# BLA Clinical Review Memorandum

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| Application Type | BLA |
| STN | 125743/0/68 |
| CBER Received Date | July 14, 2023 |
| PDUFA Goal Date | January 12, 2024 |
| Division / Office | DCEGM/OTP |
| Priority Review | No |
| Reviewer Name (BLA resubmission) | Elizabeth Sharpe, M.D. |
| Reviewer for Original BLA submission | Vijay Kumar, M.D. |
| Review Completion Date / Stamped Date | December 14, 2023 |
| Supervisory Concurrence | Shelby Elenburg, M.D.<br>Team Leader<br><br>Elizabeth Hart, M.D.<br>Branch Chief<br><br>Tejashri Purohit-Sheth, M.D.<br>Division Director |
| Applicant | Green Cross BioPharma |
| Established Name | GC5107 |
| (Proposed) Trade Name | Alyglo |
| Pharmacologic Class | Immune Globulin (Human) |
| Formulation(s), including Adjuvants, etc. | 10% Liquid |
| Dosage Form(s) and Route(s) of Administration | 300-800 mg/kg (of body weight)<br>Intravenous |
| Dosing Regimen | every 21 or every 28 days |
| Indication(s) and Intended Population(s) | Treatment of primary humoral immunodeficiency in adults |
| Orphan Designated | No |

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## GLOSSARY

| | |
|---|---|
| AE | Adverse Event |
| AR | adverse reaction |
| BIMO | Bioresearch Monitoring |
| BLA | Biologics License Application |
| BPCA | Best Pharmaceuticals for Children Act |
| CBER | Center for Biologics Evaluation and Research |
| CFR | Code of Federal Regulations |
| CI | Confidence Interval |
| CMC | chemistry, manufacturing, and controls |
| CSR | Clinical study report |
| CVID | common variable immunodeficiency |
| DCF | dosing conversion factor |
| eCRF | electronic case report form |
| eCTD | electronic Common Technical Document |
| FAS | full analysis set |
| GCP | Good Clinical Practice |
| GMC | Geometric Mean Concentration |
| GMT | Geometric Mean Titer |
| ICH | International Conference on Harmonization |
| IGIV | Immune Globulin Intravenous (Human) |
| IGSC | Immune Globulin Subcutaneous (Human) |
| ITT | Intent to Treat |
| MedDRA | Medical Dictionary for Regulatory Activities |
| PD | pharmacodynamics |
| PI | primary humoral immunodeficiency |
| PID | primary immunodeficiency |
| PK | pharmacokinetics |
| PMC | post marketing commitment |
| PT | preferred term (MedDRA) |
| QoL | Quality of life |
| SAE | serious adverse event |
| SAR | serious adverse reaction |
| SBI | serious bacterial infection |
| SC | subcutaneous |
| SOC | system organ class (MedDRA) |
| SS | safety analysis set |
| TEAE | treatment emergent adverse event |
| TEE | thromboembolic event |
| sBLA | Biologics License Application supplement |
| SD | Standard deviation |
| SOC | System Organ Class |
| USPI | United States Prescribing Information |
| XLA | X-linked agammaglobulinemia |

## 1. EXECUTIVE SUMMARY

ALYGLO (GC5107) 10% is an Immune Globulin Intravenous (IGIV) manufactured from pooled human plasma. GC Biopharma (formerly Green Cross Corporation) originally submitted a Biologics License Application (BLA) for GC5107 on February 25, 2021, for the treatment of primary humoral immunodeficiency (PI). As FDA was unable to determine whether the Ochang manufacturing establishment in South Korea was in compliance with regulations and BLA standards, FDA issued a complete response (CR) letter on February 25, 2022, noting the requirement of a pre-license inspection (PLI).

GC resubmitted this BLA on July 14, 2023 to STN125743/0/68 after a Complete Response (CR) Extension was granted on February 21, 2023. No new clinical data were provided, however, the Applicant submitted new analyses (b) (4)

PI is characterized by impaired B-cell immunity, and thus impaired ability to produce specific antibodies in response to pathogenic microorganisms. Thus, patients with PI are susceptible to recurrent, severe bacterial infections. The mainstay of treatment is lifelong maintenance administration of immunoglobulins (either intravenous [IGIV] or subcutaneous [IGSC]), to provide antibodies and prevent serious bacterial diseases.

The primary evidence of safety and effectiveness for this BLA comes from Study GC5107B_P3 which was a Phase 3, open label, single arm, historically controlled, prospective, multi-center study conducted in the US and Canada. The study enrolled 49 patients with PI who were on stable doses of immunoglobulin therapy, including 33 adults and 8 children. A total of 43 (88%) subjects completed the 12-month study; six subjects (12%) discontinued the study prematurely (5 were adults, 1 was adolescent). During the study, one adult experienced a SBI, bacterial pneumonia. The study met its primary endpoint of < 1 SBI per subject-year, which conforms to FDA Guidance and precedent for establishing efficacy of immunoglobulins for PI. The annualized SBI rate in adults was 0.03 SBI per subject-year, with an upper one-sided 99% confidence limit of 0.31.

Supportive efficacy data from the study include meaningful benefit as demonstrated by low rates of hospitalization due to infection, IV and oral therapeutic antibiotic use, missed work/school days, and unscheduled visits to physicians due to infection; the rates reported are generally comparable with rates reported for other IGIV products.

A PK sub-study in 27 subjects, including 22 adults supported the proposed dosing 300-800mg/kg every 21 or 28 days in adults. However, there were insufficient PK data to inform (b) (4) .

The safety of the product was similar to other IGIV products. No deaths or adverse events of special interest (anaphylactic shock, aseptic meningitis, hemolytic anemia/hemolysis, and acute renal failure) were observed during the study. The most common adverse reactions (ARs) noted in adults were headache (39%), nausea/vomiting (33%), fatigue (18%), nasal/sinus congestion (15%), rash (12%), arthralgia (9%), diarrhea (9%), and muscle pain/aches, infusion site pain/swelling, abdominal pain/discomfort, cough, and dizziness (6% each).

The Applicant provided substantial evidence from a single adequate and well controlled clinical trial with confirmatory evidence based on evidence from products in the same pharmacologic class. The clinical and clinical pharmacology data submitted from Study GC5107B_P3 support approval of ALYGO for the treatment of PI in adults, and the CMC issues have been adequately resolved. The proposed pharmacovigilance plan (PVP) that includes routine pharmacovigilance is acceptable to monitor post-marketing safety. In accordance with the Pediatric Research Equity Act (PREA) a PMR is being issued to assess the safety, efficacy, and PK in children 2 to <17 years.

### 1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Detailed demographics of the study population is presented in table 1.

**Table 1: GC5107_P3 Study Demographics**

| | 28-day Infusion (N=29) | 21-day Infusion (N=20) | Total (N=49) |
|---|---|---|---|
| Age in Years (at screening) (missing) | 29 (0) | 20 (0) | 49 (0) |
| Mean (SD) Age in Years (at screening) | 41.5 (21.6) | 30.7 (23.2) | 37.1 (22.7) |
| Median Age in Years (at screening) | 46.0 | 18.5 | 38.0 |
| Min, Max Age in Years (at screening) | 7, 70 | 3, 69 | 3, 70 |
| >= 2 to < 12 years age group, n (%) | 4 (13.8) | 4 (20.0) | 8 (16.3) |
| >= 12 to < 17 years age group, n (%) | 2 (6.9) | 6 (30.0) | 8 (16.3) |
| >= 17 years age group, n (%) | 23 (79.3) | 10 (50.0) | 33 (67.3) |
| Male Sex, n (%) | 16 (55.2) | 12 (60.0) | 28 (57.1) |
| Female Sex, n (%) | 13 (44.8) | 8 (40.0) | 21 (42.9) |
| White Race, n (%) | 28 (96.6) | 19 (95.0) | 47 (95.9) |
| Black or African American Race, n (%) | 0 | 0 | 0 |
| Asian Race, n (%) | 0 | 0 | 0 |
| American Indian or Alaska Native Race, n (%) | 0 | 0 | 0 |
| Native Hawaiian or Other Pacific Islander Race, n (%) | 0 | 0 | 0 |
| Other Race, n (%) | 1 (3.4) | 1 (5.0) | 2 (4.1) |
| Hispanic/Latino Ethnicity, n (%) | 2 (6.9) | 2 (10.0) | 4 (8.2) |
| Not Hispanic/Latino Ethnicity, n (%) | 27 (93.1) | 18 (90.0) | 45 (91.8) |
| Not reported/Unknown Ethnicity, n (%) | 0 | 0 | 0 |
| United States Geographic region, n (%) | 18 (62.1) | 18 (90.0) | 36 (73.5) |
| Non-United States Geographic region, n (%) | 11 (37.9) | 2 (10.0) | 13 (26.5) |
| Weight (kg) n (missing) | 29 (0) | 20 (0) | 49 (0) |
| Weight (kg) Mean (SD) | 69.7 (23.8) | 62.1 (27.3) | 66.6(24.9) |
| Weight (kg) Median | 70.5 | 64.7 | 67.3 |
| Weight (kg) Min, Max | 19.5, 138.0 | 15.1, 123.6 | 15.1, 138.0 |
| Height (cm) n (missing) | 29 (0) | 20 (0) | 49 (0) |
| Height (cm) Mean (SD) | 163.1 (15.5) | 157.17 (24.0) | 160.7 (19.4) |
| Height (cm) Median | 165.1 | 165.1 | 165.1 |
| Height (cm) Min, Max | 114.3, 185.0 | 102.0, 187.9 | 102.0, 187.9 |

Source: Reproduced from CSR-Table 14.1.5.1 (with modification to 1 decimal place)

***Reviewer Comment: There were mostly non-Hispanic white subjects enrolled in the study. The absence of other racial and ethnic groups is not concerning as ethnicity and race are not thought to influence outcomes in PI, and therefore, this imbalance does not rise to the level of a major review issue.***

### 1.2 Patient Experience Data

Published systematic reviews[1] describe the burden of disease for patients with PI and impact on activities of daily life due to recurrent infections. In the study GC5107B_P3, the Applicant collected data from subjects and their caregivers on number of days of school/work/daily activities missed due to infections. This data was captured in a diary and reviewed by investigator site staff as secondary efficacy endpoints deemed meaningful for patients with PI treated with IGIV.

Clinician reported outcomes (CROs) included infections other than SBIs, duration of infections, duration of antibiotic use, unscheduled physician visits / hospitalizations as secondary endpoints.

**Data Submitted in the Application**

| Check if Submitted | Type of Data | Section Where Discussed, if Applicable |
|---|---|---|
| ☒ | Patient-reported outcome | |
| ☒ | Observer-reported outcome | |
| ☒ | Clinician-reported outcome | |
| ☐ | Performance outcome | |
| ☐ | Patient-focused drug development meeting summary | |
| ☐ | FDA Patient Listening Session | |
| ☐ | Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel) | |
| ☐ | Observational survey studies | |
| ☐ | Natural history studies | |
| ☐ | Patient preference studies | |
| ☐ | Other: (please specify) | |
| ☐ | **If no patient experience data were submitted by Applicant, indicate here.** | |
| **Check if Considered** | **Type of Data** | **Section Where Discussed, if Applicable** |
| ☐ | Perspectives shared at patient stakeholder meeting | |
| ☐ | Patient-focused drug development meeting | |
| ☐ | FDA Patient Listening Session | |
| ☐ | Other stakeholder meeting summary report | |
| ☐ | Observational survey studies | |
| ☐ | Other: (please specify) | |

1 Song J, Zhang L, Li Y, Quan S, Liang Y, Zeng L, Liu Y. 20% subcutaneous immunoglobulin for patients with primary immunodeficiency diseases: A systematic review. Int Immunopharmacol. 2015 Apr;25(2):457-64.

## 2. CLINICAL AND REGULATORY BACKGROUND

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

Primary immunodeficiency (PID) is a heterogenous group of disorders, resulting from inborn errors of immunity, with an estimated overall prevalence in the United States of approximately 1 in 1200 live births, with the exception of immunoglobulin A (IgA) deficiency, which occurs in approximately 1 in 200 to 1 in 500 persons. Primary immunodeficiencies are broadly classified based on the component of the immune system that is primarily disrupted. Disorders of the adaptive immune system include B-cell (humoral) immune deficiencies (also referred to as antibody deficiencies), T-cell (cellular) immune deficiencies, and combined (B-cell and T-cell) immunodeficiencies.

Primary humoral immunodeficiency (PI) is a form of PID that is characterized by impaired B-cell immunity, and thus, impaired ability to produce specific antibodies in response to pathogenic microorganisms and increased susceptibility to infections. The major antibody deficiency syndromes of clinical significance include Common Variable Immunodeficiency (CVID), Severe Combined Immunodeficiency (SCID), X-linked agammaglobulinemia (XLA), Wiskott-Aldrich Syndrome, Hyper IgM Syndrome, Chronic Granulomatous Disease (CGD), and IgG subclass deficiency. Patients with PI are at increased risk for recurrent, severe respiratory tract and other infections (both viral and encapsulated bacterial in origin). Symptoms can be severe and can lead to substantial morbidity. Subjects with PI have day to day personal life disruptions with unscheduled physician office visits and hospital admissions. At present, most primary immunodeficiencies are not curable, though hematopoietic cell transplantation may be curative for some patients. Ongoing clinical trials are exploring safety and efficacy of gene therapy for different syndromes of PI. Replacement therapy with immunoglobulins provides antibodies to help prevent viral and bacterial diseases and remains the mainstay of treatment.

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

The general management of PI involves preventing and treating infections. Prevention of infections consists of avoidance measures, age-appropriate vaccination, prophylactic antibiotics, and lifelong maintenance immune globulin therapy. Treatment of infections often involves prolonged treatment courses of broad-spectrum antimicrobials.

### 2.3 Safety and Efficacy of Pharmacologically Related Products

The FDA Guidance for Industry: “Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency” (hereinafter referred to as the FDA Guidance for IG products) states that a statistical demonstration of a serious bacterial infection (SBI) rate per person-year of less than 1.0 is adequate to provide substantial evidence of effectiveness to support licensure.

Several immune globulin products (both intravenously and subcutaneously administered) have been licensed based on demonstration of a SBI rate of less than 1.0 per person-year. There are currently several licensed (Human) Immune Globulin Intravenous (IGIV) products in the U.S. indicated to treat PI: Asceniv (ADMA Biologics, Inc.), Bivigam (Biotest Pharmaceuticals Corporation), Carimune (CSL Behring AG),

Flebogamma DIF 5% and 10% (Instituto Grifols), Gammagard and Gammagard S/D (Baxter HealthCare Corp), Gammaked (Kedrion Biopharma), Gammaplex 5% & 10% (Bio Products Laboratory), and Panzyga (Octapharma Pharmazeutika Produktionsges), Privigen (CSL Behring AG).

The safety profile for immune globulins as a class is well-established. The incidence of adverse reactions (AR) reported in clinical studies supporting licensure varies according to the product, route of administration, and maximum infusion rate. Severe hypersensitivity reactions may occur with IGIV products. Common ARs for intravenously administered immune globulins typically include headache, fatigue, nausea, diarrhea, vomiting, and/or pyrexia. Immune Globulin Intravenous (Human) as a drug class carries an obligate boxed warning for thrombosis, renal dysfunction, and acute renal failure. Other rare risks associated with the use of IGIV include transmission of infectious agents (e.g., viruses), hemolysis, aseptic meningitis, transfusion associated lung injury (TRALI), hyperproteinemia and increased viscosity.

