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Applicant	OCTAPHARMA PHARMAZEUTIKA PRODUKTIONSGES.M.B.H.
Established Name	IMMUNE GLOBULIN SUBCUTANEOUS (HUMAN)
(Proposed) Trade Name	Cutaquig
Pharmacologic Class	
Formulation(s), including Adjuvants, etc	Human normal immunoglobulin G, IgG
Dosage Form(s) and Route(s) of Administration	Subcutaneous.
Dosing Regimen	Dose based on weight and trough levels. Administered weekly.
Indication(s) and Intended Population(s)	Replacement therapy in primary immunodeficiency (PI) syndromes in adults

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GLOSSARY

AEs	Adverse events
AR	Adverse Reactions
AUC	Area Under the Concentration-Time Curve
CHQ-PF50	Child Health Questionnaire-Parent Form
CI	Confidence Interval
DCF	Dosing Conversion Factor
FAS	Full Analysis Set
IgG	Immunoglobulin G
IV	Intravenous
IVIG	Intravenous Immunoglobulin
PI	Primary Immunodeficiency
PK	Pharmacokinetic
PK _{IV}	Full PK profile performed after administered intravenously
PK _{SC1}	Full PK profile at the end of the 12-week wash-in/wash-out phase administered subcutaneously
PK _{SC2}	Final PK profile after 28 administrations of Cutaquig (at steady state) administered subcutaneously
PP	Per-protocol
PT	Preferred Term
QoL	Quality of Life
SAEs	Serious Adverse Events
SARs	Suspected Adverse Reactions
SAS	Safety Analysis Set
SBI	Serious Bacterial Infections
SC	Subcutaneous
SF-36	Short Form (36) Health Survey
TEAEs	Treatment-Emergent Adverse Events

1. EXECUTIVE SUMMARY

Cutaquig is a human normal immunoglobulin G (IgG) indicated for treatment of primary immunodeficiency (PI) in adults. The administration of the immunoglobulin is via the subcutaneous (SC) route.

The applicant submitted data from a prospective, open-label, non-controlled, single-arm, multicenter Phase 3 study (SCGAM-01). Sixty-one subjects received Cutaquig SC treatment over a period of about 15 months, comprised of a 12-week wash-in/wash-out period followed by a 12-month efficacy phase. Each subject who stayed in the study for the whole period received 64 weekly infusions. The primary efficacy endpoint was the rate of serious bacterial infections (SBIs) per person-year on treatment. No SBIs were observed during the study.

Of the 61 subjects treated, 57 (93.4%) experienced at least one Treatment-Emergent Adverse Event (TEAE), including infections. There were no TEAEs leading to death or

withdrawal or other significant AEs. Five serious adverse events (SAEs) were reported in four subjects. None were assessed as related to product.

In summary, there were no statistical analysis issues in this submission. The results of this study appear to support the use of Cutaquig in all age groups to prevent SBI.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

The PI 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 characterised by hypogammaglobulinaemia with or without defective specific antibody production. Children and adults with PI have an increased risk of recurrent bacterial and viral infections that typically attack the respiratory tract (sinusitis, bronchitis, pneumonia) but can also affect the gastrointestinal tract (gastroenteritis). They can be severe and can lead to substantial morbidity. Responses to antibacterial therapy are often poor.

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

Therapeutic options for the treatment of infections in PI include standard antibiotic treatment and administration of Immunoglobulin G (IgG) as a replacement therapy. Responses to antibacterial therapy are often poor. At present, most PIs are not curable, but immunoglobulins have shown to decrease the total number of severe infections and the duration of hospitalization. Replacement therapy with polyclonal human normal immunoglobulin is the cornerstone of management for significant primary antibody deficiency disorders. Replacement therapy increases life expectancy and reduces the frequency and severity of infections, antibiotic usage and hospital admissions; however, patients remain susceptible to sporadic breakthrough infections. For most patients, replacement therapy is a lifelong requirement.

