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Applicant	Green Cross Corporation
Established Name	Immune globulin intravenous, human-stwk
(Proposed) Trade Name	ALYGLO
Pharmacologic Class	
Formulation(s), including Adjuvants, etc	
Dosage Form(s) and Route(s) of Administration	Intravenous
Dosing Regimen	300 – 900 mg/kg (of body weight) every 21 or 28 days
Indication(s) and	Treatment of primary humoral immunodeficiency (PI) in adults (b) (4)

Intended Population(s)	<p>(b) (4)</p> <p>This includes, but is not limited to, the humoral immune defect in congenital agammabulinemia, common variable immunodeficiency (CVID), X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies (SCID).</p>
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GLOSSARY

AE adverse event
GEE Generalized Estimating Equation
GB hemoglobin
ID identification
IgG immunoglobulin G
IMP Investigational Medicinal Product
IND Investigational New Drug
ITT Intent-to-Treat
IU international unit
IGIV intravenous immune globulin
IV intravenous
MedDRA Medical Dictionary for Regulatory Activities
PHID primary humoral immunodeficiency
PO oral
PP Per Protocol
SAE Serious Adverse Event
SAP Statistical Analysis Plan
SAS Statistical Analysis System
SBI serious bacterial infection
SC subcutaneous
SCIG subcutaneous immune globulin
SD standard deviation
TAEs temporally associated adverse events

1. EXECUTIVE SUMMARY

This biologics license application (BLA) is for approval of Immune Globulin Intravenous (Human) GC5107 indicated for the treatment of primary humoral immunodeficiency (PI) in adults (b) (4)

The evidence to support the safety and effectiveness of the product is based on the results of Study GC5107B_P3. The clinical trial was a Phase III, prospective, open-label, single-arm, multi-center, historically controlled study evaluating the safety, efficacy, and PK of Immune Globulin Intravenous (Human) GC5107 administered every 21 or 28 days for approximately 12 months.

The primary efficacy endpoint was the incidence of acute serious bacterial infections (SBIs) meeting the criteria described in FDA's Guidance for Industry: Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency. To meet the primary endpoint, the upper one-sided 99% confidence limit for the frequency of SBIs with GC5107 had to be less than 1.0 per subject per year. In the ITT population with 49 subjects, a single SBI (bacterial pneumonia) occurred during a cumulative total follow-up of 45.86 years, resulting in an annualized rate of acute SBIs of 0.02 per subject per year

(99% one-sided upper confidence limit: 0.21). Therefore, the study met the success criterion of the upper 99% confidence limit <1.

The SBI event occurred in the subgroup of 29 subjects treated according to the 28-day schedule (total follow-up: 26.24 years), yielding an incidence of acute SBIs of 0.04 per subject per year (99% one-sided upper confidence limit: 0.35). In the 21-day schedule group with 20 subjects (total follow-up: 19.62 years), zero SBIs were observed.

For the 49 subjects with 667 infusions, the proportion of infusions with temporally associated adverse events (TAAEs) occurring during or within one hour, 24 hours, and 72 hours after the infusion were 0.09 (95% one-sided upper confidence bound: 0.14), 0.20 (95% one-sided upper confidence bound: 0.27), and 0.24 (95% one-sided upper confidence bound: 0.31), respectively. Therefore, the primary safety objective to demonstrate that the percentage of infusions with one or more infusion-related AE was less than 40% was met.

In summary, the statistical results of study GC5107B_P3 appear to support the use of Immune Globulin Intravenous (Human) GC5107 for treatment of primary humoral immuno-deficiency (PI) in adults (b) (4)

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Primary immunodeficiency (PI) diseases are a large heterogeneous group of disorders resulting from inherited defects in the immune system development and/or function. Consequently, subjects are unable to mount an immune response to microorganisms and may experience recurrent protozoal, bacterial, fungal, and viral infections. The estimated overall prevalence of these disorders in the U.S. is approximately 1 in 1200 live births. The number of known PHID defects has increased in the last 20 years and the World Health Organization currently recognizes more than 220 different disorders that meet the definition of PI. The best-described PIs include X-linked agammaglobulinemia, common variable immune deficiency disease, selective IgA deficiency, severe combined immune deficiency, chronic granulomatous disease, Wiskott-Aldrich syndrome, X-linked hyper IgM syndrome, DiGeorge syndrome, IgG subclass deficiency, ataxia telangiectasia, leukocyte adhesion deficiency, and complement deficiencies.

