STATISTICAL ANALYSIS PLAN

STUDY TITLE: **A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO INVESTIGATE THE EFFICACY OF FENEBRUTINIB IN RELAPSING MULTIPLE SCLEROSIS**

STUDY NUMBER: GN43271

STUDY NAME: FENopta

VERSION NUMBER: 1

ROCHE COMPOUND(S): Fenebrutinib (RO7010939)

EUDRACT NUMBER: 2022-502619-13-00

IND NUMBER: 145,957

NCT NUMBER: NCT05119569

PLAN PREPARED BY: [redacted], Ph.D.

STATISTICAL ANALYSIS PLAN APPROVAL

SPONSOR: F. Hoffmann-La Roche Ltd
LEGAL REGISTERED ADDRESS: Grenzacherstrasse 124
4070 Basel, Switzerland

DATE FINAL: See electronic date stamp on the last page of this document

STATISTICAL ANALYSIS PLAN VERSION HISTORY

This Statistical Analysis Plan (SAP) was developed based on Roche SAP model document updated on 28 February 2022.

SAP Version	Approval Date	Based on Protocol (Version, Approval Date)
1	See electronic date stamp on the last page of this document	Protocol v3 dated 15 Dec 2022

TABLE OF CONTENTS

1. INTRODUCTION 6
   - 1.1 Objectives and Endpoints and Estimands 6
   - 1.2 Study Design 8
     - 1.2.1 Treatment Assignment and Blinding 10
     - 1.2.2 Independent Review Facility 11
     - 1.2.3 Data Monitoring 11
2. STATISTICAL HYPOTHESES 11
3. SAMPLE SIZE DETERMINATION 12
4. ANALYSIS SETS 12
5. STATISTICAL ANALYSES 12
   - 5.1 General Consideration 12
   - 5.2 Participant Disposition 12
   - 5.3 Primary Endpoint(s) Analysis 13
     - 5.3.1 Definition of Primary Endpoint(s) 13
     - 5.3.2 Main Analytical Approach for Primary Endpoint(s) 13
     - 5.3.3 Sensitivity Analyses for Primary Endpoint(s) 14
     - 5.3.4 Supplementary Analyses for Primary Endpoint(s) 14
       - 5.3.4.1 Subgroup Analyses for Primary Endpoint(s) 14
       - 5.3.4.2 Other Supplementary Analyses for Primary Endpoint(s) 15
   - 5.4 Secondary Endpoint(s) Analysis(ses) 15
     - 5.4.1 Key/Confirmatory Secondary Endpoint(s) 15
       - 5.4.1.1 Total number of new or enlarging T2-weighted lesions 15
       - 5.4.1.2 Proportion of Participants Free from any new Gadolinium-Enhancing T1 Lesions and new or Enlarging T2-Weighted Lesions 15
     - 5.4.2 Supportive Secondary Endpoint(s) 15
       - 5.4.2.1 Secondary safety endpoints 16
       - 5.4.2.2 Secondary PK endpoints 16
   - 5.5 Exploratory Endpoint(s) Analysis 17

5.5.1.1 Annualized relapse rate (ARR) of protocol-defined relapses 17
5.5.1.2 CSF Concentration of Fenebrutinib (CSF Sample is Optional) 18
5.5.1.3 CSF IgG Index and Oligoclonal Bands (CSF Sample is Optional) 18
5.5.1.4 CSF NfL levels (CSF sample is optional) 18
5.5.1.5 Levels of and Change in Plasma NfL and other Pharmacodynamic Biomarkers Related to Disease Activity and/or Mechanism of Action of Fenebrutinib 18
5.5.1.6 Change in Whole Blood Lymphocyte Levels 19
5.6 Other Safety Analyses 19
5.6.1 Extent of Exposure 19
5.7 Other Analyses 19
5.7.1 Summaries of Conduct of Study 19
5.7.2 Summaries of Treatment Group Comparability/Demographics and Baseline Characteristics 19
5.8 Interim Analyses 20
6. SUPPORTING DOCUMENTATION 20
7. REFERENCES 20

LIST OF TABLES

Table 1 Primary and Secondary Objectives and Corresponding Estimands 6
Table 2 Other Secondary and Exploratory Objectives and Endpoints 8

