PROTOCOL

PROTOCOL TITLE:	**A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO INVESTIGATE THE EFFICACY OF FENEBRUTINIB IN RELAPSING MULTIPLE SCLEROSIS**
PROTOCOL NUMBER:	GN43271
VERSION NUMBER:	3
ROCHE COMPOUND(S):	Fenebrutinib (RO7010939)
STUDY PHASE:	Phase II
REGULATORY AGENCY IDENTIFIER NUMBERS:	IND Number: 145957 EUDRACT Number: 2021-003772-14 EU Trial Number: 2022-502619-13-00 NCT Number: NCT05119569
SPONSOR NAME AND LEGAL REGISTERED ADDRESS:	F. Hoffmann-La Roche Ltd Grenzacherstrasse 124 4070 Basel, Switzerland
APPROVAL:	See electronic signature and date stamp on the final page of this document.

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
3	See electronic date stamp on the final page of this document.
2	13 July 2021
1	5 May 2021

PROTOCOL AMENDMENT, VERSION 3: RATIONALE

Protocol GN43271 has been amended to provide additional guidance on safety monitoring. Substantive changes to the protocol, along with a rationale for each change, are summarized below.

- Per recommendations from the independent Data Monitoring Committee (iDMC), additional monitoring visits for liver function tests (ALT, AST, total and direct bilirubin) have been added to the schedule of activities (Section 1.3). Guidance has been added for laboratory analysis of these blood tests.

The following changes have been added to further support the additional monitoring of liver function tests and provide sites with more guidance regarding patient management.

- The exclusion criterion for ALT or AST $>$ 2 x upper limit of normal has been updated to no longer allow retesting for ALT or AST 2–3 $\times$ ULN (Section 5.2).
- The criteria for discontinuation of study treatment have been edited to include participants with ALT or AST elevation between 3–5 $\times$ ULN (inclusive) persisting for 4 weeks and in absence of alternative etiology (Section 7.1).
- The safety reporting sections have been edited to clearly define the laboratory parameters that constitute adverse events of special interest (Sections 8.2.4 and 8.3.8, Appendix A3–7.6, and Appendix A6–1.1).
- Guidance on the management of patients with elevated liver function tests, including re-testing requirements and/or additional laboratory tests has been clarified (Appendix A6–2.3).
- To build on the existing safety monitoring plan for participants, detailed monitoring guidelines for participants with abnormal liver biochemical and functional tests have been added (Appendix 7). These revisions align with 2009 FDA regulatory guidance for drug induced liver injury (DILI) detection, and the 2020 Consensus by the CIOMS DILI Working Group.

The duration of the optional open-label extension (OLE) phase was extended from 96 weeks up to a maximum of 192 weeks. To align with this, the following changes were made:

- The footnote for the Study Schema was updated to clarify that there currently is an optional OLE to provide open-label fenebrutinib to all eligible participants who complete the DBT phase on study treatment (Section 1.2, Figure 1). The study design section has also been updated to include the duration of the OLE phase (Section 4.1).
- The OLE schedule of activities was updated to reflect that patients may remain in the OLE beyond 96 weeks (Section 1.3, Table 2).
- The collection of hepatic synthetic function tests was updated in the OLE schedule of activities from Weeks 36 and 96 to Weeks 12 and 24 to align with the risk period for potential hepatic transaminase elevations (Section 1.3, Table 2).

- The collection of lipids was changed to every 48 weeks following Week 48 to align with the increase in duration of the OLE phase beyond 96 weeks.

The following additional changes and clarifications have been made:

- Personal identifiable information (i.e., name and telephone number) for the Medical Monitors has been removed from the protocol (front page and Section 8.3.10). Medical Monitor contact information in Section 8.3.10 has been replaced with a sentence indicating that this information will be provided separately to sites.
- The synopsis has been simplified to align with Clinical Trials Regulation (CTR) and other guidelines.
- The language regarding the timing of the Week 12 lumbar puncture was updated to allow for more flexibility for obtaining the sample (Sections 1.3 and 8.10.1).
- The primary and secondary objectives have been updated to add language on corresponding estimands (Section 3).
- Per recommendation from the U.S. Food and Drug Administration, high dose biotin has been added to the list of prohibited concomitant medications (Section 6.8.3.1).
- The exclusion criterion regarding the presence of other neurological disorders has been clarified to specify those conditions which could interfere with the diagnosis of multiple sclerosis or with the assessments of efficacy or safety during the study (Section 5.2).
- The criterion for exclusion of patients on adrenocorticotropic hormone or systemic corticosteroid therapy has been updated to clarify that inhaled and topical corticosteroids would be permitted (Section 5.2).
- A comprehensive list of investigational medicinal products and non-investigational/ auxiliary medicinal products has been added to align with CTR requirements (Section 6 and Appendix 11)
- The responsibilities of the investigator and the role of the Medical Monitor during study conduct have been clarified (Sections 6.3.2, 6.8, and 8.2.4; Appendix A6–2.2).
- The criteria for discontinuation of study treatment has been updated for participants with thrombocytopenia in alignment with the guidance provided in Table A6-1 (Section 7.1).
- The criteria for discontinuation of study treatment for participants with ECG findings was updated to align Sections 7.1 and A6-2.4.
- It has been clarified that while magnetic resonance imaging scans are being acquired to support primary and secondary endpoints, the images will also allow for exploratory measurements (Section 8.1.1).
- The email address for withdrawal from the Research Biosample Repository after site closure has been corrected (Section 8.10.7).
- The analysis sets for efficacy and biomarker endpoints have been clarified (Sections 9.3 and 9.4.1)

- A description of the technical and organizational security measures taken to protect personal data has been added to align with CTR requirements (Appendix A1-4).
- Due to certain local requirements and an alignment of Sponsor process, it has been clarified that summaries of clinical study results may be available in health authority databases for public access in addition to redacted Clinical Study Reports (Appendix A1−6).
- The Sponsor record retention policy has been clarified (Appendix A1−7).
- Action steps for management of patients with suspected progressive multifocal leukoencephalopathy (PML) were edited to clarify that study treatment should be interrupted and the medical monitor must be notified (Appendix 8).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

TABLE OF CONTENTS

PROTOCOL AMENDMENT ACCEPTANCE FORM 11

1. PROTOCOL SUMMARY 12
   - 1.1 Synopsis 12
   - 1.2 Study Schema 14
   - 1.3 Schedule of Activities and Sample Collection Schedule 15

2. INTRODUCTION 26
   - 2.1 Study Rationale 26
   - 2.1.1 Overall Study Rationale 26
   - 2.2 Background 26
   - 2.3 Benefit–Risk Assessment 27

3. OBJECTIVES AND ENDPOINTS 28

4. STUDY DESIGN 31
   - 4.1 Overall Design 31
   - 4.2 Rationale for Study Design 31
   - 4.2.1 Rationale for Study Population 31
   - 4.2.2 Rationale for Control Group 32
   - 4.2.3 Rationale for Blinding 32
   - 4.2.4 Rationale for Biomarker Sample Collection Schedule 32
   - 4.2.5 Rationale for Endpoints 33
   - 4.2.6 Rationale for Pharmacokinetic Sample Collection Schedule 33
   - 4.2.7 Rationale for Stratification Factors 33
   - 4.2.8 Rationale for the Optional Cerebrospinal Fluid Substudy 34
   - 4.3 Justification for Dose and Schedule 34
   - 4.4 End of Study Definition 35
   - 4.5 Duration of Participation 35

5. STUDY POPULATION 35
   - 5.1 Inclusion Criteria 35
   - 5.2 Exclusion Criteria 37
   - 5.3 Lifestyle Considerations 41
   - 5.3.1 Meals and Dietary Restrictions 41

5.3.2 Caffeine, Alcohol, and Tobacco 41
5.3.3 Activity 41
5.3.4 Contraception Requirements 41
5.4 Screen Failures 41
6. STUDY TREATMENT(S) AND CONCOMITANT THERAPY 41
6.1 Study Treatments Administered 41
6.1.1 Fenebrutinib and Placebo 42
6.2 Preparation, Handling, Storage, and Accountability 43
6.3 Treatment Assignment and Blinding 43
6.3.1 Treatment Assignment 43
6.3.2 Blinding 44
6.4 Study Treatment Compliance 45
6.5 Dose Modification 45
6.6 Continued Access to Study Treatment after the End of the Study 46
6.7 Treatment of Overdose 46
6.8 Concomitant Therapy 46
6.8.1 Permitted Therapy 47
6.8.1.1 Oral Contraceptives and Hormone-Replacement Therapy 47
6.8.1.2 Symptomatic Treatments of Multiple Sclerosis 47
6.8.1.3 Treatment of Relapses 47
6.8.2 Cautionary Therapy 47
6.8.2.1 Acid-Reducing Agents 47
6.8.2.2 CYP3A- and Breast Cancer Resistance Protein-Mediated Drug Interactions 48
6.8.2.3 Statins 49
6.8.2.4 Herbal Therapies 49
6.8.3 Prohibited Therapy 49
6.8.3.1 Other Prohibited Therapies 50
6.8.4 Prohibited Food 51
6.8.5 Immunizations 51
7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION OR WITHDRAWAL 52

7.1 Discontinuation of Study Treatment 52
7.2 Participant Discontinuation or Withdrawal from the Study 53
7.3 Participants Lost to Follow-Up 54
8. STUDY ASSESSMENTS AND PROCEDURES 54
8.1 Efficacy Assessments 55
8.1.1 Magnetic Resonance Imaging 55
8.1.2 Clinical Outcome Assessments 56
8.1.3 MS Relapse Assessment 56
8.2 Safety Assessments 57
8.2.1 Physical Examinations 57
8.2.2 Vital Signs 57
8.2.3 Electrocardiograms 57
8.2.4 Clinical Safety Laboratory Assessments 58
8.2.5 Pregnancy Testing 59
8.2.6 Monitoring for Suicidal Ideation and Behavior 59
8.3 Adverse Events, Serious Adverse Events, and Other Safety Reporting 60
8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information 60
8.3.2 Method of Detecting Adverse Events and Serious Adverse Events 61
8.3.3 Follow-Up of Adverse Events and Serious Adverse Events 61
8.3.4 Regulatory Reporting Requirements for Serious Adverse Events 61
8.3.5 Pregnancy 62
8.3.6 Cardiovascular and Death Events 62
8.3.7 Anticipated Events Not Qualifying for Expedited Reporting 62
8.3.8 Adverse Events of Special Interest 62
8.3.9 Medical Monitors and Emergency Medical Contacts 63
8.4 Pharmacokinetics 63
8.5 Pharmacodynamics 64
8.6 Genetics 64
8.7 Biomarker Assessments 64
8.8 Immunogenicity Assessments 65

8.9 Health Economics and Medical Resource Utilization 65
8.10 Additional Assessments and Procedures Requiring Separate Consent 65
8.10.1 Lumbar Punctures and CSF Substudy 65
8.10.2 Samples for Research Biosample Repository 67
8.10.2.1 Overview of the Research Biosample Repository 67
8.10.3 Approval by the Institutional Review Board or Ethics Committee 68
8.10.4 Sample Collection 68
8.10.5 Confidentiality 69
8.10.6 Consent to Participate in the Research Biosample Repository 69
8.10.7 Withdrawal from the Research Biosample Repository 70
8.10.8 Monitoring and Oversight 70
9. STATISTICAL CONSIDERATIONS 70
9.1 Statistical Hypotheses 70
9.2 Sample Size Determination 71
9.3 Analysis Sets 71
9.4 Statistical Analyses 71
9.4.1 General Considerations 71
9.4.2 Primary Endpoint(s) 71
9.4.3 Secondary Endpoints 73
9.4.4 Exploratory Endpoints 74
9.4.5 Other Safety Analyses 74
9.4.6 Other Analyses 74
9.4.6.1 Summaries of Conduct of Study 74
9.4.6.2 Summaries of Treatment Group Comparability 74
9.4.6.3 Pharmacokinetic Analyses 74
9.5 Interim Analysis 74
9.6 Independent Data Monitoring Committee 74
10. REFERENCES 75

LIST OF TABLES

Table 1 Schedule of Activities 15
Table 2 Schedule of Activities: Open-Label Extension Phase 20
Table 3 Schedule of Pharmacokinetic Samples for Double-Blind Treatment 25
Table 4 *Primary and Secondary* Objectives and Corresponding *Estimands* 29
Table 5 Other Secondary and Exploratory Objectives and Endpoints 30
Table 6 Study Treatment Description 42
Table 7 List of Prohibited Medicines Due to CYP3A-Mediated Drug Interactions 50
Table 8 Schedule of CSF Substudy Pharmacokinetic and Biomarker Samples for Double-Blind Treatment 67

LIST OF FIGURES

Figure 1 Study Schema 14

LIST OF APPENDICES

Appendix 1 Regulatory, Ethical, and Study Oversight Considerations 77
Appendix 2 Clinical Safety Laboratory Tests 84
Appendix 3 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting 86
Appendix 4 Contraceptive and Barrier Guidance 104
Appendix 5 Genetics: Use and Analysis of DNA 107
Appendix 6 Safety Plan: Management of Identified and Potential Risks 108
Appendix 7 *Guidance for Recording Information in eCRFs for Participants with Abnormal Liver Enzyme and Function Tests* 119
Appendix 8 Guidance for Diagnosis of Progressive Multifocal Leukoencephalopathy 125
Appendix 9 Columbia-Suicide Severity Rating Scale Baseline/Screening Version and Since Last Visit Version 130
Appendix 10 Telephone Interviews 136
Appendix 11 *Investigational Medicinal Product and Non-Investigational Medicinal Product Designations (for Use in European Economic Area and United Kingdom)* 137
Appendix 12 Protocol Amendment History 138
Appendix 13 Abbreviations 140

PROTOCOL AMENDMENT ACCEPTANCE FORM

PROTOCOL TITLE:	**A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO INVESTIGATE THE EFFICACY OF FENEBRUTINIB IN RELAPSING MULTIPLE SCLEROSIS**
PROTOCOL NUMBER:	GN43271
VERSION NUMBER:	3
ROCHE COMPOUND(S):	Fenebrutinib (RO7010939)
SPONSOR NAME:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

Principal Investigator's Name (print)

Principal Investigator's Signature

Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by the CRO.

1. PROTOCOL SUMMARY

1.1 SYNOPSIS

PROTOCOL TITLE:	**A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO INVESTIGATE THE EFFICACY OF FENEBRUTINIB IN RELAPSING MULTIPLE SCLEROSIS**
REGULATORY AGENCY IDENTIFIER NUMBERS:	IND Number: 145957 EUDRACT Number: 2021-003772-14 EU Trial Number: 2022-502619-13-00 NCT Number: NCT05119569

STUDY RATIONALE

The purpose of this study is to assess the efficacy, safety, and pharmacokinetics of fenebrutinib, a highly selective, orally administered, adenosine triphosphate- competitive, reversible inhibitor of Bruton tyrosine kinase (BTK), compared with placebo in participants with relapsing multiple sclerosis (RMS). The BTK inhibition with fenebrutinib has the potential to reduce disease activity in multiple sclerosis by inhibiting B-cell and myeloid cell activation.

OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of fenebrutinib compared with placebo in participants with RMS. Specific objectives and corresponding endpoints for the study are outlined below.

Primary Objective	Corresponding Endpoint
• To evaluate the efficacy of fenebrutinib compared with placebo on the total number of new gadolinium-enhancing T1 MRI lesions	• Total number of new gadolinium-enhancing T1 lesions observed on MRI scans of the brain at Weeks 4, 8, and 12
Secondary Objectives	**Corresponding Endpoints**
• To evaluate the effect of fenebrutinib on MRI lesions	• 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.
• 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 (Appendix 9)
• To characterize the fenebrutinib PK profile	• Plasma concentration of fenebrutinib at specified timepoints

MRI = magnetic resonance imaging; PK = pharmacokinetic.

Primary and selected secondary objectives for the study are expressed using the estimand framework in accordance with the International Conference on Harmonization E9 (R1) statistical principles for clinical trials (ICH 2020) in Section 3.

OVERALL DESIGN AND STUDY POPULATION

This 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 gadolinium -enhancing T1 brain magnetic resonance imaging lesions in participants with RMS. The safety and pharmacokinetics of fenebrutinib will also be evaluated in the study.

Several key aspects of the study design and study population are summarized below.

Phase:	Phase II	**Population Type:**	Adult patients
Control Method:	Placebo	**Population Diagnosis or Condition:**	RMS
Interventional Model:	Parallel group	**Population Age:**	18–55 years
Test Compound{s}:	Fenebrutinib	**Site Distribution:**	Multi-site
Active Comparator:	Not applicable	**Study Intervention Assignment Method:**	Randomization
Number of Arms:	2	**Number of Participants to Be Enrolled:**	Approximately 102

STUDY TREATMENT

The investigational medicinal product for this study is fenebrutinib.

Participants will take two 100 mg tablets by mouth twice a day for a total dose of 400 mg of fenebrutinib (or placebo) every day. Participants will self-administer two 100 mg tablets in the morning and two 100 mg tablets in the evening by mouth. The tablet should be swallowed whole with some water, can be taken with or without food, and should be taken at the same time each day. Participants should be instructed that a missed fenebrutinib (or matching placebo) dose should not be taken with the next scheduled dose. Administration of fenebrutinib (or matching placebo) should be staggered with antacid use (i.e., study drug should be taken 2 hours before or 2 hours after antacid administration).

DURATION OF PARTICIPATION

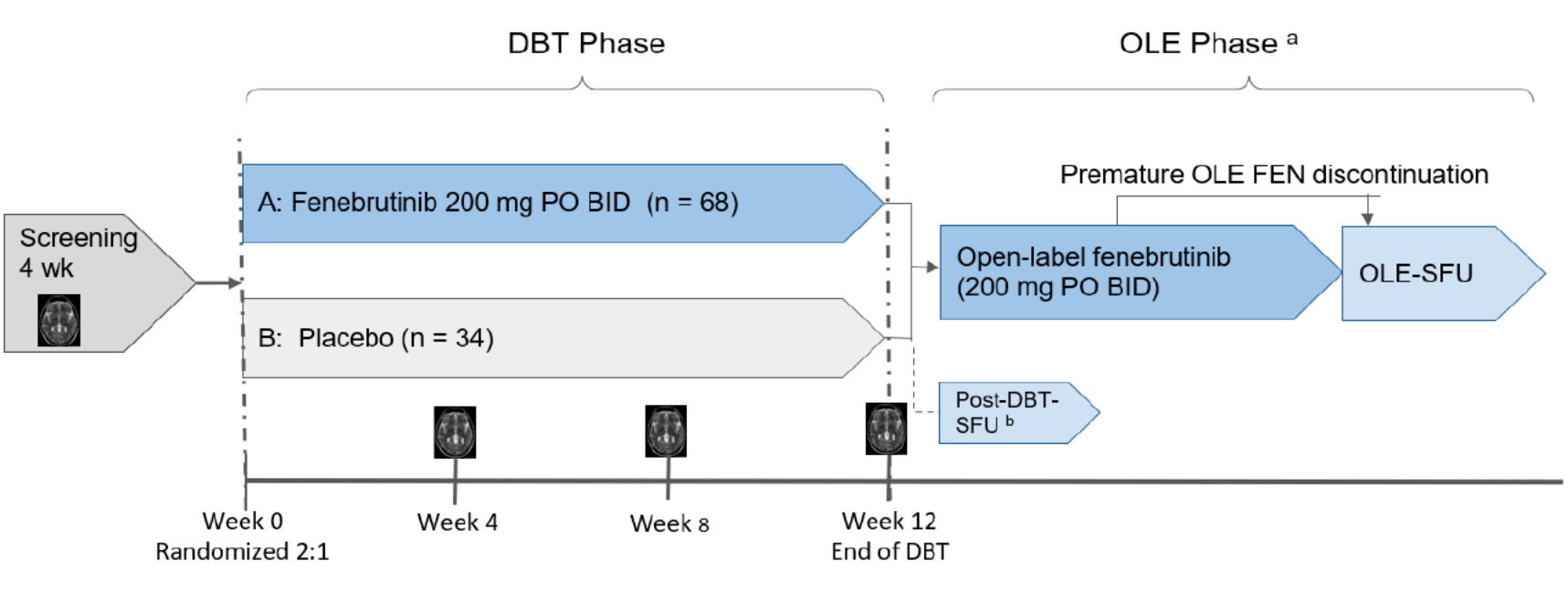
The duration of participation for each individual is expected to be 12 weeks (approximately 3 months) plus 4 weeks of safety follow up, if applicable. This will be followed by participation in an optional open-label extension (OLE) period.

COMMITTEES

Independent Committees:	Independent Data Monitoring Committee
Other Committees:	Not Applicable

1.2 STUDY SCHEMA

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.

1.3 SCHEDULE OF ACTIVITIES AND SAMPLE COLLECTION SCHEDULE

Table 1 Schedule of Activities

Visit	SCR [a]	Double-Blind Treatment									
	1	2	*3*	*4*	*5*	*6*	*7*	*8*			Safety Follow-Up Visit [e]
Study week		0	*2* [b]	4	*6* [b]	8	*10* [b]	12	UV [c]	Early D/C Visit [d]	16 (or 4 weeks after Early D/C)
Window in Days	–28 to –1	NA	±*2*	±2	±*2*	±2	±*2*	±2	NA	NA	±2
Informed consent [f]	x										
Review of eligibility criteria	x	x									
Randomization		x									
Demographic data	x										
Medical history and baseline conditions	x										
Review of contraception methods	x	x		x		x		x	x	x	x
C-SSRS	x			x		x		x	x	x	x
Vital signs [g]	x	x		x		x		x	x	x	x
Weight		x						x		x	x
Height		x									
Complete physical examination [h]	x	x						x	(x)	x	
Neurological examination [i]	x	x						x	(x)	x	
Query for potential unreported relapses		x		x		x		x	x	x	x
EDSS [j]	x	x						x	(x)	x	
12-lead ECG [k]	x	x		x				x		x	
Blood tests:[l]											
Hematology and *full* chemistry *panel*	x	x		x		x		x	(x)	x	x

Table 1 Schedule of Activities (cont.)

