


## Clinical Study Protocol

### Title Page

<b>Clinical Study Protocol Title:</b>	A Phase III, Multicenter, Randomized, Parallel Group, Double Blind, Double Dummy, Active Controlled Study of Evobrutinib Compared with an Interferon Beta 1a (Avonex®), in Participants with Relapsing Multiple Sclerosis to Evaluate Efficacy and Safety.
<b>Study Number:</b>	MS200527_0074
<b>Amendment Number</b>	1.0
<b>Merck Compound Number:</b>	M2951
<b>Study Phase:</b>	III
<b>Short Title:</b>	Phase III Study of Evobrutinib in RMS
<b>Acronym:</b>	EVOLUTION MS2
<b>Coordinating Investigator:</b>	

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<b>Replaces Version:</b>	10 Jul 2019 / Version 1.0
<b>Approval Date:</b>	05 Sep 2019
<b>Medical Monitor Name and Contact Information:</b>	PPD

## Protocol Amendment Summary of Changes

Type	Example		Notes
	Scope	Version Number	
Original protocol	Global	1.0	Initial version submitted to the first IRB or IEC
Amendment 1	Global	2.0	Based on feedback provided by Voluntary Harmonisation Procedure (VHP)

## Protocol History

Version Number	Type	Version Date
1.0	Original Protocol	10-Jul-2019
2.0	Amendment 1	05-Sep-2019

### Protocol Version 2.0 (05-Sep-2019)

This amendment is substantial based on the criteria in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

### Overall Rationale for the Amendment

- Restructuring of text on discontinuation of Study Intervention.
- Clarification of role of Sponsor's Medical Monitor.
- Clarification of statistical approach towards primary and secondary endpoints.
- Adjustment of Exclusion Criteria.
- Clarification of use of concomitant therapy.

The following elements of the protocol have been revised for clarity and specificity (see Table below).

Section # and Name	Description of Change	Brief Rationale
Full document	Correction of typos and technical issues	Clarity and consistency
5.2 Exclusion Criteria	Criterion No.7, info added regarding TB skin test at Screening	Clarification of TB skin test at Screening
5.2 Exclusion Criteria	Criterion No.38, statement added that patients should be informed that IMP contains lactose	Ensure participant safety
5.2 Exclusion Criteria	Criterion No.13, text regarding exclusion of patients with untreated hypertension and GI bleeding has been added	Clarification of participant exclusion

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria	Criterion No. 17 modified to include examples of specific ECG abnormalities	Clarification of participant exclusion
5.2 Exclusion Criteria	No. 29c modified to clarify role of Sponsor's Medical Monitor	Clarification of participant exclusion
6.3.3 Emergency Unblinding	Text has been deleted	Clarification of role of Sponsor's Medical Monitor
6.5.1 Rescue Medicine	Text modified to emphasize priority of relapse treatment over timing of MRI scan	Ensure participant safety
6.5 Concomitant Therapy, 6.5.3 Prohibited Medicines	Rules for use of antispasticity agents have been modified	Clarification of concomitant therapy
6.5.4 Other Interventions	Paracetamol has been removed	Clarification of other interventions
7.1 Discontinuation of Study Intervention	Section revised and reorganized	Clarification of discontinuation of study intervention
7.2 Participant Discontinuation/Withdrawal from the Study	Text has been revised	Clarification of participant's withdrawal from the study
8 Assessments and Procedures	Reworded to include examples of specific ECG abnormalities	Clarification of ECG assessment and procedure
8.2.3 Electrocardiograms	Information has been added regarding interpretation of ECG results	Clarification of ECG assessment and procedure
8.2.8 Columbia-Suicide Severity Rating Scale	Additional monitoring step added	Ensure proper study conduct
CCI [REDACTED]	[REDACTED]	[REDACTED]
9.4.1.1 Efficacy Analyses related to Primary Objective	Description of the Negative Binomial (NB) model from which adjusted ARR is estimated added	Clarification of statistical approach
9.4.1 Efficacy Analyses, 9.4.1.1 Efficacy Analyses related to Primary Objective, 9.4.1.2 Efficacy Analyses related to Secondary Objectives	Information added regarding missing data handling in the primary analysis of the primary endpoint (including missing data handling in the primary analyses of secondary endpoints)	Clarification of statistical approach
4.1 Overall Design, 9.4.1.2 Efficacy Analyses related to Secondary Objectives, CCI [REDACTED]	Specific promising zone boundaries added	Clarification of statistical approach

[REDACTED]

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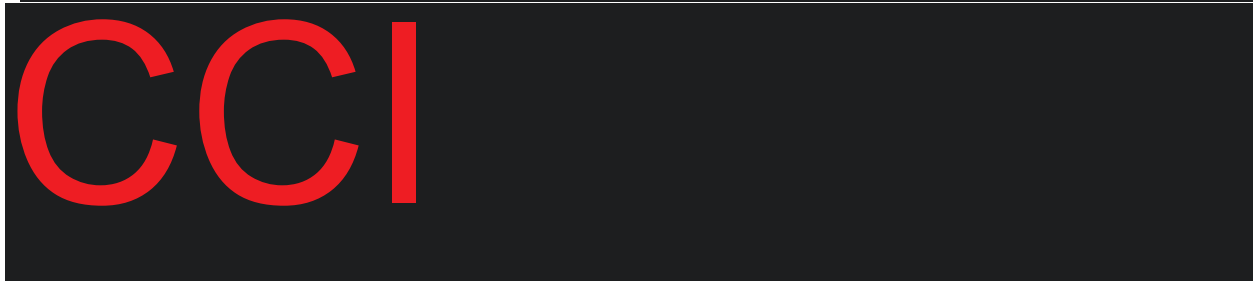
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# 1 Protocol Summary

## 1.1 Synopsis

**Protocol Title:** A Phase III, Multicenter, Randomized, Parallel Group, Double Blind, Double Dummy, Active Controlled Study of Evobrutinib compared with an Interferon Beta 1a (Avonex®), in Participants with Relapsing Multiple Sclerosis to Evaluate Efficacy and Safety.

**Short Title:** Phase III Study of Evobrutinib in RMS (EVOLUTION MS2)

**Rationale:** The purpose of this study is to characterize the efficacy and safety of evobrutinib CCI administered orally twice daily versus Interferon-beta 1a (Avonex) CCI once a week intramuscularly) in participants with Relapsing Multiple Sclerosis (RMS).

### Objectives and Endpoints:

Objectives	Endpoints (Outcome Measures)
Primary	
To demonstrate superior efficacy with evobrutinib compared to Avonex in terms of Annualized Relapse Rate (ARR)	ARR based on qualified relapses at Week 96 in participants with RMS
Secondary	
To demonstrate the efficacy of evobrutinib relative to that of Avonex on disability progression	<ul style="list-style-type: none"><li>• Time to first occurrence of 12-week confirmed Expanded Disability Status Scale (EDSS) progression over 96 weeks</li><li>• Time to first occurrence of 24-week confirmed EDSS progression over 96 weeks</li></ul>
To demonstrate the efficacy of evobrutinib relative to that of Avonex on patient reported symptoms and functional status	<ul style="list-style-type: none"><li>• Change from Baseline (CFB) in Patient Reported Outcomes Measurement Information System (PROMIS) physical function (PF) score at 96 weeks</li><li>• CFB in PROMIS Fatigue score at 96 weeks</li></ul>
To demonstrate the efficacy of evobrutinib relative to that of Avonex on magnetic resonance imaging (MRI) lesion parameters	<ul style="list-style-type: none"><li>• Total number of T1 Gd+ lesions based on assessments at Week 24, Week 48, and Week 96</li><li>• Total number of new or enlarging T2 lesions based on assessments at Week 24, Week 48, and Week 96</li></ul>

Objectives	Endpoints (Outcome Measures)
To characterize the safety and tolerability of evobrutinib.	Safety as assessed by the nature, severity, and occurrence of adverse events (AEs) and AESIs; vital signs; electrocardiograms (ECGs); absolute concentrations and change from Baseline in immunoglobulin (Ig) levels; and clinical laboratory safety parameters up to Week 108
OLE Period	
To evaluate the long-term safety, efficacy, and HRQoL of evobrutinib for an additional up to 144 weeks.	<ul style="list-style-type: none"> <li>• Efficacy and HRQoL endpoints at Weeks 48, 96, and 144               <ul style="list-style-type: none"> <li>○ ARR, based on protocol-defined qualified relapses</li> <li>○ Change from Baseline in PROMIS PF score</li> <li>○ Change from Baseline in PROMIS fatigue score</li> <li>○ Change from Baseline in Medical Outcomes Study 36 Item Short Form Health Survey (SF-36v2)</li> </ul> </li> <li>• Efficacy and HRQoL endpoints over 144 weeks               <ul style="list-style-type: none"> <li>○ Time to first occurrence of 12-week confirmed EDSS progression over 144 weeks</li> <li>○ Time to first occurrence of 24-week confirmed EDSS progression over 144 weeks</li> <li>○ Time to first occurrence of 12-week confirmed PF deterioration compared to Baseline over 144 weeks</li> </ul> </li> <li>• Efficacy endpoints at Weeks 24, 48, 96, and 144               <ul style="list-style-type: none"> <li>○ Total number of new or enlarging T2 lesions</li> <li>○ Total number of T1 Gd+ lesions</li> </ul> </li> <li>• Safety as assessed by the nature, severity, and occurrence of AEs and AESIs; vital signs; ECGs; absolute concentrations and change from Baseline in Ig levels; clinical laboratory safety parameters up to Week 144</li> </ul>

**Overall Design:** This is a Phase III, multicenter, randomized, parallel group, double blind, double dummy active controlled study of evobrutinib with an active control Avonex, in participants with RMS.

Eligible participants will be randomized 1:1 to treatment with evobrutinib CCI twice daily, or Avonex CCI once a week (intramuscularly), stratified by region and Baseline EDSS. Blinding will be accomplished using a double dummy design.

**Number of Participants:** The total sample size is planned to be CCI participants with a randomization ratio of 1:1 (approximately CCI participants per treatment group)

**Study Intervention Groups and Duration:** The 96-week Treatment Period will be preceded by a 4-week Screening Period (may be extended but cannot exceed 8 weeks) and followed by a 4-week Safety Follow-up after treatment completion or early discontinuation.

Participants experiencing initial progression of disability between Week 72 and Week 96 will continue participating in the main study for up to 12 additional weeks. The continuation period will increase the duration of participation to a maximum of 108 weeks. Upon completion of the continuation period, participants will have the option of participating in the OLE, or ending treatment (and returning for a 4-week Safety Follow-up).

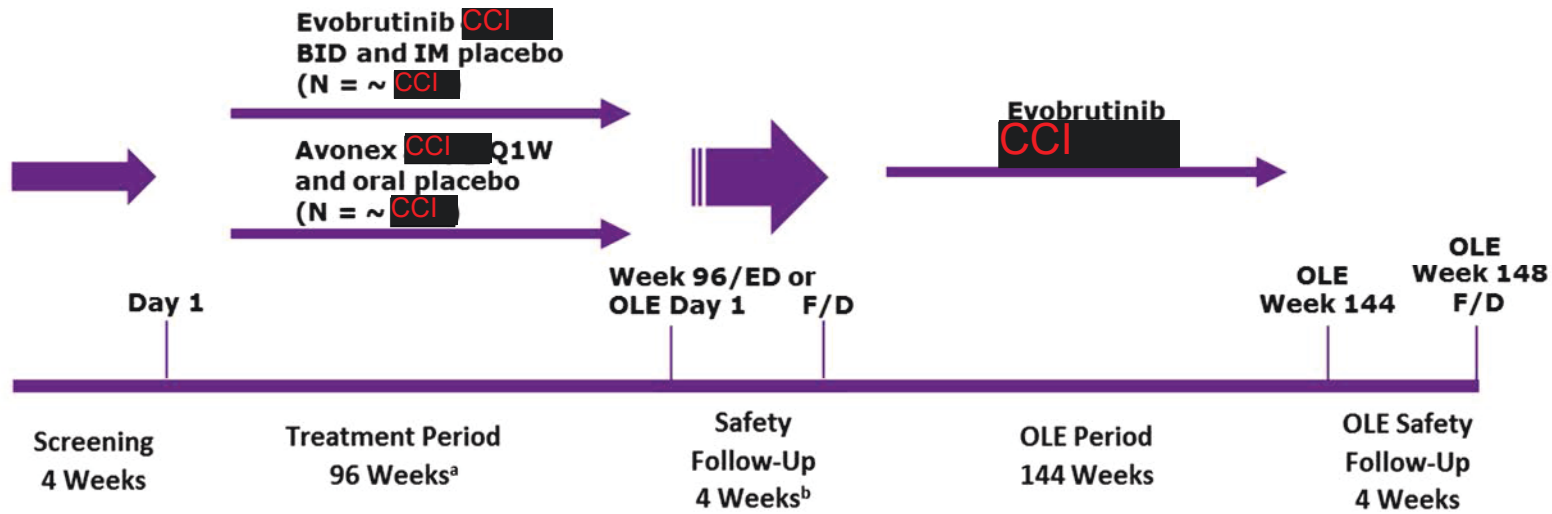
Participants who complete the 96-week double blind, double dummy Treatment Period will be offered participation in the 148-week OLE Period of the study. The double blind Week 96 visit (or up to Week 108 visit) will be considered the OLE Day 1 Visit. The Safety Follow-up Visit will be deferred until treatment is stopped in the OLE Period, due to either a participant's premature withdrawal/early termination from the OLE, termination of the study by the Sponsor, or completion of the OLE treatment period.

For participants experiencing a relapse within 4 weeks of eligibility for OLE, these participants will be allowed entry into the OLE after approval from Merck/EMD Serono provided that the treatment gap does not exceed 60 days from the last dose of study intervention received in the double blind, double dummy period (Week 96/up to Week 108 visit), and the start of the study intervention treatment in the OLE Period.

**Involvement of Special Committee(s): Yes.** Independent Data Monitoring Committee, Endpoint Adjudication Committee, and Study Steering Committee.

## 1.2 Schema

Figure 1 Study Schema



BID = Twice Daily, ED = Early Discontinuation, F/D = Follow-up/Discontinuation, IM = intramuscular, OLE = Open Label Extension, Q1W = Once Weekly.

- a Participants experiencing initial progression of disability between Week 72 and Week 96 will continue participating in the main study for up to 12 additional weeks. The continuation period will increase the duration of participation to a maximum of 108 weeks.
- b For participants who do not enter the OLE period, the F/D visit will be performed 4 weeks after the last study interventions administration. For participants entering the OLE, there will be no 4-week follow-up period between the main study and the OLE.



















AE = Adverse Event, ALP = Alkaline phosphatase, ALT = Alanine Aminotransferase, AST = Aspartate Aminotransferase, C-SSRS = Columbia-Suicide Severity Rating Scale, DNA = Deoxyribonucleic Acid, ECG = Electrocardiogram, ED = Early Discontinuation, EDSS = Expanded Disability Status Scale, EQ-5D-5L = EuroQoL 5 Dimension 5 Level, ESR = Erythrocyte Sedimentation Rate, F/D = Follow-up/Discontinuation, GGT =  $\gamma$ -Glutamyl-Transferase, h = hour, HBV = Hepatitis B Virus, HFE = High Iron Fe (human hemochromatosis protein), hsCRP = high sensitivity C reactive protein, HIV = Human Immunodeficiency Virus, ICF = Informed Consent Form, IWRS = Interactive Web Response System, LFT = Liver Function Test, MRI = Magnetic Resonance Imaging, MS = Multiple Sclerosis, CCI [REDACTED], PCR = polymerase chain reaction, CCI [REDACTED], CCI [REDACTED], PROMIS = Patient Reported Outcomes Measurement Information System, S = Screening, S2 = Screening 2, SAE = Serious Adverse Event, CCI [REDACTED] Test, CCI [REDACTED], TB = Tuberculosis, CCI [REDACTED] W = Week, WOCBP = Women Of Child Bearing Potential.

1.3.2 Schedule of Assessments – Optional Open Label Extension Period

Assessments & Procedures	Intervention Period																										U n s c h e d u l e d W e e k V i s i t	Notes: a For participants entering the OLE Period, their last visit in the main study will be their first visit in the OLE (see Section 4.1).  b The OLE F/D visit will be performed 28 d (± 3 d) after last study intervention administration.	
	OLE D1 <sup>a</sup>	W 2	W 4	W 6	W 8	W 10	W 12	W 14	W 16	W 18	W 20	W 22	W 24	W 28	W 32	W 36	W 40	W 44	W 48	W 60	W 72	W 84	W 96	W 108	W 120	W 132			W 144
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27		
Study Day ± Visit Window	1±3	1 5 ± 3	2 9 ± 3	4 3 ± 3	5 7 ± 3	71 ±3	85 ±3	99 ±3	1 3 ±3	1 7 ±3	1 4 ±3	1 5 ±3	1 6 ±3	1 9 ±3	2 5 ±3	2 8 ±3	3 1 ±3	3 7 ±7	4 0 ±7	5 5 ±7	5 8 ±7	6 3 ±7	7 7 ±7	8 5 ±7	0 4 ±7	1 0 9 ±7	1 0 3 7 ±7	1 0 3 7 ±7	
Informed Consent	X																												
Full Physical Examination	X																						X			X	X	X	Additional examinations may be completed at the discretion of the Investigator.
Serum Pregnancy Test (WOCBP only)	X																												




Assessments & Procedures	Intervention Period																								U n s c h e d u l e d V i s i t	W e e k 1 4 8 F/ D <sup>b</sup>	Notes:		
	OLE D1 <sup>a</sup>	W 2	W 4	W 6	W 8	W 10	W 12	W 14	W 16	W 18	W 20	W 22	W 24	W 28	W 32	W 36	W 40	W 44	W 48	W 60	W 72	W 84	W 9 6	W 1 0 8				W 1 1 2 0	W 1 4 4/ E D
MRI scan	X											X							X					X			X		Completed at Discontinuation Participants should meet inclusion/exclusion criteria before MRI is performed.
PROMIS fatigue and physical functioning, EQ-5D-5L	X						X					X		X					X		X		X		X	X	X	X	Completed on <b>CCI</b>

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Assessments & Procedures	Intervention Period																								U n s c h e d u l e d V i s i t	W e e k 1 4 8 F/ D <sup>b</sup>	Notes:  a For participants entering the OLE Period, their last visit in the main study will be their first visit in the OLE (see Section 4.1).  b The OLE F/D visit will be performed 28 d (± 3 d) after last study intervention administration.		
	OLE D1 <sup>a</sup>	W 2	W 4	W 6	W 8	W 10	W 12	W 14	W 16	W 18	W 20	W 22	W 24	W 28	W 32	W 36	W 40	W 44	W 48	W 60	W 72	W 84	W 96	W 108				W 120	W 144/E
Safety assessments																													



Assessments & Procedures	Intervention Period																						U n s c h e d u l e d V i s i t	W e e k 1 4 8 F/ D <sup>b</sup>	Notes:  a For participants entering the OLE Period, their last visit in the main study will be their first visit in the OLE (see Section 4.1).  b The OLE F/D visit will be performed 28 d (± 3 d) after last study intervention administration.			
	OLE D1 <sup>a</sup>	W 2	W 4	W 6	W 8	W 10	W 12	W 14	W 16	W 18	W 20	W 22	W 24	W 28	W 32	W 36	W 40	W 44	W 48	W 60	W 72	W 84				W 96	W 108	W 120
Supplemental LFT: ALP, AST, ALT, GGT, and Total Bilirubin		X	X	X	X	X		X	X	X	X	X		X	X	X	X	X		X		X				X		
																												
Evobrutinib concentration assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X	X		
Biochemistry and Hematology	X						X						X							X		X		X		X	X	X
Coagulation	X																			X			X				X	
Urinalysis/ microscopy and urine chemistry	X						X					X								X		X		X		X	X	X

Assessments & Procedures	Intervention Period																								U n s c h e d u l e d V i s i t	W e e k 1 4 8 F/ D <sup>b</sup>	Notes:		
	OLE D1 <sup>a</sup>	W 2	W 4	W 6	W 8	W 10	W 12	W 14	W 16	W 18	W 20	W 22	W 24	W 28	W 32	W 36	W 40	W 44	W 48	W 60	W 72	W 84	W 9 6	W 1 0 8				W 1 1 2 0	W 1 4 4/ E D
Vital Signs and Weight	X					X						X		X			X		X		X		X		X	X	X		
AE, SAE & AESI Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X	X	X	X	AE review to be started after ICF signed
Concomitant Medication and Procedures Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X	X	X	X		
Immunoglobulin levels	X					X						X						X		X		X		X	X		X		
<b>Study Intervention</b>																													
Dispense Study Intervention(s)	X					X						X			X			X		X					X				Dispense as needed per IWRS.
Study Intervention(s) Administration	X	Administration of study intervention																											Evobrutinib dosing will start the day after OLE Day 1. Evobrutinib must be taken in the fed state, see Section 6.1.