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

The current clinical study is the first evaluation of GC5107 in humans. The product GC5107 has not been licensed / marketed in any country for treatment of PI. However, a similar product manufactured by the applicant using (b) (4) Source Plasma is marketed in S Korea for treatment of Chronic Immune Thrombocytopenic Purpura (ITP) and Chronic Inflammatory Demyelinating Polyneuropathy (CIDP).

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

| Date | Item |
|---|---|
| January 31, 2017 | The Sponsor (named Green Cross Corporation at that time) submitted IND 16897 to conduct “An Open-Label, Single-Arm, Historically Controlled, Prospective, Multicenter Phase III Study to Evaluate the Safety, Efficacy and Pharmacokinetics of Immune Globulin Intravenous (Human) GC5107 in Subjects with Primary Humoral Immunodeficiency |
| March 02, 2017 | Teleconference placing the IND on Clinical Hold |
| March 31, 2017 | IND placed on Clinical Hold because “The IND does not contain sufficient information required under 21 CFR 312.23 to assess the risks to subjects of the proposed studies (21 CFR 312.42(b)(1)(iv)).” The Sponsor was asked to submit pausing/ study stopping rules, specify duration of monitoring for adverse events post infusion. |
| April 11, 2017 | Sponsor satisfactorily addressed all clinical hold issues identified and FDA lifted the clinical hold and allowed study to proceed. |
| October 31, 2017 | FDA corresponded agreement on the final initial Pediatric Study Plan (iPSP) submitted on August 22, 2017. |
| June 16th 2020 | Pre -BLA Meeting written response: FDA agreed with the planned waiver for pediatric patients <2 years of age.<br>FDA notified the applicant that proposed changes to the pediatric study needs to be reviewed by FDA’s Pediatric Review Committee (PeRC). |

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| | Additionally, FDA reminded the applicant that the absence of an agreed initial pediatric study plan (iPSP) can be a filing issue at the time of BLA submission. |
| October 06, 2020 | FDA communicated Non-Agreement on the Amended Agreed Initial Pediatric Study Plan (Amended Agreed iPSP-submitted on July 13, 2020) due to issues related to Pharmacokinetic endpoints and assessment schedules |
| November 23, 2020 | Applicant submitted revised iPSP Plan |
| February 09, 2021 | After discussion with PeRC, a letter acknowledging the amended agreed initial pediatric study plan (iPSP) to cover the age group (≥2 to <12 years) was sent on February 09, 2021. The revised agreement required a separate pediatric study (at least 12 children in age range ≥2 to <12 years) to be conducted under IND 16897 with estimated completion date of September 30, 2023. |
| February 25, 2021 | Applicant Green Cross Corporation submitted original BLA (125743) containing PK, efficacy, and safety data of the product GC5107 seeking indication for treatment of PI in subjects (b) (4) |
| August 03, 2021 | FDA sent Clinical Information Request #1 to submit information on PI qualifying diagnosis for all subject participants as required by eligibility criteria. Sponsor satisfactorily addressed on August 05, 2021. |
| November 17, 2021 | The application was presented before Pediatric Review Committee (PeRC). The PeRC agreed with division's recommendations to<br>1. Grant waiver of studies in Children < 2 years of age because studies are not practical.<br>2. Deferral of studies for the age group ≥ 2 years to <12 years according to Amended Agreed iPSP revised on February 4, 2021.<br>3. Requirement for new study in the age group ≥ 12 years to < 17 years because the PK data in the submitted study were insufficient to make safety or efficacy conclusions. |
| November 30, 2021 | Clinical and Clinical Pharmacology Reviewer communicated the deficiencies to the Applicant at the Late Cycle Meeting. Applicant was notified on the need to conduct another study in the age group ≥ 12 years to < 17 years to collect PK, safety, efficacy data to satisfy Pediatric Research Act – Post Marketing Requirements (PREA-PMR). |
| February 25, 2022 | FDA sent complete response letter (CRL) to the applicant. The letter states that because CBER was unable to determine that the Ochang establishment complies with the standards established in the BLA and the requirements prescribed in the applicable regulations, a pre-license inspection (PLI) of the Ochang establishment would be necessary to support approval. FDA informed the applicant that if the application is approved, the applicant will be required to conduct post-market studies to assess PK and 12-month safety and efficacy data in patients aged ≥ 12 to < 17 years of age, in addition to the pediatric study |

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|---|---|
| | in the Amended Agreed iPSP evaluating PK, safety, and efficacy of ALYGLO in at least 6 children aged ≥ 2 to < 6 years and at least 6 subjects ages ≥ 6 to < 12 years. |
| April 20, 2022 | Applicant submitted revised pediatric protocol to IND 16897 to include subjects aged ≥ 12 to <17 years |
| February 21, 2023 | FDA granted an extension for the Sponsor to resubmit the application by February 25, 2024. |
| July 14, 2023 | The applicant resubmitted the BLA, for Immune Globulin Intravenous (Human), 10% Liquid, Alyglo for the treatment of primary humoral immunodeficiency. As requested in the CRL, the submission included an amended plan for pediatric study. The applicant proposed to enroll the recommended number of additional adolescents in the on-going study that previously included only children aged ≥ 2 to < 12 years, and to delay the final study report due date to November 2026 from September 2023. |
| August 18, 2023 | In response to a clinical information request, the applicant submitted details regarding current enrollment in the pediatric study and confirmed intent to comply with U.S. regulations if the applicant opens pediatric study sites outside the U.S. (OUS). |
| November 15, 2023 | FDA requested more information about an adult subject who experienced pneumonia that was not recorded as a bacterial pneumonia. In response, the Applicant submitted justification for why the Investigator assessed the case as a viral pneumonia and thus did not fit the definition of SBI. |
| November 28, 2023 | The BIMO team notified the clinical and statistical teams that inspection revealed diary entries documenting unscheduled physician visits and missed work that was not included in the data sets or analysis for secondary endpoints. (See BIMO audit summary below.) |

Source: Table Adapted from original table in BLA Review Memo.

## 3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

### 3.1 Submission Quality and Completeness

The submission was sufficiently organized and integrated to accommodate the conduct of a complete clinical review. It was submitted electronically and formatted as an electronic Common Technical Document (eCTD) according to the FDA Guidance for Electronic Submissions. The submission contained the five modules in the common technical document structure.

### 3.2 Compliance With Good Clinical Practices And Submission Integrity

The applicant reported that the study was conducted in accordance with the guidelines of the Declaration of Helsinki on biomedical research involving human subjects and in accordance with International Conference for Harmonization (ICH): Good Clinical Practice (GCP) guidelines, European Union (EU) Directives 2001/20/EC and 2005/28/EC and the US FDA Title 21 CFR, as well as the demands of national drug and data protection laws, other applicable regulatory requirements, and any new directives or regulations that became enforceable during the course of the study.

The applicant reported that 3 major protocol deviations occurred during the study. All 3 of the deviations occurred in subjects in the 28-day infusion schedule group.

**Table 3: Summary of Major Protocol Deviations**

| Nature of Deviation | Subject ID | Additional Comments |
|---|---|---|
| Inclusion/Exclusion Criteria | (b) (6) | Subject enrolled and received 2 infusions while being worked up for Malignant Melanoma in deviation from the exclusion criterion: "Subject has a history of a malignant disease, other than properly treated carcinoma in situ of the cervix or basal cell or squamous cell carcinoma of the skin within 24 months prior to enrollment." |
| Procedure / Tests | (b) (6) | HIV-1 RNA test results were not available prior to enrollment due to insufficient sample volume |
| Procedure/ Tests | (b) (6) | HCV RNA test results were not available prior to enrollment due to insufficient sample volume |

Source: Clinical review memo from Original BLA submission, Adapted from CSR Table 10.2- Summary of Major Protocol Deviations

Subjects (b) (6) and (b) (6) were negative for HIV and HCV RNA tests – 2 and 4 weeks after 1st infusion, respectively. Subject (b) (6) was excluded from the study on the day of 2nd infusion, after receipt of pathology report confirming Melanoma.

***Reviewer Comments:***
***These protocol deviations did not affect the interpretability of safety or efficacy for this study.***

**BIMO Audit summary**

Three sites were selected based on previous inspectional history, geographic location, and the data submitted in the BLA.

Per initial BIMO Review *"The inspections verified the data reported in the BLA, including but not limited to subject eligibility, protocol deviations, IGIV infusion including any interruptions, serious bacterial infections, and adverse events for the subjects enrolled at the inspected clinical sites. No Form FDA 483s were issued for the three inspected study sites. No administrative follow-up is warranted at this time from BIMO for the inspected clinical investigators."*

During review of the BLA re-submission, the BIMO team notified the clinical and statistical teams that inspection revealed diary entries documenting unscheduled physician visits and missed work that was not included in the data sets or analysis for secondary endpoints. Clinical team review revealed that the data from the diaries that were not included in the data set / secondary endpoint analysis were either documented to be NOT due to infection or were not specified as being due to infection. Because adding the data would not affect secondary endpoint analysis, FDA did not ask the Applicant to include the missing data.

### 3.3 Financial Disclosures

| **Covered clinical study** (**GC5107_P3**): |
|---|
| Was a list of clinical investigators provided? ☒ Yes ☐ No |
| Total number of investigators identified: 64<br>(22-Principal Investigators and 42-Sub Investigators) |
| Number of investigators who are sponsor employees (including both full-time and part-time employees): 0 |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1 |
| If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0<br>Significant payments of other sorts: 1<br>Proprietary interest in the product tested held by investigator: 0<br>Significant equity interest held by investigator in sponsor of covered study: 0<br>Is an attachment provided with details of the disclosable financial interests/arrangements? ☒ Yes ☐ No (Request details from applicant)<br>Is a description of the steps taken to minimize potential bias provided? ☒ Yes ☐ No (Request information from applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0<br>Is an attachment provided with the reason? ☐ Yes ☐ No (Request explanation from applicant) |

Richard L Wasserman, MD, PhD served as Principal Investigator at the study site Allergy Partners of North Texas Research. He received retainer for ongoing consultation with the Sponsor regarding the performance of the clinical study. He completed Form FDA 3455 and disclosed potential conflicts, which were managed by delegating subject consent and data collection to qualified study staff who had no such potential conflicts. (Source: Form FDA 3455)

***Reviewer Comments:***
***Reviewer considers the adopted conflict management approach as acceptable.***

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

### 4.1 Chemistry, Manufacturing, and Controls

The Investigational Product (GC5107-10% liquid) is a new IGIV product, composed of human immunoglobulin G (IgG), produced by Green Cross Corporation in Korea. GC5107 is manufactured from human plasma pooled from more than 1,000 healthy adult donors from the USA. The manufacturing process involves Cohn fractionation, purification through (b) (4) and column chromatography (to reduce the content of thrombogenic impurities, such as Coagulation factor Xia), virus inactivation (by solvent/detergent [S/D] processing), and virus removal (by fraction I+III precipitation and nanofiltration). Formulated as a solution, GC5107 contains 100 mg/mL IgG and 250 mM glycine and has a pH of 4.8. GC5017 10% contains 100 mg/mL protein, of which not less than ≥ 96% is human IgG (and ≤ 100 µg/mL of IgA) obtained from Human Source Plasma. The functional aspects of GC5107 are equivalent to immunoglobulin in human plasma, which enables effective replacement of human immunoglobulin. All plasma units used in the manufacture of GCC 10% Intravenous Immunoglobulin (IGIV) were tested and found to be negative for human hepatitis B surface antigen (HBsAg) and antibodies to human hepatitis C virus (anti-HCV) and human immunodeficiency virus type 1 and 2 (anti-HIV-1/2) as well as Nucleic Acid Testing (NAT) for HIV-1, HAV, HBV, and HCV (using FDA licensed assays).

### 4.2 Assay Validation

Please refer to the CMC review for details.

### 4.3 Nonclinical Pharmacology/Toxicology

Please refer to the nonclinical pharmacology/toxicology review for details. No non-clinical pharmacology/toxicology review issues were identified.

### 4.4 Clinical Pharmacology

The primary PK endpoints included (1) PK parameters for total IgG (assessed in the PK population); and (2) Trough serum total IgG levels before each infusion of GC5107 in all subjects (with the interval between infusions recorded). The IgG serum trough levels were consistently above the required threshold of 500 mg/dL in adults and the data support approval for PI in adults from a clinical pharmacology perspective.

***Reviewer Comment: This Clinical and Clinical Pharmacology reviewers determined in the original submission that the PK data submitted in the*** (b) (4) ***population are insufficient (missing PK parameters, inconsistent data, and outliers) to recommend approval of Alyglo in*** (b) (4) ***who are aged*** (b) (4) ***No new PK data were included in this re-submission.***

4.4.1 Mechanism of Action

IGIV is manufactured through fractionation of large volumes of plasma pooled from thousands of healthy donors and contain immune antibodies and physiologic autoantibodies. Immune antibodies reflect the immunologic experience of the donor population. Hence the antibodies contained in IGIV will provide protection against many

bacterial, viral, and other infectious agents. This fraction of IGIV preparations is useful for passive immunization as replacement therapy.

4.4.2 Human Pharmacodynamics (PD)

GC5107 contains primarily IgG antibodies and has a distribution of immunoglobulin subclasses closely proportional to that of native human plasma. Administration of GC 5107 increases recipients' IgG levels in a dose-dependent fashion.

4.4.3 Human Pharmacokinetics (PK)

Please refer to the clinical pharmacology review for details.

For all subjects: During treatment with GC5107, the range of mean trough IgG concentration was higher in the 21-day (762.7 mg/dL to 966.0 mg/dL) compared to the 28-day infusion schedule groups (708.3 and 768.1 mg/dL). Mean serum IgG half-life was 29.58 and 28.98 for the 28-day and 21-day infusion schedule groups, respectively in the current study. Mean AUC0-t was 10190 day*mg/dL for the 28-day treatment and 6852 day*mg/dL for the 21-day treatment.

For Adult Subjects: The pharmacokinetics (PK) of ALYGLO was assessed in 22 adults (aged ≥ 17 to 70 years; 10 males and 12 females) with primary humoral immunodeficiency. The administered dose of ALYGLO during the PK assessment ranged from 313 to 821 mg/kg every 3 or 4 weeks. Blood samples for the PK study were collected after the 5$^{th}$ infusion of ALYGLO at 0.5, 2, 24, 48 hours, and Days 4, 8, 15, 22 (for the 3-week schedule) and 29 (for the 4- week schedule) post-infusion. The mean half-life was 29.6 days, and the mean clearance (baseline uncorrected) was 1.7 mL/day/kg for 28-day day dosing regimen.

The IgG trough level was collected in the intention to treat (ITT) population and the proposed target steady state trough IgG was 500 mg/dL. The mean steady state trough total IgG concentrations ranged from 706 to 768 mg/dL for the 28-day dosing regimen.