Visit	SCR[a]	Double-Blind Treatment							UV [c]	Early D/C Visit [d]	Safety Follow-Up Visit [e]
	1	2	*3*	*4*	*5*	*6*	*7*	*8*			
Study week		0	*2* [b]	4	*6* [b]	8	*10* [b]	12			16 (or 4 weeks after Early D/C)
Window in Days	–28 to –1	NA	*±2*	±2	*±2*	±2	*±2*	±2	NA	NA	±2
Limited chemistry panel: ALT, AST, total and direct bilirubin testing			*x*		*x*		*x*				
Hepatic synthetic function testing (PT, INR, aPTT)	x							x	(x)		
Lipids		x						x		x	
Flow cytometry [m]	x	x[n]		x		x		x		x	x
Total Ig, IgG, IgA, IgM	x			x		x		x		x	x
Hepatitis B screening [o]	x										
Hepatitis B virus DNA	x			(x)				(x)		(x)	
Hepatitis C screening [p]	x										
HIV screening	x										
Tuberculosis Test (QuantiFERON®-TB Gold)	x										
Plasma PK sample [q]		x		x		x		x	(x)	x	
Additional intensive PK sampling (optional) [q]		x		x							
Serum and plasma biomarkers [r]	x	x[n]		x		x		x		x	x
RNA collection (PAXgene tube)	x	x[n]						x		x	x
In clinic pregnancy test [s]	x	x		x		x		x	(x)	x	x
Urinalysis		x		x				x	(x)	x	x

Table 1 Schedule of Activities (cont.)

	SCR [a]	Double-Blind Treatment							UV [c]	Early D/C Visit [d]	Safety Follow-Up Visit [e]
Visit	1	2	*3*	*4*	*5*	*6*	*7*	*8*			
Study week		0	*2* [b]	4	*6* [b]	8	*10* [b]	12			16 (or 4 weeks after Early D/C)
Window in Days	–28 to –1	NA	*±2*	±2	*±2*	±2	*±2*	±2	NA	NA	±2
CSF collection (optional) [t]	x							x			
MRI [u]	x			x		x		x	(x)	(x)	
Concomitant medications	x	x		x		x		x	x	x	x
Adverse events	x	x		x		x		x	x	x	x
Study treatment dispensation		x		x		x		x [v]			
Study treatment compliance				x		x		x		x	
RBR: RNA, serum and plasma samples (optional) [w]	x	x[n]		x		x		x		x	x
RBR: DNA (optional) [w]		x [x]									

C-SSRS = Columbia-Suicide Severity Rating Scale; CSF = cerebrospinal fluid; DBT = double-blind treatment; D/C = discontinuation; eCRF = electronic Case Report Form; EDSS = Expanded Disability Status Scale; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; Ig = immunoglobulin; MRI = magnetic resonance imaging; OLE = open-label extension; PK = pharmacokinetic; RBR = research biosample repository; SCR. = screening; TB = tuberculosis; ULN = upper limit of normal; UV = unscheduled visit; x required, (x) not always required.

Table 1 Schedule of Activities (cont.)

[a] Participants are permitted one re-screening. As a general guideline, MRI scan, EDSS, RBR, hematology, chemistry, urinalysis, CD4, ECG, immunoglobulins, hepatitis B, C, HIV, hepatic synthetic function testing, lipids, flow cytometry, and TB screening and biomarkers samples should be repeated if there is more than 6 weeks between the screening *assessment date and* re-screening *assessment date*. All other procedures listed in the schedule of activities for the screening visit should be repeated at the re-screening visit. Any screening assessment may be repeated at a re-screening visit if judged by the investigator to be clinically necessary.

[b] *It is preferred that the blood tests performed at these visits are analyzed by the central laboratory during a clinic visit. However, if these are performed by an accredited local laboratory, the results and reference ranges must be added to the appropriate* adverse event *eCRF form* when applicable.

[c] UV may be performed, as clinically appropriate. It must be performed in the following situations: 1) if the patient is experiencing neurological worsening, 2) if the patient has $> 3 \times$ ULN AST or ALT, or 3) if the patient is experiencing symptoms that could be associated with worsening liver function. Assessments at UVs may be performed as clinically indicated. In the case of abnormalities in transamin*as*e levels or clinical indications of worsening liver function, additional laboratory testing may be required per medical monitor guidelines (see Table A6-1).

[d] Participants who discontinue from the study prior to completion should be encouraged to return to the clinic for an Early D/C visit. If a patient states intention to discontinue participation at the Week 4, Week 8, or an UV prior to Week 12, that visit should be converted to an Early D/C Visit.

[e] A Safety Follow-up Visit should be performed in 2 situations: 1) 4 weeks after early discontinuation of study drug, or 2) for participants that complete the double-blind treatment period (Week 12) who do not elect to participate in the OLE, in which the visit should be performed at Week 16.

[f] Informed consent must be documented before any study-specific screening procedure is performed.

[g] Includes respiratory rate, pulse rate, and systolic and diastolic blood pressure while the participant is in a seated position, and temperature. Temperature should be noted in the participant's notes only.

[h] Includes an evaluation of the head, eyes, ears, nose, and throat and evaluation of the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurological systems; genitourinary examinations may be performed if clinically indicated.

[i] A separate neurological examination should be performed by the treating physician if the treating physician is not performing the EDSS. During an UV, the neurological examination must be performed if the participant is experiencing neurological worsening between scheduled visits.

[j] The EDSS can performed by either the treating investigator or a separate examining investigator. The person performing the EDSS must have a valid Level C Neurostatus certification.

[k] ECG recordings must be performed after the participant has been resting in a supine position for at least 10 minutes.

[l] Participants should fast prior to the blood draws for Visits 2, 3, 4, and 5.

[m] Flow cytometry: Analysis may include, but is not limited to, the determination of B-cell and T-cell numbers and other lymphocyte subsets.

[n] *Biomarker and RBR samples should be collected prior to the administration of study drug (predose).*

Table 1 Schedule of Activities (cont.)

[o] Tests required for hepatitis B screening: HBsAg, total HBcAb, and viral DNA PCR. Participants with a positive HBsAg must be excluded. Participants with a positive HBcAb are permitted provided viral DNA PCR is negative. Participants with a positive HBcAb but negative HBV DNA PCR will have their hepatitis B viral DNA monitored as per the schedule of activities.

[p] Hepatitis C screening: HCAb must be negative.

[q] Please refer to Table 3 for more details.

[r] Biomarker samples should be collected ±3.5 days from MRI scan. Note: Not all biomarker samples will be collected at each MRI visit; however, those that are collected should be collected as close to the MRI scan as possible.

[s] All women of childbearing potential will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at specific subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[t] The Day 1 CSF collection by lumbar puncture should only be performed once other screening tests confirm that the patient qualifies for the study. Lumbar puncture can be performed anytime during the screening period or at Day 1 prior to dosing. The Week 12 lumbar puncture should to be performed between 1 to 2 hours after the administration of study drug in clinic. A contemporaneous plasma PK sample should be collected at the time of CSF collection to enable comparison of CSF and serum drug levels. *If the Week 12 lumbar puncture is missed, it can be performed at a later visit, including an OLE visit.*

[u] MRI scans should be obtained as close to the scheduled visit as possible (±3 days) and may be obtained at UV if medically warranted. MRI scan may not be performed earlier than 3 weeks after IV corticosteroid treatment for MS relapses. At the study D/C visit, an MRI scan should be obtained if an MRI scan was not performed during the prior 4 weeks.

[v] Study treatment will only be dispensed for participants continuing in the optional OLE.

[w] RBR: Not applicable at a site that has not been granted approval for RBR sampling. Performed only for patients at participating sites who have provided written informed consent to participate.

[x] A single, DNA sample will be collected for RBR at the baseline visit. If the DNA sample is not taken at Visit 2 (baseline), the sample may be taken at any subsequent timepoint during the trial.

Table 2 Schedule of Activities: Open-Label Extension Phase

Visit	Baseline [a]	Open-Label Extension Phase												UV [c]	Early D/C Visit [d]	SFU
		1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11, 13, 15, etc.*	*12, 14, 16, etc.*			
Study week	0	*2*	4	*6* [b]	8	*10* [b]	12	*14*[b]	16[b]	20[b]	24	36+ *every 24 weeks thereafter*	48 + *every 24 weeks thereafter*			+4 weeks [e]
Window in Days		±2								±5					±5	±5
Informed consent	x															
Review of eligibility criteria	x															
Review of contraception methods	x						x				x		x	x	*x*	*x*
C-SSRS	x						x				x		x		x	x
Vital signs [f]	x						x				x		x	x	x	x
Complete physical examination [g]	x						x				x		x	(x)	x	x
Query for potential unreported relapses	x						x				x			(x)	x	
EDSS [h]	x						x				x		x	(x)	x	
12-lead ECG [i]	x		x				x						*x*		x	

Table 2 Schedule of Activities: Open-Label Extension Phase (cont.)

Visit	Baseline [a]	Open-Label Extension Phase												UV [c]	Early D/C Visit [d]	SFU
		1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11, 13, 15, etc.*	*12, 14, 16, etc.*			
Study week	0	*2*	4	*6* [b]	8	*10* [b]	12	*14*[b]	16[b]	20[b]	24	36+ *every 24 weeks thereafter*	48 + *every 24 weeks thereafter*			+4 weeks [e]
Window in Days		±*2*								±*5*					±5	±5
Blood tests [j]																
Hematology and *full* chemistry *panel*	x						x				x	x	x	(x)	x	x
Limited chemistry panel: ALT, AST, total and direct bilirubin testing		*x*	x	*x*	x	*x*		*x*	x	x						
Hepatic synthetic function testing (PT, INR, aPTT)							*x*				*x*					
Total Ig, IgG, IgA, IgM	x		x		x		x				x	x	x		x	x
Hepatitis B virus DNA [k]	(x)						(x)				(x)		(x)			
Plasma PK sample [l]	x						x				x		x	(x) [m]	x	
Serum and plasma biomarkers [n]	x						x				x		*[x]*		x	x

Table 2 Schedule of Activities: Open-Label Extension Phase (cont.)

Visit	Baseline [a]	Open-Label Extension Phase												UV [c]	Early D/C Visit [d]	SFU
		1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11, 13, 15, etc.*	*12, 14, 16, etc.*			
Study week	0	*2*	4	*6* [b]	8	*10* [b]	12	*14*[b]	16[b]	20[b]	24	36+ *every 24 weeks thereafter*	48 + *every 24 weeks thereafter*			+4 weeks [e]
Window in Days		±2								±5					±5	±5
Flow cytometry [o]											x		*[x]*		x	
Lipids											x		*[x]*		x	
At home pregnancy test		*Monthly testing*														
Urine tests																
In clinic pregnancy test [p]	x						x				x		x	(x)	x	x
Urinalysis	x		x				x				x		*x*	(x)	x	x
MRI [q]	x												[x]	(x)	(x)	
Concomitant medications	x						x				x	x	x	x	x	x
Adverse events	x						x				x	x	x	x	x	x
Study treatment dispensation	x						x				x	x	x			
Study treatment compliance	x						x				x	x	x		x	
RBR RNA, serum and plasma samples (optional) [r]	x						x				x		*[x]*		x	x
Telephone interviews [s]		*Every 6 weeks (±3 days)*														

Table 2 Schedule of Activities: Open-Label Extension Phase (cont.)

C-SSRS = Columbia-Suicide Severity Rating Scale; D/C = discontinuation; eCRF = electronic Case Report Form; EDSS = Expanded Disability Status Scale; HBV = hepatitis B virus; Ig = immunoglobulin; MRI = magnetic resonance imaging; OLE = open-label extension; PK = pharmacokinetic; SFU = safety follow-up; UV= unscheduled visit; x =required, (x) =not always required*; [x] = assessment will be carried out every 48 weeks after week 48.*

[a] The baseline visit in the OLE is the same as the Week 12 visit in the DBT phase. Activities performed at the final visit of the randomized controlled period do not need to be repeated.

[b] *It is preferred that the blood tests performed at these visits are analyzed by the central laboratory during a clinic visit. However, if these are performed by an accredited local laboratory, the results and reference ranges must be added to the appropriate* adverse event eCRF when applicable*. When treatment codes become available, patients who received fenebrutinib during the DBT phase do not need to perform these visits.*

[c] UV may be performed, as clinically appropriate. It must be performed in the following situations: 1) if the patient is experiencing neurological worsening, 2) if the patient has $> 3 \times$ ULN AST or ALT, or 3) if the patient is experiencing symptoms that could be associated with worsening liver function. Assessments at UVs may be performed as clinically indicated. In the case of abnormalities in transamine levels or clinical indications of worsening liver function, additional lab testing may be required per medical monitor guidelines (see Table A6-1).

[d] Participants who discontinue from the study prior to completion should be encouraged to return to the clinic for an Early D/C visit.

[e] A SFU visit should be performed 4 weeks after early discontinuation of study drug.

[f] Includes respiratory rate, pulse rate, and systolic and diastolic blood pressure while the participant is in a seated position, and temperature. Temperature should be noted in the participant's notes only.

[g] Includes an evaluation of the head, eyes, ears, nose, and throat and evaluation of the cardiovascular, dermatologic, musculoskeletal, respiratory, and gastrointestinal systems; genitourinary examinations may be performed if clinically indicated. A separate neurological examination should be performed by the treating physician if the treating physician is not performing the EDSS. During an UV, the neurological examination must be performed if the participant is experiencing neurological worsening between scheduled visits.

[h] The EDSS can performed by either the treating investigator or a separate examining investigator. The person performing the EDSS must have a valid Level C Neurostatus certification.

[i] ECG recordings must be performed after the participant has been resting in a supine position for at least 10 minutes.

[j] Participants should fast before the blood draws.

[k] Participants with a positive HBcAb but negative HBV DNA PCR will have their hepatitis B viral DNA monitored as per the schedule of activities.

[l] To be collected predose except for the UV and Early D/C visit where sample timing is flexible.

[m] This sample is optional per the investigator's discretion

[n] Biomarker samples should be collected $\pm$ 3.5 days from MRI scan. Note: Not all biomarker samples will be collected at each MRI visit; however, those that are collected should be collected as close to the MRI scan as possible.

[o] Flow cytometry: Analysis may include, but is not limited to, the determination of B-cell and T-cell numbers and other lymphocyte subsets.

Table 2 Schedule of Activities: Open-Label Extension Phase (cont.)

[p] All women of childbearing potential will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[q] MRI scans should be obtained as close to the scheduled visit as possible (±3 days) and may be obtained at an UV if medically warranted. MRI scan may not be performed earlier than 3 weeks after IV corticosteroid treatment for MS relapses. At the Study D/C visit, an MRI scan should be obtained if an MRI scan was not performed during the prior 4 weeks.

[r] RBR: Not applicable at a site that has not been granted approval for RBR sampling. Performed only for patients at participating sites who have provided written informed consent to participate.

[s] Semi-structured telephone interviews will be conducted every *6* weeks (±3 days) between study visits (when there are dates overlapping with site visits, telephone calls will not occur). Please see *Appendix 10* for more details. If the participant answers YES to any question during the semi-structured telephone interview, the answer should be discussed and reviewed by the investigator. If warranted, the participant should return for an UV. If an unplanned pregnancy is suspected, an UV to confirm the pregnancy is required.

Table 3 Schedule of Pharmacokinetic Samples for Double-Blind Treatment

Visit	Timepoint	Sample Type
Day 1 (Week 0) and 29 (Week 4)	Prior to the morning dose, fasted [a]	PK (plasma)
	1–2 hours after dosing, fasted	PK (plasma)
Day 1 (Week 0) and Day 29 (Week 4) (if applicable) [b]	Prior to the morning dose, fasted [a]	PK (plasma
	1 hour (±10 minutes) after dosing, fasted	PK (plasma)
	2 hours (±10 minutes) after dosing, fasted	PK (plasma)
	4, 6, and 8 hours (±10 minutes) after dosing [c]	PK (plasma)
Day 57 (Week 8)	Predose [a]	PK (plasma)
Day 85 (Week 12)	Predose [a]	PK (plasma)
Unscheduled visit [d]	NA	PK (plasma)
Early D/C visit	NA	PK (plasma)

D/C = discontinuation; NA = not applicable; PK = pharmacokinetic; PPI = proton pump inhibitor.

Notes:
Morning clinic visits are preferred for all visits but are required on Days 1*, 15,* and 29. Prior to each morning clinic visit, participants should be instructed not to take their morning dose and to bring their study medication with them to their clinic visit. The dates and times of the most recent prior meal, last dose of oral study drug (prior to the clinic visit), and timing of oral study drug administration in the clinic should be recorded at each clinic visit. Use of PPIs, H_2-receptor antagonists, and/or other antacids (e.g., bismuth subsalicylate, calcium carbonate, aluminum-magnesium hydroxide) should be recorded as concomitant medications, including the date and time of last administration at each clinic visit.

Single-dose acid-reducing agents are not permitted on the day of an in-clinic visit with PK assessments.

[a] Participants should be fasting for >6 hours overnight prior to the sample collection, which must be performed at the clinic in the morning. The PK samples should be collected 5–30 minutes prior to the fenebrutinib dose.

[b] For participants participating in the intensive PK sample collection only.

[c] Fasting is not required for these samples.

[d] This sample is optional per the investigator's discretion.

2. INTRODUCTION

2.1 STUDY RATIONALE

2.1.1 Overall Study Rationale

The purpose of this study is 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). The BTK inhibition with fenebrutinib has the potential to reduce disease activity in multiple sclerosis (MS) by inhibiting B-cell and myeloid cell activation.

2.2 BACKGROUND

MS is a chronic, inflammatory, demyelinating, and degenerative disease of the CNS that affects approximately 900,000 people in the United States (Wallin et al. 2019) and 2.3 million people worldwide (GBD 2016 Multiple Sclerosis Collaborators 2019). Traditionally, MS has been classified into three clinical phenotypes: relapsing remitting MS (RRMS), secondary progressive MS (SPMS), and primary progressive MS (PPMS) (Lublin et al. 2014). SPMS and PPMS are further subdivided into active and non-active forms based on the presence or absence of disease activity (DA), defined by the presence of clinical relapses and/or T1-weighted gadolinium-enhancing (T1Gd+) lesions on magnetic resonance imaging (MRI) scan or new/enlarging T2-weighted lesions on MRI scan.

Available evidence suggests that despite the potential heterogeneity of the clinical expression of the disease, PPMS, SPMS, and RRMS belong to the same disease spectrum and that pathological mechanisms responsible for relapses/DA and progression biology are largely identical across the MS spectrum (Lassmann 2019).

Disability progression across the spectrum of MS might occur as the result of two concurrent inflammatory mechanisms: active inflammation and chronic compartmentalized inflammation. Active inflammation is responsible for the acute inflammation that can be observed on an MRI scan (as T1Gd+ lesions or new/enlarging T2 lesions) and/or that might manifest clinically as MS relapses and/or relapse -associated worsening when recovery from a previous relapse is incomplete. RMS is associated with an active inflammatory mechanism characterized by focal, bulk T-cell, and B-cell invasion and blood brain barrier leakage that give rise to classic active demyelinating plaques in the white matter.

Increasing evidence suggests that B cells (Hauser et al. 2017; Montalban et al. 2017) and myeloid cells/microglia (Howell et al. 2010) are central to the immunopathology of MS, a chronic, inflammatory and degenerative demyelinating disease of the human CNS leading to a health-related loss of quality of life due to accumulating neurological disability.

Approved disease modifying MS therapies primarily address the prevention of relapses with variable levels of efficacy. Disease modifying therapies, which include immunomodulatory, anti-inflammatory, and immunosuppressive drugs, can also, to a lesser and highly variable degree slow the development of MS-related neurological disability progression. Despite the availability of several treatments for relapsing forms of MS (RMS), ocrelizumab is to date the only drug approved in European Union and United States for participants with both RMS and PPMS. Preventing worsening of disability, especially in PMS, remains a critical unmet need (Thompson et al. 2018).

Fenebrutinib is a highly selective, orally administered, ATP-competitive, reversible inhibitor of BTK that is being developed by F. Hoffmann-La Roche Ltd (hereafter referred to as Roche) as a potential therapeutic agent for MS and other autoimmune diseases. In vitro cell-based experiments suggest that antagonism of BTK with fenebrutinib leads to inhibition of BCR-dependent B-cell proliferation and a reduction of inflammatory cytokine production from myeloid cells (including tumor necrosis factor-α [TNF-α]). Myeloid effector functions are triggered by immune complexes in vitro, and increasing evidence suggests that B cells and myeloid/microglia are central to the immunopathology of MS.

Detailed information on fenebrutinib is provided in the Fenebrutinib Investigator's Brochure.

2.3 BENEFIT–RISK ASSESSMENT

The purpose of this study is to assess the efficacy and safety of fenebrutinib, a highly selective, orally administered, ATP-competitive, reversible inhibitor of BTK, compared with placebo in participants with RMS.

BTK inhibition results in a decrease in B-cell activation and proliferation, which may explain its effects on the inflammatory pathways related to MS disease activity. BTK inhibition also has direct effects on myeloid lineage cells. As a result, there is a potential for BTK inhibition to affect microglia that are associated with the pathophysiology of MS disease progression independent of relapse. Indeed, the role of BTK inhibition in MS has been established by the results from two Phase II randomized clinical trials, one study (NCT02975349) evaluated the safety and efficacy of evobrutinib in participants with RMS (Montalban et al. 2019) and one study (NCT03889639) evaluated SAR442168 in participants with RMS (Clinicaltrials.gov 2020; Sanofi Virtual Scientific Meeting 2020). Given the similar mechanism of action, the results of these Phase II trials suggest that fenebrutinib will have a positive treatment effect on MS pathophysiology and thus support further study of this BTK inhibitor (fenebrutinib) in MS.

Clinical safety data are available from Phase I and Phase II studies in several different indications including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and chronic spontaneous urticaria (CSU). As of the writing of this protocol, more than 1200 participants and healthy volunteers have received fenebrutinib in clinical trials.

Over 650 participants have received the 200 mg twice a day (BID) dosing regimen (either blinded or open-label) that has been characterized in clinical trials in RA, SLE, and CSU. Across indications, 93 participants have received fenebrutinib at a dosage of 200 mg BID for 24 to 48 weeks; 491 participants for 48 to 96 weeks; and 8 participants for 96 weeks or more. The safety profile for the administration of fenebrutinib 200 mg BID is described in detail in the Fenebrutinib Investigator's Brochure and has been consistent across all the indications studied.

Refer to Appendix 3 for information on anticipated risks for fenebrutinib and risk mitigation measures, including guidelines for managing adverse events associated with fenebrutinib.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of fenebrutinib may be found in the Fenebrutinib Investigator's Brochure. Considering the mechanism of action of fenebrutinib, the Phase II efficacy data in other BTK inhibitors, the safety profile for fenebrutinib, and the risk mitigation measures for the study, the benefit-risk ratio is expected to be acceptable to evaluate fenebrutinib in clinical trials for MS.