Assessments & Procedures	Intervention Period																							W 1 4 8 F/ D <sup>b</sup>	U n s c h e d u l e d V i s i t	Notes:
	OLE D1 <sup>a</sup>	W 2	W 4	W 6	W 8	W 10	W 12	W 14	W 16	W 18	W 20	W 22	W 24	W 28	W 32	W 36	W 40	W 44	W 48	W 60	W 72	W 84	W 9 6			
CCI																										

AE = Adverse Event, AESI = Adverse Event of Special Interest, ALP = Alkaline phosphatase, ALT = Alanine Aminotransferase, AST = Aspartate Aminotransferase, BTK = Bruton's Tyrosine Kinase, C-SSRS = Columbia-Suicide Severity Rating Scale, d = day, DNA = Deoxyribonucleic Acid, ECG = Electrocardiogram, ED = Early Discontinuation, EDSS = Expanded Disability Status Scale, EQ-5D-5L = EuroQoL 5 Dimension 5 Level, ESR = Erythrocyte Sedimentation Rate, F/D = Follow-up/Discontinuation, GGT = γ-Glutamyl-Transferase, HBV = Hepatitis B Virus, HFE = High Iron Fe (human hemochromatosis protein), hsCRP = high sensitivity C reactive protein, ICF = Informed Consent Form, IWRS = Interactive Web Response System, LFT = Liver Function Test, MRI = Magnetic Resonance Imaging, MS = Multiple Sclerosis, CCI OLE = Open Label Extension, CCI, CCI PRO = patient reported outcomes, PROMIS = Patient Reported Outcomes Measurement Information System, S = Screening, S2 = Screening 2, SAE = Serious Adverse Event, CCI, CCI TB = Tuberculosis, CCI W = Week, WOCBP = Women Of Child Bearing Potential.

## 2 Introduction

Evobrutinib is a potent, orally administered, highly selective, irreversible inhibitor of Bruton's Tyrosine Kinase (BTK) that is being developed for the treatment of relapsing multiple sclerosis (RMS).

Complete information on the chemistry, pharmacology, efficacy, and safety of evobrutinib is in the current Investigator's Brochure.

### 2.1 Study Rationale

The purpose of this study is to characterize the efficacy and safety of evobrutinib **CCI** administered orally twice daily versus Interferon-beta 1a (Avonex) (**CCI**) once a week intramuscularly) in participants with RMS.

Evobrutinib inhibits activation of B cells via the B cell receptor. In addition, evobrutinib inhibits activation of myeloid cells by immune complexes via Fc receptors as well as the differentiation of proinflammatory macrophages. Thus, evobrutinib may be suitable for the treatment of multiple sclerosis (MS).

The main randomized, double blind, placebo-controlled Phase II study of evobrutinib with a parallel, open label, active control group (dimethyl fumarate [Tecfidera®]), in patients with RMS to evaluate efficacy, safety, tolerability, pharmacokinetics (PK), and biological activity (MS200527\_0086) is completed; the Open Label Extension (OLE) part of the study is ongoing. The study consisted of a first 24-week period, in which 267 participants were randomized to evobrutinib 25 mg once daily (n = 52), 75 mg once daily (n = 53), 75 mg twice daily (n = 54), dimethyl fumarate 240 mg twice daily (provided open label) (n = 54), or placebo (n = 54). Data from the first 24-weeks were analyzed for the primary analysis (PA). Following the 24-week period, all remaining participants continued to be treated for an additional 24-week period as follows: participants who received previously evobrutinib 25 mg once daily, 75 mg once daily, 75 mg twice daily, or dimethyl fumarate, continued to be treated with their original treatment, and participants who received placebo for the first 24-weeks were switched to evobrutinib 25 mg once daily. Treatment assignment remained blinded with the exception of dimethyl fumarate which was open label throughout the study. The first 48 weeks analysis is referred to as the Blinded Extension Analysis (BEA). For the PA, efficacy analysis consisted of the comparison between the placebo and evobrutinib treatment groups. No formal comparison between the dimethyl fumarate and the evobrutinib treatment groups was performed for either the PA or the BEA.

In the PA, the primary efficacy endpoint of the Phase II study was the total number of gadolinium-enhancing T1 lesions at Weeks 12, 16, 20, and 24. The primary efficacy analysis was a comparison of each evobrutinib dose arm versus placebo based on lesion rate (lesions per scan) ratio, adjusted for Baseline lesion activity. The primary endpoint of the study was met, and both evobrutinib 75 mg once daily (lesion rate ratio 0.30, 95% confidence interval [CI]: 0.14, 0.63; P = 0.0015 [unadjusted], P = 0.046 [adjusted according to Hochberg]) and evobrutinib 75 mg twice daily (lesion rate ratio 0.44, 95% CI: 0.21, 0.93; P = 0.0313

[unadjusted],  $P = 0.0648$  [adjusted according to Hochberg]) were associated with a reduction in T1 Gd+ lesion rate compared to placebo (Montalban 2019).

The first key secondary endpoint was annualized relapse rate (ARR) at 24-weeks. A trend towards a reduction in ARR (unadjusted [95% CI]) was seen with evobrutinib 75 mg once daily (0.13 [0.03, 0.38];  $P = 0.09$ ) and evobrutinib 75 mg twice daily (0.08 [0.01, 0.30];  $P = 0.06$ ) versus placebo (0.37, [0.17, 0.70]), with evidence of a dose response ( $P = 0.014$ ).

In the BEA, results showed an unadjusted ARR at 48 weeks of 0.11 (95% CI: 0.04, 0.25) for evobrutinib 75 mg twice daily and 0.25 (95% CI: 0.12, 0.44) for evobrutinib 75 mg once daily indicating that the efficacy trend observed during the first 24-week period was sustained during the second 24-week period, with greater clinical sustained efficacy in the 75 mg twice daily group.

These results provide evidence of evobrutinib's efficacy compared to placebo. Clinical development efforts in the MS indication will focus specifically on RMS, with potential expansion into progressive MS (PPMS and Secondary progressive multiple sclerosis [SPMS]) with subclinical central nervous system (CNS) inflammation.

Reversible elevations in transaminases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) have been observed in participants randomized to evobrutinib in the RMS Phase II study (MS200527-0086). This finding, and the overall safety and risk-benefit assessment of evobrutinib are discussed further in Section 2.3 and Section 4.3.

Taken together, efficacy and safety data from this study support progression into Phase III.

Refer to the Investigator's Brochure for further information about the nonclinical and clinical programs and Guidance for the Investigator.

## **2.2 Background**

Currently there is no cure for MS, but the course of the disease can be altered favorably with disease-modifying drugs (DMDs) with varying levels of efficacy, and distinct safety and tolerability profiles. Most active RMS patients initiate treatment with an interferon-beta or glatiramer acetate therapy. Oral DMDs including dimethyl fumarate and teriflunomide are also used as first-line agents. If responding suboptimally, patients can be treated with an alternative, second-line oral therapy such as cladribine and fingolimod, or infusion agents such as natalizumab and ocrelizumab. Generally, DMDs perceived to be more efficacious have also been shown to be associated with more significant adverse effects, ranging from serious infections (i.e., progressive multifocal leukoencephalopathy [PML]) to autoimmunity and cancer. Switching among these DMDs occurs primarily due to perceived lack of efficacy or the occurrence of adverse events (AEs), as well as individual patient preferences.

Despite the recent approvals of newer therapies for the treatment of MS, there remains an unmet need for highly effective and well-tolerated therapies for patients with MS at all stages of the disease. Early treatment with a highly efficacious, and safer DMD could be

advantageous for long term quality of life for MS patients and might slow the process of brain atrophy, which accompanies axonal damage and loss of gray and white matter.

Evobrutinib is a highly specific, oral inhibitor of BTK that inhibits B cell activation and B cell/T cell interaction, decreasing plasma cell formation and autoantibody production (Investigator Brochure, [Haselmayer 2017](#)). In addition, evobrutinib was shown to inhibit M1 macrophage survival and proinflammatory cytokine release and promotes M2 polarization of reparative human monocytes in vitro ([Alankus 2018](#)). In line with the in vitro data, evobrutinib demonstrated pharmacological efficacy in both B cell and T cell dependent mouse models of MS, by reducing CNS inflammation and amelioration of disease severity ([Boschart 2017](#), [Torke 2018](#)). Since B cell depletion studies have shown that antibody independent B cell functions play an important role in MS pathogenesis ([Bar-Or 2010](#), [Fraussen 2016](#), [Jelcic 2018](#)) and an altered innate immune system contributes to disability progression and repair in MS ([Vogel 2013](#), [Rawji 2016](#)), evobrutinib may offer advantages over current approved DMDs.

Clinical efficacy was recently demonstrated with B cell depleting anti CD20 therapies in Phase II and Phase III clinical studies in RMS and progressive MS ([Hauser 2008](#), [Hawker 2009](#), [Montalban 2016](#), [Wolinsky 2016](#)). Ocrelizumab (Ocrevus®) inhibited the formation of new inflammatory magnetic resonance imaging (MRI) lesions up to 90% ([Hauser 2008](#)) in Phase II RMS studies and high efficacy on MRI (-94%), ARR (-46%), and 24-week disease progression (-40%) was also reached in OPERA Phase I, II, and III studies against interferon-beta. Translational mechanism of action studies in anti CD20 treated RMS patients show diminished proliferation and proinflammatory differentiation of T cells ([Bar-Or 2010](#)), pointing towards abrogation of antigen presenting cell function as the primary mechanism. In addition to the role of anti CD20 in B cell antigen presentation, a recent publication of Li et al ([Li 2015](#)) describes a diminished proinflammatory myeloid cell response in ocrelizumab treated MS participants. Evobrutinib shows inhibition of myeloid cell activation by immune complexes.

Preclinical proof of concept with evobrutinib has been demonstrated for systemic lupus erythematosus/lupus nephritis, experimental autoimmune encephalomyelitis, rheumatoid arthritis (RA) and passive cutaneous anaphylaxis. Oral evobrutinib does not deplete B cells in the studies carried out to date and, upon withdrawal, restoration of immune function can be achieved in days. This is less than treatment with anti CD20 therapies, where restoration of the immune system can take months, and is important should the need to interrupt or stop therapy arise. This suggests a more favorable benefit to risk balance with respect to infections for evobrutinib versus anti CD20 therapies may be observed. In addition, BTK inhibitors might have broader efficacy than agents that cause B cell depletion, due to the importance of BTK activation downstream of various receptors expressed in myeloid cells, suggesting an additional direct effect of evobrutinib on innate immune cell activation induced by immune complexes, cytokines/chemokines, or toll-like receptor (TLR) activation ([Block 2012](#), [Lopez-Herrera 2014](#), [Whang 2014](#)). A direct myeloid inhibition activity also best explains the significant reduction of clinical score, relapse rate, and time to first relapse in T cell dependent experimental autoimmune encephalomyelitis models, in which anti CD20 antibodies do not work.



## 2.3 Benefit/Risk Assessment

In the PA of the completed MS200527-0086 study, evobrutinib significantly decreased the number of Gd+ T1 lesions at Weeks 12, 16, 20, and 24 in RMS subjects. Similar to the relationship seen for the MRI endpoints, evobrutinib 75 mg once and twice daily was associated with a lower ARR compared to placebo. These results show evobrutinib is efficacious in RMS subjects, and consequently warrant further investigation in Phase III clinical studies.



A confirmed safety finding of increases in liver transaminases has been observed from Study MS200527-0086 in subjects with RMS and the ongoing Study MS200527-0018 in subjects with SLE and was considered as important identified risk for evobrutinib. Elevations of liver transaminases were frequent, generally mild (Grade 1), asymptomatic and reversible.

During the first 52 weeks of the MS200527-0086 study, all of the instances of elevated liver enzymes occurred during the first 6 months of exposure to evobrutinib and none of the cases of elevated transaminases had any clinical signs or symptoms, and the transaminase elevations have resolved over time with the withdrawal of evobrutinib. CCI



Given these observations, this protocol excludes participants with hemochromatosis, Wilson's disease, alpha-1-antitrypsin deficiency, or any other chronic liver disease including Gilbert's disease and  $> 2 \times$  ULN values for ALT, AST, amylase, or lipase elevation at Screening. During the study, liver transaminase will be monitored every 2 weeks, particularly during the first 6 months of exposure to evobrutinib. The protocol has strict stopping criteria for liver transaminase elevations leading to treatment discontinuation and timely medical management. Also, data will be reviewed by an Independent Data Monitoring Committee (IDMC) with appropriate expertise. Beyond this, risk minimization measures proposed are considered standard for this phase of clinical development.

Investigations on embryo-fetal development in toxicological studies showed an increased incidence of malformations (mainly cleft palate) and skeletal variations in mice when compared to the control group, and abortions and/or vaginal bleeding during the last period of gestation in rabbits. In addition, an increase of resorptions, and a lower mean fetal weight were also seen.

Based on these, embryo-fetal toxicity is considered as an important potential risk in participants exposed to evobrutinib. Therefore, female participants of childbearing potential must not be pregnant, must have a negative pregnancy test at the time of enrollment and use highly effective contraception (as specified in the clinical study protocol) during the study period and 120 days after the last dose, not to donate eggs for reproduction, as risk mitigation measures.

Although no causal relationship has been established, adverse events of special interests (AESI) including infections (serious and opportunistic infections), lipase and amylase elevation, and seizure, are under close monitoring.

Due to the dominant role of CYP3A4/5 in the metabolism of evobrutinib, the compound may be a victim of DDI caused by inhibition (competitive/time-dependent) or induction of this enzyme by coadministered perpetrator drugs. The results of the completed clinical CYP DDI study (MS200527-0054) demonstrated that administration of evobrutinib with the potent CYP 3A4/5 inhibitor itraconazole resulted in a 3.35-fold increase in  $C_{max}$  and a 2.99-fold increase of AUC. Based on these observations, the administration of medications that are moderate or strong inhibitors or inducers of CYP3A4/5 is not permitted during ongoing clinical trials.

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Following the review of the totality of the safety data from the clinical studies with evobrutinib, overall, evobrutinib was well tolerated in MS patients up to 75 mg BID. The safety profile of evobrutinib has been consistent across doses and indications. No dose-related relationship has been observed for the most frequently reported TEAEs.

Overall, considering the unmet medical need in MS patients, reduction of MS activities (decreased in the number of Gd+ T1 lesions and lower ARR compare with placebo), convenience of an oral therapy and the measures put in place to mitigate the important identified and important potential risks, the benefit-risk of evobrutinib CCI BID fed supports continued clinical development of evobrutinib in this population.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of evobrutinib may be found in Section 4.2 and the Investigator's Brochure. More detailed information about the known risks and benefits of Avonex are provided in the locally approved product information (e.g. relevant SmPC or the US Prescribing Information).

Based on the available nonclinical and clinical data to date, the conduct of the study, as specified in this protocol, is considered justifiable.

### 3 Objectives and Endpoints

Objectives	Endpoints (Outcome Measures)
<b>Primary</b>	
To demonstrate superior efficacy with evobrutinib compared to Avonex in terms of ARR	ARR based on qualified relapses at Week 96 in participants with RMS
<b>Secondary</b>	
To demonstrate the efficacy of evobrutinib relative to that of Avonex on disability progression	<ul style="list-style-type: none"> <li>• Time to first occurrence of 12-week confirmed Expanded Disability Status Scale (EDSS) progression over 96 weeks</li> <li>• Time to first occurrence of 24-week confirmed EDSS progression over 96 weeks</li> </ul>
To demonstrate the efficacy of evobrutinib relative to that of Avonex on patient reported symptoms and functional status	<ul style="list-style-type: none"> <li>• Change from Baseline (CFB) in Patient Reported Outcomes Measurement Information System [PROMIS] PF score at 96 weeks</li> <li>• CFB in PROMIS Fatigue score at 96 weeks</li> </ul>
To demonstrate the efficacy of evobrutinib relative to that of Avonex on MRI lesion parameters	<ul style="list-style-type: none"> <li>• Total number of T1 Gd+ lesions based on assessments at Week 24, Week 48, and Week 96.</li> <li>• Total number of new or enlarging T2 lesions based on assessments at Week 24, Week 48, and Week 96</li> </ul>
To characterize the safety and tolerability of evobrutinib.	Safety as assessed by the nature, severity, and occurrence of adverse events (AEs) and adverse events of special interest (AESIs); vital signs; electrocardiograms (ECGs); absolute concentrations and change from Baseline in immunoglobulin (Ig) levels; and clinical laboratory safety parameters up to Week 108



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Objectives	Endpoints (Outcome Measures)
OLE Period	
<p>To evaluate the long-term safety, efficacy, and HRQoL of evobrutinib for an additional up to 144 weeks.</p>	<ul style="list-style-type: none"> <li>• Efficacy and HRQoL endpoints at Weeks 48, 96, and 144               <ul style="list-style-type: none"> <li>○ ARR, based on protocol-defined qualified relapses</li> <li>○ Change from Baseline in PROMIS PF score</li> <li>○ Change from Baseline in PROMIS fatigue score</li> <li>○ Change from Baseline in Medical Outcomes Study 36 Item Short Form Health Survey (SF-36v2)</li> </ul> </li> <li>• Efficacy and HRQoL endpoints over 144 weeks               <ul style="list-style-type: none"> <li>○ Time to first occurrence of 12-week confirmed EDSS progression over 144 weeks</li> <li>○ Time to first occurrence of 24-week confirmed EDSS progression over 144 weeks</li> <li>○ Time to first occurrence of 12-week confirmed PF deterioration compared to Baseline over 144 weeks</li> </ul> </li> <li>• Efficacy endpoints at Weeks 24, 48, 96, and 144               <ul style="list-style-type: none"> <li>○ Total number of new or enlarging T2 lesions</li> <li>○ Total number of T1 Gd+ lesions</li> </ul> </li> <li>• Safety as assessed by the nature, severity, and occurrence of AEs and AESIs; vital signs; ECGs; absolute concentrations and change from Baseline in Ig levels; clinical laboratory safety parameters up to Week 144</li> </ul>

## 4 Study Design

### 4.1 Overall Design

This is a Phase III, multicenter, randomized, parallel-group, double blind, double dummy, active controlled study of evobrutinib with an active control group Avonex, in participants with RMS.

Eligible participants will be randomized 1:1 to treatment with evobrutinib **CCI** twice daily, or Avonex **CCI** once-weekly (intramuscular injection), stratified by region and Baseline EDSS. Blinding will be accomplished using a double dummy design.

The 96-week Treatment Period will be preceded by a 4-week Screening Period (may be extended but cannot exceed 8 weeks) and followed by a 4-week Safety Follow-up after treatment completion or early discontinuation.

Participants experiencing initial progression of disability between Week 72 and Week 96 will continue participating in the main study for up to 12 additional weeks. The continuation period will increase the duration of participation to a maximum of 108 weeks. Upon completion of the continuation period, participants will have the option of participating in the OLE or ending treatment (and returning for a 4-week Safety Follow-up).

Participants who complete the 96-week double blind, double dummy Treatment Period will be offered participation in the 148-week OLE Period of the study. The purpose of the OLE Period is to allow all the participants the opportunity to receive active treatment with evobrutinib and to collect long term safety and efficacy data. The Investigator should review the optional OLE Period with the participant prior to the double blind, double dummy Week 96 visit. Signed consent will be obtained prior to participation in the OLE Period. The double blind Week 96 visit (or up to Week 108 visit) will be considered the OLE Day 1 Visit. The Safety Follow-up Visit will be deferred until treatment is stopped in the OLE Period, due to either a participant's premature withdrawal/early termination from the OLE, termination of the study by the Sponsor, or completion of the OLE treatment period.

In some cases, due to relapse, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval, regulatory-specific, or other administrative delays, a participant may experience a treatment gap between the study intervention last dose received in the double blind, double dummy period (Week 96/up to Week 108 visit) and the start of the OLE study intervention treatment. Upon Principal Investigator request, these participants may still be able to enroll in the OLE with approval from Merck/EMD Serono, on a case-by-case basis, provided that the treatment gap does not exceed 60 days from the last dose of study intervention received in the double blind, double dummy period (Week 96/up to Week 108 visit), and the start of the study intervention treatment in the OLE Period. If the day of rollover to the OLE occurs after the double blind, double dummy Safety Follow-up visit, all assessments noted at the OLE Day 1 visit will need to be completed. For participants that rollover after the Week 96/up to Week 108 visit but prior to their scheduled Safety Follow-up visit, concomitant medications and AEs will need to be reviewed and updated, and the

Principal Investigator will need to ensure that the participant remains eligible for the study (see Section 5.3). No other additional assessments other than dispensing of study intervention will need to be completed.