LIST OF FIGURES

Figure 1 Study Schema 9

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Description
AE	adverse event
ATP	adenosine triphosphate
BID	twice a day
BMI	body mass index
BTK	Bruton's tyrosine kinase
CSF	cerebrospinal fluid
CSR	Clinical Study Report
DBT	Double-blind treatment
DMC	Data Monitoring Committee
EDSS	expanded disability status scale
FSS	functional systems score
HR	hazard ratio
IA	interim analysis
ICH	International Council on Harmonization
IDMC	independent Data Monitoring Committee
IDMC-ISA	iDMC-Initial Safety Assessments
IgG	Immunoglobulin G
IxRx	interactive voice/web-based response system
MDD	minimally detectable difference
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OLE	open-label extension
PD	pharmacodynamics
PK	pharmacokinetic
RMS	relapsing multiple sclerosis
SAE	serious adverse events
SAP	Statistical Analysis Plan
SFU	safety follow-up
UHB	University Hospital Basel

1. INTRODUCTION

Study GN43271 is a Phase II study to assess the efficacy, safety, and pharmacokinetics of fenebrutinib, a highly selective, orally administered, adenosine triphosphate (ATP)-competitive, reversible inhibitor of Bruton's tyrosine kinase (BTK), compared with placebo in participants with relapsing multiple sclerosis (RMS). This Statistical Analysis Plan (SAP) provides details of the planned analyses and statistical method for the studyand supersedes analysis details specified in the protocol.

1.1 OBJECTIVES AND ENDPOINTS AND ESTIMANDS

Table 1 Primary and Secondary Objectives and Corresponding Estimands

Primary Objectives	Estimand Definition
• To evaluate the efficacy of fenebrutinib compared with placebo on the total number of new gadolinium-enhancing T1 MRI lesions	• Population: all randomized patients
	• Endpoint: Total number of new gadolinium-enhancing T1 lesions observed on MRI scans of the brain at Weeks 4, 8, and 12
	• Treatment: – 200 mg BID oral fenebrutinib – placebo
	• Intercurrent events and handling strategy: – Withdrawal from treatment: hypothetical strategy – Initiation of another MS therapy: not allowed while on study. In case of such intercurrent event: hypothetical strategy
	• Population level summary: rate ratio from Negative Binomial model
Secondary Objectives	**Estimand Definition**
• To evaluate the effect of fenebrutinib on MRI lesions	• Population: all randomized patients
	• Endpoint: 1. Total number of new or enlarging T2-weighted lesions observed on brain MRI at Weeks 4, 8, and 12 2. Proportion of participants free from any new gadolinium-enhancing T1 lesions and new or enlarging T2-weighted lesions observed on brain MRI at Weeks 4, 8, and 12

Table 1 Primary and Secondary Objectives and Corresponding Estimands

	• Treatment: – 200 mg BID oral fenebrutinib – placebo
	• Intercurrent events and handling strategy: – Withdrawal from treatment: hypothetical strategy (see Section 5.4.1) – Initiation of another MS therapy: not allowed while on study. In case of such intercurrent event: hypothetical strategy
	• Population level summary: – For Endpoint (1): rate ratio from Negative Binomial model – For Endpoint (2): odds ratio from logistic regression model

Table 2 Other Secondary and Exploratory Objectives and Endpoints

Secondary Objectives	Corresponding Endpoints
• To evaluate the safety of fenebrutinib compared with placebo	• Incidence and severity of adverse events • Change from baseline in vital signs • Change from baseline in targeted clinical laboratory test results • Proportion of participants with suicidal ideation or behavior, as assessed by Columbia-Suicide Severity Rating Scale
• To characterize the fenebrutinib PK profile	• Plasma concentration of fenebrutinib at specified timepoints
Exploratory Objectives	**Corresponding Endpoints**
• To evaluate the effect of fenebrutinib on MS relapses • To evaluate fenebrutinib concentration in the CSF • To evaluate changes in inflammatory markers in the CSF	• ARR • CSF concentration of fenebrutinib (CSF sample is optional) • CSF Immunoglobulin G (IgG) index and oligoclonal bands (CSF sample is optional) • CSF NfL levels (CSF sample is optional)
• To identify and/or evaluate biomarkers that are predictive of response to fenebrutinib, are early surrogates of efficacy, are associated with susceptibility to developing adverse events, can provide evidence of fenebrutinib activity, or can increase the knowledge and understanding of disease biology and drug safety	• Levels of and change in plasma NfL and other pharmacodynamic biomarkers related to disease activity and/or mechanism of action of fenebrutinib

