HORIZON, INC.

STATISTICAL ANALYSIS PLAN

Investigational Product: **Inebilizumab (VIB0551)**

Protocol Number: **VIB0551.P3.S2**

A PHASE 3, RANDOMIZED, DOUBLE-BLIND, MULTICENTER, PLACEBO-CONTROLLED STUDY OF INEBILIZUMAB EFFICACY AND SAFETY IN IGG4-RELATED DISEASE (SHORT TITLE: MITIGATE)

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
AC	adjudication committee
ADA	antidrug antibody(ies)
AE	adverse event
AESI	adverse event of special interest
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
ECG	electrocardiogram
[redacted]	
FAS	full analysis set
GC	glucocorticosteroids
GCP	good clinical practice
ICF	informed consent form
Ig	immunoglobulin
IgG4-RD	immunoglobulin G4-related disease
IP	investigational product
IV	intravenous(ly)
OLP	Open-label period
[redacted]	
PT	preferred term
RCP	randomized-controlled period
RI	responder index
SAE	serious adverse event
SDAY	Study day
SFP	Safety follow-up period
SOC	system organ class
TEAE	treatment-emergent adverse event
TEAESI	treatment-emergent adverse events of special interest
TESAE	treatment-emergent serious adverse event
US	United States
[redacted]	

1 INTRODUCTION

This document describes the statistical analysis for protocol VIB0551.P3.S2, A Phase 3 Randomized, Double-blind, Multicenter, Placebo-controlled Study of Inebilizumab Efficacy and Safety in immunoglobulin G4-related disease (IgG4-RD).

2 STUDY OVERVIEW

2.1 Study Objectives and Endpoints

The objectives and corresponding endpoints are listed in Table 1 below:

Table 1 Study Objectives and Endpoints

Primary objective	**Endpoints/variables**
• To evaluate the efficacy of inebilizumab in reducing the risk of a disease flare in patients with IgG4-RD.	• Time to disease flare, defined as the time in days from Day 1 (dosing) to the date of the first treated and Adjudication Committee (AC)-determined IgG4-RD flare within the 52-week randomized controlled period (RCP). The date of disease flare is defined as the date of initiation of any flare treatment (new or increased glucocorticoids (GC) treatment, other immunotherapy, or interventional procedure) deemed necessary by the Investigator for the flare.
Secondary objectives	**Endpoints/variables**
• To evaluate the safety and tolerability of inebilizumab in patients with IgG4-RD.	• Incidence of treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), and treatment-emergent adverse events of special interest (TEAESI) during the 52-week RCP and during the open-label period (OLP). • The incidence of anti-drug antibodies (ADA) directed against inebilizumab during the RCP.
• To evaluate the effect of inebilizumab on other measures of disease activity.	• Annualized flare rate for treated and AC-determined flares during the RCP. • The proportion of subjects achieving flare-free, treatment-free complete remission at Week 52, defined as the lack of evident disease activity at Week 52, no AC-determined flare during the RCP, and no treatment for flare or IgG4-RD disease control except the required 8-week GC taper. Lack of evident disease activity is defined as either an IgG4-RD Responder Index (RI, Wallace) score of 0, or a determination by the investigator that no disease activity is present based on physical, laboratory, pathology or other evidence. • The proportion of subjects achieving flare-free, corticosteroid-free complete remission at Week 52, defined as the lack of evident disease activity at Week 52, no AC-determined flare during the RCP, and no corticosteroid treatment for flare or disease control except the required 8-week GC

	taper. Time to initiation of first treatment (medication or procedure) for new or worsening disease activity by the Investigator within the RCP, regardless of AC determination of flare. • Annualized flare rate for AC-determined flares, whether or not treated, during the RCP. • Glucocorticoid use, calculated as the cumulative GC dose taken for the purpose of IgG4-RD disease control during the RCP.
Exploratory objectives	**Endpoints/variables**
[redacted]	

Baseline is defined as the last non-missing valid observation prior to the 1 Investigational product (IP) administration during RCP. In cases where measurements are taken on the same day as the first administration of IP and no time is reported, it will be assumed that these measurements are taken prior to the first administration of IP.

2.2 Study Design

This is a multicenter, randomized, double-blind (Investigator, subject, and Sponsor will be blinded to treatment assignment), placebo-controlled, parallel-cohort study to evaluate the efficacy and safety of inebilizumab for prevention of disease flare in adults with active IgG4-RD who are at high risk of recurrent flare.

The study will be conducted at approximately 60-80 sites in 20 countries. The expected duration of each subject's participation in this study is up to 400 days (screening and RCP) or, for eligible subjects who enroll in the optional OLP, up to 2,273 days (screening, RCP, interval between RCP and OLP, and OLP). A safety follow-up period (SFP) of 2 years after the last IP dose will take place for subjects who do not enter the OLP or who discontinue IP during the OLP.

Subjects will be stratified by first or subsequent IgG4-RD manifestation (i.e., newly-diagnosed vs. recurrent) and randomized 1:1 by an interactive voice/web response system (IXRS) to one of two blinded treatment groups:

- Inebilizumab group: Subjects will receive an infusion of inebilizumab 300 mg IV on Day 1, Day 15, and at Week 26.
- Placebo group: Subjects will receive an infusion of placebo on Day 1, Day 15, and at Week 26.

During the 52-week RCP, subjects will attend monthly visits for study assessments and procedures. Suspicion of flare will trigger diagnostic assessments by the Investigator. The Investigator will determine if the event meets protocol defined criteria for flare, and, independent of the flare determination, will decide if the event requires treatment. The same data reviewed by the Investigator will also be evaluated by a central, independent, and blinded AC (blinded to treatment allocation and to investigator determination of meeting flare criteria or requiring treatment) that will determine whether protocol-defined flare criteria are met.

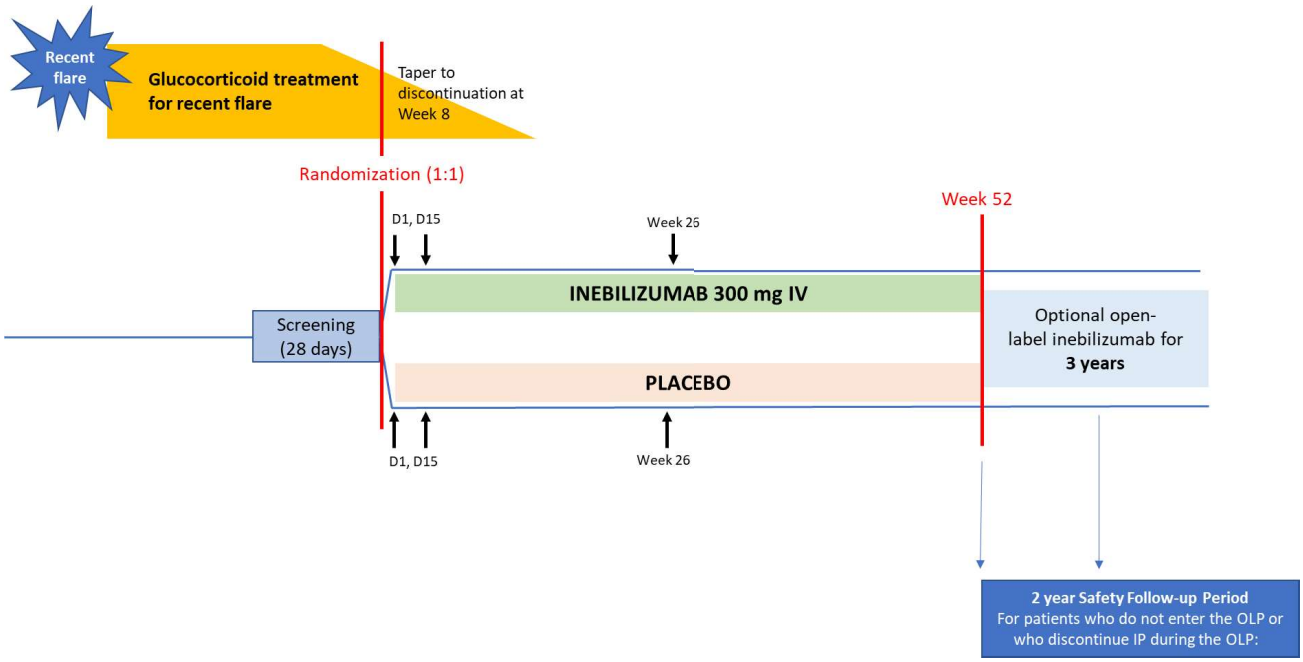
All subjects should be followed through the end of the RCP. A subject who decides to withdraw from the RCP should be asked to complete the final visit (early discontinuation visit [EDV]) for safety follow-up. Subjects who discontinue IP during the RCP without withdrawing from the study will remain in the RCP for its duration and complete the Day 365 visit.