COVID-19 Pandemic

A risk-assessment was conducted to determine whether there is any impact of the coronavirus disease 2019 (COVID-19) pandemic on the benefit-risk assessment of the conduct of this study protocol including but not limited to the patient population under study and study treatment(s) being evaluated (EMA Guidance 2021). Based on this assessment, the anticipated impact of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is no different from any other acute infection. The existing safety monitoring and management guidelines, as well as the risk minimization measures outlined in the clinical protocol are considered appropriate. Concomitant administration of an approved non-live *COVID-19* vaccine is permitted. Examples of permitted vaccines include mRNA, inactivated virus, and replication-deficient viral vector vaccines.

3. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of fenebrutinib compared with placebo in participants with RMS. Specific objectives and corresponding endpoints for the study are outlined in Table 4 *and Table 5* .

Table 4 *Primary and Secondary* **Objectives and Corresponding** *Estimands*

Primary Objective	***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
	• *Treatment:*
	  • *200 mg BID oral fenebrutinib*
	  • *placebo*
	• *Intercurrent events and handling strategy:*
	  • *Withdrawal from treatment: hypothetical strategy (see Section 9.4.3)*
	  • *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

BID = twice a day; MRI = magnetic resonance imaging

Table 5 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 *(see Appendix 9)*
• 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 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 serum 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.

4. STUDY DESIGN

4.1 OVERALL DESIGN

This 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 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 BID oral fenebrutinib or placebo for 12 weeks. The primary efficacy endpoint is the total number of new gadolinium-enhancing T1 (T1Gd+) lesions on brain MRI measured at Weeks 4, 8, and 12. The secondary efficacy outcomes are 1) the total number of new or enlarging T2 lesions on brain MRI measured at Weeks 4, 8, and 12, and 2) the proportion of participants free from any new Gd-enhancing T1 lesions and new or enlarging T2-weighted lesions observed on brain MRI at Weeks 4, 8, and 12. Drug safety will be evaluated by measuring number and severity of adverse events, changes in vital signs, and changes in laboratory parameters. 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 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.

Participants may enroll in an optional substudy in which cerebrospinal fluid (CSF) will be collected.

Patient safety will be monitored by an independent Data Monitoring Committee (iDMC) throughout the DBT phase. Further details regarding the iDMC review will be specified in a separate iDMC charter.

4.2 RATIONALE FOR STUDY DESIGN

4.2.1 Rationale for Study Population

The study will enroll participants with RMS. Participants must have recent inflammatory MS activity to enroll, defined in the inclusion criteria as two clinical relapses in the last

2 years, or one clinical relapse in the last 12 months or at least one T1 Gd+ lesion on MRI in the 6 months prior to randomization. This population will be informative for the objective of evaluating the efficacy of fenebrutinib in reducing the development of new T1 Gd+ MRI lesions.

4.2.2 Rationale for Control Group

The control arm for the study will receive matching oral placebo. A placebo comparator was chosen to enable a clear and efficient evaluation of the safety and efficacy profile of fenebrutinib monotherapy. Given the availability of approved treatments for RMS, the period of placebo exposure should be as short as possible and should not present an inappropriate risk to participating participants. The period of placebo exposure in the DBT phase will be limited to a maximum of 12 weeks. A 2:1 randomization ratio will be used to limit the number of participants in the placebo arm. Informed consent materials will clearly explain the existence of alternative approved treatments, and that by participating in the study participants are foregoing those treatments and may receive placebo for up to 12 weeks (Polman 2008).

4.2.3 Rationale for Blinding

The study is double-blinded to reduce the risk of bias in adjudication of efficacy and safety endpoints. The primary efficacy endpoint of number of new T1 Gd+ MRI lesions will be determined by an independent MRI rater who is blinded to treatment assignments. Since the study is only 12 weeks, the investigators will be blinded to the MRI results for only a short period of time.

4.2.4 Rationale for Biomarker Sample Collection Schedule

The exploratory biomarker objective for this study is to identify and/or evaluate biomarkers that are predictive of response to fenebrutinib (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to fenebrutinib, are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers), can provide evidence of fenebrutinib activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following exploratory endpoints:

- Relationship between baseline biomarkers in blood (serum and/or plasma, RNA PAXgene®) including, but not limited to neurofilament light chain, and efficacy, safety, PK, or other biomarker endpoints
- Relationship between baseline biomarkers in CSF (optional collection, CSF supernatant, and CSF cells which may include RNA sequencing) including, but not limited to neurofilament light chain, and efficacy, safety, PK, or other biomarker endpoints

- Change from baseline to post-treatment sampling in blood (serum and/or plasma) including, but not limited to neurofilament light chain, and efficacy, safety, PK, or other biomarker endpoints

Exploratory biomarker analysis results may be reported separately from the GN43271 clinical study report (CSR).

4.2.5 Rationale for Endpoints

The total number of new T1 Gd+ MRI lesions and number of new or enlarging T2 MRI lesions are the primary and secondary efficacy endpoints. These endpoints are standard Phase II efficacy outcomes for RMS. These imaging outcomes may be predictive of the ability of fenebrutinib to reduce the number of new clinical relapses, which is the endpoint that is used in Phase III studies to demonstrate efficacy. Annualized relapse rate (ARR) will be measured as an exploratory efficacy outcome in this study, though the study is not powered to identify a significant effect on this outcome.

The study will utilize standard endpoints to evaluate PK and safety, including number and severity of treatment emergent adverse events, vital signs, ECGs, laboratory parameters, and suicidal ideation.

Blood biomarkers will be measured as exploratory outcomes. Serum neurofilament light chain is a blood biomarker of neuronal damage, for which increases are associated with inflammatory activity and with MS disability progression (Thebault et al. 2022). Serum NfL will be measured to determine if fenebrutinib decreases a biomarker of neuronal injury relative to placebo-treated participants. Serum may be used to assess antigen specific antibody responses.

The rationale for CSF biomarkers is described in Section 4.2.8.

4.2.6 Rationale for Pharmacokinetic Sample Collection Schedule

The sampling schedule is designed to assess plasma fenebrutinib concentrations in participants with MS that will enable the estimation of systemic fenebrutinib exposure parameters, which may be reported separately from the Clinical Study Report. Sparse PK samples will be collected in all participants. However, to better characterize fenebrutinib pharmacokinetics, more intensive PK samples may be collected in at least 30 randomized participants (at least 20 participants receiving fenebrutinib) during the DBT phase.

4.2.7 Rationale for Stratification Factors

Randomization will be stratified based on the presence or absence of T1 Gd+ lesions on the screening MRI. The number of new MRI lesions may be higher after randomization in participants with an active MRI lesion at baseline relative to those without an active MRI lesion at baseline. Stratification by this factor will ensure that the treatment arms

are balanced with respect to the proportion of participants with a T1 Gd+ lesion on MRI at baseline.

4.2.8 Rationale for the Optional Cerebrospinal Fluid Substudy

Fenebrutinib reduces both B-cell and myeloid lineage-cell activation by binding to and blocking the function of BTK; effects on both these cell types may be important to the drug's effect on participants with MS. Persistent blood-brain barrier disruption and leakage have been reported in participants with MS. It may be important to estimate fenebrutinib's CNS exposure level in participants with MS in order to understand the drug's potential to affect CNS compartmentalized inflammation. Clinically, CSF drug levels have frequently been used to estimate drug exposure in the CNS. The optional CSF substudy proposes to collect CSF from approximately 10 participants at two timepoints. The fenebrutinib concentration may be measured in the CSF and compared to the serum concentration measured contemporaneously. To evaluate fenebrutinib's effect on antibody formation within the CNS, the CSF to serum IgG index may be measured, as will the number of unique CSF oligoclonal bands.

4.3 JUSTIFICATION FOR DOSE AND SCHEDULE

A fenebrutinib dosage of 200 mg BID was selected for evaluation in this study based on the high level of target inhibition associated with this dosage, the Phase II clinical effect observed in RA, SLE, and CSU, as well as on the body of clinical safety data for these indications (see the Fenebrutinib Investigator's Brochure).

Target inhibition was assessed using a CD63 basophil assay in Phase I, single and multiple ascending dose studies in healthy participants in which a dose- and exposure-dependent relationship with BTK inhibition was observed (Herman et al. 2018). The fenebrutinib dosage of 200 mg BID is expected to achieve a high level of target engagement (more than 90% inhibition of BTK) in the majority of participants based on simulations using a PK/PD model constructed with data from the Phase I, ascending-dose studies (Herman et al. 2018). Furthermore, a dosage of 200 mg BID is expected to maintain an extensive degree of target engagement over the entire dosing interval. On the basis of the PK/PD relationship characterized in the Phase I studies, doses higher than 200 mg BID are unlikely to significantly improve target engagement. Data from other BTK inhibitors has demonstrated that BTK inhibition is associated with decreases in the number of new T1 Gd+ lesions in the CNS in participants with MS (Montalban et al. 2019; Sanofi Virtual Scientific Meeting 2020).

The proposal to evaluate the 200 mg BID dosing regimen in this study is supported by the safety dataset in which the 200 mg BID dosing regimen has been characterized. The fenebrutinib safety profile is described in detail in the most recent version of the Fenebrutinib Investigator's Brochure. The existing clinical experience with fenebrutinib 200 mg BID in other autoimmune diseases supports testing this dosage in an MS population.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed the last visit shown in the schedule of activities.

The end of this study is defined as the date of the last visit of the last participant in the study shown in the schedule of activities for the last participant in the study globally or the date at which the last data point required for statistical analysis or safety follow-up is received from the last participant, whichever occurs later. The end of the study, including OLE, is expected to occur approximately 4 years after the last participant is enrolled.

In addition, the Sponsor may decide to terminate the study at any time.

4.5 DURATION OF PARTICIPATION

The duration of participation for each individual is expected to be 12 weeks ($approximately$ 3 months) plus 4 weeks of safety follow up, if applicable. This will be followed by participation in an optional OLE period.

5. STUDY POPULATION

Approximately 102 participants with RMS will be enrolled in this study.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 INCLUSION CRITERIA

Participants are eligible to be included in the study only if all of the following criteria apply:

- Participants who are capable of giving signed informed consent and able to complete the study protocol
- Participants who are aged 18 to 55 years inclusive at the time of signing Informed Consent Form
- A diagnosis of RMS in accordance with the revised 2017 McDonald Criteria (Thompson et al. 2018) and one of the following:
  - At least two documented clinical relapses within the last 2 years or one documented clinical relapse within 12 months of screening (but not within the 30 days prior to screening)
  - Documented evidence of the presence of at least one T1 Gd+ lesion on MRI in the 6 months prior to randomization (may include the screening MRI)

    Note: RMS may include active secondary progressive MS as defined by Lublin 2014.
- Expanded Disability Status Scale (EDSS) at screening from 0 to 5.5 points

- For women of childbearing potential: participants who agree to remain abstinent (refrain from heterosexual intercourse) or use contraception, and agreement to refrain from donating eggs, as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of $< 1\%$ per year during the treatment period and for 28 days after the final dose of fenebrutinib.

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

  Examples of contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  Hormonal contraceptive methods must be supplemented by a barrier method.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the individual. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For men: participants who agree to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agree to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 28 days after the final dose of fenebrutinib to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the individual. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of preventing drug exposure. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.

5.2 EXCLUSION CRITERIA

Participants are excluded from the study if any of the following criteria apply:

- Disease duration of >10 years from the onset of symptoms and an EDSS score at screening <2.0
- Participants who are pregnant or breastfeeding, or intending to become pregnant during the study or within 28 days after the final dose of fenebrutinib

  Women of childbearing potential must have a negative serum pregnancy test result at screening. If a urine pregnancy test is positive *at a subsequent visit*, it must be confirmed by a serum pregnancy test, ideally from the central laboratory.
- Men intending to father a child during the study or within 28 days after final dose of study drug
- A diagnosis of primary progressive MS or non-active secondary progressive MS
- Any known or suspected active infection at screening or baseline (excluding onychomycosis), or any major episode of infection requiring hospitalization or treatment with IV anti-microbials within 8 weeks prior to or during screening or treatment with oral anti-microbials within 2 weeks prior to or during screening
- History of progressive multifocal leukoencephalopathy (PML)
- History of cancer, including hematologic malignancy and solid tumors, within 10 years of screening

  Basal or squamous cell carcinoma of the skin that has been excised and is considered cured and in situ carcinoma of the cervix treated with apparent success by curative therapy $>$ 1 year prior to screening is not exclusionary
- Presence of other neurological disorders *that could interfere with the diagnosis of MS or with the assessments of efficacy or safety during the study*, including, but not limited to, the following:
  - History of ischemic cerebrovascular disorders (e.g., stroke, transient ischemic attack, spontaneous intracranial hemorrhage, or traumatic intracranial hemorrhage) or ischemia of the spinal cord
  - History or known presence of CNS or spinal cord tumor (e.g., meningioma, glioma)
  - History or known presence of potential metabolic causes of myelopathy (e.g., untreated vitamin B12 deficiency)
  - History or known presence of infectious causes of myelopathy (e.g., syphilis, Lyme disease, HTLV-1, herpes zoster myelopathy)
  - History of genetically inherited progressive CNS degenerative disorder (e.g., hereditary paraparesis, mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes [MELAS] syndrome)
  - Neuromyelitis optica spectrum disorder

  - History or known presence of systemic autoimmune disorders potentially causing progressive neurological disease (e.g., lupus, anti-phospholipid antibody syndrome, Sjögren syndrome, Behçet disease)
  - History or known presence of sarcoidosis
  - History of severe, clinically significant brain or spinal cord trauma (e.g., cerebral contusion, spinal cord compression)
- Evidence of clinically significant psychiatric, pulmonary, renal, hepatic (including Gilbert syndrome), metabolic, gastrointestinal (GI), or cardiovascular disease (including arrhythmias or QTc prolongation), or endocrine disease (including uncontrolled diabetes, non-gallstone pancreatitis, or chronic pancreatitis) that, in the investigator's opinion, would preclude patient participation
- Presence of the New York Heart Association Class III and Class IV criteria for congestive heart failure
- Screening 12-lead ECG that demonstrates clinically relevant abnormalities that may affect patient safety or interpretation of study results, including QT interval corrected through use of Fridericia's formula (QTcF) $>$ 440 ms demonstrated by at least two ECGs $>$ 30 minutes apart
- Current treatment with medications that are well known to prolong the QT interval at doses that have a clinically meaningful effect on QT, as determined by the investigator
- History of ventricular dysrhythmias or risk factors for ventricular dysrhythmias, such as long QT syndrome and other genetic risk factors (e.g., Brugada syndrome); structural heart disease; coronary heart disease (symptomatic or with ischemia demonstrated by diagnostic testing, prior coronary artery bypass grafting, or coronary lesions $>$ 70% diameter stenosis that have not been or cannot be re-vascularized); clinically significant electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia, hypocalcemia); family history of sudden, unexplained death; or cardiac ion channel genetic mutations (e.g., congenital long QT syndrome)
- Participants undergoing dialysis or estimated glomerular filtration rate (eGFR) $<$ 60 mL/min/1.73 m^2 (may be repeated if eGFR 45–59 mL/min/1.73 m^2)
- Any of the following laboratory results:
  - ALT or AST $>$ 2 $\times$ upper limit of normal (ULN)
  - Total bilirubin greater than 1.5 $\times$ ULN
  - Hemoglobin $<$ 9.5 g/dL (may be repeated if 9–9.4 g/dL)
  - White blood cell count $<$ 2000 cells/mm^3 (μL)
  - Platelet count $<$ 100 $\times$ 10^9/L (may be repeated if 80–100 $\times$ 10^9/L)
  - Absolute neutrophil count $\leq$ 1500 cells/mm^3 (μL)
  - IgG $<$ 500 mg/dL

- Any concomitant disease that may require chronic treatment with systemic corticosteroids or immunosuppressants during the course of the 12-week double-blind study period
- History of alcohol or other drug abuse within 12 months prior to screening
- Positive screening tests for active, latent, or inadequately treated hepatitis B (as evidenced by either of the following):
  - Positive hepatitis B surface antigen (HBsAg)
  - Positive hepatitis B core antibody [total HBcAb] with detectable hepatitis B virus (HBV) DNA
- Positive screening tests for hepatitis C (positive hepatitis C antibodies)
- Evidence of active or latent or inadequately treated infection with tuberculosis (TB) as defined by the following:

  A positive QuantiFERON® TB-Gold (QFT) test is found at screening. QFT testing should be performed through the central laboratory (see Table A2-1 for test requirements).

  An indeterminate QFT test should be repeated.

  A positive QFT test or two successive indeterminate QFT results should be considered *a* positive diagnostic TB test.

  An indeterminate QFT test followed by a negative QFT test should be considered a negative diagnostic TB test.
- Abnormalities in hepatic synthetic function tests (e.g., PT, INR, aPTT) judged by the investigator to be clinically significant
- History of hospitalization or transfusion for a GI bleed
- Known bleeding diathesis
- Any condition possibly affecting oral drug absorption
- History of or currently active primary or secondary (non–drug-related) immunodeficiency, including known history of HIV infection
- Inability to complete an MRI scan (contraindications for MRI scan, including but not restricted to, pacemaker, cochlear implants, intracranial vascular clips, surgery within 6 weeks of entry in the study, coronary stent implanted within 8 weeks prior to the time of the intended MRI scan) or contraindication to Gd administration
- Any previous history of organ transplantation
- Any previous treatment with bone marrow transplantation or hematopoietic stem cell transplantation
- Adrenocorticotropic hormone or systemic corticosteroid therapy within 4 weeks prior to screening or during the screening period

  Inhaled and topical corticosteroids are allowed

- Receiving an unstable dosing regimen of proton pump inhibitors (PPIs) or H_2receptor antagonist (H_2RAs) during the screening phase and/or no plan to remain at a stable dose for the duration of study treatment

  Participants must not initiate PPIs or H2RAs within 2 weeks prior to randomization.
- Treatment with IVIg or plasmapheresis within 12 weeks prior to randomization
- Sensitivity or intolerance to any ingredient (including excipients) of fenebrutinib
- Receipt of a live-attenuated vaccine within 6 weeks prior to randomization. Influenza vaccination is permitted if the inactivated vaccine formulation is administered.
- Need for systemic anticoagulation (oral or injectable) or anti-platelet agent other than nonsteroidal anti-inflammatory drugs, aspirin, and other salicylates (aspirin up to 162 mg QD is allowed)
- Previous treatment with fenebrutinib or another BTK inhibitor for any indication
- Treatment with strong CYP3A4 inhibitors, strong or moderate CYP3A4 inducers, within 7 days or 5 drug-elimination half-lives (whichever is longer) prior to randomization
- Treatment with CYP3A4 substrates with a narrow therapeutic window within 7 days or 5 drug-elimination half-lives (whichever is longer) prior to randomization
- Previous use of anti-CD20 therapies, unless the last infusion was more than 2 years prior to screening and B-cell count is normal at screening
- Previous use of fingolimod, siponimod, ozanimod, or ponesimod within 6 weeks of randomization
- Previous use of natalizumab within 6 months of randomization
- Previous treatment with azathioprine, mycophenolate mofetil, or methotrexate within 12 weeks of randomization
- Previous use of teriflunomide, unless teriflunomide plasma concentrations are $<$0.02 mg/L at screening
- Any previous treatment with cladribine, mitoxantrone, daclizumab, alemtuzumab, or cyclophosphamide
- Treatment with dimethyl fumarate or monomethyl fumarate within 4 weeks of randomization
- Treatment with any investigational agent within 5 half-lives of randomization
- Requirement for any prohibited concomitant medications
- Previous treatment with any other immunomodulatory or immunosuppressive medication not already listed above without appropriate washout as described in the applicable local label

  If the washout requirements are not described in the applicable local label, then the wash out period must be 5 times the half-life of the medication. The PD

effects of the previous medication must also be considered when determining the required time for washout.

Note: No washout is required for interferon or glatiramer acetate.

Note: Participants screened for this study should not be withdrawn from therapies for the sole purpose of meeting eligibility for the trial. Participants who discontinue their current therapy for non-medical reasons should specifically be informed of their treatment options before deciding to enter the study.

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Meals and Dietary Restrictions

Use of the following foods is prohibited during the study and for at least 7 days prior to initiation of study treatment: furanocoumarin derivatives, such as those found in grapefruit, Seville oranges, pomegranates, or star fruit juice or products.

5.3.2 Caffeine, Alcohol, and Tobacco

This study has no caffeine, alcohol, or tobacco restrictions.

5.3.3 Activity

This study has no activity restrictions.

5.3.4 Contraception Requirements

During the study, participants must use contraception or take other precautions as described in Section 5.1.

5.4 SCREEN FAILURES

Individuals who do not meet the criteria for participation in this study (screen failure) may qualify for one re-screening opportunity (for a total of two screenings per individual) at the investigator's discretion. Individuals must re-sign the consent form prior to re-screening. The investigator will *maintain a* record *of* reasons for screen failure.

6. STUDY TREATMENT(S) AND CONCOMITANT THERAPY

Study treatment is defined as any investigational treatment, marketed product, placebo, or medical device intended to be administered to a study participant according to the study protocol.

The investigational medicinal product (IMP) for this study is fenebrutinib *(or fenebrutinib-matching* placebo*). Appendix 11 identifies all investigational medical products, and auxiliary medicinal products for this study.*

6.1 STUDY TREATMENTS ADMINISTERED

Table 6 provides a description of assigned study treatments for this study.

Table 6 Study Treatment Description

	Fenebrutinib	Placebo
Use	Experimental	Placebo comparator
Type of medicinal product	IMP	IMP
Drug form	Tablet	Tablet
Unit Dose Strength(s)	100 mg	Not applicable
Dosage Level(s)	200 mg BID	2 tablets BID
Formulation(s)	Refer to pharmacy manual and Investigator's Brochure	Not applicable
Packaging	Pill bottle	Pill bottle
Labeling	Per local requirements	
Route of administration	Oral	Oral
Source	Sponsor	Sponsor

IMP = investigational medicinal product

6.1.1 Fenebrutinib and Placebo

Participants will take two 100 mg tablets PO BID for a total dose of 400 mg of fenebrutinib (or placebo) every day. Participants will self-administer two 100 mg tablets in the morning and two 100 mg tablets in the evening by mouth. The tablet should be swallowed whole with some water, can be taken with or without food, and should be taken at the same time each day. Participants should be instructed that a missed fenebrutinib (or matching placebo) dose should not be taken with the next scheduled dose. Administration of fenebrutinib (or matching placebo) should be staggered with antacid use (i.e., study drug should be taken 2 hours before or 2 hours after antacid administration). In addition, any antacids (e.g., bismuth subsalicylate, calcium carbonate, aluminum-magnesium hydroxide) should be recorded as concomitant medications.