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

During the last 20 years, several IgG preparations have been developed for SC administration. At present, Cutaquig is neither approved for marketing nor withdrawn or suspended from marketing authorization worldwide.

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

- An information request sent to Octapharma on July 26, 2013 included FDA statistical comments regarding the initial IND submission (IND 15617, June 13, 2013) which contained the protocol for pivotal study SCGAM-01. In their response of December 11, 2013, the applicant confirmed that the 95% confidence interval (CI) for the primary efficacy endpoint was replaced by the upper one-sided 99% confidence limit.

- The pre-BLA meeting correspondence (CRMTS #10629, April 4, 2017) did not include statistical questions.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

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

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

5.1 Review Strategy

The clinical development program for Cutaquig consists of Study SCGAM-01. The study is ongoing; the data cutoff date for this submission is October 27, 2017.

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

BLA 125668.0

Module 1.14	Labeling
Module 2.5	Clinical Overview
Module 2.7.3	Summary of Clinical Efficacy
Module 2.7.4	Summary of Clinical Safety
Module 2.7.6	Synopses of Individual Studies
Module 5.2	Tabular Listing of All Clinical Studies
Module 5.3.5.2	Study Report: Clinical Phase 3 study to evaluate the pharmacokinetics, efficacy, tolerability and safety of subcutaneous human immunoglobulin ((b) (4) 16.5%) in subjects with primary immunodeficiency (PI) diseases

Amendment 125668/0.4

Module 1.2	Cover letter
	Response to Information request dated February 5, 2018

Amendment 125668/0.6

Module 1.2	Cover letter
	Response to Information request dated February 23, 2018

Amendment 125668/0.8

Module 1.2	Cover letter
	Response to Information request dated April 27, 2018

Amendment 125668/0.16

Module 1.2	Cover letter
	Response to Information request dated June 29, 2018

Amendment 125668/0.25

Module 1.2

Cover letter

Response to Information request dated August 10, 2018

5.3 Table of Studies/Clinical Trials

The clinical development program for Cutaquig (also called (b) (4)) is summarized in Table 1.

Table 1. Summary of clinical studies to evaluate the pharmacokinetics (PK), efficacy, tolerability and safety of subcutaneous human immunoglobulin (*Cutaquig 16.5%*) in subjects with PI diseases

Study ID	Population/ N=Patients in study/ Gender/Age Range	Design/ Study Site/Location/ Study Period	Test Product/ Dosage/ Route of Administration	Evaluation Criteria	Objectives
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	<u>Primary objectives</u> 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. <u>Secondary objectives</u> 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.

“Source: Adapted from BLA 125668, Module 5.2, Tabular Listing of all Clinical Studies.”

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1

Study SCGAM-01 is entitled “Clinical Phase 3 study to evaluate the pharmacokinetics, efficacy, tolerability and safety of subcutaneous human immunoglobulin ((b) (4) 16.5%) in subject with primary immunodeficiency diseases.”

6.1.1 Objectives (Primary, Secondary, etc)

The primary objectives are:

- To assess the efficacy of Cutaquig in preventing SBIs (defined as bacteraemia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia and visceral abscess) compared with historical control data.
- To evaluate the pharmacokinetic (PK) characteristics of Cutaquig and to compare the area under the curve (AUC) with that of IVIG.

The secondary objectives are:

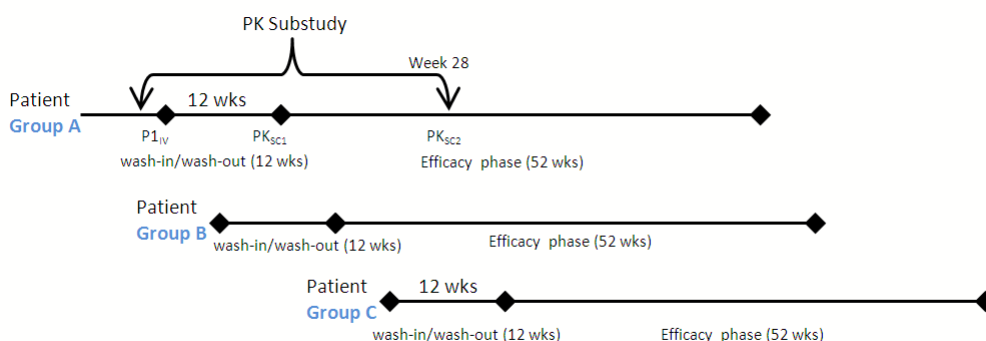
- To evaluate the tolerability and safety of Cutaquig.
- To determine the PK profile of Cutaquig.
- To assess the dosing conversion factor (DCF) when switching subjects from intravenous immunoglobulin (IVIG) treatment.

- 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

SCGAM-01 is a prospective, open-label, non-controlled, single-arm, multicenter Phase 3 study with a 12-week wash-in/wash-out period followed by a 12-month efficacy (treatment) period. The first PK evaluation ("PK_{IV}") (see Figure 1) takes place before and after the last administration of IGIV 5% or IGIV 10%, according to the subject's regular treatment schedule (previous IGIV dose). In the following 12-week wash-in/wash-out phase, weekly (± 2 days) SC doses of Cutaquig were given, at 1.5 times the previous IVIG dose adjusted for weekly dosing. After the analysis of PK data obtained at the end of the wash-in/wash-out phase ("PK_{SC1}"), the "corrected" Dosing Conversion Factor (DCF) was calculated. During the efficacy phase of the study, Cutaquig was administered subcutaneously every week (± 2 days). A minimum time of 4 days had to be kept in between two single SC infusions. Each subject who stayed in the study for the whole period received 64 Cutaquig SC weekly infusions. The study comprises three groups of subjects (see Figure 1):

Figure 1. Efficacy Phase – Groups of Subjects



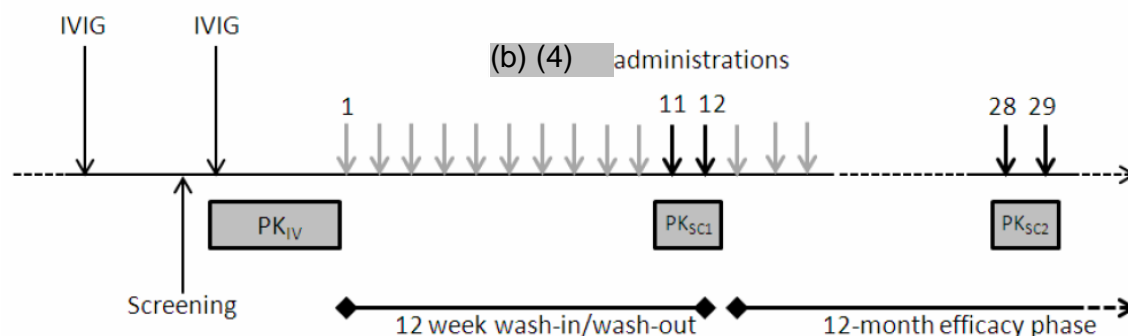
“Source: Adapted from BLA 125668, Module 5.3.5.2, Protocol and protocol amendment, Figure 2.”

Reviewer Comment. In Figure 1, Group A, I found a typographical error. Instead of Pl_{iv} it should be PK_{iv} .

Group A:

Subjects who underwent the PK substudy had three PK assessments: a full PK profile after the last administration of the previously used IVIG product before the subject was switched to Cutaquig (PK_{IV}), a full PK profile at the end of the wash-in/wash-out phase (PK_{SC1}) and a final PK profile after 28 administrations of Cutaquig (at steady state) to assess the bioavailability of total IgG with respect to the two administration methods (PK_{SC2}) (Figure 2).

