

Application Type	BLA Supplement
STN	125668/158
CBER Received Date	December 23, 2020
PDUFA Goal Date	October 23, 2021
Division / Office	OTAT
Committee Chair	Vijay Kumar, M.D.
Clinical Reviewer(s)	Vijay Kumar, M.D.
Project Manager	Eden Chane, M.S.
Reviewer Name(s)	Tingting Zhou, Ph.D.
Review Completion Date / Stamped Date	
Supervisory Concurrence	Renee C. Rees, Ph.D., Team Leader, Therapeutics Evaluation Branch
	Boguang Zhen, Ph.D., Branch Chief, Therapeutics Evaluation Branch
Applicant	OCTAPHARMA Pharmazeutika Produktionsges.m.b.H.
Established Name	Immune Globulin Subcutaneous (Human)-hipp, 16.5%
(Proposed) Trade Name	Cutaquig
Dosage Form(s) and Route(s) of Administration	A solution containing 16.5% immunoglobulin (IgG) (165 mg/mL) for subcutaneous (SC) infusion only
Dosing Regimen	Individualize the dose based on the patient's pharmacokinetic and clinical response. Dose for patients switching from intravenous immunoglobulin (IVIG): initial weekly dose = previous IVIG dose (in grams) x 1.30 / number of weeks between IVIG doses Dose for patients switching from subcutaneous immunoglobulin (SCIG): maintain the same weekly dosing as the previous SCIG
Indication(s) and Intended Population(s)	Addition of pediatric population to: Treatment of primary humoral immunodeficiency (PI) in adults

Table of Contents

Glossary 3

1. Executive Summary 4

2. Clinical and Regulatory Background 4

2.1 Disease or Health-Related Condition(s) Studied..... 4

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s) 5

2.4 Previous Human Experience with the Product (Including Foreign Experience) 5

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission 5

3. Submission Quality and Good Clinical Practices..... 6

3.1 Submission Quality and Completeness 6

3.2 Compliance With Good Clinical Practices And Data Integrity 6

5. Sources of Clinical Data and Other Information Considered in the Review..... 6

5.1 Review Strategy 6

5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review 6

5.3 Table of Studies/Clinical Trials 6

6. Discussion of Individual Studies/Clinical Trials..... 7

6.1 Trial SCGAM-01 7

6.1.1 Objectives (Primary, Secondary, etc) 7

6.1.2 Design Overview 8

6.1.3 Population 8

6.1.4 Study Treatments or Agents Mandated by the Protocol..... 9

6.1.6 Sites and Centers..... 9

6.1.8 Endpoints and Criteria for Study Success 9

6.1.9 Statistical Considerations & Statistical Analysis Plan 9

6.1.10 Study Population and Disposition 12

6.1.11 Efficacy Analyses 15

6.1.12 Safety Analyses 21

6.2 Trial SCGAM-03 21

6.2.1 Objectives (Primary, Secondary, etc) 21

6.2.2 Design Overview 21

6.2.3 Population 22

6.2.4 Study Treatments or Agents Mandated by the Protocol..... 22

6.2.6 Sites and Centers..... 22

6.2.8 Endpoints and Criteria for Study Success 23

6.2.9 Statistical Considerations & Statistical Analysis Plan 23

6.2.10 Study Population and Disposition 24

6.2.11 Efficacy Analyses 26

6.2.12 Safety Analyses 31

10. Conclusions..... 31

10.1 Statistical Issues and Collective Evidence 31

10.2 Conclusions and Recommendations 32

GLOSSARY

AE	Adverse event
AESI	Adverse event of special interest
AUC	Area under the curve
CI	Confidence interval
DCF	Dosing conversion factor
ESID	European Society for Immunodeficiencies
FDA	Food and Drug Administration
FAS	Full analysis set
IgA	immunoglobulin A
IgG	Immunoglobulin
IV	Intravenous
IVIG	Intravenous immunoglobulin
Kg	Kilogram
M	Meter
Max	Maximum
Mg	Milligram
Min	Minute/Minimum
N	Number of observations
NA	Not Applicable
PAGID	Pan-American Group for Immunodeficiency
PI	Primary humoral immunodeficiency
PMR	Post marketing requirement
PP	Per-protocol
QoL	Quality of Life
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
sBLA	supplemental Biologics License Application
SBI	Serious bacterial infection
SC	Subcutaneous
SCIG	Subcutaneous immunoglobulin
SD	Standard deviation
TEAE	Treatment-emergent adverse event
US	United States

1. Executive Summary

(b) (4) 16.5%, under the trade name CUTAQUIG, is currently indicated for the treatment of primary humoral immunodeficiency (PI) in adults. (b) (4) 16.5% is human normal immunoglobulin for weekly subcutaneous (SC) administration. Octapharma submitted the complete results from a pivotal study SCGAM-01 and a long-term safety follow up study SCGAM-03 in this supplemental Biologics License Application (sBLA) to expand the current indication to treatment of PI in pediatric subjects.

SCGAM-01 was a prospective, open-label, non-controlled, single-arm, multicenter phase III study with a 12-week wash-in/wash-out period followed by a 12-month efficacy period. A total of 75 subjects, including 37 adults and 38 pediatric subjects aged 2 or older, were enrolled in the study. No serious bacterial infections (SBIs) were reported during the study with an upper 2-sided 98% confidence interval (CI) of 0.065. By age group, the upper limit of the CI was 0.379 for young children aged ≥ 2 and < 6 years, 0.325 for older children aged ≥ 6 and < 12 years, 0.532 for adolescents aged ≥ 12 and < 17 years, and 0.130 for adults aged ≥ 17 and ≤ 75 years. Thus, the study demonstrated a SBI rate per person-year of less 1.0 for all the age groups so met its success criteria.

SCGAM-03 was a prospective, open-label, non-controlled, single-arm, multicenter Phase III safety follow-up study to SCGAM-01 that allowed de novo subjects in Canada. A total of 27 subjects, including 17 adults and 10 pediatric subjects aged 2 or older, were enrolled in the study. One SBI was observed in one adult. The rate of SBI per person-year was 0.018 overall with an upper two-sided 98% CI limit of 0.189. The rate of SBIs per person-year was 0.030 for the adult group and 0.000 for all other age groups. The upper 2-sided 98% CI limits by age groups were all < 1.0 . Thus, similar efficacy results were shown in the follow-up study.

No death occurred in either study. One subject from SCGAM-01 experienced acute deep vein thrombosis of the popliteal vein that was moderate in intensity. In SCGAM-03, the same subject experienced severe pulmonary embolism and venous thrombosis limb and consequently was discontinued treatment.

I verified the efficacy results from both studies that appear in the proposed updated label. Based on the available data, the statistical evidence supports approval of the applicant's labelling update to expand the indication to treatment of PI in pediatric subjects aged ≥ 2 years or older.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

The primary immunodeficiency syndromes are a heterogeneous group of disorders with an intrinsic defect of the tissues, cells or proteins of the immune system resulting in immune deficiency. Many of these disorders are characterized by hypogammaglobulinemia with or without defective specific antibody production.

Subjects with PI have an increased risk of recurrent bacterial or viral infections that typically attack the respiratory tract but can also affect the gastrointestinal tract.

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

Immunoglobulin (IgG) replacement therapy is used to treat subjects with PI. There are several IgG preparations that have been developed for intravenous (IV) and subcutaneous (SC) administration.

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

(b) (4) 16.5% was first approved in Canada on February 15, 2018. By November 2020, (b) (4) 16.5% has been licensed in a total of 28 countries.