***Reviewer Comment: These values are comparable to those reported in clinical trials of currently marketed IGIV products, where IgG half-life values ranged from 32 to 37 days (28-day infusion schedule) and from 20 to 34 days (21-day infusion schedule). As per the Clinical Pharmacology reviewer, overall, the clinical pharmacology data support the approval of the proposed dosing regimen of 300-800 mg/kg every 21 or 28-day infusion as replacement therapy in adults with primary humoral immunodeficiency.***

**4.5 Statistical**

The statistical reviewer reviewed the submitted data used to support the primary study endpoint analyses and no statistical concerns were identified. Please refer to the memo from the statistical reviewer.

### 4.6 Pharmacovigilance

The pharmacovigilance reviewer did not identify safety issues that would necessitate additional risk management measures beyond standard post-marketing pharmacovigilance.

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

### 5.1 Review Strategy

In the original BLA submission the clinical reviewer evaluated the clinical study report for Study GC5107B_P3; this BLA re-submission did not include additional clinical data. (b) (4), in addition to considering overall study data, the clinical, clinical pharmacology, and statistical teams re-analyzed relevant data to assess safety, efficacy, and PK in adults (b) (4). This review memo focuses on the re-analyses.

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

Documents Submitted by Applicant in Support of this BLA

- 1.3.4 Financial Certification and Disclosure
- 1.6.3: Correspondence Regarding Meetings
- 1.9.6: Other Correspondence Regarding Pediatric Exclusivity or Study Plan (includes the amended iPSP)
- 1.14.1: Draft Labeling
- 1.16: Risk Management Plan
- 1.18: Proprietary Names
- 2.5: Clinical Overview
- 5.2 Tabular Listing of Clinical Studies
- 5.3 Clinical Study Reports
- 5.4 Literature References

Information submitted during BLA re-submission review

- Responses to three information requests with supporting documentation

Documents from BIMO team sent to clinical and statistical teams for review:

- Four subject diaries
- Data table that includes which diary information was recorded in the data sets and thus included in data analysis.

## 5.3 Table of Studies/Clinical Trials

### Table 4: Table of Clinical Studies-GC5017

| Type of Study | Study Identifier | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dose Regimen; Route of Administration | Number of Subjects | Healthy Subjects or Diagnosis of Patients | Treatment Duration | Study status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| Efficacy | GC5107B_P 3 | **Overall Objective of Study GC5107B_P3:**<br>To assess the safety, efficacy, and PK of GCC 10% IGIV in subjects with PI.<br><br>**Primary Efficacy Objective:**<br>To evaluate the incidence of acute SBIs (bacterial pneumonia, bacteremia/sepsis, bacterial meningitis, visceral abscess, osteomyelitis/septic arthritis) meeting U.S. FDA guidance criteria.<br>**Primary Safety Objective:**<br>To document the proportion of infusions with temporally associated adverse events (AEs), defined as AEs that occurred during or within 1 hour, 24 hours and 72 hours following an infusion of the Investigational Medicinal Product (IMP); including AEs that were determined to be unrelated to the product.<br>**Primary PK Objectives:**<br>To assess<br>• the PK parameters for total IgG (assessed in the PK population)<br>• Trough serum total IgG levels before each infusion of GCC 10% IGIV in all subjects, with the interval between infusions recorded. | Open label, single arm, historically controlled, prospective, multicenter study | GCC 10% IGIV is a liquid immune globulin intravenous (IGIV) product that contains 100 mg/mL of human IgG and 18.8 mg/mL of glycine.<br>.<br>GCC 10% IGIV is administered IV infusion 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 | A total of 49 subjects (including 33 adults) were enrolled. | Patients with a confirmed clinical diagnosis of a PI (as defined by the IUIS criteria). | 12 Months | Completed; Full Report |

Abbreviation: AE: adverse events, IgG: Immunoglobulin G, IGIV: Immune globulin intravenous, IMP: investigational medicinal product, IUIS: international union of immunological Societies, IV: Intravenous, PK: pharmacokinetics, SBIs: Serious Bacterial Infection
Reproduced from Table 5.2-1 Source: Applicant's document Tabular listing of All Clinical Studies

## 5.4 Consultations

5.4.1 Advisory Committee Meeting (if applicable)

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

5.4.2 External Consults/Collaborations

No external consultations were needed or obtained for the Clinical Review of this application.

## 5.5 Literature Reviewed

Primary immunodeficiency diseases. Report of an IUIS Scientific Committee. 3-. Clin Exp Immunol. 1999 Oct;118 Suppl 1(Suppl 1):1-28.

Modell V, Orange J, Quinn J, et al. Global report on primary immunodeficiencies: 2018 update from the Jeffrey Modell Centers Network on disease classification, regional trends, treatment modalities, and physician reported outcomes. Immunol Res. 2018; 66:367-380

Bonagura VR. Using intravenous immunoglobulin (IVIG) to treat patients with primary immune deficiency disease. J Clin Immunol. 2013 Jan;33 Suppl 2: S90-4.

Shapiro RS, Wasserman RL, Bonagura V, Gupta S. Emerging Paradigm of Primary Immunodeficiency Disease: Individualizing Immunoglobulin Dose and Delivery to Enhance Outcomes. J Clin Immunol. 2017 Feb;37(2):190-196.

Song J, Zhang L, Li Y, Quan S, Liang Y, Zeng L, Liu Y. 20% subcutaneous immunoglobulin for patients with primary immunodeficiency diseases: A systematic review. Int Immunopharmacology. 2015 Apr;25(2):457-64.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

## 6.1 Trial #1 (of 1)

An Open-Label, Single-Arm, Historically Controlled, Prospective, Multicenter Phase III Study to Evaluate the Safety, Efficacy and Pharmacokinetics of Immune Globulin Intravenous (Human) GC5107 in Subjects with Primary Humoral Immunodeficiency. The study was conducted in USA and Canada from (b) (6) (first subject first visit; Subject (b) (6)) to (b) (6) (last subject follow-up; Subject (b) (6)).

6.1.1 Objectives (Primary, Secondary)

The main objectives of this study were to assess the safety, efficacy, and pharmacokinetics (PK) of GC5107 in subjects with Primary Humoral Immunodeficiency (PI).

The primary efficacy objective was to evaluate the incidence of acute serious bacterial infections (SBIs; bacterial pneumonia, bacteremia/sepsis, bacterial meningitis, visceral abscess, osteomyelitis/septic arthritis) meeting U.S. Food and Drug Administration

(FDA) guidance criteria (FDA/CBER, 2008). The implicit control for efficacy is the expected rate of at least 1 serious bacterial infection per patient year in the affected population. The available literature suggests that prior to the routine institution of immunoglobulin replacement therapy, patients with hypogammaglobulinemia and agammaglobulinemia due to primary humoral immunodeficiency experienced approximately four or more serious acute bacterial infections per year[2].

**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 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
- the incidence of infections other than serious bacterial infections and their correlation with trough IgG levels.

**The primary safety objective** of the study was to document the proportion of infusions with temporally associated adverse events (AEs), defined as events that occurred during or within 1 hour, 24 hours and 72 hours following an infusion of the investigational product (including AEs that were determined to be unrelated to the product).

**Secondary safety objectives** were to document and assess the following safety parameters:

- overall incidence of all AEs that occurred during or within 1 hour, 24 hours, and 72 hours following an infusion of investigational product (regardless of the causal relationship)
- frequency of all AEs occurring during the study (regardless of the causal relationship)
- frequency of suspected adverse reactions (defined as AEs classified either by the investigator or sponsor as at least possibly related to GC5107)
- proportion of AEs considered by the investigator to be GC5107-related.
- number and proportion of GC5107 infusions during which the infusion rate was decreased due to AEs
- changes in vital signs, physical examination, and laboratory results; and
- viral safety (freedom from transmission of blood borne viral diseases, including HIV-1&2, HAV, HBV, HCV, and parvovirus B19)

**The primary PK objectives** were to assess

- PK parameters for total immunoglobulin G (IgG) (assessed in the PK population); and
- trough serum total IgG levels before each infusion of GC5107 in all subjects, with the interval between infusions recorded

[2] BRUTON OC. Agammaglobulinemia. Pediatrics. 1952 Jun;9(6):722-8. PMID: 14929630.

**Secondary PK objectives** were to assess:

- PK parameters of IgG subclasses (assessed in the PK population)
- trough serum level of IgG subclasses and specific IgG antibodies before Infusions 1, 5, 9, 13 (for subjects treated according to the 28-day infusion schedule) or Infusions 1, 5, 11, 17 (for subjects treated according to the 21-day infusion schedule) for anti-Hemophilus influenzae type b, anti-Streptococcus pneumoniae serotypes, anti-Tetanus toxoid, and anti-CMV
- the number and proportion of subjects who failed to meet the target IgG trough level (500 mg/dL) at any time point equal to or after 5th infusion (estimated 5 half-lives).

6.1.2 Design Overview

The study was an open-label, single-arm, historically controlled, prospective study that was conducted at multiple sites in US and Canada.

***Reviewer Comment:*** *The study was conducted according to the June 2008 FDA guidance titled, "Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency."*

6.1.3 Population

**Summary of the Inclusion Criteria:**
Eligible subjects:

- Age 2 to 70 years
- Confirmed clinical diagnosis of a PI [as defined by the International Union of Immunological Societies –(IUIS) criteria], documented agammaglobulinemia or hypogammaglobulinemia
- Must have received 300-900 mg/kg of a licensed IGIV therapy at 21- or 28-day intervals for at least three infusions prior to enrolling in this study
- At least two documented trough IgG levels of ≥ 500 mg/dL, obtained at two infusion cycles (21 or 28 days) within 12 months prior to study enrollment

***Reviewer Comment:***
***The inclusion criteria were typical for IGIV trials and were designed to select a population of subjects with PI that would be considered at average risk of developing of a serious bacterial infection. Specifically, subjects with and without previous history of SBI were included in the trial.***

***Subjects who previously participated in a clinical trial of an experimental IGIV treatment were eligible if they received stable IGIV therapy for at least 3 infusion cycles prior to the first infusion of GC5107, and all inclusion and exclusion criteria were satisfied. Subjects who previously participated in a clinical trial of subcutaneous immune globulin (IGSC) were eligible if they switched to IGIV for three infusion cycles (21 or 28 days) prior to enrollment in this study. Allowing subjects who had been in other clinical trials for IGIV previously is reasonable because the half-life of IGIV products is approximately 30 days and hence would not be expected to interfere with the results of the study.***

**Summary of the Exclusion Criteria:**
Subjects were excluded from the study if they had any of the following:

- Secondary immunodeficiency
- Newly diagnosed PI, previously untreated with immunoglobulin
- Dysgammaglobulinemia, isolated IgG subclass deficiency, or isolated IgA deficiency with known anti-IgA antibodies
- History of a severe reaction or hypersensitivity to IGIV or other injectable forms of IgG
- Lifetime history of any thrombotic event, protein losing enteropathy, nephrotic syndrome or lymphangiectasia
- Clinical signs or symptoms of an acute infection within 7 days prior to screening, known history of or testing positive at enrollment for human immunodeficiency virus (HIV) type 1 or 2 (by nucleic acid testing [NAT]), hepatitis B virus (HBV; HBsAg and NAT), hepatitis C virus (HCV; by NAT), or hepatitis A virus (HAV; by NAT)
- Profound anemia or persistent severe neutropenia, transaminases above 2.5 times the upper limit of normal (ULN)
- History of malignant disease within 24 months prior to enrolment
- History of epilepsy or migraines not completely controlled by medication
- Presence of a severe chronic or other condition precluding safe participation in the study, or likely to interfere with the evaluation of the investigational product

***Reviewer Comments:***

***Excluding subjects who were previously untreated with IGIV will reduce the numbers of subjects who cannot tolerate IGIV and reduce the safety signals. It would be useful to study naïve subjects in clinical trials to gain a better understanding of the issues related to first time use and to inform labels regarding naïve patient dosing. However, this is not critical and may not be feasible as many diagnosed patients receive IGIV therapy and identifying a naïve population may be somewhat challenging.***

***Excluding subjects on steroids or receiving other blood products is reasonable because steroids could confound efficacy and safety results.***

6.1.4 Study Treatments or Agents Mandated by the Protocol

Eligible subjects received intravenous infusions of the study product, 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 ± 4 day or every 28 ± 4 day (depending on their pre-study IGIV treatment schedule) for 12 months of study infusions. Therefore, the total number of infusions was either 13 (28-day infusion schedule) or 17 (21-day infusion schedule). The dose regimen remained unchanged throughout the study period unless there was a medically justified need to change it.

The first infusion of GC5107 was started at an initial rate of 1.0 mg/kg/min (0.01 mL/kg/min) for 30 minutes. If well tolerated, after 30±5 minutes, the infusion rate was increased to 2.0 mg/kg/min (0.02 mL/kg/min). If well tolerated, the infusion rate was further increased to 4.0 mg/kg/min (0.04 mL/kg/min) at 60±5 minutes. If well tolerated, the infusion rate was increased to the maximum rate of 8.0 mg/kg/min (0.08 mL/kg/min) at 90±5 minutes and maintained at that rate until the infusion was completed. The second and all subsequent infusions of GC5107, if the first infusion was well tolerated, were started at an initial infusion rate of 2.0 mg/kg/min (0.02 mL/kg/min) and increased every 15±5 minutes to the maximum rate of 8.0 mg/kg/min (0.08 mL/kg/min).

***Reviewer Comments: The same rate of infusion was used irrespective of age. The lower average rates of infusion in children were by virtue of their lower weight.***

### 6.1.5 Directions for Use

The product was administered intravenously in one sitting. The tubing was flushed with saline or D5W solution at the end of the infusion to ensure that the entire dose was administered. All infusions were administered at study sites (see Section 6.1.6).