Figure 2. PK Substudy



PK_{IV} - administered intravenously; PK_{SC1} and PK_{SC2} - administered subcutaneously

“Source: Adapted from BLA 125668, Module 5.3.5.2, Protocol and protocol amendment, Figure 1”

Group B:

Subjects who do not participate in the PK substudy but who are enrolled in parallel to the ongoing PK substudy.

Group C:

Subjects who did not participate in the PK substudy and who are enrolled after the corrected DCF is known.

6.1.3 Population

Subjects who meet all of the following criteria may be enrolled:

- Age of ≥ 2 years and ≤ 75 years.
- Confirmed diagnosis of PI as defined by European Society for Immunodeficiencies (ESID) and Pan American Group for Immunodeficiency (PAGID) and requiring immunoglobulin replacement therapy due to hypogammaglobulinaemia or agammaglobulinaemia.
- On regular octagam 5% or 10% treatment for at least 6 infusions prior to entering the study at a constant dose between 300 and 800 mg/kg body weight ($\pm 20\%$ of the mean dose for the last 6 infusions).
- Availability of the IgG trough levels of two previous octagam 5% or 10% infusions before enrollment, and maintenance of ≥ 5.0 g/L in the trough levels of these two previous infusions.
- Negative result on a pregnancy test (HCG-based assay in urine) for women of childbearing potential and use of a reliable method of contraception for the duration of the study.

6.1.4 Study Treatments or Agents Mandated by the Protocol

The study was planned to start with dosing based on previous results for AUC dosing and to adjust dosing requirements as soon as the necessary PK results were available. As PK results were not available in time, the initial dose calculation was applied for all subjects.

For subjects participating in the PK substudy (Group A) and those in Group B, the Cutaquig dose during the wash-in/wash-out phase was calculated as follows:

$$\frac{\text{previous IVIG dose (in grams)} \times 1.5}{\text{number of weeks between IVIG doses}}$$

They stayed on this dose until the corrected DCF was known. If the corrected DCF was >1.5, the subsequent Cutaquig doses were calculated with the corrected DCF.

Group C subjects receive a SC dose adjusted by the corrected DCF.

6.1.6 Sites and Centers

The study was conducted at 18 active sites (who were included in the analysis): two sites in Poland, four sites in Czech Republic, one site in Hungary, seven sites in the USA, one site in Canada and three sites in Slovakia.

6.1.8 Endpoints and Criteria for Study Success

Primary endpoint

The primary efficacy endpoint is the rate of SBIs per person-year on treatment.

The FDA Guidance for Industry (2008)¹ suggests that, based on historical data, a statistical demonstration of a SBI per person-year less than 1.0 is adequate to provide substantial evidence of efficacy. Therefore, the study success is that the SBI rate is less than 1.0 per person-year with one-sided confidence 99%. Accordingly, the null hypothesis to be tested in this study is that the SBI rate is greater than or equal to 1.0 per person-year, tested at the 1% level of significance. The null hypothesis was to be rejected if the two-sided 98% confidence limit –which is the upper one-sided 99% confidence limit – was less than 1.0.

Secondary efficacy endpoints:

- 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).
- Days missed from work/school/kindergarten/day care due to infections and their treatment.

¹Guidance for Industry - Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency, 2008

- Episodes of fever.
- QoL assessments using the Child Health Questionnaire-Parent Form (CHQ-PF50) from parent or guardian of subjects <14 years of age and the Short Form (36) Health Survey (SF-36) in subjects ≥ 14 years of age.

Safety endpoints:

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

6.1.9 Statistical Considerations & Statistical Analysis Plan

Sample Size

Based on historical data, the applicant assumed that the rate of SBIs per person-year is less than 0.5. Using STPLAN 4.3 software the applicant calculated that 42 evaluable subject-years would be sufficient to test the null hypothesis that the serious infection rate is greater than or equal to 1.0 per person-year at the 1% level of significance with 90% power. The study was to enroll at least 50 subjects, each treated with Cutaquig over a period of 15 months. Assuming a drop-out rate of 15%, the number of evaluable person-years would still be at least 42.5 and thus satisfy above sample size consideration.