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

The treatment of choice for PI patients with predominant antibody deficiency is replacement therapy with human immune globulin preparations for intravenous

(IV) or subcutaneous (SC) administration (IGIV and SCIG). Therapeutic options for the treatment of infections in PHID patients include standard antibiotic treatment. Therapeutic options for treatment of PHID itself include transplantation of bone marrow- derived stem cells and gene therapy.

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

GCC 10% IGIV is being developed for the treatment of PHID. It has been approved and marketed in one country (Republic of Korea) to date (since May 12, 2017).

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

Starting in 2015, Green Cross Corporation (GCC) had four meetings with FDA related to GCC 10% intravenous immune globulin (IGIV). The meetings included a Type B (Pre-IND) meeting, Type C meetings, and a Type B (Pre-BLA) meeting.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

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

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

5.1 Review Strategy

The applicant submitted data from one completed pivotal study GC5107B_P3 to support the indication pursued in this BLA. This memo reviews data from Study GC5107B_P3.

5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review 125743/0

The following documents (and module number) in BLA 125743 were reviewed:

Module 1.14	Labeling
Module 1.2	Cover Letter
Module 2.2	Introduction
Module 2.5	Clinical Overview
Module 2.7.3	Summary of Clinical Efficacy
Module 2.7.4	Summary of Clinical Safety
Module 5.2	Tabular Listing of all Clinical Studies
Module 5.3	Clinical Study Reports
Module 5.3.5.1	Study Report of Controlled Clinical Studies Pertinent to the Claim Indication

Module 5.3.3.1	Study Report Body Chapter
Module 5.3.5.1	GC5107B_P3 Clinical Study Report
Module 5.3.5.1	GC5107B_P3 Clinical Study Report Addendum 1
Module 5.3.5.1	GC5107B_P3 Clinical Study Report Addendum 1 - Tables, Figures & Listings

5.3 Table of Studies/Clinical Trials

Study GC5107B_P3 was the only one clinical trial for the development of this product. No table is presented in this Subsection.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1 GC5107_P3

6.1.1 Objectives (Primary, Secondary, etc.)

The primary efficacy objective was to demonstrate the efficacy of GCC IGIV, 10% in preventing the development of acute serious bacterial infections (SBIs), including bacterial pneumonia, bacteremia/sepsis, bacterial meningitis, visceral abscess, and osteomyelitis/septic arthritis.

Secondary efficacy objectives were to evaluate the following parameters: the incidence of infections other than acute SBIs; the number of days missed from work/school/kindergarten/day care or unable to perform normal daily activities due to infections; the number of days that the care providers of pediatric subjects had to miss work in order to care for the child due to infections; the number of days of unscheduled physician visits and hospitalizations due to infection; the number of days on therapeutic IV antibiotics; the number of days on therapeutic oral antibiotics; time to resolution of infections; and the incidence of infections other than serious bacterial infections correlated with trough IgG levels.

6.1.2 Design Overview

Study GC5107B_P3 was a Phase III, prospective, open-label, single-arm, multi-center, historically controlled study to evaluate the safety, efficacy, and PK of Immune Globulin Intravenous (Human) GC5107 administered every 21 or 28 days for approximately 12 months in subjects with PHID enrolled at centers in Canada and USA.

Upon consenting and screening, eligible subjects received intravenous (IV) infusions of the Investigational Medicinal Product (IMP) (GC5107) at the same dose and interval as used for their previous IGIV maintenance therapy. GC5107 was administered at a dose of 300-900 mg/kg (of body weight) every 21 or 28 days (\pm 4 days; depending on their pre-study IGIV treatment schedule) for 12 months of study infusions. Subjects treated according to the 21-day schedule were to receive a total of 17 infusions, whereas subjects treated according to the 28-day schedule were to receive a total of 13 infusions during the 12-month

treatment period. The dosing regimen remained unchanged throughout the study period unless there was a medically justified need to change it. Upon completion of study treatment, subjects underwent a follow-up visit within three weeks (21-day schedule) or within four weeks (28-day schedule) after the last dose of IMP. Hence the total subject follow-up (after screening) was approximately 12 months (51 or 52 weeks).