### 6.1.6 Sites and Centers

**Table 5: List of Principal Investigators and Investigative Sites with Recruitment Data**

| Site | Investigator | Institution | Subjects Screened (N=74) | Subjects Enrolled 28-Day Infusion (N=29) | Subjects Enrolled 21-Day Infusion (N=20) | Total Subjects Enrolled (N=49) |
|---|---|---|---|---|---|---|
| 02 | Dr. Stephen Betschel | Saint Michael's Hospital Toronto, Canada | 3 | 2 | 0 | 2 |
| 04 | Dr. Jacques Hébert | Clinique Spécialisée en Allergie Québec City, Canada | 7 | 5 | 0 | 5 |
| 05 | Dr. Elie Haddad | CHU Ste-Justine - University of Montreal, Canada | 2 | 0 | 0 | 0 |
| 07 | Dr. Gordon Sussman | Gordon Sussman Clinical Research Toronto, Canada | 3 | 1 | 0 | 1 |
| 08 | Dr. Anne Ellis | Queen's University - Kingston General Hospital (KGH), Kingston, Canada | 8 | 3 | 1 | 4 |
| 09 | Dr. Bruce Ritchie | University of Alberta Hospital Edmonton, Canada | 2 | 0 | 0 | 0 |
| 10 | Dr. Juthaporn Cowan | The Ottawa Hospital Ottawa, Canada | 1 | 0 | 1 | 1 |
| 20 | Dr. Oral Alpan | O & O Alpan, LLC Fairfax, VA, USA | 5 | 2 | 2 | 4 |
| 21 | Dr. Amy Darter | Oklahoma Institute of Allergy and Asthma Clinical Research, LLC Oklahoma City, OK, USA | 7 | 1 | 2 | 3 |
| 22 | Dr. William Lumry | AARA Research Center Dallas TX, USA | 3 | 3 | 0 | 3 |
| 23 | Dr. Donald McNeil | Optimed Research, LTD Columbus, OH USA | 5 | 2 | 2 | 4 |
| 24 | Dr. Isaac Melamed | IMMUNE International Research Centers Centennial, CO USA | 4 | 0 | 3 | 3 |

| Site | Investigator | Institution | Subjects Screened (N=74) | Subjects Enrolled 28-Day Infusion (N=29) | Subjects Enrolled 21-Day Infusion (N=20) | Total Subjects Enrolled (N=49) |
|---|---|---|---|---|---|---|
| 26 | Dr. Ralph Shapiro | Midwest Immunology Clinic Plymouth, MN 55446, USA | 5 | 0 | 3 | 3 |
| 27 | Dr. Elena Perez | Allergy Associates of the Palm Beaches North Palm Beach FL USA | 5 | 5 | 0 | 5 |
| 28 | Dr. Daniel Suez | Allergy, Asthma & Immunology Clinic Irving, TX USA | 6 | 3 | 2 | 5 |
| 29 | Dr. Richard Wasserman | Allergy Partners of North Texas Research, Dallas, TX 75043 | 1 | 0 | 1 | 1 |
| 30 | Dr. Fernado Mandujano | Pediatric Pulmonary Associates of North Texas, Frisco Texas | 6 | 2 | 3 | 5 |

Data Source: Original BLA review memo, adapted from Table 6.2, Page 38 of GC5107 CSR

***Reviewer Comment:***
***Most of the investigators were from United States, where 36 (out of 49) subjects enrolled at 10 (out of 15) sites.***

6.1.7 Surveillance/Monitoring

- The Applicant Green Cross Corporation (GCC), Korea, delegated site management and clinical monitoring responsibilities to (b) (4) the responsible clinical CRO in the USA, and to (b) (4) the responsible clinical CRO in Canada.
- Medical monitoring was delegated to (b) (4) for U.S. sites, and to (b) (4) for Canadian sites.
- (b) (4) also provided safety reporting, data management and statistical services including the design and implementation of the Statistical Analysis Plan (SAP) for the study.
- Authoring of the clinical study report (CSR) was delegated to (b) (4)
- Central laboratory testing (clinical and viral safety and pharmacokinetics [PK]) was delegated to (b) (4).
- The investigational medicinal product (IMP) was manufactured, packaged, and labelled by GCC. Local re-labeling (addition of kit numbers) and distribution was the responsibility of (b) (4) for U.S. sites, and (b) (4) for Canadian sites.
- A third-party Drug Safety Monitoring Board (DSMB) monitored the safety of study subjects on a periodic basis. The main responsibilities of the DSMB included: monitoring the safety of patients enrolled in this study, through scheduled review of accumulating clinical and safety data, alerting the applicant of any safety concerns, and making recommendations to the applicant regarding the continuation of the study.
    - 4 member DSMB was chaired by (b) (4). The other members were (b) (4)

- Members of the DSMB were independent of the study Sponsor (including designees) and participating sites.

Schedule of Subject Evaluations for the 28- and 21-day Infusion Schedules are shown in tables below.

**Table 6: Schedule of Subject Evaluations-28 Day Infusion Schedule**

A time window of ±4 days was allowed for every subject visit except screening.

| **Week No.** | **-** | **0** | **0** | **4** | **4** | **8** | **12** | **16** | **16** | **16** | **16** | **16** | **16** | **16** | **16** | **16** | **16** | **20** | **24** | **28** | **32** | **36** | **40** | **44** | **48** | **52** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Infusion No.** | **Screening** | **1** | **-** | **2** | **-** | **3** | **4** | **5** | **5** | **5** | **5** | **5** | **5** | **5** | **5** | **5** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **F/U** |
| **Day No. or hours (h) or minutes (min)** | **(-28 to -1)** | **D1** | **D4 (±1)** | **D1** | **D4 (±1)** | **-** | **-** | **Pre-30 min** | **D1** | **2h** | **24h** | **48h** | **D4** | **D8** | **D15** | **D22** | **D29** | **-** | **-** | **-** | **-** | **-** | **-** | **-** | **-** | **-** |
| Informed consent/PHI | X | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Med history, eligibility, demography | X | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Physical exam[1] | X | X | X | X | X | X | X | - | X | - | - | - | - | - | - | - | - | X | X | X | X | X | X | X | X | X |
| Chest x-ray[2] | X | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Viral safety[3] | X | - | - | - | - | - | X | - | - | - | - | - | - | - | - | - | - | - | X | - | - | - | - | - | - | X |
| Vital signs[4] | X | X | X | X | X | X | X | - | X | - | - | - | - | - | - | - | - | X | X | X | X | X | X | X | X | X |
| Concomitant medications | X | X | X | X | X | X | X | - | X | - | - | - | - | - | - | - | - | X | X | X | X | X | X | X | X | X |
| Blood chemistry[5] | X | X | X | X | X | X | X | - | X | - | - | - | - | - | - | - | - | X | X | X | X | X | X | X | X | X |
| Hematology[6] | X | X | X | X | X | X | X | - | X | - | - | - | - | - | - | - | - | X | X | X | X | X | X | X | X | X |
| Urinalysis[7] | X | X | X | X | X | X | X | - | X | - | - | - | - | - | - | - | - | X | X | X | X | X | X | X | X | X |
| Trough IgG[8] | X | X | - | X | - | X | X | - | X | - | - | - | - | - | - | - | - | X | X | X | X | X | X | X | X | X |
| IgG subclasses, specific antibodies[9] | - | X | - | - | - | - | - | - | X | - | - | - | - | - | - | - | - | - | - | - | X | - | - | - | X | - |
| Diary review | - | - | X | X | X | X | X | - | X | - | - | - | - | - | - | - | - | X | X | X | X | X | X | X | X | X |
| Adverse events | X | X | X | X | X | X | X | - | X | - | - | - | - | - | - | - | - | X | X | X | X | X | X | X | X | X |
| PK analysis[10] | - | - | - | - | - | - | - | X | X | X | X | X | X | X | X | X | X | - | - | - | - | - | - | - | - | - |
| DAT/Coombs Test[11] | X | X | X | - | - | - | - | - | - | - | - | - | - | - | - | - | - | X | - | - | - | - | - | - | X | - |
| Retention sample[12] | X | X | X | X | X | X | X | - | X | - | - | - | - | - | - | - | - | X | X | X | X | X | X | X | X | X |
| Serum pregnancy test | X | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Urine pregnancy test | - | X | - | X | - | X | X | - | X | - | - | - | - | - | - | - | - | X | X | X | X | X | X | X | X | X |

Source: Schedule of Assessments Table: Study Protocol -IND16897

1 Record weight, height, vital signs, and note abnormalities in any major organ system.

2 If baseline X-ray taken within last 6 months is not available.

3 Serology and NAT for HIV-1/2 (NAT for HIV-1 only), HCV, HBV; parvovirus B19 and HAV (Serology and NAT at screening; if negative, NAT thereafter).

4 All infusion vital signs will be recorded 10-15 minutes prior to infusion, 5 minutes before each infusion rate increase, 30 min after reaching the maximum infusion rate, every 60 minutes thereafter, upon completion of the infusion, and 60 minutes after completion of the infusion. All vital sign measurements have an allowable window of ± 5 minutes.

5 Blood Chemistry: Total bilirubin, creatinine, blood urea nitrogen (BUN), ALT, AST, alkaline phosphatase, lactate dehydrogenase (LDH), glucose, sodium, potassium, chloride, CO2, serum haptoglobin and calcium will be measured. Plasma-free hemoglobin: before the 1st infusion and safety visits.

6 Hematology: Hemoglobin, hematocrit, platelets, red blood cells (RBC), white blood cells (WBC) and differential counts. Reticulocyte count: before the 1st infusion and safety visits. If hemoglobin decreases by >1 g/dL from the baseline, follow-up labs will be performed and these tests include hematology including hemoglobin, total bilirubin, serum LDH, serum haptoglobin, plasma-free hemoglobin, and urine hemosiderin 2-5 days and 7-10 days after the infusion.

7 Urine samples will be obtained for routine analysis at screening, before every infusion, at safety visit, and at FU. All urinalyses will include microscopic urinalysis performed by the central laboratory. Urinalysis will include pregnancy testing before every infusion and FU. Urine hemosiderin: before the 1st infusion.

8 Obtained IgG trough level at the time of screening can be served as one of documented IgG trough levels.

9 Trough levels of IgG subclasses and specific antibodies. Testing at Infusion 1, 5, 9, and 13.

10 PK samples will be taken after the 5th study infusion as follows: at 30 min to 10 min before infusion, 30 min (± 5 min), 2 hours (± 15 min), 24 hours (± 2 hours), 48 hours (± 2 hours) of post infusion, and on Day4(± 12 hours), Day 8 (± 1 day), Day 15 (± 1 day), and Day 22(± 1 day) and Day29 (± 2 days).
11 Take blood samples before and after infusion.
12 Retention samples: 1 mL serum samples will be stored at –70oC at the central laboratory.
Abbreviations: D=day; DAT=Direct Antiglobulin Test; F/U=follow-up; h=hours; IgG=immunoglobulin G; min=minutes; PHI=Private Health Information; PK=pharmacokinetic; Pre=pre-infusion.

**Table 7: Schedule of Subject Evaluations-21 Day Infusion Schedule**

A time window of ±4 days was allowed for every subject visit except screening.

| **Week No.** | **-** | **0** | **0** | **3** | **3** | **6** | **9** | **12** | **12** | **12** | **12** | **12** | **12** | **12** | **12** | **12** | **15** | **18** | **21** | **24** | **27** | **30** | **33** | **36** | **39** | **42** | **45** | **48** | **51** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Infusion No.** | **Screening** | **1** | **-** | **2** | **-** | **3** | **4** | **5** | **5** | **5** | **5** | **5** | **5** | **5** | **5** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14** | **15** | **16** | **17** | **F/U** |
| **Day No., or hours (h) or minutes (min)** | **(-21 to -1 d)** | **D1** | **D4 (±1)** | **D1** | **D4 (±1)** | **-** | **-** | **Pre-30 min** | **D1** | **2h** | **24h** | **48 h** | **D4** | **D8** | **D15** | **D22** | **-** | **-** | **-** | **-** | **-** | **-** | **-** | **-** | **-** | **-** | **-** | **-** | **-** |
| Informed consent/PHI | X | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Med history, eligibility, demography | X | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Physical exam[1] | X | X | X | X | X | X | X | - | X | - | - | - | - | - | - | - | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Chest x-ray[2] | X | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Viral safety[3] | X | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | X | - | - | X | - | - | - | - | - | - | - | - | X |
| Vital signs[4] | X | X | X | X | X | X | X | - | X | - | - | - | - | - | - | - | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant medications | X | X | X | X | X | X | X | - | X | - | - | - | - | - | - | - | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Blood chemistry[5] | X | X | X | X | X | X | X | - | X | - | - | - | - | - | - | - | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Hematology[6] | X | X | X | X | X | X | X | - | X | - | - | - | - | - | - | - | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Urinalysis[7] | X | X | X | X | X | X | X | - | X | - | - | - | - | - | - | - | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Trough IgG[8] | X | X | - | X | - | X | X | - | X | - | - | - | - | - | - | - | X | X | X | X | X | X | X | X | X | X | X | X | X |
| IgG subclasses, specific antibodies[9] | - | X | - | - | - | - | - | - | X | - | - | - | - | - | - | - | - | - | - | - | - | X | - | - | - | - | - | X | - |
| Diary review | - | - | X | X | X | X | X | - | X | - | - | - | - | - | - | - | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Adverse events | X | X | X | X | X | X | X | - | X | - | - | - | - | - | - | - | X | X | X | X | X | X | X | X | X | X | X | X | X |
| PK analysis [10] | - | - | - | - | - | - | - | X | X | X | X | X | X | X | X | X | - | - | - | - | - | - | - | - | - | - | - | - | - |
| DAT/Coombs[11] | X | X | X | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | X | - | - | - | - | - | - | - | - | X | - |
| Retention sample[12] | X | X | X | X | X | X | X | - | X | - | - | - | - | - | - | - | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Serum pregnancy test | X | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Urine pregnancy test | - | X | - | X | - | X | X | - | X | - | - | - | - | - | - | - | X | X | X | X | X | X | X | X | X | X | X | X | X |

Source: Schedule of Assessments Table: Study Protocol -IND16897
1 Record weight, height, vital signs, and note abnormalities in any major organ system.
2 If baseline X-ray taken within last 6 months is not available.
3 Serology and NAT for HIV-1/2 (NAT for HIV-1 only), HCV, HBV; parvovirus B19 and HAV (Serology and NAT at screening; if negative, NAT thereafter).
4 All infusion vital signs will be recorded 10-15 minutes prior to infusion, 5 minutes before each infusion rate increase, 30 min after reaching the maximum infusion rate, every 60 minutes thereafter, upon completion of the infusion and 60 minutes after completion of the infusion. All vital sign measurements have an allowable window of ± 5 minutes.
5 Blood Chemistry: Total bilirubin, creatinine, blood urea nitrogen (BUN), ALT, AST, alkaline phosphatase, lactate dehydrogenase (LDH), glucose, sodium, potassium, chloride, CO2, serum haptoglobin and calcium will be measured. Plasma-free hemoglobin: before the 1st infusion and safety visits.

6 Hematology: Hemoglobin, hematocrit, platelets, red blood cells (RBC), white blood cells (WBC) and differential counts. Reticulocyte count: before the 1st infusion and safety visits. If hemoglobin decreases by >1 g/dL from the baseline, follow-up labs will be performed and these tests include hematology including hemoglobin, total bilirubin, serum LDH, serum haptoglobin, plasma-free hemoglobin, and urine hemosiderin 2-5 days and 7-10 days after the infusion.
7 Urine samples will be obtained for routine analysis at screening, before every infusion and at FU. All urinalyses will include microscopic urinalysis performed by the central laboratory. Urinalysis will include pregnancy testing before every infusion and FU. Urine hemosiderin: before the 1st infusion.
8 Obtained IgG trough level at the time of screening can be served as one of documented IGG trough levels
9 Trough levels of IgG subclasses and specific antibodies. Testing at Infusion 1, 5, 11, and 17.
10 PK samples will be taken after the 5th study infusion as follows: at 30 min to 10 min before infusion, 30 min (± 5 min), 2 hours (± 15 min), 24 hours (± 2 hours), 48 hours (± 2 hours) of post infusion, and on Day4(± 12 hours), Day 8 (± 1 day), Day15(± 1 day), and Day 22(± 1 day).
11 Take blood samples before and after infusion.
12 Retention samples: 1 mL serum samples will be stored at –70oC at the central laboratory. Source: Schedule of Assessments Table: Study Protocol -IND16897
Abbreviations: D=day; DAT=Direct Antiglobulin Test; F/U=follow-up; h=hours; IgG=immunoglobulin G; min=minutes; PHI=Private Health Information; PK=pharmacokinetic; Pre=pre-infusion.

