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Green Cross Corporation

GC5107B_P3

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

Statistical Analysis Plan

Version: 4.0

[redacted]

SPONSOR SIGNATURE PAGE

Approved by: [redacted]

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REVISION HISTORY

Version No.	Effective Date	Summary of Change(s)
1.0	17 Jun 16	New document
2.0	19 Oct 16	• Section 4.3.1 (Disposition of Subjects), added more details to the summary of subject withdrawn from study. • Section 4.5 (Demographic and Other Baseline Characteristics ….), deleted the analysis of "Prior only" medication. • Section 4.7.1.3 (Handling of Dropouts or Missing Data), deleted the summary of missing data for the primary endpoint. • Section 4.9 (Pharmacokinetic Endpoint), QCD scientist added details for PK analysis. QCD scientist co-author the SAP • MedDRA dictionary version changed from 18.1 to 19.1 • Correct "first dose" to "first infusion", "last dose" to last infusion.
3.0	06 Aug 19	• According to Protocol v2.0 Amendment 1, added safety visits (72 hours after the end of the first and second infusion). Second Follow-up after last infusion is deleted. • According to Protocol v2.0 Amendment 2, Time windows for PK sampling points are clarified in section 4.9, in addition to Pharmacokinetic Parameters of Total IgG and Serum Levels of IgG Subclasses. • According to according Protocol v 2.0 Amendment 3, the number of pediatric subjects is changed from 12 to 8. The wording of 'evaluable' is deleted in the definition of analysis population. • According the FDA's review feedback, added ITT2 population, and geographic region. • Added imputation method to the algorithm of duration of AEs during infusion, and the duration of hospitalization. • Added the definition of follow-up time for each subject. • Added clarification for Aes that occur during or within (a) 1 hour, (b) 24 hours, and (c) 72 hours following an infusion; clarification for time of onset of Aes occurs during infusion, and AE duration;

		clarification for AE leading to discontinuation, dose interruption, and rate change. • Deleted summary of abnormal vital sign. • Clarified the PK endpoint and corresponding analysis population. • In Section 4.11, clarified any analysis that is deviated from protocol specified statistics analysis. • To clarify the meaning and to be consistent through the whole texts, some words are revised or added.
4.0	Date of last signature	• Added imputation rule for partial first lifetime IGIV infusion date. • Added imputation rule for missing or partial AE start date, when analyzing the yearly duration of infections. • Clarify the definition of infections in section 4.7.3. • Added Protocol Version 2, Amendment 1 REB Approval Dates to Appendices. • Section 4.7.3, add clarification of handle subject with no experience of event. • Section 4.4.3, add clarification of trough IgG level categorization. • Added Section 4.7.4 Exploratory Efficacy Variable

LIST OF ABBREVIATIONS

ADR	Health Canada's Adverse Drug Reaction
AE	Adverse event
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
AUMC	Area under the concentration times time versus time curve
BLQ	Below the Limit of Quantitation
CIOMS	Council for International Organizations of Medical Sciences
CI	Confidence interval
CL	Total body clearance
C_{max}	Maximum concentration
C_{min}	Minimum (trough) concentration
CMV	Cytomegalovirus
CRF	Case report form
CVID	Common variable immunodeficiency
DAT	Direct Antiglobulin (Coombs) test
DB	Database
DNA	Deoxyribonucleic acid
DSMB	Drug Safety Monitoring Board
eCRF	Electronic case report form
FDA	Food and Drug Administration
GEE	Generalized Estimating Equation
HAV	Hepatitis A virus
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
ICH	International Conference of Harmonization
IgG	Immunoglobulin G
IGIV	Immune globulin intravenous
IM	Intramuscular
IMIG	Intramuscular immune globulin
IND	Investigational New Drug
IR	Incremental recovery
ITT	Intention-to-treat
IV	Intravenous
kg	Kilogram
λ_Z	Elimination rate constant
mg	Milligram
MedDRA	Medical dictionary for regulatory activities
MRT	Mean residence time
n	Number of subjects providing data at the relevant visit
NAT	Nucleic Acid Testing
PASS	Power and Sample Size
PCR	Polymerase chain reaction

PD Spec	Protocol deviation specification
PHID	Primary humoral immunodeficiency
PK	Pharmacokinetic
PO	Oral
PN	Preferred name
PP	Per-protocol
PT	Preferred term
QCD	Quantitative Clinical Development
RNA	Ribonucleic acid
REB	Research Ethics Board
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SD	Standard deviation
SI	International System of Units
SOC	System organ class
$t_{1/2}$	Elimination half-life
T_{max}	Time point of maximum concentration (C_{max})
TEAE	Treatment emergency adverse event
Vd	Volume of distribution
V_{ss}	Volume of distribution at steady state
V_z	Volume of distribution during terminal phase
WHO	World Health Organization

1 INTRODUCTION

Primary humoral immunodeficiency (PHID) diseases occur in persons with inherited defects of their immune systems [1]. Antibody deficiencies, also referred to as B-cell or humoral immunodeficiencies, comprise the largest group of PHIDs. Common variable immunodeficiency (CVID) is the most frequent PHID with an estimated prevalence of 1 in 50,000 [2]. It is defined principally as low IgG, IgA, and/or IgM together with a significant impairment of specific antibody production in response to vaccination or natural infection.

Early treatment of PHID included subcutaneous and intramuscular (IM) injections of 16% Immune Serum Globulin. Since the introduction of IgG preparations suitable for IV use, immune globulin intravenous (IGIV) has become the standard of care for PHID patients with antibody deficiency. With the introduction of IGIV preparations, doses have increased from previous intramuscular immune globulin (IMIG) doses of 100 to 200 mg/kg/month. The optimal dose and frequency of IGIV administration must be determined individually for each subject. For subjects with PHID, monthly doses of approximately 300 to 600 mg/kg infused every 21-28 days is commonly used [3, 4]. Studies have shown that some patients, particularly those with chronic/recurrent sinopulmonary disease, do better with higher doses in the range of 800 mg/kg/dose [5, 6].