6.1.3 Population

- Male or female with confirmed clinical diagnosis of a Primary Humoral Immunodeficiency (PHID) Disease as defined by International Union of Immunological Societies (IUIS) and with documented agammaglobulinemia or hypogammaglobulinemia
- Aged 2 to 70 years
- Treated with 300-900 mg/kg of a licensed intravenous immune globulin (IGIV) therapy at 21 ± 4 or 28 ± 4 day intervals for at least 3 infusions prior to this study.
- At least two documented IgG trough levels of ≥ 500 mg/dL obtained at two infusion cycles (21 or 28 days) within 12 months prior to study treatment.
- Willingness to comply with all requirements of the protocol.
- For females of child-bearing potential: a negative serum pregnancy test at screening and agreement to employ adequate birth control measures during the study.
- For males: agreement to practice adequate birth control measures during the study.
- Informed consent form signed by the subject, parent or guardian, and an assent form for children (≥ 2 to < 12 years of age at study entry) and adolescents (≥ 12 to < 17 years of age at study entry) as appropriate per study documentation requirements and regulations of the local jurisdiction.
- Authorization to access personal health information.
- Subjects participating in a clinical trial with another experimental IGIV were eligible if they had received stable IGIV therapy for at least 3 infusion cycles (of 21 or 28 days, as applicable) prior to receiving GC5107 and all inclusion and exclusion criteria were satisfied.
- Subjects participating in a clinical trial of subcutaneous immune globulin (SCIG) could be enrolled if they were switched to IGIV for three infusion cycles (of 21 ± 4 or 28 ± 4 days) prior to enrollment in this study.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Subjects received IV infusions of the IMP (GC5107) at the same dose and interval as used for their previous IGIV maintenance therapy. GC5107 was administered at a dose of 300-900 mg/kg (of body weight) every 21 or 28 days (± 4 days; depending on their pre-study IGIV treatment schedule) for 12 months of study infusions. Subjects treated according to the 21-day schedule were to receive a total of 17 infusions, whereas subjects treated according to the 28-day

schedule were to receive a total of 13 infusions during the 12-month treatment period. The dosing regimen remained unchanged throughout the study period unless there was a medically justified need to change it.

6.1.6 Sites and Centers

Ten sites were in the US and seven sites were in Canada.

6.1.7 Surveillance/Monitoring

A third-party Drug Safety Monitoring Board (DSMB) monitored the safety of study subjects on a periodic basis. Members of the DSMB were independent of the study Sponsor (including designees) and participating sites.

6.1.8 Endpoints and Criteria for Study Success

Primary Efficacy Endpoint

The primary efficacy endpoint was the rate of acute serious bacterial infections (SBIs) meeting the FDA criteria (bacterial pneumonia, bacteremia/sepsis, bacterial meningitis, visceral abscess, osteomyelitis/septic arthritis) in subjects treated with GC5107. The rate of SBIs is defined as the mean number of validated SBIs per subject per year.

The study is considered a success if the upper limit of an exact one-sided 99% CI for the SBIs rate is less than 1.0 per subject per year according to the FDA guidance (FDA/CBER, 2008, Guidance for industry: safety, efficacy, and pharmacokinetic studies to support marketing of immune globulin intravenous (human) as replacement therapy for primary humoral immunodeficiency).

Secondary Efficacy Endpoints

- The incidence of infections other than acute SBIs.
- The incidence of infections other than SBIs correlated with trough IgG levels.
- Time to resolution of infections.
- The number of days missed from work/school/kindergarten/daycare or days unable to perform normal daily activities due to infections.
- The number of days that the care providers of pediatric subjects had to miss work in order to care for the child due to infections.
- The number of days of unscheduled physician visits due to infections.
- The number of days of hospitalizations due to infections.
- The number of days of IV therapeutic antibiotics.
- The number of days of oral (PO) therapeutic antibiotics.

Primary Safety Endpoint

The primary safety endpoint was the proportion of infusions with TAAE that occurred during or within 1 hour, 24 hours, and 72 hours following an infusion of the IMP. The success criterion is the upper one-sided 95% confidence limit less than 0.4 for the observed proportion of infusions with TAAEs (FDA/CBER, 2008).

6.1.9 Statistical Considerations & Statistical Analysis Plan

Analysis Populations

- Intent-to-Treat (ITT) Population: Defined as of all subjects who were enrolled into the study and received any amount of the IMP. This population was used for display of demographics, disposition, and for the primary safety and efficacy analyses.
- Per Protocol (PP) Population: Defined as of all subjects in the ITT population who completed the whole 12-month study period and who did not have any major protocol violations which are likely to have an impact on the validity of the data for analysis.
- ITT2 Population: Defined as all subjects in the ITT population who were enrolled into study following Protocol Version 2.0 amendment 1 (March 16, 2017) onwards. The rationale for the ITT2 population was as follows: Canadian subjects were initially enrolled under protocol Version 1.0, Amendment 3, dated March 24, 2016. As per FDA request, additional safety measures (including longer post-infusion observation times, two additional safety visits (72 hours after the end of Infusions 1 and 2), and stopping rules for IMP administration and for the study) were added to the protocol (Version 2.0, Amendment 1).