## 4.2 Scientific Rationale for Study Design

This study was designed to determine the efficacy and safety of evobrutinib in participants with RMS. The primary objective will focus on reduction of relapses relative to Avonex over 96 weeks in adult participants with RMS based on the ARR at Week 96. The OLE will allow for assessment of long term safety and efficacy of evobrutinib.

The findings in Section 2 support the pathogenic contribution of B cells to MS damage. In contrast, a failed clinical study with another B cell targeting agent, atacicept, supports the notion that certain B cell subtypes may mediate beneficial anti-inflammatory effects (Kappos 2014). Novel nondepleting B cell therapies may deliver a more favorable benefit risk profile than current B cell directed therapeutic approaches.

There is consensus in the MS community, that the use of placebo in Phase III studies with RMS participants is no longer ethical, due to the availability of established and effective therapies (Polman 2008). Interferon-beta 1a is an acknowledged therapy that has been used in past pivotal studies as a comparator and is well-suited for the objective of this study. It is currently used as part of the standard of care platform therapies in the treatment of MS and has a well-established efficacy and safety profile.

As the active treatment is oral and the active comparator is an injectable, the study will have a double dummy design. This design minimizes the potential for bias and maintains the integrity of the clinical data generated from this study. It also reduces the risk of concluding that superiority to the active comparator was driven by participant and assessor bias.

This study plans to enroll RMS participants according to the McDonald MS 2017 criteria (Thompson 2018) with an EDSS score of 0 to 5.5 at Screening who had at least 2 documented clinical attacks within the previous 2 years, who had at least 1 or more documented relapses within the 2 years before Screening with either: 1 relapse which occurred within the last year prior to randomization, OR the presence of at least 1 Gd+ T1 lesion within 6 months prior to randomization. These criteria have been implemented to further characterize the benefits of treatment with evobrutinib in a wide range of RMS participants with varying degrees of

disease activity and severity. The age range will be limited to  $\leq 55$  years with the aim to avoid confounding by neurological conditions prevalent in older participants.

The proposed study endpoints are widely accepted as clinically relevant, and have been used in numerous pivotal clinical studies in RMS. The primary endpoint for the study will be ARR over 96 weeks, based on qualified relapses. Secondary efficacy endpoints will include total number of new or enlarging T2 lesions at Week 96 (based on post-baseline assessments at Weeks 24, 48, and 96), total number of T1 Gd+ lesions at Week 96 (based on post-baseline assessments at Weeks 24, 48, and 96), and time to 12 or 24-week CDP. Prevention of relapses, prevention/delay of accumulation of sustained neurological disability, as well as effect on MRI are meaningful goals in the treatment of participants with RMS.

Patient Reported Outcomes (PROs) including those assessing fatigue and PF, are included as a secondary endpoint (PF) and CCI in the current study. Fatigue has been reported as the most bothersome symptom for MS patients among other concerns, such as bladder and bowel problems, cognitive impairment, visual disorders, musculoskeletal issues e.g. stiffness, spasm, walking difficulty and balance problems (Martin 2017, Patti 2011, Branas 2000). In turn, these are associated with impairments in various functional areas, including instrumental activities of daily living (IADLs), limitations with physical activities such as participating in sports, limitations related to ability to work or study, and social interactions (Patti 2014, Larocca 2011). The current data from randomized controlled trial studies support positive treatment effects of currently available DMDs (including, teriflunomide, dimethyl fumarate, natalizumab, and ocrelizumab) on Health-related Quality of Life (HRQoL), i.e., improving or preventing the worsening of HRQoL (Jongen 2017).

Refer to the Investigator's Brochure for further information about the nonclinical and clinical programs and Guidance for the Investigator.

### **4.3 Justification for Dose**

Selection of the Phase III dose was based on pharmacodynamic, efficacy, and safety data from the ongoing Phase IIb study MS200527-0086, and supported by clinical pharmacology studies where dosing of the tablet was included (Studies MS200527-0017 and MS200527-0019). The models describing CCI

CCI

CCI CCI CCI CCI

Thus, the criteria for selection of an efficacious dose to be used in Phase III is based on targeting exposure of  $\geq 468$  ng•h/mL CCI

Elevated ALT values were observed based on laboratory blood tests at all dose levels in 16 participants with RMS in Study MS200527-0086, with 7.4% of the participants receiving placebo, 5.8% of the participants at 25 mg once daily, 3.8% of the participants at 75 mg once daily, and 13% of the participants at 75 mg twice daily experiencing elevated ALT levels. The mechanism for the elevated ALTs has not been identified, and there is inconclusive evidence of dose-response or exposure-response relationship.

CCI

CCI

Avonex will be administered intramuscularly at the highest approved dose of CCI once a week. Refer to the locally approved product information (e.g. relevant SmPC or US Prescribing Information) for further details.

Additional information about the justification for dose for evobrutinib may be found in the Investigator's Brochure.

#### 4.4 End of Study Definition

A participant has completed the study if he/she has completed all study parts, including the Treatment Period and the last visit (Safety Follow-up Visit).

The end of the study is defined as the date of the last visit of the last participant.

## 5 Study Population

The criteria in Sections 5.1 and 5.2 are designed to enroll only participants, who are appropriate for the study; thereby, ensuring the study fulfills its objectives. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a participant is suitable for this study.

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

Before performing any study assessments that are not part of the participant's routine medical care, the Investigator will confirm that the participant or the participant's legal representative has provided written informed consent, as indicated in [Appendix 2 Study Governance](#).

### 5.1 Inclusion Criteria

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

#### Age

1. Are 18 to 55 years of age at the time of signing the informed consent.

#### Type of Participant and Disease Characteristics

2. Are diagnosed with RMS (relapsing-remitting multiple sclerosis [RRMS] or secondary progressive multiple sclerosis [SPMS] with relapses) in accordance with 2017 Revised McDonald criteria ([Thompson 2018](#)).
3. One or more documented relapses within the 2 years before Screening with either:
  - a. one relapse which occurred within the last year prior to randomization, OR
  - b. the presence of at least 1 Gd+ T1 lesion within 6 months prior to randomization.
4. Have an EDSS score of 0 to 5.5 at Baseline
  - a. Participants with an EDSS score  $\leq 2$  at Screening are only eligible for participation if their disease duration (time since onset of symptoms) is no more than 10 years.
5. Are neurologically stable for  $\geq 30$  days prior to both Screening and Baseline.

#### Sex

6. Are female or male
    - a. Female participants
      - Are **not** pregnant or breastfeeding, and at least one of the following conditions applies:
        - o **Not** a Woman of Child Bearing Potential
- OR

- If a Woman of Child Bearing Potential, use a highly effective contraceptive method (i.e., with a failure rate of < 1% per year), preferably with low user dependency, as described in [Appendix 3](#) for the following time periods:
    - Before the first dose of the study intervention(s), if using hormonal contraception:
      - Has completed at least one 4-week cycle of an oral contraception pill and either had or has begun her menses
- OR
- Has used a depot contraceptive or extended-cycle oral contraceptive for at least 28 days and has a documented negative pregnancy test using a highly sensitive assay.

AND

- A barrier method, as described in [Appendix 3](#).
  - During the Intervention Period

After the study Intervention Period (i.e., after the last dose of study intervention is administered) for at least 90 days, plus 30 days (a menstrual cycle) after the last dose of study intervention and agree not to donate eggs (ova, oocytes) for reproduction during this period.

The Investigator evaluates the effectiveness of the contraceptive method in relationship to the first dose of study intervention.
  - Have a negative serum or highly sensitive urine pregnancy test, as required by local regulations, within 4 to 8 weeks and a highly sensitive urine pregnancy test at Baseline before the first dose of study intervention. If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required.
- Additional requirements for pregnancy testing during and after study intervention are in Section [8.2.4](#).
- The Investigator reviews the medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a female with an early undetected pregnancy

### **Informed Consent**

7. Capable of giving signed informed consent, as indicated in [Appendix 2](#), which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and this protocol.



8. Participants must be contactable by email or telephone throughout the study.

## 5.2 Exclusion Criteria

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

### Medical Conditions

1. Participants diagnosed with Progressive MS, in accordance with the 2017 Revised McDonald criteria, as follows:
  - a. Participants with Primary Progressive MS.
  - b. Participants with Secondary Progressive MS without evidence of relapse.
2. Disease duration > 10 years in participants with an EDSS  $\leq$  2.0 at Screening.
3. Immunologic disorder other than MS or any other condition requiring oral, intravenous (IV), intramuscular, or intra-articular corticosteroid therapy, with the exception of well-controlled Type 2 diabetes mellitus or well controlled thyroid disease.
4. History or current diagnosis of other neurological disorders that may mimic MS, including but not limited to: neuromyelitis optica, transverse myelitis, bilateral optic neuritis of simultaneous onset, Lyme disease, HTLV-1-associated myelopathy, untreated vitamin B12 deficiency, neurosarcoidosis, and cerebrovascular disorders.
5. History or current diagnosis of PML. If a brain MRI has findings suggestive of PML, cerebrospinal fluid JC virus polymerase chain reaction (CSF JCV PCR) should be tested to rule out PML (see [Appendix 8](#)).
6. Active, clinically significant viral, bacterial, or fungal infection, or any major episode of infection requiring hospitalization or treatment with parenteral anti-infectives within 4 weeks of Screening, or completion of oral anti-infectives within 2 weeks before or during Screening, or a history of recurrent infections (i.e., 3 or more of the same type of infection in a 12-month rolling period). Vaginal candidiasis, onychomycosis, and genital or oral herpes simplex virus considered by the Investigator to be sufficiently controlled would not be exclusionary.
7. The participant:
  - Has a history of or current diagnosis of active tuberculosis (TB)OR
  - Is currently undergoing treatment for latent TB infection (LTBI)OR
  - Has an untreated LTBI as determined by documented results within 3 months of the Screening Visit of a positive TB skin test with purified protein derivative (PPD) with induration  $\geq$  5 mm

OR



- Has current household contacts with active TB, unless prophylaxis treatment has been completed and documented evidence that household contacts have completed treatment

OR

- Has a positive QuantiFERON-TB test at Screening, unless the participant has completed chemoprophylaxis for LTBI (as per applicable local guidelines) prior to the Screening Visit.

Participants with documented completed appropriate LTBI treatment would not be excluded and are not required to be tested.

Note: TB skin test with PPD will not be performed at Screening. Reference to TB skin test results above is in reference to a potential participant's past results.

8. Indeterminate QuantiFERON-TB test results may be repeated once and will be considered positive if retest results are positive. However, if results continue to be indeterminate, then the individuals will be evaluated with T-SPOT.TB at the request of the Investigator. In this case, if the T-SPOT.TB is negative, the individual may be enrolled after approval by the Medical Monitor (see Section 8 for exceptions to tests analyzed by a central laboratory). If T-SPOT.TB is not available, then for the next steps the Medical Monitor should be contacted.
9. Individuals with a diagnosis of hemochromatosis, Wilson's disease, alpha-1-antitrypsin deficiency, or any other chronic liver disease including Gilbert's disease will be excluded from the study.
10. Individuals with elevated transferrin saturation (> 50% transferrin saturation in males; and > 40% transferrin saturation in females) and/or with elevated ferritin levels > 500 µg/L will be excluded.
11. Individuals with sickle cell anemia, thalassemia and/or any chronic blood disorder requiring blood transfusions will be excluded from the study.
12. History of splenectomy at any time, or any major surgery within 2 months prior to Screening.
13. History of myocardial infarction or cerebrovascular event within 6 months prior to Screening, or current active angina pectoris, history of or current congestive heart failure New York Heart Association (NYHA) Class III or Class IV, uncontrolled seizures (remote infantile febrile seizures are not exclusionary), prolonged untreated hypertension (Systolic  $\geq$  160 mm Hg and/or diastolic  $\geq$  100 mm Hg), active GI bleeding, or any other significant active medical condition in the Investigator's opinion or Sponsor's/designee's opinion.
14. A history of attempted suicide within 6 months prior to Screening or a positive response to items 4 or 5 of the Columbia-Suicide Severity Rating Scale (C-SSRS) at Screening.

15. An episode of major depression within the last 6 months prior to Screening (clinically stable minor depression is not exclusionary).
16. History of cancer with the following exceptions:
  - A confirmed history of non-melanoma skin cancer Stage 0 (in situ) or Stage 1, considered cured > 5 years is not exclusionary.
  - A history of in situ cervical cancer, considered cured > 5 years, is not exclusionary.
  - A history of Stage I prostate cancer with normal Prostate-Specific Antigen (PSA), considered cured for > 5 years, is not exclusionary.

Any history of cancer not meeting these exceptions is exclusionary.
17. On Screening ECG, any abnormality (e.g., uncontrolled second or third degree AV conduction block, ventricular tachyarrhythmias) that in the Investigator's opinion may impact participation in the study.
18. An active infective process or any other clinically significant abnormality on Screening Chest X-ray (CXR) taken within 4 weeks of the first dose, per Investigator opinion. If a CXR has been taken within the previous 3 months and results are available and normal, the CXR does not need to be repeated.

**Prior/Concomitant Therapy**

19. Contraindication to Avonex or incompatibility with Avonex use, including:
  - a. Hypersensitivity to natural or recombinant interferon-beta, or to any excipients.
  - b. Cessation of interferon therapy due to poor tolerability or safety concerns, or suboptimal response.
20. IV or oral glucocorticoids within 4 weeks prior to randomization (inhaled corticosteroids are allowed) (see Section 8).
21. Treatment with monthly IV methylprednisolone (see Section 6.5.1).
22. Treatment with beta-interferons or glatiramer acetate within 4 weeks prior to randomization.
23. Treatment with dimethyl fumarate within 4 weeks prior to randomization provided lymphocyte count is > 1000 cells/ $\mu$ L prior to randomization.
24. Treatment with teriflunomide within 12 weeks or after the accelerated elimination procedure 12 days prior to randomization.
25. Use of lymphocyte trafficking blockers (natalizumab or fingolimod) within 48 weeks prior to randomization.
26. Use of IV Ig or plasmapheresis within 12 weeks prior to randomization.
27. Treatment with rituximab and/or ocrelizumab. Participants who have received 1 dose of rituximab or ocrelizumab, and reason for treatment discontinuation was not

- treatment failure, will be eligible to enter the study if the last dose of rituximab or ocrelizumab was at least 48 weeks prior to randomization.
28. Treatment with any other B cell depleting therapy, BTK inhibitors (including evobrutinib), mitoxantrone, or lymphocyte-depleting therapies (e.g., alemtuzumab, anti-CD4, cladribine, cyclophosphamide, total body irradiation, bone marrow transplantation).
  29. Concomitant treatment with medications commonly used for symptom management of MS patients will be exclusionary as follows:
    - a. Participants taking dantrolene are to be excluded. Participants on other antispasticity agents can be included if they have been on a stable dose over the 3 months prior to randomization.
    - b. Participants on dalfampridine (Ampyra) or fampridine can be included only if they have been on a stable dose 3 months prior to randomization.
    - c. Medications known to lower the seizure threshold are not permitted unless reviewed and the eligibility of the participant is confirmed by the Medical Monitor.
  30. Treatment with medical marijuana for MS symptoms, unless it is consistent with local MS treatment guidelines and local regulations.
  31. On anticoagulation, or antiplatelet therapy other than daily aspirin for cardioprotection. Use of fish oil supplements within 4 weeks prior to randomization.
  32. Participants currently receiving (or unable to stop using prior to receiving the first dose of study intervention) potent (strong to moderate) inducers of cytochrome P450 3A (CYP3A) (must stop at least 3 weeks prior), medications or herbal supplements known to be potent (strong to moderate) inhibitors of CYP3A (must stop at least 1 week prior), or drugs mainly metabolized by CYP3A with a narrow therapeutic index (must be stopped at least 1 day prior) (See Section 6.5).

#### **Prior/Concurrent Clinical Study Experience**

33. Participation in any investigational drug study within 6 months or 5 half-lives of the investigational drug, whichever is longest, prior to Screening.

#### **Diagnostic Assessments**

34. Any of the following:
  - a. History of or positive for human immunodeficiency virus (HIV) at Screening.
  - b. History of or positive for hepatitis C virus (HCV) antibody and/or HCV RNA by polymerase chain reaction (PCR) at Screening. However, if a participant has a history of HCV infection and has completed, documented and appropriate treatment at least 1 year prior to Screening AND is negative for HCV RNA by PCR at Screening, participants will not be excluded from the study.

Note: All participants found to be positive for anti-HCV antibody at Screening will have reflex testing performed for HCV RNA by PCR to assess study eligibility.

- c. Positive for hepatitis B surface antigen (HBsAg) at Screening.
  - d. For participants who are negative for HBsAg at Screening but are anti-hepatitis B surface antibody positive without history of vaccination for Hepatitis B and/or anti-hepatitis B core antibody positive with or without history of vaccination for Hepatitis B at Screening, reflex testing for hepatitis B virus DNA (HBV DNA) by PCR will be performed:
    - i. Hepatitis B antibody positive participants who have detectable HBV DNA are excluded.
    - ii. Hepatitis B antibody positive participants who are HBV DNA negative are not excluded from the study. However, these participants will have HBV DNA monitoring by PCR at visits noted in the Schedule of Activities (SoA) (Section 1.3).
35. Estimated glomerular filtration rate (eGFR) by the 4-variable Modification of Diet in Renal Disease equation of  $< 60 \text{ mL/min/1.73 m}^2$  or any renal condition that would preclude the administration of gadolinium (e.g., acute kidney injury).
36. ALT, AST, amylase, or lipase  $> 2 \times$  upper limit of normal (ULN) of laboratory reference range, total bilirubin  $> 1.5 \times$  ULN, or any other clinically significant laboratory abnormality.
37. Significant cytopenia, including neutrophil count  $< 1,500/\text{mm}^3$ , platelet count  $< 75,000/\text{mm}^3$ , absolute lymphocyte count  $< 1,000/\text{mm}^3$ , or a white blood cell count  $< 3500/\text{mm}^3$ .

#### **Other Exclusions**

38. Any allergy, contraindication, or inability to tolerate Avonex or evobrutinib or any of their excipients, including lactose, which is an excipient in the oral Study Intervention (e.g., evobrutinib **CCI**, placebo **CCI**).

Note: Individuals with acquired lactose intolerance are not excluded, but should be aware that the oral Study Intervention contains lactose and should be monitored for gastrointestinal symptoms related to the increased consumption of lactose in the IMP, and made aware of the risks.

39. Inability to comply with MRI scanning, including contraindications to MRI such as known allergy or other contraindications to gadolinium contrast media, claustrophobia, presence of a pacemaker, cochlear implants, ferromagnetic devices or clips, intracranial vascular clips, insulin pumps, nerve stimulators.
40. Vaccination with live or live-attenuated virus vaccine within 1 month prior to Screening.

41. Regular alcohol consumption within 6 months prior to the study defined as: an average weekly intake of > 14 units for males or > 7 units for females. One unit is equivalent to 8 g of alcohol: a half pint (~240 mL) of beer, 1 glass (125 mL) of wine or 1 (25 mL) measure of spirits.

### **5.3 Criteria for Entry into Open Label Extension Period**

#### **5.3.1 Inclusion Criteria for Open Label Extension Period**

Participants who meet the following entry criteria may participate in the OLE Period:

1. Complete the 96-week, double blind, double dummy Treatment Period, and who, in the opinion of the Investigator, may benefit from treatment with evobrutinib.
2. Are able and willing to provide written informed consent for the OLE Phase (e.g., before the first administration on OLE Day 1) and to comply with the study protocol.
3. Are willing to continue to use the contraceptive methods as described in Section 5.1 (Inclusion Criterion 6) and Appendix 3.

#### **5.3.2 Exclusion Criteria for Open Label Extension Period**

Participants will be excluded from the OLE if they meet any of the following exclusion criteria at the OLE screening (OLE Day 1):

1. Participants who did not complete study treatment in main study/Week 96 Visit or Week 108 Visit.
2. Treatment with high-dose oral or IV steroids within 30 days before OLE Day 1.
3. Contraindications to MRI, for example, presence of pacemakers or other implanted metal devices (excluding dental braces), an allergy to gadolinium based MRI contrast, renal impairment, or claustrophobia that cannot be medically managed.
4. History of suicidal ideation or an episode of clinically severe depression (as determined by the Investigator) within 12 weeks prior to OLE Day 1.
5. History of abnormal laboratory results that, in the opinion of the Investigator, are indicative of a significant cardiac, endocrine, hematologic, immunologic, metabolic urologic, pulmonary, gastrointestinal, dermatologic, psychiatric, renal, neurologic (other than MS), and/or other major diseases.
6. Any of the following abnormal blood tests during the Treatment Period requiring discontinuation of study intervention, and/or at End of Study visit or at OLE Day 1: alanine aminotransferase/serum glutamate pyruvate transaminase (ALT/SGPT), aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT), gamma glutamyl-transferase, amylase, or lipase  $\geq 2 \times$  ULN, creatinine clearance < 60 mL/min (estimated by Cockcroft-Gault equation)
7. Female participants who have a positive pregnancy test result, are pregnant, or are currently breast feeding.

