

Clinical Pharmacology BLA Review

Division of Clinical Evaluation and Pharmacology/Toxicology (DCEPT),

Office of Tissues and Advanced Therapy (OTAT)

Submission Number: 125743/00

Product Name: Immune Globulin Intravenous (Human), 10% Liquid

Proposed Indication: For the treatment of primary humoral immunodeficiency (PI)

Applicant: Green Cross Corporation

Date Submitted: February 25, 2021

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Reviewer: Million Tegenge, PhD

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Director, DCEPT, OTAT

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1. Executive Summary

In this Biologics License Application (BLA) submission, the Applicant (Green Cross Corporation) has submitted clinical data to license its Immune Globulin (human) Intravenous product (GCC 10% IGIV, ALYGLO) as replacement therapy for primary humoral immunodeficiency (PI) in (b) (4) adult subjects. ALYGLO is newly developed highly purified and concentrated human immunoglobulin G (IgG) antibodies for intravenous administration (IGIV).

The data supporting clinical pharmacology of ALYGLO were obtained from a Phase 3 study that evaluated the pharmacokinetics (PK), safety and efficacy in subjects with Primary Humoral Immunodeficiency. The PK of total IgG were measured in 27 subjects (b) (4) 22 adults aged ≥ 17 to 70 years) following the 5th infusion of ALYGLO. The administered dose of ALYGLO during the PK assessment ranged from 313 to 821 mg/kg. Blood samples for the PK study were collected 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 clearance (baseline uncorrected) was 1.7 mL/day/kg for the 28-day and 2.4 mL/day/kg for the 21-day infusion schedules. The mean half-life (baseline uncorrected) was 29.6 days and 29.0 days for the 28-day and 21-day infusion schedule, respectively. The mean steady state trough total IgG concentrations ranged from 706 to 768 mg/dL for the 28-day dosing regimen and ranged from 763 to 966 mg/dL for the 21-day dosing regimen. These steady state total IgG trough concentrations are comparable with the values obtained at baseline, which reflects the subjects' prior IgG treatment. (b) (4)

(b) (4)

(b) (4)

Overall, the clinical pharmacology data support the approval of the proposed dosing regimen of 300-900 mg/kg every 21 or 28-day infusion as replacement therapy for primary humoral immunodeficiency in adult subjects, (b) (4)

2. Recommendations

The clinical pharmacology information in this BLA is acceptable for approval of ALYGLO in adult subjects, provided that satisfactory agreement is reached between the Applicant and FDA regarding the language in Section 1, 8 and 12 of the proposed package insert. Please refer to the clinical pharmacology labeling comments in page 7 of this review memo.

3. Background

Polyclonal immune globulin preparations of human origin, including immunoglobulin intravenous (IGIV), have long been used as replacement therapy in patients with humoral immunodeficiencies. Although the mechanism of action of IGIV is not fully understood, IGIV is believed to supply a broad spectrum of opsonic and neutralizing IgG antibodies against bacteria or their toxins. ALYGLO is a ready to use, sterile, liquid preparation of highly purified and concentrated human immunoglobulin G (IgG) antibodies. ALYGLO contains 100 mg/mL protein, of which not less than 96% is human IgG obtained from source human plasma.

In this BLA submission the Applicant is seeking approval of ALYGLO as a replacement therapy for primary humoral immunodeficiency (PI) in (b) (4) adult subjects. The data supporting clinical pharmacology of ALYGLO were based on a clinical study entitled: “An Open-Label, Single-Arm, Historically Controlled, Prospective, Multicenter Phase III Study to Evaluate the Safety, Efficacy and Pharmacokinetics (PK) of Immune Globulin Intravenous (Human) GC5107 in Subjects with Primary Humoral Immunodeficiency”. The primary efficacy endpoint of the study was the incidence of serious bacterial infections (SBIs). The primary PK endpoints include assessment of:

- PK parameters of total IgG evaluated in subset of subjects (PK population).
- Trough serum total IgG levels before each infusion of GC5107 in all subjects.