Statistical Methods

Analysis of Primary Efficacy Endpoint:

The rate of validated SBIs and the 99% upper confidence limit for the validated SBI rate was calculated using a Poisson regression model accounting for the length of the observation periods per subject. SAS PROC GENMOD was used to fit this model, assuming the Poisson distribution for the number of SBIs with the logarithm as link function. The model included the natural logarithm of the length of the observation period in years as an offset to account for the different lengths of the observation periods per subject.

Analyses of Secondary Efficacy Endpoints:

Confidence intervals were calculated at the two-sided 95% level of confidence. Rates of infection, days on antibiotics, off work/school/daily activity, hospitalizations, and acute physician visits were calculated using a Poisson regression model accounting for observation time and are presented as point estimates and 95% confidence intervals.

Unless stated otherwise, the term “descriptive statistics” referred to number of subjects (n), mean, median, standard deviation (SD), minimum and maximum for continuous data and frequencies and percentages for categorical data.

Analyses of Safety Endpoints: Descriptive statistics were used for the analysis of safety for two treatment groups combined and separately. The upper one-sided 95% confidence limit of observed proportion of infusions with TAAEs for combined treatment groups was calculated using a logistic regression model.

Handling of Dropouts or Missing Data:

No imputation of missing data for early terminations was performed. Different lengths of observation were accounted for in the Poisson regression model via an offset.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Seventy-three subjects were screened (47 in the USA, and 26 in Canada). Of the 73 subjects screened, 49 subjects (36 in the USA, and 13 in Canada) were enrolled in the study and received at least one dose of IMP.

6.1.10.1.1 Demographics

The study population was predominantly White (95.9%) and non-Hispanic (91.8%), with males representing 57.1% of the population. The age range was between 3 and 70 years, with a mean of 37.1 years (see Table 1).

Table 1. Summary of Demographic Characteristics, ITT Population

	28-day Infusion (N=29)	21-day Infusion (N=20)	Total (N=49)
Age in Years (at screening)			
n (missing)	29 (0)	20 (0)	49 (0)
Mean (SD)	41.5 (21.65)	30.7 (23.23)	37.1 (22.72)
Median	46.0	18.5	38.0
Min, Max	7, 70	3, 69	3, 70
Age group, n (%)			
>= 2 to < 12 years	4 (13.8)	4 (20.0)	8 (16.3)
>= 12 to < 17 years	2 (6.9)	6 (30.0)	8 (16.3)
>= 17 years	23 (79.3)	10 (50.0)	33 (67.3)
Sex, n (%)			
Male	16 (55.2)	12 (60.0)	28 (57.1)
Female	13 (44.8)	8 (40.0)	21 (42.9)
Ethnicity, n (%)			
Hispanic/Latino	2 (6.9)	2 (10.0)	4 (8.2)
Not Hispanic/Latino	27 (93.1)	18 (90.0)	45 (91.8)
Not reported/Unknown	0	0	0
Race, n (%)			
White	28 (96.6)	19 (95.0)	47 (95.9)
Black or African American	0	0	0
Asian	0	0	0
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Other	1 (3.4)	1 (5.0)	2 (4.1)
Geographic region			
United States	18 (62.1)	18 (90.0)	36 (73.5)
Non-United States	11 (37.9)	2 (10.0)	13 (26.5)

Source: "125743, Module 5.3.5.1 Clinical Study Report GC5107B_P3, Study Report Body Chapter, Table 11-3.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

All enrolled subjects had a history of at least one prior medical condition apart from the underlying disease. The most commonly reported (frequency $\geq 50\%$) prior medical conditions/disorders by MedDRA System Organ Class (SOC) were respiratory, thoracic and mediastinal disorders (40 subjects, 81.6%), followed by infections and infestations (33 subjects, 67.3%), gastrointestinal disorders (29 subjects, 59.2%), and skin and subcutaneous tissue disorders (25 subjects, 51.0%). The most commonly reported (frequency $\geq 20\%$) prior medical conditions/disorders by MedDRA PT were asthma (23 subjects, 46.9%), hypertension (17 subjects, 34.7%), gastroesophageal reflux disease, procedural headache, rhinitis allergic (13 subjects, 26.5% each), drug hypersensitivity (12 subjects, 24.5%), chronic sinusitis, eczema, and depression (11 subjects, 22.4% each).