ARR = annualized relapse rate; CSF = cerebrospinal fluid; CTCAE = Common Terminology Criteria for Adverse Events; MRI = magnetic resonance imaging; MS = multiple sclerosis; NfL = neurofilament light chain; PK = pharmacokinetic.

1.2 STUDY DESIGN

GN43271 is a Phase II, double-blind, placebo-controlled, randomized study with a primary efficacy objective of evaluating the effect of fenebrutinib on the total number of new Gd-enhancing T1 brain magnetic resonance imaging (MRI) lesions in participants with RMS. The safety and pharmacokinetics of fenebrutinib will also be evaluated in the study.

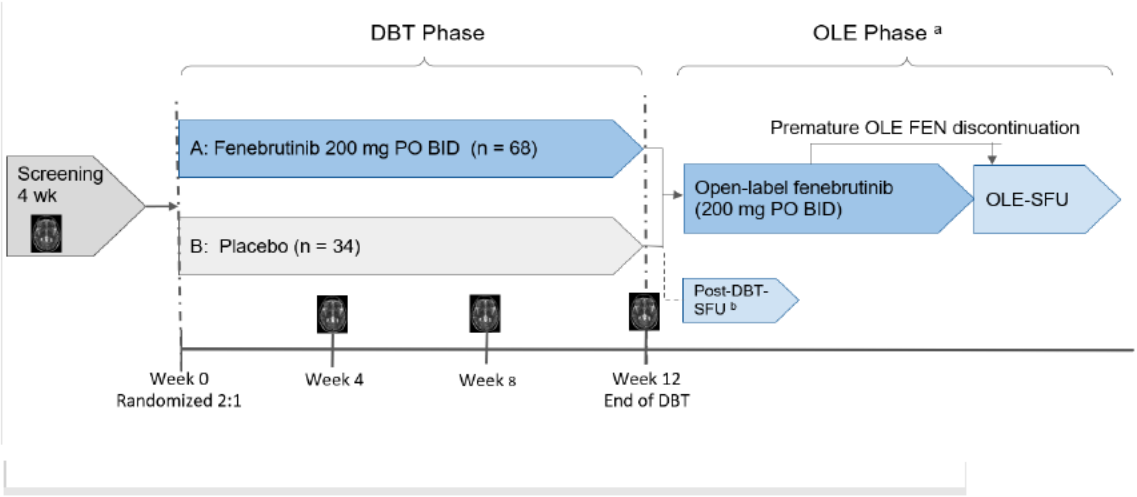
The study will enroll approximately 102 participants with RMS with recent disease activity and will consist of the following phases:

- Screening phase, of approximately 4 weeks
- Double-blind treatment (DBT) phase, where participants will be randomized in a 2:1 ratio to either 200 mg twice a day (BID) oral fenebrutinib or placebo for 12 weeks. The primary analysis will be performed when the last patient completes the Week 12 visit or withdraws.
- Optional open-label extension (OLE) phase will be available for eligible participants within the current protocol. Participants may receive up to a maximum of 192 weeks of open-label fenebrutinib in this protocol. Participants will be moved to a program level OLE (separate protocol, protocol number to be decided [TBD]) as soon as it is available.
- A safety follow-up (SFU) phase is available to participants who discontinue study drug early from either the DBT or OLE phases, who complete the DBT phase without going to OLE, or who complete the OLE phase. Participants will be followed in the SFU for approximately 4 weeks.

The study schema is shown in Figure 1.

Study GN43271 will enroll approximately 102 participants across all sites in a global enrollment phase.

Figure 1 Study Schema



BID = twice a day; DBT = double-blind trial; FEN = fenebrutinib; OLE = open-label extension; PO = by mouth; SFU = safety follow-up.

[a] An optional OLE to provide open-label fenebrutinib will be available to all eligible participants who complete the DBT phase on study treatment.