The purpose of this statistical analysis plan (SAP) is to specify the statistical analysis in more detail than stated in the clinical study protocol and to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be applied, are complete and appropriate to reach valid conclusions regarding the study objectives.

This SAP is written in accordance with principles described in the International Conference of Harmonization (ICH) Guideline E9 and is based upon the following study documents:

- Study Protocol, Version 2.0 Amendment 3 (January 04, 2019)
- electronic Case Report Form (eCRF), (RR05 October 24, 2017)

2 STUDY OBJECTIVES

The objective of this study is to assess the safety, efficacy and pharmacokinetics (PK) of GC5107 in subjects with PHID.

2.1 Primary Efficacy Endpoint/Variable

- The incidence of acute serious bacterial infections meeting United States Food and Drug Administration (FDA) guidance criteria (bacterial pneumonia, bacteremia/sepsis, bacterial meningitis, visceral abscess, osteomyelitis/septic arthritis) [3]. The upper one-sided 99% confidence limit for the frequency of acute serious bacterial infections with GC5107 must be less than 1.0 per subject per year.

2.2 Secondary Efficacy Endpoints/Variables

- 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 in order to care for the child due to infections.
- The number of days of unscheduled physician visits due to infections.
- The number of days of hospitalizations due to infections.
- The number of days of IV therapeutic antibiotics.
- The number of days of oral (PO) therapeutic antibiotics.
- Time to resolution of infections.
- The incidence of infections other than serious bacterial infections by trough IgG levels.

2.3 Primary Safety Endpoint/Variable

- The proportion of infusions with temporally associated 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).

2.4 Secondary Safety Endpoints/Variables

- 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 examination, and laboratory 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): HIV-1&2, HAV, HBV, HCV, and parvovirus B19.

2.5 Primary Pharmacokinetic Endpoints/Variables

- Pharmacokinetic parameters of total IgG (assessed in PK population).

- Trough serum total IgG levels before each infusion of GC5107 in all subjects and the interval between infusions will be recorded.

2.6 Secondary Pharmacokinetic Endpoints/Variables

- PK parameters of IgG subclasses (assessed in PK population).
- Trough serum level of IgG subclasses and specific IgG antibodies before Infusions 1, 5, 9, 13 (for 28-day infusion subject) or Infusions 1, 5, 11, 17 (for 21-day infusion subject)
    - anti-*Hemophilus influenza* type b
    - anti-*Streptococcus pneumonia* serotypes
    - anti-Tetanus toxoid
    - anti-Cytomegalovirus (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).

3 INVESTIGATIONAL PLAN

This will be a prospective, open-label, single-arm, multicenter, historically controlled, Phase III study measuring the safety, efficacy, PK, and tolerability of GC5107 in subjects with PHID.

- The study design is an open-label, uncontrolled study of at least 26 adult subjects, at least 8 adolescent subjects aged ≥ 12 to < 17 years and at least 8 child subjects aged ≥ 2 to < 12 years with well-defined PHID.
- To guard against dropout and to assure more than adequate power, up to 50 subjects will be enrolled.
- All subjects will be followed for 12 months during which infusions will be given every 21 or 28 days.
- To demonstrate efficacy, the serious bacterial infection rate will be required to have an upper one-sided 99% confidence limit less than 1.0 per subject per year.
- Pharmacokinetics will be determined after the 5th study infusion.

Duration of the Study

The study period for each subject is expected to be 14 months, including up to 28 days for screening prior to the first infusion, 12 months of study infusions, a follow-up visit at the infusion cycle month (21 or 28 days) to collect safety and efficacy data for viral marker tests (see Sections 5.8.7 of Study Protocol for additional details).

Investigators and Study Centers

A sufficient number of study sites to enroll up to 50 subjects to obtain at least 26 adult subjects, at least 8 adolescent subjects and at least 8 child subjects will be recruited. Subjects who withdraw (or are withdrawn) will not be replaced.

Randomization and Stratification

Not applicable.

Blinding

Not applicable.

Treatment Regimens

All subjects will receive intravenous infusions of investigational product at the same dose and interval as used for their previous IGIV maintenance therapy. GC5107 will be administered at a dose of 300 - 900 mg per kg (of body weight) every 21 or 28 days (± 4 days) for a period of 12 months.

Visit Schedule

The Table 1 below summarizes the timeline for the study. For detailed visit schedule, please refer to the study protocol for GC5107B_P3 (Section 5.8).

Table 1: Study Timeline

Procedure **28 day regimen** **(21 day regimen in parentheses)**	**Time**	
Screening*	Day -28 to Day -1 (Day -21 to Day -1)	Up to 28 days prior to the first infusion
Infusion 1	Week 0, D1 Baseline	12 months of infusions
Infusion 2-4 (Infusion 2-4)	Week 4 – 12 (Week 3-9)	
PK Assessment Infusion 5 (Infusion 5)	Week 16 (Week 12)	
Infusion 6 – 13 (Infusion 6 - 17)	Week 20 – 48 (Week 15- 48)	

Follow-up: 4 weeks after last infusion (3 weeks after last infusion)	Week 52 (Week 51)	3 or 4 weeks after the last investigational product infusion

Note: The screening procedures can occur only after a potential subject has signed the ICF. Results of screening must be obtained before the first study infusion.

4 STATISTICAL METHODS

4.1 Data Quality Assurance

All tables, figures and data listings to be included in the report will be independently checked for consistency, integrity and in accordance with [redacted].

4.2 General Presentation Considerations

'Baseline' is defined as the last available pre-treatment assessment, unless specified in later section. 'End of Study' is defined as the last available post-treatment assessment. 'Treatment Day' will be calculated relative to the date of the first infusion of GC5107, i.e. Treatment Day = Assessment Date - First Infusion Date + 1 (if on or after day of first infusion); or Treatment Day = Assessment Date - First Infusion Date (if before day of first infusion).

Continuous data will be summarized in terms of the mean, standard deviation (SD), median, minimum, maximum and number of observations, unless otherwise stated. Continuous data that are expected to be skewed will be presented in terms of the maximum, 75% quantile, median, 25% quantile, minimum and number of observations. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, lower quartile and upper quartile will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic.

