BLA Clinical Review Memorandum

Application Type	Original Application
STN	125668/0
CBER Received Date	29 December 2017
PDUFA Goal Date	29 December 2018
Division / Office	DCEPT/OTAT
Priority Review (Yes/No)	No
Reviewer Name(s)	L. Ross Pierce, M.D. (Lead) and Yeowon A. Kim, MD, MHS
Review Completion Date / Stamped Date	
Supervisory Concurrence	Steve Winitsky, MD, Team Lead, GMB1
	Shari Targum, MD Chief, GMB1
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	• Weekly • Initial weekly dose = previous IGIV dose (in grams) x 1.40/number of weeks between IGIV doses
Indication(s) and Intended Population(s)	Replacement therapy for primary humoral immunodeficiency (PI) in adults. This includes, but is not limited to, common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia,

	Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.
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
PI	primary (humoral) immunodeficiency
PID	primary (humoral) immunodeficiency
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing 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 original BLA for their product, Immune Globulin Subcutaneous (Human) -- Cutaquig, formerly termed (b) (4) -- which was developed as a replacement therapy in primary humoral immune deficiency (PI). Three other IGSC products were commercially available in the U.S. for treatment of PI. In addition, the Immune Globulin Intravenous (Human) product Gamunex-C is approved for subcutaneous administration. See section 2.3 for further details. Cutaquig was first approved in Canada on 15 February 2018; however, it had not yet been marketed as of 30 June 2018 (the data lock point for the 120-day safety update for this product).

A Phase 3 study conducted under IND at 18 sites in the U.S., Eastern Europe and Canada, study SCGAM-01, provides the primary evidence of safety and effectiveness for this BLA. A total of 61 subjects with PI were enrolled in study SCGAM-01: 23 pediatric subjects aged <16 years and 38 adult subjects. The pediatric cohort included four subjects aged 2 to < 5 years, 11 subjects 5 to < 12 years, and eight subjects 12 to < 16 years of age. 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 1.50 (the dosage correction factor). The dosage correction factor was used in an attempt to match the area under the curve (AUC) for serum IgG concentration after Cutaquig treatment to the AUC after prior IGIV treatment, taking into account the lower bioavailability of IGSC compared to IGIV. The study, which involved a 15-month treatment/observation period (including a 3-month washout from prior IV immunoglobulin therapy/wash-in period and a 12-month efficacy period), assessed the incidence of serious bacterial infections (SBIs) as the primary endpoint. The study was ongoing at the time of BLA and 4-month safety update submission. All adult subjects had completed participation, but eight pediatric subjects were ongoing at time of the data cutoff date. A total of six subjects (9.8%) terminated the study early, with three adolescents [37.5%] and 3 adults [7.9%], having withdrawn consent. No subjects were reported as having discontinued study medication or participation prematurely due to adverse events. The number of subject-years of exposure/observation during the 12-month primary analysis period was 4.2 for adolescents, 9.1 for younger children, and 32.5 for adults. No SBIs were observed in the trial; the study met the primary efficacy endpoint, since the upper bound of the 99% confidence interval for the incidence of SBIs (0.084) was < 1.0 SBI per subject-year.

Secondary efficacy endpoints consisted of the following:

- Annual rate of all infections regardless of 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

The outcomes of secondary efficacy endpoints were generally within the range observed in Phase 3 IND trials of other U.S.-licensed IGSC products. Results of selected secondary efficacy endpoints are shown in the following table.

Summary of Selected Secondary Efficacy Endpoints (12-month efficacy period, FAS)

Number of subjects (efficacy period)	**61**
Total number of subject years	54.77
Infections	
Annual rate of non-SBI infections per subject-year (same as rate of all infections)	3.43 (Upper one-sided 95% confidence limit: 4.57)
Systemic antibiotic use	
Number of subjects (%)	40 (65.6%)
Annual rate (treatment days per subject-year)	39.7 39.6 (Upper one-sided 95% confidence limit: 62.7)
Days out of work/school/kindergarten/day care due to infections	
Number of days	134
Annual rate (days per subject-year)	2.6 (Upper one-sided 95% confidence limit: 4.7)
Hospitalization due to infections	1
Number of days	2
Annual rate (days per subject-year)	0.037 (Upper one-sided 95% confidence limit: 0.189)

It is challenging to draw inferences regarding safety and efficacy based on pediatric subgroups due to limited sample size. That said, adolescents had a nominally lower rate of overall infections per subject-year (1.7) than children under 12 years of age (3.2) or adults (3.5). Pharmacokinetic (PK) results were available for 18 adult subjects and four pediatric subjects. Due to the small number of pediatric subjects who underwent PK testing, no inferences could be drawn regarding comparability between the PK profile in adults and that observed in pediatric subgroups.

Of 61 subjects in the Safety Analysis set, 57 (94%) reported at least one adverse event (AE), including infections. Excluding infections and infusion site reactions, 49 subjects (80%) experienced 233 AEs. The number of infection AEs was 239. Five serious AEs (SAEs) were reported, none of which appeared causally related to Cutatquig infusion. Excluding infections, the most commonly reported adverse reactions, other than local infusion site reactions, occurring in > 5% of subjects, were headache, pyrexia, diarrhea, dermatitis, and excoriation. There did not appear to be any category of adverse reactions that was more frequent among adolescents or younger children compared to adults. Overall, 75% of subjects reported local infusion site reactions, all of which were deemed to be causally related to Cutaquig infusion in this clinical review. Twenty-three percent (814/3497) of infusions were accompanied by local infusion site reactions. Fourteen subjects (23%) experienced moderate intensity local reactions and two subjects (3.3%) experienced severe intensity reactions (bruising at week 30 in one subject and severe allergic reaction at infusion sites bilaterally at week 5 in another subject). The most common local infusion site reactions were erythema, swelling, redness and pruritus. A total of nine subjects experienced 12 infusion site hematomas. The most commonly reported AEs, excluding infusion site reactions, were sinusitis (15 subjects; 25%), nasopharyngitis (14 subjects; 23%) and upper respiratory tract infection (13 patients; 21%). No thromboembolic events, hemolysis, or cases of anaphylaxis or aseptic meningitis were reported. Based on the safety data in the BLA, the safety profile of Cutaquig appears to be qualitatively similar to that of U.S.-licensed IGSC products.

The final study report for SCGAM-04, a non-IND Phase 3 study of the product that was conducted at five sites in Russia, was submitted at FDA request on 30 August 2018 as amendment 29. This study was not the subject of a Bioresearch Monitoring inspection to verify the accuracy of the data and adherence to GCP, but the results as presented by the applicant were considered supportive of a conclusion of efficacy and safety of the product for the requested indication in the Prescribing Information. The Russian study enrolled 25 subjects with PI who were followed for up to 6 months. Other than the shorter duration and size of the study, its basic design was consistent with the FDA Guidance for IGIV products, as was the case for study SCGAM-01. No SBIs were reported in the Russian study. A total of 26 non-serious infections were observed among 14 subjects during the primary treatment period, giving a rate of total infections of 2.37 per subject-year (95% CI 1.24 to 4.52). No infections were rated as severe in intensity. The mean time to resolution of infection was 9.5 days in the primary treatment period. Ten subjects used antibiotics in 19 treatment episodes, according to the study report. During the primary treatment period, six subjects had one episode of fever each, corresponding to a rate of 0.55 febrile episodes per subject-year. Three subjects had a total of four absences from work or school due to infections, corresponding to a rate of 0.01 absences per subject-year. Slight increases in SF-35v2 quality-of-life scores were observed over the course of the trial, with mean scores ranging from 41 and 58.

In study SCGAM-04, a total of 775 infusions were administered, ranging from 7 to 32 per subject. The mean dose of Cutaquig was 0.11 g/kg weekly. No deaths, SAEs, or AEs leading to premature withdrawal of subjects were reported. Fifteen subjects (60%) reported local infusion site reactions. Fifteen percent of infusions were associated with local infusion site reactions, the most common of which were erythema, pruritis, and contact dermatitis. Seven subjects (28%) had AEs that began during, or within, 72 hours of infusion. These included respiratory tract infections, “condition aggravated,” and bronchitis, musculoskeletal discomfort, dizziness, and headache. The rate of temporally related AEs per infusion was 0.015. The overall rate of AEs was 2.4 per subject, consisting of component rates of 1.36 for infection AEs and 1.04 for non-infection AEs. Viral tests remained negative throughout the study. One subject had a total serum IgG trough level < 5g/L on one occasion.

Based on the data presented in the BLA, the benefits appear to outweigh the risks of Cutaquig for the requested indication of replacement therapy in adults with PI. The clinical reviewer(s) recommend approval for the BLA

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Table 1 summarizes demographic characteristics for the SCGAM-01 study population. There are a total of 61 subjects: 23 pediatric subjects aged <16 years and 38 adult subjects. There was a slight predominance of female subjects. All subjects but one were white. Overall infections were slightly more frequent among female than male subjects (3.6 versus 2.7 infections per subject-year, respectively), though the percentages of male and female subjects with one or more infections was similar. It is challenging to make inferences based on subgroups defined by age, race, and ethnicity due to limited sample size. That said, adolescents had a nominally lower rate of overall infections per subject-year (1.7) than children under 12 years of age (3.2) or adults (3.5 infections). The number of subject-years of exposure/observation during the 12-month primary analysis period was 4.15 for adolescents, 9.1 for younger children, and 32.5 for

adults. Eight pediatric subjects had not yet completed participation in the study at the time of data analysis for the BLA.

Table 1: Demographic Characteristics of the SCGAM-01 Study Population

Parameter		Children ≥2 Years <5 Years	Children ≥5 Years <12 Years	Adolescents ≥12 Years <16 Years	Adults ≥16 Years ≤75 Years	Total All Subjects
		N = 4	N = 11	N = 8	N= 38	N = 61
Age [Years]	Median					34.00
	Min, Max					2.0, 73.0
Gender	Female	1 (25.0%)	2 (18.2%)	3 (37.5%)	27 (71.1%)	33 (54.1%)
[N (%)]	Male	3 (75.0%)	9 (81.8%)	5 (62.5%)	11 (28.9%)	28 (45.9%)
Race	White	4 (100%)	11 (100%)	8 (100%)	37 (97.4%)	60 (98.4%)
[N (%)]	Multiple	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.6%)	1 (1.6%)
Ethnicity	Not Hispanic					
[N (%)]	or Latino	4 (100%)	11 (100%)	8 (100%)	38 (100%)	61 (100%)

Adapted from Table 6, CSR, page 60 of 3029 and Table 14.1.2.1.2, CSR, page 159 of 3029

No clear differences between adult and pediatric subjects were evident in the pattern of adverse reactions reported.

1.2 Patient Experience Data

Studies SCGAM-01 and SCGAM-04 made extensive use of patient (subject) experience data in the form of patient-reported outcomes (PROs) which were secondary efficacy endpoints, including infections other than primary endpoint SBIs, duration of infections, episodes of fever, and the numbers of days of school/work/etc. missed due to infections which were recorded by subjects and/or their caregivers in subject diaries and reviewed by investigator site staff.

Patient Experience Data Relevant to this Application

				Section where discussed, if applicable
☒	The patient experience data that was submitted as part of the application include:			
	☒	Clinical outcome assessment (COA) data, such as		[e.g., Sec 6.1 Study endpoints]
		☒	Patient reported outcome (PRO)	6.1.8; 6.1.11.2
		☒	Observer reported outcome (ObsRO)	6.1.8; 6.1.11.2
		☒	Clinician reported outcome (ClinRO)	6.1.8, 6.1.11.1
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		[e.g., Sec 2.1 Analysis of Condition]
	☐	Observational survey studies designed to capture patient experience data		

	☐	Natural history studies	
	☐	Patient preference studies (e.g., submitted studies or scientific publications)	
	☐	Other: (Please specify)	
☐	Patient experience data that were not submitted in the application, but were considered in this review		
	☐	Input informed from participation in meetings with patient stakeholders	
	☐	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
	☐	Observational survey studies designed to capture patient experience data	
	☐	Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.		

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

Primary Immunodeficiency (PI) represents a heterogenous group of disorders resulting from largely inherited defects of the immune system. It is estimated that 1-2% of the population worldwide is affected[1]. 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. Patients with PI are at increased risk for recurrent, severe respiratory tract and other infections (both viral and encapsulated bacterial in origin). At present, most primary immunodeficiencies are not curable. Hematopoietic cell transplantation may be curative for some patients with PI and gene therapy is being explored. Replacement therapy with immunoglobulins, provides antibodies to help prevent viral and bacterial diseases, and is the mainstay of treatment.

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

The general management of PI involves preventing infections and treating infections. Prevention of infections consists of avoidance measures, vaccination, prophylactic antibiotics, and immune globulin therapy. Treatment of infections often involves broader 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

1 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.

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[2]. 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 four licensed Immune Globulin Subcutaneous (Human) (IGSC) products in the U.S.: Cuvitru® (Baxalta US, Inc.), Hizentra® (CSL Behring), Hyqvia® (Baxter Healthcare Corporation, Baxter BioScience), and Vivaglobin® (CSL Behring). All are indicated for replacement therapy in patients with PI. Vivaglobin is no longer marketed in the U.S. Additionally, Gamunex-C brand IGIV 10% is approved for subcutaneous administration for PI. 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 reactions (i.e. swelling, redness, heat, discomfort at the injection site), headache, fatigue, nausea, diarrhea, vomiting, and/or pyrexia. Immune Globulin Intravenous (Human) as a drug class carries an obligate boxed warning for thrombosis, renal dysfunction, and acute renal failure. Immune Globulin Subcutaneous (Human) products carry an obligate boxed warning for thrombosis.

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

There is no previous human experience with Cutaquig. It is licensed in Canada, but had not yet been marketed as of the time of U.S. BLA submission. The manufacturing of Cutaquig is based on the applicant's currently licensed IGIV products, Octagam 5% and Octagam 10%. Octagam 10% is approved for the treatment of chronic immune thrombocytopenic purpura in adults. Octagam 5% is approved for the treatment of PI.

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

Pre-BLA Meeting, Written Response, CRMTS #10629 (04 April 2017)

1. FDA advised Octapharma that a statement referring to the final iPSP is insufficient documentation for the BLA. The agreed PSP should be submitted with the BLA and should include plans for requests of any waivers or deferrals. In addition, formal requests should be submitted for each waiver and/or deferral.

2. FDA discouraged submission of a BLA until Study SCGAM-01 is completed per terms in the protocol.

3. FDA representatives stated that they cannot comment if the proposed validation of the manufacturing process is sufficient for approval. A determination of acceptability of the proposed validation for the manufacturing process can be made only be made during BLA review.

2 Guidance for Industry: Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency. U.S. Department of Health and Human Services, Food and Drug Administration, CBER, June 2008.

4. FDA confirmed that it is acceptable that Trial Summary Datasets (ts.xpt) will not be provided for non-clinical study reports in Section 4, as the study reports have been completed before 2013.

5. FDA agreed with Octapharma's proposal to submit a complete BLA.

Follow-up E-mail Correspondence (23 May 2017)

1. FDA stated that Octapharma's proposal to submit a BLA using data from Study SCGAM-01 when all adult subjects (n = 35) plus 12 pediatric subjects have completed the study and to request a deferral for the completion of the pediatric portion of the study is acceptable. However, all decisions regarding pediatric waiver and deferral requests will be made during review of the BLA submission.

2. FDA stated that interim pediatric data should be included with the BLA submission. The final pediatric clinical study report should be submitted as a separate efficacy supplement after the study is completed. Alternatively, submission of the BLA may be delayed until the final pediatric clinical study report is available for inclusion.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate the conduct of a complete 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 common technical document structure.

3.2 Compliance with Good Clinical Practices And Submission Integrity

The applicant reported 75 major protocol deviations in 40 subjects. Major deviations were most commonly due to deviation from study protocol procedures (34 deviations in 19 (31%) subjects), dosing error (21 deviations in 17 (28%) subjects), and violation of eligibility criteria (13 deviations in 11 (18%) subjects). Dosing errors were often due to not recalculating the dose after a body weight change of > 5%. Three subjects received IP beyond its expiration date and one received IP improperly stored at room temperature for five days. At least two subjects infused the IP too rapidly. Subject (b) (6) was under-dosed on two occasions "because of broken IP container." Subject (b) (6) did not receive IP on two occasions because of a broken syringe. Minor deviations were mostly due to missed or late assessments. Four subjects (Nos. (b) (6)) were excluded from the per-protocol (PP) analysis set because they terminated early during the IGIV washout/IGSC wash-in period.

Three U.S. sites and one foreign study site were the subject of FDA Bioresearch Monitoring (BIMO) inspections to assess data integrity and compliance with Good Clinical Practice (GCP). The inspected sites are listed in the table below.

FDA Bioresearch Monitoring Inspections of Study SCGAM-01

Site ID	Study Site	Location	483 Issued	Classification
11	Faculty Hospital by St. Anna in Brno	Czech Republic	Yes	VAI*
42	University of California-Irvine	Irvine, California		VAI*
43	Toledo Institute of Clinical Research	Toledo, Ohio	Yes	NAI**
47	Pediatric Pulmonary Associates of North Texas	Frisco, Texas	Yes	VAI*

*VAI = Voluntary Action Indicated
**NAI = No Action Indicated

None of the inspectional findings were judged as being significant enough to materially affect the study data or conclusions.

3.3 Financial Disclosures

Covered clinical study (name and/or number): SCGAM-01: Clinical Phase 3 study to evaluate the pharmacokinetics, efficacy, tolerability and safety of subcutaneous human immunoglobulin ((b) (4) *16.5%*) in patients with primary immunodeficiency diseases		
Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 18		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)

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

Insert text here

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

4.1 Chemistry, Manufacturing, and Controls

Please refer to CMC reviewer's memo for details.

Cutaquig is a solution manufactured from human plasma. It contains 165 mg of protein/mL, of which ≥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, (b) (4) plasma used to manufacture Cutaquig is tested for viral pathogens at both the donor and manufacturing (b) (4) levels. The pH of the product is 5.0 to (b) (4) Maltose and polysorbate 80 serve as excipients. The presence of maltose in the product represents a safety concern, in that maltose can be mistaken for glucose in some glucose meter/test strip point-of-care systems, resulting in falsely high glycose readings, which in turn can result in inappropriate use of hypoglycemics or in the masking of hypoglycemia. This risk will be mitigated by the introduction of language in the WARNINGS AND PRECAUTIONS section of the draft package insert similar to that in the licensed maltose-containing IGIV product, Octagam. No other CMC issues were identified that impacted the safety or efficacy of the product.

4.2 Assay Validation

Please refer to the CMC reviewer's memo for details. Assay validation information for the serum IgG assay was requested during the review.

4.3 Nonclinical Pharmacology/Toxicology

Please refer to the nonclinical pharmacology/toxicology reviewer's memo for details. No nonclinical pharmacology/toxicology review issues were identified that impacted the safety or efficacy of the product.

4.4 Clinical Pharmacology

Please refer to the clinical pharmacology reviewer's memo for details.

Clinical pharmacology was evaluated in Study SCGAM-01. Pharmacokinetic (PK) profiles of Cutaquig were obtained in a subset of study participants (18 adults and four pediatric subjects). The clinical pharmacology reviewer calculated the mean and median ratios of prior IGIV weekly-equivalent dose to Cutaquig dose for the PK substudy subjects in Study SCGAM-01 and for the subgroup of adult subjects who completed the study. Based on these analyses, a dosage conversion factor of 1.40 was recommended to be used in the DOSAGE AND ADMINISTRATION section of the draft

package insert; The clinical pharmacology reviewer identified methodologic difficulties with the applicant's population PK model that precluded acceptance of dosing more or less frequent than the weekly dosing regimen studied in SCGAM-01 and SCGAM-04. The draft package insert was modified accordingly. No other clinical pharmacology review issues were identified that affected safety or efficacy.

4.4.1 Mechanism of Action

Cutaquig contains a broad spectrum of IgG antibodies, some of which are directed towards infectious agents. Cutaquig's distribution of IgG subclasses is proportional to that of human plasma. Isoagglutinins toward antigens on erythrocytes as well as IgA and IgM antibodies are present but at low 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 on weekly Cutaquig to the weekly-equivalent AUC from the prior IGIV administration (mean value 1.02) fell within acceptable limits, taking variability into account.

4.5 Statistical

The statistical reviewer has verified that the primary study endpoint analyses cited by the applicant were supported by the submitted data. The statistical reviewer also verified the secondary efficacy endpoints whose outcomes were summarized in the draft package insert. The statistical reviewer prepared tables of adverse reactions from the datasets, which this reviewer used to verify the accuracy of the listing of the most frequent adverse reactions as listed in the draft package insert.

4.6 Pharmacovigilance

The pharmacovigilance reviewer did not identify substantial issues that necessitate additional risk management measures beyond standard pharmacovigilance measures.

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

5.1 Review Strategy

The applicant included data from one study in the original BLA application: IND Study SCGAM-01. There were two ongoing studies with Cutaquig at the time of BLA submission: SCGAM-03 (Clinical Phase 3 study to monitor the safety, tolerability, and efficacy of subcutaneous human immunoglobulin ((b) (4) in patients with primary immunodeficiency diseases who have completed the SCGAM-01 trial) and the non-IND study conducted in Russia, SCGAM-04 (Clinical Phase 3 Study to evaluate the efficacy, tolerability, and safety of subcutaneous immunoglobulin ((b) (4) in patients with primary immunodeficiency diseases). Data from the two ongoing studies were not included in the original submission. An information request was sent to the applicant on 14 March 2018 requesting that all interim safety data from all studies (including, but not

necessarily limited to SCGAM-01, SCGAM-03, and SCGAM-04) be submitted as an amendment in the 120-day safety update. The applicant complied with this request and stated that study SCGAM-04 was now complete and that the final study report was available upon request. FDA requested and received the final study report for SCGAM-04, the clinical review for which is described under trial #2 in this memo.

Dr. Kim summarized the results of the review of efficacy for study SCGAM-01 and contributed introductory and disease background information to this review. Dr. Pierce performed the safety review of all studies, the efficacy review of study SCGAM-04, checked the efficacy review findings, evaluated safety and efficacy in pediatric subgroups, worked with the clinical pharmacologist regarding the evaluation of dosing, and generated and reviewed the responses to all clinical information requests.