[b] Participants who complete the DBT phase on study treatment and do not wish to participate in the OLE and participants who have discontinued treatment will have a post-DBT SFU visit.

1.2.1 Treatment Assignment and Blinding

Randomization will be employed to minimize bias in treatment assignment and to provide the basis for valid statistical inference. After initial written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a participant, the study site will obtain the participant's identification number and treatment assignment from an interactive voice/web-based response system (IxRS). Participants who enroll in this study and who have completed or prematurely discontinued from treatment as specified are not permitted to be re-randomized to this study under any circumstances.

Participants will be randomly assigned to one of two treatment arms: fenebrutinib or placebo. Randomization will occur in a 2:1 ratio through use of a permuted-block randomization method to ensure a balanced assignment to each treatment arm. Randomization will be stratified by presence or absence of T1 Gd+ lesions on the screening MRI.

To maintain the integrity of the trial results and to prevent potential unblinding of the assigned arm as a result of adverse events or changes in laboratory results, the following additional measures will be implemented until the time of the primary analysis:

- Blinded, central MRI assessments: During the study, a blinded, central MRI reader will assess all MRI scans performed during the study. Of note, screening scans will be used for the assessment of patient eligibility and therefore will not be blinded. A local radiologist who is independent of the study team will review all scans at site for safety and report only significant non- multiple sclerosis (MS)-related findings to the treating investigator (or treating team).
- Blinding of laboratory parameters: Immunoglobulins (IgG, IgM, IgA, and total Ig) will be blinded until the primary database lock for the primary analysis.
- Study drug treatment allocation will remain blinded until the primary database lock for the primary analysis.

The pharmacokinetic (PK) samples must be collected from participants assigned to the comparator arm to maintain the blinding of treatment assignment; however, PK assay results for these participants are generally not needed for the safe conduct or proper interpretation of this study. Laboratories responsible for performing study drug PK assays will be unblinded to participants' treatment assignments to identify appropriate samples to be analyzed. PK samples from participants assigned to the comparator arm will not be analyzed for study drug PK concentration except at baseline or by request (e.g., to evaluate a possible error in dosing).

If study treatment unblinding is necessary for a medical emergency (e.g., in the case of a serious adverse event for which participant management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. The treatment code should not be broken except in

emergency situations. Refer to protocol Section 6.3.2 for situations where the investigator, for clinical decision making, requires the unblinding of specific MRI scans and/or laboratory results.

As per health authority reporting requirements, the Sponsor's Drug Safety representative will break the treatment code for all serious, unexpected suspected adverse reactions that are considered by the investigator or Sponsor to be related to study drug. The patient may continue to receive treatment, and the investigator, patient, and Sponsor personnel, with the exception of the Drug Safety representative and personnel who must have access to patient treatment assignments to fulfill their roles (as defined above), will remain blinded to treatment assignment.

1.2.2 Independent Review Facility

To standardize the Expanded Disability Status Scale (EDSS) assessment and data collection, data will be transferred when certain recruitment threshold has been reached and at least Week 12 of the Double Blinded Treatment Period EDSS score have been entered into the EDC for these patients. The University Hospital Basel (UHB) will perform automated algorithm check and flagged any inconsistencies if found. The sponsor will query the inconsistence and the ultimate decision of EDSS score will remain with the sites.

1.2.3 Data Monitoring

The first data review meeting should be conducted during the independent Data Monitoring Committee (iDMC)-initial safety assessment (ISA) of Phase III studies. The second safety data review may happen at the next Phase III studies iDMC meeting approximately six months later if the DBT phase has not been completed.

If a deleterious safety signal is detected by the iDMC during any data review, including an iDMC-ISA, the iDMC may recommend study discontinuation or modification of the study to the Sponsor. Further details regarding the iDMC review and iDMC-ISA will be specified in a separate iDMC charter.

2. STATISTICAL HYPOTHESES

The primary purpose of this study is estimation and hypothesis testing regarding the effect of fenebrutinib on the primary endpoint of total number of new T1 Gd+ lesions relative to placebo. Point and interval estimates of the true underlying lesion rate ratio will be presented along with the p-value.