In an optional 3-year OLP, all eligible subjects who choose to participate will receive inebilizumab. Subjects assigned to the placebo group during the RCP will receive 2 inebilizumab infusions (OLP Day 1 and Day 15), while those assigned to the inebilizumab group in the RCP will receive IV inebilizumab on OLP Day 1 and a placebo infusion on Day 15. Both groups will then receive inebilizumab infusions every 6 months for the duration of the OLP. The IXRS will assign the OLP Day 15 treatments, maintaining the blind for the RCP treatments.

In addition, all subjects who discontinue IP during the OLP, or who do not participate in the OLP, will be asked to return to the clinic for a series of follow-up visits with limited assessments, occurring every six months for a total of two years of SFP after their last IP administration. This SFP will provide data on recovery of B cell counts and immunoglobulin levels and monitor for safety events after the IP discontinuation.

A study schematic is presented in Figure 1.

Figure 1 Study Design



D = day; IV = intravenous.

2.3 Sample Size

A total of 39 flares are required to detect a relative reduction of 65% in risk for time from Day 1 (dosing) to onset of flare during the RCP with at least 90% power, two-sided $\alpha = 0.05$, and a 1:1 randomization ratio based on log-rank test for comparison. Assuming the probability of having a treated and AC-determined IgG4-RD flare during the RCP in the placebo group is 0.35 (Yunyun et al, 2017; Yunyun et al, 2019; Wang et al, 2018), a total of 160 subjects (80 subjects per treatment group) are expected to be enrolled using the following formula:

$$N = \frac{E}{\Pr(Fail)}$$

where

$$\Pr(\text{Fail}) = 0.5P_0 + 0.5P_1$$

is the weighted average of the failure probabilities P_0 and P_1 and in the placebo and inebilizumab groups, respectively. Assuming the probability of having a treated and AC-determined IgG4-RD flare during the RCP in the placebo group is 0.35 and an exponential survival distribution, the hazard rate for the placebo group is -log(1-0.35) = 0.4308. With the hypothesized treatment effect of a relative reduction of 65% in risk, the hazard rate for the inebilizumab group during the RCP is -0.35 log(1-0.35) = 0.1508. Pr(Fail) = (0.35 + [1 - exp(-0.1508)])/2 = 0.245.

The hypothesized 65% reduction in risk is an estimate based on the observed treatment effect for attack reduction with inebilizumab in the phase 3 NMOSD trial (77% reduction in risk), and limited published clinical data on the efficacy of the B cell-depleting agent rituximab in IgG4-RD.

The first 50 subjects who complete the RCP or have a treated and AC-determined IgG4-RD flare will be randomly sampled and used to simulate different sample sizes between 160 and 200 in increments of 10. For each of the sample sizes, this simulation process will be repeated 10,000 times to give a distribution of the number of flares. The target sample size is the one that achieves 39 flares 90% of the time.

If the blinded assessment from the first 50 subjects indicates that the number of flares expected with 160 subjects is less than 39, then the sample size will be adjusted based on the above exercise to the number of subjects anticipated to achieve 39 flares with a maximum of 200 subjects (100 subjects per treatment group).

3 STATISTICAL METHODS

3.1 General Considerations

The efficacy endpoints will be summarized at scheduled visits during RCP and OLP, respectively. For subjects in the OLP, the efficacy may also be summarized over the combined RCP and OLP to characterize the durability of the treatment effect, if applicable. And the summary over the combined RCP and OLP will be based on the subjects who received any dose of inebilizumab.

The safety endpoints will be summarized for the RCP, OLP, combined RCP and OLP, and SFP, respectively.

All efficacy analyses described below apply to the RCP unless stated otherwise.

The analyses with a treatment policy strategy will include all data captured during the 52-week RCP, defined as the period after first IP administration at Visit 2 (Day 1) to the conclusion of the scheduled last RCP visit at Visit 15 (Week 52), inclusive, up to but not beyond Day 1 of the OLP.

As sensitivity analyses, the analyses applying the while-on-treatment strategy for safety endpoints will include all data captured while subjects are on treatment, defined as the period after randomization at Visit 2 and 6 months (183 days) after the last treatment during the RCP, inclusive.

All statistical calculations will be primarily performed using SAS® System Version 9.4 or higher. Tabular summaries will be presented by treatment arm. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables will be summarized by descriptive statistics, including number of observations, mean, standard deviation, median, Q1, Q3, minimum, and maximum. Data listings will be sorted by treatment group and subject number.

Where appropriate, model-based estimates will be presented with their two-sided 95% confidence interval (CI) and p-values. Unless otherwise stated, nominal p-values will be reported and rounded to 4 decimal places.

3.1.1 Definition of Baseline and Study Day for Analysis Purposes

In general, baseline will be defined as the last non-missing valid observation prior to the first administration of investigational product (IP). In cases where measurements are taken on the same day as the first administration of IP and no time is reported, it will be assumed that these measurements are taken prior to the first administration of IP. Missing baseline evaluations will not be imputed and will be considered as missing.

Table 2 provides definition of baseline and study reference days for reporting purposes.

Table 2 Definition of Baseline and Study Day for Analysis Purposes

	RCP	OLP	Combined RCP and OLP (for Any Inebilizumab Exposed Analysis)	SFP
Baseline*	The last non-missing valid observation prior to the first administration of IP.	The last non-missing valid observation prior to the 1st administration of IP during OLP.	The last non-missing valid observation prior to the first administration of inebilizumab (i.e., first RCP dose in those randomized to active drug, first OLP dose in those randomized to receive placebo in the RCP).	The last non-missing valid observation prior to the first administration of IP during RCP.
Day 1	The day of first IP administration and will be denoted by Day 1 (RCP).	The day of first open-label period IP administration and will be denoted by Day 1 (OLP).	The day of first inebilizumab administration irrespective of RCP or OLP and will be denoted by Day 1 (inebilizumab).	The day after the last IP dosing date and will be denoted by Day 1(SFP)
Study day (SDAY) for each period for reporting purpose	For dates prior to Day 1 (RCP): SDAY= Date of Interest – Date of Day 1 (RCP) For dates on or after Day 1 (RCP) SDAY= Date of Interest – Date of Day 1 (RCP) + 1	For dates prior to Day 1 (OLP): SDAY= Date of Interest – Date of Day 1 (OLP) For dates on or after Day 1(OLP): SDAY= Date of Interest – Date of Day 1 (OLP) + 1	For dates prior to Day 1 (inebilizumab); SDAY= Date of Interest – Date of Day 1 (inebilizumab) For dates on or after Day 1(inebilizumab): SDAY= Date of Interest – Date of Day 1 (inebilizumab) + 1	SDAY= Date of Interest – Date of Day 1 (SFP) + 1

*In cases where measurements are taken on the same day as the first administration of IP and no time is reported, it will be assumed that these measurements are taken prior to the first administration of IP.