All participants will provide PK samples on Day 1 (baseline), on Day 29 (DBT Week 4), and at other visits as specified in Table 3. At the baseline and DBT Week 4 visits, the fenebrutinib (or matching placebo) morning dose will be administered at the morning (mandatory) clinic visit while the patient is fasting. The dates and times of the most recent prior meal, most recent antacid administration, last dose of oral study drug (prior to the clinic visit), and timing of oral study drug administration in the clinic should be recorded at each clinic visit with PK sampling.

6.2 PREPARATION, HANDLING, STORAGE, AND ACCOUNTABILITY

All IMPs required for completion of this study will be provided by the Sponsor. The study site (i.e., investigator or other authorized personnel e.g., pharmacist) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each participant, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that participants are provided with doses specified by the protocol.

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMPs supplied by the Sponsor using the interactive voice or web-based response system (IxRS) to confirm the shipment condition and content. Any damaged shipments will be replaced. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit, by temperature monitoring, for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

Only participants enrolled in the study may receive IMPs, and only authorized staff may supply or administer IMPs.

The IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor (if supplied by the Sponsor) with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the drug accountability log.

Refer to the pharmacy manual and/or the fenebrutinib Investigator's Brochure for information on IMP preparation, storage, handling, and accountability.

6.3 TREATMENT ASSIGNMENT AND BLINDING

6.3.1 Treatment Assignment

This is a randomized, double-blind study. 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 IxRS. Participants who discontinue treatment for any reason will not be

replaced, except for participants who withdraw before receiving any study treatment. 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.

6.3.2 Blinding

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 nonMS-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.

To facilitate analysis of the biological samples collected in this study, the treatment code will be released to the responsible analytical person when the samples have been received at the analytical site and are ready for assay. The result of the analysis must not be released with individual identification of the patient until after the unblinding for the primary analysis.

Study site personnel and participants will be blinded to treatment assignment until after the primary analysis. The Sponsor and its agents will also be blinded to treatment assignment, with the exception of individuals who require access to patient treatment assignments to fulfill their job roles during a study. These roles include the unblinding group responsible, clinical supply chain managers, sample handling staff, IxRS service provider, and iDMC members.

The 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. The investigator is not required to contact the Medical Monitor prior to breaking the treatment code. However, the investigator should *inform* the Medical Monitor *that* the treatment code has been broken.

If the investigator wishes to know the identity of the study drug for any reason other than a medical emergency, he or she should contact the Medical Monitor directly prior to unblinding.

The investigator should document and provide an explanation for any non-emergency unblinding. If the Medical Monitor agrees to participant unblinding, the investigator will be able to break the treatment code by contacting the IxRS.

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 an *a drug listed in Section 8.3.4*. The participant may continue to receive treatment, and the investigator, participant, and Sponsor personnel, with the exception of the Drug Safety representative and personnel who must have access to participant treatment assignments to fulfill their roles (as defined above), will remain blinded to treatment assignment.

6.4 STUDY TREATMENT COMPLIANCE

When participants self-administer study treatment at home, compliance with study treatment will be assessed.

At each clinic visit, participants will return all previously dispensed 70-mL bottles and all leftover fenebrutinib (or placebo) tablets. The site will count the leftover study drug tablets and assess compliance during DBT and during the OLE. Refer to the pharmacy manual for detailed instructions on drug storage and administration.

Details on treatment administration (e.g., dose and timing) should be noted in the source documents and on the Study Drug Administration electronic Case Report Form (eCRF). Cases of overdose, medication error, drug abuse, or drug misuse, along with any potential associated adverse events, should be reported as described in Appendix 3.

6.5 DOSE MODIFICATION

Modification of the fenebrutinib/placebo dose is not permitted.

6.6 CONTINUED ACCESS TO STUDY TREATMENT AFTER THE END OF THE STUDY

Participants may be eligible to receive fenebrutinib as part of an extension study within the current protocol, as described in Section 4.1. In addition, participants will be moved to a program level OLE (separate protocol, protocol number TBD) as soon as it is available. The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following website:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

6.7 TREATMENT OF OVERDOSE

An overdose is the administration of a drug in a quantity that is higher than the assigned dose. There is no known antidote for treating an overdose. Cases of overdose, along with any associated adverse events, should be reported as described in Appendix 3.

In the event of an overdose, the investigator should take the following steps:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any adverse event or serious adverse event and laboratory abnormalities until fenebrutinib can no longer be detected systemically (at least 5 days).
3. Obtain a plasma sample for PK analysis within 2 days from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis).

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor on the basis of clinical evaluation of the participant.

6.8 CONCOMITANT THERAPY

Previous treatment with anti-CD20 therapy (e.g., rituximab, ocrelizumab) should be reported up to 3 years prior to randomization and other MS disease modifying therapies (DMTs) should be reported up to 1 year prior to randomization. Receipt of any prior SARS-CoV-2 vaccine should be recorded in the concomitant medications eCRF. All other medications (e.g., prescription drugs, MS symptomatic therapies, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) and non-medicinal treatments (e.g., physiotherapy, occupational therapy) used by the patient within 3 months prior to initiation of study treatment will be recorded in the appropriate eCRF along with the following information:

- Reason for use
- Dates of administration, including start and end dates
- Dosage information, including dose and frequency

The Medical Monitor *may* be *consulted* if there are any questions *related to* concomitant or prior therapy.

Paracetamol or acetaminophen, at doses of ≤2 grams/day is permitted for use any time during the study.

6.8.1 Permitted Therapy

In general, investigators may manage a participant's care (including preexisting conditions) through use of supportive therapies, as clinically indicated and per local standard practice, with the exception of prohibited therapies defined in Section 6.8.3. and taking into account cautionary therapies defined in Section 6.8.2.

6.8.1.1 Oral Contraceptives and Hormone-Replacement Therapy

Participants who use oral contraceptives or hormone-replacement therapy can continue their use. All concomitant medications should be reported to the investigator and recorded on the appropriate eCRF. Participants using hormone-replacement therapy will be encouraged to use the minimal dose required to control their symptoms.

6.8.1.2 Symptomatic Treatments of Multiple Sclerosis

Participants requiring symptomatic treatment for MS (e.g., fampridine) and/or physiotherapy must be treated at a stable dose/regimen prior to the initiation of study drug and must have a plan to remain at a stable dose/regimen for the duration of the 12-week randomized controlled period. Concomitant treatments for symptoms related to MS should be kept constant throughout the randomized controlled period, but could be adapted according to patient's needs.

Participants must not start or modify their symptomatic treatment within 4 weeks of randomization. Symptomatic treatment may be initiated during the trial at the discretion of the investigator and should be kept at a stable dose as much as possible.

6.8.1.3 Treatment of Relapses

Participants who experience a relapse during the study may receive treatment with IV or oral corticosteroids, if judged to be clinically appropriate by the investigator. The following standardized treatment regimen may be used as warranted, 1 g/day IV methylprednisolone or equivalent dosing or oral steroid for a maximum of 5 consecutive days. At the discretion of the investigator, corticosteroids may be stopped abruptly or tapered over a maximum of 10 days. Such participants should not discontinue the treatment period solely based on the occurrence of a relapse, unless the patient or investigator feels he or she has met the criteria for withdrawal.

6.8.2 Cautionary Therapy

6.8.2.1 Acid-Reducing Agents

The solubility of fenebrutinib is pH-dependent, and absorption is negatively impacted by acid-reducing agents, such as PPIs and H2RAs, thereby decreasing systemic exposure.

Participants who use antacids (e.g., bismuth subsalicylate, calcium carbonate, aluminum-magnesium hydroxide) for symptomatic relief of heartburn should take fenebrutinib (or placebo) at least 2 hours before or 2 hours after antacid administration because gastric acid improves fenebrutinib absorption.

Participants may be treated with PPIs or H2RAs at up to the maximum recommended dose in accordance with the local label. The dose should remain stable for at least 2 weeks prior to initiation of study treatment and throughout study treatment.

Standalone doses of acid-reducing agents at visits requiring PK sampling is prohibited (see Table 3). Any use of PPIs, H_2RAs, and/or other antacids should be recorded as concomitant medications, including the date and time of last administration.

6.8.2.2 CYP3A- and Breast Cancer Resistance Protein-Mediated Drug Interactions

The results of a clinical drug-drug interaction study (GP39616) suggest that fenebrutinib can be classified as a mild inhibitor of CYP3A at clinically relevant doses. It is possible that fenebrutinib inhibition of CYP3A may alter the metabolism of CYP3A substrates and result in increased plasma concentrations of CYP3A substrates. Therefore, medications that are sensitive CYP3A substrates should be used with caution.

The use of hormone-replacement therapy or hormonal contraceptives containing the CYP3A substrate ethinylestradiol (with the concomitant use of a barrier method) is permitted; however, these agents should be used with caution, and participants should be counseled regarding the potential risks and benefit of these medications per the local prescribing information.

In addition, the results of Study GP39616 indicate that fenebrutinib is a moderate inhibitor of the breast cancer resistance protein (BCRP; also known as ABCG2) transporter at clinically relevant doses. There is a potential for increased plasma concentrations of drugs that are known to be substrates of the BCRP transporter. Plasma concentrations of the medications that are BCRP substrates may increase; therefore, such medications should be used with caution.

The investigator may consult the Internet reference provided below to determine whether a certain medication interacts with CYP3A or BCRP. The Internet reference is not necessarily comprehensive, and the investigator should consult local prescribing information for the concomitant medication when determining whether a concomitant medication can be safely administered with study treatment. In addition, the investigator should contact the Medical Monitor (or delegate) if questions arise prior to concomitant administration with study treatment.

https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm

6.8.2.3 Statins

Several lipid-lowering agents (statins) are metabolized by CYP3A (simvastatin, lovastatin, atorvastatin) and/or transported by BCRP (rosuvastatin, atorvastatin) and thus may be affected by drug-drug interaction with fenebrutinib. Therefore, dose adjustments of these medications should be considered (Kellick et al. 2014) as follows:

- Simvastatin: recommended maximum dose of 10 mg/day
- Lovastatin: recommended maximum dose of 20 mg/day
- Rosuvastatin: recommended maximum dose of 10 mg/day
- Atorvastatin: recommended maximum dose of 20 mg/day

The use of statins has been associated with myopathy, which can manifest as weakness, tenderness, or muscle pain with elevations of creatine kinase $>10\times$ ULN. In severe cases, myopathy can cause rhabdomyolysis with or without acute kidney injury secondary to myoglobinuria, and rare fatalities due to rhabdomyolysis have occurred. The risk of myopathy is increased by elevated plasma levels of statins. Predisposing factors for myopathy include advanced age ($\geq$65 years), female sex, uncontrolled hypothyroidism, renal impairment, or the use of concomitant medications that increase the plasma levels of the statin.

6.8.2.4 Herbal Therapies

For the purposes of this study, dietary supplements are defined as vitamins, minerals, purified food substances, and herbals with pharmaceutical properties.

Vitamins, minerals, and purified food substances are allowed in amounts not known to be associated with adverse effects (e.g., hypervitaminosis). Herbal therapies with pharmaceutical properties are allowed only if there is acceptable evidence of no CYP3A inhibition or induction (see Section 6.8.3 for a list of prohibited concomitant medications, including herbal products). Herbal therapies with pharmaceutical properties must not be administered during the study, unless there are sufficient data available to ascertain there are no drug interactions with fenebrutinib. Any questions can be directed to the Medical Monitor.

6.8.3 Prohibited Therapy

The results of Study GP39616 suggest that fenebrutinib can be classified as a moderately sensitive substrate of CYP3A at clinically relevant doses. There is a potential for a drug-drug interaction with any medication that strongly inhibits or induces this enzyme. Therefore, medications in the following categories should be prohibited for 7 days or 5 half-lives, whichever is longer, prior to the first dose of study drug and until the final dose of study drug.

- Strong CYP3A4 inhibitors
- Strong or moderate CYP3A inducers

The results of study (GP39616) suggest that fenebrutinib can be classified as a mild inhibitor of CYP3A at clinically relevant doses. Fenebrutinib may increase plasma concentrations of the medications in the following category. Therefore, the following medications should be prohibited during study treatment:

- CYP3A4 substrates with a narrow therapeutic window

Table 7 summarizes a list of prohibited medications for the reasons listed above. This list is not comprehensive, and the investigator should consult local prescribing information for the concomitant medication as well as the Internet reference provided below when determining whether a concomitant medication can be safely administered with study treatment. In addition, the investigator should contact the Medical Monitor if questions arise regarding medications not listed.

https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm

Table 7 List of Prohibited Medicines Due to CYP3A-Mediated Drug Interactions

Class	Examples of Drugs in this Class
Strong CYP3A4 inhibitors	Boceprevir, cobicistat, clarithromycin, danoprevir/ritonavir, elvitegravir/ritonavir, indinavir/ritonavir, itraconazole, idelalisib, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole*, and nirmatrelvir/ritonavir.*
Strong CYP3A inducers	Apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, and hyperforin (St. John's Wort)
Moderate CYP3A inducers	Bosentan, dexamethasone, efavirenz, etravirine, phenobarbital, primidone, phenobarbital, and rifabutin
CYP3A4 substrate with a narrow therapeutic window	Alfentanil, astemizole, cyclosporine, cisapride, dihydroergotamine, ergotamine, everolimus, fentanyl, pimozide, quinidine, sirolimus, terfenadine, and tacrolimus

Note: This list is not comprehensive, and the investigator should consult local prescribing information for the concomitant medication as well as the Internet reference provided below when determining whether a concomitant medication can be safely administered with study treatment. In addition, the investigator should contact the Medical Monitor if questions arise regarding medications not listed.

https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm

6.8.3.1 Other Prohibited Therapies

Use of the following concomitant therapies is prohibited as described below for participants in the DBT phase, OLE phase, and SFU phase:

- Investigational therapy (other than protocolmandated study treatment)

- Any Bcell targeted therapy (e.g., rituximab, alemtuzumab, atacicept, belimumab, ublituximab, ofatumumab, or ocrelizumab)
- BTK inhibitors (other than fenebrutinib)
- Any other DMT for MS (including, but not limited to, cladribine, mitoxantrone, interferons, glatiramer acetate, dimethyl fumarate and other fumarates, and fingolimod and other sphingosine-1-phosphate receptor modulators)

  The Medical Monitor should be consulted if it is unclear if a medication is considered disease modifying.
- Systemic anticoagulation (oral or injectable) or antiplatelet agent other than nonsteroidal antiinflammatory drugs, aspirin, and other salicylates (aspirin up to 162 mg four times a day (QID) is allowed)
- Use of "as needed" doses of acid-reducing agents (e.g., PPIs, H_2RAs) at visits requiring PK sampling is prohibited (chronic dosing is acceptable) (see Table 3)
- *High-dose biotin*

6.8.4 Prohibited Food

Use of the following foods is prohibited during the study and for at least 7 days prior to initiation of study treatment: furanocoumarin derivatives, such as those found in grapefruit, Seville oranges, pomegranates, or star fruit juice or products.

6.8.5 Immunizations

Participants will be excluded from study participation if they have been vaccinated with a live or live-attenuated vaccine (e.g., the intranasal live attenuated influenza vaccines, bacille Calmette Guérin, varicella) within 6 weeks of randomization. In addition, immunization with a live or live-attenuated vaccine is prohibited for the duration of study participation, including the SFU phases.

The effect of fenebrutinib upon the efficacy of vaccinations is unknown. Vaccinations with vaccines other than live or live-attenuated vaccinations are permitted during the study period. It is recommended that all vaccinations, other than live or live-attenuated vaccinations, should follow the local immunization schedule. In addition, measurement of vaccine-induced response titers should be considered to determine if individuals can mount a protective immune response as the efficacy of the vaccination may be decreased. Administration of a seasonal influenza vaccine, except for the intranasal live-attenuated influenza vaccine, is recommended but not required.

Refer to Fenebrutinib Investigator's Brochure and Appendix A6-1.4 for further details and precautions regarding vaccinations.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION OR WITHDRAWAL

7.1 DISCONTINUATION OF STUDY TREATMENT

It may be necessary for a participant to permanently discontinue (definitive discontinuation) study treatment. If study treatment is definitively discontinued, the participant should move to the Safety Follow-up Period. Refer to the schedule of activities (see Section 1.3) for data to be collected at the time of discontinuation of study treatment ("Early Discontinuation Visit") and the further follow-up evaluations that need to be completed in the Safety Follow-up Period.

Participants must permanently discontinue study treatment if they experience any of the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the participant's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the participant
- Demonstrate active hepatitis B infection
- PML
- First observation of AST or ALT elevation $>8\times$ ULN
- AST or ALT elevation $>5\times$ ULN persisting more than 2 weeks
- AST or ALT elevation $>3\times$ ULN in combination with any of the following:
  - Total bilirubin $>2\times$ ULN or clinical jaundice as defined by Hy's Law
  - INR >1.5
  - Symptoms of hepatitis, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness
  - Signs or symptoms of immune-related hepatotoxicity (fever, rash, or eosinophilia $>5\%$)
- *ALT or AST elevation between 3–5 × ULN (inclusive) persisting for 4 weeks and in absence of alternative etiology*
- Grade 3 neutropenia (ANC 500–1000/mm³) persisting more than 1 month or reoccurring
- Grade 4 neutropenia (ANC <500/mm^3)
- Grade *2* thrombocytopenia (platelet count *50,000–75*,000/mm³) persisting more than one month or reoccurring
- Grade *3* thrombocytopenia (platelet count 25,000–*50,000*/mm^3) *or Grade 4 thrombocytopenia (<25,000/mm³)*
- Malignancy (with the exception of non-serious local and resectable basal or squamous cell carcinoma of the skin)

- Pregnancy
- An episode of torsade de pointes or a new ECG finding of clinical concern or sustained (at least two ECG measurements > 30 minutes apart) QTcF that is > 500 ms and/or > 60 ms longer than the baseline value (unless there is a clear alternative cause other than study drug) as described in Appendix 6. Electrocardiogram assessment should be conducted as outlined in Section 8.2.3.
- Requirement of *chronic use of* any prohibited medication as defined in Section 6.8.3. *If any prohibited medication is considered to be medically necessary, the investigator should discuss with the Medical Monitor.*

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF.

Refer to the schedule of activities in Section 1.3 (see Table 1) for details on follow-up assessments to be performed for participants who permanently discontinue study treatment. If a participant requests to be withdrawn from treatment or follow-up assessments, this request must be documented in the source documents and signed by the investigator.

7.2 PARTICIPANT DISCONTINUATION OR WITHDRAWAL FROM THE STUDY

A participant may withdraw from the study at any time at his or her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a participant requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the schedule of activities (see Section 1.3). Refer to the schedule of activities for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The participant will be permanently discontinued both from the study treatment and from the study at that time.

If a participant withdraws consent from the study, the Sponsor may retain and continue to use any data collected before withdrawal of consent. Samples collected prior to withdrawal may be analyzed, unless the participant specifically requests that the samples be destroyed (as documented in the source documents) or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

7.3 PARTICIPANTS LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule. If the participant is unable or unwilling to comply with study visits, site personnel should assess reasons the participant is unable or unwilling to return to the clinic, and determine if there are ways to support participant participation.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, three telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he or she will be considered lost to follow-up and will be withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled individuals and for individuals who are not subsequently enrolled will be maintained at the study site.

Study procedures and their timing are summarized in the schedule of activities (see Section 1.3). Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the schedule of activities, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a *detailed* record of all participants screened and to *document* eligibility or record reasons for screening failure, as applicable.

Medical history and baseline conditions, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), and reproductive status will be recorded at baseline. Previous treatment with anti-CD20 therapy (e.g., rituximab, ocrelizumab) should be reported up to 3 years prior to randomization and other MS DMTs should be reported up to 1 year prior to randomization. Receipt of any prior SARS-CoV-2 vaccine should be recorded in the concomitant medications eCRF. All other medications (e.g., prescription drugs, MS symptomatic therapies, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) and non-medicinal treatments (e.g., physiotherapy, occupational therapy) used by the patient within 3 months prior to initiation of study treatment will be recorded in the appropriate eCRF. Demographic data, including age, sex, and self–reported race/ethnicity, will also be recorded if allowed per local regulations. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Participants will be closely monitored for safety throughout the study. Participants should be assessed for toxicity prior to each dose; treatment will be administered only if the clinical assessment and local laboratory test values are acceptable. Urgent safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

8.1 EFFICACY ASSESSMENTS

8.1.1 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is a useful tool for monitoring CNS lesions in MS. Different MRI derived parameters have been related to clinical activity and T1 weighted Gd-enhancing lesions or new and/or enlarging hyperintense T2 lesions have been related to relapses.

Radiologic evaluation for the primary efficacy parameter will be performed using a standardized MRI protocol at screening, and at Weeks 4, 8, and 12. Measurements from the screening MRI scan sequences will be used for the baseline MRI measurements; therefore, these sequences do not need to be repeated at the baseline visit. In addition, mandatory MRI scans will be obtained in participants who withdraw from study treatment (at withdrawal visit) if one was not performed during the prior 4 weeks. *While MRI scans are acquired in this study to support the primary and secondary endpoints, the set of images from each examination allows for the possibility of additional exploratory measurements.*

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. Further details on scanning acquisition sequences, methods, handling, and transmission of the scans, certification of

site MRI radiologist/technicians, and the procedures for the blinded analysis of the scans at the central reading center will be described in separate MRI acquisition procedures manuals *and Imaging Review Charters*.

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. During the DBT phase, only the local radiologist/technician at the investigational site who is assigned to this study may have access to the MRI scans, except at screening when the treating investigator may view the MRI scan. To maintain the blind, the treating investigator must not review the MRI scans obtained after randomization unless a safety concern arises. In the event that the treating investigator becomes aware of these MRI results, this should be documented in the eCRF, indicating the reason. The treating investigator may have access to MRI scans performed during the OLE phase *from their MRI facility*.

If participants receive corticosteroids for an MS relapse, every effort should be made to obtain an MRI scan prior to the first corticosteroid dose if the pre-corticosteroid scan is within 1 week of the scheduled visit. In participants receiving corticosteroids for an MS relapse, there should be an interval of 3 weeks between the last dose of corticosteroids and the MRI scan.