The null hypothesis will be tested at the $\alpha = 0.05$ level (two-sided test).

- H0 (null hypothesis): there is no statistically significant difference between the fenebrutinib group and placebo group in the total number of new T1 Gd+ lesions at the end of DBT phase.

- H1 (alternative hypothesis): there is a statistically significant difference between the fenebrutinib group and placebo group in the total number of new T1 Gd+ lesions at the end of DBT phase.

3. SAMPLE SIZE DETERMINATION

A sample size of 102 was chosen to ensure at least 90% power to detect a 60% reduction in total number of new T1 Gd+ lesions. This assumes that the placebo arm has 0.7 new lesion per post-baseline scan and assuming approximately 3% dropout by the end of study. Approximately 68 will be randomized to receive fenebrutinib and 34 randomized to receive placebo.

4. ANALYSIS SETS

All efficacy and biomarker endpoints will be analyzed on all randomized patients. Efficacy and biomarker analyses will use all randomized patients grouped by treatment as assigned by randomization.

Safety Population

The Safety Population will include all participants who received any study drug. Patient who received an incorrect medication rather than the one they were randomized will be summarized in the group according to the treatment actually received. All safety outcome measures will be analyzed using the Safety Population.

PK Population

The PK analysis population will consist of participants with sufficient data to enable estimation of key parameters, with participants grouped according to treatment received.

5. STATISTICAL ANALYSES

5.1 GENERAL CONSIDERATION

Unless otherwise specified, all baseline and efficacy analyses will be performed on all randomized patients. Participants will be analyzed according to the treatment assigned at randomization by IxRS.

All safety analysis will be based on the safety evaluable population, unless otherwise specified. Participants will be analyzed according to the treatment they actually received.

5.2 PARTICIPANT DISPOSITION

The analysis of participant disposition will be based on all randomized patients. Reasons for early discontinuation will be summarized by treatment group. The number of patients entering into the SFU phase and the OLE phase will be summarized.

5.3 PRIMARY ENDPOINT(S) ANALYSIS

The primary efficacy objective of this study is to evaluate the efficacy of fenebrutinib compared with placebo in adult patients with RMS and will be assessed based on the following endpoint:

- Total number of new gadolinium-enhancing T1 MRI lesions

5.3.1 Definition of Primary Endpoint(s)

The primary endpoint will be tested using a two-sided significance level of 0.05.

Radiologic evaluation for the primary efficacy parameter will be performed using a standardized MRI protocol at screening, and at Weeks 4, 8, and 12. All MRI scans will be read by a centralized reading center for efficacy endpoints. The centralized reading center will be blinded to treatment assignment, and the reading will be performed in the absence of clinical information. All MRI scans will also be reviewed locally by a radiologist for safety, and a MRI scan report containing only non-MS pathology will be provided to the treating investigator.

The total number of new gadolinium-enhancing T1 lesions will be calculated as the sum of the individual number of new lesions observed at Weeks 4, 8 and 12.

5.3.2 Main Analytical Approach for Primary Endpoint(s)

The primary estimand follows a hypothetical strategy and estimates the treatment effect of fenebrutinib versus placebo had the patient not experienced a protocol defined intercurrent event on the basis of the following attributes:

- Population: all randomized participants.
- Variable: total number of new T1 Gd+ lesions as described in Section 5.3.1
- Treatment:
  - 200 mg BID oral fenebrutinib
  - placebo
- Intercurrent events:
  - Withdrawal from treatment: Data after participants withdrawn from treatment will be censored, following a hypothetical strategy.
  - Initiation of another MS therapy: Initiation of another MS therapy is not allowed while on study. In case of such intercurrent event, patient will be considered as censored after initiation of another MS therapy, following a hypothetical strategy.
- Population-level-summary estimator: The total number of new T1 Gd+ lesions of primary analysis will be compared between the fenebrutinib and placebo using the negative binomial model, adjusting for stratification factor(s) (presence or absence of T1 Gd+ lesions on the screening MRI). In case of early discontinuations, different number of scans among participants may be observed. Log-transformed number of

scans will be included in the negative binomial model as an “offset” variable to account for different number of scans. The rate ratio and its two-sided 95% confidence intervals will be presented along with the p-value.