3.1.2 Analysis Windows

Analysis visit windows will be used for all visit-based assessments to map longitudinal observations to scheduled visits and, thereby, allow for by-visit analyses, since not all assessments are performed on the scheduled day. Unless otherwise specified, all longitudinal efficacy and safety data analyses will be based on the analysis visit windows except the IgG4 RI. The analysis visit windows will be calculated by bisecting the interval between adjacent scheduled visit days, or by ± 14, 30, or 60 days from the scheduled RCP, OLP, or SFP visit dates, respectively, whichever results in a shorter interval. The IgG4 RI will need the data from lab or image results, which may not be available until several weeks after the scheduled visit. Hence, the IgG4 RI will be summarized by the nominal visit per protocol.

The actual assessment day will be mapped to the windows defined for each scheduled study visit with following rules:

- If more than one assessment falls within a visit window, the closest non-missing assessment to the scheduled day will be used in the analysis.
- If two non-missing assessment actual dates are equidistant from the target day, the later visit will be used in the analysis.
- For retest values of laboratory data, the retest value (the last valid observation assessed on the same visit day) will be chosen.

3.2 Protocol Deviations

Both major and critical protocol deviations, as defined by the Protocol Deviation (PD Plan, will be summarized**.** Per the PD Plan, a major deviation is one that resulted or had the potential to result in non-life-threatening harm to an individual participant or had the potential to affect the safety and well-being of trial subjects or the reliability of clinical trial data. The event did not pose a significant risk to the overall project, overall subject safety, or overall data quality/ integrity. A critical deviation is a significant departure from GCP resulting in a life-threatening risk to an individual subject, or where the safety or well-being of trial subjects was or had significant potential to be jeopardized or caused a significant portion of the clinical trial data to be potentially unreliable.

Of particular note are deviations related to the protocol-mandated oral glucocorticoid taper that begins on RCP Day 1 and lasts for 8 weeks. Each incident of a variation from the protocol-specified taper regimen will be recorded as a minor PD. These deviations will be analyzed per subject, and a major PD will be recorded if the departure from the prescribed regimen is substantial, defined as either of the following:

- The total dose for steroid tapering is > 20% more or > 20% less than the protocol-specified total dose of 700 mg of prednisone or equivalent (i.e., > 840 mg or < 560 mg)
- The total duration for steroid tapering is > 20% longer or > 20% shorter than the protocol-specified duration of 56 days (i.e., > 67 days or < 45 days)

The list of the protocol deviations and the corresponding classification may be reviewed, finalized and documented prior to unblinding the study.

3.3 Analysis Sets

3.3.1 Full Analysis Set (FAS)

The Full Analysis Set includes all subjects who receive any dose of IP during the RCP. Subjects will be analyzed according to the treatment assignment. The efficacy analyses will be based on the Full Analysis Set.

3.3.2 Safety Analysis Set (Randomized-controlled Period)

The Safety Analysis Set includes all subjects who received any dose of IP during the RCP, and will be used for safety, [redacted], and ADA analysesFor the analyses in the RCP, subjects will be analyzed according to the treatment that they actually received. Specifically, subjects randomized to the inebilizumab group who received all placebo dose will be included in the placebo group; conversely, subjects randomized to the placebo group who received at least one dose of inebilizumab will be included in the inebilizumab group.

3.3.3 Open-label Analysis Set

The Open-Label Analysis Set includes all subjects who received any dose of inebilizumab during the OLP.

3.3.4 Any Inebilizumab Analysis Set

The Any Inebilizumab Analysis Set includes all subjects who received any dose of inebilizumab during the study. Analyses with this analysis set will be based on the data collected on or after subjects receive the first administration of inebilizumab.

[redacted]

3.3.6 Safety Follow up Analysis Set

The Safety follow up Analysis Set includes all subjects who are eligible for the SFP.

3.4 Study Subjects

3.4.1 Subject Disposition

Subject disposition will be summarized using all the screened subjects. The total number of subjects will be summarized for those who are screened; who are screen failed and who are randomized. And the numbers and the percentages of the subjects will be summarized for following groups.

- Subjects who are randomized
- Subjects who discontinued treatment during the RCP
- Subjects who early discontinued from the RCP
- Subjects who completed RCP
- Subjects who entered OLP
- Subjects who discontinued treatment during the OLP
- Subjects who early discontinued from the OLP
- Subjects who entered SFP
- Subject who discontinued from the SFP

A Kaplan-Meier (KM) curve of the time to RCP discontinuation by treatment arm will be produced.

3.4.2 Demographics, Baseline Characteristics, and Medical History

The following demographics, baseline characteristics, and medical history will be summarized for Full Analysis Set by treatment group.

3.4.2.1 Demographics

- Age (years)
- Age category (< 65, ≥65 years)
- Sex (Male and Female)
- Race (American Indian or Alaskan Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other)
- Ethnicity (Hispanicor Latino vs NotHispanic or Latino).
- Region (US vs Non-US; EU vs non-EU; Asia vs non-Asia; Japan vs non-Japan)
- Height (cm)
- Weight (kg)
- BMI (kg/m^2)
- BMI category (< 18.5, ≥18.5 – <25, ≥25 – <30, ≥ 30)

3.4.2.2 Baseline Characteristics

Table 3 provides the list of baseline characteristics to be summarized along with type of summary.

Table 3 Baseline Characteristics

• IgG4-RD manifestation (newly diagnosed vs recurrent) – n (%) • Disease duration (years) defined as the years between date of diagnosis and date of 1st administration of IP, calculated as (date of 1st IP administration – date of diagnosis + 1)/365.25 - descriptive statistics • Number of organs ever affected by IgG4-RD (1, 2, 3, etc.) • List of organs previously affected (meninges, pituitary gland, etc. – "other" counts as 1) – n (%) • Highest known IgG4 serum level – descriptive statistics • Category of highest IgG4 serum level (< median vs ≥ median) – n (%) • IgG4-RD RI – descriptive statistics • Prior non-glucocorticoid therapy for IgG4-RD (yes / no) – n (%)
[redacted]

3.4.2.3 Medical History

Medical history and procedure history for IgG4-RD will be summarized by MedDRA system organ class (SOC) and preferred term (PT).

3.4.3 Study Drug Exposure

Study drug exposure, which includes number of doses, dose amount and dose amount adjusted for weight (mg/kg) of the study drug, and durations of the study drug exposure, will be summarized for RCP, OLP, and Any Inebilizumab exposure by treatment group. In addition, treatment compliance will also be summarized for RCP.

The amount of study drug exposure: If entire dose was administered, the dose amount (mg) at a specific visit will be either 0 or 300 mg depending on what treatment the subject had received; if a subject received partial dose at a dosing visit, then the amount of study

drug at that dosing visit will be estimated based on the actual volume administered. For example, if a subject receives 175 mL (instead of the full 250 mL), the dose amount (mg) will be estimated as = 300 mg × 175 mL / 250 mL = 210 mg provided the subject received inebilizumab.

Treatment compliance for an individual subject = [Total number of doses received]/ [Total number of doses planned per protocol] ×100%.