8. Inability to comply with study requirements.

## 5.4 Lifestyle Considerations

### 5.4.1 Meals and Dietary Restrictions

Refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, pomelos, grapefruit hybrids, exotic citrus fruits, cranberries, or their juices from 7 days before the start of study intervention until after the final dose.

### 5.4.2 Caffeine, Alcohol, and Tobacco

During each dosing session, participants will abstain from alcohol for 24 hours before the start of dosing until after collection of the final PK and/or pharmacodynamic sample. See Exclusion Criterion 41 for alcohol consumption while participating in the study.

There are no restrictions on caffeine or tobacco intake.

## 5.5 Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once with approval by the Medical Monitor. The second Screening Period is a new 28-day Screening Period. Rescreened participants will be assigned a new identification number. See Section 8 for required testing to be redone at rescreening.

## 6 Study Intervention(s)

Study intervention is any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant per the study protocol.

### 6.1 Study Intervention(s) Administration

<b>Study Intervention Name:</b>	Evobrutinib	Avonex (Interferon-beta 1a)
<b>CCI</b>		
<b>CCI</b>		
<b>Route of Administration:</b>	Oral	Intramuscular

<b>Dosing Instructions:</b>	<b>CCI</b>	
	At the Day 1, Week 12, Week 24, Week 48, Week 72, and Week 96 study visits in the main study, oral study interventions should be administered during the study visit to allow pre-dose assessments (see SoA [Section 1.3.1]).	
<b>Supplier/Manufacturer:</b>	Evobrutinib and placebo will be supplied by the Sponsor.	Avonex and placebo will be supplied by the Sponsor.
<b>Packaging and Labeling</b>	Evobrutinib and placebo will be packed in blister wallets/kits. Avonex and matching placebo syringes will be packed in trays/kits. Each kit will be packaged and labeled per all applicable regulatory requirements and Good Manufacturing Practice Guidelines.	

### 6.1.1 Medical Device(s) Use

1. The Sponsor-manufactured medical devices or devices manufactured for the Sponsor by a third party that are provided for use in this study are the Avonex, single-use syringes and the Avonex placebo single-use syringes, including needle.
2. Instructions for medical device use are provided in the Instructions for Use.
3. The participant will be trained at the investigational site on the appropriate use of the single-use syringe, to minimize potential injection site reactions due to poor injection technique. The participants will also be trained on the correct storage according to the Instructions for Use. The initial training will occur on the day of randomization after which the study intervention will be dispensed. The first injection will be performed under supervision. Any refresher training or additional training will be provided as needed. The participant will be instructed to contact the site if questions or problems arise.
4. The Investigator must detect, document, and report medical device incidents, including those resulting from device malfunctions, throughout the study, as specified in Section 8.3.6.3.

### 6.2 Study Intervention(s) Preparation, Handling, Storage, and Accountability

#### Storage

All study intervention supplied to each site must be stored in their original containers carefully, safely, and separately from other drugs. The storage facility at the study site must be locked and temperature controlled. Evobrutinib and placebo must be stored below 30°C (86°F). Avonex and Avonex placebo must be stored at 2°C to 8°C. The study intervention



temperature will be monitored and documented per the standard process for refrigerated medication.

In case there has been a temperature deviation at the clinical site, the site must contact the clinical research associate without delay for further evaluation and assessment by the designated quality assurance personnel at Merck Healthcare KGaA or delegated personnel at the packaging and distribution provider. The medication with the temperature excursion should still be stored at the required temperature, but quarantined during the investigations and must be appropriately labeled as “quarantine storage”.

Detailed recommendations for the use of Avonex is described in the summary of product characteristics or prescribing information, as appropriate.

The preparation, handling and storage of the study interventions will be documented in a separate Pharmacy Manual.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

- Upon receipt of the study intervention(s), the Investigator or designee must confirm appropriate temperature conditions have been maintained during transit and any discrepancies are reported and resolved before use. Also, the responsible person will check for accurate delivery. Further guidance and information for study intervention accountability are provided in the Study Reference Manual.
- Only participants enrolled in the study may receive study intervention(s) and only authorized site staff may supply it. All study intervention(s) must be stored in a secure, environmentally-controlled, and monitored (manual or automated) area, in accordance with the labeled storage conditions, and with access limited to the Investigator and authorized site staff.
- Dispensing will be recorded on the appropriate accountability forms so that accurate records will be available for verification at each monitoring visit.
- Study intervention(s) accountability records at the study site will include the following:
  - Confirmation of receipt, in good condition and in the defined temperature range.
  - The inventory provided for the clinical study and prepared at the site.
  - The dose(s) each participant used during the study.
  - The disposition (including return, if applicable) of any unused study intervention(s).
  - Dates, quantities, batch numbers, container numbers, expiry dates, and the participant numbers.
- The Investigator site will maintain records, which adequately documents that participants were provided the doses specified in this protocol, and all study intervention(s) provided were fully reconciled.



- Unused study intervention(s) must not be discarded or used for any purpose other than the present study. No study intervention that is dispensed to a participant may be re-dispensed to a different participant.
- A Study Monitor will periodically collect the study intervention(s) accountability forms.
- Further guidance and information for the final disposition of unused study intervention(s) are provided in the Study Reference Manual.

### 6.3 Measures to Minimize Bias: Study Intervention Assignment and Blinding

#### 6.3.1 Study Intervention Assignment

Participants will be randomized in a blinded fashion to either evobrutinib or Avonex treatment in a 1:1 ratio. The randomization will be stratified by 2 factors: region (4 levels: North America, Western Europe, Eastern Europe, Rest of World) and Baseline EDSS (2 levels: < 4.0, ≥ 4.0). A unique participant identification number, assigned according to the Study Reference Manual, will be used throughout the trial.

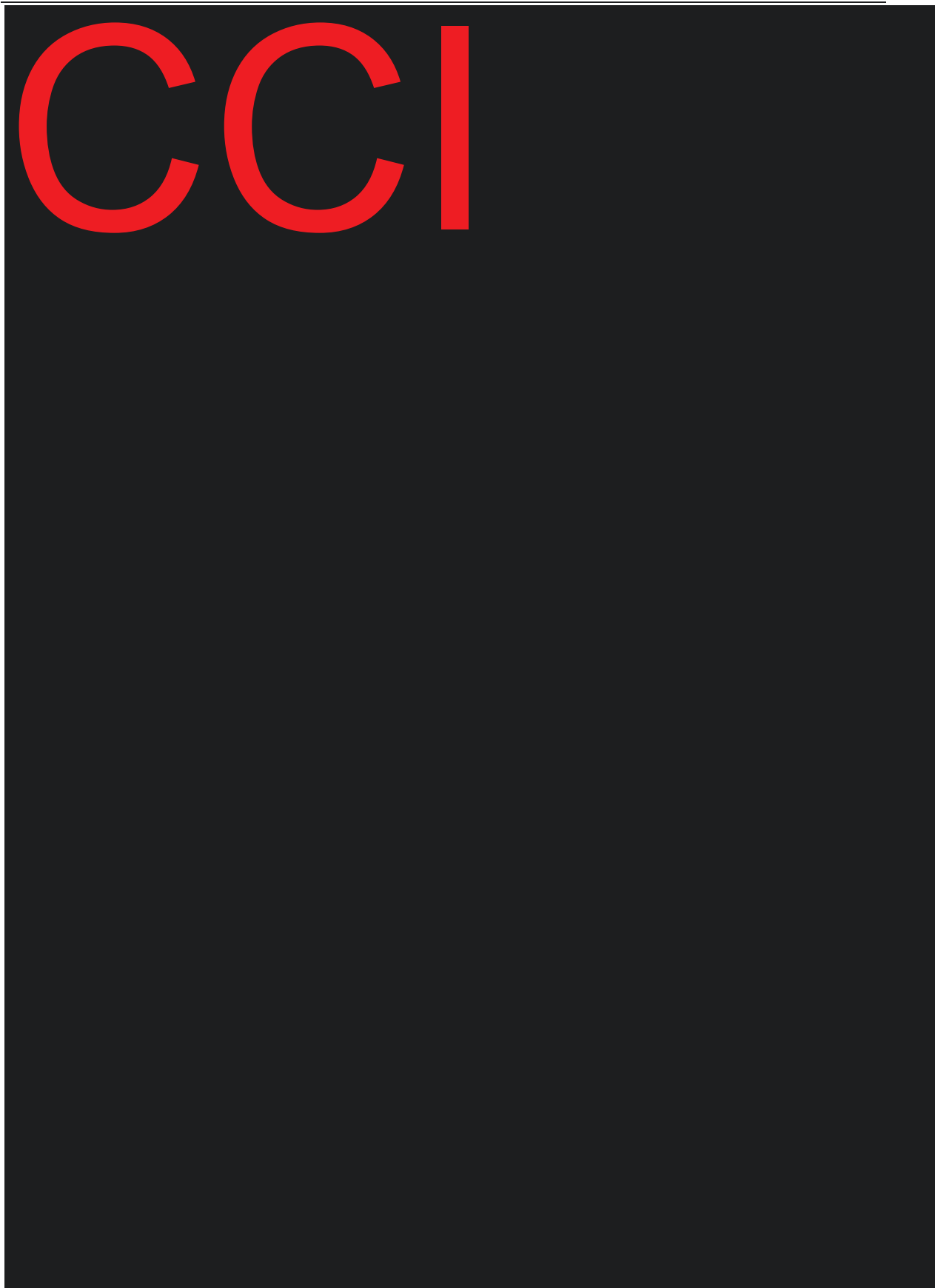
<b>Study using IWRS</b>	<p>After confirmation of participant’s eligibility and at the last practical moment prior to study intervention administration, participants will be centrally allocated to either evobrutinib or Avonex in a 1:1 ratio using an Interactive Web Response System (IWRS) and per a computer-generated randomization list.</p> <p>The IWRS will be used to assign unique participant numbers, allocate participants to study intervention group at the randomization visit, and study intervention to participants at each study intervention visit.</p> <p>Before the study is initiated, the log in information and directions for the IWRS will be provided to each site. The site will contact the IWRS prior to starting study intervention administration for each participant.</p>
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#### 6.3.2 Blinding

##### Blinding Method

- Study intervention assignment will be randomized and blinded. Blinding will be accomplished using a double-dummy design given the differences in administration between the study intervention and the active control.





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### Assignment Method Retention

- The IWRS will give the Investigator the ability to break the blind with respect to study intervention for any participant, removing the need for physical retention of the intervention assignment at the site.

### Unblinding Clinical Studies for Sample Analysis of Special Data

- The bioanalytical monitors and analytical laboratory for measurement of evobrutinib concentrations will be unblinded since obtaining the result reveals the study intervention arm for the participant. Evobrutinib concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded for the PA.

### 6.3.3 Emergency Unblinding

In an emergency, the Investigator is solely responsible for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety must always be the first consideration in this decision. The Sponsor must be notified within 24 hours after unblinding. The Investigator must provide the Sponsor the reason for unblinding without revealing the study intervention, except to the designated drug safety representative via the Emergency Unblinding Notification Form. The date of and reason for unblinding must be recorded in the source documents and CRF. Contact information for unblinding in an emergency is given on the participant emergency card provided to each participant, as noted in [Appendix 2](#) (Study Governance).

The Sponsor's drug safety department will submit any Suspected Unexpected Serious Adverse Reactions (SUSAR) reports to regulatory authorities and ethics committees with unblinded information, per applicable regulations. Only blinded information will be provided to the study team.

## 6.4 Study Intervention Compliance

The study intervention will be administered at the site on trial visit days as defined in the SoA (Section 1.3). All other administrations of study intervention will be done by the participant or participant's caregiver at home throughout the rest of the trial. Participants or participant's caregiver will be asked to record the date and time of dosing and food intake around dosing in a participant diary.

Participants will be instructed to bring all study intervention, including the used packaging/empty boxes and all blisters, to each trial visit indicated in the SoA (Section 1.3), and to allow for the assessment of compliance with study intervention. Prior to discharge from each scheduled visit, participants will be given sufficient study intervention for at-home administration until the next scheduled visit during the Treatment Period. On study visit days indicated in the SoA (Section 1.3), the previous week's study intervention adherence will be documented using pill counts.

Insufficient compliance with the protocol-specified dosing regimen is defined as receiving < 80% of the required number of scheduled doses of trial medication. Noncompliance is further addressed in Sections 7.1 and 8.4.

## 6.5 Concomitant Therapy

Record in the CRF all concomitant therapies (e.g., medicines or nondrug interventions) used from the time the participant signs the informed consent until completion of the study, including any changes. For prescription and over-the-counter medicines, vaccines, vitamins, and herbal supplements, record the name, reason for use, dates administered, and dosing information.

Contact the Medical Monitor for any questions on concomitant or prior therapy.

### Treatment for Symptoms of Multiple Sclerosis

The Treating Investigator should attempt to maintain therapies or treatments for symptoms related to MS (e.g., walking ability, spasticity, incontinence, pain, fatigue) reasonably constant throughout the study. However, if such therapies need to be added or modified during the study due to changes in the participant's clinical presentation, then this could be done at the Investigator's discretion, with the exception of those treatments listed in Section 6.5.3 (Prohibited Medications). Nonetheless, any medications that are considered necessary for the participant's well-being may be given at the discretion of the Investigator.

During the OLE, initiation of therapy with dalfampridine (Ampyra) is allowed, if indicated by the treating Investigator.

### 6.5.1 Rescue Medicine

Participants who experience a MS relapse during study intervention may receive rescue medication pursuant to the following restrictions:

1. Up to 1 g daily of methylprednisolone administered intravenous for up to 5 consecutive days. Where possible, the use of corticosteroids should be avoided in the 3 weeks prior to a scheduled MRI scan. If participants receive corticosteroids for a relapse, every effort will be made to obtain the scan prior to the first steroid dose if the pre-steroid scan is within 1 week of the scheduled visit. In all instances, the treatment of the relapse per the investigator's clinical judgement takes priority over the timing of the MRI scan.
2. Oral tapering of corticosteroid rescue medication is permitted, with a maximum of 15 days of tapering allowed.
3. In the treatment of acute exacerbations of MS, daily intramuscular or subcutaneous doses of Acthar gel, 80-120 units and not exceeding 3 weeks may be administered. An additional taper of up to 2 weeks with less frequent dosing frequency will be permitted as indicated.

## **6.5.2 Permitted Medicines**

The only permitted medications are the following:

- Medications required per the medical history that:
  - Are not specifically prohibited by the protocol during the study,
  - Are considered necessary for the participants' welfare, and
  - Will not interfere with the study intervention

Medications under the conditions described above may be given at the Investigator's discretion.

Treatment with medical marijuana for MS symptoms is permitted, if it is consistent with local MS treatment guidelines and local regulations.

Any medicines that are considered necessary to protect the participant's welfare in emergencies may be given at the Investigator's discretion, regardless if it results in a protocol deviation.

## **6.5.3 Prohibited Medicines**

Medications prohibited before the study are listed in the exclusion criteria (Section 5.2).

The following medications and therapies are not permitted during the study and would require discontinuation of the study intervention:

- Rituximab, ocrelizumab, and any other B cell depleting therapy, BTK inhibitors (including evobrutinib), mitoxantrone, or lymphocyte-depleting therapies (e.g., alemtuzumab, anti CD4, cladribine, cyclophosphamide, total body irradiation, bone marrow transplantation)
- Lymphocyte trafficking blockers (e.g., natalizumab, fingolimod)
- Intravenous Ig therapy and/or plasmapheresis and immunosuppressive treatments

- Beta-interferons (independent of study intervention) or glatiramer acetate
- Dimethyl fumarate or Teriflunomide
- Dantrolene. Other antispasticity agents are permitted at study entry if the participant has been on a stable dose over the 3 months prior to randomization. During the study, antispasticity agents can be added and/or the regimen modified based on the Investigator's clinical judgement in order to manage the participant's symptoms (see Section 6.5).
- Medications known to lower the seizure threshold should be avoided but may be used at the Investigator's discretion. Should such a medication be required, the Medical Monitor will evaluate ongoing participation in the study based on discussion with the Investigator. Dalfampridine (Ampyra) or fampridine are permitted only if the participant has been on a stable dose for 3 months prior to randomization due to the possibility of confounding effects on key study measures.
- Anticoagulation, fish oil supplements, or antiplatelet therapy other than daily aspirin for cardioprotection
- Medications known to be potent (strong to moderate) inhibitors of CYP3A, potent inducers of CYP3A, or drugs mainly metabolized by CYP3A with a narrow therapeutic index
- Biologic therapies with systemic side effects.

#### **6.5.4 Other Interventions**

Participants will be advised to use nonsteroidal anti-inflammatory drugs as needed, to counteract the side effects commonly associated with Avonex administration, or as otherwise indicated, up to the maximum recommended dose per local labeling during the trial. Caution should be exercised while using medications known to cause liver injury.

Herbal or nutritional supplements (including, but not limited to, St. John's wort, grapefruit, Seville oranges, cranberries, or juices of these fruits) known to be potent inhibitors of CYP3A must be stopped at least 1 week prior to randomization.

#### **6.6 Dose Selection and Modification**

Not applicable.

#### **6.7 Study Intervention after the End of the Study**

The Sponsor will not provide any additional care to participants after they leave the study because such care would not differ from what is normally expected for participants with relapsing forms of MS.

## 6.8 Special Precautions

See Section 7.1 for precautions related to abnormal liver function.

If any of the MRIs of the brain have findings suggestive of PML, cerebrospinal fluid JC virus polymerase chain reaction (CSF JCV PCR) should be tested to rule out PML, see Appendix 8 for further details.

## 6.9 Management of Adverse Events of Interest

Adverse events of special interests (AESI) are liver AEs (possible drug-induced, non-infectious, non-alcoholic and immune-mediated), infections (serious and opportunistic infections), lipase and amylase elevation, and seizure. All serious and nonserious AESIs must be additionally documented and reported using the appropriate Report Form as specified in Appendix 4.

### Liver adverse events

The elevations of transaminases observed in subjects treated with evobrutinib were frequent, asymptomatic, and reversible on discontinuation of evobrutinib. The mechanism is unknown.

Evobrutinib liver AESI will include transaminases and bilirubin elevations, biological Hy's Law cases based on laboratory data; any type of acute or chronic hepatitis (any grade), suspected drug-induced liver injury, acute or chronic hepatic failure, fibrosis, cirrhosis and other liver damage-related conditions.

### Infections

As per its mechanism of action, evobrutinib may impair B cell function which might lead to a decreased humoral immunity and consequently an increased risk of infection. Overall in completed studies in participants the MedDRA system organ class (SOC) CCI

Treatment of infections must be prompt and done in accordance with local standard of care depending on considerations such as the nature and severity of the infection and participant's overall health status. Any CTCAE Grade  $\geq 3$  or SAEs of infection and opportunistic infection are considered as an AESI.

### Amylase and lipase elevations

Asymptomatic elevations in amylase or lipase or both in participants treated with evobrutinib have been observed at a variety of time points and reported as TEAEs or noted as laboratory abnormalities CCI

CCI



## 7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

### 7.1 Discontinuation of Study Intervention

The Investigator should discontinue study intervention when a participant meets one of the conditions outlined below or if the Investigator believes that it is in the best interest of the participant.

If a participant's Baseline value (D1 or OLE D1, as applicable) is abnormal and/or falls within any of the conditions outlined below, consult with the Medical Monitor regarding potential discontinuation of study intervention, continued participation in study, and additional monitoring if needed. Further treatment will be at the discretion of the Investigator.

For any study treatment discontinuation related to laboratory or assessment results, the participant should be followed with additional testing as needed until a return to within normal limits or acceptable value as agreed upon by the Investigator and Medical Monitor. In cases for which permanent discontinuation of study intervention is required, no rechallenge will be allowed.

#### **Criteria for Permanent Discontinuation of Study Intervention:**

The Investigator should **permanently discontinue study intervention** and inform the Medical Monitor for the criteria outlined below.