- Handling of missing data:
  - Withdrawal from study: no imputation will be conducted for missing data. The negative binomial model with number of scans as an “offset” variable accounts for different number of scans.

If the model fails to converge due to high number of zero T1 Gd+ lesion counts, a logistic regression model will be performed on the status of new T1 Gd+ lesion post-baseline (present or not) adjusted for the same stratification factor(s). The odds ratio and its two-sided 95% confidence intervals will be presented along with the p-value. A hypothetical strategy will be used as defined above.

Number of new T1 Gd+ lesions and proportion of participants with new T1 Gd+ lesions at each scheduled visit will be summarized by treatment groups.

5.3.3 Sensitivity Analyses for Primary Endpoint(s)

To support the primary analyses, the following sensitivity analysis will be conducted:

- To test the sensitivity of the results to adjustment by the stratification factors, the primary analysis negative binomial model described above will be adjusted by the following additional covariates: sex, age (<40, ≥ 40).

5.3.4 Supplementary Analyses for Primary Endpoint(s)

5.3.4.1 Subgroup Analyses for Primary Endpoint(s)

The generalizability of primary endpoint results when comparing fenebrutinib to placebo will be investigated by estimating the treatment effect in subgroups. If there are less than 5% subjects in one subgroup, the corresponding subgroup analysis will not be produced. Summaries of primary endpoint by these subgroups will be provided:

Stratification factor:

- Presence or absence of T1Gd+ lesions at screening

Key baseline demographics:

- Age ($\geq$40 versus < 40)
- Sex (Female versus Male)
- Baseline EDSS ($>$4.0 versus $\leq$4.0)
- Region (North American versus other)

Disease characteristics:

- Prior disease modifying treatments within 6 months prior to randomization (yes or no)
- Prior steroid treatment within 3 months prior to randomization (yes or no)

5.3.4.2 Other Supplementary Analyses for Primary Endpoint(s)

To investigate the treatment effect on different estimand attribute of analysis population, the primary analysis negative binomial model described above in Section 5.3.2 may be fitted on all randomized patients excluding subjects with major protocol deviation related to incorrect amount of fenebrutinib.

5.4 SECONDARY ENDPOINT(S) ANALYSIS(SES)

5.4.1 Key/Confirmatory Secondary Endpoint(s)

The secondary efficacy endpoints are:

- Total number of new or enlarging T2-weighted lesions observed on brain MRI at Weeks 4, 8, and 12.
- Proportion of participants free from any new gadolinium-enhancing T1 lesions and new or enlarging T2-weighted lesions observed on brain MRI at Weeks 4, 8, and 12.

5.4.1.1 Total number of new or enlarging T2-weighted lesions

Total number of new or enlarging T2-weighted lesions will be calculated as the sum of the individual number of new or enlarging lesions at Weeks 4, 8, 12. The estimands for the secondary endpoint of total number of new or enlarging T2 lesions, will follow the same hypothetical strategy and have the same attributes (except for variable) as for the primary endpoint. Number of new or enlarging T2 lesions and proportion of participants with new or enlarging T2 lesions at each scheduled visit will also be summarized by treatment groups.

5.4.1.2 Proportion of Participants Free from any new Gadolinium-Enhancing T1 Lesions and new or Enlarging T2-Weighted Lesions

The secondary endpoint of proportion of participants free from any new gadoliniumenhancing T1 lesions or new or enlarging T2-weighted lesions observed on brain MRI at Weeks 4, 8, and 12 will use a logistic regression model similar as described for the primary endpoint. A hypothetical strategy will also be used as defined in Section 5.3.2.

5.4.2 Supportive Secondary Endpoint(s)

The secondary safety endpoints are:

- Incidence and severity of adverse events
- Change from baseline in vital signs
- Change from baseline in targeted clinical laboratory test results (Hematology, chemistry, hepatic synthetic function tests, lipids, and Igs)
- Proportion of participants with suicidal ideation or behavior, as assessed by Columbia-Suicide Severity Rating Scale

The secondary PK endpoint is:

- Plasma concentration of fenebrutinib at specified timepoints

5.4.2.1 Secondary safety endpoints

Safety will be assessed through summaries of exposure to study treatment, adverse events, changes in laboratory test results, changes in vital signs, and by the proportion of patients with suicidal ideation or behavior as assessed by Columbia-Suicide Severity Rating Scale (C-SSRS) scores.