The definition of duration of study drug exposure and person-years of exposure is outlined in Table 4.

Table 4 Investigational Product Exposure Summary

RCP	OLP	Combined RCP and OLP (Any Inebilizumab Exposure)
Duration of study drug exposure		
Last RCP dose date – 1st RCP dose date + 90[a]	Last OLP dose date – 1st OLP dose date + 90 [a]	Last inebilizumab dose date – 1st inebilizumab dose date + 90 [a]
Person-year definition for individual subject [b]		
(Date of last RCP day – 1st RCP dose date +1)/365.25	(Date of last OLP day – 1st OLP dose date + 1)/365.25	(Date of last study day in RCP or OLP – 1st inebilizumab dose date + 1)/365.25
[a] Based on 5 half-lives (18 days) determined from previous late-stage clinical trials [b] Total person-years will be calculated as the sum of the person-years for individual subject		

3.4.4 Prior and Concomitant Medications

Number (%) of subjects who received prior medications and concomitant medications will be summarized by WHO Drug dictionary. Rescue medications will be summarized separately from other concomitant medications. At each level of summarization, a subject is counted once if the subject reported one or more medications at that level. The prior and concomitant medications are defined as below:

- Prior medications are defined as medications with a stop date occurring before the first RCP dose date.
- Concomitant medications for RCP are defined as:
    1) Medications started on or after first RCP dose date, and on or before the end of RCP, or
    2) Medications stopped on or after first RCP dose date, and on or before the end of RCP, or
    3) Medications started before the first RCP dose date, and ongoing at the end of RCP.
- Concomitant medications for OLP are defined as:
    1) Medications started on or after the first OLP dose date, and on or before the end of OLP, or
    2) Medications stopped on or after the first OLP dose date, and on or before the end of the OLP, or

3) Medications started before the first OLP dose date, and ongoing at the end of the OLP.

Descriptive summaries and by-subject listings of corticosteroid use for protocol-specified taper, for flare treatment, and for other reasons will be provided.

3.5 Efficacy Analyses

3.5.1 Primary Efficacy Endpoint and Analysis

3.5.1.1 Primary Efficacy Endpoint and Primary Analysis

The Primary efficacy endpoint is time to disease flare, defined as the time in days from Day 1 (dosing) to the date of the first treated and AC-determined IgG4-RD flare within the 52-week RCP. The date of disease flare is defined as the date of initiation of any flare treatment (new or increased GC treatment, other immunotherapy, or interventional procedure) deemed necessary by the Investigator for the flare.

The estimand with a treatment policy strategy is defined by the following:

- Target population: Subjects in the FAS
- Variable: Time in days from Day 1 (dosing) to the date of the first treated and AC-determined IgG4-RD flare within the 52-week RCP. Date of flare onset is defined as date of onset of treatment (medication or procedure).
- Intercurrent event: All data captured during the 52-week RCP will be used for analysis. Subjects who do not complete the RCP and who have not had a treated and AC-determined flare during the RCP will be censored at the time of discontinuation.
- Population-level summary: Hazard ratio (HR) between inebilizumab versus placebo and its associated 95% CI.

To assess the robustness towards violations of the assumption of non-informative censoring of subjects who do not complete the RCP, the following sensitivity analysis will be performed:

- Target population: Subjects in the FAS
- Variable: Time in days from Day 1 (dosing) to the date of the first treated and AC-determined IgG4-RD flare within the 52-week RCP. Date of flare onset is defined as date of onset of treatment (medication or procedure).
- Intercurrent event: All data captured during the 52-week RCP will be used for analysis. Subjects who do not complete the RCP due to IgG4-RD related death or due to subject perception of lack of efficacy and who have not had a treated and AC-determined flare will be considered as having a flare with onset at the time of discontinuation / withdrawal from the RCP. Subjects who do not complete the RCP due to other reasons and who have not had a treated and AC-determined flare will be censored at the time of discontinuation / withdrawal from RCP.
- Population-level summary: HR between inebilizumab versus placebo and its associated 95% CI.

The hazard rate in the inebilizumab group will be compared to that in the placebo group using the Cox proportional hazards model with the treatment indicator (inebilizumab or placebo) and the stratification factor as the explanatory variables. The HR of inebilizumab versus

placebo will be estimated together with its associated 95% CI. The two-sided p-value for the treatment effect will be determined using Cox proportional regression model. SAS PROC PHREG will be used for fitting this model.

3.5.1.2 Additional Analysis on the Primary Efficacy Endpoint

The estimand of the additional analysis is defined by the following:

- Target population: Subjects in the FAS
- Variable: Time in days from Day 1 (dosing) to the date of the first treated and AC-determined IgG4-RD flare within the 52-week RCP. Date of flare onset is defined as date of onset of treatment (medication or procedure).
- Intercurrent event:
    - Subjects who do not complete the RCP and who have not had a treated and AC-determined flare will be censored at the time of discontinuation.
    - Subjects, who 1) receive any treatment for IgG4-RD, including GC or immunosuppressive treatment (other than GC tapered in accordance with the protocol-specified schedule during the first 8 weeks of the RCP) and/or 2) receive any prohibited GC or immunosuppressive treatment prior to experiencing a treated and AC-determined flare, will be censored at the time when relevant treatment was first received.
- Population-level summary: HR between inebilizumab versus placebo and its associated 95% CI.

The robustness towards violations of the assumption of non-informative censoring on subjects who do not complete the RCP and / or subjects who received prohibited GC or immunosuppressive treatment prior to experiencing a treated and AC-determined flare will be assessed with the following sensitivity analysis:

- Target population: Subjects in the FAS
- Variable: Time in days from Day 1 (dosing) to the date of the first treated and AC-determined IgG4-RD flare within the 52-week RCP. Date of flare onset is defined as date of onset of treatment (medication or procedure).
- Intercurrent event:
    - Subjects who do not complete the RCP due to IgG4-RD related death or due to subject perception of lack of efficacy and who have not had a treated and AC-determined flare will be considered as having a flare at the time of discontinuation / withdrawal from RCP. Subjects who do not complete the RCP due to other reasons and who have not had a treated and AC-determined flare will be censored at the time of discontinuation / withdrawal from RCP.
    - Subjects who receive the treatment for IgG4-RD, including GC or immunosuppressive treatment (other than GC tapered in accordance with the protocol-specified schedule during the first 8 weeks of the RCP) related to IgG4-RD prior to experiencing a treated and AC-determined flare will be considered as having a flare at the time of treatment.

  - Subjects who receive any prohibited GC or immunosuppressive treatment not related to IgG4-RD prior to experiencing a treated and AC-determined flare will be censored at the time when those treatment were first received.

- Population-level summary: HR between inebilizumab versus placebo and its associated 95% CI.

To assess the impact of immortal time bias, the following analysis will be performed:

- Target population: Subjects in the FAS
- Variable: Time in days from Day 1 (dosing) to the date of the first treated and AC-determined IgG4-RD flare within the 52-week RCP. Date of flare onset is defined as earliest date of subject reported new/worsening symptoms, new/worsening physical exam findings, new/worsening laboratory findings, new/worsening findings imaging, or other findings as data collected on flare assessment page.
- Intercurrent event: All data captured during the 52-week RCP will be used for analysis. Subjects who do not complete the RCP and who have not had a treated and AC-determined flare during the RCP will be censored at the time of discontinuation.
- Population-level summary: Hazard ratio (HR) between inebilizumab versus placebo and its associated 95% CI.

Data will be analyzed using the same Cox proportional hazards model as that for the primary efficacy analysis. The HR of inebilizumab versus placebo will be estimated together with its associated 95% CI and the corresponding p value.