#### For laboratory or assessment related criteria:

- a neutrophil count  $< 500 / \text{mm}^3$  (Grade 4)
- a neutrophil count 500–999 /  $\text{mm}^3$  (Grade 3) with fever
- platelet count  $< 25,000 / \text{mm}^3$  (Grade 4)



- platelet count 25,000–49,999 / mm<sup>3</sup> (Grade 3) with bleeding
- an increase in lipase to  $> 5 \times$  ULN (Grade 4)
- an increase in amylase to  $> 5 \times$  ULN (Grade 4)
- an increase in serum creatinine to  $> 3 \times$  ULN (Grade 3 or higher)
- any other laboratory abnormality of Grade 4 severity, with the exception of lymphopenia (see below)
- QTcF  $> 500$  ms OR an increase in QTcF  $> 60$  ms relative to the participant's Baseline ECG (D1) is observed and confirmed (with a second ECG).
- Detectable HBV DNA. Should this occur, consultations with specialists, such as a hepatologist, can be performed at the discretion of the Investigator and the Medical Monitor should be informed. In addition, a comprehensive hepatic/autoimmune panel is required (see below).

Note: HBV DNA is assessed only in Hepatitis B antibody-positive participants during the study (see SoA and Exclusion Criterion 34).

For other reasons:

- Pregnancy.
- Any events that endanger the safety of the participant.
- Sponsor decision to end clinical study.
- Adverse events, if discontinuation of study intervention is desired or considered necessary by the Investigator and/or participant.
- Use of prohibited medications, as defined in Section 6.5.3. Any medications that are considered necessary for the participant's well-being may be given at the discretion of the Investigator. Use of a prohibited medication may be cause for a participant to permanently discontinue study intervention; however, continuing study intervention and participation in the trial should be discussed on a case-by-case basis with the Medical Monitor.
- Lack of efficacy and/or progression of MS as defined by Investigator judgement or when a medication other than permitted medications (as defined in Section 6.5.2) is needed for treatment (see above regarding prohibited medications).

**Criteria for Temporary Discontinuation of Study Intervention:**

The Investigator should temporarily discontinue study intervention for the discontinuation criteria outlined below, inform the Medical Monitor, and perform confirmatory testing as instructed. Depending on the result of the confirmatory test, the Investigator should follow instructions as outlined below, including **permanently discontinuing study intervention** when indicated.

For any study treatment discontinuation related to laboratory or assessment results, the participant should be followed with additional testing as needed until a return to within normal limits or acceptable value as agreed upon by the Investigator and Medical Monitor. In cases

for which permanent discontinuation of study intervention is required, no rechallenge will be allowed.

Liver Function Testing criteria:

- For an increase in AST or ALT to  $> 3 \times \text{ULN}$  (Grade 2 or higher), temporarily discontinue the study intervention and recheck the value within 72 hours (and no later than 1 week).
  - **If the value is still Grade 2 or higher upon retest, the study intervention should be permanently discontinued and the Medical Monitor informed.**
  - If the value has decreased to Grade 1 or lower, the Investigator may re-initiate study intervention (see Section 7.1.1).
- For an increase in bilirubin of  $> 1.5 \times \text{ULN}$  (Grade 2 or higher), temporarily discontinue the study intervention and recheck the value within 72 hours (and no later than 1 week).
  - **If the value is still Grade 2 or higher upon retest, the study intervention should be permanently discontinued and the Medical Monitor informed.**
  - If the value has decreased to Grade 1 or lower, the Investigator may re-initiate study intervention (see Section 7.1.1).



Other Laboratory Criteria:

- For a Grade 3 decrease in neutrophil count ( $500\text{--}999 / \text{mm}^3$ ) without fever, temporarily discontinue study intervention and recheck the value within 1 week.
  - **If the value is still  $<1000 / \text{mm}^3$  (Grade 3 or higher) upon retest, permanently discontinue study intervention and inform the Medical Monitor.**

- For an improvement to Grade 2 (1000–1499 / mm<sup>3</sup>) upon retest, continue to hold the study intervention and recheck the value within 1 week.
  - If a further downward trend is observed, **permanently discontinue study intervention** and inform the Medical Monitor.
  - If no further downward trend is observed, the Investigator may re-initiate study intervention (see Section 7.1.1)
- If the neutrophil count returns to  $\geq 1500$  / mm<sup>3</sup> upon retest (i.e. returns to Grade 1 or within normal limits), the Investigator may re-initiate study intervention (see Section 7.1.1).
- For a Grade 2 decrease in neutrophil count (1000–1499 / mm<sup>3</sup>), temporarily discontinue study intervention and recheck the value within 1 week.
  - If a downward trend is observed upon retest, **permanently discontinue study intervention** and inform the Medical Monitor.
  - If no downward trend is observed, the Investigator may re-initiate study intervention (see Section 7.1.1).
- For a Grade 3 decrease in platelet count (25,000–49,999 / mm<sup>3</sup>) without bleeding, temporarily discontinue study intervention and recheck the value within 1 week.
  - **If the value is still  $< 50,000$  / mm<sup>3</sup> (Grade 3 or higher) upon retest, permanently discontinue study intervention and inform the Medical Monitor.**
  - For an improvement to Grade 2 (50,000–74,999 / mm<sup>3</sup>) upon retest, continue to hold the study intervention and recheck the value within 1 week.
    - If a further downward trend is observed upon retest, **permanently discontinue study intervention** and inform the Medical Monitor.
    - If no further downward trend is observed, the Investigator may re-initiate study intervention (see Section 7.1.1).
  - If the platelet count returns to  $\geq 75,000$  / mm<sup>3</sup> upon retest (i.e. returns to Grade 1 or within normal limits), the Investigator may re-initiate study intervention (see Section 7.1.1).
- For a Grade 2 decrease in platelet count (50,000–74,999 / mm<sup>3</sup>), temporarily discontinue study intervention and recheck the value within 1 week.
  - If a downward trend is observed upon retest, **permanently discontinue study intervention** and inform the Medical Monitor.
  - If no downward trend is observed upon retest, the Investigator may re-initiate study intervention (see Section 7.1.1).
- For an increase in amylase to  $> 2$  to  $5 \times$  ULN (Grade 3), temporarily discontinue study intervention and recheck the value within 72 hours of receipt (and no later than 1 week).
  - **If the value is still Grade 3 or higher upon retest, permanently discontinue study intervention and inform the Medical Monitor.**

- For an improvement to Grade 2 ( $> 1.5$  to  $2 \times \text{ULN}$ ) upon retest, continue to hold the study intervention and recheck the value within 1 week.
  - If the value does not decrease upon retest, **permanently discontinue study intervention** and inform the Medical Monitor.
  - If a downward trend is observed, the Investigator may re-initiate study intervention (see Section 7.1.1).
- If the amylase returns to  $\leq 1.5 \times \text{ULN}$  upon retest (i.e. returns to Grade 1 or within normal limits), the Investigator may re-initiate study intervention (see Section 7.1.1).
- For an increase in amylase to  $> 1.5$  to  $2 \times \text{ULN}$  (Grade 2), temporarily discontinue study intervention and recheck the value within 72 hours of receipt (and no later than 1 week).
  - If the value does not decrease upon retest, **permanently discontinue study intervention** and inform the Medical Monitor.
  - If a downward trend is observed, the Investigator may re-initiate study intervention (see Section 7.1.1).
- For an increase in lipase to  $> 2$  to  $5 \times \text{ULN}$  (Grade 3), temporarily discontinue study intervention and recheck the value within 72 hours of receipt (and no later than 1 week).
  - **If the value is still Grade 3 or higher, permanently discontinue study intervention and inform the Medical Monitor.**
  - For an improvement to Grade 2 ( $> 1.5$  to  $2 \times \text{ULN}$ ) upon retest, continue to hold the study intervention and recheck the value within 1 week.
    - If the value does not decrease upon retest, **permanently discontinue study intervention** and inform the Medical Monitor.
    - If a downward trend is observed, the Investigator may re-initiate study intervention (see Section 7.1.1).
  - If the lipase returns to  $\leq 1.5 \times \text{ULN}$  upon retest (i.e. returns to Grade 1 or within normal limits), the Investigator may re-initiate study intervention (see Section 7.1.1).
- For an increase in lipase to  $> 1.5$  to  $2 \times \text{ULN}$  (Grade 2), temporarily discontinue study intervention and recheck the value within 72 hours of receipt (and no later than 1 week).
  - If the value does not decrease upon retest, **permanently discontinue study intervention** and inform the Medical Monitor.
  - If a downward trend is observed, the Investigator may re-initiate study intervention (see Section 7.1.1).
- For any increase in serum creatinine  $> 1.5 \times \text{ULN}$  but  $< 3 \times \text{ULN}$  (Grade 2), temporarily discontinue study intervention and recheck the value within 72 hours of receipt (and no later than 1 week).

- If the value does not decrease upon retest, **permanently discontinue study intervention** and inform the Medical Monitor.
- If a downward trend is observed, the Investigator may re-initiate study intervention (see Section 7.1.1).
- For an absolute lymphocyte count  $< 200 / \text{mm}^3$  (Grade 4), study intervention should be temporarily discontinued, and follow-up testing should be conducted as clinically indicated
  - If the absolute lymphocyte count returns to  $800 / \text{mm}^3$  (i.e. returns to Grade 2), the Investigator may re-initiate study intervention (see Section 7.1.1).
  - If there is persistent Grade 4 lymphopenia, **permanently discontinue study intervention** and inform the Medical Monitor.
- For any other laboratory increase/decrease (as relevant) from Baseline to a clinically significant higher severity grade, temporarily discontinue study intervention and recheck the value within 72 hours of receipt (and no later than 1 week). The Investigator may re-initiate study intervention if an improving trend is observed.

For other reasons:

- At the first sign or symptom suggestive of PML, or brain MRI suggestive of PML, temporarily discontinue the study intervention and check for CSF JCV PCR. If positive, permanently withdraw the study intervention.

The SoA specifies the data to collect at study intervention discontinuation and follow-up, and any additional evaluations that need to be completed.

### 7.1.1 Temporary Discontinuation

See Section 7.1 for specific criteria for temporary discontinuation related to abnormal laboratory values. The Investigator should inform the Medical Monitor upon re-initiation of study intervention following temporary discontinuation.

### 7.1.2 Rechallenge

See Section 7.1 for specific criteria for rechallenge following temporary discontinuation for abnormal laboratory values.

## 7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time, at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.
- If a participant is permanently withdrawn from study intervention due to stopping rules (see Section 7.1), the participant should also be withdrawn from the study.
- At the time it is determined that a participant is withdrawing from the study, the participant should if possible, return for an Early Discontinuation Visit, as listed in

the SoA. The SoA specifies the data to collect at study discontinuation and follow-up, and any additional evaluations that need to be completed.

- If the participant withdraws consent for future involvement in the study, any data collected up to that point may still be used, but no future data can be generated, and any biological samples collected will be destroyed.
- Subsequent to the Early Discontinuation Visit, the participant should, if possible, enter the 4-week Safety Follow-Up Period. At the end of that 4-week period, the participant should return for the 4-week Safety Follow-Up Visit. After completing this visit, the participant would be discontinued from the study.
- A participant has the right at any time to request destruction of any biological samples taken. The investigator must document this in the site study records.

Participants who have discontinued after randomization (e.g., due to AEs or lack of efficacy) will not be replaced and will not be eligible to participate in the OLE (see Section 7.1). Participants who discontinue from the study should return for the Early Discontinuation Visit and the Safety Follow-up visit 4 weeks from the day of discontinuation of study interventions.

### **7.3 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, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain if the participant wants to or should continue in the study.
- Before a participant is deemed “lost to follow-up”, the Investigator or designee must make every effort to regain contact with the participant: 1) where possible, make 3 telephone calls; 2) if necessary, send a certified letter (or an equivalent local method) to the participant’s last known mailing address, and 3) if a participant has given the appropriate consent, contact the participant’s general practitioner for information. These contact attempts should be documented in the participant’s medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

## **8 Study Assessments and Procedures**

- Study assessments and procedures and their timing are summarized in the SoA.
- No protocol waivers or exemptions are 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 intervention.
- Adherence to the study design requirements, including those specified in the SoA, 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 screening log to record details of all participants screened, to confirm eligibility, and if applicable, record reasons for screening failure.
- Prior to performing any study assessments that are not part of the participant's routine medical care, the Investigator will obtain written informed consent as specified in [Appendix 2 Study Governance](#).
- Procedures conducted as part of the participant's routine medical care (e.g., blood count) and obtained before signing of the ICF may be used for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

The following data will be collected:

- Demography: date of birth, sex (gender), ethnicity, and race, as permitted by local regulations
- Medical history (including diagnosis and duration of MS): previous illness and surgeries (e.g., all during the past year and only major ones prior to that), concomitant illness, allergies, prior therapies for the target indication and reason for switch (i.e., relevant previous medications), therapies stopped or changed at entry into the study (includes use of drugs, alcohol, tobacco, and caffeine), special diets and, for women, menstrual status and date of last menstrual period.
- Participants will be asked to record the following information daily in a paper participant diary: dosing date and time and food intake around time of dosing.

All blood and urine tests will be analyzed by a central laboratory, with the following exceptions:

- Urine testing for  $\beta$ -human chorionic gonadotropin will be conducted at the local laboratories.
- Urine dipstick results will be interpreted locally. Please see the SoA (Section 1.3) and [Appendix 5](#) for information regarding abnormal dipstick results.

**CCI** [REDACTED] will be analyzed by the analytical laboratories specified by the Sponsor.

- HIV testing should be conducted and analyzed locally.
- In addition, ECG results will be interpreted locally by the Investigator (see Section 8.2.3).



## Screening

See the SoA (Section 1.3.1) for a list of assessments completed at Screening.

The Screening packet will be reviewed by the Medical Monitor. See [Appendix 2](#) for further details.

The Screening Period may be extended (but cannot exceed 8 weeks) for participants who have used systemic corticosteroids for their MS before Screening. For a participant to be eligible, systemic corticosteroids should not have been administered between Screening and Baseline. See [Appendix 2](#) for details of the steps to be performed.

## Retesting before Baseline

In case the Screening laboratory samples are rejected by the central laboratory or the results are not assessable or abnormal, the tests need to be repeated once within 4 weeks. Any abnormal Screening laboratory value that is clinically relevant should be retested once in order to rule out any progressive or uncontrolled underlying condition. The last value before randomization must meet study criteria. In such circumstances, the Screening Period may need to be prolonged but should not exceed 8 weeks and only after approval by the Medical Monitor.

For screen failures, see Section 5.5.

## Rescreening

Participants who are considered screen failures after a first Screening Period may undergo rescreening once, after approval by the Medical Monitor. If a participant is rescreened, all Screening tests will need to be repeated except as follows:

- a. Documented CXR and TB testing if occurred within 3 months prior to the rescreening visit.
- b. Hepatitis and HIV testing if occurred within 1 month prior to the rescreening visit.

## Unscheduled Visit

Participants should be instructed that if, at any point during the trial, they suspect that they are experiencing new or worsening neurological symptoms, including possible relapse, they should contact the Investigator as soon as possible after the onset of symptoms. If necessary, the participant should be evaluated by the Investigator within the clinic and every effort should be made to complete this evaluation within 1 week after the start of symptoms. Any assessments needed to confirm the relapse should be performed at the discretion of the Investigator. Details should be documented within the relevant section(s) of the eCRF. The definition of a qualifying and nonqualifying relapse is provided in Section 8.1.1.1.

If an MRI scan is indicated at an Unscheduled Visit for Neurological Worsening and Relapse Assessment, it should be performed prior to initiating corticosteroid therapy, where possible.



In addition, care should be taken to avoid the participant being exposed to gadolinium more than once in a 4-week period, i.e. it may be necessary to cancel the MRI scan at the next scheduled visit (all other assessments should be completed at the visit as normal). If the Unscheduled Visit is conducted for a safety concern the assessments described below should be completed and any additional assessments and further management will be at the discretion of the Investigator.

The following will be performed at an Unscheduled Visit:

- Review of concomitant medications and procedures, evaluation of AEs, disease activity assessment (relapse assessment, EDSS), complete physical examination, vital signs, and a neurologic exam
- Blood sample collection for safety assessments (hematology, chemistry, coagulation).
- Urine collection for urinalysis, and, if necessary, microscopy and protein:creatinine ratio
- Additional assessments can be performed at the discretion of the Investigator.

## **Open-label Extension Period**

After completing the Treatment Period (Weeks 1 through 96), participants will be offered the opportunity to participate in an OLE Period where all participants will receive evobrutinib. Signed consent will also be obtained prior to participation in the optional OLE Period.

Scheduled assessments will be performed according to the SoA (Section 1.3.2) before administration of the study intervention. All scheduled visits during the OLE Period may take place within the visit windows specified in the SoA. Participants who discontinue early must return for the OLE End of Treatment Visit (Week 144/Visit 26). For further details see Sections 1.3.2 and 4.

## **8.1 Efficacy Assessments and Procedures**

### **8.1.1 Neurological Assessment**

The examining neurologist (i.e., the assessor) will perform the neurological examination, document the functional system scores (FSS) and assess EDSS scores. CCI

He or she will have access only to data from assessments listed above. The examining neurologist will not be involved with any aspect of medical management of the participant and will not have access to participant data. Every effort will be made to ensure that there is no change in the examining neurologist throughout the course of the study for any individual participant. The examining neurologist will be trained and instructed not to discuss what adverse effects (if any) the participant is experiencing from their medication. The examining neurologist will receive training in performing EDSS assessments prior to the beginning of the study and must have

successfully passed an examination on performance of the Neurostatus EDSS examination within 24 months of participation. All examining neurologists will receive ongoing training on performance of the Neurostatus EDSS examination throughout the course of the study.

Prior to being examined by the examining neurologist, treating neurologists and/or study coordinators should remind participants not to discuss what (if any) adverse effects they may be experiencing; this should be documented in the source documents.

### **8.1.1.1 Qualified Relapse**

A qualifying relapse is the occurrence of new or worsening neurological symptoms attributable to MS (for > 24 hours, no fever, infection, injury, AEs, and preceded by a stable or improving neurological state for  $\geq 30$  days). The relapse should be accompanied by an increase of  $\geq 0.5$  EDSS, or 2 points increase on 1 of the FSS, or 1-point increase on  $\geq 2$  of the FSS. The increase in FSS scores must be related to the neurological symptoms which were reported as new or worsening. The change must affect the selected FSS (i.e., pyramidal, ambulation, cerebellar, brainstem, sensory, or visual, excluding bladder or bowel).

Episodic spasms, sexual dysfunction, fatigue, and mood change will not suffice to establish a relapse.



The annualized relapse rates over 96 weeks will be calculated based on qualified relapses.

### **8.1.1.2 Disability progression and Expanded Disability Status Scale**

Disability progression is defined as an increase of  $\geq 1.0$  point from the Baseline EDSS score that is not attributable to another etiology (e.g., fever, concurrent illness, or concomitant medication) when the Baseline score is 5.0 or less and an increase of  $\geq 0.5$  when the Baseline score is 5.5. Disability progression is considered sustained when the initial increase in the EDSS is confirmed at a regularly scheduled visit at least 12 weeks or 24 weeks, after the initial documentation of neurological worsening.

Confirmed disability progression, sustained for 12 and 24 weeks after the initial documentation of neurological worsening, will be analyzed as secondary endpoints.

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### 8.1.3 Patient Reported Outcomes

PRO data will be collected at the study visit with an electronic CCI device at specified study visits (see the SoA for details, Section 1.3.1). The CCI with the PRO instruments will be distributed by the Investigator staff and completed in their entirety by the participant.

PROs should be administered prior to administration of study intervention and prior to any other study assessment(s) to ensure the validity of the instruments is not compromised, and data quality meet requirements of the Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims (FDA 2009).

PRO data will be elicited from participants in this study to better characterize the clinical profile of evobrutinib. These PRO measurements are described in Sections 8.1.3.1, **CCI** and **CCI**. Please note that the methods for collecting and analyzing PRO data are different from those for the ascertainment of observed or volunteered adverse events. Due to these differences, PRO data will not be reported as adverse events and no attempt will be made to resolve any noticeable severe symptoms or functional status.

To ensure missing data are minimized, all participants will be given detailed information and training about the nature of the PRO assessments and importance of such information for the trial, at or prior to study start (based on materials provided).

Further guidance/information for study sites on procedures for collecting electronic PROs (ePROs), as well as strategies to ensure complete and high-quality PRO data will be provided in the study manual of operations.

### **8.1.3.1 Patient Reported Outcomes Measurement Information System**

The National Institute of Health Patient Reported Outcomes Measurement Information System (NIH PROMIS) comprises an extensive set of item banks and short-form measures created from the item banks that assess physical, mental, and social aspects of health in adults and children, including symptoms such as pain, fatigue, and sleep disturbance, and health domains such as physical function (PF) (Cella 2007).