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

Regulatory history with statistical implications is summarized below:

1. On December 12, 2018, (b) (4) 16.5% was approved under the trade name CUTAQUIG for treatment of PI in adults. The pediatric study would be completed as a post marketing requirement (PMR).
2. On January 16, 2019, the study protocol SCGAM-01 Version 09 submitted under amendment 60 of IND 15617, was modified to include changes in the age categories and the number of subjects to be enrolled in each age category due to enrollment difficulty. The adjustments were as follows.
 - a. ≥ 2 years and < 6 years (was < 5 years) of age: at least 4 subjects (was 10 subjects)
 - b. ≥ 6 years (was ≥ 5 years) and < 12 years of age: at least 10 subjects (was 14 subjects)
 - c. ≥ 12 years and < 17 years (was < 16 years) of age: at least 6 subjects (was 20 subjects)
 - d. ≥ 17 years (was ≥ 16 years) and ≤ 75 years of age: at least 25 to a maximum of 39 subjects
3. In March and April of 2020 when the COVID-19 pandemic started, two subjects were still participating in the study, so there were slight changes to the conduct of the study, but they were not recorded as protocol deviations:
 - a. Subject (b) (6)'s End of Study visit was completed as planned with all procedures performed but 4 days early
 - b. Subject (b) (6) had 3 subsequent visits (Week 56, 60 and End of Study) left and were provided with sufficient vials for weekly self-administration at home to avoid visits to the site. Week 56 and 60 blood samples were not done but End of Study laboratory tests were done at the local laboratory.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

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

3.2 Compliance with Good Clinical Practices and Data Integrity

The studies were conducted with good clinical practices. There were no issues with data integrity.

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

5.1 Review Strategy

This review memo reviews the complete study report of the pivotal study SCGAM-01 and the long-term safety follow-up study SCGAM-03.

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

1. Supplement BLA 125668/158.0
 - a. Module 1.14.1 Draft Labeling
 - b. Module 2.5 Clinical Overview
 - c. Module 2.7 Clinical Summary
 - d. Module 5/3/5/2 Study Reports of Uncontrolled Clinical Studies
2. Amendment BLA 125668/158.1
 - a. Module 1.2 Response to FDA information request-May 21, 2021
3. Amendment BLA 125668/158.3
 - a. Module 1.2 Response to FDA information request-June 25, 2021

5.3 Table of Studies/Clinical Trials

Two studies, SCGAM-01 and SCGAM-03, were submitted in support of this submission. See Table 1 for the study overview.

Table 1: Overview of SCGAM-01 and SCGAM-03.

Study ID	Number of Study Centers Locations & Study Period	Design	Number of Subjects by Arm	Study Drug, Route and Dose
SCGAM-01	20 Study Sites in Canada, the Czech Republic, Hungary, Poland, Russia, Slovakia, and the USA. Jun-2014 to Jun-2020	Prospective, open-label, non-controlled, single-arm, multicenter Phase 3 Study	75 PID patients were enrolled in each of the following age groups: N=12: ≥2 and <6 years N=14: ≥6 and <12 years N=12: ≥12 and <17 years N=37: ≥17 and ≤75 years	(b) (4) 16.5% Weekly subcutaneous infusions during a 12-week wash-in/wash-out phase and 12 months efficacy phase. SC doses were given at 1.5 times the previous IVIG dose adjusted for weekly dosing.
SCGAM-03	7 Study Sites 1 site in Canada and 6 sites in the USA. May-2016 – Sep-2019	Prospective, open-label, non-controlled, single-arm, multicenter, safety follow-up Phase 3 Study	27 patients were enrolled in each of the following age groups: N=2: ≥2 and <6 years N=4: ≥6 and <12 years N=4: ≥12 and <17 years N=17: ≥17 and ≤75 years	(b) (4) 16.5% Weekly subcutaneous infusions or every second week (±2 days) at the doubled weekly dose until 1) (b) (4) became commercially available in the USA; 2) Sponsor decided to terminate the trial, or 3) December 2020

Source: Adapted sBLA 125668/158; Summary of Clinical Efficacy, Table 2.7.3.6, p.12

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study SCGAM-01

The protocol for Study SCGAM-01 was titled "Clinical Phase III 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, Secondary, etc)

Primary objectives:

- Assess the efficacy of (b) (4) in preventing SBIs compared with historical control data
- Evaluate the pharmacokinetic (PK) characteristics of (b) (4) and compare the area under the curve (AUC) with that of IVIG

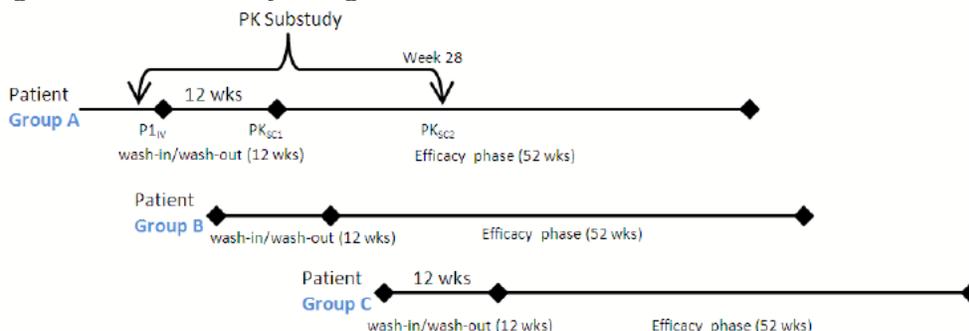
Secondary objectives:

- Evaluate the tolerability and safety of (b) (4)
- Determine the PK profile of (b) (4)
- Assess the dosing conversion factor (DCF) when switching subjects from IVIG treatment
- Develop guidance and recommendations to support further adjustments of (b) (4) dosing based on the total IgG trough level
- Assess the effect of (b) (4) on Quality of Life (QoL) measures

6.1.2 Design Overview

SCGAM-01 was a prospective, open-label, non-controlled, single-arm, multicenter phase III study with a 12-week wash-in/wash-out period followed by a 12-month efficacy period. Figure 1 presents the overall study design.

Figure 1: Overall study design of SCGAM-01



Source: Original sBLA 125668/158; Clinical study report of SCGAM-01, Figure 2, p.28

Group A: subjects who participated in the PK study

Group B: subjects who started the study while PK subjects were still in the wash-in/wash-out phase

Group C: subjects who started the study after the last subject in the PK study had completed the wash-in/wash-out phase

Reviewer comment: Due to the shift in completing the interim PK analysis relative to overall recruitment, no subjects were enrolled in Group C.

6.1.3 Population

Selected inclusion criteria:

1. Age of ≥ 2 years and ≤ 75 years
2. Confirm diagnosis of PI as defined by European Society for Immunodeficiencies (ESID) and Pan-American Group for Immunodeficiency (PAGID) and requiring IgG replacement therapy due to hypogammaglobulinemia or agammaglobulinemia
3. Subjects with at least six infusions on regular treatment with any IVIG, a minimum of the last 2 months on the same product and a constant IVIG dose between 200-800 mg/kg body weight prior to enrollment
4. Availability of the IgG trough levels of two previous IVIG infusions and at least 5.0 g/L in the trough levels of these two previous infusions prior to enrollment
5. Willingness to comply with the protocol and given written informed consent

Selected exclusion criteria:

1. Acute infection requiring intravenous antibiotic treatment within 2 weeks prior to and during the screening period
2. Known history of adverse reactions to immunoglobulin A (IgA) in other products

3. Exposure to blood or any blood product or plasma derivatives, other than IVIG treatment of PI, within the past 3 months prior to first infusion of (b) (4)
4. Requirement of any routine premedication for IgG administration
5. Treatment with immunosuppressive or immunomodulatory drugs
6. Subjects with body mass index > 40 kilogram per square meter (kg/m²)

6.1.4 Study Treatments or Agents Mandated by the Protocol

Investigational Product: (b) (4) 16.5%

Route of administration and schedule: Subcutaneously every week (± 2 days)

Dose:

- For subjects participating in the PK study and those enrolled during the wash-in/wash-out phase, SC dose was calculated as (previous IVIG dose (in grams) × 1.5) / number of weeks between IVIG doses
- The “corrected” DCF was calculated after the analysis of the PK data and the dose could be revised based on the corrected DCF for all subjects
- During the efficacy phase of the study, the dose was individualized based on the difference between each subject’s measured serum total IgG trough levels and the subject’s target serum total IgG trough level
- If the body weight changed by >5%, dose was adjusted to keep the dose constant on a milligram per kilogram (mg/kg) body weight basis.