3.5.2 Secondary Efficacy Endpoints and Analyses

The protocol defined 6 secondary efficacy endpoints. Endpoints 1, 2, and 3 are key secondary endpoints to be considered for study-wise Type I error control:

1. Annualized flare rate for treated and AC-determined IgG4-RD flares during the RCP.
2. The proportion of subjects achieving flare-free, treatment-free complete remission at Week 52,
3. The proportion of subjects achieving flare-free, corticosteroid-free complete remission at Week 52.
4. Time to initiation of first treatment (medication or procedure) for new or worsening disease activity by the Investigator within the RCP, regardless of AC determination of flare.
5. Annualized flare rate for AC-determined IgG4-RD flares, whether or not treated, during the RCP.
6. Glucocorticoid (GC) use, calculated as the cumulative GC dose taken for the purpose of IgG4-RD disease control during the RCP.

3.5.2.1 Annualized Flare Rate for treated and AC-determined IgG4-RD Flares During the RCP

The estimand with a treatment policy strategy is defined by the following:

- Target population: Subjects in the FAS

- Variable: The number of treated AC-determined IgG4-RD flares experienced during 52-week RCP
- Intercurrent event: No intercurrent events will be taken into account. All data captured during the 52-week RCP will be used for analysis.
- Population-level summary: Rate ratio between inebilizumab versus placebo and its associated 95% CI.

The number of treated and AC-determined flares will be compared between the inebilizumab group and the placebo group using a negative binomial model. The model will include covariates of treatment group (inebilizumab or placebo) and stratification factors. The logarithm of the subject's corresponding follow-up time will be used as an offset variable in the model to adjust for subjects having different exposure times during which the events occur. The estimated treatment effect (ie, the rate ratio of inebilizumab versus placebo), corresponding 95% CI, and two-sided p-value for the rate ratio will be presented.

In addition, the annualized flare rate and the corresponding 95% CI within each treatment group, and the absolute difference between treatment groups with the corresponding 95% CI, will be presented.

An additional analysis may be conducted by considering subjects, who receive 1) any treatment for IgG4-RD, including GC or immunosuppressive treatment (other than GC tapered in accordance with the protocol-specified schedule during the first 8 weeks of the RCP) and/or 2) any prohibited GC or immunosuppressive treatment, to be censored at the time when relevant treatment was first received.

3.5.2.2 The Proportion of Subjects Achieving Flare-Free, Treatment-Free Complete Remission at Week 52

Flare-free, treatment-free complete remission is defined as lack of evident disease activity at Week 52, no AC-determined flare during the RCP, and no treatment for flare or disease control except the required 8-week GC taper. Lack of evident disease activity is defined as either an IgG4- RD Responder Index (Wallace et al, 2018) score of 0, or a determination by the investigator that no disease activity is present based on physical, laboratory, pathology or other evidence.

The estimand with a composite strategy is defined by the following:

- Target population: Subjects in the FAS
- Variable: Proportion of subjects achieving flare-free, treatment-free complete remission at Week 52
- Intercurrent event: Subjects who receive treatment for flare or disease control except the required 8-week GC taper will be treated as not achieving complete remission at Week 52.
- Population-level summary: Odds ratio between inebilizumab versus placebo and its associated 95% CI.

The results of the analyses will be presented using odds ratios, together with associated 95% CI and two-sided p-value. In addition, the absolute difference of the proportions between treatment groups with the corresponding 95% CI and two-sided p-value, will also be presented.

The estimate of the treatment effect will be assessed using a logistic regression model. The response variable in the model will be whether or not a subject achieves the corresponding flare-free treatment-free complete remission at Week 52. The model will have treatment indicator (inebilizumab or placebo) and stratification factor as the explanatory variables. SAS PROC LOGISTIC and PROC GENMOD with LOGIT link will be used for fitting this model and estimate odds ratio and absolute difference of the proportions, respectively.

An additional analysis under a treatment policy strategy with the same model will be conducted, with complete remission defined as an IgG4-RD RI score of 0 at Week 52, no AC-determined flare, and no treatment for flare except the required 8-week GC taper during the RCP .

For both analyses, subjects who do not complete the RCP or are missing IgG4-RD disease activity assessment at Week 52 will be treated as not achieving complete remission at Week 52.

3.5.2.3 The Proportion of Subjects Achieving Flare-Free, Corticosteroid-Free Complete Remission at Week 52

Flare-free, corticosteroid-free complete remission is defined as lack of evident disease activity at Week 52, no AC-determined flare during the RCP, and no corticosteroid treatment for flare or disease control except the required 8-week GC taper. Lack of evident disease activity is defined as either an IgG4- RD Responder Index (Wallace et al, 2018) score of 0, or a determination by the investigator that no disease activity is present based on physical, laboratory, pathology or other evidence.

The estimand with a composite strategy is defined by the following:

- Target population: Subjects in the FAS
- Variable: Proportion of subjects achieving flare-free, corticosteroid-free complete remission at Week 52
- Intercurrent event: Subjects who receive corticosteroid for flare or disease control except the required 8-week GC taper will be treated as not achieving complete remission at Week 52.
- Population-level summary: Odds ratio between inebilizumab versus placebo and its associated 95% CI.

The results of the analyses will be presented using odds ratios, together with associated 95% CI and two-sided p-value. In addition, the absolute difference of the proportions between treatment groups with the corresponding 95% CI and two-sided p-value, will also be presented.

The estimate of the treatment effect will be assessed using a logistic regression model. The response variable in the model will be whether or not a subject achieves the corresponding flare-free corticosteroid-free complete remission at Week 52. The model will have treatment indicator (inebilizumab or placebo) and stratification factor as the explanatory variables. SAS PROC LOGISTIC and PROC GENMOD with LOGIT link will be used for fitting this model and estimate odds ratio and absolute difference of the proportions, respectively.

For both analyses, subjects who do not complete the RCP or are missing IgG4-RD disease activity assessment at Week 52 will be treated as not achieving complete remission at Week 52.

3.5.2.4 Time to Initiation of First Treatment for New or Worsening Disease Activity by the Investigator Within the RCP, Regardless of AC Determination of Flare

The estimand with a treatment policy strategy is defined by the following:

- Target population: Subjects in the FAS
- Variable: Time in days from Day 1 (dosing) to the date of the first treatment (new or increased GC treatment, other immunotherapy, or interventional procedure) for new or worsening disease activity by the investigator within the RCP, regardless of AC determination of flare within the 52-week RCP
- Intercurrent event: All data captured during the 52-week RCP will be used for analysis. Subjects who do not complete the RCP and have not received treatment for new or worsening disease activity as defined above, will be censored at the time of discontinuation.
- Population-level summary: HR between inebilizumab versus placebo and its associated 95% CI.

The hazard rate in the inebilizumab group will be compared to that in the placebo group using the Cox proportional hazards model with the treatment indicator (inebilizumab or placebo) and the stratification factor as the explanatory variables. The HR of inebilizumab versus placebo will be estimated together with its associated 95% CI.

3.5.2.5 Annualized Flare Rate for AC-Determined IgG4-RD Flares, Whether or not Treated, During the RCP

The estimand with a treatment policy strategy is defined by the following:

- Target population: Subjects in the FAS
- Variable: The number of AC-determined IgG4-RD flares, whether or not treated, experienced during 52-week RCP
- Intercurrent event: No intercurrent events will be taken into account. All data captured during the 52-week RCP will be used for analysis.
- Population-level summary: Rate ratio between inebilizumab versus placebo and its associated 95% CI.