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:

- 1.9.1: Request for [Partial] Waiver of Pediatric Studies
- 1.9.2: Request for [Partial] Deferral of Pediatric Studies
- 1.9.6: Other Correspondence Regarding Pediatric Exclusivity or Study Plans (includes the agreed iPSP and amended iPSPs)
- 1.14.1: Draft Labeling
- 1.16.1: Risk Management Plan
- 2.5: Clinical Overview
- 2.7: Clinical Summary
- 5: Clinical Study Reports and Adverse Event datasets

5.3 Table of Studies/Clinical Trials

Summary of Clinical Studies Included in this Application

Study ID	Population/ N=Patients in study/ Gender/Age Range	Design/ Study Site/Location/ Study Period	Test Product/ Dosage/ Route of Administration	Evaluation Criteria	Endpoints
SCGAM-01	PID and IgG trough levels ≥5.0 g/L N=61 28M/33F 2–73 years	Prospective, open-label, non-controlled, single-arm, multicentre Phase 3 Study 18 study sites in Canada, the Czech Republic, Hungary, Poland, Slovakia and the USA. Jun-2014 – Dec-2019	(b) (4) 16.5% Weekly subcutaneous infusions during a 12-week wash-in/wash-out phase and 12 months efficacy phase.	Pharmacokinetics, efficacy, safety	Primary endpoints: The first primary objective of the study was to assess the efficacy of (b) (4) in preventing serious bacterial infections (SBI) compared with historical control data. The second primary objective was to evaluate the PKs of (b) (4) and to compare the area under the curve (AUC) with that of IVIG. Secondary endpoints: To evaluate the tolerability and safety of (b) (4) To determine the PK profile of (b) (4) To assess the dosing conversion factor (DCF) when switching patients from IVIG treatment. To develop guidance and recommendations to support further adjustments of (b) (4) dosing based on the total IgG trough level. To assess the effect of (b) (4) on Quality of Life (QoL) measures.
SCGAM-03	PID with good tolerance of (b) (4) Target maximum N + 35 3-74 years	Prospective, open-label, uncontrolled, single-arm, multicenter, Phase 3 extension study for U.S. subjects who completed study SCGAM-01 2016 to 2018	(b) (4) 16.5% Using a "corrected" dose correction factor based on analysis of all PK subjects' data from SCGAM-01, or a value of 1.5 if the former is unknown. Weekly or every 14 days SC infusion of double the weekly dose Duration: until the product becomes commercially available in the U.S. or until the trial is terminated (~ 2.5 years)	Safety, efficacy	Safety (primary assessment): • Occurrence of all treatment-emergent adverse events (TEAEs) • 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 (haematology, clinical chemistry, basic urinalysis) Efficacy: Measurement of trough total IgG levels; monitoring for infectious diseases. Occurrence of serious bacterial infections (SBIs). Quality of life: (CHQ-PF50 or SF-36)
SCGAM-04	PID N = 25 18 to 65 years	Prospective, open-label, uncontrolled, multicenter Phase 3	Cutaquig "as prescribed"	Safety, efficacy	

Note: The secondary endpoints listed in the applicant-created portion of the above table (for study SCGAM-01 do not correspond to the actual secondary efficacy endpoints as listed in the study protocol – see section 6.1.8 of this review memo for the latter. Rather, they correspond to the study's secondary objectives.

5.4 Consultations

No consultations were needed or obtained for the review.

Outside Input Regarding Patient Experience Data:

The patient experience information in this BLA included PRO and quality of life outcomes data. FDA is unaware of any independently-conducted patient experience studies relevant to the review of this submission.

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 that needed advisory committee input.

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)

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

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1

Study SCGAM-01: Clinical Phase 3 study to evaluate the pharmacokinetics, efficacy, tolerability, and safety of subcutaneous human immunoglobulin ((b) (4) *16.5%*) in patients with primary immunodeficiency diseases

6.1.1 Objectives

Primary

- To assess the efficacy of Cutaquig in preventing serious bacterial infections (SBO) compared to historical data
- To evaluate the pharmacokinetic (PK) characteristics of Cutaquig and to compare the area under the curve (AUC) with that of IGIV

Secondary

- 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 immunoglobulin G (IgG) trough level
- To assess the effect of Cutaquig on Quality of Life (QoL) measures

6.1.2 Design Overview

Study SCGAM-01 was a prospective, open-label, uncontrolled, single arm, multi-center Phase 3 study. The study enrolled subjects with PI from ages 2 and up who had been receiving IGIV treatment. Subjects were switched from IGIV to IGSC at study start with the Cutaquig dose calculated based on the prior IGIV dose, the IGIV inter-dose interval, and a dosage correction factor to account for the lower bioavailability of IGSC vis-à-vis IGIV. The study consisted of a 12-week wash-in/wash-out period followed by a 12-

month efficacy period. The primary efficacy endpoint was the rate of serious bacterial infections (SBI; as defined in the FDA Guidance for IGIV products as bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia, and visceral abscess) per person-year on Cutaquig

There was a pharmacokinetic (PK) substudy in which a subset of study participants underwent PK assessments at three time points: (1) after the last administration of the previously used IGIV product prior to switching to Cutaquig (PK_{IV}), (2) at the end of the wash-in/wash-out phase (PK_{SC1}), and (3) after 28 administrations of Cutaquig (PK_{SC2}).

6.1.3 Population

Inclusion criteria

- Age 2 years to 75 years
- Confirmed diagnosis of PID as defined by European Society for Immunodeficiencies (ESID) and Pan-American Group for Immunodeficiency and requiring immunoglobulin replacement therapy due to hypogammaglobulinemia or agammaglobulinemia
- Previous IGIV treatment: subjects were required to have had at least 6 infusions IGIV at a dose between 200 and 800 mg/kg body weight (±20% of the mean dose for the last 6 infusions) and should have been on the same product for a minimum of 2 months prior to study entry
- Availability of IgG trough levels of two previous IVIG infusions prior to enrollment; subjects should have had trough levels ≥5.0 g/L during these infusions
- Negative pregnancy test (for women of childbearing potential) and use of a reliable method of contraception for the duration of the study

Exclusion criteria

- Acute infection requiring IV antibiotic treatment within 2 weeks prior to and during the screening period
- Known or suspected human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV) infection
- Requirement of any routine premedication for IgG administration
- Severe liver function impairment (alanine aminotransferase [ALAT] 3 times above upper limit of normal)
- Protein-losing enteropathies or proteinuria
- 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)
- History of adverse reactions to IgA
- Hypersensitivity to blood or plasma-derived products or any component of the investigational product
- 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
- Body mass index (BMI) >40 kg/m2
- 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

- History of malignancies of lymphoid cells and immunodeficiency with lymphoma
- Treatment with any investigational product within 3 months prior to first infusion of Cutaquig
- Pregnant or nursing women

Reviewer Comment: Excluding subjects 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

IGIV: Subjects participating in the PK substudy 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.
Cutaquig: Subjects received weekly subcutaneous administrations of Cutaquig during the 12-week wash-in/wash-out phase and 12-month efficacy phase, for a maximum period of 15 months. The Cutaquig dose was calculated as follows:

$$\text{Initial weekly dose (g)} = \frac{\text{previous IGIV dose (g)}}{\text{number of weeks between IGIV doses}} \times 1.5$$

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 to have been adjusted during the study if subjects' body weights changed by >5%, but this did not always occur. Notwithstanding the instructions in the protocol to use a dosage conversion factor of 1.5 as shown in the equation above, the average ratio of Cutaquig dose to the weekly-equivalent prior IGIV dose used among adults in the study was approximately 1.40. The latter value was recommended (at FDA request) in the draft package insert to calculalte the Cutaquig dose.

6.1.5 Directions for Use

Administration
Infusions were conducted with a syringe driver infusion pump. Subjects or their caregivers were trained at the study site for at least four Cutaquig administrations. Subsequently, Cutaquig could be administered at home. Administrations were given at the study site every four weeks. A maximum of six infusion sites was permitted for each administration. Infusion sites had to be at least two inches apart and had to be changed with each weekly administration.

Infusion Volume
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 ≥5 years old

- First administration: maximum of 10-15 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 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

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. For adult subjects, the maximum infusion rate could be increased further to 80 mL/hour for all sites combined starting from the 40th infusion. 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 relatively high flow rates permitted under the protocol may have contributed to the high rate of local infusion site reactions.

IgG Monitoring

Serum IgG trough levels were monitored throughout the study. Subjects who did not participate in the PK substudy 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 in the PK substudy had additional IgG measurements taken for PK profiling after the last administration of the previously used IGIV product prior to switching to Cutaquig (PK_{IV}), at the end of the wash-in/wash-out phase (PK_{SC1}), and after 28 administrations of Cutaquig (PK_{SC2}).

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. From the BIMO inspectional findings, however, it was apparent that

Cutaquig doses had not been titrated upward based on observed differences between serum IgG trough levels during Cutaquig administration and the target trough level calculated from the trough IgG level during prior IGIV treatment, which was intended to match the AUCs of IGIV and IGSC. Despite this, the dosage adjustment factor of 1.50 used in the trial was successful in achieving a group mean AUC for serum IgG at week 28 that was not lower than the AUC on prior IGIV for the subset of 22 subjects who underwent PK testing.

6.1.6 Sites and Centers

Twenty-one study sites were opened for the study; however, 18 sites enrolled subjects. Of the 18 active sites, 7 were in the U.S., 4 in the Czech Republic, 3 in Slovakia, 2 in Poland, 1 in Canada, and 1 in Hungary. The site numbers, countries of location, and investigators are listed below:

Site	**Investigator**
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 01 (Poland):	Grazyna Pulka
Site 02 (Poland):	Anna Pituch-Noworolska
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

6.1.7 Surveillance/Monitoring

For international study sites, study monitoring was performed by (b) (4)), a contract research organization. Monitoring of the U.S. sites was organized internally by the sponsor. 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 *Haemophilus influenza*, cytomegalovirus (CMV), tetanus, and measles were performed by (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 adverse event (AE) monitoring. The following assessments were performed at study site visits as outlined in the protocol schedule of assessments: laboratory parameters, weight, patient diary review, physical exam including vital signs, quality of life (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 patient diaries were transcribed onto eCRFs.

An independent data monitoring committee periodically reviewed study data with an emphasis on thromboembolic events (TEEs) and clinically significant hemolysis.

6.1.8 Endpoints and Criteria for Study Success

Efficacy
Primary Endpoint: Rate of serious bacterial infections (SBIs) per subject-year of observation on Cutaquig (SBI defined as bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia, and visceral abscess)

Secondary Endpoints:
- Annual rate of all infections regardless of 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

Pharmacokinetic
Primary Endpoint: Area under the curve (AUC) from time 0 (start of infusion) to the end of the nominal dosing period, standardized to 1 week (AUC_T) at steady-state conditions

Secondary Endpoints:
- PK profiles of total IgG, of IgG subclasses (IgG1, IgG2, IgG3, IgG4) and of antigen-specific antibodies against *Haemophilus 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)
- Trough levels of specific antibodies against *Haemophilus influenzae*, *Streptococcus pneumoniae* (types 4, 6B, 9V, 14, 18C, 19F, 23F), CMV, tetanus and measles
- IGIV to Cutaquig dosing conversion factor (DCF)

Safety
- Treatment-emergent adverse events (TEAEs) throughout the entire 65-week treatment period starting with the first infusion of Cutaquig
- Temporally associated TEAEs
- Proportion of infusions with at least one temporally associated AE
- Suspected adverse reactions (SARs)
- TEAEs by rate of infusion
- Local injection site reactions
- Vital signs (blood pressure, pulse, body temperature, respiratory rate)
- Laboratory parameters (hematology, clinical chemistry, hemolysis markers, viral markers)

6.1.9 Statistical Considerations & Statistical Analysis Plan

Please refer to the statistical reviewer's memo for details.

Efficacy

The full analysis set (FAS) was used for the primary assessment of efficacy. The SBI rate was calculated as the number of SBIs divided by person-years, starting with the end of the 12-week wash-in/wash-out period until the end of the study. A compound Poisson model was used to determine the SBI rate and the two-sided 98% confidence interval (CI). The null hypothesis was that the SBI rate is greater than equal to 1.0 per person-year, tested at the 1% level of significance. The null hypothesis was rejected if the two-sided 98% CI (which is the upper one-sided 99% CI) was less than 1.0.

The rate of other infections was calculated per person-year. The duration of infection was summarized using descriptive statistics.

Antibiotic use was reported as a list of medications, number of subjects treated with antibiotics, number of treatment episodes, and number of treatment days. Hospitalizations due to infections, episodes of fever, and absences from work or school were summarized using descriptive statistics. Quality of life data were also presented descriptively, along with the change from baseline.

Pharmacokinetics
Dose-dependent PK calculations for Cutaquig used actual potencies of the batches. Such calculations for IGIV used the nominal IgG content. PK analysis was performed by non-compartmental methods using actual elapsed time from the start of infusion and with the assumption that steady-state conditions are observed at the time of PK assessments. PK parameters were summarized using descriptive statistics. The final PK profile (PK_{SC2})of subjects in the PK substudy was evaluated for bioequivalence to IGIV. Two one-sided tests (TOST) analysis of the mean AUC_T ratio of the final adjusted Cutaquig and IGIV doses was performed.

Safety
Descriptive statistics were used to analyze safety. Treatment emergent adverse events (TEAEs) were classified as temporally associated if event onset was during the infusion or within 72 hours after the end of infusion. The proportion of infusions with one or more temporally associated AEs and the upper one-sided 95% CI were calculated. The calculation of the CI took into account the observed intra-patient correlation, as multiple infusions in a single subject cannot be assumed to be statistically independent. Adverse reactions were defined as adverse events that began during or within 72 hours of the end of the last Cutaquig infusion, plus those adverse events falling outside this time window that were deemed by either the investigator or sponsor to be at least possibly related (or of indeterminate relationship) to Cutaquig administration.

Determination of Sample Size
It was calculated that 42 person-years would provide 90% power to reject the null hypothesis of a SBI rate ≥1.0 at a 1% level of significance (Type 1 error rate of 0.01) and assuming a true SBI rate of less than 0.5 per year. Assuming a drop-out rate of 15%, the target for enrollment was set at a minimum of 50 subjects. It was calculated that 20 subjects for the PK substudy would provide 85% power for equivalence testing of the paired [IGIV and IGSC] geometric mean ratio, assuming that intrasubject variability does not exceed 0.25 and that the correlation between AUC_{TSC} and AUC_{TIV} is at least 0.4.

Missing Data
In general, missing data were not imputed. Person-year calculations were based on observed values only. Regarding AEs, if the start date and time of an AE were missing,

the AE was assumed to be treatment-emergent. Missing start dates and times were not replaced. Medications were assumed to be concomitant if it could not be determined that the medication was not administered during the Cutaquig treatment period.

6.1.10 Study Population and Disposition

Insert text here

6.1.10.1 Populations Enrolled/Analyzed

The analysis populations were defined as follows:

- Safety Analysis Set (SAS): all enrolled subjects who received any Cutaquig
- Full Analysis Set (FAS): subjects in the SAS who met eligibility criteria and for whom post-baseline data were available
- Per-Protocol Set (PP): subjects in the FAS but excluding those with major protocol violations which may have an impact on the analysis of the primary efficacy endpoint. Four subjects were excluded from the Per-Protocol set who terminated prior to the Primary Treatment Period.
- PK Evaluable Set 1: subjects who have sufficient PK data for the IGIV trough levels prior to switching to Cutaquig and also after the 11th infusion of Cutaquig to determine $AUC_{\tau IV}$ and $AUC_{\tau SC}$, respectively. Subjects with protocol violations or medical conditions likely to influence trough levels or AUC values were excluded.
- PK Evaluable Set 2: subjects who have sufficient PK data for the IGIV trough levels prior to switching to Cutaquig and also after the 28th infusion of Cutaquig to determine $AUC_{\tau IV}$ and $AUC_{\tau SC}$, respectively. Subjects with protocol violations or medical conditions likely to influence trough levels or AUC values were excluded.

Efficacy endpoints were analyzed using both the FAS and PP. Safety endpoints were analyzed using the SS. The PK Evaluable Sets were used for PK analyses.

6.1.10.1.1 Demographics

Demographic characteristics for the SCGAM-01 study population are summarized in Table 1 and Section 1.1. Of the 61 subjects in the Safety Analysis Set, 23 subjects (37.8%) were aged <16 years. There was a slight predominance of female subjects (54.1%). All but one subject was white (98.4%) and none were Hispanic or Latino.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The majority of subjects (53 of 61, 86.9%) had CVID. Three subjects (4.9%) had XLA and 5 subjects (8.2%) had other immunodeficiencies: 2 subjects had hypogammaglobulinemia, and there was one subject each with IgG deficiency, hypogammaglobulinemia IgG1, and selective deficiency of IgG_1 and IgG_2. The most common (i.e. occurring in ≥20% of subjects) findings from the medical history by preferred term (PT), excluding immunodeficiency, were asthma (27 of 61 subjects, 44.3%), rhinitis allergic (23 subjects, 37.7%), gastroesophageal reflux disease (17 subjects, 27.9%), and chronic sinusitis (13 subjects, 21.3%).

Mean (SD) body weight of all subjects in the Phase 3 IND study was 57.0 (22.2) kg. Median body weight was 60.9 kg (range 13.0 to 98.6 kg). Among the adult subjects age > 16 years, Mean (SD) body weight was 68.6 (12.5) kg and median body weight was 67.3 kg (range 44.3 to 98.6 kg). Mean (SD) BMI among adults was 24.5 (4.1) and the median BMI among adults was 23.8 (range 18.6 to 40.0).

There were three (7.9%) current smokers and 7 (18.4%) ex-smokers in the study, all among adults. Maximum alcohol consumption was recorded at 14 units per week.

Baseline chest x-rays were abnormal and clinically significant for one subject (subject (b) (6) left lowere lobe atelectasis), normal for 44 subjects and abnormal but not clinically significant for 15 subjects.

The distribution of ABO blood types, which is relevant to the risk of hemolysis from IgG products, was a follows: 27 subjects with Type A, 5 subjects with Type AB, 7 subjects with Type B, and 17 subjects with Type 0. ABO blood type was missing for 5 subjects.

Medical history findings that may overlap with adverse reactions documented in the setting of immune globulin use include drug hypersensitivity (11 subjects, 18.0%), fatigue (7 subjects, 11.5%), headache (5 subjects, 8.2%), migraine (5 subjects, 8.2%), hypersensitivity (6 subjects, 9.8%), nausea (2 subjects, 3.3%), urticaria (1 subject, 1.6%), Coombs test positive (1 subject, 1.6%), hemoglobin urine present (1 subject, 1.6%), and deep vein thrombosis (1 subject, 1.6%).

More subjects had previously been treated with IGIV on an every 4-week schedule (47 subjects, 77%) than on an every 3-week schedule (14 subjects, 23%). The mean commercial IGIV dose over the prior 6 infusions was 438.1 mg/kg.

Thirteen subjects (21.3%) had a baseline medical history of chronic sinusitis (11 adults and 2 adolescents). Twenty-seven subjects (44.3%) had a baseline medical history of asthma (12 adults and 15 pediatric subjects).

Medications for obstructive airways disease were the most common type of prior medication and were being taken by 33 subjects (54%). Antihistamines for systemic use were being used by 21 subjects (34.4%).

6.1.10.1.3 Subject Disposition
A total of 61 subjects were enrolled, of which 38 were age 16 and above, and 23 were pediatric subjects age ≥ 2 to < 16 years of age. All enrolled subjects received treatment with the investigational product (IP). As of the 27 October 2017 data cutoff date of the original BLA, 35 adults and 12 pediatric subjects (total of 47 subjects) had completed the study and 8 pediatric subjects were continuing in the study. No adults were ongoing evaluation under the study at the time of data cutoff. A total of six subjects (9.8%) terminated the study early (three adolescents [37.5%] and 3 adults [7.9%]).

Subjects were included in the various analysis sets as shown in Applicant's Table 5 below.

Table 5: Number of Patients per Analysis Set

	Children ≥2 Years <5 Years N=4 N (%)	Children ≥5 Years <12 Years N=11 N (%)	Adolescents ≥12 Years <16 Years N=8 N (%)	Adults ≥16 Years ≤75 Years N=38 N (%)	Total All Patients N=61 N (%)
Enrolled (Total Set)	4 (100.0%)	11 (100.0%)	8 (100.0%)	38 (100.0%)	61 (100.0%)
Safety Analysis Set	4 (100.0%)	11 (100.0%)	8 (100.0%)	38 (100.0%)	61 (100.0%)
Full Analysis Set (FAS)	4 (100.0%)	11 (100.0%)	8 (100.0%)	38 (100.0%)	61 (100.0%)
Per-Protocol Set (PP)	4 (100.0%)	11 (100.0%)	5 (62.5%)	37 (97.4%)	57 (93.4%)
Pharmacokinetic Evaluable Set 1	0 (0.0%)	2 (18.2%)	2 (25.0%)	19 (50.0%)	23 (37.7%)
Pharmacokinetic Evaluable Set 2	0 (0.0%)	2 (18.2%)	1 (12.5%)	19 (50.0%)	22 (36.1%)

Secondary efficacy endpoint - Total Infections

A total of 188 infections were observed among 52 of the 61 trial subjects during the 12 months following the initial 12-week washout/wash-in period (primary observation period). The rate of other infections per person-year was 3.43 overall (upper 95% CI: 4.57). The above applicant analysis included eight pediatric subjects whose participation was still ongoing at the time of database lock. In order to avoid seasonal influences, the applicant was asked to provide the results of the corresponding analysis performed on the subset of subjects that excluded ongoing subjects who had not completed the 15 month study total study period. For this subgroup, the overall rate of all/other infections over the primary (up to 12 month) treatment period was 3.24 per person-year of observation (upper 95% CI = 4.45 infections per person-year).. The overall rate of all/other infections over the total (up to 15 month) treatment period was very similar at 3.33 per person-year of observation (upper 95% CI = 4.56 infections per person-year)..

Including the 3 month IGIV washout/IGSC wash-in period, a total of 239 infections were observed among 54 subjects. Upper respiratory tract infections were the most frequently reported type of infection (108 infections). Lower respiratory tract and genitourinary tract infections were reported less frequently (19 infections each). No infections were classified as serious. One infection in an adolescent was rated severe in intensity. Three-quarters of the infections were mild (136/188) and one-quarter (51/188) moderate in intensity.