6.1.6 Sites and Centers

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

6.1.8 Endpoints and Criteria for Study Success

Primary efficacy endpoint:

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

Selected secondary efficacy endpoints:

- Rate of all infections of any kind of seriousness
- Use of antibiotics
- Hospitalizations due to infection
- Days missed from work/school/kindergarten/day care due to infections

Criteria for study success:

The upper two-sided 98% CI for the SBI rate per person-year was less than 1.0 during the primary treatment period with (b) (4), which was defined as the time between the 12th infusion of (b) (4) and the end of the (b) (4) treatment period.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Statistical Hypotheses

Null: SBI rate is greater than or equal to 1.0 per person-year

Alternative: SBI rate is less than 1.0 per person-year

Sample Size Estimation

Assuming the observed SBI frequency is less than 0.5 per year, 42 evaluable patient-years would be enough to test the null hypothesis at 1% significance level with 90% power. Assuming a drop-out rate of 15%, at least 50 subjects were planned, according to the following age categories:

- aged ≥ 2 to <6 years (young children): at least 4 subjects
- aged ≥ 6 to <12 years (older children): at least 10 subjects
- aged ≥ 12 to <17 years (adolescents): at least 6 subjects
- aged ≥ 17 to ≤ 75 years (adults): at least 25 to a maximum of 39 subjects

The PK study aimed to achieved at least 20 evaluable subjects who completed the PK profiles. Assuming an intrasubject variability of at most 0.25, expressed as coefficient of variation and a correlation between AUC_{Tsc} and AUC_{Tiv} of at least 0.4, 20 subjects would have a power of 87.5% for the equivalence test for the paired geometric mean ratio.

Analysis Populations

- Safety analysis set: all subjects who received at least part of one infusion of (b) (4)
- Full analysis set (FAS): all subjects of the safety analysis set who satisfied all major eligibility criteria and for whom any post-baseline data is available
- Per-protocol (PP): all subjects of the FAS except those who had major protocol violations such as the following which could impact the analysis of the primary efficacy endpoint
 - Violations of the study entry criteria
 - Administration of any other blood or plasma-derived or of another other immunoglobulin preparations
 - Use of any prohibited concomitant medication
 - Failure to attend two scheduled consecutive visits OR three or more scheduled visits for reasons other than clinical reasons

Statistical Methods

Primary efficacy endpoint:

Rate of SBI

Point estimate of the SBI rate and the two-sided 98% CI were presented. Calculation of the CI accounted for intra-subject correlation in infections by using a compound Poisson process. Let C_i denote the number of infections for the i^{th} subject and C the total number of infections. The adjusted CI was calculated as follows:

$$e^{\ln(r)-2.33 \sqrt{\sum c_i^2 / c^2}} ; e^{\ln(r)+2.33 \sqrt{\sum c_i^2 / c^2}}$$

Two sensitivity analyses were added in the final analysis: 1) the originally planned two-sided 98% CI was calculated assuming a scenario that one bacterial infection was

observed in the study; and 2) the CI was calculated assuming a standard Poisson distribution instead of the compound Poisson process model.

Secondary efficacy endpoints:

All infections of any kind of seriousness

The rate of other infections was calculated per person-year as follows and presented with the upper limit of a two-sided 90% CI assuming a compound Poisson process model. The duration of infection was summarized using descriptive statistics by type of infection and by severity. The individual characteristics of each infection such as time to resolution was listed.

Rate of other infections during primary treatment period = (total number of other infections occurring in the primary treatment periods) / (sum of primary treatment periods)

Use of antibiotics (number of days and annual rate)

All such medications were reported. The number of subjects treated with antibiotics, the number of treatment episodes, and the number of treatment days were tabulated. The upper limit of a two-sided 90% CI was calculated for the number of treatment days per person-year assuming the compound Poisson process model.

Hospitalizations due to infection

All hospitalizations due to infection were listed with duration and reason. The number of subjects hospitalized, the number of hospitalizations, and the number of days in hospital were tabulated and summarized descriptively. The upper limit of a two-sided 90% CI was calculated for the number of days in hospital per person-year assuming a compound Poisson process model.

Days missed from work/school/kindergarten/day care due to infections

All absences from work or school were listed with duration and reason. The individual absence rates (calculated as shown below) were summarized descriptively. The upper limit of a two-sided 90% CI was calculated for number of days absent from work/school per person-year assuming a compound Poisson process model.

Rate of absence from work or school = $(1/200) \times (\text{number of days absent from work or school}) / (\text{person-years on (b) (4) treatment})$, assuming 200 working/school days per year.

Reviewer comment: In this memo, I present the two-sided 95% CI results for the endpoints: all other infections, antibiotic use, hospitalization due to infection and days missed from work/school due to infection.

Subgroup analyses

The analyses for efficacy endpoints were analyzed overall and by age groups and sex.

Handling of Missing Data

In general, no missing data were imputed. Person-year computations were based on observed values only.

For all calculations related to dosing and PK parameters, missing weight measurements were imputed with the last available body weight.

For an adverse event (AE) with partially or completely missing start date or time, the AE was assumed to be treatment-emergent if it could not be shown that the AE did not occur or worsen during the treatment emergent period.

A medication was assumed to be concomitant if it could not be shown that the medication was not administered during the (b) (4) treatment period.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Table 2 shows the number of subjects per age group in each enrollment group and in each analysis set. All 75 enrolled subjects received at least one administration of the study medication so were included in both the safety analysis set and the FAS. The PP set included 71 subjects after excluding 4 subjects who terminated early before the start of the primary treatment period.

Table 2: Number of subjects in each enrollment group and in each analysis set.

	Children ≥ 2 and <6 years N=12 N (%)	Children ≥ 6 and <12 years N=14 N (%)	Adolescents ≥ 12 and <17 years N=12 N (%)	Adults ≥ 17 and ≤75 years N=37 N (%)	Total N=75 N (%)
Treated in enrollment Group A	5 (41.7%)	8 (57.1%)	7 (58.3%)	19 (51.4%)	39 (52.0%)
Treated in enrollment Group B	7 (58.3%)	6 (42.9%)	5 (41.7%)	18 (48.6%)	36 (48.0%)
Treated in enrollment Group C	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Safety Analysis Set	12 (100.0%)	14 (100.0%)	12 (100.0%)	37 (100.0%)	75 (100.0%)
Full Analysis Set (FAS)	12 (100.0%)	14 (100.0%)	12 (100.0%)	37 (100.0%)	75 (100.0%)
Per-Protocol Set (PP)	12 (100.0%)	14 (100.0%)	9 (75.0%)	36 (97.3%)	71 (94.7%)

Source: Adapted sBLA 125668/158; Clinical Study Report of SCGAM-01, Table 6, p.63 and Table 3, p.60.

N=number of subjects; %=percentage

6.1.10.1.1 Demographics

Table 3 provides a summary of demographic data. Overall, 36 females and 39 males participated in the study, with a higher proportion of males in the pediatric groups and a higher proportion of females in the adult group. The youngest subject was 2 years old and the oldest was 73 years old. The mean age was 4.17 years old in the young children group, 7.93 years in the older children group, 14.08 years in the adolescent group, and 47.46 years in the adult group. All subjects were white, except one multiracial adult subject.