The number of treated AC-determined flares will be compared between the inebilizumab group and the placebo group using a negative binomial model. The model will include covariates of treatment group (inebilizumab or placebo) and stratification factors. The logarithm of the subject's corresponding follow-up time will be used as an offset variable in the model to adjust for subjects having different exposure times during which the events occur. The estimated treatment effect (ie, the rate ratio of inebilizumab versus placebo), corresponding 95% CI, and two-sided p-value for the rate ratio will be presented.

In addition, the annualized flare rate and the corresponding 95% CI within each treatment group, and the absolute difference between treatment groups with the corresponding 95% CI, will be presented.

3.5.2.6 Glucocorticoid Use

The estimand is defined by the following:

- Target population: Subjects in the FAS
- Variable: Cumulative GC dose taken for the purpose of disease control during the 52-week RCP
- Intercurrent event: All data captured during the 52-week RCP will be used for analysis. GC use for a purpose other than controlling IgG4-RD or for protocol-specified steroid tapering will not be included in the analysis.
- Population-level summary: Difference in means GC dose between inebilizumab versus placebo and its associated 95% CI.

Total GC use per subject and daily GC use per subject will be summarized and analyzed by analysis of covariance models with treatment indicator (inebilizumab or placebo) and stratification factor as the explanatory variables. Results will be presented in terms of least square means (LSMEANS), treatment differences in LSMEANS, 95% Cis, and p-values.

3.5.3 Subgroup Analyses

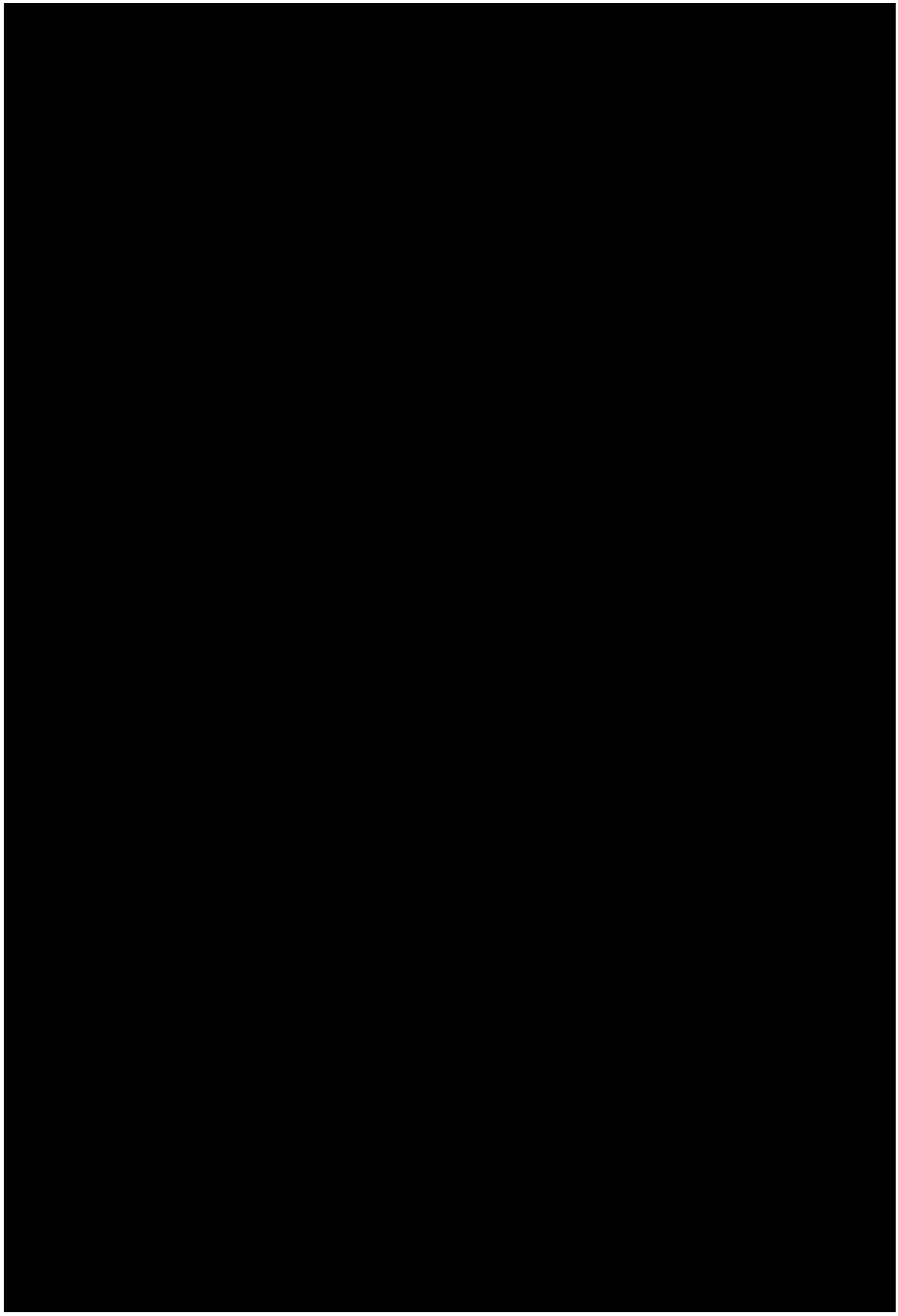
Consistency of treatment effect measured by primary and 3 key secondary endpoints in the following subgroups will be investigated:

- Age (< 65 vs ≥ 65)
- Sex (male vs female)
- Region (US vs non-US; EU vs non-EU; and Asia vs non-Asia)
- Serum IgG4 concentrations at baseline (< median vs ≥ median)
- [redacted]
- Racial/ethnic subgroups as needed for national/regional regulatory filings
- First or subsequent IgG4-RD manifestation (i.e., newly diagnosed vs. recurrent)
- Anti-drug antibody (ADA) status at any time during RCP including baseline (positive vs. negative) if data allows

The nominal p-value and 95% Cis of treatment effect will be provided for each subgroup analysis. Forest plots will be generated to visually present the consistency of treatment effect in different subgroups with overall treatment effect. Interaction tests would be conducted to evaluate the consistency of the treatment effect among the different categories of each subgroup variable.

3.5.4 Exploratory Efficacy Endpoints and Analyses

[redacted]



3.6 Safety Analysis

Safety endpoints will be summarized separately for the RCP, OLP, SFP, and combined RCP and OLP. Safety data from the RCP and OLP will be presented based on the Safety Analysis Set and on the Open-label Analysis Set, respectively. Safety data from the combined RCP and OLP will be analyzed based on the Any Inebilizumab Analysis Set.

3.6.1 Adverse Events

Adverse event and serious adverse event collection begins after the subject signs the informed consent document and continues until the end of study visit. AEs and SAEs collected during the RCP will be analyzed using a treatment policy strategy (which includes all data captured during the RCP), and a while-on-treatment strategy (which includes all data captured while subjects are on treatment). AEs and SAEs collected during the OLP, SFP and combined RCP and OLP, will be analyzed using a treatment policy strategy. For subjects who withdraw from the study, data collected up until the last visit will be included. Table 5 defines TEAEs for different analyses.

Table 5 Definition of TEAEs for Different Analyses

RCP (Treatment Policy)	RCP (While-on-treatment)	OLP	Combined RCP and OLP (Any Inebilizumab Analysis Set)	SFP
A TEAE is defined as any AE with onset date on or after the first RCP IP dose, and on or before the end of RCP.	A TEAE is defined as any AE with onset date on or after the first RCP IP dose, and on or before 6 months (183 Days) after the last RCP dose.	A TEAE is defined as any AE with onset date on or after first OLP IP dose and up to the end of OLP (prior to the SFP entry if a subject enrolled into SFP).	A TEAE is defined as any AE with onset date on or after the first inebilizumab dose (either RCP or OLP) and up to and including the day prior to the end of RCP (if a subject didn't enroll into OLP) or the end of OLP (i.e., the day prior to the SFP entry, if a subject rolled over to OLP).	TEAE is defined as any AE with onset date after the last IP dose during the study.