Hospitalizations for infections

A single (adolescent) subject was hospitalized for infection during the 12 month primary efficacy evaluation period, according to the clinical study report (CSR, page 60). The duration of hospitalization was two days. The number of days in hospital per subject-year was 0.037 days.

Episodes of Fever

During the primary observation period four (6.6%) subjects each had one episode of fever and one (1.6%) subject had 2 episodes (total 5 subjects; 8.2%). Overall, 0.110 episodes of fever per person-year were observed. Three febrile subjects were adults, one was an older child and one was adolescent.

Time to resolution of infections

In the primary observation period (efficacy period), the mean and median times to resolution of all infections were 24.0 and 10.0 days, respectively. For the overall study period, the mean and median times to resolution of all infections were 22.6 and 10.0 days, respectively. The single severe infection required 21 days to resolve.

Use of Antibiotics

During the primary observation period, 41 subjects (67.2%) used antibiotics; throughout the whole study 44 subjects (72.1%) used antibiotics. The mean number of antibiotic treatment episodes per subject-year was 2.14 and the number of treatment days per subject-year was 51.8. The number of treatment episodes ranged between one (in 14 subjects) and 9 (in one subject) and the total number of days on antibiotic treatment ranged between 4 and 372 days.

Reviewer Comment: The mean number of antibiotic treatment episodes per subject was less than the mean number of total infections per subject. This may have reflected an assessment of many infections having been of viral rather than bacterial in origin.

Absences from Work or School Due to Infection

During the primary observation period 16 subjects had 29 absences from work or school due to infections with a total of 134 days of absence. The rate of absence from work or school per person-year was 0.012, assuming 200 working/school days per year, with similar rates for absences seen in the adult and adolescent groups. The rate of absences per subject-year was 2.45.

Quality of Life

In children under 14 years of age, the CHQ-OPF50 questionnaire was used to assess quality of life (QoL). This instrument 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. Physical and psychosocial summary scores are transformed to a scale from 0 to 100. Higher scores indicate more positive functioning/better health status. Data collection was incomplete, with 15 questionnaires completed at week 28 and 11 at the end-of-study visit. No major changes over time were observed.

In subjects aged 14 years and older, the SF-36 was used to assess QoL. Higher scores indicate a better health state. The transformed scale is 0 to 100 standardized to a mean score 50 and standard deviation of 10 in the general U.S. population. Responses are combined to create eight SF-36 scales: physical function, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health. Two further summaries can be derived from the norm-based scale scores, using a weighted sum: physical health score and mental health score. Mean SF-36v2 scores ranged between 42 and 53. The summary mental health score was 51.81 at the End of Study Visit and the physical health score was 48.55 at this time point. Overall there were increases between Week 1 and the End of Study Visit in mean scores for both summary scores (physical health and mental health) and for 7 of the 8 scales (there was a mean decrease of 0.03 for bodily pain). The largest increase was seen in the general health score (mean increase of 3.97 points).

Comparison of Cutaguig Efficacy Outcomes to those of Two other IGSC Products

Efficacy outcomes of the primary and secondary endpoints shown in the table below were similar between Cutaquig and the two other (U.S.-licensed) IGSC products listed.

Efficacy Endpoints for Two Other (U.S.-Licensed) IGSC Products

Efficacy Endpoint	**Hizentra**	**Cuvitru**
SBI Rate	0	0.012 SBIs/subject-year
Total Infection Rate	2.76 infections/subject year	3.03 infections/subject year
Antibiotic Use Rate	48.5 days/subject year	57.59 days/subject year
Absences School/Work Rate	2.06 days/subject year	1.16 days/subject year
Hospitalization for Infection Rate	0.2 days/subject year	0.06 days/subject year

6.1.11.3 Subpopulation Analyses

Primary efficacy endpoint – SBI incidence

No SBIs were reported for any subgroup.

Pediatric subgroups were limited in size and person-years of exposure to IP. The young children age group (2 to < 5 years) had 3.75 subject-years of exposure. The older children age group (5 to < 12 years) had 10.20 subject-years of IP exposure. Four of the 8 adolescents had 20 or fewer IP infusions, resulting in 4.26 subject-years IP exposure in the age group 12 to < 16 years. By comparison, adults age 16 and above had 36.56 person-years of IP exposure.

Secondary efficacy endpoint - Total Infections/Other Infections

Thirteen infections (all mild) were reported in the 4 children enrolled in the youngest age cohort (ages 2 to < 5 years), with infections in the upper and lower respiratory tract and gastrointestinal tract. Forty infections were reported in 9 older children (ages 5 to <12 years), all but 3 of which were mild intensity, with infections in the upper and lower respiratory tract, ear infections, gastrointestinal tract, genitourinary tract and not (elsewhere) classified. Eleven infections were reported in 5 subjects (2.58 infections/person-year) in the adolescent group (age 12 to < 16 years), with infections in the upper and lower respiratory tract and an ear infection; 6 were mild, 4 were moderate and 1 was severe. The rates of other infections per subject-year and the corresponding one-sided upper 95% confidence intervals are shown in the table below.

Other (non-SBI) Infection Rates by Age Subgroups

Parameter	2-<5 yrs	5 - <12 yrs	12 - <16 yrs	> 16 yrs	All
Number of person-years exposure	3.75	10.20	4.26	36.56	54.77
Total number (rate) of other infections per person-year	3.468	3.921	2.582	3.391	3.432
One-sided 95% CI – upper limit	8.410	7.196	5.937	4.907	4.572

CI=Confidence interval; N=Number of patients; n=Number of infections
Source: Adapted from Applicant's Table 9 on page 66 of 3029 of FSR.

The rate of total infections was somewhat lower among adolescents at 2.6 infections per subject-year, but the number of subject-years of IP exposure and evaluation was limited. The total infection rate was otherwise fairly consistent among younger children, older children, and adults.

Time to resolution of infections

Mean and median times to resolution of all infections for age subgroups are shown in Applicant's Table 10 below.

Table 10: Time to Resolution of Other Infections in the Primary Observation Period (Full Analysis Set, N=61)

Time to Resolution of Infections [Days]	Children ≥2 Years <5 Years N=4 N (%)	Children ≥5 Years <12 Years N=11 N (%)	Adolescents ≥12 Years <16 Years N=8 N (%)	Adults ≥16 Years ≤75 Years N=38 N (%)	Total All Patients N=61 N (%)
n	13	40	11	124	188
Mean (SD)	30.00 (57.340)	31.53 (64.702)	15.55 (11.139)	21.77 (42.634)	24.05 (48.046)
Median	7.00	13.00	12.00	10.00	10.00
Min, Max	3.0, 165.0	1.0, 292.0	7.0, 47.0	2.0, 316.0	1.0, 316.0

N=Number of patients; n=number of infections; SD=standard deviation
Source: FSR page 67 of 3029

Use of Antibiotics

Two older children, one adolescent and seven adult subjects had >100 days in total of antibiotic treatment. Six subjects had individual antibiotic treatments of >100 days: in the two older children (subjects (b) (6)), the adolescent (subject (b) (6) and in one adult (subject (b) (6) it was long-term prophylactic treatment, in one adult (Patient (b) (6) it was topical acne treatment and in one adult (Patient (b) (6) it was topical inhalation treatment

6.1.11.4 Dropouts and/or Discontinuations

A total of six subjects (9.8%) terminated the study early (three adolescents [37.5%] and 3 adults [7.9%]). Premature withdrawals were described as being due to subject decision' In the case of two subjects who withdrew prematurely, it was stated that the [IP] infusion took too long.

6.1.11.5 Exploratory and Post Hoc Analyses

See appendix for results of analyses of infections and of adverse reactions excluding ongoing pediatric subjects who had not completed 12 months of Cutaquig administration during the primary efficacy period.

6.1.12 Safety Analyses

6.1.12.1 Methods

Exposure to IP

Thirty-seven subjects (60.7%) received all 64 scheduled IP infusions. Seven subjects (11.5% received 63 infusions and three subjects received 65 infusions. Eight subjects were still continuing in the study as of the data cutoff for the BLA analyses. Forty-six of 61 subjects (75.4%) did not have more than 2 infusions outside the treatment window of 2 days; 38 subjects (62.3%) had all IP infusions within the protocol-mandated treatment window.

"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 and Adverse Reactions

Of 61 subjects in the Safety Analysis set, 57 (94%) reported at least one adverse event (AE), including infections. Infusion site reactions are described in the next paragraph.

Excluding infections and infusion site reactions, 49 subjects (80%) experienced 233 events. The number of infection AEs was 239. The most commonly reported AEs excluding infusion site reactions were sinusitis (15 subjects, 25%), nasopharyngitis (14 subjects; 23%) and upper respiratory tract infection (13 patients; 21%). Five subjects (8%) reported 9 headache AEs (one of the most common AEs associated with IGIV). Excluding infections and infusion site reactions, commonly reported TEAEs were diarrhea and arthropod bite (both reported in 7 subjects; 11.5%) and pyrexia (6 patients; 9.8%). The highest frequency of AEs occurred during months one and three. The highest frequency of temporally associated AEs occurred during month one (12 subjects (20%) reported 24 such AEs). Excluding infections and local infusion site reactions, forty-nine (21.0%) of AEs were moderate in intensity and three (1.3%; appendicitis, nephrolithiasis, asthma) were rated severe in intensity. Among infection AEs, 27.2% were moderate and 0.4% (one case of respiratory syncytial virus bronchiolitis) were considered severe.

Overall, 75% of subjects reported local infusion site reactions. Twenty-three percent of infusions (814/3497) were accompanied by local infusion site reactions. Fourteen subjects (23%) experienced moderate intensity local reactions and two subjects (3.3%) experienced severe intensity reactions (bruising at the abdominal infusion site at week 30 and severe allergic reaction at lower back infusion sites bilaterally at week 5 in subject (b) (6) Moderate and severe local infusion site reactions were more commonly reported among adults. Interestingly, a greater percentage of home infusions were associated with moderate or severe local infusion site reactions than was the case with infusions given in the clinic. The most common local infusion site reactions were erythema, swelling, redness and pruritus. A total of nine subjects experienced 12 infusion site hematomas. This reviewer considers all local infusion site reactions to be causally related to IP administration. Specific local infusion site reactions are provided in the applicant's Table 31 below.

Table 31: Summary of Category and Type of Infusion Site Reaction by Patient (Frequency >5.0% of the Total Patients) (Safety Analysis Set, N=61)

	Children ≥2 Years <5 Years N=4	Children ≥5 Years <12 Years N=11	Adolescents ≥12 Years <16 Years N=8	Adults ≥16 Years ≤75 Years N=38	Total All Patients N=61
Number of patients (%) number of infusion site reactions by category[1]					
Skin lesions	2 (50.0%) 21	7 (63.6%) 78	4 (50.0%) 15	28 (73.7%) 342	41 (67.2%) 456
Space-occupying lesions	1 (25.0%) 3	5 (45.5%) 75	3 (37.5%) 38	22 (57.9%) 319	31 (50.8%) 435
Local sensation or perception	0 (0.0%) 0	3 (27.3%) 3	2 (25.0%) 4	17 (44.7%) 168	22 (36.1%) 175
Other	0 (0.0%) 0	1 (9.1%) 1	1 (12.5%) 1	10 (26.3%) 72	12 (19.7%) 74
Haematomas	1 (25.0%) 1	3 (27.3%) 4	1 (12.5%) 1	4 (10.5%) 6	9 (14.8%) 12
Procedural events	0 (0.0%) 0	1 (9.1%) 1	3 (37.5%) 3	2 (5.3%) 4	6 (9.8%) 8
Number of patients (%) number of infusion site reactions of …					
Erythema	2 (50.0%) 21	1 (9.1%) 50	2 (25.0%) 7	20 (52.6%) 160	25 (41.0%) 238
Swelling	0 (0.0%) 0	4 (36.4%) 72	3 (37.5%) 19	16 (42.1%) 257	23 (37.7%) 348
Redness	0 (0.0%) 0	7 (63.6%) 24	3 (37.5%) 6	12 (31.6%) 159	22 (36.1%) 189
Pruritus	0 (0.0%) 0	0 (0.0%) 0	2 (25.0%) 2	12 (31.6%) 137	14 (23.0%) 139
Mass	0 (0.0%) 0	3 (27.3%) 3	1 (12.5%) 1	6 (15.8%) 14	10 (16.4%) 18
Oedema	1 (25.0%) 3	0 (0.0%) 0	1 (12.5%) 17	8 (21.1%) 47	10 (16.4%) 67
Pain	0 (0.0%) 0	2 (18.2%) 2	1 (12.5%) 2	6 (15.8%) 11	9 (14.8%) 15
Bruising	0 (0.0%) 0	2 (18.2%) 2	1 (12.5%) 1	3 (7.9%) 4	6 (9.8%) 7
Haematoma	1 (25.0%) 1	2 (18.2%) 2	0 (0.0%) 0	2 (5.3%) 2	5 (8.2%) 5
Induration	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	5 (13.2%) 7	5 (8.2%) 7
Extravasation	0 (0.0%) 0	1 (9.1%) 1	2 (25.0%) 2	1 (2.6%) 2	4 (6.6%) 5
Infusion site reaction (NEC)	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	4 (10.5%) 4	4 (6.6%) 4
Not further specified	0 (0.0%) 0	1 (9.1%) 1	1 (12.5%) 1	2 (5.3%) 2	4 (6.6%) 4
Warmth	0 (0.0%) 0	1 (9.1%) 1	0 (0.0%) 0	3 (7.9%) 5	4 (6.6%) 6

1 Space-occupying lesions: Swelling; Oedema; Infiltration; Nodule; Mass
Skin lesions: Erythema; Eruption; Inflammation; Rash; Urticaria; Hives; Redness; Allergic
Local Sensation or Perception: Pruritus; Tenderness; Paraesthesia; Pain; Warmth
Haematomas: Bruising; Haematoma
Other: Infusion Site Reaction (NEC); Discomfort; Induration; Not Further Specified
Procedural Events: Extravasation; Leaking; Tape Allergy

The most frequent adverse reactions (suspected adverse reactions/adverse reactions) occurring in > 5% of study subjects are listed in the table below:

Table: Adverse Reactions other than Local Infusion Site Reactions Occurring in > 5% of Subjects

Adverse Reaction Preferred Term	Number of Subjects	Percent of Subjects	Number of Events
Sinusitis	9	14.8	14
Acute Sinusitis	4	7.5	6
Rhinitis	5	8.2	6
Nasopharyngitis	9	14.8	16
Pyrexia	5	8.2	6
Dermatitis	6	9.8	7
Headache	4	6.6	5
Bronchitis	4	6.6	5
Cough	4	6.6	5
Diarrhea	5	8.2	8
Excoriation	4	6.6	4

Note: This reviewer excluded "arthropod bite" from the above listing as it was judged not reasonable to conclude a causal relationship between this AE and IP administration.

Most of the above adverse reactions appear infection-related and could be considered to have resulted from an insufficient therapeutic effect of the IP in preventing all types of infections. See Applicant's Tables 2.1.1 under Question 5 in the Appendix entitled "Applicant's Response to FDA Clinical Information Request dated 14 March 2018" for the complete tabular listings of adverse reactions by age category and by sex.

No AEs were described as having led to death or premature withdrawal from the study. Five SAEs were reported, including one serious infection in an adolescent. (see section 6.1.12.4 below). All SAEs were considered unrelated or unlikely relalted to Cutaquig administration by the investigator/applicant or this reviewer.

The overall percentages of subjects who experienced one or more AEs excluding infections and infusion site reactions were generally similar across in each age stratum. Excluding infections and infusion site reactions, overall, 42 of 61 subjects (69%) experienced 135 temporally associated AEs (AEs that began during or within 72 hours of the last IP infusion). The rate one or more temporally associated AEs per infusion was 3.35% excluding infections and infusion site reactions. Flow rates over 70 mL per hour were associated with higher rates of temporally associated AEs. The overall rate of AEs per infusion was 3.9%. A total of 43 subjects (70%) experienced one or more suspected adverse reactions.

Including infections but excluding infusion site reactions, overall, 51 of 61 subjects (84%) experienced 268 temporally associated AEs. A total of 52 subjects (85%) experienced one or more suspected adverse reactions.

6.1.12.3 Deaths

No deaths were reported as of the data cutoff date.

6.1.12.4 Nonfatal Serious Adverse Events

Five SAEs were reported:

- One benign thyroid neoplasm resected in an adult female age 63 years with a history of partial thyroidectomy
- One case of appendicitis in an adult after the 3rd IP infusion
- One case of worsened (cluster of four) grand mal convulsions 20 days after IP infusions were begun in a 13-year-old male child with autism and a 13-year history of seizure disorder.
- One hospitalization for acute exacerbation of asthma during the 2nd month of IP administration in an adolescent female with a history of asthma. . "Viral tests were positive for rhinovirus."
- One serious infection (respiratory syncytial virus bronchiolitis) after 31 weeks of IP administration in the same adolescent who had the SAE of asthma.

Narratives were provided and reviewed for each of the above SAEs. This reviewer considers that each of the above SAEs were unlikely to be related to IP administration. The investigators concluded that the grand mal seizures was unlikely related and the other SAEs were not related to IP administration.

6.1.12.5 Adverse Events of Special Interest (AESI)

No thromboembolic events, hemolysis, or cases anaphylaxis or of aseptic meningitis were reported.

6.1.12.6 Clinical Test Results

Two subjects (Nos. (b) (6)) had free hemoglobin reported as an AE, one subject (No. (b) (6) had Coombs direct test positive reported as an AE, and one subject had haptoglobin decreased reported as an AE. Four subjects (Nos. (b) (6)) had treatment-emergent positive Coombs direct test. None of the latter had hemoglobin drops of $\geq$ 2 g/dL. One subject (#(b) (6) had a rise in serum LDH from normal to clinically significantly high (343 IU/L) at week 4. One subject (#(b) (6) had normal hemoglobin at baseline that fell to clinically significantly low at week 28. Two subjects (Nos. (b) (6)) had treatment-emergent positive hemoglobinuria. Median hemoglobin did not drop in any age group from baseline to end-of-treatment. Median serum creatinine rose slightly in all age groups. The maximum serum creatinine value at the end-of-treatment was 118.5 micromol/L (typical upper limit of normal for females is 90 and for males is 110 micromol/L). Median serum urea change from baseline to end-of-treatment was more variable across age categories but values were available for less than a quarter of study subjects.

REVIEWER COMMENT: Most of the reported changes above in laboratory values are consistent with hemolysis, but no clinical diagnoses of hemolysis were reported in the study. Most IGIV-associated hemolysis is thought to be extravascular hemolysis with nadir hemoglobin achieved approximately 7 to 10 days following administration.

Viral Testing

Subject (b) (6) had a positive HBsAg test at the end of study visit on (b) (6) with concurrent negative HBV viral load. HBsAg and HBV viral load were negative at follow-*up* testing the next month on (b) (6) . The subject's serum ALT and AST values remained within normal limits throughout the study. (The subject's serum ALT

was 15 (ULN (ULN 33) and AST was 22 (ULN 30) at screening on (b) (6). Serum ALT was 12 and AST was 21 at week 1 on (b) (6) Serum ALT was 16 and AST was 22 at week 4 on 03 Aug 2015. Serum ALT was 13 and AST was 24 at week 16 on (b) (6). Serum ALT was 14 and AST was 25 at week 28 on (b) (6). Serum ALT was 15 and AST was 22 at week 40 on (b) (6). Serum ALT was 16 and AST was 24 at week 52 on (b) (6). Serum ALT was 14 and AST was 22 at the end-of-study visit on (b) (6).)

Treatment-emergent positive parvovirus B19 viral load was observed in one older child (No (b) (6) and two adults (Nos. (b) (6)) at week 28 and in two adults (Nos. (b) (6) and (b) (6) at end-of-study.

Treatment-emergent positive hepatitis A virus (HAV) viral load was observed in one adult subject (#(b) (6)) at week 28 and in two subjects (Nos. (b) (6)) at end-of-study.

No positive results for HIV-1/2 antibody or viral load or for HCV viral load were observed.

Reviewer Comment: The presence of a positive viral load test for parvovirus B19 and for HAV does not necessarily mean that intact infectious virus is present. From the data presented it is not possible to determine whether the instances of treatment-emergent parvovirus B19 viral load in four subjects or of treatment-emergent positive HAV viral load tests in two subjects represent community-acquired infection or viral transmission from the IP.

6.1.12.7 Dropouts and/or Discontinuations

No AEs were reported to have resulted in premature withdrawal from the study.

6.1.13 Study Summary and Conclusions

Phase 3 IND study SCGAM-01 met its primary efficacy endpoint. No serious bacterial infections, 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 outcomes of secondary efficacy endpoints were consistent with the product being effective. No deaths or premature withdrawals from the study due to AEs were reported. Not unexpectedly for an IGSC product, a relatively high rate of local infusion site reactions were reported, including nine hematomas, but no cases of infusion site ulceration or necrosis were reported. Most adverse reactions other than local infusion site reactions appeared related to infection. One case of urticaria was the only immediate hypersensitivity reaction reported. Laboratory findings were consistent with possible hemolysis in three subjects, but hemolysis was not reported as an adverse reaction. No cases of thromboembolic events or cases of aseptic meningitis were reported.

6.2 Trial #2

Protocol SCGAM-04

Study Title:

Clinical Phase 3 study to evaluate the efficacy, tolerability and safety of subcutaneous human immunoglobulin ((b) (4) in patients with primary immunodeficiency syndrome.

The final study report for study, SCGAM-04, conducted at five sites in Russia, was submitted at FDA request on 30 August 2018 as amendment 29. This study was not the subject of a BIMO inspection to verify the accuracy of the data and adherence to GCP, but the results as presented by the applicant were considered supportive of a conclusion of efficacy and safety of the product for the requested indication in PI, notwithstanding the limited power of the study due to its modest size and short duration.

6.2.1 Objectives (Primary, Secondary, etc)

To evaluate the efficacy of (b) (4) [Cutaquig] in preventing serious bacterial infections (SBIs) compared with historical control data.

To evaluate the tolerability and safety of (b) (4) [Cutaquig].