4. Summary of Clinical Pharmacology Findings

- A total of 27 subjects comprised the PK population of which 15 subjects were treated with every 28-day infusion and 12 subjects were treated with every 21-day infusion schedule.
- All subjects included in the PK population were White (100%), with a comparable proportion of males (13 subjects, 48.1%) and females (14 subjects, 51.9%). The age range was between 13 and 70 years.

- The PK population included 22 adults (aged ≥ 17 years; 10 males, 12 females),
(b) (4)
received GC5107 according to the 21-day infusion schedule for PK assessments.
- PK was evaluated after the 5th infusion ($\sim 5\times$ half-life of IgG) and the administered dose of ALYGLO during the PK assessment ranged from 313 to 821 mg/kg.
- For the PK population, the mean administered 21-day dosing regimen for adult
(b) (4) subjects was 657 ± 120 mg/kg (b) (4) respectively.
The mean administered dose for adult subjects in the 28-day dosing regimen was 507 ± 104 mg/kg.
- The mean clearance (baseline uncorrected) was 1.7 mL/day/kg for the 28-day and 2.4 mL/day/kg for the 21-day infusion schedules. The mean half-life (baseline uncorrected) was 29.6 days and 29.0 days for the 28-day and 21-day infusion schedule, respectively.
- The mean clearance (baseline adjusted) was 8.4 mL/day/kg for the 28-day and 8.1 mL/day/kg for the 21-day infusion schedules. The mean half-life (baseline adjusted) was 6 days and 10 days for the 28-day and 21-day infusion schedule, respectively.
- (b) (4)
(b) (4)
(b) (4)
(b) (4)
- 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. For the ITT population, the target steady state trough level was not achieved at least on one occasion during the trial in:
 - a. (b) (4)
 - b. (b) (4)
 - c. 15% adults (5 out of 33, ≥ 17 years of age).
These data indicate that (b) (4)
(b) (4)
(b) (4)

- The overall mean steady state trough total IgG concentrations ranged from 705.7 to 768.1 mg/dL for the 28-day dosing regimen, and ranged from 762.7 to 966.0 mg/dL for the 21-day infusion group.
- These steady state total IgG trough values following administration of ALYGLO were comparable with the values obtained at baseline (726.7 mg/dL for the 28-day dosing group and 820.3 mg/dL for the 21-day dosing group). This baseline IgG trough values reflects previous IgG treatments.
- Overall, the PK of ALYGLO follows the same pattern as other FDA licensed IGIV products and the proposed dosing regimen of 300-900 mg/kg every 21 or 28-day infusion is acceptable as replacement therapy for primary humoral immunodeficiency in adult subjects. (b) (4)

5. Clinical Pharmacology Labeling Comments

1. INDICATIONS AND USAGE

ALYGLO (Immune Globulin Intravenous, Human-XXXX) is a 10% immune globulin liquid for intravenous injection, indicated for the treatment of primary humoral immunodeficiency (PI) in adults (b) (4)

To Applicant: (b) (4)

8.4. Pediatric Use

(b) (4)

12. CLINICAL PHARMACOLOGY

12.3. Pharmacokinetics

Serum concentrations of total IgG were measured in 27 subjects (b) (4) 22 adults aged ≥ 17 to 70 years) following the 5th infusion of ALYGLOIGIV. The administered dose of ALYGLO during the PK assessment ranged from 313 mg/kg to 821 mg/kg. After 5th infusion, Blood samples for PK analyses were collected until Day 22 (± 1 day) or Day 29 (± 2 days) for subjects treated according to the 21 days and 28 days schedule, respectively. (b) (4)

Table 5 summarizes the PK parameters of ALYGLO based on serum concentration of total IgG.

To Applicant: We have included dosing information for PK assessments. PK data from (b) (4)

Please update Table 5 to include PK parameters reflecting both baseline unadjusted and adjusted total IgG level. Please also include updated parameters for clearance and AUC0-last based on the analysis per your response to our clinical pharmacology information request. Please remove AUC0-24 as it is not providing any useful information.