An adverse event of special interest (AESI) is one of scientific and/or medical interest specific to understanding safety and action of the IP. The following are considered AESIs in this study:

- Anaphylaxis and serious hypersensitivity reactions
- Infusion-related reactions (IRR)
- Immune complex disease
- Cytopenia
- Serious and/or opportunistic infections, including Progressive Multifocal Leukoencephalopathy (PML).

The AESIs (investigator reported) will be summarized by Category and PT. The risk difference and corresponding 95% CI calculated by the Miettinen and Nurminen score method in cumulative incidences of AESIs by week 52 between inebilizumab and placebo groups may be presented as appropriate. In addition, the time to first instance of an AESI and duration of the AESI will be summarized by treatment group when appropriate.

In addition, following sponsor identified AESIs will also be summarized: IRR, anaphylaxis, serious hypersensitivity reactions, immune complex disease, cytopenia, serious infections, and opportunistic infections. The detailed definition of sponsor identified AESIs will be included in the statistical programming plan (SPP).

AEs will be coded to the corresponding system organ class (SOC) and preferred terms (PT) using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA). In addition, summary of AEs and SAEs by SOC and FDA Medical Query (FMQ) will also be provided for RCP and the combined period of RCP and OLP.

The number and percentage of subjects reporting TEAEs and TESAEs will be summarized for each treatment group by SOC and PT, by severity, and by relationship to the IP. If the same AE occurs multiple times within a particular subject, the highest severity and level of relationship observed will be reported.

TEAEs and TESAEs will be summarized as described in Table 6.

TEAEs per 100 Person-years for a specific reporting period will be calculated as

$$= 100 \times \frac{\text{Total number of TEAEs for specific reporting period}}{\text{Total Person years for specific reporting period}}$$

The person-year for while-on-treatment analyses will be defined as (Date of 6 months [183 Days] after the last RCP dose – 1st RCP dose date +1)/365.25. See Table 4 for the definition of person-years for other analyses.

Table 6 Type of TEAE Analyses by Period

Overall summary of TEAEs
TEAEs by SOC and PT
TEAEs with severity ≥ Grade 3 by SOC and PT
TEAEs resulting in permanent discontinuation of the IP by SOC and PT
TEAEs (≥5% in inebilizumab) by SOC and PT
TEAEs by SOC, PT and by highest severity
TEAEs by PT sorted by frequency in inebilizumab group
TEAEs by FMQ sorted by Frequency in Inebilizumab Group
TESAEs by SOC and PT
TESAEs by PT sorted by frequency in inebilizumab group
TESAEs by FMQ sorted by Frequency in Inebilizumab Group
TESAEs by Seriousness Criteria
TEAEs with Severity ≥ Grade 3 and/or TESAEs by SOC and PT
IP Related TEAEs by SOC, PT
IP Related TEAEs with Severity ≥ Grade 3 by SOC and PT
IP Related TEAEs by SOC, PT and by Highest Severity
IP Related TESAEs by SOC and PT
IP Related TEAEs with Severity ≥ Grade 3 and/or TESAEs by SOC and PT
AESI by Category, PT and by Highest Severity
Overview of TEAEs per 100 Person-years by SOC and PT
TEAEs per 100 Person-years by SOC and PT
Overview of TESAEs per 100 Person-years

TESAEs per 100 Person-years by SOC and PT
All deaths

Overall summary of TEAEs and summary of TEAEs by SOC and PT for treatment policy and while-on-treatment will be investigated when appropriate by age (< 65 vs ≥ 65), sex (male vs female), region (US vs non-US; EU vs non-EU; Japan vs Non-Japan; and Asia vs non Asia), serum IgG4 concentrations at baseline (< median vs ≥ median), [redacted] racial/ethnic subgroups as needed for national/regional regulatory submissions, first or subsequent IgG4-RD manifestation (i.e., newly-diagnosed vs. recurrent), and by ADA status at any time during RCP including baseline (positive vs negative) if data allows.

Listings will be provided for all TEAEs and non-treatment emergent AEs.

3.6.2 Clinical Laboratory Evaluation

Blood and urine samples will be collected for laboratory safety tests at baseline as well as throughout the study. Laboratory toxicities will be defined based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5 for the tests with objective criteria and version 4 for the tests with subjective criteria. The international system of units will be used for all the lab data.

The analysis for the laboratory results is listed in Table 7.

Table 7 Laboratory Results Analysis

Laboratory dataset	Planned Analysis
Hematology, Chemistry, and Coagulation	• Summary of worst post-baseline toxicity grade • Summary of at least 2-grade shift from the baseline to the worst post-baseline toxicity grade • Summary of shift from the baseline relative to the normal range • Summary of observed values, and changes and percent changes from the baseline
Urinalysis	• Summary of observed values, and changes and percent changes from the baseline
Serum Immunoglobulins	• Summary of observed values, changes and percent changes from the baseline

To evaluate the association between reduced Ig levels and infections/serious infections/opportunistic infections, those AEs will be summarized by the worst Ig Level during the combined RCP and OLP by the categories listed in Table 8.

[redacted]

[redacted]

3.6.3 Other Safety Evaluations

3.6.3.1 Vital Signs

The observed values, along with the changes from baseline, will be summarized by visit and by treatment for systolic and diastolic blood pressure (mmHg), pulse rate (beats/min), respiratory rate (breaths/min), body temperature (ºC), and body weight (kg). Shift analysis of following BMI categories will be performed:

- Underweight (<18.5 kg/m^2)
- Normal weight (≥18.5 kg/m^2 – <25 kg/m^2)
- Overweight (≥25 kg/m^2 – <30 kg/m^2)
- Obese (≥ 30 kg/m^2).

For vital sign assessments collected on the dosing day, the vital sign data will be presented by time points of interest as well. The time points of interest are as follows:

- Pre-dose assessment.
- During dosing: 15 minutes, 45 minutes, 75 minutes after start of infusion.
- After dosing: immediately after infusion, 60 minutes post-infusion.

In addition, a summary of subjects with clinically significant vital signs values (meeting any of following criteria) will also be provided:

- Systolic blood pressure: < 90 mmHg, > 140 mmHg, > 160 mmHg
- Diastolic blood pressure: < 50 mmHg, > 90 mmHg, > 100 mmHg
- Pulse rate: < 60 beats/min, > 100 beats/min
- Respiratory rate: < 12 breaths/min, > 20 breaths/min
- Body temperature: < 36°C, >38°C
- Body weight: decrease of ≥ 7% from baseline and increase of ≥ 7% from baseline.

3.6.3.2 Electrocardiogram

The observed values, along with the changes from baseline, will be summarized for ventricular heart rate (bpm), PR interval (msec), QRS duration (msec), QT interval (msec), and the corrected QT interval (QTc) based on Bazette approach and based on Fridericia approach. The number (%) of subjects meeting the following criteria will be summarized:

- QTc > 450 msec
- QTc > 480 msec

- QTc > 500 msec
- QTc increases from baseline > 30 msec
- QTc increases from baseline > 60 msec

In addition, the overall clinical evaluation of electrocardiogram results (normal, abnormal, not clinically significant abnormal, potentially clinically significant abnormal) will be summarized.