Table 3: Demographic data (FAS)

		Children ≥ 2 and <6 years N=12	Children ≥ 6 and <12 years N=14	Adolescents ≥ 12 and <17 years N=12	Adults ≥ 17 and ≤75 years N=37	Total N=75
Age (years)	Mean (SD)	4.17 (1.115)	7.93 (1.439)	14.08 (1.379)	47.46 (13.617)	27.81 (21.911)
	Median	4.50	8.00	14.00	46.00	16.00
	Min, Max	2.0, 5.0	6.0, 10.0	12.0, 16.0	20.0, 73.0	2.0, 73.0
Sex	Male [N (%)]	11 (91.7%)	9 (64.3%)	9 (75.0%)	10 (27.0%)	39 (52.0%)
	Female [N (%)]	1 (8.3%)	5 (35.7%)	3 (25.0%)	27 (73.0%)	36 (48.0%)
Race	White [N (%)]	12 (100.0%)	14 (100.0%)	12 (100.0%)	36 (97.3%)	74 (98.7%)
	Multiple [N (%)]	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.7%)	1 (1.3%)
BMI [kg/m ²]	Mean (SD)	16.28 (2.770)	17.91 (4.395)	20.78 (5.271)	24.64 (4.091)	21.43 (5.356)
	Median	15.45	17.10	19.80	23.90	21.20
	Min, Max	13.2, 21.5	12.0, 27.8	13.7, 32.0	18.60, 40.0	12.0, 40.0

Source: Adapted sBLA 125668/158; Clinical Study Report of SCGAM-01, Table 7, p.64

BMI=body mass index; Min=minimum; Max=maximum; N=number of subjects; SD=standard deviation; %=percentage; kg=kilogram; m=meter

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Table 4 provides the baseline subject characteristics for all the enrolled subjects. Of the 75 subjects, 56 subjects (74.7%) had common variable immunodeficiency (CVID), 6 subjects (8.0%) had X-linked agammaglobulinemia, and 13 subjects (17.3%) had other types of immunodeficiency. In total, 50 subjects (66.7%) had a normal chest x-ray, 20 subjects (26.7%) had an abnormal chest x-ray that was not clinically significant, 4 subjects (5.3%) had an abnormal chest x-ray that was clinically significant, and 1 subject (1.3%) had missing chest x-ray result. Sixty-five subjects (87.6%) took other prior medications. Three subjects (4.0%) had prior non-drug therapy.

Table 4: Baseline characteristics and history of primary immunodeficiency at screening (FAS)

Number (%) of patients with...	Children ≥2 Years <6 Years N=12 N (%)	Children ≥6 Years <12 Years N=14 N (%)	Adolescents ≥12 Years <17 Years N=12 N (%)	Adults ≥17 Years ≤75 Years N=37 N (%)	Total All Patients N=75 N (%)
History of PI					
CVID	4 (33.3%)	6 (42.9%)	10 (83.3%)	36 (97.3%)	56 (74.7%)
XLA	4 (33.3%)	1 (7.1%)	1 (8.3%)	0 (0.0%)	6 (8.0%)
Other	4 (33.3%)	7 (50.0%)	1 (8.3%)	1 (2.7%)	13 (17.3%)
Chest x-ray					
Normal	8 (66.7%)	8 (57.1%)	11 (91.7%)	23 (62.2%)	50 (66.7%)
Abnormal CS	2 (16.7%)	1 (7.1%)	0 (0.0%)	1 (2.7%)	4 (5.3%)
Abnormal NCS	1 (8.3%)	5 (35.7%)	1 (8.3%)	13 (35.1%)	20 (26.7%)
Missing	1 (8.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)
Any prior medication	9 (75.0%)	13 (92.9%)	10 (83.3%)	33 (89.2%)	65 (86.7%)
Any prior non-drug therapy	1 (8.3%)	0 (0.0%)	0 (0.0%)	2 (5.4%)	3 (4.0%)

Source: Original sBLA 125668/158; Clinical Study Report of SCGAM-01, Table 8, p.66
 CS=clinically significant; CVID=common variable immunodeficiency; N=number of subjects; NCS=non-clinically significant; PI=primary immunodeficiency; XLA=X-linked agammaglobulinemia

6.1.10.1.3 Subject Disposition

A total of 75 subjects were enrolled in the study. All subjects received the study medication, but 7 subjects (4 adolescents and 3 adults) withdrew from the study prematurely. Six subjects withdrew from the study themselves and one subject was withdrawn due to non-compliance. Thus, 68 subjects completed the study. The seven subjects withdrawn from the study prematurely had at least one administration of the study medication.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The efficacy results on SBIs during the primary treatment period for the FAS are shown in Table 5. No SBIs were reported at any time during the study. Based on the standard Poisson distribution, the upper limit of the 2-sided 98% CI was 0.065 in the primary treatment period. By age group, the upper limit of the CI was 0.379 for young children, 0.325 for older children, 0.532 for adolescents, and 0.130 for adults. All upper CI bounds were less than 1.0, which meets the study success criteria. The same conclusion was drawn using the total treatment period and/or using the PP analysis set.

In one sensitivity analysis, one SBI was assumed to occur and the upper limit of the 2-sided 98% CI was 0.145 in the primary observation period assuming a compound Poisson process model proposed initially in the protocol. Thus, the sensitivity analysis supported the conclusion from the primary analysis.

Table 5: Efficacy results on SBIs during the primary treatment period (FAS)

Parameters/ Age	Children ≥ 2 to < 6 years (N=12)	Children ≥ 6 to < 12 years (N=14)	Adolescents ≥ 12 to < 17 years (N=12)	Pediatrics ≥ 2 to <17 years (N=38)	Adults ≥ 17 to ≤ 75 years (N=37)	Total (N=75)
Number of person- years exposure	12.16	14.16	8.66	34.99	35.54	70.53
Total number of SBIs	0	0	0	0	0	0
Two-sided 98% CI- upper limit*	0.379	0.325	0.532	0.132	0.130	0.065

Source: Adapted sBLA 125668/158; Clinical Study Report of SCGAM-01, Table 14.2.1.1.1, p.277

N=number of subjects; CI=confidence interval; %=percentage

*Post-hoc alternative method for CIs was based on the standard Poisson distribution. See Ulm (1990) for more details.

*Reviewer comment: Since no SBIs were observed during the study, it was not possible to calculate the CI using the originally planned compound Poisson process model. Using the method described by Ulm “A Simple Method to Calculate the Confidence Interval of a Standardized Mortality Ratio (SMR), American Journal of Epidemiology, Volume 131, Issue 2, February 1990, Pages 373–375”, the upper limit of rate of SBI was calculated as $\chi^2_{2(Y+1), (1-\alpha/2)} / (2 * \text{total exposure duration})$, where Y is the observed number of SBIs and $\chi^2_{2(Y+1), (1-\alpha/2)}$ is the chi-square quantile for upper tail probability on $2(Y+1)$ degrees of freedom.*

6.1.11.2 Analyses of Secondary Endpoints

The Occurrence of Other Infections of any Kind of Seriousness

Table 6 shows the efficacy results on all other infections of any kind during the primary treatment period. As there were no SBIs, all infections during the study were non-serious SBIs. A total of 231 infections were observed in 61 subjects during the primary observation. The rate of other infections per person-year was 3.275 overall and the upper two-sided 95% CI limit was 4.472. The rate of other infections was similar across the age groups, between 2 and 4 infections per person-year, and the upper two-sided 95% CI limit was 8.275 for young children, 5.118 for older children, 6.041 for adolescents, and 5.364 for adults. Similar conclusions were seen in the PP analysis set.