Categorical data will be summarized in terms of the number of subjects providing data at the relevant time point (n), frequency counts and percentages. . Any planned collapsing of categories will be detailed in the SAP text and the data displays.

Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentages will be calculated using N as the denominator unless otherwise indicated. If sample sizes are small, the data displays will show the percentages, but any textual report will describe frequencies only.

Changes from baseline in categorical data will be summarized using shift tables where appropriate. For continuous variables, actual values and changes from baseline will be summarized using descriptive statistics across infusion schedule and overall by visit.

P-values greater than or equal to 0.001, in general, will be presented to three decimal places. P-values less than 0.001 will be presented as "<0.001".

Confidence intervals will be presented to one more decimal place than the raw data.

All report outputs will be produced using SAS® version 9.3 or a later version in a secure and validated environment.

4.3 Study Subjects

4.3.1 Disposition of Subjects

A clear accounting of the disposition of all subjects who enter the study will be provided, from screening to study completion.

The following subject data will be presented by infusion schedule and overall:

- A summary of the number of subjects screened for entry into the study and the number and percentage of subjects excluded prior to the first infusion of GC5107 by major reason and overall (Analysis population: All Subjects)
- A summary of the number of subjects treated (with at least one dose of study medication) per center (Analysis population: All Subjects Enrolled)
- A summary of the number and percentage of subjects treated (with at least one dose of study medication), withdrawing after enrollment but prior to first infusion, withdrawing after first infusion and completing each visit of the study. (Analysis population: All Subjects Enrolled). Withdrawals after enrollment but prior to first infusion and withdrawals after first infusion should also be summarized by major reason.

In addition, by-subject listings of eligibility details, visit dates and withdrawal/study completion details (including reason for discontinuation and duration of treatment prior to discontinuation) will be provided.

4.3.2 Protocol Deviations

Protocol deviations will be identified on an ongoing basis by the clinical study team and assessed as "minor" or "major" in consultation with the Sponsor. Major protocol deviations are defined as those deviations from the study protocol that are likely to have an impact on the subject's rights, safety, well-being, and/or on the validity of the data for analysis The impact of major protocol deviations on the efficacy and/or safety results will be investigated by assessing the robustness of the study results and conclusions to the choice of analysis population (see Section 4.4), both including and excluding data potentially affected by major protocol deviations.

Protocol deviations and any action to be taken regarding the exclusion of subjects or affected data from specific analyses are defined in Protocol Deviation Specification (PD Spec).

A summary of the number and percentage of subjects with a major protocol deviation by type of deviation will be given by infusion schedule and overall (Analysis population: All Subjects Enrolled). A by-subject listing of major protocol deviations will also be provided.

4.4 Analysis Populations

The primary safety and efficacy analysis will be based on the intention-to-treat (ITT) population. The ITT population will consist of all subjects who are enrolled into the study and received any amount of investigational product.

The per-protocol (PP) population will also be analyzed for efficacy. The PP population will consist of all subjects in the ITT population who complete the whole 12-month study period and who do not have any major protocol violations, which are likely to have an impact on the validity of the data for analysis.

The intention-to-treat (ITT2) second population will consist of all ITT subjects who are enrolled into study following Protocol Version 2.0 amendment 1 (March 16, 2017) onwards. Subjects who are enrolled into study following Protocol Version 1.0 amendment 3 will be excluded. Protocol Version 2, Amendment 1 REB approval dates of each site is listed in Appendices. This population will be used to perform a sensitivity analysis for the assessment of the primary efficacy and safety endpoint.

All PK analyses will be based on the PK population. The PK population will be defined as a subset of adult and adolescent subjects in the ITT population who participate in the PK study and have at least one PK sample collected. At least 20 adult and adolescent subjects will be in the PK population. Blood samples required for PK analysis will be taken before and after the 5th study infusion for those subjects who consent to the PK portion of the study.

Upon database release, protocol deviation and analysis population outputs will be produced and will be sent to the Sponsor for review. An analysis population classification meeting (data review meeting) will be arranged to discuss the outputs and to decide which subjects and/or subject data will be excluded from certain analyses. Decisions made regarding the exclusion of subjects and/or subject data from analyses will be documented and approved by the Sponsor.

A summary of the number and percentage of subjects completing each visit of the study will be given overall for each analysis population (Analysis population: All Subjects Enrolled).

A by-subject listing of analysis population details will also be provided. This listing will be presented overall and will include: center, subject identifier, inclusion/exclusion flag for each population and reason for exclusion from each population. All subjects enrolled will appear on this listing. If subject data has been partially excluded, visit will also appear on this listing.

4.5 Demographic and Other Baseline Characteristics, Medical History and Prior and Concomitant Medications

Demographic data and baseline characteristics which will be summarized descriptively by infusion schedule and overall for the ITT include age (at screening), sex, race, ethnicity, height (at screening), weight (at screening), duration since first lifetime IGIV infusion, IGIV dose level prior to study enrollment, IgG level prior to first lifetime IGIV infusion, and trough IgG level at most recent IGIV therapy. Demographic and baseline characteristic data will be summarized according to their nature of assessment. No formal testing of demographic or baseline characteristics will be performed. A corresponding listing will be provided.

Partial first lifetime IGIV infusion date will be imputed. When day part of date is missing, year and month part are available, infusion date will be imputed to the first day of the month. When year part is available, both month and day part is missing, infusion date will be imputed to the first day of the year.

For general medical history, all relevant medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary (Version 19.1 or later) and summarized by system organ class (SOC) and preferred term (PT) by infusion schedule and overall, based on the ITT population. An overall by-subject listing will also be provided.

For any recorded medical event medication other than study drugs, medication start and stop dates will be compared to the date of first infusion of study medication to allow medications to be classified as either both Prior and Concomitant or Concomitant only.

If a medication starts before the date of first infusion of study medication and stops on or after the date of first infusion of study medication then the medication will be classified as both Prior and Concomitant. Medications will be classified as Concomitant only if they have a start date on or after the date of first infusion of study medication.