6.2.2 Design Overview

Non-IND Phase 3 study SCGAM-04 was a prospective, open-label, non-controlled, single-arm, multicenter Phase 3 study in adults subjects with PI with an 8-week wash-in/wash-out period followed by a 6-month efficacy period. Subjects were administered Cutaquig via weekly subcutaneously infusion at a dose calculated by dividing the dose of the previous Immune Globulin Intravenous (Human) (IGIV) product by the number of weeks between doses. Apparently, no dosage adjustment factor was used to account for the lower bioavailability of IGSC vis-à-vis IGIV. The final study report for SCGAM-04, conducted at five sites in Russia, was submitted at FDA request on 30 August 2018 as amendment 29. The Russian study enrolled 25 subjects with PI that were followed for up to 6 months during the active treatment period. Other than the shorter duration and size of the study, its basic design was modeled after the FDA Guidance for IGIV products, as was the case for study SCGAM-01.

6.2.3 Population

Twenty-five subjects with PI were enrolled.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Cutaquig.

6.2.5 Directions for Use

Cutaquig was infused subcutaneously weekly via infusion pump.

6.2.6 Sites and Centers

The study was conducted at five Russian sites: The investigators at the five sites were Dr. Elena Latysheva (Site 1); Prof. Luidmila Sizyakina (Site 2), Prof. Anna Shcherbina (Site 3), Prof. Irina Tuzankina (Site 4), and Dr. Vadim Rassokhin (Site 5).

6.2.7 Surveillance/Monitoring

Subjects were followed periodically over a period of 8 months (2 months washout/wash-in period and six-months primary treatment period for analysis purposes).

6.2.8 Endpoints and Criteria for Study Success

Serious bacterial infections (SBIs) were defined as in protocol SCGAM-01 and the FDA Guidance for IGIV products. Secondary efficacy endpoints were essentially the same as in protocol SCGAM-01.

6.2.9 Statistical Considerations & Statistical Analysis Plan

Descriptive statistics were used to describe study outcomes.

6.2.10 Study Population and Disposition

Key study inclusion criteria:

- Confirmed diagnosis of PI requiring immunoglobulin replacement therapy due to hypogammaglobulinaemia or agammaglobulinaemia. Previously treated with at least 4 infusions on regular treatment with any IVIG, with a constant IVIG dose of between 200 and 800 mg/kg body weight.

- Availability of at least 2 immunoglobulin G (IgG) trough levels of 4 previous IVIG infusions before enrolment and maintenance of ≥5.0 g/L in the trough levels of these 4 previous infusions.

Key study exclusion criteria:

- Acute infection requiring intravenous (IV) antibiotic treatment within 2 weeks prior to and during the Screening period.

- Treatment with immunosuppressive drugs.

- Patients with a history of adverse reactions to immunoglobulin A, malignancies of lymphoid cells and immunodeficiency with lymphoma, severe liver impairment, renal function impairment, known protein-losing enteropathies or proteinuria, or known or suspected human immunodeficiency virus (HIV), hepatitis C virus (HCV) or hepatitis B virus (HBV) infection

6.2.10.1 Populations Enrolled/Analyzed

Twenty-five subjects were enrolled and comprise the full analysis and safety sets. Twenty-four subjects comprised the per-protocol analysis set.

6.2.10.1.1 Demographics

Ten men and 15 women were enrolled. The mean age was 35.2 years and the ages ranged from 18 years to 64 years old. Race and ethnicity were not provided in the study report. Median body weight was 69 kg and median BMI was 23 kg/m^2.

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The most common findings from the medical history were chronic bronchitis (15 subjects [60%]), chronic sinusitis (8 patients [32%]), and chronic tonsillitis (6 patients [24%]). The

majority of subjects (23 subjects; 92.0%) had common variable immunodeficiency and 2 subjects had X-linked agammaglobulinaemia.

6.2.10.1.3 Subject Disposition
Twenty-five subjects were enrolled. One subject withdrew prematurely. Twenty-four subjects completed the study.

6.2.11 Efficacy Analyses

Other than the shorter duration and size of the study, its basic design and endpoints were modeled after the FDA Guidance for IGIV products, as was the case for study SCGAM-01.

6.2.11.1 Analyses of Primary Endpoint(s)

No SBIs were reported in the Russian study.

6.2.11.2 Analyses of Secondary Endpoints

A total of 26 non-serious infections were observed among 14 subjects during the primary treatment period, giving a rate of total infections of 2.37 per subject-year (95% CI 1.24 to 4.52). No infections were rated severe in intensity.

The mean time to resolution of infection was 9.5 days in the primary treatment period.

Ten subjects used antibiotics in 19 treatment episodes, according to the study report.

During the primary treatment period six subjects had one episode of fever each, corresponding to a rate of 0.55 febrile episodes per subject-year.

Three subjects had a total of four absences from work or school due to infections, corresponding to a rate of 0.01 absences per subject-year.

Slight increases in SF-35v2 quality-of-life scores were observed over the course of the trial with mean scores ranging from 41 and 58.

6.2.11.3 Subpopulation Analyses

No subgroup analyses were conducted in this small study.

6.2.11.4 Dropouts and/or Discontinuations

One subject discontinued the study prematurely during the washout/wash-in period. The reason for this subject's dropout was not located in the study report, but it was stated that no discontinuations due to AEs occurred.

6.2.12 Safety Analyses

6.2.12.1 Methods

Adverse events were analyzed on per-subject and per-infusion bases.

6.2.12.2 Overview of Adverse Events

In study SCGAM-04, a total of 775 infusions were administered, ranging from 7 to 32 infusions per subject. The mean dose of Cutaquig was 0.11 g/kg weekly. No deaths, SAEs, or AEs leading to premature withdrawal of subjects were reported. Fifteen subjects (60%) reported local infusion site reactions. Fifteen percent of infusions were associated with local infusion site reactions, the most common of which were erythema, pruritis, and contact dermatitis. Seven subjects (28%) had AEs that began during or within 72 hours of infusion. These included respiratory tract infections, "condition aggravated," and bronchitis, musculoskeletal discomfort, dizziness, and headache. The rate of temporally related AEs per infusion was 0.015. The overall rate of AEs was 2.4 per subject, consisting of component rates of 1.36 for infection AEs and 1.04 for non-infection AEs. Viral tests remained negative throughout the study. One subject had a total serum IgG trough level < 5g/L on one occasion.

6.2.12.3 Deaths

No deaths occurred during study SCGAM-04.

6.2.12.4 Nonfatal Serious Adverse Events

No SAEs were reported.

6.2.12.5 Adverse Events of Special Interest (AESI)

No AEs of special interest were reported.

6.2.12.6 Clinical Test Results

Viral tests remained negative throughout the study.

6.2.12.7 Dropouts and/or Discontinuations

One subject discontinued the study prematurely.

6.2.13 Study Summary and Conclusions

The reported results of study SCGAM-04 are considered supportive of a conclusion of safety and efficacy for the requested indication in PI in adults.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1

No integrated summary of efficacy was submitted, because efficacy data from only the single Phase 3 clinical study was included in the original BLA. Other studies had not been completed at the time of original BLA submission, but non-IND Russian Phase 3 study SCGAM-04 was subsequently completed prior to the 120-day safety update data cutoff date and the final report submitted at FDA request.

No SBIs were reported for any of the three studies as of 28 June 2018.

Study SCGAM-01 was a prospective, open-label, uncontrolled, single arm, multi-center Phase 3 study. Subjects with PI from ages 2 and up were enrolled who had been receiving IGIV treatment. Subjects were switched from IGIV to IGSC at study start with the Cutaquig dose calculated based on the prior IGIV dose, the IGIV inter-dose interval,

and a dosage correction factor to account for the lower bioavailability of IGSC vis-à-vis IGIV. The study consisted of 12-week wash-in/wash-out period followed by a 12-month efficacy period.

SCGAM-04 was a prospective, open-label, uncontrolled, single-arm, multicenter Phase 3 clinical study evaluating the efficacy of Cutaquig in preventing SBIs compared with historical control data, as well as, the tolerability and safety of Cutaquig. The study involved an eight-week wash-in/wash-out period, followed by a six-month efficacy period. This completed trial enrolled 25 subjects (10 males and 15 females) with primary humoral immune deficiency who were between the ages of 16 and 75 years of age. No SBIs were observed in the study. The rate of non-serious and total infections per person-year was 2.37 (upper 95% CI limit 4.54). One-third of infections were moderate and two-thirds were mild in intensity. Only a single subject had a trough serum IgG level below 5 g/L (on one occasion). The results as describe were considered supportive of a conclusion of efficacy and safety for the requested indication.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

No integrated summary of safety was included in the original submission, which contained only data from the single Phase 3 IND clinical study, SCGAM-01.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

Study SCGAM-01 was a prospective, open-label, uncontrolled, single arm, multi-center Phase 3 study. Subjects with PI from ages 2 and up were enrolled who had been receiving IGIV treatment. Subjects were switched from IGIV to IGSC at study start with the Cutaquig dose calculated based on the prior IGIV dose, the IGIV inter-dose interval, and a dosage correction factor to account for the lower bioavailability of IGSC vis-à-vis IGIV. The study consisted of 12-week wash-in/wash-out period followed by a 12-month efficacy period.

No deaths or premature withdrawals from the study SCGAM-01 due to AEs were reported. Not unexpectedly for an IGSC product, a relatively high rate of local infusion site reactions were reported, including nine hematomas, but no cases of infusion site ulceration or necrosis were reported. Most adverse reactions other than local infusion site reactions appeared related to infection. One case of urticaria was the only immediate hypersensitivity reaction reported. Laboratory findings were consistent with possible hemolysis in three subjects, but hemolysis was not reported as an adverse reaction. No cases of thromboembolic events or cases of aseptic meningitis were reported.

SCGAM-03 is a prospective, open-label, uncontrolled, single-arm, multicenter, Phase 3 extension study for U.S. subjects who completed study SCGAM-01. The study was initiated in 2016 and was ongoing at the time of BLA submission. Safety data from ongoing study SCGAM-03 were included in the 120-day safety update (SU).

Data were requested for the non-IND Russian study. SCGAM-04 (non-IND Phase 3 study) and were included in the 120-day safety update which was received on 26 July 2018 and which had a data cutoff date of 30 June 2018. This completed trial enrolled 25 subjects (10 males and 15 females) between the ages of 16 and 75 years. SCGAM-04 was a prospective, open-label, uncontrolled, single-arm, multicenter Phase 3 clinical study evaluating the efficacy of Cutaquig in preventing SBIs compared with historical control data, as well as, the tolerability and safety of Cutaquig. The study involved an eight-week wash-in/wash-out period, followed by a six-month efficacy period. The study was to enroll 20-25 subjects at approximately five sites in Russia.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

A total of 106 subjects with primary humoral immunodeficiency collectively received more than 5072 infusions of the investigational product (IP).

As of 31 May 2018, 63 subjects, including 25 subjects < 16 years, had been enrolled in study SCGAM-01, of which 54 had completed the study. As of that date, 3 subjects, all pediatric, are ongoing.

As of 31 May 2018, the extension study of SCGAM-01, study SCGAM-03, had enrolled 19 subjects in the U.S., 18 of whom had received IP.

8.2.3 Categorization of Adverse Events

All local infusion site reactions were deemed causally related to Cutaquig in this review.

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

The maximum follow-up time in study SCGAM-01 was 15 months, compared to eight months for Russian study SCGAM-04. Additional follow-up of a subset of SCGAM-01 subjects occurred under extension protocol SCGAM-03.

8.4 Safety Results

8.4.1 Deaths

There were no deaths in any of the studies.

8.4.2 Nonfatal Serious Adverse Events

The SAEs reported in SCGAM-01 are listed in the applicant's Table 3 below. None were considered related to IP by the applicant, investigators, or this reviewer.

Table 3: SCGAM-01: Cumulative SAE listing

Country Center No	AE No	Patient Sex Age/DOB	Product	Batch No.	Last Dose [ml]	Last treatment start date/time end date/time	SAE Start date/time End date/time	SAE Verbatim PT LLT	SAE Serious Severity Outcome	SAE Action (study drug) Action (general) Inv. causality
POL 02 7		(b) (6) Male (b) (6)	Cutaquig 16.5%	M705B8145	25	(b) (6)	06MAY2018/ 09MAY2018:12:30	ACUTE ARTHRITIS/ Arthritis/ Acute arthritis	Yes/ MODERATE/ RECOVERED/ RESOLVED	DOSE NOT CHANGED/ MEDICATION OR STARTED/ NOT RELATED THERAPY
HUN 32 2		(b) (6) Female (b) (6)	Cutaquig 16.5%	C436A8136, C436B8134	75		07OCT2015/ 12OCT2015	TUMOR OF THYROID GLAND/ Thyroid neoplasm/ Thyroid tumor	Yes/ MILD/ RECOVERED/ RESOLVED	DOSE NOT CHANGED/ NONE/ NOT RELATED
USA 41 2		(b) (6) Female (b) (6)	Cutaquig 16.5%	C343A8131	144		04NOV2014:18:00/ 17NOV2014:12:00	ACUTE APPENDICITIS/ Appendicitis/ Acute appendicitis	Yes/ SEVERE/ RECOVERED/ RESOLVED	DOSE NOT CHANGED/ MEDICATION OR STARTED/ NOT RELATED THERAPY
USA 46 9		(b) (6) Male (b) (6)	Cutaquig 16.5%	M616B8142, M616A8145	62		31AUG2017:08:15/ 31AUG2017:08:40	WORSENING OF SEIZURES, EXPERIENCED 4 CLUSTERED TONIC CLONICSEIZURES/ Grand mal convulsion/ Tonic-clonic seizures	Yes/ MILD/ RECOVERED/ RESOLVED	DOSE NOT CHANGED/ MEDICATION OR STARTED/ UNLIKELY THERAPY
USA 47 4		(b) (6) Female (b) (6)	Cutaquig 16.5%	C526A8141	90		14OCT2016/ 23NOV2016	SEVERE PERSISTENT ASTHMA WITH ACUTE EXACERBATION/ Asthma/ Exacerbation of asthma	Yes/ SEVERE/ RECOVERED/ RESOLVED	DOSE NOT CHANGED/ MEDICATION OR STARTED/ NOT RELATED THERAPY
8		(b) (6) Female (b) (6)	Cutaquig 16.5%	C526A8141	90		17MAR2017/ 06APR2017	ACUTE BRONCHIOLITIS DUE TO RSV/ Respiratory syncytial virus	Yes/ SEVERE/ RECOVERED/	DOSE NOT CHANGED/ MEDICATION OR STARTED/ THERAPY

In extension study SCGAM-03, there were six SAEs reported:

> Subdural hematoma after head injury
> C3-C4 disc replacement
> Laminectomy for degenerative joint disease (DJD) with spondylosis
> Spinal stenosis with spondylolisthesis resulting in leg pain
> Status asthmaticus x 2 episodes in one subject

This reviewer concurs with the applicant's and investigators' assessments that the above SAEs were likely unrelated to IP.

> In addition, a report of cellulitis of abdominal wall, considered related by investigator/sponsor, was reported.

No SAEs were reported in study SCGAM-04.

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 patient's and investigator's decision."

In study SCGAM-04 there were no premature discontinuations due to AEs.

8.4.4 Common Adverse Events and Suspected Adverse Reactions

The most common AEs across the three studies were erythema, swelling, redness, pruritis, infusion site erythema, infusion site pruritis, and contact dermatitis.

Across the three studies through the safety update (SU) cutoff date, a total of 18 adverse events that were classified by the sponsor as adverse reactions were reported.

In study SCGAM-04 there were 18 subjects (72%) who reported a total of 59 AEs, of which 34 were infections. Excluding infections, none were severe, 9 AEs were moderate, and 17 AEs were mild in intensity. Three subjects had one AE each that was considered related to IP by the investigator (dizziness, headache, and musculoskeletal discomfort, all mild in intensity).

Suspected Adverse Reactions + Adverse Reactions per Investigator/Sponsor in SCGAM-01, SCGAM-02, and SCGAM-04 (Applicant's Table 2 from SU)

Subject ID	Age	Start Date of Event	Verbatim	LLT	Infusional AE *	Investig.	Severity	Serious?	AE Outcome	AE Latency**
(b) (6)	37	19-OCT-2015	Feverishness	Fever	Yes	Possible	Mild	No	Recovered/resolved	0,1
	43	25-JAN-2016	Positive direct coombs test	Direct Coombs test positive	Yes	Possible	Moderate	No	Recovered/resolved	0
	16	18-AUG-2015	High level of free hemoglobin	Free haemoglobin present	Yes	Possible	Mild	No	Recovered/resolved	0
	7	19-JAN-2016	Temperature increased	Body temperature increased	Yes	Possible	Mild	No	Recovered/resolved	0,45
	7	19-JAN-2016	Vomiting	Vomiting	Yes	Possible	Mild	No	Recovered/resolved	0,45
	34	24-FEB-2015	Abdominal swelling	Swelling abdomen	Yes	Probable	Moderate	No	Recovered/resolved	0,22
	55	13-APR-2016	Headache	Headache	Yes	Probable	Mild	No	Recovered/resolved	0,14
	55	18-APR-2016	Headache	Headache	Yes	Probable	Mild	No	Recovered/resolved	0,15
	12	11-MAY-2015	Myalgia	Myalgia	Yes	Probable	Moderate	No	Recovered/resolved	0,15
	63	19-SEP-2016	Stomach cramping during infusion	Stomach cramps	Yes	Possible	Mild	No	Recovered/resolved	0
	7	25-MAY-2017	Intermittent headache	Intermittent headache	Yes	Possible	Mild	No	Recovered/resolved	0
	71	18-MAY-2017	Decreased haptoglobin	Haptoglobin decreased	Yes	Possible	Mild	No	Unknown	1,49
	71	18-MAY-2017	Increased plasma hemeglobin	Hemoglobin increased	Yes	Possible	Mild	No	Unknown	1,49
	49	17-JAN-2017	Increased plasma free hemoglobin	Free haemoglobin present	No	Probable	Mild	No	Unknown	7,21
	62	24-JUN-2017	Cellulitis of abdominal wall	Cellulitis of abdominal wall	Yes	Possible	Mild	No	Recovered resolved	1,07
Scgam-03										
Scgam-04	>18	2017	Musculoskeletal discomfort	Musculoskeletal discomfort	Yes	Possible	Mild	No	Recovered resolved	<72 hours
Scgam-04	>18	2017	Dizziness	Dizziness	Yes	Possible	Mild	No	Recovered resolved	<72 hours
Scgam-04	>18	2017	Headache	Headache	Yes	Possible	Mild	No	Recovered resolved	<72 hours

* during or within 72 hrs after end of infusion

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, 75% of subjects reported local infusion site reactions. Twenty-three percent of infusions (814/3497) were accompanied by local infusion site reactions. Fourteen subjects (23%) experienced moderate intensity local reactions and two subjects (3.3%) experienced severe intensity reactions (bruising at the abdominal infusion site at week 30 and severe allergic reaction at lower back infusion sites bilaterally at week 5 in subject (b) (6) The most common local infusion site reactions were erythema, swelling, redness and pruritus

In SCGAM-04, 15 of 25 subjects (60%) experienced 201 infusion site reactions during 116 of 775 infusions (15%). Four subjects experienced moderate and 11 subjects experienced mild infusion site reactions. No infusion site reactions were rated severe. Erythema was reported in 12.9% of infusions, pruritis in 8.9%, and contact dermatitis in 1.2% of infusions.

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.

The sponsor states in the safety update that no reports of hypersensitivity reactions, aseptic meningitis, suspected viral transmission, or TEEs were received for study SCGAM-04. However, in section 20.1.4 of the SU, it states that the following were

reported in two subjects each: "allergic" and "urticarial" in studies SCGAM-01/SCGAM-03.

Although not diagnosed as hemolysis, the AEs of "high level of free hemoglobin" in study SCGAM-01 subject (b) (6) "decreased haptoglobin" and "increased plasma hemoglobin" in subject (b) (6) and "increased plasma free hemoglobin" in subject (b) (6) are consistent with the possibility of hemolysis.

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

Not analyzed.

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/sponsor opinion otherwise.

8.5.3 Product-Demographic Interactions

See Appendix.

8.5.5 Product-Product Interactions

Not analyzed.

8.5.8 Immunogenicity (Safety)

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

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. Three subjects in the U.S. Phase 3 trial had AEs that are consistent with the possibility of hemolysis. However, no drops in hemoglobin $\geq$ 2 g/dL were observed in the trial.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

The number of subject-years exposure to IP in the U.S. Phase 3 study is insufficient to adequately define product efficacy and safety in any of the pediatric age strata. Additional pediatric data from study SCGAM-01 will be submitted as a PREA-mandated efficacy supplement following study completion.

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 breasfed child, and the effects of Cutaquig® on milk production/excretion. Immunoglobulins, in particular IgA and IgM, are excreted into the milk.[3]

9.1.3 Pediatric Use and PREA Considerations

The original BLA application triggers PREA, as new immunoglobulin products are considered to contain new active ingredients.

An initial Pediatric Study Plan (iPSP) was received on 03 April 2014 and reviewed by PeRC on 18 September 2014. A revised iPSP was reviewed on 03 December 2014 by PeRC, and was accepted as an agreed iPSP on 04 December 2014. An amended iPSP, including a waiver request for the 0-2 year pediatric population and a deferral request for children and adolescents aged 2-16 years, was received on 31 March 2016, but was not reviewed by PeRC because of administrative oversight. An amended iPSP, dated 19 October 2017, included milestone revisions of the pediatric development plan. The amended iPSP was unable to be reviewed by PeRC before the BLA was submitted, but in January, 2018 PeRC stated that it did not need to review the 19 October 2017 PSP. Rather, it would review OBRR's pediatric assessment and recommendations regarding the requested partial pediatric waiver and deferral. PeRC discussed this BLA at its 31 October 2018 meeting and agreed with the requests for a partial pediatric waiver for children under 2 years of age and a partial pediatric deferral for pediatric subjects ages 2 years to < 17 years.

As of the 27 October 2017 data cutoff date of the original BLA, 12 pediatric subjects had completed the study and 8 pediatric subjects were ongoing. The pediatric data submitted with the original BLA are incomplete, and are judged by this reviewer to be inadequate to support a pediatric labeling claim. For example, for adolescent subjects aged 12 to < 17 years of age, there are only slightly more than four subject-years of exposure among subjects who completed the study and only slightly more than five subject-years of exposure if one includes subjects who had not completed the study as of the data cutoff date. Only 4 pediatric subjects had participated in the PK study. Hence, a PREA post-marketing requirement (PMR) is necessary to ensure completion the pediatric assessment.