Table 6: Efficacy results on other infections of any kind during the primary treatment period (FAS)

Parameters/ Age	Children ≥ 2 to < 6 years (N=12)	Children ≥ 6 to < 12 years (N=14)	Adolescents ≥ 12 to < 17 years (N=12)	Pediatrics ≥ 2 to <17 years (N=38)	Adults ≥ 17 to ≤ 75 years (N=37)	Total (N=75)
Number of person-years exposure	12.16	14.16	8.66	34.99	35.54	70.53
Total number of other infections	51	35	23	109	122	231
Total number of other infections per person- year	4.193	2.471	2.656	3.115	3.432	3.275
Two-sided 95% CI	(2.124, 8.275)	(1.193, 5.118)	(1.168, 6.041)	(2.024, 4.795)	(2.197, 5.364)	(2.399, 4.472)

Source: Adapted sBLA 125668/158; Clinical Study Report of SCGAM-01, Table 10, p.70 and Table 14.2.2.1.1 p.397.

N=number of subjects; CI=confidence interval; %=percentage

Use of Systematic Antibiotics

Table 7 summarizes the use of systemic antibiotics in the primary observation period. During the primary treatment period, 49 (65.3%) subjects used antibiotics systemically in 132 treatment episodes over 3330 treatment days. The number of treatment episodes per person-year was 1.872 and the number of treatment days per person-year was 47.214, with a two-sided 95% CI upper limit of 78.593. By age groups, the number of treatment days per person-year was 32.390 (95% CI upper limit: 86.253) for young children, 62.275 (95% CI upper limit: 203.723) for older children, 105.429 (95% CI upper limit: 337.189) for adolescents and 32.102 (95% CI upper limit: 60.075) for adults. The adolescents seemed to have the greatest number of days of systematic antibiotic use, although the proportions of subjects with antibiotic use were similar across the age groups.

Table 7: Use of systemic antibiotics in the primary observation period (FAS)

Parameters/ Age	Children ≥ 2 to < 6 years (N=12)	Children ≥ 6 to < 12 years (N=14)	Adolescents ≥ 12 to < 17 years (N=12)	Pediatrics ≥ 2 to <17 years (N=38)	Adults ≥ 17 to ≤ 75 years (N=37)	Total (N=75)
Patients with use of antibiotics [N (%)]	9 (75.0%)	7 (50.0%)	8 (66.7%)	24 (63.2%)	25 (67.6%)	49 (65.3%)
Number of treatment episodes [n]	29	14	13	56	76	132
Number of treatment episodes per person- year	2.384	0.988	1.501	1.601	2.138	1.872
Number of treatment days [n]	394	882	913	2189	1141	3330
Number of treatment days per person-year	32.390	62.275	105.429	62.566	32.102	47.214
Two-sided 95% CI	(12.163, 86.253)	(19.037, 203.723)	(32.965, 337.189)	(30.975, 126.376)	(17.154, 60.075)	(28.363, 78.593)

Source: Adapted sBLA 125668/158; Clinical Study Report of SCGAM-01, Table 13, p.74
N=number of subjects; n=number of episodes/days; CI=confidence interval; %=percentage

Reviewer comment: Although the proportions of subjects with systemic antibiotic use were similar among the age groups, the adolescents had the highest number of treatment days per person-year. This could be due to some pediatric subjects with long periods of systemic antibiotic use. For example, there were 10 subjects with 100 treatment days or more. In the adult group, there were 5 subjects (subject (b) (6), (b) (6), (b) (6), (b) (6), (b) (6)) with treatment days of 118, 183, 127, 101, and 215, respectively. In the adolescent group, there were 2 subjects (subject (b) (6), (b) (6)) with treatment days of 385 and 373, respectively. In the older children group, there were 2 subjects (subject (b) (6), (b) (6)) with treatment days of 370 and 375, respectively. In the young children group, there was one subject (subject (b) (6)) with 169 treatment days.

Hospitalization due to Infection

Table 8 shows the results on hospitalization due to infection during the primary treatment period. There were 4 hospitalizations due to infection during the primary treatment period, 1 in a young child and 3 in adolescents. There were 29 days in hospital and the total number of days in hospital per person-year was 0.411 with a two-sided 95% CI upper limit of 1.292. The total number of days in hospital per person-year was 0.247 (95% CI upper limit: 1.751) for young children, and 3.002 (95% CI upper limit: 10.552) for adolescents. Based on the post-hoc alternative method for the CI

calculation for zero rates, the upper limit of two-sided 95% CI for was 0.261 for older children and 0.104 for adults.

Table 8: Hospitalization due to infection during the primary treatment period (FAS)

Parameters/ Age		Children ≥ 2 to < 6 years (N=12)	Children ≥ 6 to < 12 years (N=14)	Adolescents ≥ 12 to < 17 years (N=12)	Pediatrics ≥ 2 to <17 years (N=38)	Adults ≥ 17 to ≤ 75 years (N=37)	Total (N=75)
Number of person years exposure		12.16	14.16	8.66	34.99	35.54	70.53
Number of patients hospitalized		1 (8.3%)	0 (0.0%)	3 (25.0%)	4 (10.5%)	0 (0.0%)	4 (5.3%)
Number of hospitalizations	0	11 (91.7%)	14 (100.0%)	9 (75.0%)	34 (89.5%)	37 (100.0%)	71 (94.7%)
	1	1 (8.3%)	0 (0.0%)	3 (25.0%)	4 (10.5%)	0 (0.0%)	4 (5.3%)
Total number of days in hospital		3	0	26	29	0	29
Total number of days in hospital per person-year		0.247	0.000	3.002	0.829	0.000	0.411
Two-sided 95% CI		(0.0347, 1.751)	0.261*	(0.854, 10.552)	(0.264, 2.605)	0.104*	(0.131, 1.292)

Source: Adapted sBLA 125668/158; Clinical Study Report of SCGAM-01, Table 14.2.4.1.1, p.939

N=number of subjects; CI=confidence interval; %=percentage; NA=not applicable

*Post-hoc alternative method for CIs for zero rates was based on the standard Poisson distribution. See Ulm (1990) for more details.

Absences from Work or School due to Infection

Table 9 summarizes the results on absence from work or school due to infection during the primary treatment period. During the primary treatment period, 24 (32.0%) subjects had 52 absences from work or school due to infections with a total of 252 days of absence. The total number of days absent from work or school due to infection per person-year was 3.573 with a two-sided 95% CI upper limit of 6.025. Similar rates for absences were seen across the age groups, except for the young children group where the rate was the highest at 8.467 days per person-year (95% CI upper limit: 20.734).

Table 9: Absences from work or school due to infections in the primary treatment period (FAS)

Parameters/ Age	Children ≥ 2 to < 6 years (N=12)	Children ≥ 6 to < 12 years (N=14)	Adolescents ≥ 12 to < 17 years (N=12)	Pediatrics ≥ 2 to <17 years (N=38)	Adults ≥ 17 to ≤ 75 years (N=37)	Total (N=75)
Number of subjects with absences from work/school [N (%)]	7 (58.3%)	5 (35.7%)	4 (33.3%)	16 (42.1%)	8 (21.6%)	24 (32.0%)
Total number of absences work/school	17	10	8	35	17	52
Total number of absences work/school per person-year	1.398	0.706	0.924	1.000	0.478	0.737
Total number of days absent from work/school	103	42	35	180	72	252
Total number of days absent from work/school per person-year	8.467	2.965	4.042	5.145	2.026	3.573
Two-sided 95% CI	(3.458, 20.734)	(1.076, 8.173)	(1.363, 11.989)	(2.816, 9.400)	(0.718, 5.712)	(2.119, 6.025)

Source: Adapted sBLA 125668/158; Clinical Study Report of SCGAM-01, Table 14, p.76
N=number of subjects; n=number of episodes; CI=confidence interval; %=percentage.