3.6.3.3 Physical Examination

The findings from physical examinations will be recorded. Those clinically significant abnormal findings that meet criteria for an AE will be reported as such. All abnormal physical exam findings (including not clinically significant and potentially clinically significant) will be listed.

3.8 Immunogenicity

The ADA analysis will be based on the Safety Analysis Set. The ADA status in Table 9**Error! Reference source not found.** will be summarized by the categories included in the table and the ADA titer may be summarized for ADA positive subjects. The impact of ADA on safety may be evaluated if needed.

Table 9 Definition of ADA Status

ADA Status	Definition
Prevalence (Positive during the study)	ADA positive observed at least once during the study (baseline included)
Incidence (treatment emergent ADA)	ADA positive post-baseline only or boosted their pre-existing ADA titer (≥ 4-fold increase) during the study period
Negative during the study	ADA positive not observed at any visit during the study (baseline included)
Baseline positive	ADA positive observed at baseline regardless of the post-baseline ADA status
Post-baseline positive	ADA positive observed at least once during post-baseline regardless of the baseline ADA status
Only baseline positive	ADA positive observed at baseline but not observed at any time post-baseline
Only post-baseline positive (treatment-induced)	ADA positive not observed at baseline but observed at least once post-baseline
Both baseline and post-baseline positive	ADA positive observed at baseline and observed at least once post-baseline

Persistent positive	Treatment-induced ADA positive at ≥ 2 post-baseline assessments (with ≥ 16 weeks between first and last positive) or positive at last post-baseline assessment
Transient positive	Treatment-induced ADA post-baseline positive but does not fulfil the criteria of persistent positive

ADA = anti-drug antibodies.

4 PLANNED ANALYSIS

Two analyses are planned for this study. The primary analysis will be conducted after the last subject enrolled in the study has completed the RCP or discontinued prematurely. All the data collected by the date of the last visit during the RCP (or within 5 business days after the scheduled visit window for the last visit in case any data may be collected after the last scheduled visit, for example, image data etc.) will be included in the primary analysis. The final analysis will be performed after all subjects have completed the study or discontinued prematurely.

5 MULTIPLICITY ADJUSTMENT

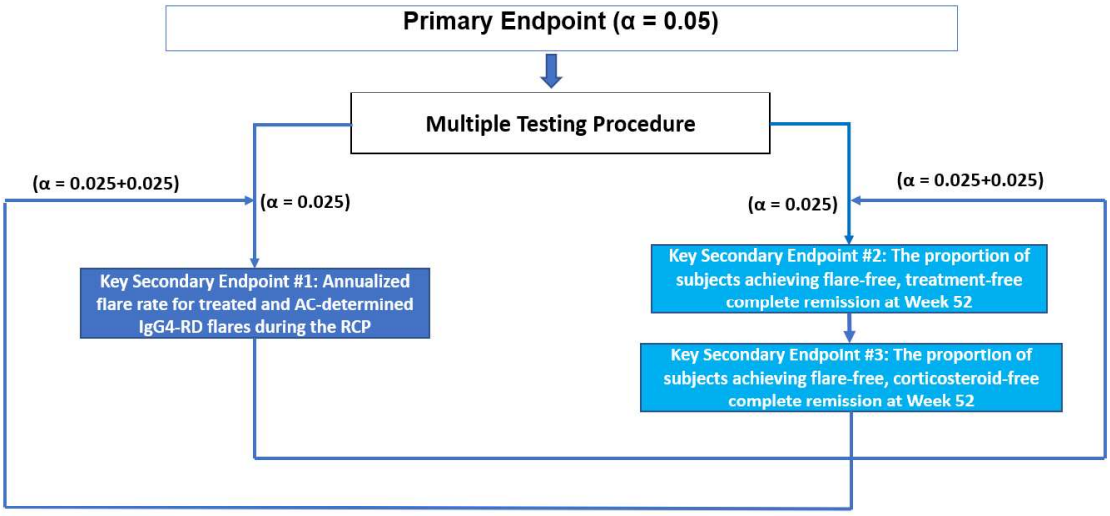
The primary null hypothesis will be tested at two-sided $\alpha = 0.05$. If, and only if, the treatment group comparison is statistically significant, the secondary hypotheses will be tested.

The 3 key secondary endpoints to be considered for study-wise type I error control are:

1. Annualized flare rate for treated, AC-determined flares during the RCP.
2. The proportion of subjects achieving flare-free, treatment-free complete remission at Week 52.
3. The proportion of subjects achieving flare-free, corticosteroid-free complete remission at Week 52.

Null hypotheses for the key secondary endpoint #1 and #2 will be tested in parallel with α = 0.025.The key secondary endpoint #2 and #3 will be tested sequentially: if the null hypotheses is rejected for the key secondary endpoint #2, the null hypothesis for the key secondary endpoint #3 will be tested with α = 0.025. If the null hypothesis for the key secondary endpoint #1 is rejected, the alpha will be recycled to test the key secondary endpoint #2 and #3 sequentially. On the other hand, if both the null hypotheses for the key secondary endpoint #2 and #3 are rejected, the alpha will be recycled to test the null hypothesis for the key secondary endpoint #1. (See Figure 2)

Figure 2 Multiple Testing Procedure for Key Secondary Endpoints



6 REFERENCE

Wallace ZS, Khosroshahi A, Carruthers MD, Perugino CA, Choi H, Campochiaro C, et al. An international multispecialty validation study of the IgG4-related disease responder index. Arthritis Care Res (Hoboken). 2018;70(11):1671-78.

Wang L, Zhang P, Wang M, Feng R, Lai Y, Peng L, et al. Failure of remission induction by glucocorticoids alone or in combination with immunosuppressive agents in IgG4-related disease: a prospective study of 215 patients. Arthritis Res Ther. 2018 Apr 10;20(1):65.

Yunyun F, Yu C, Panpan Z, Hua C, Di W, Lidan Z, et al. Efficacy of Cyclophosphamide treatment for immunoglobulin G4-related disease with addition of glucocorticoids. Sci Rep. 2017;7(1):6195. doi: 10.1038/s41598-017-06520-5. Epub 2017 Jul 21.

Yunyun F, Yu P, Panpan Z, Xia Z, Linyi P, Jiaxin Z, et al. Efficacy and safety of low dose Mycophenolate mofetil treatment for immunoglobulin G4-related disease: a randomized clinical trial. Rheumatology (Oxford). 2019;58(1):52-60.

7 REVISION HISTORY

Version #	Description of Change
Version 1.0	Initial version
Version 2.0	Updated per protocol version 9 (dated 08AUG2023. The major updates are • Change the key secondary endpoints and the analyses. • Change OLP to 3 years and add SFP.
Version 3.0	Per FDA review comments • Update multiplicity adjustment method • Update analysis window • Add details of statistical methods for clarification purpose

8 APPROVALS

Confirmation by the study biostatistician (or designee), biostatistics management (or designee), and the study clinical colleague or therapeutic lead (or designee) that the review of this statistical analysis plan is complete, and there is agreement on the content.

[redacted] Senior Manager, Biostatistics	DocuSigned by: [redacted] 6F2351D6E74343E...	15-May-2024 | 2:47:17 PM PDT
Name, Title	Signature/Date	
[redacted] Executive Director, Biostatistics	DocuSigned by: [redacted] FF1A63043C2F467...	15-May-2024 | 3:50:24 PM PDT
Name, Title	Signature/Date	
[redacted] Executive Medical Director, Clinical Development	DocuSigned by: [redacted] 959F6886E4F7415...	15-May-2024 | 2:47:25 PM PDT
Name, Title	Signature/Date	