PSP v4.0 (dated 19 October 2017) states that at least 25 pediatric subjects (5 subjects between ≥2 years and <5 years, 5 subjects between ≥5 years and <12 years, and 15 subjects between ≥12 years and <16 years) would be enrolled, with at least 14 subjects participating in the PK substudy. During the BLA review, the applicant requested a reduction in the numbers of pediatric subjects to be evaluated for PK. In conjunction with the Clinical Pharmacology reviewer, CBER modified the required number of pediatric subjects to be evaluated for PK in each pediatric age category and this was communicated to the applicant, who provided updated milestones for a PREA PMR to complete SCGAM-01 and submit a report that would compare efficacy and safety between pediatric age cohorts and between pediatric and adult subjects. CBER expects

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

the following minimum number of pediatric subjects to be evaluated by PK, broken down by pediatric age stratum:

a. Age 2 to < 6 years: 2 subjects

b. Age 6 to < 12 years: 6 subjects

c. Age 12 to < 17 years: 4 subjects

9.1.4 Immunocompromised Patients

Cutaquig® is indicated for primary immunodeficiency.

9.1.5 Geriatric Use

The small number of geriatric subjects (i.e., 3 adult subjects were aged >65 years) precluded assessment of efficacy and safety in the geriatric population.

10. CONCLUSIONS

Based on the submitted data, Cutaquig appears to be safe and effective for replacement therapy in primary humoral immune deficiency.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

See table below.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Primary Immunodeficiency (PI) represents a heterogenous 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. • 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.	• PI and its antibody deficiency syndromes are serious, chronic conditions associated with considerable morbidity and mortality. • 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.
Unmet Medical Need	• There are multiple immunoglobulin products (both intravenous and subcutaneous) approved for PI, including three subcutaneous immunoglobulin products: Hyqvia®, Hizentra®, and Cuvitru®. Gamunex-C, an IGIV, is also indicated for subcutaneous administration in PI.	• There is no unmet medical need.
Clinical Benefit	• One open-label, single arm, multi-center clinical trial was conducted in 61 subjects, including 23 pediatric subjects aged ≥2 to <16 years. Efficacy data were submitted for a total of 47 subjects who completed the study (35 adults and 12 pediatric subjects) and interim data were submitted on 8 pediatric subjects who were continuing in the study at the time of the data cutoff for the BLA. The trial design is consistent with the *FDA Guidance for Industry: Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Immunodeficiency*. • No serious bacterial infections (SBIs) were reported at any time during the study for the Full Analysis and the Per Protocol Sets. The study met its primary efficacy endpoint, in that the upper limit of the 99% confidence interval for the proportion of SBIs was <1.0. Per the *FDA Guidance for Industry: Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Immunodeficiency*, a statistical demonstration of a SBI rate per person-year less than 1.0 is considered adequate to provide substantial evidence of efficacy. Outcomes of secondary efficacy endpoints were similar to those described in the package inserts of U.S.-licensed IGSC products.	• Cutaquig was clinically effective; no SBIs were reported during the study and the upper limit of the 99% confidence interval for the proportion of SBIs was <1.0. Insufficient data on pediatric subjects was submitted to establish efficacy and safety for patients under 17 years of age. Secondary efficacy outcome measures were considered supportive of a conclusion of efficacy for Cutaquig.
Risk	• The most common risks of Cutaquig® administration identified in the clinical studies are local infusion site reactions. Erythema, swelling, redness, and pruritis were common. However, a majority of infusion site reactions were mild and resolved in a timely fashion without sequelae. • The most frequent systemic adverse reactions (suspected adverse reactions plus adverse reactions) occurring in the setting of Cutaquig® administration were infections. The most frequent adverse reactions, excluding infections and local reactions, include diarrhea, pyrexia, headache, cough, dermatitis, asthma, and excoriation. • There were no deaths, thrombotic events, clinical hemolysis events, anaphylaxis, or aseptic meningitis events reported. The 5 SAEs that occurred in SCGAM-01 were assessed as unlikely related or not related to Cutaquig®. • There may be a risk of falsely elevated glucose readings with some glucose meters/strips that do not use a glucose-specific assay method, resulting in misinterpretation of maltose contained in the product as glucose.	• The frequency (i.e. percent of subjects) with local infusion site reactions observed with Cutaquig* is higher than that observed with other approved SCIG products (i.e., Hyqvia*, Hizentra*, and Cuvitru*). However, the rate of local reactions per infusion is comparable. • The presence of maltose in the product merits inclusion of a warning/precaution regarding the risk of obtaining falsely elevated glucose readings when using non-glucose-specific glucose meters/strips. • The rate of infections, both serious and non-serious combined was similar to the rates reported during clinical trials of U.S-licensed IGSC products. The clinical
	• It cannot presently be excluded that any or all all risks of IGIV listed in WARNINGS AND PRECAUTIONS for IGIV product, such as thrombosis or hemolysis, may also occur following Cutaquig® administration; however, based on their lack of observation of confirmed cases in study SCGAM01 and its extension, the maximum incidence of any of the listed reactions in adults is expected to be less than 10%. The incidence of biochemical findings consistent with possible hemolysis in SCGAM-01 was ~ 5%.	benefit is considered to outweigh the known and potential risks.
Risk Management	• Subcutaneous immune globulin products carry an obligate boxed warning for thrombosis. • Other serious risks of immune globulin products include hypersensitivity and anaphylaxis, especially in IgA deficient patients with antibodies to IgA, decline in renal function, hemolysis, TRALI, aseptic meningitis, and transmission of infectious agents.	• Patients should be monitored for signs and symptoms of hypersensitivity, aseptic meningitis syndrome, hemolysis, and TRALI. • Patients should be informed that Cutaquig* is manufactured from human plasma and hence, may contain transmissible infectious agents. • Routine postmarketing surveillance is recommended.

11.2 Risk-Benefit Summary and Assessment

Given the substantial morbidity and mortality risk from serious bacterial infections inherent in PI and the generally favorable safety profile observed in the IND Phase 3 trial and its extension study, notwithstanding the frequent but generally mild local infusion site reactions, the assessment of benefit:risk is considered favorable.

11.3 Discussion of Regulatory Options

The regulatory options for this BLA submission are approval or a complete response; the latter is considered inappropriate for the clinical review discipline, given the completeness of the submission and the demonstration that the clinical benefits of Cutaquig® outweigh its risks.

11.4 Recommendations on Regulatory Actions

The clinical reviewers recommend approval for the BLA.

11.5 Labeling Review and Recommendations

The applicant was requested to revise the draft package insert (PI) as follows:

- Revise the dose adjustment factor for switching from IGIV to Cutaquig to be consistent with the factor used during SCGAM-01 (1.40).
- Revise the recommended dosing frequency to that used during SCGAM-01 (weekly dosing only).
- Emphasize that, before starting Cutaquig, patients are to be stabilized on IGIV for a period of at least three months.
- Add the risk of obtaining falsely elevated blood glucose readings when using non-glucose-specific glucose meters/strips because of the maltose content of the product.

11.6 Recommendations on Postmarketing Actions

Routine post-marketing surveillance is appropriate for the product. The application triggers PREA; however, there is an insufficient amount of complete data from pediatric subjects in the BLA to satisfy the requirement for pediatric assessment. Therefore, a PREA post-marketing requirement (PMR) is necessary to ensure completion of Phase 3 study SCGAM01, which had eight pediatric subjects who were still participating in the study as of the original BLA data cutoff date. Submission of the complete pediatric data, including PK data, from the Phase 3 study should permit a pediatric assessment for this product and indication.

APPENDICES

Applicant's Response to FDA Clinical Information Request dated 14 March 2018

1. Please include all available interim safety data from all clinical studies in a 120-day safety update. This should include, but not necessarily be limited to data from study protocols SCGAM-01 (IND Phase 3 study), SCGAM-03 (IND Phase 3 extension study), and SCGAM-04 (non-IND Phase 3 study).

Applicant Response

All available interim safety data from all clinical studies will be included in the first 120-day safety update report following the acceptance of filing of the BLA for Cutaquiq. The first 120-day safety update report will have the DLP 30-Jun-2018 and will be submitted to FDA until 30-Jul-2018.

Reviewer Comment: Noted.

2. Please submit the initial protocol, the final protocol, and a summary of all protocol amendments and their dates of implementation for protocol SCGAM-03 and non-IND study SCGAM-04.

Applicant Response

Please find the requested protocols together with a summary of the amendments and their dates of implementation of SCGAM-03 in Module 5, section 5.3.5.2.

*The same package was compiled for the non-IND study SCGAM-0**4** and is provided as attachment to the response document.*

Clinical trial SCGAM-04 is being conducted in Russia only.

Reviewer Comment: Noted.

3. Please clarify whether your analysis of the rate of total infections was limited to the subset of SCGAM-01 subjects who completed the 12-month post-washout portion of the study and subjects who discontinued the study prematurely. If not, please submit an analysis for this subgroup, as well as separate analyses of adults and pediatric subjects < 17 years of age from this subgroup. This will help to avoid seasonal bias that could result from inclusion of active subjects who have not completed the study.

Applicant Response

The initial analysis of the total infection rate was based on all available patients, including patients still ongoing. We have thus repeated the analysis on basis of the full analysis set, excluding ongoing subjects as requested.

To address the request of separate analyses for adults and pediatric subjects < 17, we have applied the age strata specified by FDA in question #6, i.e. the age groups 2 to <12, 12 to < 17, 17 to 65, and > 65 years, and also repeated the same analysis for each sex.

The results of these analyses are provided in the following tables:

Table Number	Population	Table Heading
1.1.1	FAS excluding ongoing subjects	Rate of other infections
1.1.2	FAS excluding ongoing subjects - subgroup male	Rate of other infections
1.1.3	FAS excluding ongoing subjects - subgroup female	Rate of other infections

Table 1.1.1
Rate of Infections
Full Analysis Set Excluding Ongoing Subjects

Overall all infections, Treatment Period: Primary

Parameter	Categories/ Sample Characteristics	Age (years) >=2 to <12 years (N=9)	Age (years) >=12 to <17 years (N=7)	Age (years) >=17 to <=65 years (N=34)	Age (years) >65 years (N=3)	Total (N=53)
Number of person years exposure		9.07	4.15	32.49	3.05	48.76
Number of patients with other infections	Yes	7 (77.8%)	4 (57.1%)	30 (88.2%)	3 (100.0%)	44 (83.0%)
Number of other infections per patient	0	2 (22.2%)	3 (42.9%)	4 (11.8%)	0 (0.0%)	9 (17.0%)
	1	1 (11.1%)	2 (28.6%)	10 (29.4%)	1 (33.3%)	14 (26.4%)
	2	0 (0.0%)	1 (14.3%)	1 (2.9%)	1 (33.3%)	3 (5.7%)
	3	1 (11.1%)	1 (14.3%)	8 (23.5%)	0 (0.0%)	10 (18.9%)
	4	3 (33.3%)	0 (0.0%)	2 (5.9%)	1 (33.3%)	6 (11.3%)
	5	0 (0.0%)	0 (0.0%)	2 (5.9%)	0 (0.0%)	2 (3.8%)
	6	1 (11.1%)	0 (0.0%)	3 (8.8%)	0 (0.0%)	4 (7.5%)
	7	1 (11.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.9%)
	9	0 (0.0%)	0 (0.0%)	2 (5.9%)	0 (0.0%)	2 (3.8%)
	12	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (1.9%)
	13	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (1.9%)
Time to Resolution [days]	N	29	7	115	7	158
	Mean (SD)	38.21 (66.753)	59.14 (113.466)	19.87 (34.424)	9.57 (7.764)	24.52 (47.575)
	Median	15.00	15.00	10.00	7.00	10.00
Time to Resolution [days]	Minimum, Maximum	2.0, 292.0	11.0, 316.0	2.0, 232.0	4.0, 26.0	2.0, 316.0
	Q1, Q3	7.00, 19.00	12.00, 31.00	6.00, 17.00	4.00, 11.00	6.00, 18.00
Total Number of other infections		29	7	115	7	158
Total Number of other infections per person-year		3.196	1.689	3.539	2.295	3.240
One sided 95% CI - Upper Limit		6.298	4.196	5.238	6.737	4.451

Table 1.1.1
Rate of Infections
Full Analysis Set Excluding Ongoing Subjects

Overall all infections, Treatment Period: Total

Parameter	Categories/ Sample Characteristics	Age (years) >=2 to <12 years (N=9)	Age (years) >=12 to <17 years (N=7)	Age (years) >=17 to <=65 years (N=34)	Age (years) >65 years (N=3)	Total (N=53)
Number of person years exposure		10.97	5.29	39.50	3.68	59.44
Number of patients with other infections	Yes	7 (77.8%)	5 (71.4%)	31 (91.2%)	3 (100.0%)	46 (86.8%)
Total Number of other infections		41	10	138	9	198
Total Number of other infections per person-year		3.738	1.890	3.493	2.446	3.331
One sided 95% CI - Upper Limit		7.498	4.512	5.161	7.211	4.563

Reviewer Comment: The overall rate of all/other infections over the primary (up to 12 month) treatment period was 3.24 per person-year of observation (upper 95% CI = 4.45 infections per person-year). The rate was lowest among adolescent subjects, however this subgroup had only slightly over 4 subject-years of investigational product exposure and follow-up. The overall rate of all/other infections over the total (up to 15 month) treatment period was similar at 3.33 per person-year of observation (upper 95% CI = 4.56 infections per person-year).

Table 1.1.2
Rate of Infections
Full Analysis Set Excluding Ongoing Subjects - Male

Overall all infections, Treatment Period: Primary

Parameter	Categories/ Sample Characteristics	Age (years) >=2 to <12 years (N=8)	Age (years) >=12 to <17 years (N=6)	Age (years) >=17 to <=65 years (N=9)	Age (years) >65 years (N=1)	Total (N=24)
Number of person years exposure		8.08	3.10	8.12	1.02	20.32
Number of patients with other infections	Yes	7 (87.5%)	3 (50.0%)	8 (88.9%)	1 (100.0%)	19 (79.2%)

Table 1.1.1
Rate of Infections
Full Analysis Set Excluding Ongoing Subjects

Severity: Moderate, Treatment Period: Primary

Parameter	Categories/ Sample Characteristics	Age (years) >=2 to <12 years (N=9)	Age (years) >=12 to <17 years (N=7)	Age (years) >=17 to <=65 years (N=34)	Age (years) >65 years (N=3)	Total (N=53)
Number of person years exposure		9.07	4.15	32.49	3.05	48.76
Number of patients with other infections	Yes	1 (11.1%)	2 (28.6%)	18 (52.9%)	1 (33.3%)	22 (41.5%)

Table 1.1.1
Rate of Infections
Full Analysis Set Excluding Ongoing Subjects

Severity: Moderate, Treatment Period: Total

Parameter	Categories/ Sample Characteristics	Age (years) >=2 to <12 years (N=9)	Age (years) >=12 to <17 years (N=7)	Age (years) >=17 to <=65 years (N=34)	Age (years) >65 years (N=3)	Total (N=53)
Total Number of other infections		2	4	50	1	57
Total Number of other infections per person-year		0.182	0.756	1.266	0.272	0.959
One sided 95% CI - Upper Limit		0.945	2.070	2.186	1.408	1.563

[Reviewer Comment: No infections rated severe in intensity were reported.]

Subgroup analyses by Sex of Combined Infections excluding ongoing subjects

Table 1.1.2
Rate of Infections
Full Analysis Set Excluding Ongoing Subjects - Male

Overall all infections, Treatment Period: Total

Parameter	Categories/ Sample Characteristics	Age (years) >=2 to <12 years (N=8)	Age (years) >=12 to <17 years (N=6)	Age (years) >=17 to <=65 years (N=9)	Age (years) >65 years (N=1)	Total (N=24)
Number of person years exposure		9.76	4.04	9.87	1.23	24.90
Number of patients with other infections	Yes	7 (87.5%)	4 (66.7%)	8 (88.9%)	1 (100.0%)	20 (83.3%)

Table 1.1.2
Rate of Infections
Full Analysis Set Excluding Ongoing Subjects - Male

Overall all infections, Treatment Period: Primary

Parameter	Categories/ Sample Characteristics	Age (years) >=2 to <12 years (N=8)	Age (years) >=12 to <17 years (N=6)	Age (years) >=17 to <=65 years (N=9)	Age (years) >65 years (N=1)	Total (N=24)
Total Number of other infections		29	6	18	2	55
Total Number of other infections per person-year		3.591	1.933	2.217	1.969	2.707
One sided 95% CI - Upper Limit		7.075	5.390	4.552	10.200	4.231

Table 1.1.3
Rate of Infections
Full Analysis Set Excluding Ongoing Subjects - Female

Overall all infections, Treatment Period: Primary

Parameter	Categories/ Sample Characteristics	Age (years) >=2 to <12 years (N=1)	Age (years) >=12 to <17 years (N=1)	Age (years) >=17 to <=65 years (N=25)	Age (years) >65 years (N=2)	Total (N=29)
Number of person years exposure		1.00	1.04	24.37	2.03	28.44
Number of patients with other infections	Yes	0 (0.0%)	1 (100.0%)	22 (88.0%)	2 (100.0%)	25 (86.2%)

Table 1.1.3
Rate of Infections
Full Analysis Set Excluding Ongoing Subjects - Female

Overall all infections, Treatment Period: Total

Parameter	Categories/ Sample Characteristics	Age (years) >=2 to <12 years (N=1)	Age (years) >=12 to <17 years (N=1)	Age (years) >=17 to <=65 years (N=25)	Age (years) >65 years (N=2)	Total (N=29)
Number of person years exposure		1.21	1.25	29.64	2.45	34.55
Number of patients with other infections	Yes	0 (0.0%)	1 (100.0%)	23 (92.0%)	2 (100.0%)	26 (89.7%)

Table 1.1.3
Rate of Infections
Full Analysis Set Excluding Ongoing Subjects - Female

Overall all infections, Treatment Period: Primary

Parameter	Categories/ Sample Characteristics	Age (years) >=2 to <12 years (N=1)	Age (years) >=12 to <17 years (N=1)	Age (years) >=17 to <=65 years (N=25)	Age (years) >65 years (N=2)	Total (N=29)
Total Number of other infections		0	1	97	5	103
Total Number of other infections per person-year		0.000	0.961	3.980	2.458	3.621
One sided 95% CI - Upper Limit			4.979	6.211	9.542	5.537

Combined infections excluding ongoing subjects

Table 1.1.1
Rate of Infections
Full Analysis Set Excluding Ongoing Subjects

Overall all infections, Treatment Period: Primary

Parameter	Categories/ Sample Characteristics	Age (years) >=2 to <12 years (N=9)	Age (years) >=12 to <17 years (N=7)	Age (years) >=17 to <=65 years (N=34)	Age (years) >65 years (N=3)	Total (N=53)
Number of person years exposure		9.07	4.15	32.49	3.05	48.76
Number of patients with other infections	Yes	7 (77.8%)	4 (57.1%)	30 (88.2%)	3 (100.0%)	44 (83.0%)

Table 1.1.1
Rate of Infections
Full Analysis Set Excluding Ongoing Subjects

Overall all infections, Treatment Period: Primary

Parameter	Categories/ Sample Characteristics	Age (years) >=2 to <12 years (N=9)	Age (years) >=12 to <17 years (N=7)	Age (years) >=17 to <=65 years (N=34)	Age (years) >65 years (N=3)	Total (N=53)
Time to Resolution [days]	Minimum, Maximum Q1, Q3	2.0, 292.0 7.00, 19.00	11.0, 316.0 12.00, 31.00	2.0, 232.0 6.00, 17.00	4.0, 26.0 4.00, 11.00	2.0, 316.0 6.00, 18.00
Total Number of other infections		29	7	115	7	158
Total Number of other infections per person-year		3.196	1.689	3.539	2.295	3.240
One sided 95% CI - Upper Limit		6.298	4.196	5.238	6.737	4.451

Lower Respiratory Tract Infections

Table 1.1.1
Rate of Infections
Full Analysis Set Excluding Ongoing Subjects

Other Infections: Lower resp. tract infections, Treatment Period: Primary

Parameter	Categories/ Sample Characteristics	Age (years) >=2 to <12 years (N=9)	Age (years) >=12 to <17 years (N=7)	Age (years) >=17 to <=65 years (N=34)	Age (years) >65 years (N=3)	Total (N=53)
Number of person years exposure		9.07	4.15	32.49	3.05	48.76
Number of patients with other infections	Yes	3 (33.3%)	0 (0.0%)	6 (17.6%)	0 (0.0%)	9 (17.0%)
Number of other infections per patient	0	6 (66.7%)	7 (100.0%)	28 (82.4%)	3 (100.0%)	44 (83.0%)
	1	2 (22.2%)	0 (0.0%)	5 (14.7%)	0 (0.0%)	7 (13.2%)
	3	1 (11.1%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	2 (3.8%)
Time to Resolution [days]	N	5		8		13
	Mean (SD)	18.60 (4.336)		10.38 (4.749)		13.54 (6.064)
	Median	18.00		9.00		12.00
	Minimum, Maximum	15.0, 26.0		6.0, 21.0		6.0, 26.0
	Q1, Q3	16.00, 18.00		7.50, 11.50		8.00, 18.00
Total Number of other infections		5	0	8	0	13
Total Number of other infections per person-year		0.551	0.000	0.246	0.000	0.267

Reviewer Comment: A total of 13 lower respiratory tract infections were reported among nine subjects.