6.1.11.3 Subpopulation Analyses

Subgroup analyses of infection rates by age category and the analysis of infection rates for the combined pediatric groups are shown in Table 5.

Subgroup analyses of SBIs by sex showed that the upper limit of the 2-sided 98% CI was 0.129 for female vs 0.132 for male in the primary treatment period. By age group, the upper limit of the CI was 4.534 for young female children, 0.911 for older female children, 1.468 for female adolescents, and 0.174 for female adults. Among the males, by age group the upper limit of the CI was 0.413 for young children, 0.506 for older children, 0.834 for adolescents, and 0.504 for adults. Subgroup analyses of SBIs by sex showed that all the upper limits were <1.0, except for the young female children group (N=1) and the young female adolescent group (N=3). Due to the small samples in the age groups, those subgroup findings might not be reliable.

Out of the 75 subjects, 74 subjects were White, so subgroup analyses by race were not informative.

By region, adult subjects in North America were treated with antibiotics on more occasions (2.955 vs. 1.274 treatment episodes per persons-year) and for a longer time (48.817 vs. 14.418 treatment days per person-year) than adult subjects in Europe.

6.1.11.4 Dropouts and/or Discontinuations

No missing data were imputed for the seven subjects (7/75, 9.3%) who did not complete the study, and person-year computation was based on observed values. Given no SBIs were observed during the study, there was no reason to believe that these seven subjects would have abnormally high SBI rates. The results presented by the applicant appear reasonable.

6.1.12 Safety Analyses

6.1.12.3 Deaths

No deaths occurred during the study.

6.1.12.4 Nonfatal Serious Adverse Events

Excluding infusion sites, twelve serious adverse events (SAEs) were reported in 9 subjects (12.0%): 2 adults (5.4%), 3 adolescents (25.0%), 3 older children (21.4%), and 1 young child (8.3%). Five of the SAEs were infections. The SAEs were not considered to be related to (b) (4) and no action was taken with the study drug because of the SAEs.

6.1.12.5 Adverse Events of Special Interest (AESI)

One acute deep vein thrombosis of the popliteal vein that was moderate in intensity was reported in subject (b) (6). This event was considered not to be related to the study drug.

6.2 Trial SCGAM-03

The protocol for study SCGAM-03 is titled “Clinical Phase III 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.”

6.2.1 Objectives (Primary, Secondary, etc)

Primary objective: to assess the medium to long term safety and tolerability of (b) (4)

Secondary objectives:

- Assess the effect of (b) (4) on QoL measures
- Obtain further data on the efficacy of (b) (4)

6.2.2 Design Overview

SCGAM-03 was a prospective, open-label, non-controlled, single-arm, multicenter Phase III safety follow up study to Study SCGAM-01. Subjects received weekly or bi-weekly doses of the investigational product over a period of up to 4.5 years for subjects previously enrolled in Study SCGAM-01 and 12 months for de novo subjects in Canada.

6.2.3 Population

US study sites for SCGAM-01 subjects:

Selected inclusion criteria:

1. Completion of the main study SCGAM-01 with good tolerance of (b) (4)
2. Consented to the study and willingness to comply with all aspects of the protocol, including blood sampling for the duration of the study

Selected exclusion criteria:

1. No IgG treatment for greater than 5 weeks between the last infusion of (b) (4) in the SCGAM-01 study and the first infusion of (b) (4) in the SCGAM-03 study
2. Exposure to blood or any blood product or derivative, other than IgG used for regular PI treatment, within the 3 months before the first infusion in the SCGAM-03 study

Canadian site for de novo subjects who were receiving SCIG treatment in Canada but had not participated in the SCGAM-01 study:

Selected inclusion criteria:

1. Age of ≥ 18 years and ≤ 75 years
2. Confirmed diagnosis of PI as defined by ESID and PAGID and required immunoglobulin replacement therapy due to hypogammaglobulinemia or agammaglobulinemia
3. Availability of the IgG trough levels of two previous SCIG infusions before enrollment and maintenance of ≥ 5.0 g/L in the trough levels of these two previous infusions
4. Willingness to comply with all aspects of the protocol, including blood sampling for the duration of the study

Selected exclusion criteria:

1. Known history of adverse reactions to IgA in other products
2. Exposure to blood or any blood product or plasma derivatives, other than IVIG treatment of PI, within the past 3 months prior to first infusion of (b) (4)
3. Requirement of any routine premedication for IgG administration
4. Treatment with immunosuppressive or immunomodulatory drugs
5. Subjects with body mass index > 40 kg/m²

6.2.4 Study Treatments or Agents Mandated by the Protocol

Investigational Product: (b) (4) 16.5%

Route of administration and schedule: Subcutaneously every week (± 2 days) or every other week (± 2 days) at double the weekly dose

Dose:

- SCGAM-01 subjects: the same dose as the Week 64 infusion of study SCGAM-01
- De novo subjects in Canada: the same dose as their previous commercial SCIG product dose

6.2.6 Sites and Centers

Seven sites were initiated: 6 sites in the US and 1 site in Canada.

6.2.8 Endpoints and Criteria for Study Success

Primary safety endpoints:

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

Selected secondary efficacy endpoints:

- Occurrence of SBIs
- Annual rate of all infections of any kind or seriousness
- Use of antibiotics
- Hospitalizations due to infection
- Days missed from work/school/kindergarten/day care due to infections

6.2.9 Statistical Considerations & Statistical Analysis Plan

Sample Size Estimation

Approximately 45 subjects were planned

- Approximately 35 subjects who completed Study SCGAM-01
- Approximately 10 de novo subjects who did not participate in SCGAM-01 but could be enrolled at the clinical site in Canada

Analysis Populations

- Safety analysis set (SAF): all subjects who received at least part of one infusion of (b) (4) within this extension study
- Full analysis set (FAS): all subjects of the safety analysis set who satisfied all eligibility criteria and for whom any post screening data in the extension study were available
- Per-protocol (PP): all subjects in the FAS except those with major protocol violations which may have impacted the analyses of the primary endpoints

Statistical Method

Primary safety analysis

Safety analysis included descriptive statistics, tabulations, listing of all TEAEs, safety laboratory results, viral markers, vital signs, and physical examination findings.

Secondary efficacy analysis

The same analyses were used as those in SCGAM-01 study.

Subgroup analyses

The analyses for efficacy endpoints were analyzed overall and by age groups.

Handling of Missing Data

The same missing data handling methods as in SCGAM-01 study were applied. In general, missing data were not imputed.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

Table 10 shows the number of subjects per age group in each analysis set. No subjects were excluded from the PP set. All three analysis populations (SAF, FAS and PP) were the same including all 27 subjects.

Table 10: Number of subjects per analysis set

	Children ≥2 Years <6 Years N=2	Children ≥6 Years <12 Years N=4	Adolescents ≥12 Years <17 Years N=4	Adults ≥17 Years ≤75 Years N=17	All Patients N=27
Safety Analysis Set (SAF)	2 (100.0%)	4 (100.0%)	4 (100.0%)	17 (100.0%)	27 (100.0%)
Full Analysis Set (FAS)	2 (100.0%)	4 (100.0%)	4 (100.0%)	17 (100.0%)	27 (100.0%)
Per Protocol Set (PP)	2 (100.0%)	4 (100.0%)	4 (100.0%)	17 (100.0%)	27 (100.0%)

Source: Original sBLA 125668/158; Clinical Study Report of SCGAM-03, Table 10, p.61
N=number of subjects; %=percentage

6.2.10.1.1 Demographics

Table 11 provides a summary of some baseline characteristics. Overall, 10 males and 17 females participated in the study. There was a higher proportion of females in the adult age group than in the pediatric groups. The youngest subject was 6 years old and the oldest was 73 years old. The mean age was 6.50 years for the young children group, 9.00 years for the older children group, 14.25 years for the adolescent group and 56.12 years for the adult group. Most of the subjects (92.6%) were White.