If medication start and/or stop dates are missing or partial, the dates will be compared as far as possible with the date of first infusion of study medication. Medications will be assumed to be Concomitant only, unless there is clear evidence (through comparison of partial dates) to suggest that the medication started prior to the first infusion of study medication. If there is clear evidence to suggest that the medication started prior to the first infusion of study medication, the medication will be assumed to be both Prior and Concomitant.

Prior and concomitant medications will be coded using the WHO Drug dictionary WHODDE (DEC 2015 or later) and will be summarized per Anatomical Therapeutic Chemical level 3 (ATC 3) and preferred name (PN) by infusion schedule and overall. By-subject listings will be provided for both Prior and Concomitant medications and Concomitant only medications, respectively.

4.5.1 Prohibited Medications

Other IGIVs will be prohibited for one infusion cycle (21 or 28 days) prior to the first infusion of GC5107 until the completion of Follow-up visit. High dose steroids and other immunosuppressive/cytotoxic drugs are prohibited during the study period except when required for emergency use. Oral and parenteral corticosteroid are allowed if the average dose is <0.15 mg of prednisone equivalent/kg/day and 2 mg of prednisone equivalent /kg/day for up to 24 days two times per year. While daily doses could exceed this limit, the long term average dose is to be kept below this limit. Topical, intranasal and inhaled steroids are permitted.

4.6 Treatment Compliance

Treatment compliance for GC5107 is defined as the ratio, expressed as a percentage, of the actual total volume of GC5107 administered to a subject (ml) over the course of interval to the total volume of GC5107 intended to be administered over that same interval. Total volume intended to be administered is the sum of planned dose volume, the Total volume of assigned dose in CRF, at each infusion during the treatment period. Non-compliant is defined as <80% or >120% compliance.

A summary of the treatment compliance measures by interval, including the number and percentage of compliant and non-compliant subjects per definition above by infusion schedule and overall, will be produced based upon the ITT population.

A by-subject listing of treatment compliance data will be provided.

4.7 Efficacy Evaluation

4.7.1 Analysis and Data Conventions

Confidence intervals will be calculated at the two-sided 95% level of confidence except for the primary efficacy and safety endpoints which will be one-sided 99% and 95% respectively.

This study is designed to test for non-inferiority of GC5107 which will be compared with historically-based standards. The null hypothesis is 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. Symbolically, this is expressed as follows:

H_0: average incidence of serious acute bacterial infections on GC5107 $\geq$ 1.0 per subject per year
H_1: average incidence of serious acute bacterial infections on GC5107 < 1.0 per subject per year

A one-sided test based on a generalized linear models procedure for Poisson regression with α=0.01 will be used to test this hypothesis. Equivalently, the upper one-sided 99% confidence limit would be less than 1.0.

Adverse Event related efficacy endpoint are defined based on treatment emergency adverse event (TEAE) only, including acute serious bacterial infections, infection other than acute serious bacterial infections, incidence of infections, duration of infections, time to resolution of infection.

4.7.1.1 Multi-center Studies

For the purpose of the summaries and analyses, the term ‘Site’ will be used to define each investigator site.

For the primary efficacy variable, the statistical model to be used for the estimation of treatment effects will not adjust for differences between centers. Adjustment for center will not be performed in the analysis of the secondary efficacy variables.

4.7.1.2 Adjustments for Covariates

Not applicable.

4.7.1.3 Handling of Dropouts or Missing Data

All analyses and descriptive summaries will be based on the observed data. Unless otherwise specified, missing data will not be imputed.

When analyzing the yearly duration of infections or fever episode, missing or partial AE start date will be imputed according to following rule:

- If year, month and day are all missing then assign to treatment start date.
- If month-day are missing, year is
    - The same as the year of treatment start date then assign the month-day of treatment start date.
    - Earlier than the year of treatment start date then assign to December 31.
    - After the year of treatment start date then assign January 1.
- If day are missing, year-month is
    - The same as the year-month of treatment start date, then assign the day of treatment start date.
    - Earlier than the year-month of treatment start date, then assign to the last day of the month (31 for month Jan, Mar, May, July, Aug, Oct, and Dec; 30 for month Apr, Jun, Sep, Nov, 28 or 29 for month Feb).
    - After the year-month of treatment start date, then assign the first day of the month 1.

The end dates of ongoing infections or fever episode will be imputed to the last visit date.

When analyzing the duration of hospitalization due to infections, the end dates of ongoing hospitalization will be imputed to the last visit date.

When analyzing the duration of AEs during infusion, the infusion start time will be used to impute the missing AE start time, the last available time (23:59pm) of AE stop date will be used to impute the missing AE stop time.

4.7.1.4 Multiple Comparisons/Multiplicity

No adjustments for multiplicity are required.

4.7.1.5 Interim Analyses

There is no interim analysis planned for this study.

4.7.1.6 Examination of Subgroups

The uniformity of the treatment effect for the primary efficacy and primary safety variables will be examined for the following subgroups:

1. Age (≥ 2 to < 12 years, ≥ 12 to < 17 years, ≥ 17 years)
2. Sex (Male, Female)
3. Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other)
4. Geographic region (United States, Non-United States)

Summaries of the primary efficacy and primary safety variable by subgroup will be produced based on the ITT population. Same summaries by subgroup will be repeated, based on the ITT2 population. No formal statistical test will be performed within subgroups.

4.7.2 Primary Efficacy Variable – Incidence of Acute Serious Bacterial Infections

The primary variable for the assessment of efficacy is the incidence of acute serious bacterial infections (pneumonia, bacteremia and septicemia, osteomyelitis/septic arthritis, bacterial meningitis, visceral abscess) per subject during the 12-month study observation period, calculated for the ITT population. The primary variable will be analyzed by infusion schedule and overall.

A formal statistical analysis (a non-inferiority test) will be applied for the primary efficacy endpoint. A 99% one-sided upper confidence limit for the incidence of serious acute bacterial infections will be derived, and conformance with the FDA standard will be considered acceptable if this limit is less than 1.0 per subject per year.