The mean disease duration since first lifetime IGIV infusion was approximately 8.77 years. All subjects had been receiving IGIV infusions at regular 21- or 28-day intervals prior to enrollment, at a dose level between 319 and 826 mg/kg (mean 538.5 mg/kg). The mean IGIV dose was lower among subjects treated at the 28-day vs. the 21-day schedule (501.2 vs. 592.7 mg/kg, respectively). Trough IgG levels during most recent IGIV therapy prior to enrollment were above 500 mg/dL in all subjects (range between 521 and 1286 mg/dL), with no notable differences between the two infusion schedules (see Table 2 for details).

Table 2. Relevant Disease Characteristics at Baseline, ITT Population

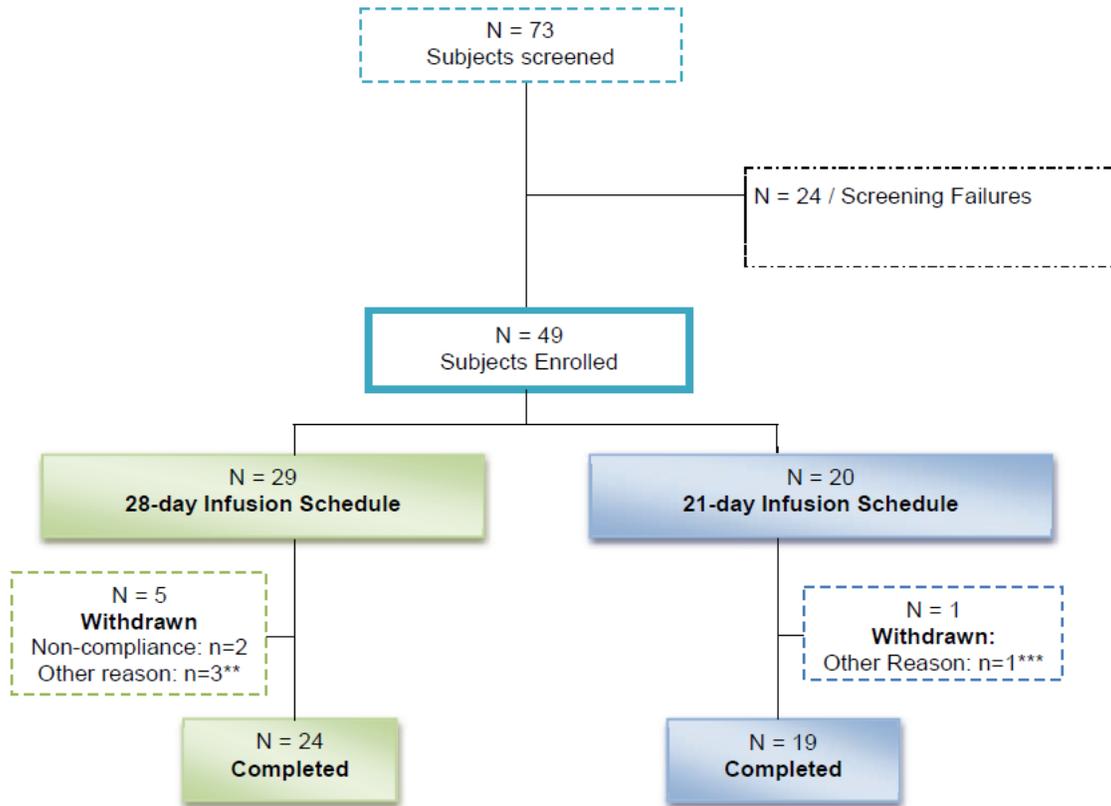
	28-day Infusion (N=29)	21-day Infusion (N=20)	Total (N=49)
Duration Since First Lifetime IGIV Infusion (years) [1]			
n (missing)	28 (1)	20 (0)	48 (1)
Mean (SD)	8.78 (8.328)	8.75 (6.675)	8.77 (7.606)
Median	7.05	9.25	8.45
Min, Max	0.2, 27.3	0.1, 18.8	0.1, 27.3
IGIV Dose Level Prior to Study Enrollment (mg/kg)			
n (missing)	29 (0)	20 (0)	49 (0)
Mean (SD)	501.2 (94.04)	592.7 (135.88)	538.5 (120.55)
Median	497.0	572.5	520.0
Min, Max	319, 693	324, 826	319, 826
IgG Level Prior to First Lifetime IGIV Infusion (mg/dL)			
n (missing)	23 (6)	17 (3)	40 (9)
Mean (SD)	393.6 (166.80)	335.4 (202.33)	368.9 (182.59)
Median	457.0	329.0	394.0
Min, Max	10, 628	6, 679	6, 679
Trough IgG Level at During Most Recent IGIV Therapy (mg/dL)			
n (missing)	29 (0)	20 (0)	49 (0)
Mean (SD)	930.0 (186.80)	941.7 (195.53)	934.8 (188.47)
Median	947.0	932.0	945.0
Min, Max	521, 1286	563, 1280	521, 1286