Reviewer Comment. The applicant's estimates are in agreement with the FDA Guidance (2008) which considers between 40 and 50 subjects sufficient to demonstrate an infection rate of less than one per person per year.

Analysis populations

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

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

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

Reviewer Comment. The applicant included pediatric and adolescent subjects in the FAS and PP sets. According to the indication , it is sufficient to meet the primary endpoint for the adult part of these populations.

Interim Analysis

A PK interim analysis was to be conducted after all PK_{SCI} data were available to revise the initial DCF of 1.5 to the corrected value according to the AUC and to obtain a titration scheme to be used by the investigator to achieve the associated target trough levels. This PK interim analysis was done at the same time as the analysis presented in the CSR.

Statistical Methods

Descriptive summaries are presented for each of the primary and secondary endpoints. Summaries are completed for all subjects overall and by age group. Continuous, quantitative variable summaries include the number of subjects with non-missing values (N), mean, standard deviation, median, minimum and maximum, first and third quartile. Categorical, qualitative variable summaries include the frequency and percentage of subjects who are in the particular category. In general the denominator for the percentage calculation is based upon the total number of subjects in the analysis population unless otherwise specified.

Primary Efficacy Endpoint

The SBI rate was calculated as (number of SBI) / (person-years) during the efficacy period after completion of the 12-week wash-in/wash-out phase to ensure that any occurring infection could be unambiguously attributed to steady-state treatment with Cutaquig . A two-sided 98% CI was calculated that accounts for intra-subject correlation in incidents following a compound Poisson process model.

Secondary Efficacy Endpoints

The rate of infections other than SBI will be calculated per person-year and presented with the 95% CI. The rate of other infections will be analyzed and presented using the same method as the rate of serious bacterial infections. However, a 95% confidence interval will be calculated.”

Missing Data

Missing data were not imputed; calculations pertaining to person-year computations were based on observed values only. No analysis of the patterns of missing data was done.

In case of AEs, if the start date and time of an AE were partially or completely missing, the AE was assumed to be treatment-emergent if it could not be definitely shown that the AE did not occur or worsen during the treatment period (worst case approach). Missing start dates and times were not replaced.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Sixty-one evaluable subjects were enrolled and received at least one dose of study drug. Both the SAS and FAS are comprised of 61 subjects. Four subjects were excluded from the PP set because they terminated early in the study, well before the start of the treatment period; therefore the PP population is comprised of 57 subjects. The numbers of subjects per age group included in each analysis set are provided in Table 2.

Table 2: Number of Subjects 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%)

“Source: Adapted from BLA 125668, Module 5.3.5.2, Report Body, Table 5”

6.1.10.1.1 Demographics

Overall, 33 female subjects and 28 male subjects participated in this study, with a higher proportion of male subjects in the child and adolescent groups, and a higher proportion of women in the adult group. The youngest subject enrolled was 2 years old and the oldest was 73 years old. In the adult group, the mean age was 46.6 years and 71.1% of the subjects were female. The demographic data for the FAS are presented in Table 3.

Table 3: Demographic Data (FAS, N=61)