6. Appendix

6.1. Study#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 overall objective of the study was to assess the safety, efficacy, and pharmacokinetics (PK) of GC5107 in subjects with Primary Humoral Immunodeficiency (PHID). The primary PK objectives were to evaluate:

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

The 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-*Haemophilus influenzae* type b, anti-*Streptococcus pneumoniae* serotypes, anti-Tetanus toxoid, and anti-CMV
- Number and proportion of subjects who failed to meet the target IgG trough level (500 mg/dL) at any time point equal to or subsequent to 5th infusion (estimated 5 half-lives).

Eligible subjects received intravenous infusions of the study product 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 days or every 28 ± 4 days (depending on their pre-study IGIV treatment schedule) for 12 months of study infusions. The dose could be adjusted by the investigator according to the individual subject's need and body weight.

Blood samples were collected from all subjects (intention-to-treat (ITT) population) at screening, prior to each infusion of GC5107 and at the follow-up visit to determine the serum trough levels of total IgG. In addition, samples to determine IgG subclasses and trough levels of specific antibodies were collected at the 1st, 5th, 9th, and 13th infusion for subjects on the 28-day infusion schedule, and at the 1st, 5th, 11th, and 17th infusion for subjects on the 21-day infusion schedule. Blood samples were collected from a subset of subjects (PK population) after the 5th infusion of IMP to determine the serum concentration of total IgG, IgG subclasses, and to derive the PK parameters for total IgG. Blood samples for PK analysis were obtained at 10-30 pre-infusion and at the following sampling points post-infusion (after the 5th infusion):

- 0.5, 2, 24, 48 hours
- 4, 8, 15, 22 days.
- Additional 29-day sample was collected for those subjects on the 28-day infusion schedule.

Demographics, and Dosing Information (ITT Population)

The total population of 49 enrolled subjects included 33 adults (aged ≥17 years; 15 males, 18 females), eight adolescents (aged ≥12 to <17 years; six males, two females) and eight children (aged ≥2 to <12 years; seven males, one female). All subjects had been receiving IGIV infusions at regular 21- or 28-day intervals prior to enrollment, at a dose level between 319 and 826 mg/kg (mean =538.5 mg/kg). The mean IGIV dose was lower among subjects treated at the 28-day vs. the 21-day schedule (501.2 vs. 592.7 mg/kg, respectively). The dose administered during the present study ranged from (b) (4) (b) (4) 319-817 mg/kg (adults). Dosing frequency of GC5107 is summarized for each age group as follows:

- Every 28-days: 23 adults, 2 adolescents and 4 children
- Every 21-days: 10 adults, 6 adolescents and 4 children

Pharmacokinetic Parameters of Total IgG Following Administration of GC5107

A total of 27 subjects comprised the PK population, including 15 subjects treated according to the 28-day infusion schedule and 12 subjects treated according to the 21-day infusion schedule. All subjects included in the PK population were White (100.0%), with a similar proportion of males (13 subjects, 48.1%) and females (14 subjects, 51.9%). The age range was between 13 and 70 years, with 6 subjects aged above 65 years. The PK population included 22 adults (aged ≥ 17 years; 10 males, 12 females), (b) (4)

The administered dose of IMP during the PK assessment ranged from 313 mg/kg to 821 mg/kg. The mean administered 21-day dosing regimen for adult (b) (4) was 657 ± 120 mg/kg (b) (4) respectively. The mean administered dose for adult subjects in the 28-day dosing regimen was 507 ± 104 mg/kg (Table 1).

Table 1: Summary of dosing administered during the PK evaluation

| Age Group | Dose (mg/kg) |
|------------------------------|-------------------------|
| 21-Day Dosing Regimen | |
| (b) (4) | |
| ≥ 17 years (n=7) | 657 ± 120 (462-821) |
| 28-Day Dosing Regimen | |
| (b) (4) | |
| ≥ 17 years (n=13) | 507 ± 104 (313-691) |