To estimate the event rate and develop the appropriate one-sided 99% upper confidence limit, a generalized linear models procedure for Poisson regression will be used. This will allow for the possibility of over-dispersion resulting from extra-Poisson variation. This procedure involves estimating a scale parameter of over-dispersion [4]. The mean event rate is estimated by regressing the response on a vector of 1's. Event rates for individuals will be calculated by dividing the number of events for that individual by the total amount of follow-up time. The distribution of these event rates across individuals will be presented using a histogram.

A secondary analysis will also be conducted, assuming a Poisson distribution for the occurrence of primary endpoints, with no over-dispersion. The first step is calculating the annualized infection rate observed for each subject. The annualized infection rate for each individual will be calculated by dividing the number of events for that individual by his or her amount of follow-up time.

These infection rates will be transformed using a square root transformation (since the data are expected to be approximately Poisson), and the mean and variance calculated, weighting by the number of months data available for each subject. The upper 99% one-sided confidence limit for the population mean (on the transformed scale) will then be calculated using standard normal distribution theory, and the resulting limit will be squared (to back-transform it to the original scale) for comparison with the target value of 1 per subject per year.

The influence of outliers will be investigated by repeating the primary analysis with any outlying values excluded.

Total amount of follow-up time for each subject is defined as (date of last visit – first infusion date + 1)/365.25 for subjects who complete the study; and defined as (date of withdrawal – first infusion date + 1)/365.25 for subjects who withdraw from the study.

A sensitivity analysis to assess the robustness of the study conclusions to the choice of analysis population will be performed on the PP population and ITT2 population for the primary efficacy variable.

The homogeneity of the treatment effect for a number of important subgroups (i.e. age, sex, race) will be investigated as described in 4.7.1.6.

A by-subject listing of the primary efficacy data will be provided.

4.7.3 Secondary Efficacy Variables

Secondary efficacy endpoints are:

- The incidence of infections other than acute serious bacterial infections meeting FDA guidance criteria.
- The number of days missed from work/school/kindergarten/day care 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 in order to care for the child due to infections.
- The number of days of unscheduled physician visits due to infections.
- The number of days of hospitalizations due to infections.
- The number of days of IV therapeutic antibiotics.
- The number of days of oral (PO) therapeutic antibiotics.
- Time to resolution of infections.
- The incidence of infections other than serious bacterial infections by trough IgG levels. The categories of trough IgG levels will be determined by looking at the distribution of trough IgG levels at the study completion. Incidence will be summarized by total group mean of trough IgG level throughout treatment, including the trough IgG level from infusion 1 to follow up assessment (< mean Trough IgG, >= mean Trough IgG).

These endpoints will be analyzed descriptively by infusion schedule and overall based on ITT and PP populations, respectively. Subject with no experience of specific event will be included in the analysis as zero incidence, zero day, or zero time duration. For hospitalizations, the number and (total) duration for each subject will be calculated and converted to a figure per year. These data will be presented using the standard set of summary statistics (except that the mean and SD will be calculated weighting for the duration of data available for each subject).

Infections is defined as TEAE coded to MedDRA system organ class 'Infections and infestations', or otherwise suggestive of an infection by medical review.

4.7.4 Exploratory Efficacy Variable

Exploratory efficacy endpoint is fever episode. Fever episode is defined as TEAEs with preferred term "Pyrexia". Incidence of fever episode per subject during the 12-month study observation period, will be analyzed by infusion schedule and overall based on ITT, ITT2, and PP populations. Incidence rate and one-sided 99% upper confidence limit will be estimated by the primary efficacy analysis method, generalized linear models for Poisson regression with over-dispersion. The total duration of fever episode for each subject will be calculated and converted to a figure per year. These data will be presented using the standard set of summary statistics (except that the mean and SD will be calculated weighting for the duration of data available for each subject).

A by-subject listing of the fever episode will be provided.

4.8 Safety Evaluation

All safety endpoints will be summarized by infusion schedule and overall based upon the ITT population as defined in Section 4.4.

4.8.1 Primary Safety Endpoint

The primary safety endpoint will be analyzed with the objective of demonstrating that the percentage of infusions with one or more infusion-related AE is less than 40% [3]. In order to estimate the overall probability of the occurrence of an AE possibly related to infusion for study subjects, as well as a one-sided 95% upper confidence bound, the Generalized Estimating Equation (GEE) method of Zeger and Liang [7] will be used. The response variable will be defined as the logit of the probability of an AE associated with an infusion, and the overall probability and the confidence bound will be estimated under a model with a compound symmetry working correlation structure. This approach allows the outcome of having an AE associated with an infusion to be correlated across infusions within individuals. A demonstration of adequate safety requires that the one-sided 95% upper confidence bound of the probability that an infusion is associated with an AE is below 0.40.

Sensitivity analyses will be undertaken by performing the same analysis under a model with an independence working correlation structure. Same analysis will be repeated, based on the ITT2 population.

4.8.2 Extent of Exposure

Exposure as measured by duration of treatment and amount of study drug used during the treatment period will be summarized. Duration of treatment (days) will be calculated as last infusion date – first infusion date + 1.

A summary of the number of infusions per subject, the number of subjects at each planned dose range per 100 mg/kg at Infusion 1 (e.g. 300-<400, 400-<500), weeks on study, and weeks on study drug by infusion schedule and overall, will be produced based upon the ITT population.

Treatment compliance will be summarized as described in Section 4.6.

A corresponding listing containing treatment compliance and exposure information will also be provided.

4.8.3 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 19.1 or later.

Treatment-emergent adverse events will be tabulated and are defined as those adverse events that either start or worsen in severity on or after the date/time of first infusion of study treatment until one infusion cycle (21 or 28 days) after the last study infusion.

Where dates are missing or partially missing, adverse events will be assumed to be treatment-emergent, unless there is clear evidence (through comparison of partial dates) to suggest that the adverse event started prior to the first infusion of study treatment or one infusion cycle (21 or 28 days) after the last infusion of study treatment.