Parameter	Categories/ Sample Characteristics	Age (years) ≥2 to < 5 (N=4)	Age (years) ≥5 to < 12 (N=11)	Age (years) ≥12 to < 16 (N=8)	Age (years) ≥16 to ≤ 75 (N=38)	Total (N=61)
Age [years]	N	4	11	8	38	61
	Mean (SD)	3.00 (1.155)	6.82 (1.888)	13.38 (1.061)	46.63 (14.369)	32.23 (21.959)
	Median	3.00	6.00	13.50	45.50	34.00
	Minimum, Maximum	2.0, 4.0	5.0, 10.0	12.0, 15.0	16.0, 73.0	2.0, 73.0
	Q1, Q3	2.00, 4.00	5.00, 9.00	12.50, 14.00	37.00, 58.00	12.00, 50.00
Gender	Male	3 (75.0%)	9 (81.8%)	5 (62.5%)	11 (28.9%)	28 (45.9%)
	Female	1 (25.0%)	2 (18.2%)	3 (37.5%)	27 (71.1%)	33 (54.1%)
ABO Rhesus blood type	Missing	0 (0.0%)	2 (18.2%)	2 (25.0%)	1 (2.6%)	5 (8.2%)
	A	1 (25.0%)	4 (36.4%)	4 (50.0%)	18 (47.4%)	27 (44.3%)
	AB	0 (0.0%)	1 (9.1%)	1 (12.5%)	3 (7.9%)	5 (8.2%)
	B	2 (50.0%)	1 (9.1%)	0 (0.0%)	4 (10.5%)	7 (11.5%)
	O	1 (25.0%)	3 (27.3%)	1 (12.5%)	12 (31.6%)	17 (27.9%)
Race	White	4 (100.0%)	11 (100.0%)	8 (100.0%)	37 (97.4%)	60 (98.4%)
	Multiple	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.6%)	1 (1.6%)
Ethnicity	Not Hispanic or Latino	4 (100.0%)	11 (100.0%)	8 (100.0%)	38 (100.0%)	61 (100.0%)

“Source: Adapted from BLA 125668, Module 5.3.5.2, Report Body, Table 14.1.2.1.1”

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The most common findings from the medical history by PT (Preferred Term)(apart from immunodeficiency) were asthma (27 subjects [44.3%]), allergic rhinitis (23 subjects [37.7%]), gastroesophageal reflux disease (17 subjects [27.9%]) and chronic sinusitis (13 subjects [21.3%]). All 61 subjects in the SAS/FAS used concomitant medication and 20 (32.8%) used non-drug therapies (mainly surgery and dental work).

6.1.10.1.3 Subject Disposition

Out of the 61 enrolled subjects, all subjects received study treatment, and 6 subjects (3 adolescents and 3 adults) were withdrawn from the study prematurely after at least one administration of study medication. Forty-seven subjects have completed the study and eight subjects were ongoing at the time of the data cut-off. A detailed overview on the number of subjects by age group who were enrolled, who received treatment, who terminated early and who completed the study is given in Table 4.

Table 4: Subject Disposition by Age (All Subjects, N=61)

	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%)
Treated in Enrolment Group A	0 (0.0%)	2 (18.2%)	3 (37.5%)	20 (52.6%)	25 (41.0%)
Treated in Enrolment Group B	4 (100.0%)	9 (81.8%)	5 (62.5%)	18 (47.4%)	36 (59.0%)
Treated in Enrolment Group C	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ongoing	2 (50.0%)	4 (36.4%)	2 (25.0%)	0 (0.0%)	8 (13.1%)
Completed	2 (50.0%)	7 (63.6%)	3 (37.5%)	35 (92.1%)	47 (77.0%)
Early- terminated	0 (0.0%)	0 (0.0%)	3 (37.5%)	3 (7.9%)	6 (9.8%)

N=number of subjects

“Source: Adapted from BLA 125668, Module 5.3.5.2, Report Body, Table 3”

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

No SBIs were observed during the study and the applicant calculated the upper 99% confidence limit as 0.084 which is less than 1.0 per perso-year.

***Reviewer Comment.** In the original submission the applicant did not calculate the upper confidence limit for SBI because the pre-specified statistical method did not permit to calculate CIs in the case of zero events. Upon our information request of August 10, 2018, the applicant calculated the confidence limit using the method described by Ulm (Simple Method to Calculate the Confidence Interval of a Standardized Mortality Ratio (SMR), American Journal of Epidemiology, Volume 131, Issue 2, 1 February 1990, Pages 373–375). Their estimate of the upper 99% confidence limit for FAS is 0.084. I calculated the upper 99% confidence bound using StatXact 10. My calculations confirmed the applicant’s estimate. The applicant did not calculated the upper confidence limit for the adult subpopulation only. My estimate of the upper confidence limit for the adult subpopulation only is 0.126. Therefore the study was successful in achieving the success criterion since the upper one-sided 99% confidence limit for the observed SBI rate per subject per year is <1.0.*

6.1.11.2 Analyses of Secondary Endpoints

A total of 188 non-serious infections were observed in 52 subjects over 54.77 person years in the efficacy period. The rate of other infections per person-year was 3.432 overall (upper 95% CI: 4.572) (see Table 5). The median time to resolution of infections was 10 days, with longer times for moderate infections (16 days) than mild infections (8 days). The severe infection resolved in 21 days.