The PROMIS physical function (PF) item bank was identified as having great potential for the evobrutinib program due to several factors, despite limited previous use in MS (Amtmann 2018), and lack of an MS-specific short form. First, the content includes all key aspects of physical function domain, such as IADL, lower extremity (mobility), back and neck (central), and upper extremity functioning domains (Rose 2014). Second, the development process of PROMIS items included a rigorous development and calibration process, ensuring the technical quality of items. Further, items capture the full continuum of PF, from low to high levels, which is a useful characteristic for capturing changes over time. A short form specific to MS has recently been derived with input from MS patients (n = 57) and is currently undergoing validation (Kamudoni 2018). Measures from the PF item bank are scored on a T-score metric (higher scores = higher PF). The minimal clinically important difference (MCID) score cut-off for the short form is yet to be established. A provisional MCID estimate of 5 points is proposed, based on previous research on the PF item bank (Yost 2011, Amtmann 2018).

The PROMIS Fatigue item bank includes 95 items assessing the experience (frequency, duration and intensity) as well as the impacts of fatigue on physical, mental and social activities (Lai 2011). Psychometric properties of this bank have been established across different clinic populations (Cella 2016). An 8-item short-form specific to MS, derived based on input from clinicians (n = 36) and participants with MS (n = 48), is available (Cook 2012). This short form is currently undergoing further validation. Measures from the fatigue item bank are scored on a T-score metric (higher scores = higher fatigue); a provisional MCID

estimate of 4 points is proposed based on previous research on the fatigue item bank (Yost 2011, Amtmann 2018).

The PROMIS approach offers flexibility in the selection of items and how these are administered, including use of bespoke measures, fixed short forms, or computerized adaptive testing. PROMIS based short forms for physical functioning and fatigue are currently in preparation for FDA qualification as a drug development tool (DDT) in MS (MS Working Group, 2018; DDT COA, 2018).

Physical function deterioration is defined as a reduction in PROMIS PF T-score  $\geq 5.0$  compared to Baseline PROMIS PF T-score sustained for at least 12 weeks.





## 8.2 Safety Assessments and Procedures

The safety profile of the study intervention will be assessed through the recording, reporting and analysis of baseline medical conditions, adverse events (AEs), physical examination findings, vital signs, electrocardiograms, and laboratory tests including Ig and subclass concentration.

Comprehensive assessment of any potential toxicity experienced by each participant will be conducted starting when the participants give informed consent and throughout the study. The Investigator will report any AEs, whether observed by the Investigator or reported by the participant; the reporting period is specified in Section 8.3.1.

### 8.2.1 Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

- Investigators should pay special attention to clinical signs related to previous serious illnesses.

Any physical exam abnormality findings, which are identified as clinically significant before the ICF is signed, will be captured on the Medical History eCRF. After the ICF is signed, any new physical exam abnormality findings will be captured on the Adverse Event form.

### **8.2.2 Vital Signs**

- Height at Screening and weight will also be measured and recorded. Weight will be measured and recorded at each visit where vital signs are recorded as noted in the SoA.
- Oral temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed semisupine with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).
- Vital signs will be measured in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse and respiratory rate.

### **8.2.3 Electrocardiograms**

- Triplicate 12-lead ECG will be obtained as outlined in the SoA using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, intervals.
- At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes and should occur in a resting state without prior procedure such as blood draw.
- The 12-lead ECG recordings will be obtained after 10 minutes of rest in a semisupine position.
- ECG results will be interpreted locally by the Investigator. In the event of findings that could represent clinically relevant cardiac issues (including but not limited to new or worsening arrhythmia, significant changes in ECG parameters, signs and/or symptoms that could represent cardiac events such as syncope, chest pain, etc.), additional evaluations can be performed per the Investigator's clinical judgement. (including but not limited to repeat ECGs, echocardiography, evaluation by a cardiologist).



## 8.2.4 Clinical Safety Laboratory Assessments

- Blood and urine samples will be collected for the clinical laboratory tests listed in [Appendix 5](#), at the time points listed in the SoA. All samples should be clearly identified.
- Additional tests may be performed at any time during the study, as determined necessary by the Investigator or required by local regulations.
- The tests will be performed by the central laboratory. See [Appendix 5](#) for exceptions.
- Local laboratory results are only required when central laboratory results are not available in time for study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make a study intervention decision or response evaluation, the results must be entered in the CRF.
- The Sponsor must receive a list of the local laboratory normal ranges before shipment of study intervention(s). Any changes to the ranges during the study must be forwarded to the Sponsor or designated organization.
- The Investigator must review each laboratory report, document their review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents.
- Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.
- Pregnancy testing (serum or highly sensitive urine, as required by local regulations) will be conducted at monthly intervals during study intervention administration.
- Pregnancy testing (serum or highly sensitive urine, as required by local regulations) will be conducted at the end of relevant systemic exposure of the study intervention and correspond with the time frame for female participant contraception in [Section 5.1](#).

## 8.2.5 Pregnancy

Pregnancy testing (urine or serum as required by local regulations) should be conducted as summarized in the SoA ([Section 1.3](#)) during intervention.

Urine pregnancy testing will be performed at home or at the site. Urine pregnancy test kits will be provided to the participants at site visits. The Investigator and/or delegated site staff will train the relevant participants to self-administer the urine pregnancy test, and will contact the participant by telephone to confirm completion of urine pregnancy testing and discuss results.

### **8.2.6 Immunoglobulin levels**

Blood samples for Ig levels (IgM, IgA, IgG, and IgE) will be collected as noted in the SoA (Section 1.3).

Samples will be analyzed by the central laboratory selected by the Sponsor. Samples will be collected, labeled, processed, stored, and shipped according to the instructions in the Laboratory Manual.

Results will not be disclosed to the sites, Sponsor, or representative prior to database lock to avoid unblinding. However, the IDMC will have access to these data as applicable.

### **8.2.7 Chest X-ray**

Posteroanterior CXRs will be performed as noted in the SoA (Section 1.3) according to local standard practice. Participants who had a CXR performed for clinical reasons within 3 months prior to Day 1 do not need to have the CXR repeated. The CXR should show no evidence of active infective process, or any other clinically significant abnormalities. The overall evaluation (normal/abnormal) will be recorded on the eCRF, and if abnormal, the specific abnormality will be recorded. Abnormal evaluations will be judged as clinically significant or not clinically significant by the Investigator. The CXR will be performed and read locally.

### **8.2.8 Columbia-Suicide Severity Rating Scale**

The Columbia-Suicide Severity Rating Scale (C-SSRS) will be used for prospective suicidality assessment. C-SSRS is a tool used to assess the lifetime suicidality of a participant and to track suicidal events through the treatment. The structured interview prompts recollection of suicidal ideation, including the intensity of the ideation, behavior and attempts with actual/potential lethality.

The scale will be administered by the Treating Physician at the timepoints indicated in the SoA (Section 1.3). The C-SSRS “Screening/Baseline” will be collected at Screening and Baseline and the C-SSRS “since last visit” will be collected at subsequent visits.

Subjects who answer “yes” to any suicidal behavior questions or to suicidal ideation questions 4 or 5 on the C-SSRS during the study should be referred for appropriate psychiatric care and the Medical Monitor notified.

Please note: assessing the risk of suicide is a difficult and complex task when applied to the individual participant. Certainly, no single clinical scale can replace a thorough medical examination and suicide risk assessment. Ultimately, the determination of the presence of suicidality depends on clinical judgment.

### **8.2.9 Independent Data Monitoring Committee, Endpoint Adjudication Committee, and Study Steering Committee**

#### **Independent Data Monitoring Committee**

An IDMC will be formed for this study to monitor interim safety and disease activity data on a regular basis to ensure ongoing surveillance of participant safety and to monitor the conduct of the study to protect its integrity, including recommendations about additional monitoring measures or risk mitigation procedures that may be deemed necessary to protect the study participants. After consideration, the Sponsor will inform the IDMC of any decision that will be taken in response to the IDMC recommendations. The IDMC will consist of a minimum of at least 3 expert members who are independent of the Sponsor. The members will be appointed by the Sponsor based on their expertise in biostatistics, MS and additional members with expertise in hepatology who are available on an ad hoc basis. All IDMC members will have experience in the conduct of clinical studies. Members will not be Investigators in the study, nor will they have any conflict of interest with the Sponsor. Sponsor representatives and study Investigators are not eligible for membership on the IDMC. Details regarding IDMC roles, responsibilities, activities, and possible recommendations will be provided in a separate IDMC charter.

The IDMC will review CCI [REDACTED]. The recommendations of the IDMC will not contain unblinded data or other information that could lead to Investigators or Sponsor representatives becoming unblinded. An independent statistician, who is not involved with study conduct and not a member of IDMC, is responsible for producing the CCI [REDACTED] for IDMC review.



### Study Steering Committee

A Study Steering Committee (SSC) will provide direction and oversight to the study from an Investigator's perspective, including protocol creation and amendments, study execution, and evaluation of study results at the end of study. Investigators in this clinical study and other experts who are not otherwise involved in the trial may serve on this committee.

### 8.3 Adverse Events and Serious Adverse Events

The definitions of an Adverse Event (AE) and a Serious Adverse Event (SAE) are in [Appendix 4](#).

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

The AE reporting period for safety surveillance begins when the participant is initially included in the study (date of first signature of informed consent/date of first signature of first informed consent) and continues until the Safety Follow-up Visit.

Any SAE assessed as related to study intervention must be recorded and reported, as indicated in [Appendix 4](#), whenever it occurs, irrespective of the time elapsed since the last administration of study intervention.

The method of recording, evaluating, and assessing causality of AEs (including SAEs) and the procedures for completing and transmitting SAE reports are in [Appendix 4](#).

### **8.3.2 Method of Detecting Adverse Events and Serious Adverse Events**

At each study visit, the participant will be queried on changes in his or her condition. During the reporting period, any unfavorable changes in the participant's condition will be recorded as AEs, regardless if reported by the participant or observed by the Investigator.

Complete, accurate and consistent data on all AEs experienced for the duration of the reporting period (defined below) will be reported on an ongoing basis in the appropriate section of the CRF. All SAEs and nonserious AESIs must be additionally documented and reported using the appropriate Report Form as specified in [Appendix 4](#).

### **8.3.3 Follow-up of Adverse Events and Serious Adverse Events**

AEs are recorded and assessed continuously throughout the study, as specified in Section 8.3.1 and are assessed for their outcome at the Safety Follow-up Visit. All SAEs ongoing at the Safety Follow-up Visit must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the participant is documented as "lost to follow-up". Reasonable attempts to obtain this information must be made and documented. It is also the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed. Further information on follow-up procedures is given in [Appendix 4](#).

### **8.3.4 Regulatory Reporting Requirements for Serious Adverse Events**

The Sponsor will send appropriate safety notifications to Health Authorities in accordance with applicable laws and regulations.

The Investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (particularly deaths) involving study participants to the IEC/IRB that approved the study.

In accordance with ICH GCP, the Sponsor/designee will inform the Investigator of findings that could adversely affect the safety of participants, impact the conduct of the study or alter the IEC's/IRB's approval/favorable opinion to continue the study. In line with respective regulations, the Sponsor/designee will inform the Investigator of AEs that are both serious and unexpected and considered to be related to the administered product ("suspected unexpected serious adverse reactions" or SUSARs). The Investigator should place copies of Safety Reports in the Investigator Site File. National regulations regarding Safety Report notifications to Investigators will be considered.

When specifically required by regulations and guidelines, the Sponsor/designee will provide appropriate Safety Reports directly to the concerned lead IEC/IRB and will maintain records of these notifications. When direct reporting is not clearly defined by national or site-specific regulations, the Investigator will be responsible for promptly notifying the concerned IEC/IRB of any Safety Reports provided by the Sponsor/designee and of filing copies of all related correspondence in the Investigator Site File.

For studies covered by the European Directive 2001/20/EC, the Sponsor's responsibilities regarding the reporting of SAEs/SUSARs/Safety Issues will be carried out in accordance with that Directive and with the related Detailed Guidance documents.

### **8.3.5 Pregnancy**

Only pregnancies the Investigator considers to be related to the study intervention (e.g., resulting from a drug interaction with a contraceptive method) are AEs. However, all pregnancies with an estimated conception date during the period defined in Section 8.3.1 (Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information) must be recorded in the AE page/section of the CRF for both pregnancies in female participants and pregnancies in female partners of male participants. The Investigator must notify the Sponsor/designee in an expedited manner of any pregnancy using the Pregnancy Report Form, which must be transmitted by the same process specified for SAE reporting in [Appendix 4](#), section on Reporting Serious Adverse Events and Adverse Events of Special Interest.

Investigators must actively follow up, document and report on the outcome of all these pregnancies, even if the participants are withdrawn from the study.

The Investigator must notify the Sponsor/designee of these outcomes using the Pregnancy Report Form. If an abnormal outcome occurs, the SAE Report Form will be used if the participant sustains an event and the Parent-Child/Fetus Adverse Event Report Form if the child/fetus sustains an event. Any abnormal outcome (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) must be reported in an expedited manner, as specified in Section 8.3.1, while normal outcomes must be reported within 45 days after delivery.

In the event of a pregnancy in a participant occurring during the study, the participant must be discontinued from study intervention. The Sponsor/designee must be notified without delay and the participant must be followed as indicated above.

### **8.3.6 Medical Device Incidents (Including Malfunctions)**

- Medical devices are being provided for use in this study as Avonex and Avonex placebo are supplied in single-use prefilled syringes. To fulfill regulatory reporting obligations worldwide, the Investigator is responsible for the detection and documentation of events meeting the definitions of incident or malfunction that occur during the study with such devices.
- The definition of a Medical Device Incident is in [Appendix 6](#).
- Incidents meeting the definition of an AE or a SAE will also follow the processes outlined in Section 8.3 (Adverse Events and Serious Adverse Events) and [Appendix 6](#).

#### **8.3.6.1 Time Period for Detecting Medical Device Incidents**

- Medical device incidents or malfunctions of the device that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.
- If the Investigator learns of any incident at any time after a participant has ended study participation, and such incident is considered reasonably related to a medical device provided for the study, the Investigator will promptly notify the Sponsor.
- The method of documenting Medical Device Incidents is provided in [Appendix 6](#).

#### **8.3.6.2 Follow-up of Medical Device Incidents**

- All medical device incidents involving an AE will be followed and reported in the same manner as other AEs, as specified in Section 8.3.3. This applies to all participants, including those who discontinue study intervention.
- The Investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the incident.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the Investigator.

#### **8.3.6.3 Prompt Reporting of Medical Device Incidents to Sponsor**

- Medical device incidents will be reported to the Sponsor within 24 hours after the Investigator determines that the event meets the protocol definition of a medical device incident.
- The investigator/site will send the Medical Device Incident Report Form to the Sponsor. The investigator/site will complete the IMP Complaint receipt form and send to Clinical Trial Supplies (CTS). If the server is unavailable, then use site communication with the Sponsor.
- The Sponsor will be the contact for the receipt of medical device reports and SAE.

### 8.3.6.4 Regulatory Reporting Requirements for Medical Device Incidents

- The Investigator will promptly report all incidents occurring with any medical device provided for use in the study for the Sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.
- The Investigator or responsible person per local requirements (e.g., the head of the medical institution) will comply with the applicable local regulatory requirements relating to the reporting of incidents to the IRB/IEC.

## 8.4 Treatment of Overdose

For this study, any dose of study intervention greater than the highest total daily dose included in the protocol or planned for a participant in the study within a 24-hour time period  $\pm$  6 hours will be considered an overdose.

The Sponsor does not recommend specific treatment for an overdose, but assistive/supportive measures, as necessary, should be provided.

Even if it not associated with an AE or a SAE, any overdose is recorded in the CRF and reported to drug safety in an expedited manner. Overdoses are reported on a SAE Report Form, following the procedure in [Appendix 4](#), section on Reporting Serious Adverse Events and Adverse Events of Special Interest.

A large, stylized logo consisting of the letters 'C', 'C', and 'I' in a bold, red, sans-serif font. The 'C's are circular with a gap at the bottom, and the 'I' is a simple vertical bar. The logo is centered on a solid black rectangular background.

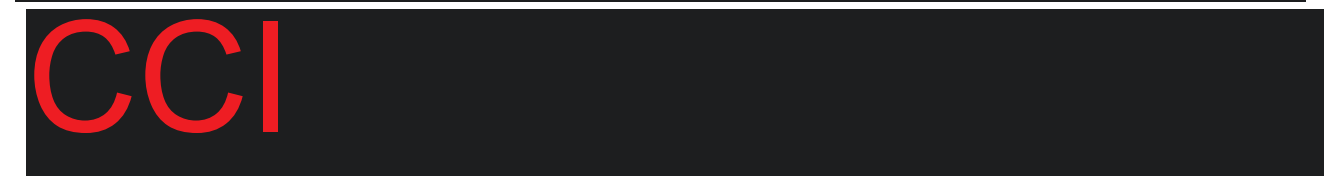
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## 9 Statistical Considerations

### 9.1 Statistical Hypotheses

#### 9.1.1 Statistical Hypotheses related to Primary Objective

The primary endpoint, ARR based on 96 weeks of follow-up and qualified relapse events from participants enrolled in the present study, will be assessed for superiority via a 1-sided test of the null hypothesis  $H_0: rRR \geq 1$ , where rRR denotes qualified relapse rate ratio comparing evobrutinib to Avonex. The alternative hypothesis is  $H_1: rRR < 1$ . The rRR effect measure will be estimated from a negative binomial (NB) model for qualified relapse count that adjusts for covariates based on stratification factors.

#### 9.1.2 Statistical Hypotheses related to Secondary Objectives

There are four efficacy secondary endpoints and two HRQoL secondary endpoints: time to first occurrence of 12-week confirmed disability progression (CDP) over 96 weeks (pooled), time to first occurrence of 24-week CDP over 96 weeks (pooled), Change from Baseline (CFB) in PROMIS Physical Function (PF) score at 96 weeks (pooled), CFB in PROMIS Fatigue score at 96 weeks (pooled), total number of T1 Gd+ lesions based on assessments at Week 24, 48, and 96, and total number of new or enlarging T2 lesions based on assessments at Week 24, 48, and 96.

The secondary endpoint, time to 12-week CDP (pooled), will be assessed for superiority via a 1-sided stratified logrank test of the null hypothesis  $H_0: S_e(t) \leq S_c(t)$ , where  $S_e(t)$  denotes the survival function for time to 12-week CDP in the experimental (evobrutinib) arm,  $S_c(t)$  denotes the survival function for time to 12-week CDP in the control (Avonex) arm, and the variable  $t$  denotes time since randomization. The alternative hypothesis is  $H_1: S_e(t) > S_c(t)$ . Strata in the logrank test will be based on randomization strata and study ID. The secondary endpoint time to 24-week CDP (pooled) will be analyzed similarly, with a similar null hypothesis tested.

The secondary endpoint, CFB in PROMIS PF score at 96 weeks (pooled), will be assessed for superiority via a 1-sided test of the null hypothesis  $H_0: \Delta_{PF} \leq 0$ , where  $\Delta_{PF}$  denotes difference in PROMIS Physical Function score Change From Baseline (CFB) at 96 weeks least-squares mean, comparing evobrutinib to Avonex, based on pooled data (higher score corresponds to improved physical function). The alternative hypothesis is  $H_1: \Delta_{PF} > 0$ . Covariates in the model used to model CFB will be based on randomization strata and study ID. The secondary endpoint CFB in PROMIS Fatigue score at 96 weeks (pooled) will be analyzed similarly, with a similar null hypothesis tested.

The secondary endpoint, total number of T1 Gd+ lesions based on scans at Weeks 24, 48, and 96, from participants enrolled in the present study, will be assessed for superiority via a 1-sided test of the null hypothesis  $H_0: IRR \geq 1$ , where IRR denotes lesion rate ratio comparing evobrutinib to Avonex. The alternative hypothesis is  $H_1: IRR < 1$ . The IRR effect measure will be estimated from a NB model for total number of T1 Gd+ lesions that adjusts for

covariates based on stratification factors. The secondary endpoint total number of active T2 lesions based on scans at Weeks 24, 48, and 96, will be analyzed similarly, with a similar null hypothesis tested.





### 9.3 Populations for Analyses

The analysis populations are specified below. The final decision to exclude participants from any analysis population will be made during a blinded data review meeting prior to database lock and unblinding.