6.1.8 Endpoints and Criteria for Study Success

EFFICACY ENDPOINTS:
Primary Efficacy Endpoint: The incidence of acute serious bacterial infections meeting Food and Drug Administration (FDA) guidance criteria (bacterial pneumonia, bacteremia/sepsis, bacterial meningitis, visceral abscess, osteomyelitis/septic arthritis) of <1 SBI / year.

Secondary Efficacy Endpoints (no testing order prespecified):
- The incidence of infections other than acute serious bacterial infections meeting FDA guidance criteria.
- 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 provider of the pediatric subject had to miss work to care for the child due to infections.
- The number days of unscheduled physician visits due to infections.
- The number of days of hospitalizations due to infections.
- The number of days of intravenous (IV) therapeutic antibiotics.

**Reviewer Comments:**

1. ***The primary efficacy endpoint conforms to the FDA guidance of < 1 SBI / patient / year as adequate to support licensure of Immunoglobulin for treatment of PI.***

2. ***The secondary efficacy endpoints were not ordered. The objective of the secondary endpoints was to collect patient experience data (patient/ care giver and clinician reported outcomes) required for licensure of biological products. They are descriptive statistics and there are no "win" criteria. Absence of ordering of the secondary endpoint testing does not affect the ability to interpret the conclusions of the data.***

3. ***For this BLA re-submission, the applicant proposed an indication of treatment of PI in*** (b) (4)

6.1.9 Statistical Considerations & Statistical Analysis Plan

This study was designed to establish the superiority of GC5107 compared with historically based rates of SBI in untreated individuals. All statistical outputs were produced using Statistical Analysis System (SAS®) version 9.4 in a secure and validated environment.

The null hypothesis was that the incidence of serious acute bacterial infections in subjects treated with GC5107 is greater than or equal to 1.0 per subject per year. The

alternative hypothesis is that the incidence of serious acute bacterial infections is less than 1.0 per subject per year. A one-sided test based on a generalized linear models' procedure for Poisson regression with α=0.01 was used to test this hypothesis. Confidence intervals were calculated at the two-sided 95% level of confidence except for the primary efficacy and safety endpoints which were one-sided 99% and 95% respectively.

All analyses and descriptive summaries were based on the observed data. Missing data were not imputed, except as specified. For analysis of the duration of hospitalization due to infections, the end dates of ongoing hospitalizations were imputed to the last visit date. For analyzing the duration of AEs during infusion, the infusion start time was used to impute the missing AE start time, and the last available time (23:59 pm) of AE stop date was used to impute the missing AE stop time.

***Reviewer Comment:***
***There were two treatment groups in this study: subjects on a 21-day infusion schedule (GC5107 infusion administered every 21 days) and subjects on a 28-day infusion schedule (GC5107 infusion administered every 28 days). Although, the 2 groups were compared for efficacy in a post-hoc analysis, the numbers are too small to draw any conclusions.***

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Analysis populations

Analyses were performed based on the following data sets:

- 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 is 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. Efficacy analyses were repeated on the PP population.
- 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. This population is used to perform a sensitivity analysis for the primary efficacy and safety endpoints.
- Pharmacokinetic Population: Defined as a subset of adult and adolescent subjects in the ITT population who participated in the PK study and have at least one PK sample collected. PK parameters of total IgG and IgG subclasses were analyzed on the PK population.

**Table 8: Number of Subjects in Analysis Data Sets**

| Actual, n | 28-day Infusion Schedule | 21-day Infusion Schedule | Total |
|---|---|---|---|
| Enrolled and treated, n | 29 | 20 | 49 |
| Completed, n (%) | 24 | 19 | 43 |
| ITT/Safety Population, n | 29 | 20 | 49 |
| ITT2 Population, n | 19 | 19 | 38 |
| Per Protocol, n | 24 | 19 | 43 |
| PK Population | 15 | 12 | 27 |

Data Source: Adapted from Table 14.1.4 Page 182 of GC5107 CSR

***Reviewer Comment:***

- ***Protocol version 1.0 was approved by Health Canada (March 24, 2016). All Canadian subjects were enrolled per Version 1.0.***
- ***Protocol Version 2.0 included modifications based on US FDA feedback on the protocol (summary of the pharmacology, pharmacokinetics and toxicology studies, study stopping rules, 1-hour post infusion monitoring, and reporting of AE 72 hour after the infusion). All U.S. subjects were enrolled under protocol Version 2.0, Amendment 1, dated March 16, 2017.***
- ***The ITT population includes those who prematurely discontinued the study. The clinical team separately analyzed these subjects for SBI and non SBI. See Table 21 below.***

6.1.10.1.1 Demographics

The study population is 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.

Table 9: Age Distribution

| Age in Years (at screening) | 28-day Infusion (N=29) | 21-day Infusion (N=20) | Total (N=49) |
|---|---|---|---|
| n (missing) | 29 (0) | 20 (0) | 49 (0) |
| Mean (SD) | 41.5 (21.6) | 30.7 (23.2) | 37.1 (22.7) |
| Median | 46.0 | 18.5 | 38.0 |
| Min, Max | 7, 70 | 3, 69 | 3, 70 |

Data Source: Adapted from Table 11-3 Page 86 of GC5107 CSR

Table 10: Sex Distribution

| Sex, n (%) | 28-day Infusion (N=29) | 21-day Infusion (N=20) | Total (N=49) |
|---|---|---|---|
| Male | 16 (55.2) | 12 (60.0) | 28 (57.1) |
| Female | 13 (44.8) | 8 (40.0) | 21 (42.9) |

Data Source: Adapted from Table 11-3 Page 86 of GC5107 CSR

Table 11: Age Group and Sex Distribution

| Age group (n) and Sex (M/F) | 28-day Infusion (N=29) | 21-day Infusion (N=20) | Total (N=49) |
|---|---|---|---|
| >= 2 to < 12 years (M/F) | 4 (4/0) | 4 (3/1) | 8 (7/1) |
| >= 12 to < 17 years (M/F) | 3 (2/1) | 5 (4/1) | 8 (6/2) |
| >= 17 years (M/F) | 22 (10/12) | 11 (5/6) | 33 (15/18) |

Data Source: Adapted from Table 11-3 Page 86 of GC5107 CSR

***Reviewer Comment: In the pediatric age group, only 3/16 study participants were female. Except for X-linked Agammaglobulinemia as cause of PI, the other causes of PI do not have any gender predilection. The safety and efficacy data are comparable for both sexes.***

**Table 12: Race Distribution**

| Race, n (%) | 28-day Infusion (N=29) | 21-day Infusion (N=20) | Total (N=49) |
|---|---|---|---|
| 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) |

Data Source: Adapted from Table 11-3 Page 86 of GC5107 CSR

**Table 13: Ethnicity Distribution**

| Ethnicity, n (%) | 28-day Infusion (N=29) | 21-day Infusion (N=20) | Total (N=49) |
|---|---|---|---|
| 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 |

Data Source: Adapted from Table 11-3 Page 86 of GC5107 CSR

***Reviewer Comment: During review of the original BLA submission, FDA sent an information request to the applicant to comment on the generalizability of the results to the overall population, because 96% of subjects were of White race and 92% were non-Hispanic/Latino. The applicant submitted the estimated population prevalence of PI in US utilizing data from the Commercial Claims and Encounters (CCE) for 2001–2007 and Multi-State Medicaid (MC) databases for 2001–2005. The prevalence of any PI among Whites (W) was more than 2 times higher than among either Blacks (B) or Hispanics (H) (W=47.6 per 100,000, B=19.2, H=22.0).***

***Ideally the study population would match the distribution of PI in the community. It is possible that PI is underdiagnosed / recognized in certain ethnic groups, particularly Black and Hispanic populations, due to socio-economic factors. During review of published literature and approved labels for use of IVIG, we did not see any difference in rate of infection based on race or ethnicity. As the pathophysiology of PI is unlikely to be distinct amongst the different subpopulations, the findings are likely generalizable to the different races and ethnicities.***

**Table 14: Geography Distribution**

| Geographic region, n (%) | 28-day Infusion (N=29) | 21-day Infusion (N=20) | Total (N=49) |
|---|---|---|---|
| United States | 18 (62.1) | 18 (90.0) | 36 (73.5) |
| Non-United States (Canada) | 11 (37.9) | 2 (10.0) | 13 (26.5) |

Data Source: Adapted from Table 11-3 Page 86 of GC5107 CSR

***Reviewer Comment: Only adult subjects were enrolled at Canadian Sites. All 16 study participants in the pediatric age group who were enrolled were treated at US sites.***

**Table 15: Weight Distribution**

| Weight (kg) | 28-day Infusion (N=29) | 21-day Infusion (N=20) | Total (N=49) |
|---|---|---|---|
| n (missing) | 29 (0) | 20 (0) | 49 (0) |
| Mean (SD) | 69.75 (23.1) | 62.12 (27.3) | 66.64 (24.9) |
| Median | 70.5 | 64.7 | 67.3 |
| Min, Max | 19.5, 138.0 | 15.1, 123.6 | 15.1, 138.0 |

Data Source: Adapted from Table 11-3 Page 86 of GC5107 CSR

**Table 16: Height Distribution**

| Height (cm) | 28-day Infusion (N=29) | 21-day Infusion (N=20) | Total (N=49) |
|---|---|---|---|
| n (missing) | 29 (0) | 20 (0) | 49 (0) |
| Mean (SD) | 163.1 (15.4) | 157.17 (24.0) | 160.65 (19.4) |
| Median | 165.1 | 165.1 | 165.10 |
| Min, Max | 114.3, 185.0 | 102.0, 187.9 | 102.0, 187.9 |

Data Source: Adapted from Table 11-3 Page 86 of GC5107 CSR

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The most common underlying cause of PI was Common Variable Immunodeficiency (35 subjects). The other etiologies included Hypogammaglobulinemia (10) X-linked Agammaglobulinemia (2), Bruton's Hypogammaglobulinemia (2).

***Reviewer Comment: The distribution of study subjects is in line with the distribution of PI in general population.***

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 disease duration since first lifetime IGIV infusion was approximately 8.8 years. The previous IGIV product used by subjects were Gammagard (12 subjects), Octagam (10), Gamunex (10), Privigen (7), (b) (4) (3). The other IGIV products (Gamuked, Gammaplex etc.,) were used by 1 subject each.

***Reviewer Comment: All subjects had previously been on a single brand of IGIV (except 1 subject*** (b) (6) ***who used 3) and suggests that most subjects were well controlled on their previous IVIG therapy.***

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.

***Reviewer Comment: The higher dose in the 21-day dosed subjects is counter-intuitive but may reflect a clinical decision based on patient's history of infections to treat these patient with higher doses and shorter intervals.***

No subject had a history of bacterial meningitis, osteomyelitis, or septic arthritis. Two subjects had a history of skin abscess, but no subjects had a history of visceral abscess. The most reported (frequency ≥20%) prior additional 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). 34 subjects had normal chest X-rays (70%) and 14 subjects had abnormal but not clinically significant chest X-rays. 1 subject had abnormal but not clinically significant CT scan of the Chest.

The majority of subjects in the ITT population (46 subjects, 93.9%) were taking at least one prior or concomitant medication (prescription or non-prescription).
The most commonly used (frequency ≥30%) prior or concomitant medications by Anatomical Therapeutic Chemical (ATC) class were inhalant adrenergic (25 subjects, 51.0%), other analgesics and antipyretics (21 subjects, 42.9%), antihistamines for systemic use (20 subjects, 40.8%), non-steroidal anti-inflammatory and antirheumatic products (16 subjects, 32.7%), and vitamin A and D supplements (15 subjects, 30.6%).

***Reviewer Comment: The comorbidities noted are expected in patients with PI who are in the age range of enrolled subjects. The concomitant medications do not confound the interpretation of safety signals.***

Treatment Compliance:
Of the 29 subjects treated according to the 28-day schedule, 24 (82.8%) received all 13 protocol prescribed IGIV infusions. The remaining five subjects received between one and 11 (total of 23) GC5107 infusions. A total of 335 GC5107 infusions were administered according to the 28-day schedule (88.9% of the planned number of 377 GC5107 infusions in this infusion schedule group).

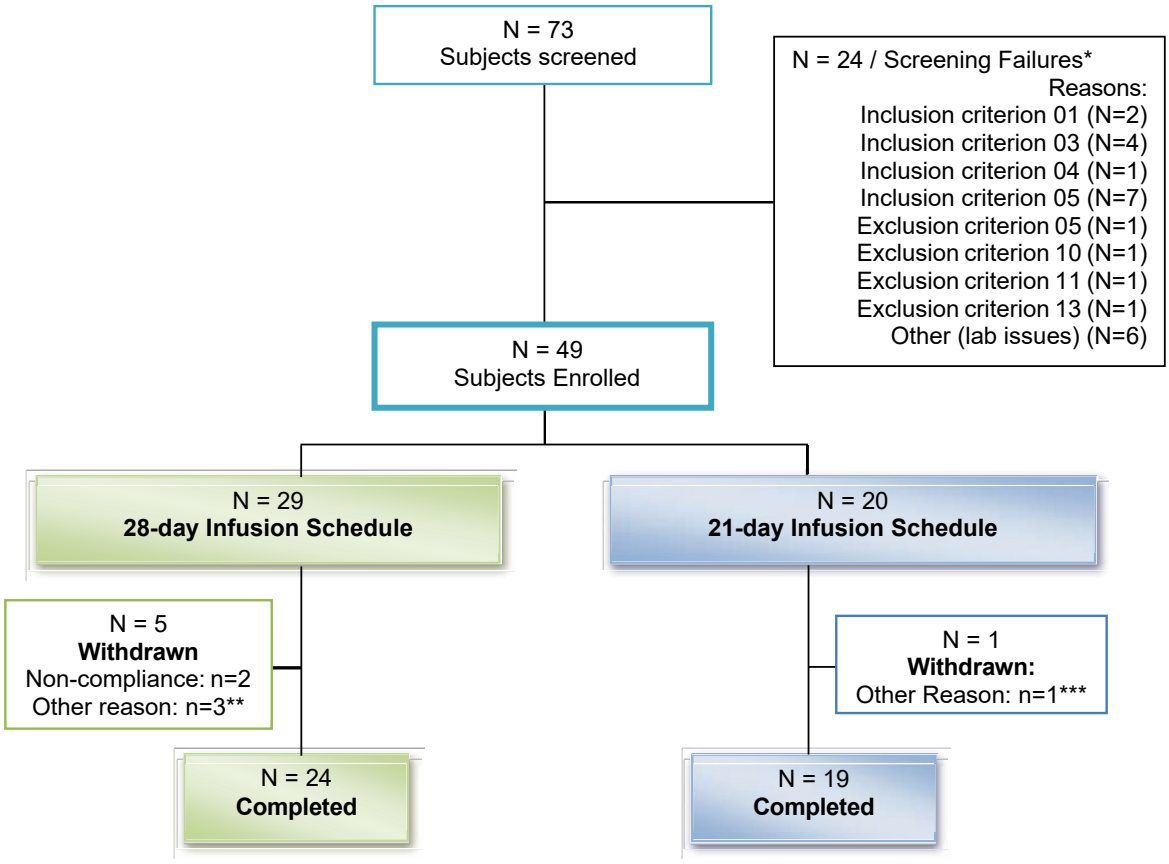
Of the 20 subjects treated according to the 21-day schedule, 19 (95.0%) received all 17 protocol prescribed IGIV infusions. The remaining one subject received nine infusions of GC5107. A total of 332 GC5107 infusions were administered according to the 21-day schedule, (97.6% of the planned number of 340 GC5107 infusions in this infusion schedule group).