Table 5: Summary of Other Infections, Rate of Other Infections per Person-Year

Infections	All subjects N=61 N (%) n
Any other	52 (85.2%) 188
Ear	4 (6.6%) 4
Eye	1 (1.6%) 2
Gastrointestinal tract	9 (14.8%) 13
Genitourinary tract	10(16.4%)19
Upper respiratory tract	43 (70.5%) 108
Lower respiratory tract	14 (23.0%) 19
Skin	3 (4.9%) 3
Not (elsewhere) classified	17(27.9%) 20
Mild	48 (78.7%) 136
Moderate	26(42.6%) 51
Severe	1(1.6%) 1
Number of person-years exposure	54.77
Total of other infections per person-year	3.432
One-sided 95% CI –upper limit	4.572

CI=Confidence interval; N=Number of subjects; n=Number of infections.

“Source: Adapted from BLA 125668, Module 5.3.5.2, Report Body, Table 9”

***Reviewer Comment.** I confirmed the applicant’s calculation of the point estimate (other infections/number of person-years). To verify the upper 95% confidence limit, an information request was sent on June 29, 2018, requesting the applicant calculate 95% CI using SAS PROC GENMOD or PROC GLIMMIX. The applicant used the overdispersed Poisson regression model in PROC GENMOD to recalculate the CI. The new result is 4.114. This result is close to the value presented in Table 5.. However, the applicant claims that the original calculations using a compound Poisson process model (Kegler, Epidemiologic Perspectives & Innovations 2007, 4:1) “cannot be reproduced exactly by PROC GENMOD or PROC GLIMMIX” and the analyses originally provided are more conservative.*

Two-thirds (41/61, 67.2%) of subjects used antibiotics during the efficacy period. The number of treatment episodes per person-year was 2.136, the number of treatment days was 2835, and the number of treatment days per person-year was 51.759. The majority of antibiotic use was systemic: 40 (65.6%) subjects used systemic antibiotics and the number of treatment days per person-year was 39.618.

There was one hospitalization due to infection that lasted for two days, for a total of 0.037 (2/54.77, Upper one-sided 95% confidence limit: 0.189) hospitalization days per person-year.

During the efficacy period sixteen subjects (28.1%) out of 57 school/work age subjects in the full analysis set (51.03 person-years) had 29 absences from work or school due to infections with a total of 134 days of absence. The rate of days missed from work or school per person-year was, assuming 200 working/school days per person -year.

During the efficacy period 5 (8.2%) subjects each had at least one episode of fever with total 6 of episodes of fever, giving 0.110 episodes of fever per person-year.

Overall, there were no major changes in the mean and median of Child Health Questionnaire-Parent Form (CHQ-PF50) scores over time. Mean SF-36 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. Overall there were increases (i.e., improved QoL), albeit slight, between Week 1 and the end of study visit in mean scores for both summary scores (physical health and mental health) and also for 7 of the 8 scales.

6.1.11.3 Subpopulation Analyses

No subgroup analyses were necessary since the number of SBIs was zero.

6.1.11.4 Dropouts and/or Discontinuations

Three adolescents withdrew from the study (Subject (b) (6) after 33 days, Subject (b) (6) after 56 days and Subject (b) (6) after 20 days), as well as three adults (Subject (b) (6) after 224 days, Subject (b) (6) after 14 days and Subject (b) (6) after 271 days). The reason for withdrawal from the study was the subject's decision in each case. Estimated or derived data were not used to deal with missing data. The analyses of annualized SBI rate were done per subject-year for all FAS subjects, and thus included an adjustment for length of time each subject was followed. Therefore no imputation of missing data for early terminations was needed or performed.