Adverse events will be listed individually by body system with subject identification numbers and the overall incidences of all AEs that occur during or within (a) 1 hour, (b) 24 hours, and (c) 72 hours following an infusion of investigational product, regardless of other factors that may impact a possible causal association with product administration. When no exact start time is available, only knowing the start date of adverse event, adverse events on the same day of the infusion will be considered as “during or within 1 hour”, adverse events on the next day of the infusion will be considered as “within 24 hours”, and adverse events within the next three days of the infusion will be considered as “within 72 hours”.

The following will be reported: (a) the total number of infusions with AEs that occur during or within 72 hours of an infusion, (b) the total number of infusions, and (c) the mean number of such temporally associated AEs per infusion (a/b).

For each subject and for the study as a whole, the number of infusions administered, the total number of AEs reported at any time during the study (including AEs that the Sponsor or the investigator determine were not product related), the number of AEs temporally associated with infusions, and the number and percentage of infusions temporally associated with one or more AEs will be reported.

For AEs that occur during infusion, (1) the infusion rate in effect at the time of onset of AEs; (2) the time of onset of AEs (minutes), calculated as AE start time – infusion start time; and (3) the time of AEs duration (minutes), calculated as AE end date/time – AE start date/time, will be reported and analyzed. We will list serious adverse events (SAEs), AEs by severity, AEs by body system, and our determination of which AEs were product related and which were not.

We will list the mean number of AEs temporally associated with infusions per infusion, the proportion of infusions administered to subjects for whom "infusional" AEs have been reported, the proportion of subjects who experience one or more AEs at any time during the trial.

We will list AEs as following the most recent infusion of the investigational product, described by its appropriate ordinal number (for example, following the first infusion, second infusion, third infusion). The listings will include separate reports of all AEs (even if the AE is determined to be unrelated to product) and of AEs judged by investigators to be associated with the infusion of the product.

Adverse event summaries will be ordered in terms of decreasing frequency for SOC, and PT within SOC, in the treatment group, and then alphabetically for SOC, and PT within SOC.

For each subject and each adverse event, the worst severity recorded will be attributed and used in the by-severity summaries. Similarly, the worst causality (most related to treatment) will be attributed and used in the by-causality summaries. If severity or causality is missing, the worst case will be assumed.

A by-subject listing of all adverse events (including non-treatment-emergent events) will be provided. This listing will be presented by treatment group and will include: center, subject identifier, age, sex, race, ethnicity, adverse event (SOC, PT, and verbatim term), date of onset, date of resolution, duration, severity, seriousness, action taken, outcome and causality.

4.8.4 Deaths, Serious Adverse Events, and Other Significant Adverse Events

AEs leading to death, SAEs and other significant AEs (i.e. leading to drug withdrawal, dose interruption or reduction, and premature discontinuation) will be summarized descriptively and also listed. AE Leading to discontinuation is defined as AE with action taken of "Patient withdrawn from study therapy", or "Patient taken off study". AE Leading to dose Interruption is defined as AE with action taken of "Infusion interrupted", or "Infusion terminated", or "Infusion skipped". AE Leading to rate change is defined as AE with action taken of "Infusion slowed".

4.8.5 Clinical Laboratory Evaluation

Clinical laboratory tests include hematology, clinical chemistry and urinalysis. All clinical laboratory parameters will be presented in the International System of Units (SI) (except for hemoglobin, which will be presented in g/dL) and classified as “Normal”, “Low” or “High” (and “Abnormality Clinically Significant” or “Abnormality Non Clinically Significant” if “Low” or “High”) based on normal ranges supplied by the central laboratory. Each clinical laboratory parameter will be summarized by infusion schedule and overall for each visit, respectively.

For by-visit summaries, the last non-missing assessment (including repeat assessments) recorded at each visit will be summarized. If visit windows are to be used, the non-missing assessment closest to the mid-point of the visit window will be summarized (including repeat assessments). For across visit summaries (e.g. maximum post-baseline value), scheduled, unscheduled and repeat assessments will be considered.

A subject will be defined as having a treatment-emergent laboratory abnormality if any of the following conditions are satisfied for a specific laboratory parameter:

- Laboratory result within the normal range at Baseline and either a result below the lower limit of the normal range or above the upper limit of the normal range at any post-baseline time point on or before 3 months after the last dose of study treatment.
- Laboratory result below the lower limit of the normal range at Baseline and a laboratory result above the upper limit of the normal range at any post-baseline time point on or before 3 months after the last dose of study treatment.
- Laboratory result above the upper limit of the normal range at Baseline and a laboratory result below the lower limit of the normal range at any post-baseline time point on or before 3 months after the last dose of study treatment.

If a clinical laboratory parameter is continuous or numeric, statistics like mean, SD, median, minimum and maximum will be presented in the way described in Section 4.2. Value change of post-dose Visits from baseline will be summarized in the same way as well. If a clinical laboratory parameter is categorical, frequency and percentage will be provided for each category for this particular parameter at each visit.

All abnormal laboratory data assessed during the study including the data assessed at Final Visit (Follow-up) will be listed on an individual basis as actual values at each visit as well as the change from baseline and analyzed similarly. In addition, shift tables will be used to show the laboratory parameter deviations with respect to the normal ranges of laboratory values from baseline to each post-dose Visit, respectively (i.e. "Normal" vs. "Low" or "High", respectively).

By-subject listings of all laboratory data and abnormal laboratory data will be provided separately by treatment group, with abnormal values highlighted (not needed if for listing of abnormal laboratory data), and including center, subject identifier, age, sex, race, ethnicity, weight and visit. Laboratory reference ranges should also be listed.

Viral safety data and DAT/Coombs test will be listed and summarized by planned visit. Table 2 below summarizes the viral safety test at screening and during study. Changes from baseline in viral safety test will be summarized using shift tables where appropriate.