Table 11: Demographic and baseline characteristics (FAS)

Parameter	Children ≥2 Years <6 Years N=2	Children ≥6 Years <12 Years N=4	Adolescents ≥12 Years <17 Years N=4	Adults ≥17 Years ≤75 Years N=17	All Patients N=27
Age (Years)					
Mean (SD)	6.50 (0.707)	9.00 (1.826)	14.25 (0.957)	56.12 (11.895)	39.26 (24.353)
Median	6.50	9.00	14.50	59.00	51.00
Min, Max	6.0, 7.0	7.0, 11.0	13.0, 15.0	25.0, 73.0	6.0, 73.0
Gender					
Male	2 (100.0%)	2 (50.0%)	2 (50.0%)	4 (23.5%)	10 (37.0%)
Female	0 (0.0%)	2 (50.0%)	2 (50.0%)	13 (76.5%)	17 (63.0%)
Race					
White	2 (100.0%)	4 (100.0%)	4 (100.0%)	15 (88.2%)	25 (92.6%)
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.9%)	1 (3.7%)
Multiple	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.9%)	1 (3.7%)
Ethnicity					
Not Hispanic or Latino	2 (100.0%)	4 (100.0%)	4 (100.0%)	17 (100.0%)	27 (100.0%)

Source: Original sBLA 125668/158; Clinical Study Report of SCGAM-03, Table 11, p.62
 BMI=body mass index; CVID=common variable immunodeficiency; Max=maximum; N=number of subjects; PID=primary immunodeficiency disease; SD=standard deviation; %=percentage

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

All subjects had prior medical history. About 77.8% of the subjects had history of infections. Most of the subjects (88.9%) had CVID.

6.2.10.1.3 Subject Disposition

In total, 27 subjects were screened and enrolled into the extension study. All 27 subjects received the study treatment, and 23 subjects completed the study. Four subjects were withdrawn from the study: two subjects changed treatment, one subject withdrew consent, and one subject (Subject (b) (6)) was discontinued treatment due to diagnosis of pulmonary embolism, previous event of deep vein thrombosis, and a family history of blood clots. Most subjects were adults. Table 12 provides a detailed overview of the number of subjects in the study by age group.

Table 12: Subject disposition by age (FAS)

	Children ≥2 Years <6 Years N=2 N (%)	Children ≥6 Years <12 Years N=4 N (%)	Adolescents ≥12 Years <17 Years N=4 N (%)	Adults ≥17 Years ≤75 Years N=17 N (%)	All Patients N=27 N (%)
Enrolled (excluding Screen Failures)	2 (100.0%)	4 (100.0%)	4 (100.0%)	17 (100.0%)	27 (100.0%)
Completed	2 (100.0%)	4 (100.0%)	2 (50.0%)	15 (88.2%)	23 (85.2%)
Terminated Early	0 (0.0%)	0 (0.0%)	2 (50.0%)	2 (11.8%)	4 (14.8%)

Source: Original sBLA 125668/158; Clinical Study Report of SCGAM-03, Table 8, p.59
N=number of subjects; %=percentage

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

No primary efficacy analyses were performed as the primary objective of this study was to assess the medium-to-long term safety tolerability of (b) (4).

6.2.11.2 Analyses of Secondary Endpoints

The Occurrence of SBIs and all Other Infections of any Kind of Seriousness

Table 13 shows the efficacy results on SBIs and other types of infections. One SBI (bacteremia/sepsis) was reported. The rate of SBI per person-year was 0.018 overall (upper two-sided 98% CI limit: 0.189). The rate of SBIs per person-year was 0.030 for the adult group and 0.000 for all other age groups. All upper 98% CI limits were < 1.0.

A total of 118 other infections were reported among 25 subjects. The rate of all other infections per person-year was 2.182 overall (95% CI upper limit: 3.916). The rates were lower for young and older children than for adolescent and adult subjects.

Reviewer Comment: Because the number of subjects in the pediatric age groups were small, the age group comparisons might not be useful.

Table 13: Efficacy results on SBIs and all other infections (FAS)

Parameters/ Age	Children ≥ 2 to < 6 years (N=2)	Children ≥ 6 to < 12 years (N=4)	Adolescents ≥ 12 to < 17 years (N=4)	Pediatrics ≥ 2 to <17 years (N=10)	Adults ≥ 17 to ≤ 75 years (N=17)	Total (N=27)
Number of person years exposure	5.05	8.02	7.58	20.65	33.44	54.09
Serious Bacterial Infections (SBIs)						
Total number of SBIs	0	0	0	0	1	1
Total number of SBIs per person-year	0	0	0	0	0.030	0.018
Two-sided 98% CI-upper limit	NA	NA	NA	NA	0.306	0.189
Two-sided 98% CI-upper limit*	0.913	0.574	0.607	0.223	0.199	0.123
All other Infections						
Total number of all other infections	8	12	22	42	76	118
Total number of all other infections per person-year	1.585	1.497	2.901	2.034	2.273	2.182
Two-sided 95% CI	(0.280, 8.964)	(0.335, 6.688)	(0.813, 10.355)	(0.863, 4.797)	(1.048, 4.931)	(1.216, 3.916)

Source: Adapted sBLA 125668/158; Clinical Study Report of SCGAM-03, Table 13-14, p.68, 79
 CI=confidence interval; N=number of subjects; SBI=serious bacterial infection; SD=standard deviation;
 %=percentage.

*Post-hoc alternative method for CIs for zero rates was based on the standard Poisson distribution. See
 Ulm (1990) for more details.

Use of Systematic Antibiotics

During the study, 19 subjects (70.4%) used antibiotics systemically for a total of 90 treatment episodes, as shown in Table 14. Overall, the number of treatment episodes per person-year was 1.664 and the number of treatment days per person-year was 46.038 with a two-sided 95% CI upper limit of 99.370. Adolescents reported the highest number of treatment days per person year at 108.784 (95% CI upper limit: 465.368).

Table 14: Use of systemic antibiotics (FAS)

Parameters/ Age	Children ≥ 2 to < 6 years (N=2)	Children ≥ 6 to < 12 years (N=4)	Adolescents ≥ 12 to < 17 years (N=4)	Pediatrics ≥ 2 to <17 years (N=10)	Adults ≥ 17 to ≤ 75 years (N=17)	Total (N=27)
Number of person years exposure	5.05	8.02	7.58	20.65	33.44	54.09
Subjects with use of antibiotics [N (%)]	1 (50.0%)	1 (25.0%)	4 (100.0%)	6 (60.0%)	13 (76.5%)	19 (70.4%)
Number of treatment episodes	3	6	12	21	69	90
Number of treatment episodes per person-year	0.595	0.748	1.582	1.017	2.063	1.664
Number of treatment days	52	581	825	1458	1032	2490
Number of treatment days per person-year	10.305	72.476	108.784	70.619	30.861	46.038
Two-sided 95% CI	(1.452, 73.159)	(10.209, 514.514)	(25.429, 465.368)	(22.668, 220.003)	(12.151, 78.380)	(21.329, 99.370)

Source: Adapted sBLA 125668/158; Clinical Study Report of SCGAM-03, Table 17, p.73
N=number of subjects; n=number of episodes; CI=confidence interval; %=percentage

Reviewer comment: Similar to SCGAM-03, the adolescents had the highest number of treatment days per person-year. This could be due to some pediatric subjects with long periods of systemic antibiotic use. There were 6 subjects with 100 treatment days or more. In the adult group, there were 3 subjects (b) (6), (b) (6), and (b) (6) with treatment days of 100, 231, 407, respectively. In the adolescent group, there were 2 subjects (b) (6) and (b) (6) with treatment days of 560 and 246, respectively. In the older children group, there was one subject (b) (6) with 581 treatment days. In the young children group, there was no such subject. Out of the 6 subjects, 4 subjects (b) (6), (b) (6), (b) (6) and (b) (6) also had long periods of systemic antibiotic use in SCGAM-01.