6.1.12 Safety Analyses

6.1.12.3 Deaths

No deaths occurred during the study.

6.1.12.4 Nonfatal Serious Adverse Events (SAE)

Five serious adverse events (SAEs) were reported in four subjects; none were assessed as related to product. The details of all five SAEs are presented in Table 6.

Table 6: Listing of Serious Adverse Events

Patient sex	Age group	MedDRA Preferred Term	Reason for seriousness	Intensity	Relationship to study medication	Outcome
Female	Adults ≥16 Years ≤75 Years	Thyroid neoplasm	Hospitalisation	Mild	Not related	Recovered/ resolved
Female	Adults ≥16 Years ≤75 Years	Appendicitis	Hospitalisation and medically important condition	Severe	Not related	Recovered/ resolved
Male	Children ≥5 Years <12 Years	Grand mal convulsion	Medically important condition	Mild	Unlikely	Recovered/ resolved
Female	Adolescents ≥12 Years <16 Years	Asthma	Hospitalisation	Severe	Not related	Recovered/ resolved
		Respiratory syncytial virus bronchiolitis	Hospitalisation	Severe	Not related	Recovered/ resolved

MedDRA = Medical Dictionary for Regulatory Activities;

“Source: Adapted from BLA 125668, Module 5.3.5.2, Report Body, Table 32”

6.1.12.5 Adverse Events of Special Interest (AESI)

No thromboembolic events were observed.

Infection TEAEs are considered AEs of special interest in PI subjects. A total of 239 infections were observed in 54 (88.5%) subjects over the efficacy period. Just over one-quarter (29.5%, 18/61) of the subjects experienced 1 or 2 infection TEAEs, 15 (24.6%) subjects experienced between 3 and 4, 10 (16.4%) subjects experienced 11, 3 subjects (4.9%) experienced 15, 5 subjects (8.1%) experienced 19, and 3 subjects (4.9%) experienced 26. One subject reported a treatment-unrelated infection SAE of severe intensity (respiratory syncytial virus bronchiolitis); all other AEs of infections were non-serious, non-severe and treatment unrelated. Upper respiratory tract infections were reported most frequently. Three-quarters of the infections in the efficacy period were mild and one-quarter moderate in intensity; there was one severe infection which resulted in hospitalization.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

Efficacy

Data from one prospective, open-label, non-controlled, single-arm, multicenter Phase 3 study (SCGAM-01) were submitted in support of the BLA. The study is ongoing (data cutoff was October 27, 2017); 28 male and 33 female (total 61) subjects were enrolled: 4 subjects $2 \leq$ years of age < 5 , 11 subjects $5 \leq$ years of age < 12 , 8 subjects $12 \leq$ years of age < 16 and 38 subjects $12 \leq$ years of age ≤ 75 . Forty-seven subjects completed the study.

No SBIs were reported at any time during the study. With zero SBIs in 54.77 person years of treatment in the efficacy period, the study had a rate of 0.0 SBIs per subject per year (upper one-sided 99% confidence limit 0.084), and therefore was successful in achieving the success criterion since the upper one-sided 99% confidence limit for the observed SBI rate per subject per year is < 1.0 .

Secondary efficacy endpoints further demonstrated the low incidence of infection, therapeutic antibiotic use, days missed from work/school/daycare, and unscheduled medical visits and hospitalizations.

Safety

There were no TEAEs leading to death or withdrawal or other significant AEs. All five SAEs were considered unrelated to study medication. There was one AE of infection that was considered severe and unrelated. There were no deaths or thromboembolic events.

10.2 Conclusions and Recommendations

There were no statistical issues in this submission. The results of the study appear to support the use of Cutaquig in adults with PI to prevent SBIs.