Source: Reviewer Analysis

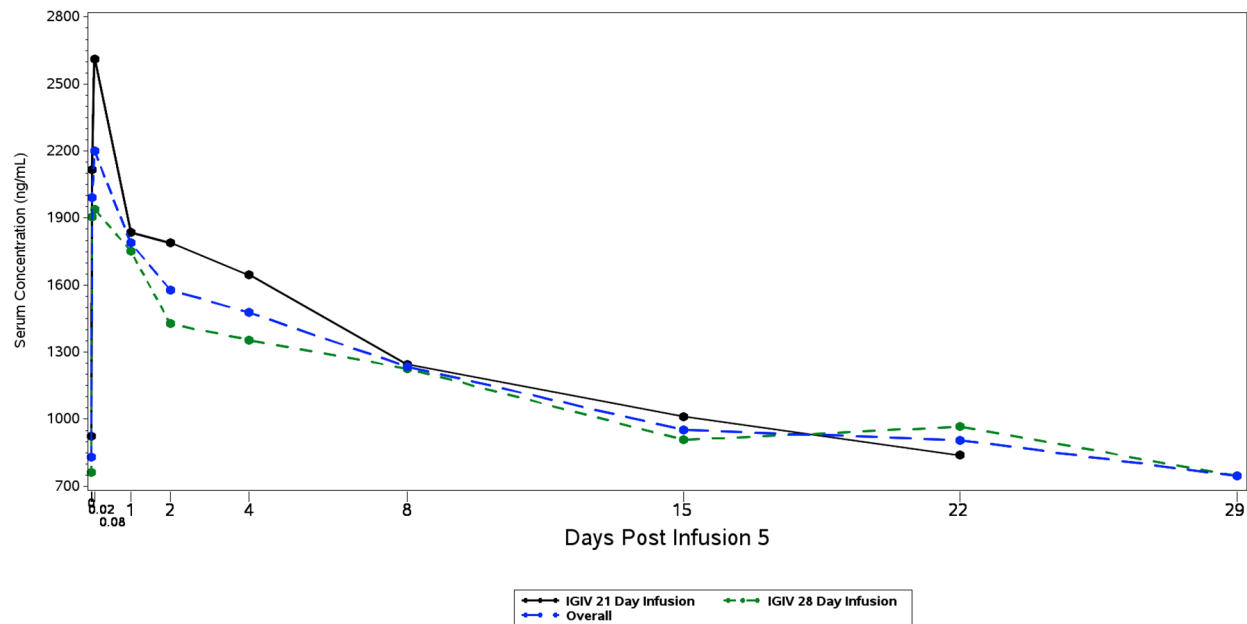
PK parameters of total IgG (uncorrected for baseline) is summarized in Table 2. The mean uncorrected total IgG C_{max} values were 2122 mg/dL and 2245 mg/dL for the 28-day and 21-day infusion schedule groups, respectively. The mean clearance was 1.7 mL/day/kg for the 28-day and 2.4 mL/day/kg for the 21-day infusion schedules. The mean half-life was 29.6 days and 29.0 days for the 28-day and 21-day infusion schedules, respectively (Table 2). The baseline uncorrected concentrations of total IgG were generally higher in the 21-day vs 28-day infusion schedule up to 15 days post-infusion (Figure 1).

Table 2: Pharmacokinetics of Total IgG (Uncorrected for baseline) After the 5th Infusion of GC5107 (PK Population)

| Infusion Schedule | | AUC _{0-tau} (day*mg/dL) | CL (mL/day/kg) | V _{ss} (mL/kg) | V _z (mL/kg) | MRT (day) | T _{1/2} (day) | C _{max} (mg/dL) |
|---------------------------|------|-------------------------------------|-------------------|----------------------------|---------------------------|--------------|---------------------------|-----------------------------|
| 28-day Infusion (N=15) | N | 15 | 15 | 3 | 3 | 3 | 11 | 15 |
| | Mean | 31020 | 1.683 | 48.24 | 49.40 | 27.38 | 29.58 | 2122 |
| | SD | 6100.7 | 0.42885 | 4.4040 | 5.1507 | 8.4026 | 11.017 | 350.29 |
| | Min | 24500 | 0.7723 | 44.18 | 46.34 | 19.44 | 13.17 | 1501 |
| | Max | 46680 | 2.449 | 52.92 | 55.35 | 36.18 | 51.51 | 2668 |
| 21-day Infusion (N=12) | N | 11 | 11 | 2 | 2 | 2 | 10 | 11 |
| | Mean | 26220 | 2.420 | 63 | 65.86 | 20.15 | 28.98 | 2245 |
| | SD | 4316.9 | 0.65482 | 0.54446 | 5.8575 | 1.3356 | 25.294 | 405.98 |
| | Min | 18470 | 1.675 | 62.62 | 61.72 | 19.21 | 13.12 | 1601 |
| | Max | 34320 | 3.404 | 63.39 | 70.01 | 21.10 | 99.80 | 3129 |

Source: Table 14.4.1.1; updated PK analysis based on clinical pharmacology information request.