8.1.2 Clinical Outcome Assessments

Disability will be measured using the EDSS. The EDSS is based on a standardized neurological examination, incorporating functional systems (visual, brainstem, pyramidal, cerebellar, sensory, bowel and bladder, and cerebral [or mental]) that are rated and then scored as a functional systems score (FSS), and ambulation, which is scored as ambulation score. Each FSS is an ordinal clinical rating scale ranging from 0 to 5 or 6 and an ambulation score that is rated from 0 to 1*6*. These ratings are then used in conjunction with observations, as well as information, concerning ambulation and use of assistive devices to determine the total EDSS score. The EDSS is a disability scale that ranges in 0.5-point steps from 0 (normal) to 10.0 (death) (Kurtzke 1983; Kappos 2011). All FSS, ambulation score, and total EDSS scores will be captured electronically. Note that the following items do not need to be scored for this study: sexual dysfunction and fatigue.

8.1.3 MS Relapse Assessment

All new or worsening neurological events compatible with MS representing a clinical relapse will be reported in the appropriate eCRF. The EDSS/FSS evaluation can be performed by the Principal Investigator or by a designated sub-investigator. Whenever possible, the same rater should evaluate a patient throughout the study. The EDSS should be performed within 7 days from the onset of the relapse. If the change or intensification of existing neurological symptoms are more likely attributed to a transient systemic infection, then a referral to the examining investigator may not be warranted.

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 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.

Derivation of protocol-defined relapses will be performed by the Sponsor. Clinical relapses (i.e., regardless of whether or not they meet the criteria for a protocol-defined relapse) will be recorded in the eCRF.

8.2 SAFETY ASSESSMENTS

8.2.1 Physical Examinations

A complete physical examination will include, at a minimum, assessments of the head, eyes, ears, nose, and throat and evaluation of the cardiovascular, dermatologic, musculoskeletal, respiratory, and gastrointestinal systems; genitourinary examinations may be performed if clinically indicated. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. A neurological examination includes, but is not limited to, an assessment of mental status, level of consciousness, cranial nerve function, motor function, sensory function, reflexes, and coordination. During an unscheduled visit, the neurological examination must be performed if the patient is experiencing neurological worsening between scheduled visits.

8.2.2 Vital Signs

Vital signs will be measured in a seated position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, pulse, and respiratory rate.

8.2.3 Electrocardiograms

Single 12-lead ECGs will be obtained as outlined in the schedule of activities (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR interval, QRS interval, and QT interval. QT interval corrected through use of Fridericia's formula (QTcF) can be calculated by the ECG machine or using standard

formulas. Refer to Appendix 6 for QTc withdrawal criteria and any additional QTc readings that may be necessary.

Lead placement should be as consistent as possible. ECG recordings must be performed after the participant has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws). Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre–ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG reports. Paper copies of ECG tracings will be kept as part of the participant's permanent study file at the site. The following should be recorded on the appropriate eCRF: heart rate, RR interval, QRS interval, PR duration, uncorrected QT interval, and QTcF based on machine readings of the individual ECG tracings. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF. If considered appropriate by the Sponsor, ECGs may be analyzed retrospectively at a central laboratory.

If at a particular postdose timepoint the mean QTcF is $>$500 ms and/or $>$60 ms longer than the baseline value, another ECG must be recorded, ideally within the next 5 minutes, and ECG monitoring should continue until QTcF has stabilized on two successive ECGs. The Medical Monitor should be notified. Standard-of-care treatment may be instituted at the investigator's discretion. If a PK sample is not scheduled for that timepoint, an PK sample should be obtained. A decision on study drug discontinuation should be made, as described in Appendix 6 (Section A6–2.4). The investigator should also evaluate the participant for potential concurrent risk factors (e.g., electrolyte abnormalities, co-medications known to prolong the QT interval, severe bradycardia).

8.2.4 Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical laboratory tests to be performed and to the schedule of activities (see Section 1.3) for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the Adverse Event CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms

- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment
- ALT or AST > 3 × ULN unless attributed to a specific clinical diagnosis that is to be reported as the primary adverse event term *(see Section 8.3.1 for more information on AE categories)*.

Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 4 weeks *of the final* dose of study treatment should be repeated until the values return to normal or baseline or are *considered to be stable and* no longer considered clinically significant by the investigator. If such values do not return to normal or baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the Sponsor notified.

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the schedule of activities.

If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., serious adverse event or adverse event or dose modification), the results must be recorded on the eCRF.Samples collected for safety laboratory tests will be destroyed no later than the time of completion of the final Clinical Study Report.

8.2.5 Pregnancy Testing

The schedule for pregnancy testing for enrolled female participants is outlined in Section 1.3 and will be conducted as outlined in Appendix 4.

8.2.6 Monitoring for Suicidal Ideation and Behavior

Participants being treated with fenebrutinib should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior, especially at the beginning and end of the course of treatment, or at the time of dose changes, either increases or decreases. Consideration should be given to discontinuing the study medication in participants who experience signs of suicidal ideation or behavior, following a risk assessment.

Screening assessment of suicidal ideation and behavior or treatment-emergent suicidal ideation and behavior will be monitored during Study GN43271 using the Columbia-Suicide Severity Rating Scale (C-SSRS).

8.3 ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, AND OTHER SAFETY REPORTING

The definitions of adverse event and serious adverse event can be found in Appendix 3.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an adverse event or serious adverse event and remain responsible for following up adverse events that are serious, are considered related to the study treatment or study procedures, or caused the participant to discontinue the study treatment (see Section 7).

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Event/*Special Situations* Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. All other medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the General Medical History and Baseline Conditions eCRF, not the Adverse Event eCRF.

All adverse events will be reported from the start of treatment until 28 days after the final dose of study treatment at the timepoints specified in the schedule of activities (see Section 1.3).

All serious adverse events will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated serious adverse event data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek adverse event or serious adverse event information after conclusion of study participation. However, if the investigator learns of any serious adverse event, including a death, at any time after a participant has been discharged from the study, and he or she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the Sponsor.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of adverse events and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about adverse event occurrences.

8.3.3 Follow-Up of Adverse Events and Serious Adverse Events

After the initial adverse event or serious adverse event report, the investigator is required to proactively follow each participant at subsequent visits or contacts. All adverse events will be followed until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the participant is lost to follow-up (as defined in Section 7.3), or the participant withdraws consent. Further information on follow-up procedures is provided in Appendix 3.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the investigator to the Sponsor of a serious adverse event is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory authorities about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards or Ethics Committees (IRBs/ECs), and investigators.

For all studies except those utilizing medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

To determine reporting requirements for serious adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the document listed below:

Drug	Document
Fenebrutinib	Fenebrutinib Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

An investigator who receives an investigator safety report describing a serious adverse event or other specific safety information (e.g., summary or listing of serious adverse events) from the Sponsor will review and then file it and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5 Pregnancy

Female participants of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 28 days after the final dose of fenebrutinib.

Male participants will be instructed through the Informed Consent Form to immediately inform the investigator if a female partner becomes pregnant during the study or within 28 days after the final dose of fenebrutinib.

If a pregnancy is reported, the investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.

All pregnancies reported during the study should be followed until pregnancy outcome, with follow-up information on the infant collected according to procedures outlined in Appendix 4. The Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events.

8.3.6 Cardiovascular and Death Events

Information on reporting deaths is provided in Appendix 3.

8.3.7 Anticipated Events Not Qualifying for Expedited Reporting

Events not qualifying for expedited reporting will not be defined for this study.

8.3.8 Adverse Events of Special Interest

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware

of the event; see Section A3–5 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST *(>3×ULN)* in combination with *either an elevated total* bilirubin *(>2×ULN)* or clinical jaundice, as defined by Hy's Law (see Section A3–7.6)
- *Cases of an elevated ALT and/or AST 3–5×ULN, INR>1.5, total bilirubin≤2×ULN, and absence of clinical jaundice*
- *Cases of elevated ALT and/or AST 5–8×ULN, total bilirubin≤2×ULN and absence of clinical jaundice*
- *Cases of elevated ALT and/or AST>8×ULN, total bilirubin≤2×ULN and absence of clinical jaundice*
- Suspected transmission of an infectious agent by a study treatment, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a participant exposed to a medicinal product. This term applies only when a contamination of the study treatment is suspected.

Laboratory results for adverse events of special interest pertaining to hepatic transaminase elevations should be closely monitored, as the AESI category should be upgraded to reflect the most severe liver enzyme results, where required.

8.3.9 Medical Monitors and Emergency Medical Contacts

*To ensure the safety of study participants, access to Medical Monitors is available 24 hours per day, 7 days per week. A*n Emergency Medical Call Center will *also* be available 24 hours per day, 7 days per week. The Emergency Medical Call Center will connect the investigator with an Emergency Medical Contact, provide medical translation service if necessary, and track all calls. Contact information, including toll-free numbers for the Emergency Medical Call Center, will be distributed to investigators.

8.4 PHARMACOKINETICS

Plasma samples of approximately 9 mL will be collected for measurement of plasma concentrations of fenebrutinib as specified in the schedule of activities (see Section 1.3).

Optional additional intensive PK sample collection will be performed at the Day 1 and Day 2*9* visits for participants that consent to it. The intensive PK sampling involves collection of blood samples according to the schedule shown in Table 3.

Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples will be used to evaluate the pharmacokinetics of fenebrutinib. Samples collected for analyses of fenebrutinib plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Genetic analyses will not be performed on these plasma samples. Participant confidentiality will be maintained.

All PK samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed to allow for assay development and validation (if needed).

Information on unblinding of personnel responsible for performing PK assays is provided in Section 6.3.

8.5 PHARMACODYNAMICS

Refer to Section 8.7 for information on exploratory pharmacodynamic biomarkers.

8.6 GENETICS

Refer to Section 8.10 for information on genetic biomarkers.

8.7 BIOMARKER ASSESSMENTS

The following biomarker samples will be collected, as applicable, from participants at all sites:

- Serum and plasma samples for determination of fluid biomarkers of neuro*nal*- and glial *activity*, B cell and myeloid cell *biology*, and the relationship between fenebrutinib exposure and selected pharmacodynamic biomarkers including but not limited to serum and/or plasma neurofilament light chain
- Flow cytometry: Analysis may include, but is not limited to, the determination of B-cell numbers (CD19+) and other lymphocyte subsets

Blood samples for collection of RNA may be measured for exploratory biomarker analyses and may include but not be limited to neuro*nal*- and glial *activity*, B cell and myeloid cell *biology*, and the relationship between fenebrutinib exposure to RNA gene expression. Analyses may involve extraction of RNA for use of next-generation sequencing (NGS) of a comprehensive panel of genes. NGS methods will not include whole genome sequencing (WGS) or whole exome sequencing (WES).

Biomarker samples requiring separate consent are described in Section 8.10.

Screening blood samples, including those collected from individuals who do not enroll in the study, may be used for future research and/or development of disease-related tests or tools.

Biomarker samples will be collected according to the schedule outlined in Section 1.3 (see Table 1). Biomarker samples will be sent to one or several central laboratories, academic laboratories or to the Sponsor or a designee. Instructions for the collection and handling of biomarker samples, including sampling procedures, storage conditions, and shipment instructions, are provided in the laboratory manual.

Unless the participant gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 8.10) biomarker samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or participants unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

8.8 IMMUNOGENICITY ASSESSMENTS

Immunogenicity assessments are not applicable for this study.

8.9 HEALTH ECONOMICS AND MEDICAL RESOURCE UTILIZATION

Health economics and medical resource utilization assessments will not be performed in this study.

8.10 ADDITIONAL ASSESSMENTS AND PROCEDURES REQUIRING SEPARATE CONSENT

8.10.1 Lumbar Punctures and CSF Substudy

Consenting participants will undergo optional lumbar puncture for collection of CSF at the Baseline and Week 12 visits.

The Informed Consent Form will contain a separate section that addresses optional lumbar punctures. The investigator or authorized designee will explain to each participant the objectives, methods, and potential hazards of undergoing optional lumbar punctures. Participants will be told that they are free to choose not to undergo optional lumbar punctures and may withdraw their consent at any time and for any reason. A separate, specific signature will be required to document a participant's agreement to undergo optional lumbar punctures. Participants who choose not to undergo optional lumbar punctures will not provide a separate signature. The investigator should document whether or not the participant has given consent to undergo optional lumbar

punctures and (if applicable) the date of consent, by completing the Sample Informed Consent/Withdrawal eCRF.

Table 8 summarizes CSF substudy PK and biomarker collection during the double-blind treatment phase, according to the schedule outlined in Section 1.3 (see Table 1). The baseline lumbar puncture can be performed at Day 1 prior to receiving the first dose of study drug, or it can be performed during the screening period prior to Day 1. However, the baseline lumbar puncture should only be performed once other screening tests have been performed and it has been confirmed that the participant qualifies for the study. The lumbar puncture performed at the Week 12 visit should be performed between 1 to 2 hours after the administration of study drug in clinic. At the Week 12 lumbar puncture, a contemporaneous blood sample for PK measurement should be collected at the same time as the lumbar puncture is performed to enable comparison of CSF and plasma drug concentration. *If the Week 12 lumbar puncture is missed, it can be performed at a later visit, including an OLE visit.*

Inflammatory markers in the CSF will be measured as described in Section 4.2.8.

Samples may be used for exploratory biomarker research as described in Section 8.7. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual. Refer to Section 8.7 for information on duration of sample storage and availability of data from biomarker analyses.

Table 8 Schedule of CSF Substudy Pharmacokinetic and Biomarker Samples for Double-Blind Treatment

Visit	Timepoint	Sample Type
Screening (Day −28 to Day –1) or Day 1 (Week 0) after patient has qualified for study	NA	Biomarkers (CSF, serum[a])
Day 85 (Week 12)	1-2 hours after dosing	PK (CSF, plasma), biomarkers (CSF, serum)

CSF = cerebrospinal fluid; NA = not applicable; PPI = proton pump inhibitor; PK = pharmacokinetic

[a] Sample will come from the main study in order to avoid duplication. This is not an additional sample to the main study

Notes:

- Morning clinic visits are preferred for all visits but are required on Day 1. Prior to each morning clinic visit, participants should be instructed not to take their morning dose and to bring their study medication with them to their clinic visit. The dates and times of the last dose of oral study drug (prior to the clinic visit) and timing of oral study drug administration in the clinic should be recorded at each clinic visit. Use of PPIs, H_2-receptor antagonists, and/or other antacids (e.g., bismuth subsalicylate, calcium carbonate, aluminum-magnesium hydroxide) should be recorded as concomitant medications, including the date and time of last administration at each clinic visit.
- Single-dose acid-reducing agents are not permitted on the day of an in-clinic visit with PK assessments.
- At Week 12, PK CSF and plasma samples should be taken contemporaneously when feasible.

8.10.2 Samples for Research Biosample Repository

8.10.2.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR samples will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for participants in the future.

Samples for the RBR will be collected from participants who give specific consent to participate in this optional research. RBR samples will be analyzed to achieve one or more of the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety

- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

8.10.3 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 8.10.6) will not be applicable at that site.

8.10.4 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to fenebrutinib, diseases, or drug safety:

- Plasma samples collected as indicated in the schedule of activities
- Serum samples collected as indicated in the schedule of activities
- RNA samples collected as indicated in the schedule of activities
- DNA sample collected as indicated in the schedule of activities
- Leftover blood, serum, plasma, cerebrospinal fluid, and any derivatives thereof (e.g., DNA, RNA, proteins, peptides)

The above samples may be sent to one or more laboratories for analysis of germline or somatic variants via WGS, WES, or other genomic analysis methods. Genomics is increasingly informing researcher's understanding of disease pathobiology. The WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which participants are more likely to respond to a drug or develop adverse events.

Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

All RBR samples are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the

IRB/EC–approved Informed Consent Form and applicable laws (e.g., health authority requirements).

8.10.5 Confidentiality

All RBR samples and associated data will be labeled with a unique participant identification number.

Participant medical information associated with RBR samples is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the participant, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses of RBR samples, data derived from these analyses will generally not be provided to study investigators or participants unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR samples must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

8.10.6 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each participant the objectives, methods, and potential hazards of participation in the RBR. Participants will be told that they are free to choose not to provide optional RBR samples and may withdraw their consent at any time and for any reason during the storage period. A separate, specific signature will be required to document a participant's agreement to provide optional RBR samples. Participants who choose not to provide optional RBR samples will not provide a separate signature. The investigator should document whether or not the participant has given consent to provide optional RBR samples and (if applicable) the date(s) of consent, by completing the Sample Informed Consent/Withdrawal eCRF.

In the event of an RBR participant's death or loss of competence, the participant's samples and data will continue to be used as part of the RBR research.

8.10.7 Withdrawal from the Research Biosample Repository

Participants who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the Sample Informed Consent/Withdrawal eCRF. If a patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global.rcr-withdrawal@roche.com

A patient's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a patient's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

8.10.8 Monitoring and Oversight

All RBR samples will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to an individual's participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

9. STATISTICAL CONSIDERATIONS

The primary analysis will be performed after the last patient completes the Week 12 visit or withdraws. The analysis will be performed by the Sponsor. Significance testing of the primary and secondary endpoints will account for multiplicity and control family-wise type I error. All hypothesis tests will be 2-sided unless otherwise specified.

9.1 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.

9.2 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 3% dropout by the end of study. Approximately 68 will be randomized to receive fenebrutinib and 34 randomized to receive placebo.

9.3 ANALYSIS SETS

All patients

*E*fficacy 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.

9.4 STATISTICAL ANALYSES

The Statistical Analysis Plan (SAP) will be finalized prior to unblinding and database lock for the primary analysis, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints.

9.4.1 General Considerations

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.

9.4.2 Primary Endpoint(s)

The primary endpoint is the total number of new T1 Gd+ lesions observed on MRI scans of the brain at Weeks 4, 8, and 12. The total number of *new* T1 Gd−enhanced lesions is

the sum of the individual number of *new* T1 Gd−enhanced lesions at Weeks 4, 8, and 12.

The primary estimand follows a hypothetical strategy and estimates the treatment effect of fenebrutinib versus placebo had the patient not experienced an 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 8.1.1
- 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) (Section 6.3.1). 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 including 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:

- Data after participants withdrawn from treatment will be censored.
- For the intercurrent event of withdrawal from treatment:

  Those withdrawn because of lack of efficacy or death and having no T1 Gd+ lesions are considered as having T1 lesions

  Otherwise, no imputation will be conducted.

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. Sensitivity analyses may also be performed for the primary endpoint and documented in the SAP.

9.4.3 Secondary Endpoints

The estimands for the secondary endpoint of total number of new or enlarging T2 lesions, as defined in Section 3 (Table 3), will follow the same hypothetical strategy and have the same attributes 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.

The secondary endpoint of 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 will use a logistic regression model similar as described for the primary endpoint. A hypothetical strategy will also be used:

- Data after participants withdrawn from treatment will be censored.
- For the intercurrent event of withdrawal from treatment:

  Those withdrawn because of lack of efficacy or death and having no T1 Gd+ lesions or new or enlarging T2 lesions are considered as not free from lesions.

  Otherwise, no imputation will be conducted.

Safety will be assessed through summaries of exposure to study treatment, adverse events, changes in laboratory test results, and changes in vital signs.

All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities thesaurus terms, and adverse event severity will be graded according to the most current version of 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 sign (pulse rate, respiratory rate, blood pressure, pulse oximetry, and temperature) will be displayed by time, with grades identified where appropriate. 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.

9.4.4 Exploratory Endpoints

Analyses on exploratory efficacy endpoints will be performed as data allows and further details will be described in the SAP.

9.4.5 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.

9.4.6 Other Analyses

9.4.6.1 Summaries of Conduct of Study

Enrollment, study treatment administration, and discontinuation from the study will be summarized by treatment arm. The reasons for study treatment discontinuation will also be tabulated. Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be summarized by treatment arm.

9.4.6.2 Summaries of Treatment Group Comparability

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.

9.4.6.3 Pharmacokinetic Analyses

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. Relationships between PK and PD, efficacy, and safety endpoints may be explored.

Additional PK analyses will be conducted as appropriate and as specified in the SAP. The exploratory PK analyses may be reported separately.

9.5 INTERIM ANALYSIS

There is no plan to conduct interim analysis.

9.6 INDEPENDENT DATA MONITORING COMMITTEE

Refer to Section 4.1 for information on the iDMC for this study.

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Appendix 1
Regulatory, Ethical, and Study Oversight Considerations

TABLE OF CONTENTS

A1-1. Regulatory and Ethical Considerations
A1-2. Financial Disclosure
A1-3. Informed Consent Process
A1-4. Data Protection
A1-5. Administrative Structure
A1-6. Dissemination of Clinical Study Data
A1-7. Data Quality Assurance
A1-8. Source Documents
A1-9. Study and Site Closure
A1-10. Publication Policy
A1-11. Protocol Deviations

A1–1. REGULATORY AND ETHICAL CONSIDERATIONS

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences international ethical guidelines
- Applicable International Council for Harmonisation (ICH) Guideline for Good Clinical Practice
- Applicable laws and regulations

The protocol, Informed Consent Form, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an Institutional Review Board or Ethics Committee (IRB/EC) by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any substantial amendments to the protocol will require IRB/EC and health authority approval (as locally required) before implementation of changes, with the exception of administrative changes or changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
- Notifying the IRB/EC of serious adverse events or other significant safety findings, as required by IRB/EC procedures
- Providing oversight of the conduct of the study at the site and ensuring adherence to requirements of 21 CFR (U.S. sites only), the ICH Guideline for Good Clinical Practice, the IRB/EC, Regulation (E.U.) No. 536/2014 (E.U. sites only), and all other applicable local regulations

A1–2. FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 4.4).

A1–3. INFORMED CONSENT PROCESS

The investigator or authorized designee will explain the nature of the study to the patient or his or her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50 (U.S. sites only), the ICH Guideline for Good Clinical Practice, and the IRB/EC.

The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the Informed Consent Form.

If the Informed Consent Form is revised (through an amendment or an addendum) to communicate information that might affect a patient's willingness to continue in the study, the patient or the patient's legally authorized representative must re-consent by signing the most current version of the Informed Consent Form or the addendum, in accordance with applicable laws and IRB/EC policy.

A copy of each Informed Consent Form must be provided to the patient or the patient's legally authorized representative.

Participants who are re-screened are required to sign a new Informed Consent Form.

The Informed Consent Form will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each patient the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a patient's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.

A1–4. DATA PROTECTION

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. In the event of a data security breach, appropriate mitigation measures will be implemented.

Participants will be assigned a unique identifier by the Sponsor. Any patient records or datasets that are transferred to the Sponsor will contain the identifier only; the patient's name or any information that would make the patient identifiable will not be transferred.