Table 2. Viral Safety Assessment

Category	**At Screening**	**At other following visits**
HBV serology	HBs Ag, anti-HBs Ab, anti-H Bc Ab	HBs Ag
HBV NAT	HBV DNA	HBV DNA
HCV serology	Total anti-HCV Ab	
HCV NAT	HCV RNA	HCV RNA
HAV serology	Total anti-HAV Ab	
HAV NAT	HAV PCR	HAV PCR
HIV serology	HIV Ab	
HIV NAT	HIV-1 RNA	HIV-1 RNA
Parvovirus B19 IgG	Parvovirus B19 IgG	
Parvovirus B19 IgG DNA	Parvovirus B19 IgG DNA	Parvovirus B19 IgG DNA

4.8.6 Vital Signs, Physical Findings and Other Observations Related to Safety

For this study, vital signs include systolic and diastolic blood pressure, heart rate, respiratory rate, body temperature, and weight. Each vital sign parameter will be analyzed as continuous variable in the way described in Section 4.2. For by-visit summaries, the last non-missing assessment (including repeat assessments, if any) recorded at each visit will be used for summarization.

Abnormalities identified during the physical examination will be summarized across infusion schedule and overall by visit. Clinical significance of the abnormalities will be evaluated and presented. In addition, a shift table will be produced to summarize the change from baseline in categorical data. The three categories for both the physical examination are as follows: normal, abnormal-not clinically significant, and abnormal-clinically significant. A by-subject listing will also be provided for physical examinations.

4.8.7 Drug Safety Monitoring Board (DSMB)

An independent third-party DSMB will monitor the safety of the subjects on a periodic basis. Members of the DSMB will be independent of the study Sponsor and participating sites. Safety parameters that will be evaluated by the DSMB and the Sponsor will include:

- Serious, including life-threatening or fatal adverse drug experiences that are clearly related to the investigational product.
- Other IND Safety Reports, The Council for International Organizations of Medical Sciences (CIOMS) and Health Canada's Adverse Drug Reaction (ADR) which are submitted to the FDA according to 21CFR 312.32 requirements and submitted to Health Canada, respectively.
- Adverse drug reactions and suspected adverse drug reactions that are considered unexpected.
- Suspected thrombotic events.

If at any time during the study, a subject is confirmed to have had a serious (including life-threatening or fatal) adverse drug experience that is clearly related to the investigational drug, the DSMB will conduct a review.

4.9 Pharmacokinetic Endpoints

4.9.1 Assessment of Pharmacokinetics

Derivation of PK parameters will be the responsibility of Early Phase, Quantitative Clinical Development (QCD), [redacted]. PK parameters will be calculated by non-compartmental analysis methods from the concentration-time data using WinNonlin (WNL) Professional (Version 8.0 or higher) following these guidelines:

- Actual sampling times relative to dosing rather than nominal times will be used in the calculation of all derived PK parameters (corrected and not corrected per baseline).
- Baseline will be defined as pre-infusion concentration
- There will be no imputation of missing data.
- Any subjects with missing concentration data will be included in the PK analysis set provided that at least C_{max} and AUC_{0-t} can be reliably calculated.
- All Below the Limit of Quantitation (BLQ) values pre-dose and before the first quantifiable concentration will be substituted by zeros. Thereafter, BLQ values between evaluable concentrations will be substituted by missing before the calculation of the PK variables. Terminal BLQ values will be disregarded.

4.9.1.1 IgG Trough Levels

Blood samples for the preparation of serum will be collected from all subjects at screening prior to each infusion of GC5107 and at the Follow-up visit to determine the trough levels of total IgG.

4.9.1.2 IgG Subclasses/Specific Antibodies – Trough Levels (pre-infusion of GC5107)

28-day Infusion Subjects: IgG subclasses, specific antibodies trough levels - at Infusions 1, 5, 9, and 13.

21-day Infusion Subjects: IgG subclasses, specific antibodies trough levels - at Infusions 1, 5, 11, and 17.

4.9.1.3 Pharmacokinetic Parameters of Total IgG and Serum Levels of IgG Subclasses

Blood samples will be collected from at least 20 subjects before and after the 5th infusion of investigational product. The samples will be used to measure the serum concentrations of total IgG and IgG subclasses. The PKs of total IgG will be determined.

The following PK parameters for total IgG will be determined using uncorrected values and baseline-corrected values when IgG values prior to immunoglobulin therapy are available.

- Plasma concentration-time curve
- Half life will be calculated as ln_2/λ_Z
- Area under the curve ($AUC_{0\text{-}t}$, $AUC_{0\text{-}24h}$ and $AUC_{0\text{-}inf}$) and the area under the concentration times time versus time curve (AUMC) will be calculated by linear–log trapezoidal method (linear method will be employed for all incremental trapezoids arising from increasing concentrations and the logarithmic method will be used for those arising from decreasing concentrations
- Volume of distribution (V_d) will be estimated as V_z and V_{ss}. No values will be specifically generated or reported for V_d. Maximum concentration (C_{max}) will be obtained directly from the concentration-time data
- Minimum (trough) concentration (C_{min}) will be obtained directly from the concentration-time data at pre-dose
- Time of maximum concentration (T_{max})
- Clearance (CL) will be calculated as dose/$AUC_{0\text{-}inf}$
- IR (incremental recovery) will be estimated as (C_{max}- C_{min})/dose per body weight
- IR_{30min} (incremental recovery) will be estimated as (C_{30min}- C_{min})/dose per body weight, where C_{30min} is the observed Total IgG concentration at 30min post-infusion
- λ_z will be estimated at terminal phase by linear regression after log-transformation of the concentrations
    - Only those data points that are judged to describe the terminal log-linear decline will be used in the regression.

  - A minimum number of three data points in the terminal phase will be used in calculating λ_z with the line of regression starting at any post-C_{max} data point (C_{max} should not be part of the regression slope). The adjusted correlation coefficient (R^2 adjusted) in general should be greater than 0.90. Any value less than 0.90 may be used at the PK Scientist's best knowledge and judgment.
  - The interval used to determine λz should be equal or greater than 1.5-fold the estimated half-life or otherwise used at the PK Scientist's best knowledge and judgment.
- λ (lower) will be the lowest time used to estimate λ_z
- λ (upper) will be the highest time used to estimate λ_z
- V_z will be calculated as CL/λ_Z
- V_{ss} will be calculated as $CL \times MRT$
- MRT will be calculated as $(AUMC_{0\text{-}inf}/AUC_{0\text{-}inf}) - TI/2$ where TI = infusion duration
- %AUC ext will be calculated as $(1-[AUC_{0\text{-}t}/AUC_{0\text{-}inf}]) \times 100$

The following PK parameters for IgG subclasses will be measured: C_{max}, C_{min}, and $t_{1/2}$.