The cumulative total of GC5107 infusions administered during the study was 667 (93.0% of the target number of 717 GC5107 infusions in the two infusion schedule groups combined).

6.1.10.1.3 Subject Disposition

Subject disposition during screening is depicted in Figure 1 below.

***Figure 1 Disposition of Subjects***




Data Source: Reproduced from Figure 1, Page 81 of GC5107 CSR

***Reviewer Comments: Approximately 1/3 of the subjects were screen failures. 7 of the 24 screen failures were in subjects without confirmed diagnosis of PI (Inclusion Criterion #1), not having received at least 3 doses of another IVIG prior to screening (Inclusion Criterion #3) or have IgG trough level of ≥ 500mg/dl (Inclusion Criterion #4). 7 were in subjects who were not willing to comply with the protocol (Inclusion Criterion #5).***

***The primary reasons for screen failure were failure to meet inclusion criteria (14/23) and lack of access to some laboratory testing (6/23). Six subjects were excluded due to non-availability of viral testing labs. Six of the 24 screen failures (five unique subjects) were subsequently re-screened and enrolled in the study (Subjects*** (b) (6) ***).***

Subject disposition during the treatment part of the study is depicted in the table below.

**Table 17: Disposition of subjects**

| Disposition/Reason | 28-day Infusion n (%) | 21-day Infusion n (%) | Total n (%) |
|---|---|---|---|
| Enrolled | 29(100) | 20(100) | 49(100) |
| Treated | 29(100) | 20 (100) | 49(100) |
| Not Treated | 0 | 0 | 0 |
| Completed | 24 (83) | 19 (95) | 43 (88) |
| Discontinued | 5 (17) | 1 (5) | 6 (122) |
| Withdrawal after Enrollment but prior to First Infusion | 0 | 0 | 0 |
| Withdrawal after First Infusion | 5 (17) | 1 (5) | 6 (12) |
| Primary Reason for Withdrawal after First Infusion | 5 | 1 | 6 |
| Subject/Parent decision | 0 | 0 | 0 |
| Adverse Event | 0 | 0 | 0 |
| Protocol Violation | 0 | 0 | 0 |
| Non-compliance | 2 (7) | 0 | 2 (4) |
| 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) | 1 (5) | 4 (8) |

Data Source: Reproduced from Table 10-1 Page 82 of GC5107 CSR

All 49 enrolled subjects were included in the safety analysis.
Reasons for withdrawal of 6 subjects:

- Withdrawal of consent (Subjects (b) (6) and (b) (6)) both after 1st treatment.
- Subject (b) (6) was undergoing evaluation but was not aware of melanoma diagnosis till after the 2nd infusion. Subject was withdrawn by the Applicant due to melanoma diagnosis.
- Two subjects (b) (6) were lost to follow up after being on the study for 324 and 197 days respectively and were withdrawn due to noncompliance.
- Inability to obtain IV access (Subject (b) (6) – withdrew after 167 days.

All withdrawn subjects were adults except subject (b) (6) who was 16 years of age.

***Reviewer Comment: As 3 subjects withdrew within 2 treatments, the duration of exposure was too short to detect non infusion reaction adverse events. No concerning safety signals were noted in the other 3 subjects.***

6.1.11 Efficacy Analyses

All 49 subjects who were enrolled in this study and received at least one dose of GC5107, are included in the ITT population, and are included in efficacy analysis.

6.1.11.1 Analyses of Primary Endpoint(s)

A 99% one-sided upper confidence limit of less than 1.0 per subject per year for the incidence of acute SBIs was predefined as an indicator of acceptable efficacy and conformance with FDA standards.

**Table 18: Incidence of Acute SBI**

| Acute Serious Bacterial Infections Meeting FDA Guidance Criteria | 28 Day Infusion (N=29) | 21 Day Infusion (N=20) | Total (N=49) |
|---|---|---|---|
| Total Number of all infections | 1 | 0 | 1 |
| Bacterial Pneumonia | 1 | 0 | 1 |
| Bacteremia/Sepsis | 0 | 0 | 0 |
| Bacterial Meningitis | 0 | 0 | 0 |
| Visceral Abscess | 0 | 0 | 0 |
| Osteomyelitis/Septic Arthritis | 0 | 0 | 0 |

Data Source: Adapted from Table 11-7 Page 92 of GC5107 CSR

In the ITT population, a single primary endpoint event of acute SBI (bacterial pneumonia in the 28-day schedule group) occurred during a cumulative total follow-up of 45.86 years, resulting in an incidence of acute SBIs of 0.02 events per subject per year. There was no SBI reported in the 21-day schedule group.

**Reviewer Comments:**

1. ***The SBI of Bacterial Pneumonia occurred in an adult subject. Recalculation of the incidence of acute SBI based on only the adult population is 1 in 33 subjects is 0.03 events per subject per year.***
2. ***A second case of pneumonia in an adult subject was reported in the adverse event data set but not assessed as an SBI by the Applicant. In response to a clinical information request, the Applicant included documentation indicating that this second case of pneumonia was a viral pneumonia and thus did not meet the definition of SBI.***

Brief Synopsis of SBI in Subject (b) (6)

A 59-year-old, non-Hispanic White male (Subject (b) (6)) with history of PID developed bacterial pneumonia on February 24, 2018 (Study Day 89). He received his first GC5107 infusion (28-day infusion group) on (b) (6), and his last GC5107 infusion prior to this event on (b) (6) (Infusion 4). He had a history of recurrent pneumonia prior to enrolling in the study while on IGIV. He had multiple comorbid conditions including Type 2 Diabetes, Hypertension, Hepatic Cirrhosis.

Six days prior to the event of bacterial pneumonia, the subject was treated for bronchitis (onset on February 16, 2018) with a 10-day regimen of Augmentin (amoxicillin/clavulanic acid) 875/125 twice a day (February 19-24, 2018) and Bromfed DM syrup (brompheniramine, dextromethorphan and pseudoephedrine) 10 mL (February 19-24, 2018). On (b) (6), the subject presented to urgent care with complaints of chest discomfort, fever, and myalgia. Subject was sent home after nasal swab came back negative for Influenza. The subject presented to ER after GC5107 infusion.

Chest X Ray confirmed diagnosis of pneumonia. CT scan revealed multifocal bronchopneumonia with probable reactive mediastinal and hilar lymphadenopathy; there was no evidence of pleural effusion, acute pulmonary embolus, or pneumothorax.

Subject was empirically treated in the hospital with Intravenous antibiotics (IV piperacillin/tazobactam). Subject did not require supplemental oxygen support. Subject showed clinical improvement and was discharged home, 3 days later (b) (6), with final discharge diagnoses of community acquired multifocal pneumonia of undetermined bacterial origin. (Cultures were negative). This event of bacterial pneumonia was assessed as SAE (because of hospitalization) severe in intensity and not related to the GC5107 by the Investigator.

***Reviewer Comment: After reviewing the detailed narrative summary, this reviewer concurs that a) this event was SBI and b) the event was severe in intensity requiring hospitalization; The subject completed the study (received 9 more treatments with GC5107) and trough levels were > 500mg/dL***

6.1.11.2 Analyses of Secondary Endpoints

Incidence of Infections Other Than Acute SBIs Meeting FDA Guidance Criteria

In the ITT population, 38 subjects (77.6%) experienced a total of 135 infections other than acute SBIs during a cumulative total follow-up of 45.9 patient-years, resulting in a mean incidence (±SD) of 2.9±2.5 infections per subject per year (range from 0 to 12.24 infections).

The most frequent infections (number of subjects / %) observed during the study were sinusitis (17/ 34.6%), bronchitis (6 /12.2%), Influenza (6 /12.2%) nasopharyngitis (6 /12.2%) urinary tract infection (5/10.2%), gastroenteritis (3/6.1%) and otitis media (3 / 6.1%).

Comparison of incidence of infections (between the 2 infusion groups) is shown in Table 19 and relationship to mean IgG trough level is shown in Table 20 below.

**Table 19: Comparative Incidence of Infections other than Acute SBI**

| Infections other than Acute Serious Bacterial Infections | 28-day Infusion (N=29) | 21-day Infusion (N=20) | Total (N=49) |
|---|---|---|---|
| Total Number | 64 | 71 | 135 |
| Number of Subjects with At Least One Infection other than Acute Serious Bacterial Infections Meeting FDA Guidance Criteria, n (%) | 21 (72.4) | 17 (85.0) | 38 (77.6) |
| Total Amount of Follow-up Time (year) | 26.24 | 19.62 | 45.86 |
| Mean (SD) (number per subject per year) | 2.4 (1.9) | 3.6 (2.9) | 2.9 (2.5) |
| Median (number per subject per year) | 2.0 | 3.5 | 2.0 |
| Min, Max | 0, 8.0 | 0, 12.2 | 0, 12.2 |

Data Source: Adapted from Table 11-9 Page 96 of GC5107 CSR

**Table 20: Incidence of non SBI Infections in relation to IgG trough level**

| Non SBI Infections in relation to trough level | 28-day Infusion (N=29) | 21-day Infusion (N=20) | Total (N=49) |
|---|---|---|---|
| Total Number of Infections | 64 | 71 | 135 |
| Total group mean trough | 775.2 | 775.2 | 775.2 |
| < mean Trough IgG, n | 42 | 15 | 57 |
| >= mean Trough IgG, n | 22 | 56 | 78 |
| Number of Subjects with At Least One Infection other than Acute Serious Bacterial Infections Meeting FDA Guidance Criteria, n (%) | 21 (72.4) | 17 (85.0) | 38 (77.6) |
| < mean Trough IgG | 14 (48.3) | 5 (25.0) | 19 (38.8) |
| >= mean Trough IgG | 7 (24.1) | 12 (60.0) | 19 (38.8) |
| Total Amount of Follow-up Time (year) | 26.2 | 19.6 | 45.9 |
| Follow up time for < mean Trough IgG | 16.1 | 5.8 | 21.9 |
| Follow up time for >= mean Trough IgG | 10.2 | 13.8 | 23.9 |

Data Source: Adapted from Table 11-10 Page 97 of GC5107 CSR

***Reviewer Comment: The annual rate of infections other than acute SBIs was numerically 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, respectively). It is counter intuitive. It is possible that the investigators may have adjusted the doses for individual subjects based on history of greater disease severity or frequency of non SBIs in each subject to have higher trough levels as noted in more frequent infusion group. Such changes may have been done prior to the study enrollment as no subject switched to a more frequent infusion group during the study.***

***Of note, the rate of non SBIs/ subject / year are comparable to data from other recently approved IVIG products (Privigen - 3.55; Bivigam- 3.7, Gammaplex - 3.1, Asceniv-3.4).***

Number of Days of Hospitalizations Due to Infections

In the ITT population, 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 bacterial pneumonia) and two days (Subject (b) (6), 21-day infusion schedule; hospitalized for influenza), yielding a mean duration of hospitalizations of 0.1±0.53 days.

***Reviewer Comment: The rate of hospitalization due to infections is in line with data from clinical studies of other IVIG products (Asceniv 1/59; Bivigam 2/58). The subjects' Immunization status / response of subjects for pneumococcal and influenza vaccines were not tested in this study.***

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.

Number of Days of IV Therapeutic Antibiotics

Only 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 bacterial pneumonia).

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. 16 subjects in 28-day infusion group and 13 subjects in the 21-day infusion group received antibiotics; the mean number of days of oral antibiotic use were 13.3 and 13,1 respectively.

Number of Days Missed or Unable to Perform Daily Activities Due to Infections [in the ITT population of all subjects (n=49)]

25 subjects (51.0%) missed at least one day from work/school/kindergarten/daycare or were unable to perform normal daily activities due to infections. On average, subjects missed 7.1±18.0 days (range, from 0 to 96 days) from work/school/kindergarten/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)

***Reviewer Comments:***

1. ***The rate of unscheduled physician visits, need for antibiotics, missed days from work / school/ daycare due to infections are in line with data from clinical studies of other IVIG products.***

6.1.11.3 Subpopulation Analyses

(b) (4)

(b) (4)

Subpopulation Analysis of Study participants ≥17 years of age.

Demographics: There were 33 (22 female and 25 male) adult subjects with ages ranging 17-70 years enrolled in the study. Forty-five subjects were reported to be of white race. Other than the two adults with reported race as “other,” all subjects were white. One subject of white race was reported to be of Hispanic or Latino ethnicity. 29 of them had had Combined Variable Immune deficiency (CVID), 2 had Bruton’s disease, 1 had hypogammaglobulinemia, and one had agammaglobulinemia as the cause of PI.

Study Disposition: Of the 33 adult age group study participants, 5 withdrew from the study (two due to withdrawal of consent, one due to melanoma that was existing at the time of enrollment, two subjects were lost to follow up).

Efficacy: There was one SBI (bacterial pneumonia) reported in this population (0.03 acute SBIs per subject-year). The annual rate of non SBI infections were 2.4 infections per subject-year. I subject (3%) received intravenous (IV) antibiotics for 3 days. 19 subjects (58%) received oral antibiotics for 11 +/- 14 days. 14 subjects (42%) missed at least one day from work/school/ability to perform normal daily activities due to infection. 19 adult subjects (58%) had at least one day of unscheduled physician visits. Two subjects were hospitalized due to infection (one for 2 hospitalizations with one day/hospitalization and one for 1 hospitalization for 3 days). The annual rate of hospitalizations due to infection was 0.1 +/- 0.4 hospitalizations per year.