Participants must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to participants, who will be required to give consent for their data to be used as described in the Informed Consent Form.

Participants must be informed that their medical records may be examined by auditors or other authorized individuals representing the Sponsor or Sponsor collaborators and licensees, by appropriate IRB/EC members, and by inspectors from health authorities.

A1–5. ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 35 sites globally will participate to enroll approximately *102* participants. Enrollment and randomization will occur through an interactive voice or web-based response system.

Central facilities will be used for certain assessments throughout the study (e.g., specified laboratory tests, biomarker and pharmacokinetic analyses), as specified in Section 8 and Appendix 2. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected. When discussed with the Sponsor or its CRO, local laboratory tests can be used instead of central laboratory tests in certain situations (e.g., urgent safety evaluations, lack of an adequate collection kit at the site).

An iDMC will be employed to monitor and evaluate patient safety throughout the study. An IRF will collect, store, and potentially review imaging data.

A1–6. DISSEMINATION OF CLINICAL STUDY DATA

Study data, which may include imaging data, may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and*/or* other summar*ies of clinical study results may be available in heath authority databases for public access as required by local regulation, and* will be provided upon

request. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following website:

https://www.roche.com/innovation/process/clinical-trials/data-sharing/

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or participants unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication.

A1–7. DATA QUALITY ASSURANCE

All patient data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided prior to study initiation, in the various functional monitoring plans (including, but not limited to, Quality Tolerance Limit Management Plan and Trial Monitoring Plan).

The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).

Study monitors will perform ongoing monitoring activities as specified in the Trial Monitoring Plan to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, the ICH Guideline for Good Clinical Practice, and all applicable regulatory requirements.

Records and documents pertaining to the conduct of this study, including signed Informed Consent Forms, must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

The Sponsor will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

A1–8. SOURCE DOCUMENTS

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the Case Report Form (CRF) or entered in the electronic Case Report Form (eCRF) that are transcribed from source documents must be consistent with the source documents, or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the Trial Monitoring Plan.

A1–9. STUDY AND SITE CLOSURE

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a site closure visit has been performed.

The investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include, but are not limited to, the following:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the Sponsor's procedures, or the ICH Guideline for Good Clinical Practice
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IRBs/ECs, the health authorities, and any contract research organizations used for the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participants and should ensure appropriate patient therapy and/or follow-up.

A1–10. PUBLICATION POLICY

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of results of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

A1–11. PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

Appendix 2
Clinical Safety Laboratory Tests

The tests detailed in Table A2-1 will be performed by the central laboratory, with the exception of the urine pregnancy test which will be performed at the site.

Local laboratory results are only required in the event that the central laboratory results are not available in time for study treatment administration and/or response evaluation. If a local sample is required, it is important that a sample for central analysis be obtained at the same time. Additionally, if the local laboratory results are used to make either a study treatment decision or a response evaluation, the results must be entered on the electronic Case Report Form.

Additional tests may be performed at any time during the study if determined to be necessary by the investigator or if required by local regulations.

Table A2-1 Protocol-Required Safety Laboratory Assessments

Central Laboratory Tests
• Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells). • Chemistry panel (serum or plasma): bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total and direct bilirubin, ALP, ALT, AST, urate, and LDH, amylase, lipase*, and GGT*. • Coagulation: INR, aPTT, and PT • HIV serology: HIV-1 antibody/HIV-1/2 antibody/HIV-2 antibody • HBV serology: HBsAg, HBsAb, and total HBcAb for all individuals; HBV DNA for individuals with negative HBsAg and HBsAb tests and a positive total HBcAb test Individuals with a positive quantitative HBV DNA at screening (must be < 500 IU/mL per the eligibility criteria) will undergo additional HBV DNA tests as outlined in the schedule of activities (see Section 1.3). • HCV serology: HCV antibody for all individuals; HCV RNA for individuals with a positive HCV antibody test • Lipids: cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides • Quantitative immunoglobulins: IgA, IgG, and IgM • Pregnancy test All women of childbearing potential will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. • Urinalysis, including dipstick (pH, specific gravity, glucose, protein, ketones, and blood) and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, and bacteria) • Tuberculosis test: QuantiFERON®-TB Gold Note: This test should be performed at the central laboratory; however, in the event of extenuating circumstances and with Sponsor approval, an appropriately accredited local laboratory may be used, and Roche will collect the results.
Local Laboratory Tests
• Urine pregnancy tests will be performed at screening and specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus.

Investigators must document their review of each laboratory safety report.

Laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel {until the study has been unblinded}.

Appendix 3
Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

TABLE OF CONTENTS

A3-1. Definition of Adverse Event
A3-2. Definition of Serious Adverse Event
A3-3. Recording and Follow-Up of Adverse Events and Serious Adverse Events
A3-3.1 Adverse Event and Serious Adverse Event Recording
A3-3.2 Assessment Of Severity
A3-3.3 Assessment of Causality
A3-3.4 Follow-Up of Adverse Events and Serious Adverse Events
A3-3.4.1 Investigator Follow-Up
A3-3.4.2 Sponsor Follow-Up
A3-4. Reporting of Serious Adverse Events
A3-4.1 Serious Adverse Event Reporting to the Sponsor via an Electronic Collection Tool
A3-4.2 Serious Adverse Event Reporting to the Sponsor via Paper CRF
A3-5. Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest
A3-5.1 Events That Occur prior to Study Treatment Initiation
A3-5.2 Events That Occur after Study Treatment Initiation
A3-6. Reporting Adverse Events That Occur after the Adverse Event Reporting Period
A3-7. Procedures for Recording Adverse Events
A3-7.1 Diagnosis Versus Signs and Symptoms
A3-7.2 Adverse Events That Are Secondary to Other Events
A3-7.3 Persistent of Recurrent Adverse Events
A3-7.4 Abnormal Laboratory Values
A3-7.5 Abnormal Vital Sign Values
A3-7.6 Abnormal Liver Enzymes and Function Tests
A3-7.7 Deaths
A3-7.8 Preexisting Medical Conditions
A3-7.9 Lack of Efficacy or Worsening of Multiple
A3-7.10 Hospitalization or Prolonged Hospitalization
A3-7.11 Cases of Overdose , Medication Error, Drug Abuse, or Drug Misuse

A3–1. DEFINITION OF ADVERSE EVENT

Adverse Event Definition

An adverse event is any untoward medical occurrence in a patient or clinical study patient temporally associated with the use of a study treatment, whether or not considered related to the study treatment.

Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the Adverse Event Definition

The following events meet the definition of adverse event:

- Any clinically relevant, abnormal laboratory test results (hematology, clinical chemistry, or urinalysis), or other safety assessments (e.g., ECG, radiological scans, vital sign measurements), including those that worsen from baseline. Refer to Section 8.2.4 for reporting requirements of abnormal laboratory results as adverse events.
- Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition
- New condition detected or diagnosed after study treatment administration, even though it may have been present before the start of the study
- Signs, symptoms, or clinical sequelae of a suspected drug–drug interaction
- Signs, symptoms, or clinical sequelae of a suspected overdose of either study treatment or a concomitant medication

  Overdose per se will not be reported as an adverse event or serious adverse event unless it is an intentional overdose taken with possible suicidal or self-harming intent. Such overdoses should be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an adverse event or serious adverse event. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an adverse event or serious adverse event if they fulfill the definition of an adverse event or serious adverse event.

Events NOT Meeting the Definition of Adverse Event

The following events do not meet the definition of adverse event:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient's condition
- The disease or disorder being studied or expected progression, including MS relapses, signs, or symptoms of the disease or disorder being studied, unless more severe than expected for the patient's condition
- Medical or surgical procedure (e.g., endoscopy, appendectomy)

  The condition that leads to the procedure is the adverse event.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of a preexisting disease or condition present or detected at the start of the study that do not worsen

A3–2. DEFINITION OF SERIOUS ADVERSE EVENT

If an event is not an adverse event per the definition in Section A3–1, it cannot be a serious adverse event even if serious conditions are met (e.g., hospitalization for signs or symptoms of the disease under study, death due to progression of disease).

A serious adverse event is defined as any untoward medical occurrence that, at any dose:

- Results in death
- Is life threatening

  The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization

  In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are adverse events. If a complication prolongs hospitalization or fulfills any other seriousness criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event should be considered serious.

  Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an adverse event.

- Results in persistent disability or incapacity

  The term "disability" means a substantial disruption of a person's ability to conduct normal life functions.

  This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly or birth defect
- Other situations:

  Medical or scientific judgment should be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE]; see Section A3–3.2); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the electronic Case Report Form (eCRF).

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event) (see Section A3–5 for reporting instructions).

A3–3. RECORDING AND FOLLOW-UP OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

A3–3.1 ADVERSE EVENT AND SERIOUS ADVERSE EVENT RECORDING

When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The investigator will then record all relevant adverse event or serious adverse event information on the eCRF.

It is **not** acceptable for the investigator to send photocopies of the patient's medical records to the Sponsor in lieu of completion of the Adverse Event eCRF.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before submission to the Sponsor.

The investigator will attempt to establish a diagnosis of the event on the basis of signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs or symptoms) will be documented as the adverse event or serious adverse event.

A3–3.2 ASSESSMENT OF SEVERITY

The investigator will assess the severity of each adverse event reported during the study through use of the NCI CTCAE (v5.0) grading scale. The investigator will use the grading scale in Table 1 for assessing the severity of adverse events that are not specifically listed in the NCI CTCAE.

Table A3-1 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute.
Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Examples of instrumental activities of daily living include preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by participants who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section A3–5 for reporting instructions), per the definition of serious adverse event in Section A3–2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section A3–5 for reporting instructions), per the definition of serious adverse event in Section A3–2.

A3–3.3 ASSESSMENT OF CAUSALITY

The investigator is obligated to assess the relationship between study treatment and each occurrence of each adverse event or serious adverse event.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying diseases, concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration, will be considered and investigated.

The investigator will also consult the Investigator's Brochure and/or prescribing information (for marketed products) in his or her assessment.

For each adverse event or serious adverse event, the investigator **must** document in the medical notes that he or she has reviewed the adverse event or serious adverse event and has provided an assessment of causality.

There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data to the Sponsor.

The investigator may change his or her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

A3–3.4 FOLLOW-UP OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

A3–3.4.1 Investigator Follow-Up

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathologic examinations, or consultation with other health care professionals.

If a patient dies during participation in the study or during a recognized follow-up period, the investigator will provide the Sponsor with a copy of any post-mortem findings, including histopathology.

New or updated information will be recorded in the originally completed CRF.

The investigator will submit any updated serious adverse event data to the Sponsor within 24 hours of receipt of the information. New or updated information should be recorded on the originally completed Adverse Event eCRF. For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results

- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

During the adverse event reporting period (defined in Section 8.3.1), resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

A3–3.4.2 Sponsor Follow-Up

For serious adverse events and adverse events of special interest, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

A3–4. REPORTING OF SERIOUS ADVERSE EVENTS

A3–4.1 SERIOUS ADVERSE EVENT REPORTING TO THE SPONSOR VIA AN ELECTRONIC COLLECTION TOOL

The primary mechanism for reporting a serious adverse event to the Sponsor will be the electronic data collection tool, as described in Section A3–5.

If the electronic system is unavailable, the site will use the paper *Clinical trial Adverse Event/Special Situations Form*, as described in Section A3–5, to report the event within 24 hours.

The site will enter the serious adverse event data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the electronic data collection tool will be taken off line to prevent the entry of new data or changes to existing data.

If a site receives a report of a new serious adverse event from a study patient or receives updated data on a previously reported serious adverse event after the electronic data collection tool has been taken off line, the site can report this information on a paper *Clinical trial Adverse Event/Special Situations Form*, as described in Section A3–5.

A3–4.2 SERIOUS ADVERSE EVENT REPORTING TO THE SPONSOR VIA PAPER CRF

Under certain circumstances, serious adverse events may be reported to the Sponsor through use of a paper *Clinical trial Adverse Event/Special Situations Form*, as described in Section A3–5.

A3–5. REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS AND ADVERSE EVENTS OF SPECIAL INTEREST

A3–5.1 EVENTS THAT OCCUR PRIOR TO STUDY TREATMENT INITIATION

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention (e.g., biopsy, discontinuation of medications) should be reported. The paper Clinical Trial Adverse Event/*Special Situations* Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either by faxing or by scanning and emailing the form, using the fax number or email address provided to investigators.

A3–5.2 EVENTS THAT OCCUR AFTER STUDY TREATMENT INITIATION

After initiation of study treatment, serious adverse events and adverse events of special interest will be reported 4 weeks after the final dose of study treatment. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after the investigator becomes aware of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Adverse Event/*Special Situations* Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either by faxing or by scanning and emailing the form, using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur more than 4 weeks after the final dose of study treatment are provided in Section A3–6.

A3–6. REPORTING ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 4 week after the final dose of study treatment), if the event is believed to be related to prior exposure to study treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Adverse Event/*Special Situations* Form, using the fax number or email address provided to investigators.

A3–7. PROCEDURES FOR RECORDING ADVERSE EVENTS

When an adverse event occurs, it is the responsibility of the investigator to review all documentation related to the event (e.g., hospital progress notes, laboratory reports, and diagnostics reports). The investigator will then record all relevant adverse event information on the Adverse Event eCRF. It is not acceptable for the investigator to send photocopies of the patient's medical records to the Medical Monitor in lieu of completion of the eCRF. Investigators should use correct medical terminology and concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations. Only one adverse event term should be recorded in the event field of the Adverse Event eCRF.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before submission to the Sponsor.

A3–7.1 DIAGNOSIS VERSUS SIGNS AND SYMPTOMS

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

A3–7.2 ADVERSE EVENTS THAT ARE SECONDARY TO OTHER EVENTS

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

A3–7.3 PERSISTENT OF RECURRENT ADVERSE EVENTS

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware that the event became serious; see Section A3–5 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

A3–7.4 ABNORMAL LABORATORY VALUES

Not every abnormal laboratory value qualifies as an adverse event. A laboratory value abnormality that is associated with the underlying disease should not be reported as an adverse event unless judged by the investigator to be more severe than expected.
A laboratory value abnormality that is not associated with the underlying disease must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dose modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment
- ALT or AST $> 3 \times$ upper limit of normal (ULN) unless this is attributed to a specific clinical diagnosis that is to be reported as the primary adverse event term

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event (except for ALT/AST $> 3 \times$ ULN, which must always be reported as an adverse event in this protocol).

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin $5 \times$ ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section A3–7.4 for details on recording persistent adverse events).

A3–7.5 ABNORMAL VITAL SIGN VALUES

Not every abnormal vital sign value qualifies as an adverse event. A vital sign abnormality that is associated with the underlying disease should not be reported as an adverse event unless judged by the investigator to be more severe than expected.

A vital sign abnormality that is not associated with the underlying disease must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dose modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (e.g., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section A3–7.4 for details on recording persistent adverse events).

A3–7.6 ABNORMAL LIVER ENZYMES AND FUNCTION TESTS

An elevated ALT and/or AST ($>3\times$ULN) must be reported as an adverse event in this protocol (refer to table A6-1).

- *Cases of potential drug-induced liver injury that include an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice, as defined by Hy's Law (refer to Table A6-1).*
- *Cases of elevated ALT and/or AST 3–5 $\times$ ULN, INR >1.5, total bilirubin $\leq 2\times$ULN, and absence of clinical jaundice*
- *Cases of elevated ALT and/or AST 5–8 $\times$ ULN, total bilirubin $\leq 2\times$ULN and absence of clinical jaundice*
- *Cases of ALT or AST $>8\times$ULN, total bilirubin $\leq 2\times$ULN and absence of clinical jaundice*

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section A3–7.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either as a serious adverse event or an adverse event of special interest (see Section A3–5).

Abnormal liver enzymes will warrant close observation and ruling out of alternative causes (refer to Table A6-1 and Appendix 7).

A3–7.7 DEATHS

All deaths that occur during the protocol-specified adverse event reporting period (see Section 8.3.1), regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section A3–5). This includes death attributed to an MS relapse.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

If the death is attributed solely to progression of multiple sclerosis, "multiple sclerosis progression" should be recorded on the Adverse Event eCRF. Deaths that occur after the adverse event reporting period should be reported as described in Section A3–6.

A3–7.8 PREEXISTING MEDICAL CONDITIONS

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

A3–7.9 LACK OF EFFICACY OR WORSENING OF MULTIPLE SCLEROSIS

Medical occurrences or symptoms of deterioration that are anticipated as part of the expected pattern of progression of the underlying disease, or other MS-related symptoms should not be recorded as adverse events. Clinical MS relapses will be recorded on a dedicated eCRF. However, deterioration that is judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study should be recorded as an adverse event. If there is any

uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event. When recording an unanticipated worsening of MS on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors. Occasional isolated symptoms that according to the investigator are caused by MS, but do not constitute a full MS relapse, should be reported as an adverse event, with the causality "Disease under study" (see Section A3–5).

A3–7.10 HOSPITALIZATION OR PROLONGED HOSPITALIZATION

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section A3–2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Planned hospitalization required by the protocol unless prolonged
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The patient was hospitalized for an elective procedure that was planned prior to the study, was scheduled during the study despite the fact that the condition had not worsened, or was scheduled during the study when treatment became necessary because of the expected normal progression of the condition. Such events should still be recorded as medical procedures in the On Study Surgeries and Procedures eCRF.

  The patient has not experienced an adverse event
- Hospitalization following an MS relapse as long as the reason for hospitalization is to receive standard treatment with high dose corticosteroids

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

A3–7.11 CASES OF OVERDOSE , MEDICATION ERROR, DRUG ABUSE, OR DRUG MISUSE

Overdose (accidental or intentional), medication error, drug abuse, and drug misuse (hereafter collectively referred to as "special situations") are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Intentional overdose: intentional administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.
- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm
- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse

  In cases where drug is to be self administered by the patient, drug misuse could involve the drug being administered to someone other than the patient.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria or qualifies as an adverse event of special interest, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5). For fenebrutinibmatching placebo, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the adverse event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Drug abuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug abuse" box.

- Drug abuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug misuse" boxes.

In addition, all special situations associated with fenebrutinib and matching placebo, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter fenebrutinib and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter fenebrutinib and "intentional overdose" as the event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter fenebrutinib and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter fenebrutinib and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.
- Drug abuse that does not qualify as an overdose: Enter fenebrutinib and "drug abuse" as the event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter fenebrutinib and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the fenebrutinib and "drug misuse" as the event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter fenebrutinib and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug misuse" boxes.
- Drug administered to someone other than the patient: Enter fenebrutinib and "patient supplied drug to third party" as the event term. Check the "Drug misuse" box.

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

Appendix 4
Contraceptive and Barrier Guidance

TABLE OF CONTENTS

A4-1. Pregnancies in Female Participants
A4-2. Pregnancies In Female Partners Of Male Participants
A4-3. Abortions
A4-4. Abnormal Pregnancy Outcomes

A4–1. PREGNANCIES IN FEMALE PARTICIPANTS

Female participants of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 4 weeks after the final dose of fenebrutinib. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after the investigator becomes aware of the pregnancy), either by faxing or by scanning and emailing the form, using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the participant, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the participant should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly or birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

A4–2. PREGNANCIES IN FEMALE PARTNERS OF MALE PARTICIPANTS

Male participants will be instructed through the Informed Consent Form to immediately inform the investigator if a female partner becomes pregnant during the study or within 4 weeks after the final dose of fenebrutinib. The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male participant exposed to study treatment. When permitted by the site, the pregnant partner would need to sign an Authorization for the Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

An investigator who is contacted by the male participant or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

A4–3. ABORTIONS

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

A4–4. ABNORMAL PREGNANCY OUTCOMES

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomaly, birth defect, ectopic pregnancy) in a female participant exposed to study treatment or the female partner of a male participant exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5).

Appendix 5
Genetics: Use and Analysis of DNA

Genetic biomarker assessments will not be performed in this study.

Appendix 6
Safety Plan: Management of Identified and Potential Risks

Fenebrutinib is not approved, and clinical development is ongoing. The safety plan for participants in this study is based on clinical experience with fenebrutinib in completed and ongoing studies. The anticipated important safety risks for fenebrutinib are outlined below. Please refer to the Fenebrutinib Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of study participants. Eligibility criteria have been designed to exclude individuals at higher risk for toxicities. Participants will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for treatment interruption or discontinuation, are provided below.

A6–1. RISKS ASSOCIATED WITH FENEBRUTINIB

A6–1.1 HEPATIC TRANSAMINASE ELEVATIONS

In clinical Phase 2 studies to date, participants treated with fenebrutinib have been found to be at an increased risk of transaminase elevations than participants on placebo.

Between 1% and 10% of participants in the fenebrutinib 200 mg BID treatment arms of blinded randomized studies and OLEs experienced Grade 2 or higher transaminase elevations (ALT/AST of 3-5 × ULN or higher), compared with fewer than 1% of participants in the placebo arms across studies.

Participants enrolled in clinical trials with fenebrutinib will be monitored for the risk of hepatotoxicity with regular measurement of transaminases as outlined in the schedules of activities (see Table 1). They should receive appropriate supportive care as clinically indicated, with hepatotoxicity managed in accordance with the study protocols and site institutional guidelines. Cases of potential drug-induced liver injury that include *the categories below must be reported to Sponsor as an adverse event of special interest within 24 hours of awareness (see Section 8.3.8).*

- *Cases of elevated ALT or AST (3 × ULN) in combination with either an elevated total bilirubin (> 2 × ULN) or clinical jaundice, as defined by Hy's Law (see A3□7.6)*
- *Cases of an elevated ALT and/or AST 3–5 × ULN, INR > 1.5, total bilirubin ≤ 2 × ULN, and absence of clinical jaundice*
- *Cases of elevated ALT and/or AST 5-8 x ULN, total bilirubin ≤ 2 x ULN and absence of clinical jaundice*
- *Cases of elevated ALT and/or AST > 8 x ULN, total bilirubin ≤ 2 x ULN and absence of clinical jaundice*

Guidelines for management of study treatment in the event hepatic transaminase elevation/hepatotoxicity is observed in participants are provided in Table A6–1 *and Appendix 7*.