Analysis Set	Description
Screening (SCR)	All participants, who provided informed consent, regardless of the participant's randomization and study intervention status in the study.
Full Analysis Set (FAS)	All participants who were randomized to study intervention. Participants will be analyzed per the intervention group to which they were randomized (i.e., intention-to-treat principle).
Per-Protocol (PP)	All FAS participants, who comply with the protocol in meeting criteria that could impact the proper evaluation of key objectives of the study. Clinically important protocol deviations that would lead to a participant being excluded from the PP Analysis Set will be finalized prior to database lock. Participants will be analyzed per the intervention group to which they were randomized.
Safety (SAF)	All participants, who were administered any dose of any study intervention. Participants will be analyzed per the actual study intervention they received.
Quality of life (QoL)	All FAS participants who have received at least one dose of any study intervention and have at least one Baseline and one post Baseline QoL assessment (among the following: SF-36, EQ-5D-5L, etc). Participants will be analyzed according to randomized treatment.
Open Label Extension (OLE)	All participants who receive at least 1 dose of evobrutinib during the OLE.

The following subgroups of the FAS will be considered for efficacy analyses:

- sex, age, region, severity of disease, ethnic origin, prior treatment history (including but not limited to type, number and duration of prior treatments as well as reason for switch), EDSS.

### 9.4 Statistical Analyses

This section provides a description of the statistical methods to be used to analyze efficacy, safety, and other endpoints. Prior to locking the database, a detailed Integrated Analysis Plan (IAP) will be finalized.

Unless otherwise specified, the FAS will be the PA set for all efficacy analyses, PRO analyses, and reporting of demographic and Baseline characteristics. The Safety analysis set will be used for all safety data reporting.

The secondary objectives based on disability progression and patient reported symptoms and functional status will be evaluated based on pooled data from the present study and the second Phase III study (i.e., MS200527\_0073).

### 9.4.1 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	
ARR over 96 weeks	Primary analysis based on NB model of qualified relapse count over 96 weeks, adjusted for Baseline covariates defined by randomization strata; test based on adjusted relapse rate ratio (evobrutinib versus comparator) from the model. Estimation of treatment effect (and 95% 2-sided CI) based on adjusted relapse rate ratio from NB model. In the primary analysis of ARR, missing data assumed to be missing at random, with missing data status noninformative for qualified relapse.
Secondary efficacy and HRQoL	
Time to 12-week CDP	Analyzed for participants pooled from both Phase III studies. Primary analysis based on stratified logrank test of distribution of time to 12-week CDP with strata defined by randomization strata and study ID (i.e., study 0073 or 0074), CCI [REDACTED] Estimation of treatment effect (and 95% 2-sided CI) based on hazard ratio from stratified Cox model of 12-week CDP hazard rate. Cumulative distribution function for time to 12-week CDP will be estimated via Kaplan-Meier method by treatment group. In the primary analysis of time to 12-week CDP, censoring assumed to be noninformative for 12-week CDP.
Time to 24-week CDP	Analyzed for participants pooled from both Phase III studies. Primary analysis based on stratified logrank test of distribution of time to 24-week CDP with strata defined by randomization strata and study ID. Estimation of treatment effect (and 95% 2-sided CI) based on hazard ratio from stratified Cox model of 24-week CDP hazard rate. Cumulative distribution function for time to 24-week CDP will be estimated via Kaplan-Meier method by treatment group. In the primary analysis of time to 24-week CDP, censoring assumed to be noninformative for 24-week CDP.
PROMIS physical function (PF) score CFB at Week 96	Analyzed for participants pooled from both Phase III studies. Primary analysis based on MMRM analysis where score CFB at Week 96 is modeled, with adjustment for baseline PROMIS PF score and covariates defined by randomization strata and study ID; test based on difference (evobrutinib versus comparator) in least squares means of Week 96 CFB from the model. Estimation of treatment effect (and 95% 2-sided CI) based on adjusted difference in least-squares means from the model. Cumulative distribution function for Week 96 CFB will be estimated by treatment group. In the primary analysis of PROMIS PF CFB, missing data assumed to be missing at random, with missing data status noninformative for CFB.
PROMIS fatigue score CFB at Week 96	Analyzed for participants pooled from both Phase III studies. Primary analysis based on MMRM analysis where score CFB at Week 96 is modeled, with adjustment for baseline PROMIS Fatigue score and covariates defined by randomization strata and study ID; test based on difference (evobrutinib versus comparator) in least squares means of Week 96 CFB from the model. Estimation of treatment effect (and 95% 2-sided CI) based on adjusted difference in least-squares means from the model. Cumulative distribution function for Week 96 CFB will be estimated by treatment group. . In the primary analysis of PROMIS Fatigue CFB, missing data assumed to be missing at random, with missing data status noninformative for CFB.

Endpoint	Statistical Analysis Methods
Total T1 Gd+ lesions over scans at Weeks 24, 48, and 96	Primary analysis based on NB model of total lesion count, adjusted for Baseline lesion activity and covariates defined by randomization strata; test based on adjusted lesion rate ratio (evobrutinib versus comparator) from model. Estimation of treatment effect (and 95% 2-sided CI) based on adjusted lesion rate ratio from NB model. In the primary analysis of lesion rate, missing data assumed to be missing at random, with missing data status noninformative for lesion count.
Total new or enlarging T2 lesions over scans at Weeks 24, 48, and 96	Primary analysis based on NB model of total lesion count, adjusted for Baseline lesion activity and covariates defined by randomization strata; test based on adjusted lesion rate ratio (evobrutinib versus comparator) from model. Estimation of treatment effect (and 95% 2-sided CI) based on adjusted lesion rate ratio from NB model. In the primary analysis of lesion rate, missing data assumed to be missing at random, with missing data status noninformative for lesion count.





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CCI, CDP = Confirmed disability progression, CFB = change from baseline, CCI, CI = confidence interval, CUA = combined unique active, EDSS = Expanded Disability Status Scale, EQ-5D-5L = EuroQoL 5 Dimension 5 Levels, Gd = gadolinium, HRQoL = health-related quality of life, CCI, MMRM = Mixed Effect model for repeated measures, NB = negative binomial, CCI, CCI, PROMIS = Patient Reported Outcomes Measurement Information System, SD = standard deviation, CCI, CCI, CCI

### 9.4.1.1 Efficacy Analyses related to Primary Objective

Analysis of the primary efficacy endpoint, ARR over 96 weeks, will be based on the Full Analysis set (FAS) and include all available data during the 96-week Treatment Period, as well as data from participants assigned to an additional 12 weeks of treatment. ARR will be analyzed via a NB model for qualified relapse count, with offset equal to the log of time on study in years, and adjustment for covariates defined by randomization strata. The adjusted qualified relapse rate ratio (RR) comparing evobrutinib to Avonex will be estimated from the NB model. The adjusted RR, 95% 2-sided CI, and 1-sided p-value will be reported, together with adjusted ARR for each intervention group from the model, unadjusted ARR for each intervention group calculated nonparametrically, and associated 95% 2-sided CI. The analysis of ARR will be based on data from this study alone. In the primary analysis of ARR, missing data will be assumed missing at random, with missing data status noninformative for qualified relapse.

Unadjusted annualized relapse rate over 96 weeks is calculated by dividing the total number of qualified relapse events experienced by all participants in a given arm through week 96 by the person-time (in years) observed for those participants through week 96, based on participants in the Full Analysis Set (FAS).

Adjusted annualized relapse rate over 96 weeks in each arm will be estimated using a NB model that adjusts for region (4 levels: North America, Western Europe, Eastern Europe, Rest of World) and baseline EDSS (< 4.0 versus  $\geq 4.0$ ), based on participants in the FAS.

This NB model assumes a common dispersion parameter for all patients, independent of treatment or baseline covariates. The adjusted relapse rate ratio estimate is given by exponentiation of the estimate for the treatment coefficient from the NB model. In the primary analysis, only observed events and observation time will be included in the analysis; there will be no imputation of events for patients discontinuing study early.

Sensitivity analyses are specified in Section 9.4.1.3.

### 9.4.1.2 Efficacy Analyses related to Secondary Objectives

The hypotheses tested in support of secondary efficacy objectives are described, and the inheritance of alpha graphically depicted, in Section 9.4.4.4.

Analysis of the secondary efficacy endpoint, time to 12-week CDP, will be based on the PA sets pooled from the present study and the second Phase III study, and include all 12-week CDP events where the initial disability event occurred during the first 96 weeks of treatment with subsequent confirmation, at least 12 weeks later, occurring on treatment. For participants assigned to an additional 12 weeks of treatment, for a total of 108 weeks of treatment, confirmation (or lack thereof) at Week 108 will be included in the analysis. Participants who did not have onset of CDP by completion of assigned treatment, by the time of early discontinuation of treatment, or who are lost to follow up, will be censored at the date of the last EDSS assessment during the 96-week Treatment Period. In the primary analysis of time to 12-week CDP, censoring will be assumed noninformative for 12-week CDP.



The PA of time to 12-week CDP will report the hazard ratio comparing evobrutinib to Avonex estimated via a stratified Cox model, 95% 2-sided CI, and 1-sided p-value for the **CCI** test, together with a Kaplan-Meier estimate of cumulative probability of experiencing 12-week CDP over time for each intervention group. In general, a participant not experiencing a 12-week CDP event while on treatment will have time to 12-week CDP censored at the last EDSS assessment. Prior to pooling, the validity of pooling data across the present study and the second Phase III study will be assessed by ensuring consistency of demographics, Baseline characteristics, ARR and 12-week CDP results.

The secondary endpoint, time to 24-week CDP, will be analyzed only at the time of the PA, so a conventional stratified logrank test will be used, not the **CCI** test. In all other respects, the analysis of the 24-week CDP endpoint will be the same as that of the 12-week CDP endpoint.

The secondary efficacy endpoint, Change from Baseline (CFB) in PROMIS Physical Function (PF) score at Week 96, will be analyzed based on pooled data via Mixed-Effect Model for Repeated Measures (MMRM), with adjustment for Baseline score and covariates defined by randomization strata and study ID. The difference (comparing evobrutinib and Avonex) in

least-squares mean CFB, 95% 2-sided CI, and 1-sided p-value will be reported. For each intervention group, the adjusted least-squares mean Week 96 score CFB and associated 95% 2-sided CI will be reported, as will the estimated cumulative distribution function for Week 96 score CFB. In the primary analysis of PROMIS PF CFB, missing data will be assumed missing at random, with missing data status noninformative for CFB. The CFB in PROMIS Fatigue score at Week 96 endpoint will be analyzed in the same manner as CFB in PROMIS PF score at Week 96.

The secondary efficacy endpoint, total number of T1 Gd+ lesions over scans at Weeks 24, 48, 96, will be analyzed via a NB model for total T1 Gd+ lesion count, with offset equal to the log of number of scans, and adjustment for Baseline lesion activity and covariates defined by randomization strata. The adjusted lesion RR comparing evobrutinib to Avonex estimated from the NB model, 95% two-sided CI, and 1-sided p-value will be reported, together with adjusted lesion rate for each intervention group and associated 95% 2-sided CI. The analysis of total number of T1 Gd+ lesions will be based on data from the present study only. In the primary analysis of lesion rate, missing data will be assumed missing at random, with missing data status noninformative for lesion count. The total number of new or enlarging T2 lesions endpoint will be analyzed in the same manner as total number of T1 Gd+ lesions.

### **9.4.1.3 Sensitivity Analyses**

The following sensitivity analyses for the primary endpoint ARR over 96 weeks will be considered and detailed in the IAP:

1. analysis in which multiple imputation is used to evaluate the potential influence of informative drop-outs according to drop-out reason. For each imputed data set, participants who discontinued treatment early during the 96-week Treatment Period without qualified relapse in the 30 days prior to discontinuation will be (a) imputed to relapse according to the control ARR if the drop-out reason was unrelated to treatment (i.e., unrelated to lack of efficacy or safety issues), and (b) assumed to have a qualified relapse event at the date of discontinuation if the drop-out reason was related to treatment;
2. analysis in which 100% of participants who discontinued treatment early during the 96-week Treatment Period without qualified relapse in the 30 days prior to discontinuation, are assumed to have a qualified relapse event at the date of discontinuation
3. analysis including all available data during the 96-week Treatment Period, data from participants assigned to an additional 12 weeks of treatment, and data from the Safety Follow-up;
4. analysis based on PP analysis set, to be performed if at least 10% of FAS participants are excluded from the PP analysis set;
5. analysis restricted to participants in FAS set who received study intervention, to be performed if at least 1% of FAS participants did not receive study intervention;

6. analysis with additional covariates in the NB model, such as number of relapses occurring within 2 years prior to study entry, baseline presence/absence of T1 Gd+ lesions, prior MS treatment, and age;
7. analysis of time to qualified relapse, with qualified relapse considered a recurrent event, and qualified relapse hazard ratio, comparing evobrutinib to Avonex, estimated from the time to recurrent event model.

The following sensitivity analyses for the secondary efficacy endpoint time to 12-week CDP will be considered and detailed in the IAP:

1. analysis in which multiple imputation is used to evaluate the potential influence of informative initial progression events that could not be confirmed due to drop-out, according to drop-out reason. For each imputed data set, participants who discontinued treatment early during the 96-week Treatment Period after having an initial progression event, but prior to 12-week confirmation, will be (a) imputed to have a 12-week CDP event according to the control distribution for 12-week CDP if the drop-out reason was unrelated to treatment (i.e., unrelated to lack of efficacy or safety issues), and (b) assumed to have a 12-week CDP event at the date of initial progression if the drop-out reason was related to treatment;
2. analysis in which 100% of participants who discontinued treatment early during the 96-week Treatment Period after having an initial progression event, but prior to 12-week confirmation, are assumed to have a 12-week CDP event at the date of initial progression;
3. analysis based on PP analysis set, to be performed if at least 10% of FAS participants are excluded from the PP analysis set;
4. analysis with additional covariates in the stratified Cox model, such as number of relapses occurring within 2 years prior to study entry, baseline presence/absence of T1 Gd+ lesions, prior MS treatment, and age.

Sensitivity analyses for time to 24-week CDP will be similar.

The following sensitivity analyses for the secondary HRQoL endpoint PROMIS Physical Function (PF) score CFB at Week 96 will be considered and detailed in the IAP:

1. analysis in which multiple imputation is used to evaluate the potential influence of informative drop-outs. For each imputed data set, participants who discontinued treatment early during the 96-week Treatment Period will be imputed to have a score CFB value at a given timepoint according to the control score CFB distribution at that timepoint;
2. analysis based on PP analysis set, to be performed if at least 10% of FAS participants are excluded from the PP analysis set;

Sensitivity analyses for PROMIS Fatigue score CFB at Week 96 will be similar.

The following sensitivity and supplemental analyses for the secondary efficacy endpoint total T1 Gd+ lesions (or new/enlarging T2 lesions) will be considered and detailed in the IAP:

1. analysis in which multiple imputation is used to evaluate the potential influence of informative drop-outs. For each imputed data set, participants who are missing one or more scans planned during the 96-week Treatment Period will be imputed to have a lesion count at the missing scans according to the control lesion rate;
2. (supplemental) lesion count at a single scan modeled as Poisson-distributed, with a random effect for participant, and adjustment for Baseline lesion activity and covariates defined by randomization strata. This model will compare treatment on the basis of conditional adjusted lesion rate ratio, where conditioning is on the random effect.
3. (supplemental) total lesion count compared between arms on the basis of distribution location shift (Hodges-Lehmann estimate) and Wilcoxon rank sum test, stratified according to randomization strata, and baseline lesion activity.

## 9.4.2 Safety Analyses

All safety analyses will be performed on the Safety Analysis population.

Endpoint	Statistical Analysis Methods
Primary	Not applicable.
Secondary	
Adverse Events	Descriptive statistics, AESI summaries, 3-Tier AE summaries
Clinical Laboratory Test Values	Descriptive statistics, shift tables, boxplots, individual participant line plots, Kaplan-Meier analyses of time to event, Evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) figures
CCI	CCI
ECG Parameters	Descriptive statistics
Vital Signs	Descriptive statistics
CCI	

### 9.4.2.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All treatment-emergent AEs (TEAEs) will be summarized by intervention group. Treatment-emergent AEs are defined as AEs that occurred or worsened on or after the first dose of study intervention. The number and percentage of participants who experienced at least 1 TEAE will be summarized by SOC and preferred term. The percentage will be based on the number of participants in each intervention group. Treatment-emergent AEs will also

be summarized by relationship to intervention and by severity within each intervention group. Deaths, SAEs, AESIs, and AEs leading to study discontinuation will be tabulated and presented in data listings. Participant level data listings of all AEs will be presented.

Summary and analysis of AEs will be performed based on the 3-tier approach (Crowe 2009) as further detailed in the IAP. Tier 1 AEs and AESIs will be pre-defined in the IAP.

#### **9.4.2.2 Clinical Laboratory Test Values**

Clinical laboratory results (chemistry, hematology, and urinalysis) will be summarized using descriptive statistics for each visit by intervention group. Observed values at each visit and changes from Baseline to each post-baseline visit will be presented. For clinical laboratory parameters with associated normal ranges, number and percentage of participants having high/low/normal findings for worst on-treatment laboratory value will be summarized by intervention group; shift tables will be used to summarize changes from Baseline finding to worst on-treatment finding. For clinical laboratory parameters with National Cancer Institute (NCI)- Common Terminology Criteria for Adverse Events (CTCAE) grades, shift tables will be used to summarize changes from Baseline grade to worst on-treatment grade. The distribution of selected laboratory parameters by time point and intervention group will be displayed via boxplots. All laboratory data will be provided in participant data listings.

Analyses of liver enzyme tests will include Kaplan-Meier estimates of time to ALT or AST events, plots supporting evaluation of Drug-Induced Serious Hepatotoxicity (eDISH), and individual participant profiles.

#### **9.4.2.3 Vital Signs**

Observed values at each visit and changes from Baseline to each post-baseline visit in vital signs (blood pressure, pulse rate, respiratory rate, and temperature) will be summarized by time point and intervention group using descriptive statistics. Similar summaries of descriptive statistics will be provided for the vital signs collected before and after the first dose of study intervention. Out-of-range values of vital signs will be tabulated as appropriate. All vital signs will be provided in participant data listings.

#### **9.4.2.4 Electrocardiogram Parameters**

Observed values at each visit and change from Baseline to Week 96 in ECG parameters (e.g., PR, HR, QRS, RR, QT, and QTc) will be summarized by intervention group using descriptive statistics. QTc will be reported based on Fridericia's method. Percentage and counts of participants with normal and abnormal ECG findings will be summarized by intervention group. Out-of-range values of ECG parameters will be tabulated as appropriate. All ECG data will be provided in participant data listings.

For all ECG parameters, the results for categorical analysis will be summarized by intervention group and visit (or time point) in frequency tables with counts and percentages of participants.

Categories will cover absolute values and changes from Baseline:

HR:

- Absolute < 50 bpm, < 40 bpm, < 30 bpm
- Change from Baseline > 20 bpm, > 30 bpm, > 40 bpm

PR:

- Absolute > 200 msec and > 220 msec
- Change from Baseline

QRS:

- Absolute > 110 msec

QTc:

- Absolute > 450 msec, > 480 msec, and > 500 msec
- Change from Baseline > 30 msec and > 60 msec

Electrocardiogram parameters will be summarized using descriptive statistics for continuous variables such as QTc intervals, and frequency counts and percentages for categorical variables.

#### **9.4.2.5 Concomitant Medication and Procedures**

Prior and concomitant medications will each be categorized by therapeutic class and preferred term using World Health Organization (WHO) Drug coding dictionary. The number and percent of participants using each prior and concomitant medication will be summarized by therapeutic class and preferred drug name for each intervention group. Participants who reported more than 1 medication for a particular preferred term will be counted once for each preferred term and therapeutic class.

Concomitant procedures will be classified by medical review. The number of and percent of participants experiencing each prior and concomitant procedure will be summarized by type of procedure for each intervention group.

#### **9.4.2.6 Columbia-Suicide Severity Rating Scale**

Results of the C-SSRS will be listed for each visit by participant.





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#### **9.4.3.2 Demographics, Baseline Characteristics, Disposition, and Compliance**

Participant demographics, such as age, sex, race, will be summarized by intervention group using descriptive statistics. Baseline disease characteristics (including MS history and MRI characteristics), such as Baseline EDSS, number of relapses in the 1 year and 2 years prior to randomization, time (in years) since onset of MS symptoms, time (in years) since MS diagnosis, Baseline number of T1 Gd+ lesions, Baseline number of T2 lesions, and Baseline T2 lesion volume, prior MS study treatment will also be summarized.

Disposition of participants (i.e., discontinuation from treatment by reason, discontinuation from study by reason) and compliance of participants to intervention will be summarized by intervention group using descriptive statistics.