The following table summarizes efficacy results in adult subjects.

| Category | Result (N=33) |
|---|---|
| Follow-up time (in person years) | 30.3 |
| Annualized rate of confirmed acute SBIs (events per person-year) | 0.03 |
| Annualized rate of other infections (events per person-year) | 2.4 |
| Number of subjects with use of therapeutic antibiotics | 19 (58%) |
| Number of days of therapeutic antibiotics: median (min, max) | 14 (5, 63) |
| Number of subjects missed at least one day from work/school or days unable to perform normal daily activities due to infection | 14 (42%) |
| Number of days off work/school or days unable to perform normal daily activities due to infection: median (min, max) | 6 (1, 80) |
| Number of subjects with hospitalizations due to infection | 2 (6%) |
| Total days of hospitalization due to infection | 5 (One subject for 2 days and one subject for 3 days) |
| Annualized rate of hospitalization due to infection (days per person-year) | 0.2 |

6.1.11.4 Dropouts and/or Discontinuations

**Please see section 6.1.10.1.3 of this memo (titled Subject Disposition) for description of dropouts and discontinuation from the study.**

***Reviewer Comment: Of the 6 subjects who dropped out from the study, 2 of them received only 1 dose, 1 of them received 2 doses.***
***No SBI was observed in the other 3 subjects. Non-SBIs noted in these 3 subjects are shown in table below. This reviewer (based on the information on infections) does not think that the dropouts/ discontinuations affected the interpretability of the study.***

**Table 21: Non SBI in 3 subjects who discontinued the study**

| Subject ID | Days on the Study | Non SBI (number of infections) |
|---|---|---|
| (b) (6) | 324 | Acute Sinusitis (1)<br>Rhinitis (1)<br>Influenza (1) |
| (b) (6) | 197 | Oral Candidiasis (1) |
| (b) (6) | 167 | Influenza (1)<br>Gastroenteritis (1)<br>Upper Respiratory Infection (1)<br>Bronchitis (1) |

Data Source: Reviewer Analysis of Subject Data

6.1.11.5 Exploratory and Post Hoc Analyses (adults and pediatric subjects)

The applicant performed an exploratory analysis of the incidence of fever episodes. In the ITT population, 13 subjects (26.5%) experienced a total of 19 fever episodes. Based on a cumulative total follow-up time of 45.86 years, the overall incidence of fever episodes was 0.41 with no notable difference between the 28-day compared to the 21-

day infusion schedule group. The mean duration of fever episodes was 1.1±2.27 days in the total ITT population.

Reviewer Comment: all adverse events of fever occurred only in pediatric subjects.

6.1.12 Safety Analyses

6.1.12.1 Methods

Safety analyses focused on the following endpoints:

Primary Safety Endpoint: The proportion of infusions with temporally associated adverse events (AEs) that occur during or within 1 hour, 24 hours, and 72 hours following an infusion of investigational product (including AEs that were determined to be unrelated to the product). The primary safety endpoint was descriptive in nature with no prespecified success criteria.

Secondary Safety Endpoints:

- The overall incidence of all AEs that occur during or within 1 hour, 24 hours, and 72 hours following an infusion of investigational product.
- The frequency of all AEs that occur during the study regardless of the investigator's assessment of their relationship to investigational product.
- The frequency of suspected adverse reactions as defined by all AEs either classified by investigator or sponsor as at least possibly related to GC5107.
- Changes in vital signs, physical examinations, and laboratory test results.
- The number and proportion of GC5107 infusions for which the infusion rate was decreased due to AEs.
- The proportion of AEs considered by the investigator to be investigational product related.
- Viral safety (freedom from transmission of blood-borne viral diseases): the human immunodeficiency virus (HIV) 1&2, hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), and parvovirus B19.

Safety Analysis was conducted in the ITT Population which included all subjects who were enrolled into the study and received any amount of the GC5107.

Subjects were asked to complete a diary and record all AEs that occurred after the previous study infusion with special emphasis on adverse events during the first 24, 48 and 72 hours after infusion. During the treatment and follow-up periods, subjects underwent the following evaluations: adverse event monitoring, recording of concomitant medications (throughout the study) and review of subject diaries at each visit. Physical Exam was conducted at each visit, multiple vital signs assessments at each visit (including 10 to 15 minutes pre infusion, 5 minutes before each infusion rate increase, 30 minutes after reaching the maximum infusion rate, as well as immediately after and 60 minutes after the infusion was completed).

Routine safety laboratory tests (hematology, blood chemistry and urinalysis) completed before each infusion, and at the follow-up Visit after last infusion. Measurements of

direct antiglobulin (DAT/Coombs) were performed before and after the 1st infusion, three days after the 1st infusion, and before and after the 6th and 13th infusions (for subjects on the 28- day infusion schedule) or before and after the 8th and 17th infusions (for subjects on the 21- day infusion schedule). Blood samples were obtained at screening to exclude subjects who were positive by NAT (nucleic acid test) for each of the following viruses: HIV, HCV, HBV, and HAV. Samples were tested by serology and NAT for HIV-1/2 (NAT for HIV-1 only), HCV and HBV. Tests for HAV and Parvovirus B19 were performed by NAT (throughout the study) and serology (only at baseline).
The subject diaries included questions to ascertain both the patient experience with the treatment (AEs) and impact on day-to-day functioning (e.g., unscheduled physician visits, days missed from day care/ school/ work). The Schedule of assessments included monitoring for infusion associated reaction (within 60 minutes), temporally related AEs (within 72 hours). The monitoring included assessments for hemolytic anemia and transmission of viral diseases because both have been associated with this class of products (Human Immunoglobulin).

***Reviewer Comment: safety assessments are appropriate for pivotal IGIV clinical studies***

6.1.12.2 Overview of Adverse Events

All Subjects

All 49 enrolled subjects experienced at least one AE during the study. A total of 743 AEs were reported during the study (average of 15.2 events per subject). Approximately half of the total population (26 subjects, 53.1%) experienced a total of 113 AEs assessed by the investigator as at least possibly related to the GC5107. The majority of the AEs were mild (588/743, or 79.1% of all AEs) or moderate in intensity (143/743, or 19.2% of all AEs). Nine subjects (18.4%) experienced only mild AEs, and for 33 subjects (67.3%), the highest AE intensity was moderate. Seven subjects (14.3%) experienced a total of 12 severe AEs; four subjects (8.2%) experienced a total of five treatment-emergent SAEs during the study. In the 21-day infusion group, 20 subjects experienced 251 AEs (average 12.6 per subject); 12 subjects (60.0%) experienced 29 AEs classified as at least possibly related to GC5107 (average 1.5 events per subject).

Temporally Associated Adverse Reactions in >5% of study participants are shown below.

**Table 22a: Temporally Associated Adverse Reactions (ARs) in >5% of study subjects**

| Adverse Reaction (AR) | Number of Subjects with AR | % of Study Population (n=49) |
|---|---|---|
| Headache | 24 | 49% |
| Nausea | 12 | 24.5% |
| Fatigue | 9 | 18.4% |
| Nasal congestion | 5 | 10.2% |
| Cough | 4 | 8.2% |
| Diarrhea | 4 | 8.2% |
| Abdominal pain upper | 3 | 6.1% |
| Arthralgia | 3 | 6.1% |
| Infusion site extravasation | 3 | 6.1% |
| Oropharyngeal pain | 3 | 6.1% |
| Pain | 3 | 6.1% |
| Pyrexia | 3 | 6.1% |
| Sinus congestion | 3 | 6.1% |
| Urticaria | 3 | 6.1% |

Data Source: Original BLA Reviewer Analysis of Adverse Reactions

***Reviewer Comment from Reviewer of Original BLA submission:***
***Although there were small differences between the two infusion schedules in the proportion of subjects experiencing any AE during or within 1 hour, 24 hours, and 72 hours after an GC5107 infusion ( the frequency of severe AE and Serious AE was numerically higher in the 28-day infusion compared to the 21-day infusion group [severe AEs: 6 subjects (20.7%) vs. 1 subject (5.0%), respectively; SAEs: 3 subjects (10.3%) vs. 1 subject (5.0%), respectively]), given the small numbers, no conclusions related to causality can be reached.***

<u>The following overview includes data from only adult subjects enrolled in the study.</u>

All 33 enrolled adult subjects experienced at least one AE during the study. A total of 482 AEs were reported during the study (average of 14.6 events per subject). Approximately half of the total adult population (19 subjects, 58%) experienced a total of 84 AEs assessed by the investigator as at least possibly related to the GC5107. The majority of AEs were mild (341/482, or 71% of all AEs) or moderate intensity (127/482 or 26% of all AEs). Only one subject experienced only mild AEs, and for 24 subjects (72%), the highest AE intensity was moderate. Eight subjects (24%) experienced a total of 14 severe AEs. In the 28-day infusion group, 23 subjects experienced 393 AEs (average 11.9 events per subject); 11 subjects (%) experienced 72 AEs classified as at least possibly related to GC5107 (average 6.5 events per subject). 5 subjects (15.2%) experienced a total of 6 treatment-emergent serious adverse events (SAEs) during the study.

In the 28-day infusion group, 29 subjects experienced 492 AEs (average 17.0 events per subject); 14 subjects (48.3%) experienced 84 AEs classified as at least possibly related to GC5107 (average 2.9 events per subject).

In the 21-day infusion group, 23 subjects experienced 393 AEs (average 17 per subject); 8 subjects (34.7%) experienced 12 AEs classified as at least possibly related to GC5107 (average 1.5 events per subject).

Temporally Associated Adverse Reactions in >5% of adult study participants are shown below.

**Table 22b: Temporally Associated Adverse Reactions (ARs) in >5% of adult study subjects**

| **Adverse Reactions (ARs)** | **No. of Subjects Reporting ARs (Percentage of Subjects) [N[1]=33]** | **No. of Infusions with ARs (Percentage of Infusions) [N[2]=427]** |
|---|---|---|
| Headache | 13 (39) | 38 (8.9) |
| Nausea/Vomiting | 11 (33) | 21 (4.9) |
| fatigue | 6 (18) | 18 (4.2) |
| Nasal/sinus congestion | 5 (15) | 7 (1.6) |
| Rash | 4 (12) | 4 (0.9) |
| Arthralgia/joint pain | 3 (9) | 4 (0.9) |
| diarrhea | 3 (9) | 3 (0.7) |
| Muscle pain/aches | 2 (6) | 9 (2.1) |
| Infusion site pain/swelling | 2 (6) | 6 (1.4) |
| Abdominal pain/discomfort | 2 (6) | 3 (0.7) |
| Cough | 2 (6) | 3 (0.7) |
| Dizziness | 2 (6) | 3 ((0.7) |

* Adverse events that occurred during or within 72 hours after the end of an infusion
[1] Total number of subjects
[2] Total number of infusions

*Reviewer Comment:* (b) (4) *, ARs in adults are compared to ARs in children in the following table 22b.*

Adverse Reactions: Comparison between Adult and Pediatric Subjects

**Table 22c: Temporally Associated Adverse Reactions (ARs) in >5% of all study subjects (comparison of adults and children)**

| AR (<72h post infusion) Dictionary derived term | Adults 17+ (N=33) N (# infusions) | Children under 17 (N=16) N (# infusions) | All (N=49) N (# infusions) |
|---|---|---|---|
| Headache | 13 (38) | (b) (4) | |
| Nausea/Vomiting | 11 (21) | | |
| fatigue | 6 (18) | | |
| Nasal/sinus congestion | 5 (7) | | |
| Rash | 4 (4) | | |
| Arthralgia/joint pain | 3 (4) | | |
| diarrhea | 3 (3) | | |
| Muscle pain/aches | 2 (9) | | |
| Infusion site pain/swelling | 2 (6) | | |
| Abdominal pain/discomfort | 2 (3) | | |
| Cough | 2 (3) | | |
| Dizziness | 2 (3) | | |
| Menstrual disorder | 2 (3) | | |
| Pyrexia (fever) | 0 (0) | | |

Data Source of Table 22a and 22b: Reviewer analysis of adverse reactions

6.1.12.3 Deaths
No Deaths occurred during the study.

6.1.12.4 Nonfatal Serious Adverse Events

A total of five treatment-emergent SAEs occurred in four subjects (8.2%) during the study. Three out of 29 subjects (10.3%) experienced four SAEs in the 28-day schedule group, and one out of 20 subjects (5.0%) experienced a single SAE during the study. Brief description of SAEs:

28 Day Schedule:
- 3 out of 29 subjects (10.3%) experienced 4 SAEs
  - Subject (b) (6) experienced two SAEs (bacterial pneumonia and acute myocardial infarction
  - 4 -assessed as severe in intensity [# days post infusion (dpi)/infusion #]
    - Urticaria -Subject (b) (6) - 68yr/F; 26 dpi /#7; 4-day hospitalization
    - Pneumonia bacterial - Subject (b) (6) -59yr/M; 0 dpi /#4; 4-day hospitalization
    - Acute myocardial infarction- Subject (b) (6) -59yr/M; 22 dpi /#11; 3-day hospitalization and drug eluting stent
    - Squamous cell carcinoma of the tongue - Subject (b) (6) -69/F;1 dpi/ #12 – chemotherapy – completed study.

21 Day Schedule:
- 1 out of 20 subjects (5.0%) experienced a 1 SAE
  - 1 was assessed as moderate
  - Influenza- Subject (b) (6) -29/M; 14 dpi / #2- 2-day hospitalization

***Reviewer Comments: In addition to the five treatment-emergent SAEs, there was one case of pre-existing malignant melanoma in Subject (b) (6), who was enrolled in the study despite this exclusionary condition. Subject (b) (6) was withdrawn from the study due to this protocol deviation.***

***There was no severe AEs or hospitalizations reported in subjects <17 years of age.***

6.1.12.5 Adverse Events of Special Interest (AESI)

No cases of anaphylactic shock, aseptic meningitis, hemolytic anemia/hemolysis, and acute renal failure were observed during the study. Although thromboembolic events such as stroke, pulmonary embolism, deep vein thrombosis were not observed, there was 1 instance of myocardial infarction in Subject (b) (6), requiring angioplasty and placement of drug eluting stent during a 3-day hospitalization.

***Reviewer Comment: This subject had multiple risk factors (such as age > 55 years, diabetes for > 30 years; hypertension with left ventricular hypertrophy). Therefore, it is unlikely that the myocardial infarction was related to the use of IGIV.***

6.1.12.6 Clinical Test Results

Vital signs:
During the study, the number of fever episodes (defined as number of subjects / total episodes) were 9 and 11 in the 28-day infusion group and were 4 and 8 in the 21-day infusion group. In total throughout the study, 13 subjects had at least 1 episode of fever with total of 19 episodes. Three subjects had concomitant tachycardia – one rated as mild (Subject (b) (6)- resolved on the same day); 2 others also rated as mild (Subjects (b) (6)) were not resolved at the last follow up visit. Two subjects had worsening of hypertension – unresolved at the follow visit (Subject (b) (6)- rated as moderate, Subject (b) (6) – rated as mild). No instances of hypotension were reported.

(b) (4), and four adult subjects during the treatment period. Two adult subjects had decreased weight (Subject (b) (6) with weight change of -12.5%; Subject (b) (6) - with weight change of -11.9%). All other study participants had weight gain during the study (ranging from 12.9% to 18.7%).

***Reviewer comment: Weight gain in 1 adult subject was related to use of prednisone;*** (b) (4) ***No infections were reported with lower trough level. Therefore, this reviewer does not think that the weight gain was product related.***

Abnormalities in Physical Exam:
Shifts from normal baseline to abnormal post-baseline physical examination findings were noted in one to four subjects for cardiovascular, respiratory, musculoskeletal, neurologic, and integumentary systems. Subject (b) (6) had irregular heartbeat and Subject (b) (6) had palpable lymph node – both unresolved at last follow visit. These were rated as mild and unrelated to GC5107.

Hematological Abnormalities:
Three subjects had clinically significant abnormalities. Subject (b) (6) had iron deficiency anemia (lowest hemoglobin was 10.8 g/dl) rated as mild, resolved (in 87 days) and unrelated to GC5107. Subject (b) (6) had history of immune thrombocytopenia and had fluctuating platelet count from 50-160 (x $10^9$/L) throughout the study. Subject (b) (6) had thrombocytopenia (lowest 114 x $10^9$/L) resolved in 30 days, rated as mild and unrelated to GC5107.