A6–1.2 INFECTIONS

Fenebrutinib is a reversible antagonist of BTK signaling in immune cells (B cells, myeloid cells, but not T cells) that may lead to immunomodulatory effects and an increased risk of infection in healthy participants. Infections, including pneumonia and fatal influenza infections, have occurred in adult participants with B-cell malignancies treated with fenebrutinib. Serious infections, including a case of tuberculosis (TB), have been reported in blinded, open-label, and completed studies of fenebrutinib in autoimmune indications. As a safety precaution, the study protocol contains exclusion criteria for infections (including chronic infections such as hepatitis B) and potential infection risk and guidelines for study treatment management in the event of infection.

All participants in the study should be monitored for fever and potential infectious complications, including opportunistic infections and TB, and should be evaluated promptly. Physicians or a health care provider should give participants advice to prevent potential transmission of and exposure to endemic infections according to local or Centers for Disease Control and Prevention guidelines. Participants should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of an infection. All infections occurring during the study, including, but not limited to, respiratory infections, cutaneous infections, urinary tract infections, systemic viral infections, and episodes of suspicious or febrile diarrhea, should be evaluated using serology or polymerase chain reaction, if available, and cultured, if feasible, and any identified organisms noted in the eCRF.

Guidelines for management of study treatment in the event that infections are observed in participants are provided in Table A6-1.

A6–1.3 HEPATOTOXICITY

Based on the clinical data, transaminase elevations are considered a risk associated with fenebrutinib (see Section A6-1.1). Hepatotoxicity is a potential risk as it is unknown whether more severe drug-induced liver injury can be caused by fenebrutinib.

Guidelines for management of study treatment in the event of hepatic transaminase elevations/hepatotoxicity is observed in participants are provided in Table A6-1 *and Appendix 7*, and refer to the Fenebrutinib Investigator's Brochure for further details.

A6–1.4 EFFECT ON VACCINATIONS

The effect of fenebrutinib upon the efficacy of vaccinations is unknown. It is recommended that appropriate vaccinations for per local guidelines be up to date before study participation. Refer to Section 5.2 for the exclusion criteria and Section 6.8.5 for vaccination requirements. In addition, immunization with a live or live-attenuated vaccine is prohibited for the duration of study participation, including during the safety follow-up (SFU).

A6–1.5 BLEEDING

The effect of BTK inhibition as a potential risk factor for bleeding is unknown. Bleeding was not observed in nonclinical studies with fenebrutinib. Bleeding events, including Grade $\geq$ 3 GI bleeding, have been reported in participants with hematological cancer treated with fenebrutinib, and Grade $\geq$ 2 bleeding has been reported in participants enrolled in blinded studies for autoimmune diseases.

See Section 5.1 and Section 5.2 for inclusion and exclusion criteria regarding bleeding risk. Participants should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of clinically significant bleeding.

Guidelines for management of study treatment in the event that bleeding is observed in participants are provided in Table A6-1. Refer to the Fenebrutinib Investigator's Brochure for further details.

A6–1.6 CYTOPENIAS

Cytopenias have been observed in the ongoing Phase I study of fenebrutinib in oncology participants (Study GO29089) and in the completed Phase II studies of fenebrutinib in participants with rheumatoid arthritis (RA) (Studies GA29350 and GA30067) and systemic lupus erythematosus (SLE) (Studies GA30044 and GA30066). The cytopenias have been monitorable and clinically manageable, although some participants with SLE, enrolled in studies with fenebrutinib, have had protocol-mandated discontinuations because of cytopenias. Participants should be monitored regularly with hematology laboratory evaluations, as outlined in the schedules of activities (see Section 1.3), and should receive appropriate supportive care as clinically indicated. Participants should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of cytopenias (e.g., persistent fever, bruising, bleeding, pallor). Cytopenias should be managed according to local clinical guidelines.

Guidelines for managing study treatment in the event that cytopenia is observed are provided in Table A6-1. Refer to the Fenebrutinib Investigator's Brochure for further details.

A6–1.7 GASTROINTESTINAL EFFECTS

Reversible body weight gain and food consumption changes have been observed in animals. Mild diarrhea, nausea, and abdominal pain have been reported in participants with B-cell malignancies; however, the events have resolved and have not led to study treatment discontinuation. Healthy participants in the multiple-ascending dose Study GA29347 reported events of mild self-limited nausea. Across studies with immune indications receiving blinded or open-label treatment, approximately 5% of enrolled participants have reported nausea, vomiting, diarrhea, or other GI symptoms; these events occurred with similar frequencies in the fenebrutinib and placebo arms.

Throughout the study, participants will be monitored for GI adverse events. Symptomatic treatment according to the investigator's clinical judgment should be provided. Refer to the Fenebrutinib Investigator's Brochure for further details.

A6–1.8 CARDIOVASCULAR EFFECTS

Fenebrutinib is considered to have a low potential to cause QT interval prolongation or to directly affect other cardiovascular parameters in humans at therapeutic exposures.

Analysis of ECG data from the single-and multiple-ascending dose studies in healthy participants did not demonstrate any significant increase in either QRS interval or QTcF intervals. However, cardiac safety will be evaluated in all participants at baseline and throughout this study, with routine monitoring of vital signs (including heart rate and blood pressure), routine safety ECGs, and collection of adverse events, until ECG effects can be ruled out (see Section 8.3.6 and Section 8.2.3).

For management of participants with sustained QTcF prolongation (QTcF that is $>$500 ms or $>$60 ms longer than the baseline value), see Section 8.3.6 and Section A6-2.4. The investigator should also evaluate the patient for potential concurrent risk factors (e.g., electrolyte abnormalities, concomitant medications known to prolong the QT interval, severe bradycardia). Refer to the Fenebrutinib Investigator's Brochure for further details.

A6–1.9 VASCULAR INFLAMMATION

Vascular inflammation (vasculitis) was observed in dogs administered fenebrutinib in the 4-week toxicity study, and these changes were not completely reversed by the end of the 4-week recovery period; however, these changes were not observed in the 9-month toxicity study. The translatability of these findings to humans is unknown; however, Beagle dogs are susceptible to spontaneous development of polyarteritis syndrome (Snyder et al. 1995) and may be more sensitive to any drug-induced effects. All participants enrolled in the study will be monitored for adverse events suggestive of vasculitis as part of routine monitoring. Creatinine, complete blood count, and urinalysis

are monitored in participants as outlined in schedules of activities (see Section 1.3). Refer to the Fenebrutinib Investigator's Brochure for further details.

A6–1.10 MALIGNANCY

The effect of BTK inhibition on the development of malignancies is not known; however, malignancies have been identified as a potential concern for immunomodulatory agents. Malignancies have been reported in participants with X-linked agammaglobulinemia (XLA), including lymphoreticular malignancies, gastric and colorectal adenocarcinoma, and squamous cell carcinoma of the lung. No hyperplastic or neoplastic changes have been observed in nonclinical toxicology studies of fenebrutinib up to 4 weeks duration. Malignancies have been observed in participants enrolled in clinical trials of fenebrutinib in immune indications (RA and SLE). Based on the limited clinical experience to date (short studies that cannot adequately characterize the risk of malignancy, no obvious pattern of malignancies was observed), it is not possible to determine if fenebrutinib may have played a role in the development of any of the malignancies.

Participants with a history of cancer, including hematologic malignancy and solid tumors, within 10 years of screening will be excluded from the study. Basal or squamous cell carcinoma of the skin that has been excised and is considered cured and in situ carcinoma of the cervix treated with apparent success by curative therapy more than 1 year prior to screening are not exclusionary.

Participants should follow local, age-appropriate cancer screening recommendations. Guidelines for management of participants who develop malignancies are provided in Table A6-1. Refer to the Fenebrutinib Investigator's Brochure for further details.

A6–1.11 EMBRYO-FETAL TOXICITY

Based on data from animal models, fenebrutinib is currently classified as a suspected teratogen. Fetal malformations, including domed heads, considered the result of dilated ventricles in the brain, and multiple malformations (gastroschisis and cardiovascular malformations) in one animal were seen in rabbits in the Segment II studies. In rats, cleft palate and fetal skeletal variations consisting of changes in the numbers of ossification sites (increased thoracic vertebrae; reduced lumbar vertebrae) contributed to an increased number of ribs that were seen in the Segment II studies. Maternal toxicity, consisting of body weight changes (i.e., reduced gain or loss) and reduced food consumption was observed in rabbit does and rat dams. Seven pregnancies have occurred in women enrolled in clinical trials of fenebrutinib. There have been no reports to date of fetal malformations. Fenebrutinib should not be administered to pregnant women or to women trying to become pregnant (see Section 5.1 and Section 4.1 for details). See Section 5.2 and Section 4.1 for details for women who are pregnant, nursing (breastfeeding), or intending to become pregnant. All participants must adhere

to the protocol contraception guidelines. For pregnancy testing requirements and contraceptive guidelines, see Section 5.1 and Section 4.1.

See Section 5.3.4 for male contraception requirements.

Refer to the Fenebrutinib Investigator's Brochure for further details.

A6–2. MANAGEMENT OF PARTICIPANTS WHO EXPERIENCE ADVERSE EVENTS

A6–2.1 DOSE MODIFICATIONS

Dose modifications are not allowed.

A6–2.2 TREATMENT INTERRUPTION

Fenebrutinib may be withheld in participants who experience toxicity considered to be related to study drug. If fenebrutinib has been withheld for >28 days because of toxicity, the participant should be discontinued from fenebrutinib, unless resumption of treatment is approved by the investigator following consultation with the Medical Monitor. Fenebrutinib may be withheld for reasons other than toxicity (e.g., surgical procedures) at the investigator's discretion following consultation with the Medical Monitor. The investigator may consult the Medical Monitor to determine the acceptable length of treatment interruption.

A6–2.3 MANAGEMENT GUIDELINES

All participants in the study should be monitored for fever and potential infectious complications, including opportunistic infections and tuberculosis, and should be evaluated promptly. Participants should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of an infection.

Participants will be asked to promptly report to the investigator any episode of jaundice, dark urine, or severe abdominal symptoms.

Participants will be asked to promptly report to the investigator any bleeding events.

Guidelines for management of specific adverse events provided in the subsections below are for guidance purposes only and are not intended to supersede the medical opinion of the treating investigator.

Table A6-1 Guidelines for Management of Participants Who Experience Adverse Events

Event	Action to Be Taken
Infection [a]	
Serious Infection	• Withhold study drug during antimicrobial//antiviral treatment. • Study drug may resume following full clinical resolution and re-assessment of benefit-risk for the treated patient.
Bleeding events	
Grade 1 or 2	• Maintain study drug dosing.
Grade ≥ 3	• For Grade ≥ 3 bleeding events, withhold study drug and initiate emergency therapy according to institutional guidelines. Study drug may be resumed after the event resolves.
Neutropenia [b]	
Grade 1 (ANC $<$ LLN–1500/mm^3) or 2 (ANC $<$ 1500–1000/mm/mm$^{3)}$	• Maintain study drug dosing.
Grade 3: ANC $<$ 1000–500/mm^3	• For the first event, hold study drug and recheck CBC in 7 days. • If neutrophil count has recovered to Grade 1 ($>$ 1500/mm^3) or has returned to the normal range, study drug can be resumed. • Discontinue study drug if event persists more than one month or event reoccurs.
Grade 4: ANC $<$ 500 mm^3	• Discontinue study drug.
Thrombocytopenia[c]	
Grade 1: PLT $<$ LLN–75,000/mm^3	• In the absence of bleeding event(s), maintain study drug dosing.
Grade 2: PLT $<$ 75,000–50,000/mm^3	• For the first event, hold study drug and recheck CBC in 7 days. • If platelet count has recovered to Grade 1 or has returned to the normal range, study drug can be resumed. • Discontinue study drug if event persists more than one month or event reoccurs.
Grade ≥ 3: PLT $<$ 50,000/mm^3	• Discontinue study drug.
Malignancy	
Any malignancy	• Discontinue study drug with the exception of non-serious local and resectable basal or squamous cell carcinoma of the skin.

Table A6-1 Guidelines for Management of Participants Who Experience Adverse Events (cont.)

Event	Action to Be Taken
Liver function test elevation	
AST or ALT > 3.0–5.0 × ULN	• Repeat testing of ALT, AST, ALP, total and *direct* bilirubin, *GGT,* CPK, LDH, complete blood count with differential, coagulation tests*, and the "LFT unscheduled" lab kit* within 48–72 hours; inquire about symptoms, co-medications, co-morbidities, and alternative causes *(refer to Appendix 7)*. The medical monitor will provide guidance on additional lab testing that may be required. • If ALT or AST > 3 × ULN is confirmed on repeat testing, continue close observation (repeat testing of ALT, AST, ALP, and total bilirubin) every 48–72 hours until transaminases stabilize, then weekly until AST and ALT < 3 × ULN. Maintain study drug dosing. • If study drug was stopped, re-challenge is allowed. • *Permanently discontinue study drug if AST or ALT > 3.0 × ULN persists for 4 weeks in absence of alternative etiology or if close observation is not possible.* • Record as an adverse event.
AST or ALT > 5.0–8.0 × ULN	• Repeat testing of ALT, AST, ALP, total and *direct* bilirubin, *GGT,* CPK, LDH, complete blood count with differential*,* coagulation tests*, and the "LFT unscheduled" lab kit* within 48–72 hours; inquire about symptoms, co-medications, co-morbidities, and alternative causes *(refer to Appendix 7)*. The medical monitor will provide guidance on additional lab testing that may be required. • Continue close observation (repeat testing of ALT, AST, ALP, and total bilirubin) every 48–72 hours until transaminases stabilize, then weekly until AST and ALT < 3 × ULN. • Discontinue study drug if AST or ALT > 5 × ULN persist more than 2 weeks or if close observation is not possible. • Re-challenge is not permitted. • Report as an adverse event of special interest within 24 hours.

Table A6-1 Guidelines for Management of Participants Who Experience Adverse Events (cont.)

AST or ALT > 8.0 × ULN	• Permanently discontinue study drug. • Repeat testing of ALT, AST, ALP, total and *direct* bilirubin, *GGT,* CPK, LDH, complete blood count with differential*,* coagulation tests *and the "LFT unscheduled" lab kit* within 48–72 hours; inquire about symptoms, co-medications, co-morbidities, and alternative causes *(refer to Appendix 7)*. The medical monitor will provide guidance on additional lab testing that may be required. • Continue close observation (repeat testing of ALT, AST, ALP, and total bilirubin) every 48–72 hours until transaminases stabilize, then weekly until AST and ALT < 3 × ULN. • Report as an adverse event of special interest within 24 hours.
AST or ALT > 3 × ULN in combination with fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (> 5%)	• Permanently discontinue study drug. • Repeat testing of ALT, AST, ALP, total and *direct* bilirubin, *GGT,* CPK, LDH, complete blood count with differential*,* coagulation tests*, and the "LFT unscheduled" lab kit* within 48–72 hours; inquire about symptoms, co-medications, co-morbidities, and alternative causes *(refer to Appendix 7)*. The medical monitor will provide guidance on additional lab testing that may be required. • Continue close observation (repeat testing of ALT, AST, ALP, and total bilirubin) every 48–72 hours until transaminases stabilize, then weekly until AST and ALT < 3 × ULN. • Record as an adverse event or an adverse event of special interest as appropriate.

Table A6-1 Guidelines for Management of Participants Who Experience Adverse Events (cont.)

AST or ALT > 3 × ULN in combination with a total bilirubin > 2 × ULN or INR > 1.5, or clinical jaundice	• Permanently discontinue study drug. • Rapid evaluation, including *repeat testing of ALT, AST, ALP, total and direct bilirubin, GGT, CPK, LDH, complete blood count with differential,coagulation tests, and the "LFT unscheduled" lab kit within 48-72 hours; inquire about symptoms, co-medications, co-morbidities, and* work-up for alternative etiologies, and hepatology or subspecialist consultation is required *(refer to Appendix 7).* The medical monitor will provide guidance on additional lab testing that may be required. • *Continue close observation (repeat testing of ALT, AST, ALP, and total bilirubin) every 48-72 hours until transaminases stabilize, then weekly until AST and ALT < 3 ´ ULN.* • Report as an adverse event of special interest within 24 hours, (see Section 8.3.8).
ALT and/or AST 3-5 × ULN, INR > 1.5, total bilirubin ≤ 2 ´ ULN, and absence of clinical jaundice	• *Permanently discontinue study drug.* • *Rapid evaluation, including repeat testing of ALT, AST, ALP, total and direct bilirubin, GGT, CPK, LDH, complete blood count with differential,coagulation tests, and the "LFT unscheduled" lab kit within 48-72 hours; inquire about symptoms, co-medications, co-morbidities, and work-up for alternative etiologies, and hepatology or subspecialist consultation is required (refer to Appendix 7). The medical monitor will provide guidance on additional lab testing that may be required.* • *Continue close observation (repeat testing of ALT, AST, ALP, and total bilirubin) every 48-72 hours until transaminases stabilize, then weekly until AST and ALT < 3 ´ ULN.* • *Report as an adverse event of special interest within 24 hours, (see Section 8.3.8).*

LFT = liver function test; LLN = lower limit of normal; PLT = platelet count; ULN = upper limit of normal

[a] Appropriate laboratory investigations, including but not limited to cultures, should be performed to establish the etiology of any serious infection.

[b] Patients withdrawn from the study because of a reduced neutrophil count must be followed closely for signs of infection, with treatment as deemed appropriate by the investigator, and must have a repeat WBC count with differential performed weekly until the ANC is above 1000 cells/mm^3 (1.0×10^9/L). If the ANC does not return to above 1000 cells/mm^3 (1.0×10^9/L) within 2 months (or sooner if deemed necessary by the investigator), a hematology referral is recommended.

[c] Patients withdrawn from the study because of a reduced platelet count must have a repeat platelet count checked weekly until the count is above 100,000 cells/mm^3 (100×10^9/L). Additional management and treatment should be as deemed appropriate by the investigator. If the platelets do not return to above 100,000 cells/mm^3 (100×10^9/L) within 2 months (or sooner if deemed necessary by the investigator), a hematology referral is recommended.

A6–2.4 MANAGEMENT OF INCREASES IN QT INTERVAL

Study drug should be discontinued in participants who develop any of the following, unless there is a clear alternative cause for the changes:

- Sustained (at least two ECG measurements $>$30 minutes apart) QT interval corrected through use of Fridericia's formula (QTcF) that is $>$500 ms and/or $>$60 ms longer than the baseline value
- An episode of torsades de pointes or a new ECG finding of clinical concern

Of note, if there is a new intraventricular conduction block, the increase in QRS complex duration should be subtracted from the QTcF change, because this represents an increase in QTcF unrelated to alterations in repolarization. Also of note, it is not uncommon to record arrhythmias such as non-sustained ventricular tachycardia, supraventricular tachycardia, pauses, or atrial fibrillation in healthy volunteers receiving placebo during periods of extended ECG monitoring. Therefore, it is critical that expert cardiology advice be sought to confirm any ECG changes and to ascertain the likelihood of a drug-induced arrhythmia versus the background occurrence of this arrhythmia. In such a situation, saving all available ECG data is highly suggested.

Management of participants with sustained QTcF prolongation should include close monitoring, with ECGs repeated at least hourly until two successive ECGs show resolution of the findings, correction of any electrolyte abnormalities, and possible discontinuation of other concomitant medications that are known to prolong the QT interval. Consultation with a cardiologist or electrophysiologist is recommended, to help in the management of such participants.

Appendix 7

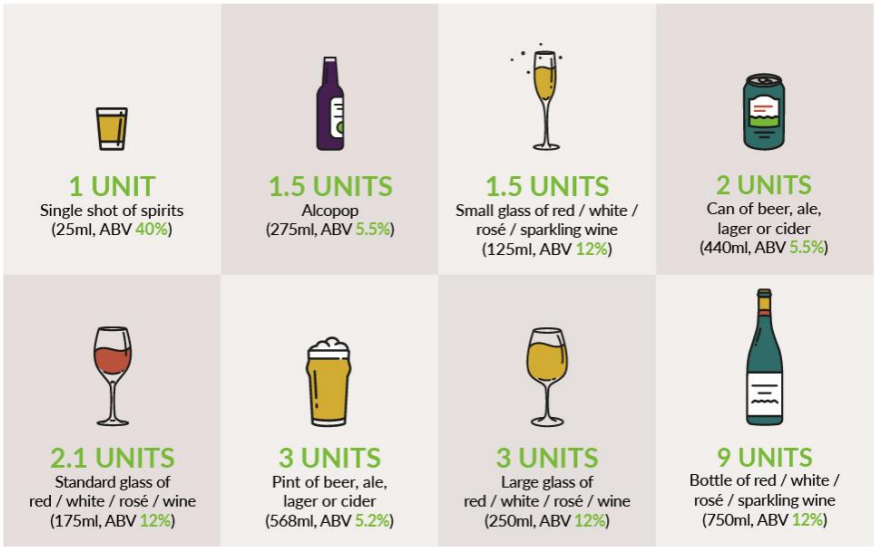
Guidance for Recording Information in eCRFs for Participants with Abnormal Liver Enzyme and Function Tests

For any patient with ALT/AST > 3 ´ ULN, please ask the questions below and record the relevant information in the appropriate eCRF.