All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and adverse event severity will be graded according to the most current version of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE). All adverse events, serious adverse events, adverse events leading to death, adverse events of special interest, and adverse events leading to study treatment discontinuation that occur on or after the first dose of study treatment (i.e., treatment-emergent adverse events) will be summarized by mapped term, appropriate thesaurus level, and severity grade. For events of varying severity, the highest grade will be used in the summaries. Deaths and cause of death will be summarized.

Relevant laboratory and vital signs will be displayed by time and grade identified when associated with an adverse event. Additionally, a shift table of selected laboratory tests will be used to summarize the baseline and maximum postbaseline severity grade. Changes in vital signs will be summarized.

Proportion of participants with suicidal ideation or behavior, as assessed by Columbia-Suicide Severity Rating Scale, will be summarized.

5.4.2.2 Secondary PK endpoints

The PK analysis will include tabulation of plasma concentration data and summarization of plasma concentrations by visit, with participants grouped according to treatment received. Descriptive summary statistics may include the arithmetic mean, median, range, standard deviation, and coefficient of variation, as appropriate.

Interpatient variability will be evaluated, and potential sources of variability may be assessed.

Systemic fenebrutinib exposure may also be evaluated using a population PK approach. Relationships between exposure and pharmacodynamics (PD), efficacy, and safety endpoints may be explored.

Additional PK analyses may be conducted during and/or at the end of the study as appropriate. The exploratory PK analyses may be reported separately.

5.5 EXPLORATORY ENDPOINT(S) ANALYSIS

Analyses on exploratory efficacy endpoints may be performed as data allows and results may be reported separately from the GN42371 Clinical Study Report.

The exploratory endpoints for this study may include, but are not limited to, the list below.

- Annualized relapse rate (ARR) of protocol-defined relapses
- Cerebrospinal fluid (CSF) concentration of fenebrutinib (CSF sample is optional)
- CSF IgG index and oligoclonal bands (CSF sample is optional)
- CSF NfL levels (CSF sample is optional)
- Levels of and change in plasma NfL and other pharmacodynamic biomarkers related to disease activity and/or mechanism of action of fenebrutinib

5.5.1.1 Annualized relapse rate (ARR) of protocol-defined relapses

For this study, a protocol-defined relapse is defined as the occurrence of new or worsening neurological symptoms attributed to MS and immediately preceded by a relatively stable or improving neurological state of at least 30 days. Symptoms must persist for > 24 hours and should not be attributable to confounding clinical factors (e.g., fever, infection, injury, adverse reactions to concomitant medications). The new or worsening neurological symptoms must be accompanied by objective neurological worsening consistent with an increase of at least one of the following:

- Half a step (0.5 point) on the EDSS
- Two points on one of the selected functional systems score (FSS) listed below
- One point on two or more of the selected FSS listed below

The change must affect the following selected FSS: pyramidal, ambulation, cerebellar, brainstem, sensory, or visual. Episodic spasms, sexual dysfunction, fatigue, mood change, or bladder or bowel urgency or incontinence will not suffice to establish a relapse. Note that the following items need not be scored: sexual dysfunction and fatigue.

The annualized protocol-defined relapse rate will be calculated using a negative binomial regression model, adjusting for stratification factor (presence or absence of T1 Gd+ lesions at screening).

Log-transformed follow-up time will be included in the negative binomial model as an “offset” variable to account for different follow-up durations. For every patient, the follow-up time starts from the first study treatment, and ends at the end of study DBT phase/discontinuation from study. The rate ratio and its two-sided 95% confidence intervals will be presented along with the p-value.

5.5.1.2 CSF Concentration of Fenebrutinib (CSF Sample is Optional)

The fenebrutinig CSF concentration will be summarized by visit, with participants grouped according to treatment received. Descriptive summary statistics may include the arithmetic mean, median, range, standard deviation, and coefficient of variation, as appropriate.

Additional CSF or brain PK analyses may be conducted during and/or at the end of the study as appropriate. The exploratory PK analyses may be reported separately.