Use of Antibiotics

Table 1.2.1
Use of antibiotics
Full Analysis Set Excluding Ongoing Subjects

Treatment Period: Total, All Patients

Parameter	Categories/ Sample Characteristics	Age (years) >=2 to <12 years (N=9)	Age (years) >=12 to <17 years (N=7)	Age (years) >=17 to <=65 years (N=34)	Age (years) >65 years (N=3)	Total (N=53)
Number of person years exposure		10.97	5.29	39.50	3.68	59.44
Number of patients with use of Antibiotics	Yes	6 (66.7%)	4 (57.1%)	25 (73.5%)	2 (66.7%)	37 (69.8%)
Number of treatment episodes with Antibiotics	0	3 (33.3%)	3 (42.9%)	9 (26.5%)	1 (33.3%)	16 (30.2%)
	1	2 (22.2%)	2 (28.6%)	8 (23.5%)	1 (33.3%)	13 (24.5%)
	2	1 (11.1%)	0 (0.0%)	5 (14.7%)	0 (0.0%)	6 (11.3%)
	3	1 (11.1%)	1 (14.3%)	3 (8.8%)	1 (33.3%)	6 (11.3%)
–	4	1 (11.1%)	1 (14.3%)	1 (2.9%)	0 (0.0%)	3 (5.7%)
	5	0 (0.0%)	0 (0.0%)	2 (5.9%)	0 (0.0%)	2 (3.8%)
T	7	1 (11.1%)	0 (0.0%)	2 (5.9%)	0 (0.0%)	3 (5.7%)
	8	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (1.9%)
	9	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (1.9%)
	10	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (1.9%)
P	11	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (1.9%)
–						
T	Total number of treatment episodes with Antibiotics	18	9	93	4	124
days with use of Antibiotics						
Total number of treatment days with use of Antibiotics per person-year		7.904	13.546	72.486	15.083	48.677

Table 1.2.1
Use of antibiotics
Full Analysis Set Excluding Ongoing Subjects

Treatment Period: Total, Region: Europe

Parameter	Categories/ Sample Characteristics	Age (years) >=2 to <12 years (N=4)	Age (years) >=12 to <17 years (N=1)	Age (years) >=17 to <=65 years (N=16)	Age (years) >65 years (N=1)	Total (N=22)
Total number of treatment days with use of Antibiotics per person-year		27.169	239.442	18.115	0.000	29.030

Table 1.2.2
Use of antibiotics
Full Analysis Set Excluding Ongoing Subjects - Male

Treatment Period: Total, All Patients

Parameter	Categories/ Sample Characteristics	Age (years) >=2 to <12 years (N=8)	Age (years) >=12 to <17 years (N=6)	Age (years) >=17 to <=65 years (N=9)	Age (years) >65 years (N=1)	Total (N=24)
Total number of treatment days with use of Antibiotics per person-year		17.930	86.552	18.344	22.013	29.440

Table 1.2.2
Use of antibiotics
Full Analysis Set Excluding Ongoing Subjects - Male

Treatment Period: Primary, All Patients

Parameter	Categories/ Sample Characteristics	Age (years) >=2 to <12 years (N=8)	Age (years) >=12 to <17 years (N=6)	Age (years) >=17 to <=65 years (N=9)	Age (years) >65 years (N=1)	Total (N=24)
Number of person years exposure		8.08	3.10	8.12	1.02	20.32
Number of patients with use of Antibiotics	Yes	5 (62.5%)	3 (50.0%)	4 (44.4%)	1 (100.0%)	13 (54.2%)
Number of treatment episodes with Antibiotics	0	3 (37.5%)	3 (50.0%)	5 (55.6%)	0 (0.0%)	11 (45.8%)
	1	1 (12.5%)	1 (16.7%)	0 (0.0%)	1 (100.0%)	3 (12.5%)
	2	1 (12.5%)	1 (16.7%)	1 (11.1%)	0 (0.0%)	3 (12.5%)
	3	2 (25.0%)	1 (16.7%)	2 (22.2%)	0 (0.0%)	5 (20.8%)
	5	0 (0.0%)	0 (0.0%)	1 (11.1%)	0 (0.0%)	1 (4.2%)
	6	1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.2%)
Total number of treatment episodes with Antibiotics		15	6	13	1	35
Total number of treatment episodes with Antibiotics per person-year		1.857	1.933	1.601	0.985	1.723

Table 1.2.3
Use of antibiotics
Full Analysis Set Excluding Ongoing Subjects - Female

Treatment Period: Total, All Patients

Parameter	Categories/ Sample Characteristics	Age (years) >=2 to <12 years (N=1)	Age (years) >=12 to <17 years (N=1)	Age (years) >=17 to <=65 years (N=25)	Age (years) >65 years (N=2)	Total (N=29)
Number of person years exposure		1.21	1.25	29.64	2.45	34.55
Number of patients with use of Antibiotics	Yes	1 (100.0%)	0 (0.0%)	21 (84.0%)	1 (50.0%)	23 (79.3%)
Number of treatment episodes with Antibiotics	0	0 (0.0%)	1 (100.0%)	4 (16.0%)	1 (50.0%)	6 (20.7%)
	1	1 (100.0%)	0 (0.0%)	8 (32.0%)	1 (50.0%)	10 (34.5%)
	2	0 (0.0%)	0 (0.0%)	4 (16.0%)	0 (0.0%)	4 (13.8%)
	3	0 (0.0%)	0 (0.0%)	2 (8.0%)	0 (0.0%)	2 (6.9%)
	4	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	1 (3.4%)
	7	0 (0.0%)	0 (0.0%)	2 (8.0%)	0 (0.0%)	2 (6.9%)
	8	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	1 (3.4%)
	9	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	1 (3.4%)
	10	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	1 (3.4%)
	11	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	1 (3.4%)
Total number of treatment episodes with Antibiotics		1	0	78	1	80

Table 1.3.1
Hospitalisation due to Infection
Full Analysis Set Excluding Ongoing Subjects

Treatment Period: Total

Parameter	Categories/ Sample Characteristics	Age (years) >=2 to <12 years (N=9)	Age (years) >=12 to <17 years (N=7)	Age (years) >=17 to <=65 years (N=34)	Age (years) >65 years (N=3)	Total (N=53)
Number of person years exposure		10.97	5.29	39.50	3.68	59.44
Number of hospitalizations	0	9 (100.0%)	7 (100.0%)	34 (100.0%)	3 (100.0%)	53 (100.0%)
Total number of hospitalizations		0	0	0	0	0
Total Number of hospitalizations per person-year		0.000	0.000	0.000	0.000	0.000
Number of days in hospital	0	9 (100.0%)	7 (100.0%)	34 (100.0%)	3 (100.0%)	53 (100.0%)
Total number of days in hospital		0	0	0	0	0
Total number of days in hospital per person-year		0.000	0.000	0.000	0.000	0.000
Total number of episodes of fever		3	1	3	0	7
Total number of episodes of fever per person-year		0.274	0.189	0.076	0.000	0.118

Table 1.4.1
Episodes of Fever
Full Analysis Set Excluding Ongoing Subjects

Treatment Period: Primary

Parameter	Categories/ Sample Characteristics	Age (years) >=2 to <12 years (N=9)	Age (years) >=12 to <17 years (N=7)	Age (years) >=17 to <=65 years (N=34)	Age (years) >65 years (N=3)	Total (N=53)
Number of person years exposure		9.07	4.15	32.49	3.05	48.76
Number of patients with fever	Yes	1 (11.1%)	1 (14.3%)	3 (8.8%)	0 (0.0%)	5 (9.4%)
Number of episodes of fever	0	8 (88.9%)	6 (85.7%)	31 (91.2%)	3 (100.0%)	48 (90.6%)
	1	0 (0.0%)	1 (14.3%)	3 (8.8%)	0 (0.0%)	4 (7.5%)
	2	1 (11.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.9%)
Total number of episodes of fever		2	1	3	0	6
Total number of episodes of fever per person-year		0.220	0.241	0.092	0.000	0.123

Fever Episodes by Sex

Table 1.4.2
Episodes of Fever
Full Analysis Set Excluding Ongoing Subjects - Male

Treatment Period: Primary

Parameter	Categories/ Sample Characteristics	Age (years) >=2 to <12 years (N=8)	Age (years) >=12 to <17 years (N=6)	Age (years) >=17 to <=65 years (N=9)	Age (years) >65 years (N=1)	Total (N=24)
Number of person years exposure		8.08	3.10	8.12	1.02	20.32
Number of patients with fever	Yes	1 (12.5%)	0 (0.0%)	1 (11.1%)	0 (0.0%)	2 (8.3%)
Number of episodes of fever	0	7 (87.5%)	6 (100.0%)	8 (88.9%)	1 (100.0%)	22 (91.7%)
	1	0 (0.0%)	0 (0.0%)	1 (11.1%)	0 (0.0%)	1 (4.2%)
	2	1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.2%)
Total number of episodes of fever		2	0	1	0	3
Total number of episodes of fever per person-year		0.248	0.000	0.123	0.000	0.148

Table 1.4.3
Episodes of Fever
Full Analysis Set Excluding Ongoing Subjects - Female

Treatment Period: Primary

Parameter	Categories/ Sample Characteristics	Age (years) >=2 to <12 years (N=1)	Age (years) >=12 to <17 years (N=1)	Age (years) >=17 to <=65 years (N=25)	Age (years) >65 years (N=2)	Total (N=29)
Number of person years exposure		1.00	1.04	24.37	2.03	28.44
Number of patients with fever	Yes	0 (0.0%)	1 (100.0%)	2 (8.0%)	0 (0.0%)	3 (10.3%)
Number of episodes of fever	0	1 (100.0%)	0 (0.0%)	23 (92.0%)	2 (100.0%)	26 (89.7%)
	1	0 (0.0%)	1 (100.0%)	2 (8.0%)	0 (0.0%)	3 (10.3%)
Total number of episodes of fever		0	1	2	0	3
Total number of episodes of fever per person-year		0.000	0.961	0.082	0.000	0.105

Absences from Work or School

Table 1.5.1
Absences from Work or School due to Infection
Full Analysis Set Excluding Ongoing Subjects

Treatment Period: Primary

Parameter	Categories/ Sample Characteristics	Age (years) >=2 to <12 years (N=7)	Age (years) >=12 to <17 years (N=7)	Age (years) >=17 to <=65 years (N=34)	Age (years) >65 years (N=3)	Total (N=51)
Number of person years exposure		7.05	4.15	32.49	3.05	46.74
Number of patients with absences from work or school	Yes	3 (42.9%)	1 (14.3%)	8 (23.5%)	0 (0.0%)	12 (23.5%)
Number of absences from work or school	0	4 (57.1%)	6 (85.7%)	26 (76.5%)	3 (100.0%)	39 (76.5%)
	1	2 (28.6%)	0 (0.0%)	5 (14.7%)	0 (0.0%)	7 (13.7%)
	2	1 (14.3%)	1 (14.3%)	1 (2.9%)	0 (0.0%)	3 (5.9%)
	3	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (2.0%)
	7	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (2.0%)
Total number of absences from work or school		4	2	17	0	23
Total number of absences from work or school per person-year		0.567	0.482	0.523	0.000	0.492

Missed days in school/work: the question is not applicable for children below 6(as most of these do not visit kindergarden), thus this age group is excluded from the analysis of this secondary endpoint.

Table 1.5.1
Absences from Work or School due to Infection
Full Analysis Set Excluding Ongoing Subjects

Treatment Period: Primary

Parameter	Categories/ Sample Characteristics	Age (years) >=2 to <12 years (N=7)	Age (years) >=12 to <17 years (N=7)	Age (years) >=17 to <=65 years (N=34)	Age (years) >65 years (N=3)	Total (N=51)
Rate of absence from work or school per person-year		0.018	0.007	0.011	0.000	0.011

Table 1.5.2
Absences from Work or School due to Infection
Full Analysis Set Excluding Ongoing Subjects - Male

Treatment Period: Total

Parameter	Categories/ Sample Characteristics	Age (years) >=2 to <12 years (N=6)	Age (years) >=12 to <17 years (N=6)	Age (years) >=17 to <=65 years (N=9)	Age (years) >65 years (N=1)	Total (N=22)
Number of person years exposure		7.32	4.04	9.87	1.23	22.46
Number of patients with absences from work or school	Yes	3 (50.0%)	1 (16.7%)	2 (22.2%)	0 (0.0%)	6 (27.3%)
Number of absences from work or school	0	3 (50.0%)	5 (83.3%)	7 (77.8%)	1 (100.0%)	16 (72.7%)
	1	1 (16.7%)	0 (0.0%)	2 (22.2%)	0 (0.0%)	3 (13.6%)
	2	2 (33.3%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	3 (13.6%)
Total number of absences from work or school		5	2	2	0	9
Total number of absences from work or school per person-year		0.683	0.495	0.203	0.000	0.401

Missed days in school/work: the question is not applicable for children below 6(as most of these do not visit kindergarden), thus this age group is excluded from the analysis of this secondary endpoint.

Reviewer Comment:
Adolescents generally had the lowest rate of all infections. The rates of all infections in other pediatric and adult age categories were generally similar, notwithstanding the comparatively small size of several subgroups.

The incidence of all infections was similar among males and females.

4. BLA supplement section 2.5.5.5 Serious Adverse Events states in part that all five serious adverse events (SAEs) reported in study SCGAM-01 “were assessed as unrelated to treatment by the responsible investigator.” Please provide your, as sponsor, assessment of the possible relationship between each of these SAEs and prior administration of the investigational product. Please include data on the time interval between the prior infusion and the onset of each SAE as part of your discussion of your causality assessments.

Applicant Response

> *Please find attached the sponsor assessment of the possible relationship between the five SAEs and prior administration of* (b) (4) *including data on the time interval between the prior infusion and the onset of each SAE.*

Sponsor assessment of the causal relationship between SAEs and prior administration of Cutaquig

Pat. ID	AE (MedDRA-PT)	Age/ Gender	Infusional AE?	Latency*	AE Duration	AE Severity	AE Seriousness Criteria	AE Outcome	Investigator Causality	Sponsor Causality
(b) (6)	Thyroid neoplasm	63/f	Yes	55 hrs	5 days	MILD	Hospitalization required or prolonged	RECOVERED/ RESOLVED	NOT RELATED	NOT RELATED Patient had partial thyroidectomy 25 years ago. Recently, struma relapsed and patient was hospitalized for re-thyroidectomy. Histology: hyperplastic enlargement of thyroid gland w/o any signs of malignancy. No action was taken with the study drug.
	Appendicitis	34/f	Yes	31 hrs	13 days	SEVERE	Hospitalization required or prolonged Medically important condition	RECOVERED/ RESOLVED	NOT RELATED	NOT RELATED The patient experienced abdominal pain and presented to the emergency department. CT scan revealed appendicitis. Patient underwent emergency laparoscopic appendectomy. No action was taken with the study drug.
	Grand mal convulsion	10/m	No	187 hrs	25 min	MILD	Medically important condition	RECOVERED/ RESOLVED	UNLIKELY	NOT RELATED Medical history included seizure disorder since 2003. Long latency. Neurologist increased anti-epileptic medications prior to discharge. No action was taken with the study drug.
	Asthma	13/f	Yes	5 hrs	40 days	SEVERE	Hospitalization required or prolonged	RECOVERED/ RESOLVED	NOT RELATED	NOT RELATED Medical history which include severe and persistent asthma since 2005, whooping cough due to *Bordetella pertussis* and allergic rhinitis. Due to acute exacerbation, patient was admitted to hospital. No action was taken with the study drug.
	Respiratory syncytial virus bronchiolitis	13/f	Yes	38 hrs	20 days	SEVERE	Hospitalization required or prolonged	RECOVERED/ RESOLVED	NOT RELATED	NOT RELATED Same patient as above. Laboratory results revealed a virus panel positive for respiratory syncytial virus. No action was taken with the study drug.

* time between prior infusion of octanorm and onset of SAE.

Reviewer Comment:

This reviewer concurs with the assessment that none of the above reported SAEs were causally related to Cutaquig administration.

5. Please submit a table of all adverse reactions (AR) for study SCGAM-01 using the following definition of AR: Either the AE was classified at least possibly related to IP administration according to investigator and/or applicant OR the AE began within 72 hours following the end of the IP infusion, OR the investigator's causality assessment was missing.

Applicant Response:

This definition of AR actually matches the definition of suspected adverse reactions (SARs) used in the analysis.

We have thus prepared a table of SARs by SOC and PT (systemic with infections, but excluding infusion site reactions) for the safety set, again excluding ongoing subjects, and stratified by the age groups suggested by FDA in question 6 (2 to < 12,

12 to < 17, 17 to 65, and > 65 years), per sex and in total. Please refer to Tables 2.1.1, 2.1.2, and 2.1.3.

Table 2.1.1
Number of Patients with Suspected Adverse Reactions by System Organ Class and Preferred Term
Safety Analysis Set Excluding Ongoing Subjects

systemic with infections and w/o infusion site reactions

MedDRA SOC MedDRA Preferred Term	Age (years) >=2 to <12 (N=9)		Age (years) >=12 to <17 (N=7)		Age (years) >=17 to <=65 (N=34)		Age (years) >65 years (N=3)		Total (N=53)	
Any Suspected Adverse Reactions	8 (88.9%)	55	4 (57.1%)	19	30 (88.2%)	146	3 (100.0%)	14	45 (84.9%)	234
Infections and infestations	6 (66.7%)	18	4 (57.1%)	7	26 (76.5%)	67	3 (100.0%)	7	39 (73.6%)	99
Acarodermatitis	0 (0.0%)	0	0 (0.0%)	0	1 (2.9%)	1	0 (0.0%)	0	1 (1.9%)	1
Acute sinusitis	1 (11.1%)	1	0 (0.0%)	0	3 (8.8%)	5	0 (0.0%)	0	4 (7.5%)	6
Appendicitis	0 (0.0%)	0	0 (0.0%)	0	1 (2.9%)	1	0 (0.0%)	0	1 (1.9%)	1
Bacterial infection	0 (0.0%)	0	0 (0.0%)	0	1 (2.9%)	1	0 (0.0%)	0	1 (1.9%)	1
Blastocystis infection	0 (0.0%)	0	0 (0.0%)	0	1 (2.9%)	1	0 (0.0%)	0	1 (1.9%)	1
Bronchitis	1 (11.1%)	2	0 (0.0%)	0	3 (8.8%)	3	0 (0.0%)	0	4 (7.5%)	5
Campylobacter infection	0 (0.0%)	0	0 (0.0%)	0	2 (5.9%)	2	0 (0.0%)	0	2 (3.8%)	2
Chronic sinusitis	0 (0.0%)	0	1 (14.3%)	1	1 (2.9%)	1	0 (0.0%)	0	2 (3.8%)	2
Cystitis	0 (0.0%)	0	0 (0.0%)	0	1 (2.9%)	1	0 (0.0%)	0	1 (1.9%)	1
Ear infection	1 (11.1%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.9%)	1
Fungal infection	0 (0.0%)	0	0 (0.0%)	0	1 (2.9%)	1	0 (0.0%)	0	1 (1.9%)	1
Gastroenteritis	0 (0.0%)	0	0 (0.0%)	0	1 (2.9%)	1	0 (0.0%)	0	1 (1.9%)	1
Gastroenteritis viral	1 (11.1%)	1	0 (0.0%)	0	1 (2.9%)	1	0 (0.0%)	0	2 (3.8%)	2
Gastrointestinal infection	1 (11.1%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.9%)	1
Herpes simplex	0 (0.0%)	0	0 (0.0%)	0	1 (2.9%)	1	0 (0.0%)	0	1 (1.9%)	1
Herpes zoster	0 (0.0%)	0	0 (0.0%)	0	1 (2.9%)	1	0 (0.0%)	0	1 (1.9%)	1
Influenza	0 (0.0%)	0	0 (0.0%)	0	3 (8.8%)	3	0 (0.0%)	0	3 (5.7%)	3
Laryngitis	0 (0.0%)	0	0 (0.0%)	0	1 (2.9%)	1	0 (0.0%)	0	1 (1.9%)	1
Nasopharyngitis	1 (11.1%)	1	0 (0.0%)	0	6 (17.6%)	13	2 (66.7%)	2	9 (17.0%)	16
Onychomycosis	0 (0.0%)	0	0 (0.0%)	0	1 (2.9%)	1	0 (0.0%)	0	1 (1.9%)	1
Oral candidiasis	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (33.3%)	1	1 (1.9%)	1
Oral herpes	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (33.3%)	2	1 (1.9%)	2
Otitis media	1 (11.1%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.9%)	1
Pharyngitis	1 (11.1%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.9%)	1
Pharyngitis streptococcal	0 (0.0%)	0	0 (0.0%)	0	1 (2.9%)	1	0 (0.0%)	0	1 (1.9%)	1
Respiratory syncytial virus infection	1 (11.1%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.9%)	1
Respiratory tract infection	1 (11.1%)	1	0 (0.0%)	0	1 (2.9%)	1	0 (0.0%)	0	2 (3.8%)	2
Rhinitis	1 (11.1%)	2	1 (14.3%)	1	3 (8.8%)	3	0 (0.0%)	0	5 (9.4%)	6
Rhinovirus infection	1 (11.1%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.9%)	1
Sinusitis	0 (0.0%)	0	2 (28.6%)	3	6 (17.6%)	9	1 (33.3%)	2	9 (17.0%)	14
Staphylococcal infection	0 (0.0%)	0	0 (0.0%)	0	1 (2.9%)	1	0 (0.0%)	0	1 (1.9%)	1
Tinea infection	0 (0.0%)	0	1 (14.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (1.9%)	1
Tooth infection	0 (0.0%)	0	0 (0.0%)	0	1 (2.9%)	1	0 (0.0%)	0	1 (1.9%)	1
Upper respiratory tract infection	3 (33.3%)	3	1 (14.3%)	1	2 (5.9%)	2	0 (0.0%)	0	6 (11.3%)	6
Urinary tract infection	1 (11.1%)	1	0 (0.0%)	0	2 (5.9%)	5	0 (0.0%)	0	3 (5.7%)	6
Urinary tract infection fungal	0 (0.0%)	0	0 (0.0%)	0	1 (2.9%)	1	0 (0.0%)	0	1 (1.9%)	1
Viral sinusitis	0 (0.0%)	0	0 (0.0%)	0	1 (2.9%)	1	0 (0.0%)	0	1 (1.9%)	1
Vulvovaginal candidiasis	0 (0.0%)	0	0 (0.0%)	0	1 (2.9%)	1	0 (0.0%)	0	1 (1.9%)	1
Vulvovaginal mycotic infection	0 (0.0%)	0	0 (0.0%)	0	1 (2.9%)	2	0 (0.0%)	0	1 (1.9%)	2