Positive Direct Antiglobulin (Coombs Test)

**Table 23: Summary of Positive Coombs Test**

| Number of Subjects with positive test | 28-day Infusion group n=29(100%) | 21-day Infusion group n=20(100%) | Total n=49(100%) |
|---|---|---|---|
| At Baseline | 0 | 2 (10%) | 2 (1%) |
| At any time during study (treatment Emergent) | 8 (27.6%) | 7 (35%) | 15 (30.6%) |
| At last assessment | 4 (13.8%) | 4 (20%) | 8 (16.3%) |
| Clinically Significant Hemolysis | 0 | 0 | 0 |

Data Source: Table reconstructed based on tables 12-21 and 14.3.4.7.1 of GC5107 CSR

***Reviewer Comment: If the hemoglobin decreased by >1 g/dL from baseline, the protocol required follow-up testing (hemoglobin, total bilirubin, serum LDH, serum haptoglobin, plasma-free hemoglobin, and urine hemosiderin) completed 2-5 days and 7-10 days after the infusion. No AEs indicative of hemolysis were reported during the study. Hemolytic anemia (HA) is a well-known adverse reaction with this class of products (Immunoglobulins). Therefore, although no cases of HA were noted in this clinical trial, the product label should include hemolytic anemia in Warnings and Precautions section.***

Change in Serum chemistries during the study:

The most common shifts to above-normal values at end-of-treatment occurred for alkaline phosphatase [two subjects (8.3%) in the 28-day and one subject (5.3%) in the 21-day infusion schedule group]; creatinine [three subjects (12.5%) in the 28-day and no subjects in the 21-day infusion schedule group.

***Reviewer Comment: No consistent pattern or clinically meaningful changes from baseline were observed in mean or median blood chemistry parameters during the study. Although impaired renal function and Acute Renal Failure have been described with this class of products, it was not observed during the study.***

Urine Analysis Results:
Clinically significant urinalysis abnormalities (i.e., reported as AEs) occurred in five subjects.

Three subjects (Subjects (b) (6) – had pyuria and bacteriuria consistent with urinary infection); one Subject ((b) (6)) had moderate hematuria -resolved in 1 day - associated with nephrolithiasis and pyelonephritis. Subject (b) (6) had multiple urinary

abnormalities including proteinuria (resolved), pyuria and positive fungal test (resolved in 26 days).

***Reviewer Comment: Urinary abnormalities are associated with increased risk of infection and resolved with treatment. This reviewer thinks that these cases of urinary abnormalities were not attributable to GC5107.***

Results of Viral testing conducted during the study

At Baseline:

- Parvovirus B19 IgG (Index), HAV serology (total anti-HAV antibody), and HBsAb (total) were tested only at baseline and were positive in all subjects.
- HBcAb was tested only at baseline and was positive in 32 (65.3%) of subjects.
- HCV Ab was tested only at baseline and was negative in all subjects.
- HIV Ab was tested only at baseline and was negative in all subjects.

During the study:

- HBsAg, HCV RNA, and HIV-1 RNA remained negative at each post-baseline assessment time-point.

- HBV DNA turned positive in 2 subjects ( (b) (6) ). In both subjects, HBV DNA was not detected at follow up visit and HBsAg remained negative throughout the study.

***Reviewer Comment: Administration of Immunoglobulin products carries the risk of transmission of viruses. Although the sample size was small, it is reassuring that no viral transmission was reported during the 12-month duration of the study.***

6.1.12.7 Dropouts and/or Discontinuations

Please see section 6.1.10.1.3 of this memo (titled Subject Disposition) for description of dropouts and discontinuation from the study.

***Reviewer Comment: Of the 6 subjects who dropped out from the study, 2 of them received only 1 dose, 1 of them received 2 doses. The 3 other subjects were included in ITT population data set for safety assessments. One of these subjects switched to subcutaneous administration due to lack of IV access after 6 months of the study and had no SBIs. 2 subjects who dropped out of the study (due to noncompliance) had no SBI prior to drop out. Therefore, the dropouts/ discontinuations did not affect the interpretability of the study (primary efficacy of SBI), although the impact on secondary efficacy endpoints is unclear.***

6.1.13 Study Summary and Conclusions

The study met its objective as the incidence of serious acute bacterial infections (in subjects with PI treated with the investigational product GC 5107) was less than 1.0 per subject per year (in accordance with FDA guidance) disproving the null hypothesis. No deaths occurred during the study. There were no adverse events AEs leading to discontinuation from the study. The most common AEs noted in adults were headache (39%), nausea/vomiting (33%), fatigue (18%), nasal/sinus congestion (15%), rash (12%), arthralgia (9%), diarrhea (9%), and muscle pain/aches, infusion site

pain/swelling, abdominal pain/discomfort, cough, dizziness, and menstrual disorder (6% each). The secondary efficacy endpoints and safety data are comparable to other approved Immunoglobulin products. No new concerning safety signals or Adverse Events of Special Interest (AESI) were observed).

7. INTEGRATED OVERVIEW OF EFFICACY

No integrated summary of efficacy was submitted, nor was it required as a single pivotal study was submitted. See Section 6 for the efficacy data provided and analyzed in this submission.

8. INTEGRATED OVERVIEW OF SAFETY

No integrated summary of safety was included in the BLA submission, nor was it required as the submission was comprised of a single pivotal study. See section 6 for the safety data provided and analyzed in this submission.

9. ADDITIONAL CLINICAL ISSUES

**9.1 Special Populations**

9.1.1 Human Reproduction and Pregnancy Data

No clinical studies were conducted in pregnant subjects, and no data are available to indicate whether GC 5107 can cause fetal harm when administered to pregnant women or can affect reproductive capacity. However, immunoglobulin products have been shown to cross the placenta, increasingly after 30 weeks of gestation. The draft labeling indicates that GC 5107 should only be administered to pregnant women if clinically indicated.

9.1.2 Use During Lactation

GC 5107 has not been evaluated in lactating subjects.

9.1.3 Pediatric Use and PREA Considerations

Although the Applicant submitted a pediatric assessment for adolescents as part of the adult study, the clinical review team does not agree that this assessment is complete. The safety, efficacy and pharmacokinetic data for the pediatric age subjects are presented below.

Demographics: There were 16 (3 female and 13 male) pediatric study participants with 8 each of two age groups (≥2 to <12 years; (≥12 to <17 years). Age of study participants ranged from 3-16 years. All were reported to be of white race, and non-Hispanic ethnicity. (b) (4)

.

Study Disposition: (b) (4)

Efficacy Data in the Pediatric Subjects: (b) (4)

Safety Data: (b) (4)

Pharmacokinetic (PK) Data in the Adolescent Subjects: (b) (4)

**Reviewer Comments:**

(b) (4)

***, in the CR letter, FDA requested the Applicant propose another plan to assess PK and one year of safety and efficacy in 6 additional subjects ages ≥12 to <17 years. No new clinical data were submitted in this BLA-resubmission.***

***The Applicant is requesting a deferral of pediatric studies in age group ≥ 2 to < 17 years. With the agreed iPSP, the Applicant was granted a waiver for subjects aged 0 to < 2 years because necessary studies are impossible or highly impracticable due to the rarity of diagnosis in this age group. The existing amended agreed iPSP (Feb 09, 2021) includes a separate ongoing study GC5107D (An Open-Label, Single-Arm, Historically Controlled, Prospective, Multicenter Phase III Study to Evaluate the Pharmacokinetics and Safety of Immuno- Globulin Intravenous (Human) 10% GC5107 in Pediatric Subjects ≥ 2 to < 12 Years of Age with Primary Humoral Immunodeficiency) with the following timelines.***

- ***Final Protocol Submission: May 15, 2018***
- ***Study Completion: March 31, 2023***

• ***Final Report Submission: September 30, 2023.***

***With this BLA resubmission the Applicant proposes to enroll 6 subjects age ≥12 years to < 17 years in the ongoing study GC5107D, in addition to already planned subjects ages ≥ 2 to < 12 Years, with the following amended timeline:***

***Protocol Submission Date: May 15, 2018***
***Amended Protocol Submission Date: April 20, 2022***
***Study Initiation Date: December 21, 2020***
***Study Completion Date: May 30, 2026***
***Final Report Submission: November 30, 2026***

***Given the historical duration of time needed to enroll subjects in each age group, the amended timeline is acceptable. The ongoing study is designed to collect PK and 1 year of safety and efficacy data. Therefore, enrolling 6 additional subjects aged ≥12 years to < 17 years is adequate to fulfill the FDA request in the CR letter. The clinical team anticipates that the proposed study may be adequate to determine safety, efficacy, and PK in subjects aged ≥12 years to < 17 years. The Clinical Team recommends granting the deferral of studies in age group ≥ 2 to < 17 years as proposed by the Applicant in this submission and summarized above.***

9.1.4 Immunocompromised Patients

GC 5107 is indicated for primary immunodeficiency.

9.1.5 Geriatric Use

Eight adults > 65 years of age were enrolled and treated in the study. Sample size is too small to derive any definitive conclusions, however, findings appeared to be similar in this subpopulation compared to the overall population.

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

Not applicable

10. CONCLUSIONS

The applicant submitted a single adequate and well controlled study, Study GC5107_P3, which was conducted according to FDA Guidance and was adequately designed to demonstrate safety and efficacy of GC5107 for treatment of PI. The study met its primary efficacy endpoint 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) meeting FDA criteria was less than 1.0 per subject per year in the population of subjects with PI receiving GC5107 infusions every 21 or 28 days for 12 months. Efficacy was also supported by low rates of hospitalization due to an infection, IV therapeutic antibiotic use, missed workdays for care providers of pediatric patients, and unscheduled visits to physicians due to infection. The rate of missed work/school/daycare days due to infection, and oral therapeutic antibiotic use during the study was in the range of rates reported for other IGIV products.

The proportion of infusions with one or more infusion-related AEs was less than 40%; therefore, the study also met its primary safety endpoint. The study demonstrated that

12 months of treatment with GC5107 was well tolerated, with no deaths, no SAEs attributed to GC5107, and no AEs leading to withdrawal. The type and frequency of AEs were consistent with the known safety profile of other licensed IVIG treatments.

Clinical Reviewer recommends the following:

- Granting license for use of Alyglo / GC5107, for treatment of PI in adults ≥ 17 years of age.
- Post Marketing Requirement (under PREA) to conduct PK, safety, and efficacy study in the pediatric population (age group ≥2 to <17 years).
- Waiver of requirement for clinical studies in children < 2 years of age.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

### 11.1 Risk-Benefit Considerations

The applicant submitted a single adequate and well controlled study, Study GC5107_P3, that provides substantial evidence of effectiveness and safety. Confirmatory evidence is derived from other members of same pharmacologic class. Data submitted to the BLA establish a substantial benefit for treatment of PI in adults such as prevention of serious bacterial infection, and reduction in rate of missed work, hospitalizations due to infections, antibiotic use, and annual rate of infection. The most common AEs noted in adults were headache (39%), nausea/vomiting (33%), fatigue (18%), nasal/sinus congestion (15%), rash (12%), arthralgia (9%), diarrhea (9%), and muscle pain/aches, infusion site pain/swelling, abdominal pain/discomfort, cough, dizziness, and menstrual disorder (6% each). The benefit-risk profile is favorable.

### 11.2 Risk-Benefit Summary and Assessment

Risk-Benefit Summary presented in table below.

| Decision Factor | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Analysis of Condition | • Primary Immunodeficiency (PID) represents a heterogenous group of disorders resulting from inherited defects of the immune system.<br>• Patients with PI are at increased risk for recurrent, severe bacterial infections. | • PID are serious, chronic conditions associated with considerable morbidity and mortality.<br>• Immunoglobulin replacement therapy (administered by the intravenous or subcutaneous routes) has been shown to reduce the incidence of serious infections through provision of passive immunity. |
| Unmet Medical Need | • Numerous formulations of intravenous immunoglobulin products are approved for treatment of PI. | • There is currently no unmet need.<br>• There is potential for supply chain disruptions and shortages, so there is a public health benefit for having additional approved immunoglobulin replacement products on the market. |
| Clinical Benefit | • Study participants received IVIG Infusions on a 28-day schedule (n=29) or 21-day schedule (n=20)<br>• There was 1 event of SBI reported during a cumulative total follow-up of 45.9 years in the pivotal study. In adults, the incidence of acute SBIs was 0.03 events per subject per year, with an upper one-sided 99% confidence limit of 0.31.<br>• Subjects treated with GC5107 had similar rate of missed school/work, hospitalizations due to infections, antibiotic use, and annual rate of infection, to the other IGIV approved for treatment of PI. | • The study met its primary endpoint because the incidence of SBIs was less than 1.0 per subject per year (in accordance with FDA Guidance) disproving the null hypothesis.<br>• The product is effective at preventing SBIs in adults ≥ 17 years of age with PI. |
| Risk | • Class-specific risks for Immune Globulin products (AESI) include the following: Thrombosis, Hypersensitivity reactions, Acute renal failure, Hyperproteinemia, Aseptic Meningitis, Hemolysis, Transfusion-related acute lung injury (TRALI), Transmissible infectious agent, Laboratory test interference.<br>• The most common adverse reactions, observed in ≥ 5% of study subjects, were headache, nausea/vomiting, fatigue, nasal/sinus congestion, rash, arthralgia, diarrhea, muscle pain/aches, infusion site pain/swelling, abdominal pain/discomfort, cough, and dizziness. | • ARs with GC5107 are similar to other approved IGIV products<br>• There were no AESI attributed to GC5107. |

| Decision Factor | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Risk Management | • The risks of GC5107 can be managed by clinical monitoring throughout the Infusion and periodic laboratory monitoring of renal function and for hemolysis.<br>• Patients should be educated and monitored for signs and symptoms of hypersensitivity, thrombosis, aseptic meningitis, and TRALI. | • If GC5107 were approved for adults aged ≥ 17 years, labelling and routine pharmacovigilance plan, would be adequate to manage the risks. |

### 11.3 Discussion of Regulatory Options

In the original application, (b) (4) The data are adequate to support approval in adults with a post-marketing required pediatric study.

### 11.4 Recommendations on Regulatory Actions

The clinical team recommends approval of this BLA for ALYGLO for the treatment of primary humoral immunodeficiency in adults.

### 11.5 Labeling Review and Recommendations

The review committee negotiated revisions to the PI, to include Sections 1, 2, 6, 12, and 14. The proposed labeling was reviewed by the Advertising and Promotional Labeling Branch (APLB) and was found acceptable.

### 11.6 Recommendations on Post-marketing Actions

Post-marketing Requirements are necessary for completion of deferred pediatric studies, required under the Pediatric Research Equity Act (PREA) (21 CFR 314.55(b) and 601.27(b)) for the age range ≥ 2 to < 17 years of age.

The Applicant will be required to enroll 6 subjects age ≥12 years to < 17 years in the ongoing study GC5107D, in addition to already planned subjects ages ≥ 2 to < 12 years, with the following amended timeline:

Study Completion Date: May 30, 2026
Final Report Submission: November 30, 2026