Liver Related Signs and Symptoms	
1). Does the subject have any of the following liver-related signs and symptoms?: *a) Fever* *b) Nausea* *c) Vomiting* *d) Abdominal pain* *e) Abdominal tenderness* *f) Joint pain/ arthralgia* *g) Joint swelling* *h) Rash* *i) Urticaria* *j) Mucosal inflammation or ulceration* *k) Asterixis* *l) Confusion/ disorientation* *m) Coma* *n) Jaundice* *o) Ascites* *p) Peripheral oedema* *q) Palmar erythema* *r) Fatigue* *s) Lymphadenopathy* *t) Dark urine* *u) Other liver-related signs or symptoms*	*If **"Yes"** to Question 1:, if ALT/AST >5 x ULN, please report each symptom on the DILI Signs and Symptoms eCRF.* *If ALT/AST > 3 and ≤5 ´ ULN, please report each sign and symptom in the additional case details of the Abnormal Liver Enzyme Adverse Event eCRF (unless a specific diagnosis has been established that accounts for the symptom, in which case the specific diagnosis should be recorded).*

Medical history: Liver-Related Diseases	
2. Does the subject have a history of any of the following? *a) Hepatitis A* *b) Hepatitis B* *c) Hepatitis C* *d) Hepatitis D* *e) Hepatitis E* *f) Autoimmune hepatitis* *g) Haemochromatosis* *h) Non-alcoholic fatty liver disease (NAFLD)* *i) Non-alcoholic steatohepatitis (NASH)* *j) Gallbladder disease (e.g., gallbladder stones, cholecystitis, bile duct stones)* *k) Alcohol-related liver disease (e.g., alcohol related cirrhosis, alcohol related hepatitis, steatosis)* *l) Drug-induced liver injury (DILI) (Specify suspected drugs)* *m) Jaundice or hyperbilirubinaemia* *n) HIV infection* *o) Tuberculosis* *p) Congestive heart failure* *q) Right heart failure* *r) Hepatic metastasis* *s) Diabetes* *t) Inflammatory bowel disease (Crohn's disease or ulcerative colitis)* *u) Hypotension*	*If "Yes" to question 2:* *please report each liver-related disease on the Medical History/Baseline conditions eCRF as per protocol Section 8.2.1*

v) Systemic infection or sepsis
w) Seizures
x) Recent drop in blood pressure or shock
y) Herpes infection
z) Uncontrolled diabetes mellitus

Risk Factors for Conditions Associated with Liver Disease	
Has any of the following occurred within 1 week before the hepatic event?	
3. Did the subject engage in vigorous physical exercise?	*If "Yes"' for Question 3, please record in the "Additional Case Details" field of the hepatic adverse event that was reported.*
4. Has the subject taken acetaminophen (paracetamol)?	*If "Yes" for Questions 4-6: please report on the Concomitant Medications eCRF (as per protocol Section 6.8).*
5. Have any other new medications or supplements been taken?	
6. Did the subject eat wild mushrooms?	
Has any of the following occurred within 3 months before the hepatic event?	
7. Has the subject gained or lost weight considered to be clinically significant?	*If "Yes" for Question 7: please report on an Adverse Event eCRF (unless a diagnosis of liver injury has been established).*
8. Has the subject consumed alcohol?	*If "Yes" for Question 8: please complete the Alcohol Use History eCRF.*
	*Please use chart when providing units in the Alcohol Use History eCRF*
9. Has the subject been exposed to an environmental or industrial toxin or a chemical agent?	*If "Yes" for Question 9, please record in the "Additional Case Details" field of the hepatic adverse event that was reported.*
10. Has the subject received parenteral nutrition?	*If "Yes" for questions 10, please report on the On Study Surgery and Procedure eCRF*

11. Has the subject used recreational drugs or injection drugs? *a) Methamphetamines* *b) Cocaine* *c) Ecstasy* *d) Ketamine* *e) Narcotics* *f) Other, specify*	*If "Yes" for Question 11, please report on the Concomitant Medications eCRF.*
12. Has the subject had a blood transfusion?	*If "Yes" for Question 12, please record on the On Study Surgery and procedures eCRF.*
Please add any other risk factors to the Additional Case Details and Event Narrative field in the Adverse Event eCRF reporting elevated liver enzymes.	

Hepatic Imaging Studies	
13. Were imaging studies performed? • *Magnetic resonance imaging (MRI)/ magnetic resonance cholangiopancreatography (MRCP)* • *Abdominal ultrasound* • *CT scan* • *ERCP (Endoscopic retrograde cholangiopancreatography)*	*If "Yes" for Question 13, please report in the On Study Surgery and Procedures eCRF and see Question 14 below*
14. Were any abnormalities noted on an imaging study?	*If "Yes" to Question 14, please report on an Adverse Event eCRF (unless a specific diagnosis has been established that accounts for the imaging finding, in which case the specific diagnosis should be recorded)*

Liver biopsy	
15. Was a liver biopsy performed?	*If "Yes" for Question 15, please report in the On Study Surgery and Procedures eCRF and see Question 16 below*
16. Were any abnormalities noted on the liver biopsy?	*If "Yes" for Question 16, Please report on an Adverse Event eCRF (unless a specific diagnosis has been established that accounts for the imaging finding, in which case the specific diagnosis should be recorded).*

Family History	
17. Do any of the subject's first-degree relatives have α-1 antitrypsin deficiency, hereditary haemochromatosis, or autoimmune liver disease?	*If Yes for Question 17, please record in the "Additional Case Details" field of the hepatic adverse event that was reported.*

Local Laboratory Tests	
Hepatic tests should be monitored during the event (as per Table 1 of the Safety Monitoring Plan (see Appendix 6) until resolution or return to baseline levels, regardless of whether the study drug is continued or not.	
18. Were local laboratory tests performed?	*If "Yes" for Question 18, please provide results of laboratory tests with reference ranges on the adverse event eCRF when applicable.*

Appendix 8
Guidance for Diagnosis of Progressive Multifocal Leukoencephalopathy

ACTION STEPS IF PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY IS SUSPECTED

Participants with suspected progressive multifocal leukoencephalopathy (PML), defined as a new or worsening neurological symptom that necessitates magnetic resonance imaging (MRI) and/or lumbar puncture and cerebrospinal fluid (CSF) analyses to rule out PML, should be withheld from study treatment until PML is ruled out by complete serial clinical evaluations and appropriate diagnostic testing. The Medical Monitor should be contacted by email and should be immediately contacted by telephone.

If the clinical presentation is suggestive of PML, further investigations should include brain MRI evaluation as soon as possible. If MRI evaluation reveals lesions suspicious for PML (see Figure A8-1), a lumbar puncture with evaluation of the CSF for the detection of JC virus (JCV) DNA using a validated sensitive assay should be undertaken. A diagnosis of PML can potentially be made by evaluating clinical and MRI findings plus the identification of JCV in the CSF (see Table A8-1).

There is no known treatment or cure for PML. Treatment considerations are discussed in the medical literature (Calabrese et al. 2007)

MRI ASSESSMENT

Although there are no pathognomonic findings that differentiate PML from multiple sclerosis (MS), a brain MRI scan that includes fluid-attenuated inversion recovery (FLAIR) and T2-weighted and T1-weighted sequences, with and without gadolinium (Gd), should be performed to assess participants with neurological changes suggestive of PML (see Figure A8-1).

Comparison with a baseline scan may assist with interpretation of the findings on the newly acquired MRI scan (see Table A8-2) for differences in lesion characteristics that may help differentiate between PML and MS).

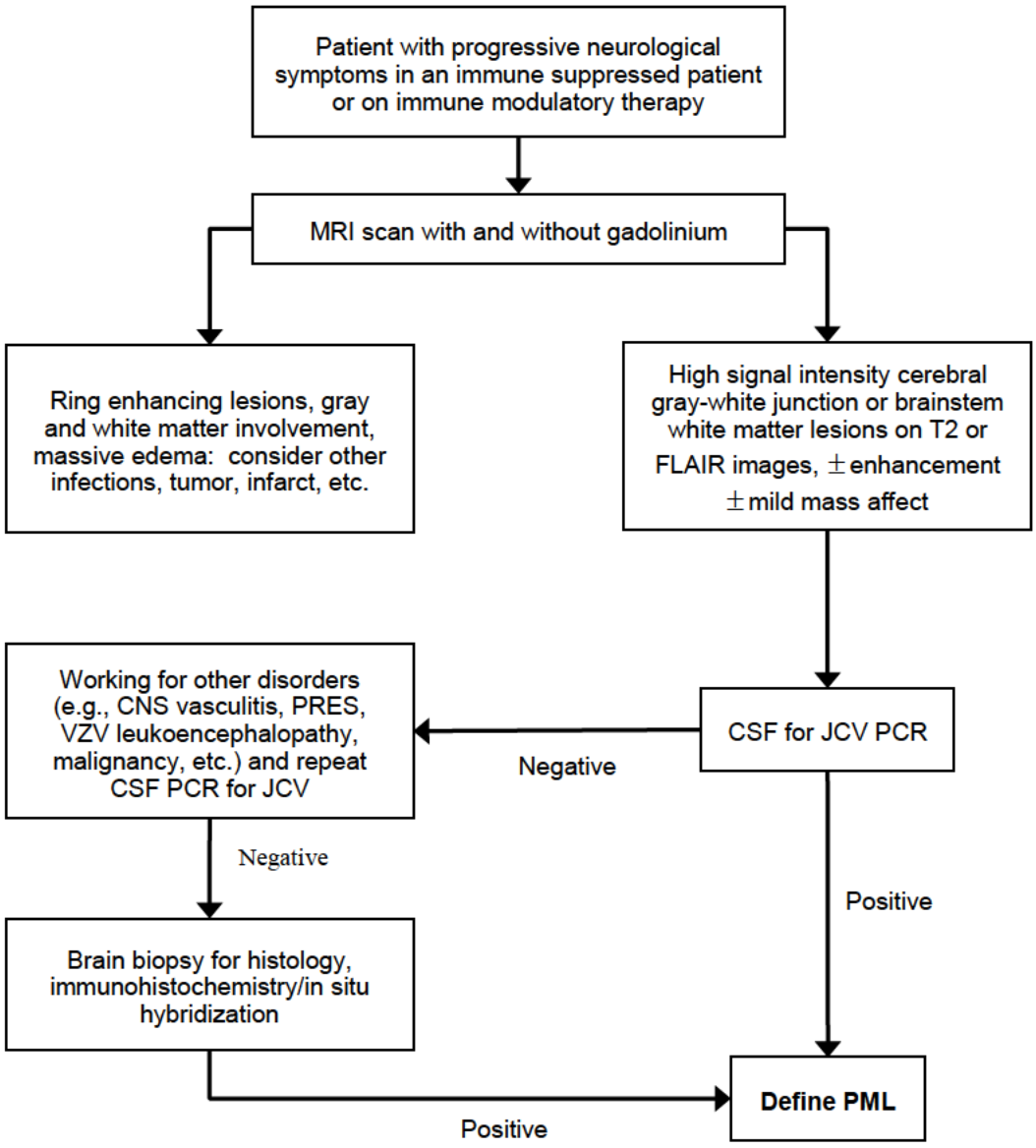
CSF ASSESSMENT

The detection of JCV DNA in the CSF of a patient with clinical and MRI features suggestive of PML establishes the diagnosis of PML.

If JCV DNA is not detected in CSF and if clinical suspicion of PML remains high, a repeat lumbar puncture should be performed.

If diagnosis remains uncertain and suspicion of PML remains high, a brain biopsy may be considered to establish a definitive diagnosis.

Figure A8-1 Diagnostic Algorithm Framework for PML



CSF = cerebrospinal fluid; FLAIR = fluid-attenuated inversion recovery; JCV = JC virus; MRI = magnetic resonance imaging; MS = multiple sclerosis; PML = progressive multifocal leukoencephalopathy; PRES = posterior reversible encephalopathy syndrome; PCR = polymerase chain reaction; VZV = varicella zoster virus.

Source: Berger et al. 2013

Table A8-1 Clinical Signs and Symptoms Typical of MS and PML

	MS	PML
Onset	**Acute**	**Subacute**
Evolution	• Over hours to days • Normally stabilized • Resolve spontaneously even without therapy	• Over weeks • Progressive
Clinical presentation	• Diplopia • Paresthesia • Paraparesis • Optic neuritis • Myelopathy	• Cortical symptoms/signs • Behavioral and neuropsychological alteration • Retrochiasmal visual defects • Hemiparesis • Cerebellar symptoms/signs (e.g., gait abnormalities, limb incoordination)

MS = multiple sclerosis; PML = progressive multifocal leukoencephalopathy.

Source: Adapted from Kappos et al. 2007.

Table A8-2 MRI Lesion Characteristics Typical of PML and MS

Feature	MS (relapse)	PML
Location of new lesions	Mostly focal; affect entire brain and spinal cord, in white and possibly gray matter	Diffuse lesions, mainly subcortical and rarely periventricular, located almost exclusively in white matter, although occasional extension to gray matter has been seen; posterior fossa frequently involved (cerebellum)
Borders	Sharp edges; mostly round or finger-like in shape (especially periventricular lesions), confluent with other lesions; U-fibers may be involved	Ill-defined edges; irregular in shape; confined to white matter; sparing gray matter; pushing against the cerebral cortex; U-fibers destroyed
Mode of extension	Initially focal; lesions enlarge within days or weeks and later decrease in size within months	Lesions are diffuse and asymmetric, extending homogeneously; no confluence with other lesions; confined to white-matter tracks, sparing the cortex; continuous progression
Mass effect	Acute lesions show some mass effect	No mass effect even in large lesions (but lesion slightly abuts cerebral cortex)

Table A8-2 MRI Lesion Characteristics Typical of PML and MS - (cont.)

Feature	MS (relapse)	PML
On T2-weighted sequence	• Acute lesions: hyperintense center, isointense ring, discrete hyperintensity outside the ring structure • Subacute and chronic lesions: hyperintense with no ring structure	Diffuse hyperintensity, slightly increased intensity of newly involved areas compared with old areas, little irregular signal intensity of lesions
On T1-weighted sequence	Acute lesions: densely hypointense (large lesions) or isointense (small lesions); increasing signal intensity over time in 80%; decreasing signal intensity (axonal loss) in about 20%	Slightly hypointense at onset, with signal intensity decreasing over time and along the affected area; no reversion of signal intensity
On FLAIR sequence	Hyperintense, sharply delineated	Hyperintensity more obvious; true extension of abnormality more clearly visible than in T2-weighted images
With enhancement	• Acute lesions: dense homogeneous enhancement, sharp edges • Subacute lesions: ring enhancement • Chronic lesions: no enhancement	Enhancement is possible, particularly in natalizumab-associated PML (Maas et al. 2016); in participants with HIV, some peripheral enhancement is possible, especially under therapy
Atrophy	Focal atrophy possible due to focal white-matter degeneration; no progression	No focal atrophy

FLAIR = fluid-attenuated inversion recovery; MS = multiple sclerosis; PML = progressive multifocal leukoencephalopathy.

Source: Adapted from Yousry TA et al. 2006.

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Maas RP, Muller-Hansma AH, Esselink RA, et al. Drug-associated progressive multifocal leukoencephalopathy: a clinical, radiological, and cerebrospinal fluid analysis of 326 cases. J Neurol 2016;263:2004–21.

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Appendix 9
Columbia-Suicide Severity Rating Scale
Baseline/Screening Version and Since Last Visit Version

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COLUMBIA-SUICIDE SEVERITY

RATING SCALE

(C-SSRS)

Baseline/Screening Version

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

Appendix 9: Columbia-Suicide Severity Rating Scale Baseline/Screening Version and Since Last Visit Version

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past 12 Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it… and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** ___ ***Type # (1-5)*** ___ ***Description of Ideation*** ___ Past X Months - ***Most Severe Ideation:*** ___ ***Type # (1-5)*** ___ ***Description of Ideation*** ___	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	___	___
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	___	___
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	___	___
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	___	___
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	___	___

Appendix 9: Columbia-Suicide Severity Rating Scale Baseline/Screening Version and Since Last Visit Version

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Lifetime	Past 1 Years
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	**Yes** ☐ **No** ☐ Total # of Attempts _____	**Yes** ☐ **No** ☑ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of interrupted _____	**Yes** ☐ **No** ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of aborted _____	**Yes** ☐ **No** ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

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C-SSRS Since Last Visit - United States/English - Mapi.
C-SSRS-SinceLastVisit_AU5.1_eng-USori.doc

Appendix 9: Columbia-Suicide Severity Rating Scale Baseline/Screening Version and Since Last Visit Version

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Since Last Visit**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it.....and I would never go through with it".* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them".* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** _____ _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

Appendix 9: Columbia-Suicide Severity Rating Scale Baseline/Screening Version and Since Last Visit Version

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	**Yes** ☐ **No** ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	**Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** ☐ **No** ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** ☐ **No** ☐
Suicide:	**Yes** ☐ **No** ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

Appendix 10
Telephone Interviews

The purpose of the semi-structured interview is to identify and collect information on any changes in the *participant*'s health status that may warrant an unscheduled visit (e.g., new or worsening neurological symptoms, suspected unplanned pregnancy). The telephone interview will be conducted by treating team personnel familiar with the *participant*(s) (see Table 2).

The questions below will be asked and the *participant*'s answers during the telephone interview will be recorded:

1. Since your last visit or telephone interview, have you had any new or worsening neurological symptoms (such as sudden changes in your thinking, alterations in your thinking, alterations in your behavior, visual disturbance, extremity weakness, limb coordination problems or gait abnormalities) that have persisted over more than one day?
2. Since your last visit or telephone interview, have you had any new or worsening medical problems?
3. How do you feel overall? Have you lost your appetite, are you nauseous, fatigued, have changes in your sleep patterns?
4. Since your last visit or telephone interview, have you had any infections or signs suggestive of infection, such as fever, headache, sore throat, cough, altered digestive transit, and/or burning sensation while urinating?
5. For female *participants*, since your last visit or telephone interview, have you had a positive urine pregnancy test?
6. Since your last visit or telephone interview, have you taken any new medicines (including medicines to treat multiple sclerosis, steroid medicines, or medicines that reduce the acid in your stomach)?

If the *participant* answered YES to any question, discuss and review the *participant*'s answer(s) with the treating investigator. If warranted, the *participant* should return for an unscheduled visit. If an unplanned pregnancy is suspected, an unscheduled visit to confirm the pregnancy is required.

All relevant information should be recorded in the appropriate *electronic Case Report Form*.

Appendix 11

Investigational Medicinal Product and Non-Investigational Medicinal Product Designations (for Use in European Economic Area and United Kingdom)

Table 1 Investigational, Authorized Auxiliary, and Unauthorized Auxiliary Medicinal Product Designations for European Economic Area

Product Name	*IMP/AxMP Designation*	*Marketing Authorization Status in EEA*	*Used within Marketing Authorization*
Fenebrutinib	*IMP (test product)*	*Not Authorized*	*Not applicable*
Placebo	*IMP (Placebo)*	*Not Authorized*	*Not applicable*

EEA = European Economic Area; IMP = investigational medicinal product; AxMP = authorised auxillary medicinal product.

Table 2 Investigational and Non-Investigational Medicinal Product Designations for European Economic Area /and/ United Kingdom

Product Name	*IMP/NIMP Designation*	*Marketing Authorization Status in U.K.*	*Used within Marketing Authorization*
Fenebrutinib	*IMP (test product)*	*Not Authorized*	*Not applicable*
Placebo	*IMP (Placebo)*	*Not Authorized*	*Not applicable*

EEA = European Economic Area; IMP = investigational medicinal product; NIMP = non-investigational medicinal.

Appendix 12
Protocol Amendment History

A rationale for the current amendment precedes the Table of Contents.

PROTOCOL AMENDMENT, VERSION 2: 13 JULY 2021

Protocol GN43271 has been amended to provide additional guidance on safety reporting, and eligibility criteria. Substantive changes to the protocol, along with a rationale for each change, are summarized below.

- The following changes have been added to clarify the reporting procedures for cases of transaminase increases:
  - Text has been added to specify that all laboratory reports of ALT or AST $> 3 \times$ upper limit of normal (ULN) are to be reported as adverse events (Sections 8.2.4, A3–1, A3–7.4, A3–7.6, and Table A6–1).
  - Text has been added to specify that all laboratory reports of ALT or AST $> 5 \times$ ULN are to be reported as Adverse Events of Special Interest (Sections 8.3.8, A3–7.6, A6–1.1, and Table A6–1).
  - The Schedule of Activities has been updated to include elevated ALT or AST $> 3 \times$ ULN as a clinically appropriate reason for an unscheduled visit to be performed.
- The pharmacokinetic and biomarker samples and collection timepoints have been updated in the Schedule of Activities and Pharmacokinetic and Biomarker Samples for Open-Label Extension Phase (Section 1.3, Tables 2 and 3).
- Details regarding the administration of Coronavirus disease –2019 vaccines were added to provide clarity (Section 2.3).
- The exclusion criterion regarding a white blood cell count of < 4000 cells/mm^3 (μL) was changed to < 2000 cells/mm^3 (μL) as a more appropriate critically low value (Section 5.2).
- QFT test only screening procedure for patients with a history of Bacille Calmette-Guérin vaccination was removed from the exclusion criterion for patients with active or latent or inadequately treated infection with tuberculosis (Section 5.2) because QFT is the only testing option for all patients.
- The eligibility requirement on disease-modifying therapy washout periods prior to study entry was amended to unify across different drug labels/countries and account for the long term pharmacodynamic effect of selected treatments (Section 5.2).
  - Exclusion criterion was revised to reduce previous use of fingolimod, siponimod, ozanimod, or ponesimod from 8 to 6 weeks prior to randomization (Section 5.2).
  - Exclusion criterion was revised to remove previous use of natalizumab for more than 1 year prior to randomization (Section 5.2).

- Text regarding screen failure and re-screening has been revised to clarify that medical monitor permission is required to re-screen a patient more than once (Section 5.4).
- Text has been updated to clarify the regulatory requirements for substantial amendments and to align with the current Roche process (Section A1−1).
- Text has been updated to clarify platelet count ranges for adverse event management of thrombocytopenia (Appendix 6, Table A6−1).
- The EUDRACT number was corrected to update a mistake in the first request in the title page.

Appendix 13
Abbreviations

Abbreviation or Term	Definition
ATP	adenosine triphosphate
BCRP	breast cancer resistance protein
BTK	Brutons tyrosine kinase
COVID-19	coronavirus disease 2019
CRO	contract research organization
CSF	cerebrospinal fluid
CTR	*Clinical Trial Regulation*
C-SSRS	Columbia-Suicide Severity Rating Scale
CSU	chronic spontaneous urticaria
D/C	discontinuation
DBT	double blind trial
DMT	disease modifying therapies
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
EDSS	expanded disability status scale
FSS	functional systems score
Gd	gadolinium
H_2RA	H_2 receptor agonist
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
ICH	International Council for Harmonisation
IMP	investigational medicinal product
iDMC	independent Data Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IxRS	interactive voice or web-based response system
MRI	magnetic resonance imaging
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events

Abbreviation or Term	Definition
NfL	*neurofilament light chain*
NGS	*next-generation sequencing*
OLE	*open label extension*
PD	pharmacodynamic
PK	pharmacokinetic
PML	progressive multifocal leukoencephalopathy
PPI	proton pump inhibitor
PPMS	primary progressive MS
QTcF	QT interval corrected through use of Fridericia's formula
RA	rheumatoid arthritis
RBR	Research Biosample Repository
RMS	relapsing MS
RRMS	relapsing remitting MS
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SFU	safety follow up
SLE	systemic lupus erythematosus
SPMS	secondary progressive MS
T1Gd+	T1-weighted gadolinium-enhancing
TB	tuberculosis
TEAE	treatment emergent adverse event
ULN	upper limit of normal
WES	whole exome sequencing
WGS	whole genome sequencing

Signature Page for Protocol - GN43271 - FENEBRUTINIB - v3 - Global/Core - Publis
System identifier: RIM-CLIN-461344

Approval Task	[redacted] Company Signatory 15-Dec-2022 14:23:37 GMT+0000