Hospitalization due to Infection

Table 15 shows the results of hospitalization due to infection. There were three hospitalizations due to infection reported during the study. Two adult subjects were hospitalized for infection for a total of 10 days. No pediatric subjects were hospitalized due to infection. Overall, the total number of days in hospital per person-year due to infection was 0.185 days (two-sided 95% CI upper limit: 0.823).

Table 15: Hospitalization due to infection (FAS)

Parameters/ Age		Children ≥ 2 to < 6 years (N=2)	Children ≥ 6 to < 12 years (N=4)	Adolescents ≥ 12 to < 17 years (N=4)	Pediatrics ≥ 2 to <17 years (N=10)	Adults ≥ 17 to ≤ 75 years (N=17)	Total (N=27)
Number of person years exposure		5.05	8.02	7.58	20.65	33.44	54.09
Number of patients hospitalized		0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (11.8%)	2 (7.4%)
Total number of hospitalizations	0	2 (100.0%)	4 (100.0%)	4 (100.0%)	10 (100.0%)	15 (88.2%)	25 (92.6%)
	1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.9%)	1(3.7%)
	2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.9%)	1(3.7%)
Total number of days in hospital		0	0	0	0	10	10
Total number of days in hospital per person-year		0.000	0.000	0.001	0	0.299	0.185
Two-sided 95% CI		0.730*	0.460*	0.487*	0.179*	(0.0672, 1.330)	(0.0416, 0.823)

Source: Adapted sBLA 125668/158; Clinical Study Report of SCGAM-03, Table 14.2.4.1, p.394-395

N=number of subjects; CI=confidence interval; %=percentage; NA=not applicable

*Post-hoc alternative method for CIs for zero rates was based on the standard Poisson distribution. See Ulm (1990) for more details.

Absences from Work or School due to Infection

Overall, 10 subjects had 33 absences from work or school due to infection, with a total of 130 days of absence. The total number of days absent from work or school due to infection per person-year was 2.404 (two-sided 95% CI upper limit of 5.543). The total days of absence from work/school were highest among young children (4.756; two-sided 95% CI upper limit of 25.157) and the lowest among adults (1.645; two-sided 95% CI upper limit of 6.512).

Table 16: Absences from work or school due to infections (FAS)

Parameters/ Age	Children ≥ 2 to < 6 years (N=2)	Children ≥ 6 to < 12 years (N=4)	Adolescents ≥ 12 to < 17 years (N=4)	Pediatrics ≥ 2 to <17 years (N=10)	Adults ≥ 17 to ≤ 75 years (N=17)	Total (N=27)
Number of person-years exposure	5.05	8.02	7.58	20.65	33.44	54.09
Subjects with absences from work/school [N (%)]	2 (100.0%)	2 (50.0%)	2 (50.0%)	6 (60.0%)	4 (23.5%)	10 (37.0%)
Total number of absences from work/school	6	8	10	24	9	33
Total number of absences from work/school per person-year	1.189	0.998	1.319	1.162	0.269	0.610
Total number of days absent from work/school	24	27	24	75	55	130
Total number of days absent from work/school per person-year	4.756	3.368	3.165	3.633	1.645	2.404
Two-sided 95% CI	(0.899, 25.157)	(0.509, 22.267)	(0.521, 19.222)	(1.285, 10.268)	(0.415, 6.512)	(1.042, 5.543)

Source: Adapted sBLA 125668/158; Clinical Study Report of SCGAM-03, Table 19, p.75
 N=number of subjects; CI=confidence interval; %=percentage

6.2.11.3 Subpopulation Analyses

Subgroup analyses of infection rates by age category and the analysis of infection rates for the combined pediatric groups are shown in Table 13. Because of the low numbers of pediatric subjects (6 male and 4 females total), and a low number of male adult (N=4), comparisons by sex might not be informative. In addition, since all pediatric subjects were White and only 2 adult subjects were non-White, subgroup analyses by race would not be meaningful.

6.2.11.4 Dropouts and/or Discontinuations

No missing data were imputed, and person-year computations were based on observed values only. Given only one SBI was observed among the 27 subjects and none of the 4 (4/27, 14.8%) subjects who did not complete the study experienced SBIs before withdrawing, there was no reason to believe these four subjects would have abnormally high SBI rates. The results presented by the applicant appear reasonable.

6.2.12 Safety Analyses

6.2.12.3 Deaths

No death occurred during the study

6.2.12.4 Nonfatal Serious Adverse Events

A total of 16 SAEs were reported among 7 subjects: 4 adult subjects, 2 adolescents and 1 older child. Three of the SAEs were infections. None of these events were considered related to (b) (4). One adolescent (Subject (b) (6)) experienced pulmonary embolism and was discontinued treatment per Sponsor decision.

6.2.12.5 Adverse Events of Special Interest (AESI)

One adolescent (Subject (b) (6)) experienced severe pulmonary embolism, venous thrombosis limb and autoimmune thyroiditis. The subject also had an event of deep vein thrombosis during SCGAM-01 study and a family history of blood clots. The subject was discontinued treatment per Sponsor decision.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

I verified the primary efficacy and some secondary efficacy results of the pivotal study SCGAM-01 and some secondary efficacy results of the long-term follow up safety study SCGAM-03.

SCGAM-01 was a prospective, open-label, non-controlled, single-arm, multicenter phase III study with a 12-week wash-in/wash-out period followed by a 12-month efficacy period. The study enrolled 75 subjects: 37 adults and 38 pediatric subjects aged 2 or older. No SBIs were observed during the study. The upper limit of the 2-sided 98% CI for SBI rate was 0.065 per person-year overall. By age group, the upper limit of the CI was 0.379 for young children, 0.325 for older children, 0.532 for adolescents, and 0.130 for adults. Because all upper CI bounds were less than 1.0, the study met its success criteria that the SBI rate per person year is less than 1.0.

The rate of other infections was also similar across the age groups, between 2 and 4 infections per person-year. The adolescents reported the greatest number of days of systematic antibiotic use at 105.429 days. The total number of days hospitalized per person-year was 0.082 for young children, and 0.346 for adolescents. There was no hospitalization in the older children and in the adults. Similar rates for absences from work/school were seen across the age groups, except for the young children group where the rate was the highest at 8.467 days per person-year.

Similar efficacy results were seen in the follow-up study SCGAM-03. SCGAM-3 enrolled 27 subjects: 17 adults and 10 children aged 2 or older. One SBI was observed in one adult during the study. The number of SBI per person-year was 0.018 overall with an upper two-sided 98% CI limit of 0.189. The number of SBI per person-year was 0.030 in the adult group and 0.000 in all the pediatric age groups. In terms of all other infections,

the young and older children had lower rates than adolescents and adults. Adolescents also reported the highest number of days of systematic antibiotic use per person-year at 108.784. No pediatric subjects were hospitalized due to infection and two adult subjects were hospitalized for infection for a total of 10 days. The young children reported the highest number of days of absent from work/school at 4.756 days.

No death occurred in either study. However, one subject from SCGAM-01 experienced acute deep vein thrombosis of the popliteal vein that was moderate in intensity. The same subject continued onto SCGAM-03 and experienced severe pulmonary embolism, venous thrombosis limb and autoimmune thyroiditis. Consequently, the applicant decided to discontinue treatment for the subject.

10.2 Conclusions and Recommendations

Based on the results of the pivotal study SCGAM-01 and the long-term follow-up study SCGAM03, adequate statistical evidence supports approval of the proposed indication of treatment of PI in adults and pediatric subjects (2 years of age and older).