Figure 1. Baseline Uncorrected Geometric Mean IgG Serum Concentration by Time Points for 21-day and 28-day Infusion Schedule



Source: CSR, Figure 14.4.1.3

PK parameters for baseline adjusted total IgG is summarized in Table 3. Baseline-adjusted concentration data were obtained by subtracting the pre-infusion baseline concentration from post-baseline (on-treatment) serum concentrations. The IgG concentration profiles based on baseline adjusted values is displayed in Figure 2. The mean clearance was 8.4 mL/day/kg for the 28-day and 8.1 mL/day/kg for the 21-day infusion schedules. The mean half-life was 6 days and 10 days for the 28-day and 21-day infusion schedules, respectively (Table 3).

Table 3: Pharmacokinetics of Baseline-adjusted Total IgG After the 5th Infusion of GC5107 (PK Population)

| Infusion Schedule | | T _{1/2} (day) | T _{max} (day) | C _{max} (mg/dL) | C _{min} (mg/dL) | IR [(mg/dL)/ (mg/kg)] | AUC _{0-inf} (day*mg/dL) | AUC _{0-t} (day*mg/dL) | AUC Ext (%) | V _{ss} (mL/kg) | V _z (mL/kg) | CL (mL/day/kg) | MRT (day) |
|------------------------|------|---------------------------|---------------------------|-----------------------------|-----------------------------|-----------------------------|-------------------------------------|-----------------------------------|----------------|----------------------------|---------------------------|-------------------|--------------|
| 28-day Infusion (N=15) | N | 11 | 15 | 15 | 15 | 15 | 11 | 15 | 11 | 11 | 11 | 11 | 11 |
| | Mean | 5.996 | 0.2455 | 1353 | 0 | 2.698 | 10930 | 10190 | 11.27 | 47.35 | 44.65 | 8.397 | 9.152 |
| | SD | 3.0308 | 0.33851 | 352.88 | 0 | 0.59964 | 8185.3 | 7240.9 | 10.446 | 16.812 | 18.037 | 9.0532 | 4.6188 |
| | Min | 0.6088 | 0.07500 | 833.0 | 0 | 1.955 | 1170 | 1119 | 0.08129 | 26.04 | 22.35 | 1.696 | 1.131 |
| | Max | 9.829 | 1.080 | 1955 | 0 | 3.965 | 31310 | 28420 | 38.94 | 83.40 | 81.52 | 34.09 | 15.35 |
| 21-day Infusion (N=12) | N | 8 | 12 | 11 | 12 | 11 | 6 | 11 | 6 | 6 | 6 | 6 | 6 |
| | Mean | 9.556 | 0.7025 | 1321 | 0 | 2.184 | 8156 | 6852 | 9.533 | 56.85 | 57.43 | 8.082 | 7.101 |
| | SD | 9.9996 | 0.98993 | 352.57 | 0 | 0.69977 | 23160 | 30430 | 5.5285 | 24.907 | 28.295 | 2.8524 | 2.5530 |
| | Min | 2.556 | 0.07431 | 546.0 | 0 | 1.358 | 5317 | 2524 | 4.054 | 26.28 | 22.22 | 5.999 | 4.362 |
| | Max | 32.46 | 3.113 | 1773 | 0 | 3.602 | 11450 | 10850 | 17.22 | 91.11 | 97.19 | 12.58 | 11.33 |
| Total (N=27) | N | 19 | 27 | 26 | 27 | 26 | 17 | 26 | 17 | 17 | 17 | 17 | 17 |
| | Mean | 7.495 | 0.4486 | 1339 | 0 | 2.481 | 9952 | 8780 | 10.65 | 50.70 | 49.16 | 8.286 | 8.428 |
| | SD | 6.8738 | 0.72791 | 346 | 0 | 0.68151 | 6739.4 | 5991.4 | 8.8592 | 19.809 | 22.207 | 7.3343 | 4.0486 |
| | Min | 0.6088 | 0.07431 | 546.0 | 0 | 1.358 | 1170 | 1119 | 0.08129 | 26.04 | 22.22 | 1.696 | 1.131 |
| | Max | 32.46 | 3.113 | 1955 | 0 | 3.965 | 31310 | 28420 | 38.94 | 91.11 | 97.19 | 34.09 | 15.35 |