Source: "125743, Module 5.3.5.1 Clinical Study Report GC5107B_P3, Study Report Body Chapter, Table 11-4.

6.1.10.1.3 Subject Disposition

Of the 73 subjects screened, 49 subjects (36 in the USA, and 13 in Canada) were enrolled in the study and received at least one dose of IMP. Figure 1 presents subject disposition in study GC5107B_P3. The majority of subjects completed the study.

Figure 1. Disposition of Subjects



Source: “125743, Module 5.3.5.1 Clinical Study Report GC5107B_P3, Study Report Body Chapter, Figure 1”.

A total of six subjects (12.2%) discontinued the study prematurely, including five subjects treated according to the 28-day schedule, and one subject treated according to the 21-day schedule. All withdrawals occurred after the first dose of IMP. The reasons for withdrawal are summarized in Table 3.

Table 3. Reasons for Early Termination

Disposition/Reason	28-day Infusion n (%)	21-day Infusion n (%)	Total n (%)
Enrolled	29	20	49
Treated	29 (100.0)	20 (100.0)	49 (100.0)
Not Treated	0	0	0
Completed	24 (82.8)	19 (95.0)	43 (87.8)
Discontinued	5 (17.2)	1 (5.0)	6 (12.2)
Withdrawal after Enrollment but prior to First Infusion	0	0	0
Withdrawal after First Infusion	5 (17.2)	1 (5.0)	6 (12.2)
Primary Reason for Withdrawal after First Infusion			
Subject/Parent decision	0	0	0
Adverse Event	0	0	0
Protocol Violation	0	0	0
Non-compliance	2 (6.9)	0	2 (4.1)
Continued participation will pose a risk to the subject	0	0	0
Female became pregnant	0	0	0
Subject administered other IgG product after the first infusion of GC5107	0	0	0
Subject was administered hyperimmune serum	0	0	0
Other	3 (10.3)*	1 (5.0)**	4 (8.2)

Percentages are based on enrolled subjects.

Source: “125743, Module 5.3.5.1 Clinical Study Report GC5107B_P3, Study Report Body Chapter, Table 10-1”.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

In the ITT population of 49 subjects, a single primary endpoint event of acute SBIs (bacterial pneumonia) occurred during a cumulative total follow-up of 45.86 years resulting in an annualized rate of acute SBIs of 0.02 per subject per year (99% one-sided upper confidence limit: 0.21). In the 21-day schedule group of 20 subjects zero SBIs were observed. In the 28-day schedule group of 29 subjects (total follow-up: 26.24 years), the incidence of acute SBIs was 0.04 per subject per year (99% one-sided upper confidence limit: 0.35). The estimates were acquired using SAS PROC GENMOD Poisson regression.

A secondary (sensitivity) analysis of the primary efficacy endpoint was also conducted, assuming a Poisson distribution for the occurrence of primary endpoints and making use of the result that the square root transformation yields a variable that is approximately normally distributed with a standard deviation independent of the mean and approximately equal to 0.5. Sensitivity analyses of the primary endpoint in the ITT population yielded an overall incidence of acute SBIs of <0.01 per subject per year, with a 99% one-sided upper confidence limit of 0.01. Among subjects treated according to the 28-day schedule the incidence of acute SBIs was <0.01(upper confidence limit 0.02). In each of these analyses,

the 99% one-sided upper confidence limit for the incidence of acute SBIs remained far below 1 per subject per year.