5.5.1.3 CSF IgG Index and Oligoclonal Bands (CSF Sample is Optional)

Change from baseline of IgG Index may be summarized descriptively by visits. The LS mean of placebo adjusted treatment effect of fenebrutinib may be estimated by a MMRM model at Week 12.

Change from baseline of CSF IgG Oligoclonal Band status (positive/negative) may be summarized descriptively by visits.

Change from baseline of Albumin Index may be summarized descriptively by visits. The LS mean of placebo adjusted treatment effect of fenebrutinib may be estimated by a MMRM model at Week 12.

5.5.1.4 CSF NfL levels (CSF sample is optional)

Change from baseline of CSF NfL may be summarized descriptively by visits. The LS mean of placebo adjusted treatment effect of fenebrutinib may be estimated by a MMRM model at Week 12.

5.5.1.5 Levels of and Change in Plasma NfL and other Pharmacodynamic Biomarkers Related to Disease Activity and/or Mechanism of Action of Fenebrutinib

Change from baseline of NfL may be summarized descriptively by visits. The LS mean of placebo adjusted treatment effect of fenebrutinib may be estimated by a MMRM model at Week 12.

Change from baseline of plasma CCL4 level may be summarized descriptively by visits. The LS mean of placebo adjusted treatment effect of fenebrutinib may be estimated by a MMRM model at Week 12.

Change from baseline of plasma CXCL13 level may be summarized descriptively by visits. The LS mean of placebo adjusted treatment effect of fenebrutinib may be estimated by a MMRM model at Week 12.

5.5.1.6 Change in Whole Blood Lymphocyte Levels

Change from baseline of blood B cell count (CD3-CD19+ cells/mcL) may be summarized descriptively by visits. The LS mean of placebo adjusted treatment effect of fenebrutinib may be estimated by a MMRM model at Week 12.

Change from baseline of blood CD3+ T cell count (CD3+CD45+ cells/μL) may be summarized descriptively by visits. The LS mean of placebo adjusted treatment effect of fenebrutinib may be estimated by a MMRM model at Week 12.

Change from baseline of Helper T cell count (CD3+CD4+ cells/μL) may be summarized descriptively by visits. The LS mean of placebo adjusted treatment effect of fenebrutinib may be estimated by a MMRM model at Week 12.

Change from baseline of blood Cytotoxic T cell count (CD3+CD8+ cells/μL) may be summarized descriptively by visits. The LS mean of placebo adjusted treatment effect of fenebrutinib may be estimated by a MMRM model at Week 12.

Change from baseline of blood NK cell count (CD3-CD16+CD56+ cells/μL) may be summarized descriptively by visits. The LS mean of placebo adjusted treatment effect of fenebrutinib may be estimated by a MMRM model at Week 12.

5.6 OTHER SAFETY ANALYSES

In addition to the analyses as specified for the secondary safety endpoint, study treatment exposure (such as treatment duration, total dose received and treatment interruptions) will be summarized with descriptive statistics.

The ECG data will be displayed by time. Changes in ECGs will be summarized.

5.6.1 Extent of Exposure

Study treatment exposure (such as treatment duration, total dose received, and number of doses and dose interruptions) will be summarized with descriptive statistics.

5.7 OTHER ANALYSES

5.7.1 Summaries of Conduct of Study

Enrollment and study treatment administration will be summarized by treatment arm. Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be summarized by treatment arm.

5.7.2 Summaries of Treatment Group Comparability/Demographics and Baseline Characteristics

Demographics and baseline characteristics (including age, sex, T1 Gd+ lesions, etc.) will be summarized by treatment arm. Baseline data are the last data obtained prior to initiation of study treatment. Descriptive statistics (mean, standard deviation, median,

and range) will be presented for continuous variables and counts and percentages will be presented for categorical variables.

5.8 INTERIM ANALYSES

There is no plan to conduct interim analysis.

6. SUPPORTING DOCUMENTATION

This section is not applicable, since there is no additional supporting document.

7. REFERENCES

Not applicable

Signature Page for Statistical Analysis Plan - GN43271
System identifier: RIM-CLIN-467214

Approval Task	[redacted] Scientific content approver 10-Feb-2023 20:42:21 GMT+0000