Source: CSR, Table 11-14

Reviewer comments: The PK of GC5107 follows the similar pattern as other FDA licensed IGIV products. (b) (4)

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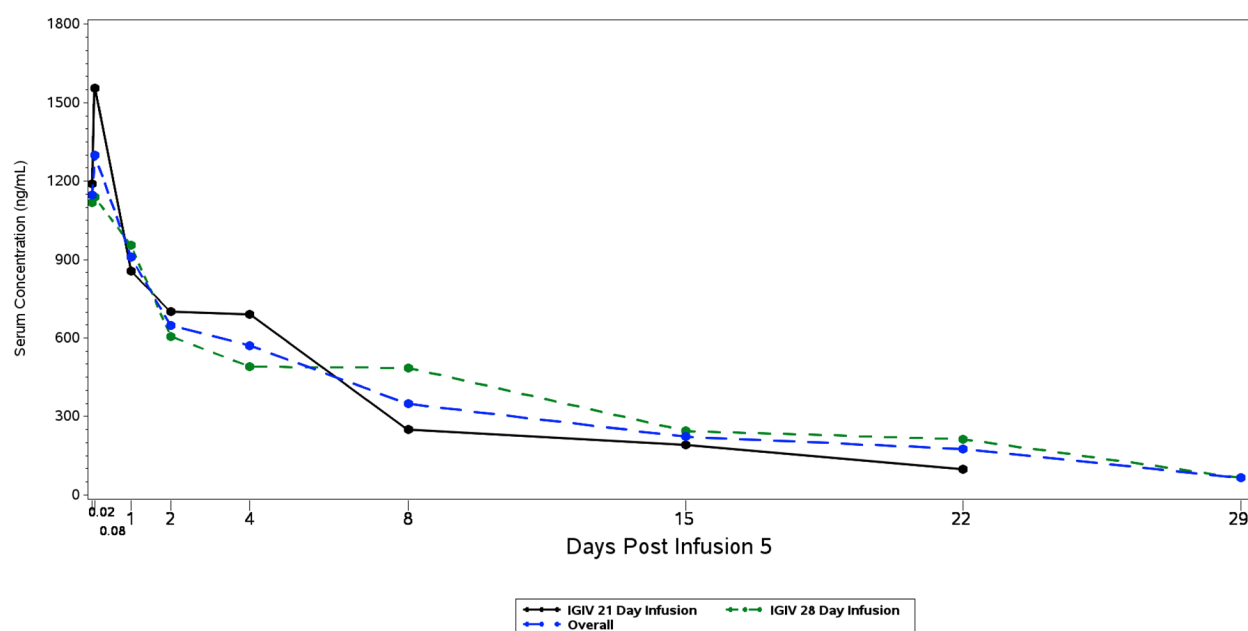
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(b) (4)

Figure 2. Baseline Adjusted Geometric Mean IgG Serum Concentration by Time Point for 21-day and 28-day Infusion Schedule



Source: CSR, Figure 14.4.1.2

Trough Concentrations of Total IgG

The trough IgG concentrations before each infusion of GC5107 are summarized in Table 4. The baseline mean serum trough levels (i.e., prior to the first infusion of GC5107) for total IgG were 726.7 mg/dL and 820.3 mg/dL for the 28-day and 21-day infusion groups, respectively. For the 28-day infusion group, mean steady state trough total IgG concentrations ranged from 705.7 to 768.1 mg/dL from Infusion 5 through Infusion 13. For the 21-day infusion group, mean steady state trough total IgG concentrations ranged from 762.7 to 966.0 mg/dL from Infusion 5 through Infusion 17 (Table 4).