In the PP population, the event of acute SBI (bacterial pneumonia in the 28-day schedule group) occurred during a cumulative total follow-up of 43.23 years, resulting in an incidence of acute SBIs of 0.02 per subject per year (99% one-sided upper confidence limit: 0.24).

In the ITT2 population, the event of acute SBI (bacterial pneumonia in the 28-day schedule group) occurred during a cumulative total follow-up of 36.71 years, resulting in an incidence of acute SBIs of 0.03 per subject per year (99% one-sided upper confidence limit: 0.27).

6.1.11.2 Analyses of Secondary Endpoints

The incidence of infections other than acute SBIs

In the ITT population, 38 out of 49 subjects (77.6%) experienced a total of 135 infections other than acute SBIs during a cumulative total follow-up of 45.86 years, resulting in a mean incidence (\pm SD) of 2.9 ± 2.47 infections per subject per year (range from 0 to 12.24 infections). The annual rate of infections other than acute SBIs was higher among subjects in the 21-day compared to the 28-day dosing group (mean 3.6 ± 2.91 vs 2.4 ± 1.93 infections per subject per year).

Incidence of infections other than acute serious bacterial infections by trough IgG levels

In the ITT population, the total group mean trough IgG Level was 775.2. The number of infection events other than acute SBIs in the group with trough IgG Level ≥ 775.2 was 78 vs. 57 in the group with trough IgG Level ≤ 775.2 . The mean infection rate per subject per year for the two groups are 3.3 (SD: 2.80) and 2.6 (SD:1.99), respectively.

Time to resolution of infections

In the ITT population, 38 subjects (77.6%) experienced a total of 136 infections (including one acute SBI and 135 other infections). The average durations of these infections ranged from approximately 3 days for pyrexia of unknown origin to approximately 30 days for bronchitis. Individual infections with a known start-and stop date and a maximum duration exceeding 30 days included scleritis (179 days), bronchiectasis (up to 100 days), bronchitis (up to 63 days), bacteriuria (up to 57 days), cellulitis (60 days), sinusitis (up to 47 days), otitis media (up to 46

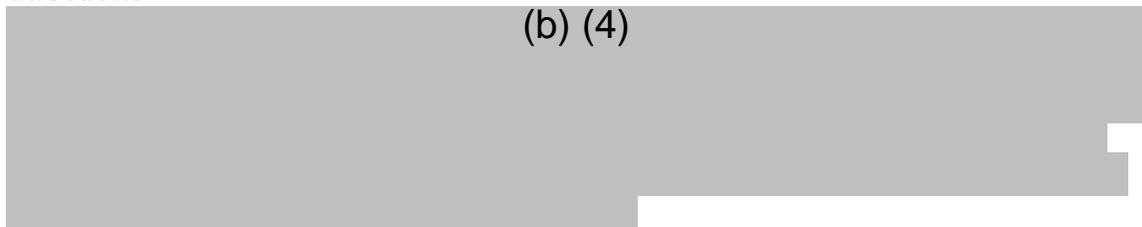
days), gastrointestinal viral infection (41 days), herpes zoster (34 days), and urinary tract infection (up to 31 days).

Number of Days Missed or Unable to Perform Daily Activities Due to Infections

In the ITT population, 25 subjects (51.0%) missed at least one day from work/school/daycare or were unable to perform normal daily activities due to infections. On average, subjects missed 7.1 ± 18.04 days (range, from 0 to 96 days) from work/school/daycare or were unable to perform normal daily activities due to infections during the study period.

Number of Days Missed by Care Providers of Pediatric Subjects Due to Infections

(b) (4)



Number of Days of Unscheduled Physician Visits Due to Infections

A total of 32 subjects (65.3%) in the ITT population had at least one day of unscheduled physician visits due to infections during their study participation. The mean number of days of unscheduled physician visits due to infections was 2.3 ± 3.75 days (range, from 0 to 24 days).

Number of Days of Hospitalizations Due to Infections

Two subjects (4.1%) required hospitalization due to an infection. The durations of these hospitalizations were three days (Subject (b) (6), 28-day infusion schedule; hospitalized for pneumonia bacterial) and two days (Subject (b) (6) 21-day infusion schedule; hospitalized for influenza).

Number of Days of IV Therapeutic Antibiotics

One subject (2.0%) received IV therapeutic antibiotics for a total of three days during his study participation (Subject (b) (6), 28-day infusion schedule; treated for pneumonia bacterial).