PK blood samples will be obtained at 30 min to 10 min pre-infusion, 30 min (± 5 min), 2 hours (± 15 min), 24 hours (± 2 hours), 48 hours (± 2 hours) of post infusion, and Day 4 (± 12 hours), Day 8 (± 1 day), Day 15 (± 1 day), and Day 22 (± 1 day) and Day 29 (± 2 days) (if applicable) . The subjects must have given informed consent for participating in these assessments. The samples for total IgG PK and the samples for IgG subclasses will be analyzed by the selected central laboratory.

4.9.2 Statistical Analysis of Pharmacokinetics

All PK endpoints will be analyzed descriptively. Where relevant, confidence intervals will also be presented. An exception to this will be mean trough levels, which will be compared to steady state trough levels on previous treatment regimens for all subjects. In the event of changes in dose or dosing interval, some adjustment of mean values (using data from the PK profile) may be required. Pharmacokinetic parameters, outlined in Section 4.9.1, will be summarized by infusion schedule and overall.

In the PK population, a descriptive analysis by infusion schedule and overall will be performed to the following endpoint.

- PK parameter of total IgG
- Serum concentration of total IgG
- PK parameter of IgG subclasses
- Serum concentration of IgG subclasses

In the ITT population, a descriptive analysis by infusion schedule and overall will be performed to the following endpoint.

- Trough serum total IgG level

- Trough serum level of IgG subclasses
- Trough serum level of specific IgG antibodies against Hemophilus influenza type b, Streptococcus pneumonia serotypes, Tetanus toxoid, and Cytomegalovirus.

4.10 Determination of Sample Size

The power of this study to establish that the true infection rate is less than 1 per subject per year depends primarily on the unknown true infection rate. However, on the assumption that the distribution of the number of infections per year is approximately Poisson, an estimate of the power can be made for a range of assumptions about the true infection rate.

The analyses of these data will be based on a generalized linear model for Poisson regression and non-inferiority of the investigational product will be claimed if the upper 99% one-sided confidence limit for the mean is less than 1.

To calculate the power, we will assume that observations follow a Poisson distribution, and make use of the standard result in statistical theory that the square root transformation yields a variable that is approximately normally distributed with a standard deviation (SD) independent of the mean and approximately equal to 0.5.

The following table shows the power of a study with 42 subjects to achieve an upper 99% confidence limit less than 1, for various true values of the population mean infection rate. These results were obtained using Power and Sample Size (PASS).

Table 4: Mean Infection Rates and Power of Study Sample Size

True population infection rate per subject per year		Power
Absolute	Square-root transformed	
0.4	0.6325	98.86%
0.5	0.7071	91.03%
0.56	0.7483	79.60%

With 42 subjects, the study therefore has about 80% power provided that the true rate of acute bacterial infections in the study population is below 0.56 per subject per year, under the Poisson assumption.

To guard against dropout and to assure more than adequate power, up to 50 subjects will be enrolled.

It should be noted, however, that these are not conservative estimates of power. In practice, the data may show some over-dispersion relative to the Poisson distribution assumed in these calculations, partly due to different subjects having different susceptibilities (or

exposures), i.e. the presence of some intra-subject correlation, but also due to some subjects having less than a full year of observation. The method of analysis proposed for the primary endpoint takes due account of any such over-dispersion. However, it is not included in the power calculation described above. Therefore, though the power may be slightly less than that calculated in the table above, the study should still be adequately powered to demonstrate non-inferiority for a population in which the true incidence of serious acute bacterial infections is below 0.56 per subject per year.

[redacted]

4.11 Changes in the Conduct of the Study or Planned Analysis

Any deviation from the procedures described within this analysis plan will be described in the clinical study report. Per FDA's request, ITT2 population is added into the analysis plan. ITT2 population will be used to perform a sensitivity analysis of the primary efficacy and primary safety endpoints. FDA also requested to add subgroup of geographic region (United States, non- United States) as well as age, sex and race which were planned initially, to evaluate the uniformity of the treatment effect for the primary efficacy and primary safety variables. Protocol section 9.1.7. specified the following planned analysis for AEs that occur during an infusion: "the time AEs change materially in intensity and/or resolve" will be reported and analyzed. In the SAP section 8.4.3, the planned analysis had been modified to "the time of AEs duration," as the exact time of AE changing intensity is not collected in the eCRF. Only AE duration is available to analyze the time AEs resolved.

5 REFERENCES

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6 APPENDICES

Protocol Version 2, Amendment 1 REB Approval Dates

REB approval date of Canada site

Site Number	REB Approval Date
01	02 Aug 2017
02	23 Feb 2018
03	02 Aug 2017
04	02 Jun 2017
05	02 Aug 2017
06	13 Jun 2017
07	02 Jun 2017
08	29 May 2017
09	17 Jul 2017
10	23 Oct 2017

All US sites started the study under Protocol version 2.0 amendment 1.

[redacted] Statistical Analysis Plan 20191104 v4.0.pdf
This document contains a total of 36 pages including any signature page/s.

[redacted] Electronic Signature Page

This page is the manifestation of the electronic signature(s) used in compliance [redacted] International's electronic signature policies and procedures and in compliance with applicable regulations.

UserName: [redacted]
Title: Principal Biostatistician, GDO
Date: Tuesday, 05 November 2019, 01:53 AM GMT Standard Time
Meaning: Document contents approved.
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UserName: [redacted]
Title: QCD Scientific Director, TMS
Date: Tuesday, 05 November 2019, 12:28 PM GMT Standard Time
Meaning: Document contents approved.
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