Table 2.1.1
Number of Patients with Suspected Adverse Reactions by System Organ Class and Preferred Term
Safety Analysis Set Excluding Ongoing Subjects

systemic with infections and w/o infusion site reactions

MedDRA SOC MedDRA Preferred Term	Age (years) >=2 to <12 (N=9)		Age (years) >=12 to <17 (N=7)		Age (years) >=17 to <=65 (N=34)		Age (years) >65 years (N=3)		Total (N=53)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0%)	0	0 (0.0%)	0	2 (5.9%)	2	0 (0.0%)	0	2 (3.8%)	2
Thyroid neoplasm	0 (0.0%)	0	0 (0.0%)	0	1 (2.9%)	1	0 (0.0%)	0	1 (1.9%)	1
Uterine leiomyoma	0 (0.0%)	0	0 (0.0%)	0	1 (2.9%)	1	0 (0.0%)	0	1 (1.9%)	1
Blood and lymphatic system disorders	1 (11.1%)	2	1 (14.3%)	2	2 (5.9%)	2	0 (0.0%)	0	4 (7.5%)	6
Eosinophilia	1 (11.1%)	2	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.9%)	2
Leukopenia	0 (0.0%)	0	1 (14.3%)	1	1 (2.9%)	1	0 (0.0%)	0	2 (3.8%)	2
Lymphadenitis	0 (0.0%)	0	0 (0.0%)	0	1 (2.9%)	1	0 (0.0%)	0	1 (1.9%)	1
Neutropenia	0 (0.0%)	0	1 (14.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (1.9%)	1
Immune system disorders	1 (11.1%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.9%)	1
Hypersensitivity	1 (11.1%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.9%)	1
Nervous system disorders	0 (0.0%)	0	0 (0.0%)	0	7 (20.6%)	8	0 (0.0%)	0	7 (13.2%)	8
Carpal tunnel syndrome	0 (0.0%)	0	0 (0.0%)	0	1 (2.9%)	1	0 (0.0%)	0	1 (1.9%)	1
Headache	0 (0.0%)	0	0 (0.0%)	0	4 (11.8%)	5	0 (0.0%)	0	4 (7.5%)	5
Sinus headache	0 (0.0%)	0	0 (0.0%)	0	2 (5.9%)	2	0 (0.0%)	0	2 (3.8%)	2
Eye disorders	0 (0.0%)	0	0 (0.0%)	0	3 (8.8%)	5	0 (0.0%)	0	3 (5.7%)	5
Blepharitis	0 (0.0%)	0	0 (0.0%)	0	1 (2.9%)	1	0 (0.0%)	0	1 (1.9%)	1
Cataract	0 (0.0%)	0	0 (0.0%)	0	1 (2.9%)	1	0 (0.0%)	0	1 (1.9%)	1
Conjunctivitis	0 (0.0%)	0	0 (0.0%)	0	1 (2.9%)	1	0 (0.0%)	0	1 (1.9%)	1
Eye irritation	0 (0.0%)	0	0 (0.0%)	0	1 (2.9%)	1	0 (0.0%)	0	1 (1.9%)	1
Vitreous floaters	0 (0.0%)	0	0 (0.0%)	0	1 (2.9%)	1	0 (0.0%)	0	1 (1.9%)	1
Ear and labyrinth disorders	2 (22.2%)	2	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	2 (3.8%)	2
Ear pain	1 (11.1%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.9%)	1
Motion sickness	1 (11.1%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.9%)	1
Respiratory, thoracic and mediastinal disorders	3 (33.3%)	5	1 (14.3%)	2	4 (11.8%)	6	1 (33.3%)	2	9 (17.0%)	15
Asthma	0 (0.0%)	0	0 (0.0%)	0	1 (2.9%)	1	0 (0.0%)	0	1 (1.9%)	1
Cough	2 (22.2%)	2	0 (0.0%)	0	2 (5.9%)	3	0 (0.0%)	0	4 (7.5%)	5
Dysphonia	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (33.3%)	1	1 (1.9%)	1
Nasal congestion	2 (22.2%)	3	1 (14.3%)	2	0 (0.0%)	0	0 (0.0%)	0	3 (5.7%)	5
Oropharyngeal pain	0 (0.0%)	0	0 (0.0%)	0	1 (2.9%)	1	1 (33.3%)	1	2 (3.8%)	2
Sinus congestion	0 (0.0%)	0	0 (0.0%)	0	1 (2.9%)	1	0 (0.0%)	0	1 (1.9%)	1
Gastrointestinal disorders	5 (55.6%)	11	2 (28.6%)	2	11 (32.4%)	13	1 (33.3%)	3	19 (35.8%)	29
Abdominal discomfort	0 (0.0%)	0	0 (0.0%)	0	1 (2.9%)	1	0 (0.0%)	0	1 (1.9%)	1
Abdominal distension	0 (0.0%)	0	0 (0.0%)	0	2 (5.9%)	2	0 (0.0%)	0	2 (3.8%)	2
Abdominal pain	0 (0.0%)	0	1 (14.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (1.9%)	1
Abdominal pain upper	1 (11.1%)	3	0 (0.0%)	0	1 (2.9%)	1	0 (0.0%)	0	2 (3.8%)	4
Cheilitis	1 (11.1%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.9%)	1

Table 2.1.1
Number of Patients with Suspected Adverse Reactions by System Organ Class and Preferred Term
Safety Analysis Set Excluding Ongoing Subjects

systemic with infections and w/o infusion site reactions

MedDRA SOC MedDRA Preferred Term	Age (years) >=2 to <12 (N=9)		Age (years) >=12 to <17 (N=7)		Age (years) >=17 to <=65 (N=34)		Age (years) >65 years (N=3)		Total (N=53)	
Dental caries	0 (0.0%)	0	0 (0.0%)	0	1 (2.9%)	1	0 (0.0%)	0	1 (1.9%)	1
Diarrhoea	1 (11.1%)	2	0 (0.0%)	0	6 (17.6%)	6	1 (33.3%)	3	8 (15.1%)	11
Gastrooesophageal reflux disease	1 (11.1%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.9%)	1
Haemorrhoids	0 (0.0%)	0	0 (0.0%)	0	1 (2.9%)	1	0 (0.0%)	0	1 (1.9%)	1
Nausea	0 (0.0%)	0	0 (0.0%)	0	1 (2.9%)	1	0 (0.0%)	0	1 (1.9%)	1
Umbilical hernia	0 (0.0%)	0	1 (14.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (1.9%)	1
Vomiting	3 (33.3%)	4	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	3 (5.7%)	4
Skin and subcutaneous tissue disorders	2 (22.2%)	4	1 (14.3%)	1	5 (14.7%)	5	0 (0.0%)	0	8 (15.1%)	10
Dermatitis	0 (0.0%)	0	0 (0.0%)	0	1 (2.9%)	1	0 (0.0%)	0	1 (1.9%)	1
Dermatitis allergic	1 (11.1%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.9%)	1
Dermatitis contact	0 (0.0%)	0	0 (0.0%)	0	2 (5.9%)	2	0 (0.0%)	0	2 (3.8%)	2
Intertrigo	1 (11.1%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.9%)	1
Rash	0 (0.0%)	0	1 (14.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (1.9%)	1
Skin discolouration	1 (11.1%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.9%)	1
Skin lesion	0 (0.0%)	0	0 (0.0%)	0	1 (2.9%)	1	0 (0.0%)	0	1 (1.9%)	1
Solar dermatitis	0 (0.0%)	0	0 (0.0%)	0	1 (2.9%)	1	0 (0.0%)	0	1 (1.9%)	1
Urticaria	1 (11.1%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.9%)	1
Musculoskeletal and connective tissue disorders	0 (0.0%)	0	1 (14.3%)	1	10 (29.4%)	18	0 (0.0%)	0	11 (20.8%)	19
Arthralgia	0 (0.0%)	0	0 (0.0%)	0	2 (5.9%)	2	0 (0.0%)	0	2 (3.8%)	2
Back pain	0 (0.0%)	0	0 (0.0%)	0	1 (2.9%)	1	0 (0.0%)	0	1 (1.9%)	1
Muscle spasms	0 (0.0%)	0	0 (0.0%)	0	3 (8.8%)	3	0 (0.0%)	0	3 (5.7%)	3
Musculoskeletal pain	0 (0.0%)	0	0 (0.0%)	0	2 (5.9%)	4	0 (0.0%)	0	2 (3.8%)	4
Myalgia	0 (0.0%)	0	1 (14.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (1.9%)	1
Neck pain	0 (0.0%)	0	0 (0.0%)	0	1 (2.9%)	1	0 (0.0%)	0	1 (1.9%)	1
Pathological fracture	0 (0.0%)	0	0 (0.0%)	0	1 (2.9%)	2	0 (0.0%)	0	1 (1.9%)	2
Rotator cuff syndrome	0 (0.0%)	0	0 (0.0%)	0	1 (2.9%)	1	0 (0.0%)	0	1 (1.9%)	1
Scoliosis	0 (0.0%)	0	0 (0.0%)	0	1 (2.9%)	2	0 (0.0%)	0	1 (1.9%)	2
Spondylolisthesis	0 (0.0%)	0	0 (0.0%)	0	1 (2.9%)	1	0 (0.0%)	0	1 (1.9%)	1
Synovial cyst	0 (0.0%)	0	0 (0.0%)	0	1 (2.9%)	1	0 (0.0%)	0	1 (1.9%)	1
Renal and urinary disorders	1 (11.1%)	1	0 (0.0%)	0	2 (5.9%)	2	0 (0.0%)	0	3 (5.7%)	3
Dysuria	1 (11.1%)	1	0 (0.0%)	0	2 (5.9%)	2	0 (0.0%)	0	3 (5.7%)	3
Reproductive system and breast disorders	0 (0.0%)	0	0 (0.0%)	0	1 (2.9%)	1	0 (0.0%)	0	1 (1.9%)	1
Pelvic congestion	0 (0.0%)	0	0 (0.0%)	0	1 (2.9%)	1	0 (0.0%)	0	1 (1.9%)	1
General disorders and administration site conditions	1 (11.1%)	1	2 (28.6%)	2	5 (14.7%)	5	0 (0.0%)	0	8 (15.1%)	8
Device leakage	0 (0.0%)	0	0 (0.0%)	0	1 (2.9%)	1	0 (0.0%)	0	1 (1.9%)	1
Fatigue	0 (0.0%)	0	0 (0.0%)	0	2 (5.9%)	2	0 (0.0%)	0	2 (3.8%)	2
Malaise	0 (0.0%)	0	1 (14.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (1.9%)	1
Mucosal inflammation	0 (0.0%)	0	1 (14.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (1.9%)	1
Pyrexia	1 (11.1%)	1	0 (0.0%)	0	2 (5.9%)	2	0 (0.0%)	0	3 (5.7%)	3
Investigations	2 (22.2%)	3	2 (28.6%)	2	5 (14.7%)	5	1 (33.3%)	2	10 (18.9%)	12
Blood sodium decreased	0 (0.0%)	0	1 (14.3%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (1.9%)	1
Body temperature increased	1 (11.1%)	1	0 (0.0%)	0	1 (2.9%)	1	0 (0.0%)	0	2 (3.8%)	2
Coombs direct test positive	0 (0.0%)	0	0 (0.0%)	0	1 (2.9%)	1	0 (0.0%)	0	1 (1.9%)	1
Free haemoglobin present	0 (0.0%)	0	1 (14.3%)	1	1 (2.9%)	1	0 (0.0%)	0	2 (3.8%)	2
Haemoglobin increased	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (33.3%)	1	1 (1.9%)	1
Haptoglobin decreased	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (33.3%)	1	1 (1.9%)	1
Influenza A virus test positive	1 (11.1%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.9%)	1
Parvovirus B19 test positive	1 (11.1%)	1	0 (0.0%)	0	1 (2.9%)	1	0 (0.0%)	0	2 (3.8%)	2
Urine analysis abnormal	0 (0.0%)	0	0 (0.0%)	0	1 (2.9%)	1	0 (0.0%)	0	1 (1.9%)	1
Injury, poisoning and procedural complications	4 (44.4%)	7	0 (0.0%)	0	6 (17.6%)	7	0 (0.0%)	0	10 (18.9%)	14
Arthropod bite	2 (22.2%)	2	0 (0.0%)	0	3 (8.8%)	4	0 (0.0%)	0	5 (9.4%)	6
Excoriation	2 (22.2%)	2	0 (0.0%)	0	2 (5.9%)	2	0 (0.0%)	0	4 (7.5%)	4
Fall	1 (11.1%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.9%)	1
Laceration	0 (0.0%)	0	0 (0.0%)	0	1 (2.9%)	1	0 (0.0%)	0	1 (1.9%)	1
Scar	1 (11.1%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.9%)	1
Scratch	1 (11.1%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (1.9%)	1

Tables of adverse reactions excluding infusion site reactions by sex – Male

Table 2.1.2
Number of Patients with Suspected Adverse Reactions by System Organ Class and Preferred Term
Safety Analysis Set Excluding Ongoing Subjects - Male

systemic with infections and w/o infusion site reactions

MedDRA SOC MedDRA Preferred Term	Age (years) >=2 to <12 (N=8)		Age (years) >=12 to <17 (N=6)		Age (years) >=17 to <=65 (N=9)		Age (years) >65 years (N=1)		Total (N=24)	
Any Suspected Adverse Reactions	8 (100.0%)	55	3 (50.0%)	16	7 (77.8%)	27	1 (100.0%)	2	19 (79.2%)	100
Infections and infestations	6 (75.0%)	18	3 (50.0%)	6	7 (77.8%)	13	1 (100.0%)	2	17 (70.8%)	39
Acarodermatitis	0 (0.0%)	0	0 (0.0%)	0	1 (11.1%)	1	0 (0.0%)	0	1 (4.2%)	1
Acute sinusitis	1 (12.5%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (4.2%)	1
Bacterial infection	0 (0.0%)	0	0 (0.0%)	0	1 (11.1%)	1	0 (0.0%)	0	1 (4.2%)	1
Bronchitis	1 (12.5%)	2	0 (0.0%)	0	2 (22.2%)	2	0 (0.0%)	0	3 (12.5%)	4
Chronic sinusitis	0 (0.0%)	0	1 (16.7%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (4.2%)	1
Ear infection	1 (12.5%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (4.2%)	1
Gastroenteritis	0 (0.0%)	0	0 (0.0%)	0	1 (11.1%)	1	0 (0.0%)	0	1 (4.2%)	1
Gastroenteritis viral	1 (12.5%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (4.2%)	1
Gastrointestinal infection	1 (12.5%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (4.2%)	1
Nasopharyngitis	1 (12.5%)	1	0 (0.0%)	0	3 (33.3%)	4	0 (0.0%)	0	4 (16.7%)	5
Otitis media	1 (12.5%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (4.2%)	1
Pharyngitis	1 (12.5%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (4.2%)	1
Respiratory syncytial virus infection	1 (12.5%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (4.2%)	1
Respiratory tract infection	1 (12.5%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (4.2%)	1
Rhinitis	1 (12.5%)	2	0 (0.0%)	0	2 (22.2%)	2	0 (0.0%)	0	3 (12.5%)	4
Rhinovirus infection	1 (12.5%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (4.2%)	1
Sinusitis	0 (0.0%)	0	2 (33.3%)	3	1 (11.1%)	1	1 (100.0%)	2	4 (16.7%)	6
Tinea infection	0 (0.0%)	0	1 (16.7%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (4.2%)	1
Upper respiratory tract infection	3 (37.5%)	3	1 (16.7%)	1	1 (11.1%)	1	0 (0.0%)	0	5 (20.8%)	5
Urinary tract infection	1 (12.5%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (4.2%)	1
Blood and lymphatic system disorders	1 (12.5%)	2	1 (16.7%)	2	1 (11.1%)	1	0 (0.0%)	0	3 (12.5%)	5
Eosinophilia	1 (12.5%)	2	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (4.2%)	2
Leukopenia	0 (0.0%)	0	1 (16.7%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (4.2%)	1
Lymphadenitis	0 (0.0%)	0	0 (0.0%)	0	1 (11.1%)	1	0 (0.0%)	0	1 (4.2%)	1
Neutropenia	0 (0.0%)	0	1 (16.7%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (4.2%)	1
Immune system disorders	1 (12.5%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (4.2%)	1
Hypersensitivity	1 (12.5%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (4.2%)	1
Nervous system disorders	0 (0.0%)	0	0 (0.0%)	0	1 (11.1%)	1	0 (0.0%)	0	1 (4.2%)	1
Headache	0 (0.0%)	0	0 (0.0%)	0	1 (11.1%)	1	0 (0.0%)	0	1 (4.2%)	1
Ear and labyrinth disorders	2 (25.0%)	2	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	2 (8.3%)	2
Ear pain	1 (12.5%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (4.2%)	1
Motion sickness	1 (12.5%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (4.2%)	1
Respiratory, thoracic and mediastinal disorders	3 (37.5%)	5	1 (16.7%)	2	1 (11.1%)	1	0 (0.0%)	0	5 (20.8%)	8
Cough	2 (25.0%)	2	0 (0.0%)	0	1 (11.1%)	1	0 (0.0%)	0	3 (12.5%)	3
Nasal congestion	2 (25.0%)	3	1 (16.7%)	2	0 (0.0%)	0	0 (0.0%)	0	3 (12.5%)	5
Gastrointestinal disorders	5 (62.5%)	11	1 (16.7%)	1	3 (33.3%)	3	0 (0.0%)	0	9 (37.5%)	15
Abdominal pain	0 (0.0%)	0	1 (16.7%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (4.2%)	1
Abdominal pain upper	1 (12.5%)	3	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (4.2%)	3
Cheilitis	1 (12.5%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (4.2%)	1
Diarrhoea	1 (12.5%)	2	0 (0.0%)	0	2 (22.2%)	2	0 (0.0%)	0	3 (12.5%)	4
Gastrooesophageal reflux disease	1 (12.5%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (4.2%)	1
Nausea	0 (0.0%)	0	0 (0.0%)	0	1 (11.1%)	1	0 (0.0%)	0	1 (4.2%)	1
Vomiting	3 (37.5%)	4	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	3 (12.5%)	4
Skin and subcutaneous tissue disorders	2 (25.0%)	4	1 (16.7%)	1	0 (0.0%)	0	0 (0.0%)	0	3 (12.5%)	5
Dermatitis allergic	1 (12.5%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (4.2%)	1
Intertrigo	1 (12.5%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (4.2%)	1
Rash	0 (0.0%)	0	1 (16.7%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (4.2%)	1
Skin discolouration	1 (12.5%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (4.2%)	1
Urticaria	1 (12.5%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (4.2%)	1
Musculoskeletal and connective tissue disorders	0 (0.0%)	0	1 (16.7%)	1	2 (22.2%)	5	0 (0.0%)	0	3 (12.5%)	6
Muscle spasms	0 (0.0%)	0	0 (0.0%)	0	1 (11.1%)	1	0 (0.0%)	0	1 (4.2%)	1
Musculoskeletal pain	0 (0.0%)	0	0 (0.0%)	0	1 (11.1%)	3	0 (0.0%)	0	1 (4.2%)	3
Myalgia	0 (0.0%)	0	1 (16.7%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (4.2%)	1
Rotator cuff syndrome	0 (0.0%)	0	0 (0.0%)	0	1 (11.1%)	1	0 (0.0%)	0	1 (4.2%)	1

Table 2.1.2
Number of Patients with Suspected Adverse Reactions by System Organ Class and Preferred Term
Safety Analysis Set Excluding Ongoing Subjects - Male

systemic with infections and w/o infusion site reactions

MedDRA SOC MedDRA Preferred Term	Age (years) >=2 to <12 (N=8)		Age (years) >=12 to <17 (N=6)		Age (years) >=17 to <=65 (N=9)		Age (years) >65 years (N=1)		Total (N=24)	
Renal and urinary disorders	1 (12.5%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (4.2%)	1
Dysuria	1 (12.5%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (4.2%)	1
General disorders and administration site conditions	1 (12.5%)	1	1 (16.7%)	1	1 (11.1%)	1	0 (0.0%)	0	3 (12.5%)	3
Mucosal inflammation	0 (0.0%)	0	1 (16.7%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (4.2%)	1
Pyrexia	1 (12.5%)	1	0 (0.0%)	0	1 (11.1%)	1	0 (0.0%)	0	2 (8.3%)	2
Investigations	2 (25.0%)	3	2 (33.3%)	2	1 (11.1%)	1	0 (0.0%)	0	5 (20.8%)	6
Blood sodium decreased	0 (0.0%)	0	1 (16.7%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (4.2%)	1
Body temperature increased	1 (12.5%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (4.2%)	1
Free haemoglobin present	0 (0.0%)	0	1 (16.7%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (4.2%)	1
Influenza A virus test positive	1 (12.5%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (4.2%)	1
Parvovirus B19 test positive	1 (12.5%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (4.2%)	1
Urine analysis abnormal	0 (0.0%)	0	0 (0.0%)	0	1 (11.1%)	1	0 (0.0%)	0	1 (4.2%)	1
Injury, poisoning and procedural complications	4 (50.0%)	7	0 (0.0%)	0	1 (11.1%)	1	0 (0.0%)	0	5 (20.8%)	8
Arthropod bite	2 (25.0%)	2	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	2 (8.3%)	2
Excoriation	2 (25.0%)	2	0 (0.0%)	0	1 (11.1%)	1	0 (0.0%)	0	3 (12.5%)	3
Fall	1 (12.5%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (4.2%)	1
Scar	1 (12.5%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (4.2%)	1
Scratch	1 (12.5%)	1	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (4.2%)	1