Number of Days of Oral Therapeutic Antibiotics

In the ITT population, a total of 29 subjects (59.2%) received oral therapeutic antibiotics during their study participation. The average number of days of oral therapeutic antibiotic use was 13.2 ± 22.09 (range from 0 to 127 days).

6.1.11.3 Subpopulation Analyses

Given that only one subject experienced acute SBIs in the study (bacterial pneumonia in an adult White male subject enrolled in the U.S.; 28-day infusion

schedule group), only one subgroup has an estimated incidence of acute SBIs in each demographic and geographic region category; in the remaining subgroups, the incidence of primary endpoint events was not estimable. For the demographic and regional subgroups that included the subject with acute SBIs, the 99% one-sided upper confidence limit for the incidence of acute SBIs remained below 1.0 per subject per year.

6.1.11.4 Dropouts and/or Discontinuations

Of the 49 enrolled subjects, six (12.2%) withdrew from the study prematurely, and 43 subjects (87.8%) completed the 12-month treatment period and subsequent follow-up assessments (24 subjects treated according to the 28-day schedule, and 19 subjects treated according to the 21-day schedule). All withdrawals occurred after the first dose of IMP. Withdrawals were not replaced. The analyses of annualized SBI rate were done per subject-year for all 49 subjects exposed to IMP and included an adjustment for length of time each subject was followed. Therefore, no imputation of missing data for early terminations was performed.

6.1.12 Safety Analyses

6.1.12.3 Deaths

There were no AEs leading to death or discontinuation from the study.

6.1.12.4 Nonfatal Serious Adverse Events

The percentage of subjects experiencing at least one treatment-emergent SAE was relatively low (8.2%) given the underlying disease, and importantly, none were attributed to the IMP. Serious infections occurred in two subjects (one in each infusion schedule group). Bacterial origin was confirmed in one of these cases (pneumonia bacterial in Subject (b) (6)) and this SAE also qualified as a primary efficacy endpoint event. The other serious infection was due to influenza (Subject (b) (6), 21-day infusion schedule).

6.1.12.5 Adverse Events of Special Interest (AESI)

In the total ITT population (N=49 subjects, 667 infusions), the proportion of infusions with TAAEs occurring during or within one hour after the infusion was 0.09 (95% one-sided upper confidence bound: 0.14), the proportion of infusions with TAAEs occurring during or within 24 hours after the infusion was 0.20 (95% one-sided upper confidence bound: 0.27), and the proportion of infusions with TAAEs occurring during or within 72 hours after the infusion was 0.24 (95% one-sided upper confidence bound: 0.31). Therefore, the primary safety objective to demonstrate that the percentage of infusions with one or more infusion-related AE was less than 40% was met.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

Of the 49 enrolled subjects, one subject in the 28-day schedule group had an acute serious bacterial infection (bacterial pneumonia). It occurred in the context of a cumulative total follow-up of 45.86 years, resulting in an annualized rate of acute SBIs of 0.02 per subject per year (99% one-sided upper confidence limit: 0.21). Among the 29 subjects treated according to the 28-day schedule (total follow-up: 26.24 years), the incidence of acute SBIs was 0.04 per subject per year (99% one-sided upper confidence limit: 0.35). In the 21-day schedule group zero SBIs were observed. Therefore, the study met the success criterion of the upper 99% confidence limit <1.

For the 49 subjects with 667 infusions, the proportion of infusions with TAAEs occurring during or within one hour, 24 hours, and 72 hours after the infusion were 0.09 (95% one-sided upper confidence bound: 0.14), 0.20 (95% one-sided upper confidence bound: 0.27), and 0.24 (95% one-sided upper confidence bound: 0.31), respectively. Therefore, the primary safety objective to demonstrate that the percentage of infusions with one or more infusion-related AE was less than 40% was met.

10.2 Conclusions and Recommendations

Study GC5107B_P3 met its primary efficacy objective by demonstrating that the upper one-sided 99% confidence limit for the rate of acute SBIs (bacterial pneumonia, bacteremia/sepsis, bacterial meningitis, visceral abscess, osteomyelitis/septic arthritis) was less than < 1.0 per subject per year in the population of subjects with PHID receiving GCC 10% IGIV infusions every 21 or 28 days for 12 months. The primary safety objective to demonstrate that the percentage of infusions with one or more infusion-related AE was less than 40% was also met. The statistical results of study GC5107B_P3 support the use of Immune Globulin Intravenous (Human) GC5107 for treatment of primary humoral immuno-deficiency (PI) in adults (b) (4)