Table 4: Summary of Trough Total IgG Concentrations Before Each GC5107 Infusion (ITT Population)

| Infusion Sched. | Stat. | Infusion Number | | | | | | | | | | | | | | | | |
|------------------------|-------|-----------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 |
| 28-day Infusion (N=29) | N | 29 | 28 | 26 | 26 | 26 | 26 | 26 | 24 | 25 | 25 | 25 | 24 | 24 | NA | NA | NA | NA |
| | Mean | 726.7 | 734.0 | 750.7 | 721.8 | 730.8 | 708.3 | 732.5 | 711.3 | 737.8 | 756.4 | 731.1 | 768.1 | 705.7 | | | | |
| | SD | 159.11 | 148.45 | 239.12 | 147.43 | 171.03 | 155.32 | 158.84 | 162.89 | 173.76 | 178.63 | 178.06 | 323.39 | 139.07 | | | | |
| | Min | 427 | 395 | 415 | 466 | 417 | 435 | 460 | 458 | 457 | 482 | 319 | 410 | 515 | | | | |
| | Max | 1031 | 1120 | 1398 | 967 | 1156 | 1076 | 1037 | 975 | 1072 | 1275 | 1042 | 1969 | 961 | | | | |
| 21-day Infusion (N=20) | N | 20 | 20 | 20 | 20 | 20 | 19 | 20 | 20 | 20 | 18 | 19 | 19 | 19 | 19 | 19 | 19 | 19 |
| | Mean | 820.3 | 837.5 | 824.3 | 830.6 | 798.1 | 801.3 | 762.7 | 790.9 | 832.7 | 854.4 | 894.0 | 898.7 | 880.9 | 928.8 | 828.7 | 966.0 | 860.3 |
| | SD | 196.89 | 145.55 | 142.09 | 159.29 | 144.42 | 189.21 | 176.87 | 120.44 | 147.25 | 222.82 | 294.62 | 169.84 | 187.51 | 189.67 | 262.65 | 293.04 | 157.34 |
| | Min | 471 | 565 | 514 | 432 | 507 | 506 | 496 | 601 | 621 | 623 | 570 | 605 | 615 | 647 | 326 | 602 | 623 |
| | Max | 1202 | 1184 | 1084 | 1036 | 999 | 1150 | 1141 | 1055 | 1160 | 1636 | 1922 | 1229 | 1408 | 1329 | 1587 | 1603 | 1228 |
| Total (N=49) | N | 49 | 48 | 46 | 46 | 46 | 45 | 46 | 44 | 45 | 43 | 44 | 43 | 43 | 19 | 19 | 19 | 19 |
| | Mean | 764.9 | 777.1 | 782.7 | 769.1 | 760.0 | 747.6 | 745.6 | 747.4 | 780.0 | 797.4 | 801.5 | 825.8 | 783.1 | 928.8 | 828.7 | 966.0 | 860.3 |
| | SD | 179.65 | 154.52 | 204.09 | 160.50 | 161.84 | 174.66 | 165.69 | 149.02 | 167.64 | 201.80 | 246.36 | 271.92 | 182.78 | 189.67 | 262.65 | 293.04 | 157.34 |
| | Min | 427 | 395 | 415 | 432 | 417 | 435 | 460 | 458 | 457 | 482 | 319 | 410 | 515 | 647 | 326 | 602 | 623 |
| | Max | 1202 | 1184 | 1398 | 1036 | 1156 | 1150 | 1141 | 1055 | 1160 | 1636 | 1922 | 1969 | 1408 | 1329 | 1587 | 1603 | 1228 |

Source: CSR, Table 14.4.2

The number and proportion of subjects who failed to meet the target trough IgG level of 500 mg/dL at any time point at or following the 5th infusion of GC5107 are summarized in Table 5. As shown more subjects in the 28-day compared to the 21-day infusion groups (9 of 26 subjects [34.6%] vs 3 of 20 subjects [15.0%], respectively) had at least one trough IgG concentration level measured below the 500 mg/dL target between Infusion 5 and the Follow-up visit (Table 5). At individual time-points between Infusion 5 and the Follow-up visit, up to four subjects in the 28-day, and no more than one subject in the 21-day infusion schedule group failed to meet the target trough IgG level of 500 mg/dL (Table 5). The following is demographic characteristics of the 12 subjects with at least one trough IgG concentration below the target 500 mg/dL:

- (b) (4)
- (b) (4)
- Five adults (aged 22 to 69 years, 5/12 subjects, 42%),
- Ten males (10/12 subjects, 83.3%)

There were 18 measurements of trough IgG levels below the 500 mg/dL target in the 12 subjects. However, none of the 12 subjects with at least one below-target trough IgG

level experienced a serious infection, and only one of the 12 subjects experienced a non-serious infection within four weeks (one IMP cycle) after a below target trough IgG measurement.

Also, trough levels for specific antibodies were evaluated. The mean trough levels of *anti-Haemophilus Influenzae type B*, *anti-Streptococcus pneumoniae*, and anti-tetanus toxoid antibodies are comparable to pre-treatment values throughout the treatment period in both 21-day and 28-day infusion groups. All subjects tested positive for anti-CMV IgG antibodies. Currently, the clinical application of trough level of antibodies against specific pathogens is not fully understood.

Reviewer comments: For the ITT population, the proposed target steady state trough level of 500 mg/dL is not achieved at least on one occasion in:

- (b) (4)
- (b) (4)
- 15% adults (5 out of 33, ≥ 17 years of age)

It should be noted that the optimum trough level for IgG products is not known but a meta-analysis study suggested that the risk of pneumonia can be significantly reduced by higher trough IgG levels.¹ In the present study, the overall mean steady state total IgG level following treatment with GC5107 is comparable with baseline IgG level (corresponding with subject previous IgG treatment). These trough data and the overall PK profile of the GC5107 indicate that the proposed dosing regimen is acceptable as replacement therapy for primary humoral immunodeficiency in adult subjects. (b) (4)

¹ Orange, J.S.; Grossman, W.J.; Navickis, R.J.; Wilkes, M.M. Impact of Trough IgG on Pneumonia Incidence in Primary Immunodeficiency: A Meta-Analysis of Clinical Studies. Clin. Immunol. 2010, 137, 21–30.

Table 5: Number and Proportion of Subjects Who Failed to Meet the Target IgG Trough Level (500 mg/dL) At or After the 5th Infusion (ITT Population)

| | 28-day Infusion (N=29) n/n` (%) | 21-day Infusion (N=20) n/n` (%) | Total (N=49) n/n` (%) |
|--|--|--|-----------------------------|
| Number of subjects who failed to meet the target IgG trough level (500 mg/dL) at least once at or after the 5th Infusion | 9/26 (34.6) | 3/20 (15.0) | 12/46 (26.1) |
| Infusion 5 | 3/26 (11.5) | 0/20 (0.0) | 3/46 (6.5) |
| Infusion 6 | 1/26 (3.8) | 0/19 (0.0) | 1/45 (2.2) |
| Infusion 7 | 1/26 (3.8) | 1/20 (5.0) | 2/46 (4.3) |
| Infusion 8 | 4/24 (16.7) | 0/20 (0.0) | 4/44 (9.1) |
| Infusion 9 | 2/25 (8.0) | 0/20 (0.0) | 2/45 (4.4) |
| Infusion 10 | 1/25 (4.0) | 0/18 (0.0) | 1/43 (2.3) |
| Infusion 11 | 2/25 (8.0) | 0/19 (0.0) | 2/44 (4.5) |
| Infusion 12 | 1/24 (4.2) | 0/19 (0.0) | 1/43 (2.3) |
| Infusion 13 | 0/24 (0.0) | 0/19 (0.0) | 0/43 (0.0) |
| Infusion 14 | | 0/19 (0.0) | 0/19 (0.0) |
| Infusion 15 | | 1/19 (5.3) | 1/19 (5.3) |
| Infusion 16 | | 0/19 (0.0) | 0/19 (0.0) |
| Infusion 17 | | 0/19 (0.0) | 0/19 (0.0) |
| Follow Up Visit | 0/24 (0.0) | 1/20 (5.0) | 1/44 (2.3) |

Source: CSR, Table 14.4.5