Tables of adverse reactions by sex excluding infusion site reactions – Female

Table 2.1.3
Number of Patients with Suspected Adverse Reactions by System Organ Class and Preferred Term
Safety Analysis Set Excluding Ongoing Subjects - Female

systemic with infections and w/o infusion site reactions

MedDRA SOC MedDRA Preferred Term	Age (years) >=2 to <12 (N=1)		Age (years) >=12 to <17 (N=1)		Age (years) >=17 to <=65 (N=25)		Age (years) >65 years (N=2)		Total (N=29)	
Any Suspected Adverse Reactions	0 (0.0%)	0	1 (100.0%)	3	23 (92.0%)	119	2 (100.0%)	12	26 (89.7%)	134
Infections and infestations	0 (0.0%)	0	1 (100.0%)	1	19 (76.0%)	54	2 (100.0%)	5	22 (75.9%)	60
Acute sinusitis	0 (0.0%)	0	0 (0.0%)	0	3 (12.0%)	5	0 (0.0%)	0	3 (10.3%)	5
Appendicitis	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	1	0 (0.0%)	0	1 (3.4%)	1
Blastocystis infection	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	1	0 (0.0%)	0	1 (3.4%)	1
Bronchitis	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	1	0 (0.0%)	0	1 (3.4%)	1
Campylobacter infection	0 (0.0%)	0	0 (0.0%)	0	2 (8.0%)	2	0 (0.0%)	0	2 (6.9%)	2
Chronic sinusitis	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	1	0 (0.0%)	0	1 (3.4%)	1
Cystitis	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	1	0 (0.0%)	0	1 (3.4%)	1
Fungal infection	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	1	0 (0.0%)	0	1 (3.4%)	1
Gastroenteritis viral	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	1	0 (0.0%)	0	1 (3.4%)	1
Herpes simplex	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	1	0 (0.0%)	0	1 (3.4%)	1
Herpes zoster	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	1	0 (0.0%)	0	1 (3.4%)	1
Influenza	0 (0.0%)	0	0 (0.0%)	0	3 (12.0%)	3	0 (0.0%)	0	3 (10.3%)	3
Laryngitis	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	1	0 (0.0%)	0	1 (3.4%)	1
Nasopharyngitis	0 (0.0%)	0	0 (0.0%)	0	3 (12.0%)	9	2 (100.0%)	2	5 (17.2%)	11
Onychomycosis	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	1	0 (0.0%)	0	1 (3.4%)	1
Oral candidiasis	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (3.4%)	1
Oral herpes	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	2	1 (3.4%)	2
Pharyngitis streptococcal	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	1	0 (0.0%)	0	1 (3.4%)	1
Respiratory tract infection	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	1	0 (0.0%)	0	1 (3.4%)	1
Rhinitis	0 (0.0%)	0	1 (100.0%)	1	1 (4.0%)	1	0 (0.0%)	0	2 (6.9%)	2
Sinusitis	0 (0.0%)	0	0 (0.0%)	0	5 (20.0%)	8	0 (0.0%)	0	5 (17.2%)	8
Staphylococcal infection	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	1	0 (0.0%)	0	1 (3.4%)	1
Tooth infection	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	1	0 (0.0%)	0	1 (3.4%)	1
Upper respiratory tract infection	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	1	0 (0.0%)	0	1 (3.4%)	1
Urinary tract infection	0 (0.0%)	0	0 (0.0%)	0	2 (8.0%)	5	0 (0.0%)	0	2 (6.9%)	5
Urinary tract infection fungal	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	1	0 (0.0%)	0	1 (3.4%)	1
Viral sinusitis	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	1	0 (0.0%)	0	1 (3.4%)	1
Vulvovaginal candidiasis	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	1	0 (0.0%)	0	1 (3.4%)	1
Vulvovaginal mycotic infection	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	2	0 (0.0%)	0	1 (3.4%)	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0%)	0	0 (0.0%)	0	2 (8.0%)	2	0 (0.0%)	0	2 (6.9%)	2
Thyroid neoplasm	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	1	0 (0.0%)	0	1 (3.4%)	1
Uterine leiomyoma	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	1	0 (0.0%)	0	1 (3.4%)	1
Blood and lymphatic system disorders	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	1	0 (0.0%)	0	1 (3.4%)	1
Leukopenia	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	1	0 (0.0%)	0	1 (3.4%)	1
Nervous system disorders	0 (0.0%)	0	0 (0.0%)	0	6 (24.0%)	7	0 (0.0%)	0	6 (20.7%)	7
Carpal tunnel syndrome	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	1	0 (0.0%)	0	1 (3.4%)	1
Headache	0 (0.0%)	0	0 (0.0%)	0	3 (12.0%)	4	0 (0.0%)	0	3 (10.3%)	4
Sinus headache	0 (0.0%)	0	0 (0.0%)	0	2 (8.0%)	2	0 (0.0%)	0	2 (6.9%)	2
Eye disorders	0 (0.0%)	0	0 (0.0%)	0	3 (12.0%)	5	0 (0.0%)	0	3 (10.3%)	5
Blepharitis	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	1	0 (0.0%)	0	1 (3.4%)	1
Cataract	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	1	0 (0.0%)	0	1 (3.4%)	1
Conjunctivitis	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	1	0 (0.0%)	0	1 (3.4%)	1
Eye irritation	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	1	0 (0.0%)	0	1 (3.4%)	1
Vitreous floaters	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	1	0 (0.0%)	0	1 (3.4%)	1
Respiratory, thoracic and mediastinal disorders	0 (0.0%)	0	0 (0.0%)	0	3 (12.0%)	5	1 (50.0%)	2	4 (13.8%)	7
Asthma	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	1	0 (0.0%)	0	1 (3.4%)	1
Cough	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	2	0 (0.0%)	0	1 (3.4%)	2
Dysphonia	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (3.4%)	1
Oropharyngeal pain	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	1	1 (50.0%)	1	2 (6.9%)	2
Sinus congestion	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	1	0 (0.0%)	0	1 (3.4%)	1
Gastrointestinal disorders	0 (0.0%)	0	1 (100.0%)	1	8 (32.0%)	10	1 (50.0%)	3	10 (34.5%)	14
Abdominal discomfort	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	1	0 (0.0%)	0	1 (3.4%)	1
Abdominal distension	0 (0.0%)	0	0 (0.0%)	0	2 (8.0%)	2	0 (0.0%)	0	2 (6.9%)	2
Abdominal pain upper	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	1	0 (0.0%)	0	1 (3.4%)	1
Dental caries	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	1	0 (0.0%)	0	1 (3.4%)	1
Diarrhoea	0 (0.0%)	0	0 (0.0%)	0	4 (16.0%)	4	1 (50.0%)	3	5 (17.2%)	7

Table 2.1.3
Number of Patients with Suspected Adverse Reactions by System Organ Class and Preferred Term
Safety Analysis Set Excluding Ongoing Subjects - Female

systemic with infections and w/o infusion site reactions

MedDRA SOC MedDRA Preferred Term	Age (years) >=2 to <12 (N=1)		Age (years) >=12 to <17 (N=1)		Age (years) >=17 to <=65 (N=25)		Age (years) >65 years (N=2)		Total (N=29)	
Haemorrhoids	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	1	0 (0.0%)	0	1 (3.4%)	1
Umbilical hernia	0 (0.0%)	0	1 (100.0%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (3.4%)	1
Skin and subcutaneous tissue disorders	0 (0.0%)	0	0 (0.0%)	0	5 (20.0%)	5	0 (0.0%)	0	5 (17.2%)	5
Dermatitis	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	1	0 (0.0%)	0	1 (3.4%)	1
Dermatitis contact	0 (0.0%)	0	0 (0.0%)	0	2 (8.0%)	2	0 (0.0%)	0	2 (6.9%)	2
Skin lesion	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	1	0 (0.0%)	0	1 (3.4%)	1
Solar dermatitis	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	1	0 (0.0%)	0	1 (3.4%)	1
Musculoskeletal and connective tissue disorders	0 (0.0%)	0	0 (0.0%)	0	8 (32.0%)	13	0 (0.0%)	0	8 (27.6%)	13
Arthralgia	0 (0.0%)	0	0 (0.0%)	0	2 (8.0%)	2	0 (0.0%)	0	2 (6.9%)	2
Back pain	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	1	0 (0.0%)	0	1 (3.4%)	1
Muscle spasms	0 (0.0%)	0	0 (0.0%)	0	2 (8.0%)	2	0 (0.0%)	0	2 (6.9%)	2
Musculoskeletal pain	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	1	0 (0.0%)	0	1 (3.4%)	1
Neck pain	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	1	0 (0.0%)	0	1 (3.4%)	1
Pathological fracture	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	2	0 (0.0%)	0	1 (3.4%)	2
Scoliosis	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	2	0 (0.0%)	0	1 (3.4%)	2
Spondylolisthesis	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	1	0 (0.0%)	0	1 (3.4%)	1
Synovial cyst	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	1	0 (0.0%)	0	1 (3.4%)	1
Renal and urinary disorders	0 (0.0%)	0	0 (0.0%)	0	2 (8.0%)	2	0 (0.0%)	0	2 (6.9%)	2
Dysuria	0 (0.0%)	0	0 (0.0%)	0	2 (8.0%)	2	0 (0.0%)	0	2 (6.9%)	2
Reproductive system and breast disorders	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	1	0 (0.0%)	0	1 (3.4%)	1
Pelvic congestion	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	1	0 (0.0%)	0	1 (3.4%)	1
General disorders and administration site conditions	0 (0.0%)	0	1 (100.0%)	1	4 (16.0%)	4	0 (0.0%)	0	5 (17.2%)	5
Device leakage	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	1	0 (0.0%)	0	1 (3.4%)	1
Fatigue	0 (0.0%)	0	0 (0.0%)	0	2 (8.0%)	2	0 (0.0%)	0	2 (6.9%)	2
Malaise	0 (0.0%)	0	1 (100.0%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (3.4%)	1
Pyrexia	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	1	0 (0.0%)	0	1 (3.4%)	1
Investigations	0 (0.0%)	0	0 (0.0%)	0	4 (16.0%)	4	1 (50.0%)	2	5 (17.2%)	6
Body temperature increased	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	1	0 (0.0%)	0	1 (3.4%)	1
Coombs direct test positive	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	1	0 (0.0%)	0	1 (3.4%)	1
Free haemoglobin present	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	1	0 (0.0%)	0	1 (3.4%)	1
Haemoglobin increased	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (3.4%)	1
Haptoglobin decreased	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	1 (50.0%)	1	1 (3.4%)	1
Parvovirus B19 test positive	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	1	0 (0.0%)	0	1 (3.4%)	1
Injury, poisoning and procedural complications	0 (0.0%)	0	0 (0.0%)	0	5 (20.0%)	6	0 (0.0%)	0	5 (17.2%)	6
Arthropod bite	0 (0.0%)	0	0 (0.0%)	0	3 (12.0%)	4	0 (0.0%)	0	3 (10.3%)	4
Excoriation	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	1	0 (0.0%)	0	1 (3.4%)	1
Laceration	0 (0.0%)	0	0 (0.0%)	0	1 (4.0%)	1	0 (0.0%)	0	1 (3.4%)	1

Reviewer Comment: Noted. Excluding ongoing subjects, there did not appear to be any category of adverse reaction that was more frequent among adolescents or younger children compared to adults.

6. Please submit subgroup analyses for secondary efficacy variables, [suspected adverse reactions plus adverse reactions using the above definition of AR], SAEs, and withdrawals due to AEs by age groups 2 to < 12, 12 to < 17, 17 to 65, and > 65 years, sex, and race.

   Applicant Response

   All tables submitted as part of the response to this IR match age groups as defined by FDA above. In addition analyses per sex group are provided as requested. As all but one participant of SCGAM-01 were of race 'WHITE', we did not attempt any stratification by race.

   The following tables are submitted:

Table Number	Population	Table Heading
1.2.1	FAS excluding ongoing subjects	Use of antibiotics
1.2.2	FAS excluding ongoing subjects - subgroup male	Use of antibiotics
1.2.3	FAS excluding ongoing subjects - subgroup female	Use of antibiotics
1.3.1	FAS excluding ongoing subjects	Hospitalisation due to Infection
1.3.2	FAS excluding ongoing subjects - subgroup male	Hospitalisation due to Infection
1.3.3	FAS excluding ongoing subjects - subgroup female	Hospitalisation due to Infection
1.4.1	FAS excluding ongoing subjects	Episodes of Fever
1.4.2	FAS excluding ongoing subjects - subgroup male	Episodes of Fever
1.4.3	FAS excluding ongoing subjects - subgroup female	Episodes of Fever
1.5.1	FAS excluding ongoing subjects	Absences from Work or School due to Infection
1.5.2	FAS excluding ongoing subjects - subgroup male	Absences from Work or School due to Infection
1.5.3	FAS excluding ongoing subjects - subgroup female	Absences from Work or School due to Infection

Reviewer Comment:

See Table 2.1.1 under Applicant Response to comment #5. See Tables under Applicant Response to comment #1 for subgroup analyses of secondary efficacy endpoints by age groups and by sex. This reviewer agrees that the subgroup consisting of one black subjects is too small for meaningful subgroup analysis.

Applicant 30 August 2018 Response to FDA's 27 August 2018 Clinical Information Request

1. The 120-day safety update reports six SAEs in extension study SCGAM-03, including 2 episodes of status asthmaticus in one subject. Please submit a detailed narrative of the status asthmaticus SAEs, including information on the timing of the onset of the SAEs in relation to the start and end times of the most recent investigational product SC infusions.

Applicant's Response:

Please note that both SAEs are coming from the ongoing study, the data is still being cleaned of these cases. After 120-day safety update report was finalised start and end dates of the SAEs in question have been clarified and now confirmed by the Investigator as 06 Mar 2018 - 8 Mar 2018 and 18 Apr 2018 – 20 Apr 2018 respectively. The dates reported in the safety update report actually represent the

start and end dates of the underlying adverse event "deterioration of asthma" in both cases.

SAE "Status asthmaticus" 06 Mar 2018 – 08 Mar 2018
A 15 year-old Caucasian female (weight 56.6 kg, height 159 cm, born on (b) (6) , patient ID (b) (6)) with Primary Immunodeficiency Disease was screened on (b) (6) . The first infusion of (b) (4) 16.5% (week 2) was 90 ml and was administered on (b) (6) . The most recent infusion dose, prior to hospitalization, of (b) (4) 16.5 % (week 24) was 90 ml and was administered on (b) (6) . **[Reviewer Comment: The (b) (6) infusion was well before week 24.]**

An investigator reported that the patient experienced Status Asthmaticus. The event was assessed by the investigator as serious with reported criterion of hospitalization.

Medical/surgical history included severe persistent asthma since (b) (6) , common variable immunodeficiency since (b) (6) , recurrent bronchitis since (b) (6) , and allergic rhinitis since (b) (6) , anxiety since (b) (6) and Vitamin D deficiency since (b) (6) .

Concomitant medications at the time of the event included Advair for asthma since (b) (6) , azithromycin for immunodeficiency since (b) (6) , Levalbuterol for asthma since (b) (6) , ipratropium bromide for asthma since (b) (6) , Pulmicort for asthma since (b) (6) Vitamin D for deficiency since (b) (6) , Zyrtec for allergic rhinitis since (b) (6) , Nasonex for allergic rhinitis since (b) (6) (b) (6) guaifenesin/dextromethorphan since (b) (6) , Acetaminophen with Codeine since (b) (6) , Prozac for anxiety since (b) (6) , and Spiriva for asthma since (b) (6) .

On (b) (6) , the subject presented with a cough. Despite aggressive home treatments with aerosols and oral medications she continued to cough requiring frequent aerosols during the day. On (b) (6) , oral Prednisone was started at 40 mg 3 times a day for 2 days, then 2 times a day for 2-4 days, then once a day for 2-4 days, then 20 mg once a day for 2-4 days. Azithromycin 250 mg was increased from 3 times a week to once daily for 7 days. On (b) (6) , the decision was made to hospitalize the subject due to her failure to respond to any home treatment with the diagnosis of status asthmaticus. Status asthmaticus was successfully treated and the subject was discharged from the hospital on (b) (6) with status asthmaticus reported as resolved. Resolution date for asthma deterioration related symptoms was reported as (b) (6) .

The Primary Investigator assessed the severity of the serious event, Status Asthmaticus, as severe and causality as not related to the study drug. The event outcome was reported as resolved on (b) (6) .

SAE "Status Asthmaticus" 18 Apr 2018 – 20 Apr 2018
A 15 year-old Caucasian female (weight 61.2 kg, height 159 cm, born on (b) (6) (b) (6) patient ID (b) (6)) with Primary Immunodeficiency Disease was screened on (b) (6) . The first infusion of (b) (4) 16.5% (week 2) was 90 ml and was administered on (b) (6) . The most recent infusion dose, prior to hospitalization, of (b) (4) 16.5 % (week 24) was 90 ml and was administered on

16 Apr 2018.

An investigator reported that the patient experienced Asthma Exacerbation. The event was assessed by the investigator as serious with reported criterion of hospitalization.

Medical/surgical history included severe persistent asthma since (b) (6), common variable immunodeficiency since (b) (6), recurrent bronchitis since (b) (6), and allergic rhinitis since (b) (6), anxiety since (b) (6) and Vitamin D deficiency since (b) (6).

Concomitant medications at the time of the event included Advair for asthma since (b) (6), azithromycin for immunodeficiency since (b) (6) Levalbuterol for asthma since (b) (6), ipratropium bromide for asthma since (b) (6), Pulmicort for asthma since (b) (6), Vitamin D for deficiency since (b) (6), Zyrtec for allergic rhinitis since (b) (6), Nasonex for allergic rhinitis since (b) (6) (b) (6) guaifenesin/dextromethorphan since (b) (6), Acetaminophen with Codeine since (b) (6), Prozac for anxiety since (b) (6), and Spiriva for asthma since (b) (6).

On (b) (6), the subject started with a dry barky cough associated with a low grade fever (99.0 F). On (b) (6), the subject was seen in clinic. Upon exam, the cough was paroxysmal and the subject was hacking. The subject was started on aggressive aerosols with Levaluterol every 4 hours while awake, Tylenol #3 1 tablet twice a day as needed, Tessalon Perles 300 mg TID, and Mucinex DM 1 tab BID. The subject's symptoms progressively worsened and on (b) (6) she was admitted to hospital due to failure to responds the at home treatment with the diagnosis of status asthmaticus. Status asthmaticus was successfully treated and the subject was discharged from the hospital on (b) (6) with status asthmaticus reported as resolved. Resolution date for asthma deterioration related symptoms was reported as (b) (6).

The Primary Investigator assessed the severity of the serious event, Asthma Exacerbation, as severe and causality as not related to the study drug. The event outcome was reported as resolved on (b) (6).

Reviewer Comment:

The diagnosis of severe persistent asthma preceded the initial administration of Cutaquig by more than two years. However, it is interesting to note that severe persistent asthma was diagnosed 4.5 months after the diagnosis of common variable immunodeficiency (CVI) was made. Presumably, the subject was treated with IGIV and/or IGSC since the time of diagnosis and before severe asthma was diagnosed, raising the possibility that IGIV/IGSC treatment with products other than Cutaquig may have played a causal role in aggravating the subject's pulmonary symptoms. That said, Advair was prescribed for asthma starting 2 weeks prior to the diagnosis of CVI, and other medications for asthma had been prescribed as early as 10 years prior to the diagnosis of CVI. The most recent dose of Cutaquig was prior to and on the day of hospitalization for the first episode of status asthmaticus. However, the subject's worsening of asthma appears to have begun 11 days earlier. The subject had been receiving Cutaquig

for approximately four months prior to the onset of the event, making a causal relationship between Cutaquig and the SAE unlikely.

The onset of the illness leading to the 2nd episode of status asthmaticus began 7 days prior to the last administration of Cutaquig prior to hospitalization. If the subject were adhering to the study schedule, she would have received a Cutaquig infusion on the day her cough began. Hospitalization occurred 2 days following Cutaquig administration. Causality appears to be unlikely related to Cutaquig for the reasons stated above, but the possibility that Cutaquig may have been a contributing/aggravating factor cannot be entirely excluded.

2. Please submit a detailed narrative for the AE in study SCGAM-03 consisting of cellulitis of abdominal wall, considered related by investigator/sponsor.

Applicant's Response:

On Friday (b) (6) *, the subject* (b) (6) *performed a routine subcutaneous infusion of* (b) (4) *on her abdomen at home. The following day, she noticed two of the four infusion sites were erythematous, warm, and swollen to approximately 4 cm in diameter. She denied having a fever. On* (b) (6) *, the subject contacted on-call physician assistant at the investigational site and was recommended to start a course of cephalexin 500 mg BID for 10 days. On* (b) (6) *,* (b) (6) *the subject presented to investigational site for a follow-up with the physician regarding the erythema and swelling. At that time, one of the infusion site reactions had resolved, while the other continued to progress. Based on the presentation, the subject was sent to Emergency Department for concern of cellulitis and to rule-out potential abscess.*

Once in the ER, the subject was diagnosed with cellulitis of the abdominal wall. An ultrasound of the site was performed which revealed no fluid collection or abscess. She was given a dose of IV clindamycin and was sent home with oral clindamycin 300 mg QID for 7 days, with instructions to follow up in clinic. The subject was reevaluated by Investigator on (b) (6) *, and it was noted that the cellulitis was healing well. Her infusion that day was observed for appropriate technique and she was instructed to switch infusion site to her thighs, instead of abdomen. The subject was seen again on* (b) (6) *by the physician for follow-up, who noted the reaction was continuing to resolve.*

Reviewer Comment:

While the possibility of bacterial contamination of the product is a possibility, given that two of four infusion sites showed signs of inflammation, no similar cases have been reported in the trial and it is plausible that skin flora or skin contaminants were carried to the subcutaneous space during needle placement. Observance of good technique in using antiseptic on the infusion site prior to needle placement is not expected to sterilize the skin and bacteria can reside in hair follicles that resist antiseptic application, which could lead to cellulitis as the needle may displace superficial bacteria to deeper structures.

3. Please submit the final study report for completed non-IND Russian study SCGAM-04, which you indicated in the safety update is available upon request.

Applicant's Response:

Please refer to the clinical study report of study SCGAM-04 in Module 5, section 5.3.5.2.

Please note that clinical study SCGAM-04 was conducted in patients in Russia to provide efficacy and safety data to support marketing authorization in the Russian Federation. Therefore the study database was not set up to match the data standards listed in the FDA Data Standards Catalog (Appendix 16.4 Individual Patient Data Listings not available in CDISC format).

All data collected is however included in pdf format in the Patient Data Listings (Appendix 16.2 to the study report).

Reviewer Comment:

Noted. Results of the non-IND Russian study SCGAM-04 are summarized in the body of this memo under Trial #2.

4. Please submit the final protocol and a summary of all protocol amendments for study SCGAM-04. These appear to be missing from the IND amendment that was to contain them in response to an earlier information request.

Applicant's Response:

Please refer to section 16.1.1 of the clinical study report of study SCGAM-04 provided in Module 5, section 5.3.5.2.

Reviewer Comment:

Noted. The design of the non-IND Russian study SCGAM-04 are summarized in the body of this memo under Trial #2.