#### **9.4.3.3 Patient Reported Outcome Analyses**

The endpoint change from Baseline (CFB) in PRO score at a given time point (Week 48 or Week 96), will be compared between evobrutinib and Avonex via a Mixed-Effect Model for Repeated Measures (MMRM) based on pooled data, adjusted for Baseline PRO score and



covariates defined by randomization strata and study ID. The adjusted difference in least-squares mean change from Baseline at a given time point (Week 48 or Week 96), comparing evobrutinib to Avonex, 2-sided 95% CI, and 1-sided p-value will be reported. A similar analysis will be performed for all PRO score change from Baseline endpoints. CCI

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#### 9.4.3.5 Analysis of Open Label Extension Period Endpoints

Efficacy and HRQoL data collected during the 144-week OLE Period will be summarized. Details will be provided in the IAP.

Safety data collected during the 144-week OLE Period will be analyzed as described in Section 9.4.2.

#### 9.4.4 Sequence of Analyses

Three analyses are planned for the study: CCI

(2) a primary analysis (PA), performed by the Sponsor, with timing and endpoint evaluation as described in Section 9.4.4.2, and (3) a final analysis (FA), performed by the Sponsor, triggered when 100% of participants enrolled in the OLE complete the OLE, or discontinue prematurely from the OLE. The IA will not be performed for futility.

If the sample size is not increased at the time of the IA, and the PA of the present study occurs prior to the PA of the second Phase III study, there will be an analysis of endpoints based on data pooled from the two studies at the time of the PA of the second Phase III study.

In addition, analyses will be performed at regular intervals for the purpose of safety monitoring by the IDMC, as described in the IDMC Charter.

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#### 9.4.4.2 Primary Analysis

If the sample size is not increased when the IA is performed, the PA of the present study will be triggered when the last participant reaches 96 weeks of treatment or discontinues from treatment prematurely during the blinded Treatment Period, and completes Safety Follow-up, or discontinues from the study prematurely during the blinded Treatment Period. Given that the primary analyses of this study and the second Phase III study are unlikely to coincide, endpoints based on data pooled from both studies will be evaluated at the time of the last study-specific PA.

If the sample size is increased when the IA is performed, the PA will be triggered when the recalculated number of events from the pooled studies is reached based on events occurring during the blinded Treatment Period, or when the last participant from both studies reaches 96 weeks of treatment or discontinues from treatment prematurely during the blinded Treatment Period, and completes Safety Follow-up or discontinues from study prematurely during the blinded Treatment Period, whichever occurs first.

After protocol deviations are determined, and the database is locked for the primary analysis, the drug codes will be broken and made available for the primary data analysis. All endpoints based on Baseline to Week 96 data will be evaluated.

### 9.4.4.3 Final Analysis

The final analysis will occur only when the last participant enrolled in the OLE completes the OLE or discontinues prematurely, the protocol deviations are determined, and the database is locked for the final analysis. All endpoints based on OLE data will be evaluated.

### 9.4.4.4 Multiplicity



To control trial-wise and family-wise type I error at the 1-sided 0.025 level in the presence of multiple endpoint testing, a graphical approach to sequentially rejective multiple testing will be employed (Bretz 2009, Hung 2013). The 1-sided null hypotheses in the graph are as follows, where “Study 1” denotes the present study, and “Study 2” denotes the second Phase III study:

Primary Endpoint Null Hypotheses:

$H_{011}$ :  $rRR_1 \geq 1$ , where  $rRR_1$  denotes qualified relapse rate ratio comparing evobrutinib to Avonex in Study 1

$H_{012}$ :  $rRR_2 \geq 1$ , where  $rRR_2$  denotes qualified relapse rate ratio comparing evobrutinib to Avonex in Study 2

Secondary Endpoint Null Hypotheses:

$H_{02}$ :  $S_{12e}(t) \leq S_{12c}(t)$ , where  $S_{12e}(t)$  denotes the survival function for time to 12-week CDP in the experimental (evobrutinib) arm based on pooled data,  $S_{12c}(t)$  denotes the survival function for time to 12-week CDP in the comparator (Avonex) arm based on pooled data, and the variable  $t$  denotes time since randomization.

$H_{03}$ :  $S_{24e}(t) \leq S_{24c}(t)$ , where  $S_{24e}(t)$  and  $S_{24c}(t)$  denote the survival functions for time to 24-week CDP based on pooled data

$H_{04}$ :  $\Delta_{PF} \leq 0$ , where  $\Delta_{PF}$  denotes difference in PROMIS Physical Function score Change From Baseline (CFB) at 96 weeks least-squares mean, comparing evobrutinib to Avonex, based on pooled data (higher score corresponds to improved physical function) .

$H_{05}$ :  $\Delta_{Fatigue} \leq 0$ , where  $\Delta_{Fatigue}$  denotes difference in PROMIS Fatigue score CFB at 96 weeks least-squares mean, comparing evobrutinib to Avonex, based on pooled data (higher score corresponds to reduced fatigue).

$H_{061}$ :  $IRR_{61} \geq 1$ , where  $IRR_{61}$  denotes T1 Gd+ lesion rate ratio comparing evobrutinib to Avonex in Study 1

$H_{062}$ :  $IRR_{62} \geq 1$ , where  $IRR_{62}$  denotes T1 Gd+ lesion rate ratio comparing evobrutinib to Avonex in Study 2

$H_{071}$ :  $IRR_{71} \geq 1$ , where  $IRR_{71}$  denotes new or enlarging T2 lesion rate ratio comparing evobrutinib to Avonex in Study 1

$H_{072}$ :  $IRR_{72} \geq 1$ , where  $IRR_{72}$  denotes new or enlarging T2 lesion rate ratio comparing evobrutinib to Avonex in Study 2.

At the primary analysis, the primary efficacy endpoint, ARR, will be tested at the  $0.025 - \alpha_1/2$  (1-sided) level in each study, assuming  $\alpha_1$  (1-sided) is spent in the conduct of the IA of 12-week CDP based on pooled data. [Figure 2](#) shows the multiple testing procedure (MTP) involving study-specific endpoints and pooled endpoints, with the simplifying assumption that  $\alpha_1 = 0$ .

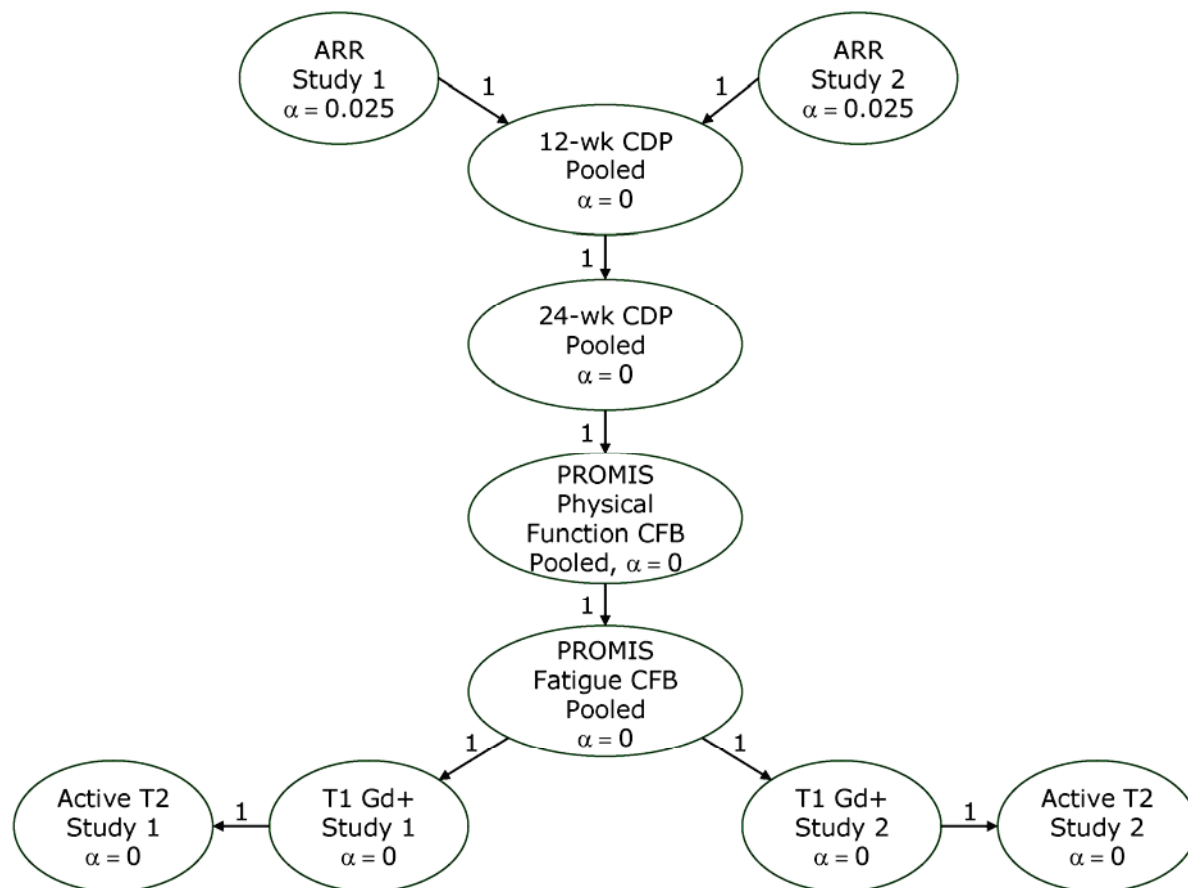
At the primary analysis, the 12-week CDP pooled endpoint will be tested at the  $0.025 - \alpha_1$  level, 1-sided, only if ARR is significant in both studies at the  $0.025 - \alpha_1/2$  level, 1-sided.

If the 12-week CDP pooled endpoint is significant at the  $0.025 - \alpha_1$  level, 1-sided, the subsequent pooled endpoints (24-week CDP, PROMIS PF CFB at Week 96, PROMIS Fatigue CFB at Week 96) will be tested in a hierarchical order at  $0.025 - \alpha_1$  level, 1-sided.

If all the pooled endpoints (12-week CDP, 24-week CDP, PROMIS PF CFB at Week 96, PROMIS Fatigue CFB at Week 96) are significant at the  $0.025 - \alpha_1$  level, 1-sided, then the T1 Gd+ endpoint will be tested within each study at the  $0.025 - \alpha_1/2$  level, 1-sided.

If the T1 Gd+ endpoint within a study is significant at the  $0.025 - \alpha_1/2$  level, 1-sided, then the active T2 endpoint for that study will be tested at the same level.

Figure 2 Multiplicity Graph



ARR = Annualized Relapse Rate, CDP = Confirmed Disability Progression, CFB = change from baseline, Gd<sup>+</sup> = gadolinium positive, PROMIS = Patient Reported Outcomes Measurement Information System, T1 and T2 = type of Magnetic Resonance Image, Wk = Week.

## 10 References

**CCI**

Amtmann D, Bamer AM, Kim J, et al. People with multiple sclerosis report significantly worse symptoms and health related quality of life than the US general population as measured by PROMIS and NeuroQol outcome measures. *Disabil Health J.* 2018;11(1):99-107.

Bar-Or A, Fawaz L, Fan B, et al. Abnormal B-cell cytokine responses a trigger of T-cell-mediated disease in MS? *Ann Neurol.* 2010;67(4):452-61.

Block H, Zarbock A. The Role of the Tec Kinase Bruton's Tyrosine Kinase (Btk) in Leukocyte Recruitment. *Int Rev Immunol.* 2012;31:104-18.

Boschart U, Crandall T, Pereira A, et al. T Cell Mediated Experimental CNS Autoimmunity Induced by PLP in SJL Mice is modulated by Evobrutinib (M2951) a Novel Bruton's Tyrosine

Kinase Inhibitor. EMD Serono Research and Development Institute, Billerica, Massachusetts, USA. 2017 P678.

Brañas P, Jordan R, Fry-Smith A, et al. Treatments for fatigue in multiple sclerosis: a rapid and systematic review. *Health Technol Assess.* 2000;4(27):1-61.

Bretz F, Maurer W, Brannath W, et al. A graphical approach to sequentially rejective multiple test procedures. *Stat Med.* 2009;28:586-604.

Cella D, Gershon R, Lai JS, et al. The future of outcomes measurement: item banking, tailored short-forms, and computerized adaptive assessment. *Qual Life Res.* 2007;16:133-41.

Cella D, Lai JS, Jensen SE, et al. PROMIS Fatigue Item Bank had Clinical Validity across Diverse Chronic Conditions. *J Clin Epidemiol.* 2016;73:128-34.

Cook KF, Bamer AM, Amtmann D, et al. Six Patient-Reported Outcome Measurement Information System Short Form Measures Have Negligible Age- or Diagnosis-Related Differential Item Functioning in Individuals With Disabilities. *Arch Phys Med Rehabil.* 2012;93:1289-91.

Crowe BJ, Xia HA, Berlin JA, et al. Recommendations for safety planning, data collection, evaluation and reporting during drug, biologic and vaccine development: a report of the safety planning, evaluation, and reporting team. *Clin Trials.* 2009;6(5):430-40.

**CCI**

De Stefano N, Iannucci G, Sormani MP, et al. MR correlates of cerebral atrophy in patients with multiple sclerosis. *J Neurol.* 2002;249(8):1072-7.

Drug Development Tools Clinical Outcome Assessments #000069: PROMIS® Physical Functioning Item Bank. Available at:  
<https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm626855.htm>. Accessed 11 April 2019.

Fraussen J, de Bock L, Somers V et al. B cells and antibodies in progressive multiple sclerosis: Contribution to neurodegeneration and progression. *Autoimmun Rev.* 2016;15(9):896-9.

**CCI**

Hauser SL, Waubant E, Arnold DL, et al. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. *N Engl J Med.* 2008;358(7):676-88.

Hawker K, O'Connor P, Freedman MS, et al. Rituximab in Patients with Primary Progressive Multiple Sclerosis, Results of a Randomized Double-Blind Placebo-Controlled Multicenter Trial. *Ann Neurol.* 2009;66:460–71.

Hung HMJ and Wang S. Multiple comparisons in complex clinical trial designs. *Biometrical Journal*. 2013;55:420-9.

Jelcic L, Nimer FA, Wang J, et al. Memory B cells Activate Brain-Homing, Autoreactive CD4+ T Cells in Multiple Sclerosis. *Cell* 2018;175(1): Epub.

Jongen PJ. Health-Related Quality of Life in Patients with Multiple Sclerosis: Impact of Disease-Modifying Drugs. *CNS Drugs*. 2017;31(7):585-602.

Kamudoni P, Henke C, Barrett A, et al. A new PROMIS physical function short form for use in relapse and progressive multiple sclerosis types. *Qual Life Res*. 2018;27(1):S1–S190.

Kappos L, Hartung H-P, Freedman MS, et al. Atacept in multiple sclerosis (ATAMS): a randomised, placebo-controlled, double-blind, phase 2 trial. *Lancet Neurol*. 2014;13:353–63.

Lai JS, Cella D, Choi S, et al. How item banks and their application can influence measurement practice in rehabilitation medicine: a PROMIS fatigue item bank example. *Arch Phys Med Rehabil*. 2011;92:S20-7.

LaRocca NG. Impact of Walking Impairment in Multiple Sclerosis Perspectives of Patients and Care Partners. *Patient*. 2011;4(3):189-1.

Li R, Rezk A, Miyazaki Y, et al. Proinflammatory GM-CSF-producing B cells in multiple sclerosis and B cell depletion therapy. *Sci Transl Med*. 2015;7(310):1-10.

López-Herrera G, Vargas-Hernández A, González-Serrano ME et al. Bruton's tyrosine kinase-an integral protein of B cell development that also has an essential role in the innate immune system. *Journal of Leukocyte Biology*. 2014;95:243-50.

Martin SA, Olayinka-Amao OC, Henke C, et al. Conceptual Model and Instrument Review in Multiple Sclerosis. ISPOR-EU: 4-8 November 2012; Glasgow, Scotland.

**CCI**

McHorney CA, Ware JE Jr, Rogers W, et al. The validity and relative precision of MOS short and long form health status scales and Dartmouth COOP charts. *Med Care*. 1992;30(Suppl 5):MS253-65.

**CCI**

Montalban X, Hemmer B, Rammohan K, et al. A Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Phase III Trial to Evaluate Efficacy and Safety of Ocrelizumab in Primary Progressive Multiple Sclerosis. Poster session presented at: Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS) Forum; 2016 Feb 18-20; New Orleans, LA.

**CCI**

Multiple Sclerosis Working Group, presented at the Ninth Annual PRO Consortium Workshop. Available at:  
[https://c-path.org/wp-content/uploads/2018/05/2018\\_MS\\_WG\\_Poster.pdf](https://c-path.org/wp-content/uploads/2018/05/2018_MS_WG_Poster.pdf). Accessed 11 April 2019.

Patti F, Amato MP, Trojano M, et al. Quality of life, depression and fatigue in mildly disabled patients with relapsing-remitting multiple sclerosis receiving subcutaneous interferon beta-1a: 3-year results from the COGIMUS (COGnitive Impairment in MUltiple Sclerosis) study. *Mult Scler*. 2011;17(8):991-1001.

Patti F, Vila C. Symptoms, prevalence and impact of multiple sclerosis in younger patients: a multinational survey. *Neuroepidemiology*. 2014;42:211-8.

Polman CH, Reingold SC, Barkhof F, et al. Ethics of placebo-controlled clinical trials in multiple sclerosis: a reassessment. *Neurology*. 2008;70(13 Pt 2):1134-40.

Poser CM and Brinar W. Epilepsy and multiple sclerosis. *Epilepsy Behav*. 2003;4(1):6-12.

Rawji KS, Mishra MK, Michaels NJ, et al. Immunosenescence of microglia and macrophages: impact on the ageing central nervous system. *Brain*. 2016;139:653-61.

Rose M, Bjorner JB, Gandek B, et al. The PROMIS Physical Function item bank was calibrated to a standardized metric and shown to improve measurement efficiency. *J Clin Epidemiol*. 2014;67:516-26.

Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol*. 2018;17(2):162-173.

**CCI**

Vogel DYS, Vereyken EJF, Glim JE et al. Macrophages in inflammatory multiple sclerosis lesions have an intermediate activation status. *J Neuroinflammation*. 2013;10(35):pub.

**CCI**

Wattjes M, Richert ND, Killestein J, et al. The chameleon of neuroinflammation: magnetic resonance imaging characteristics of natalizumab-associated progressive multifocal leukoencephalopathy. *Mult Scler*. 2013;19:1826-40.

**CCI**

Wolinsky J, Arnold DL, Bar-Or A, et al. Efficacy of Ocrelizumab in Patients With PPMS With and Without T1 Gadolinium-Enhancing Lesions at Baseline in a Phase III, Placebo-Controlled Trial. Poster session presented at: Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS) Forum; 2016 Feb 18-20; New Orleans, LA.

Yost KJ, Eton DT, Garcia SF, et al. Minimally important differences were estimated for six PROMIS-Cancer scales in advanced-stage cancer patients. *J Clin Epidemiol*. 2011;64(5):507-16.



Yousry TA, Pelletier D, Cadavid D, et al. Magnetic resonance imaging pattern in natalizumab-associated progressive multifocal leukoencephalopathy. *Ann Neurol.* 2012;72:779-87.

11 Appendices

## Appendix 1 Abbreviations

CCI	
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine aminotransferase
ARR	Annualized Relapse Rate
AST	Aspartate aminotransferase
AUC	Area under the curve
AV	Atrioventricular
BEA	Blinded Extension Analysis
BID	Twice daily
CCI	
CCI	CCI
CDP	Confirmed disability progression
CFB	Change from baseline
CCI	CCI
CI	Confidence interval
CNS	Central nervous system
CP	Conditional power
CRF	Case Report Form
CRO	Contract Research Organization
CSF	Cerebrospinal fluid
CSR	Clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CTS	Clinical Trial Supplies
CUA	Combined unique active
CXR	Chest X-ray
CYP3A	Cytochrome P450 3A
DAC	Data Analysis Center

DMD	Disease-modifying drugs
EAC	Endpoint Adjudication Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
EDSS	Expanded Disability Status Scale
eGFR	Estimated glomerular filtration rate
<b>CCI</b>	
FA	Full Analysis
FAS	Full Analysis Set
F/D	Follow-up/Discontinuation
FDA	Food and Drug Administration
FLAIR	Fluid-attenuated inversion recovery
FSH	Follicle-stimulating hormone
FSS	Functional system scores
GCP	Good Clinical Practice
Gd	Gadolinium
HCV	Hepatitis C virus
HFE	High Iron Fe (human hemochromatosis protein)
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life
<b>CCI</b>	
HRT	Hormonal replacement therapy
IA	Interim analysis
IAP	Integrated Analysis Plan
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IRB	Institutional Review Board

IWRS	Interactive Web Response System
LFT	Liver function test
LTBI	Latent TB infection
MCID	Minimal clinically important difference
MedDRA	Medical Dictionary of Regulatory Activities
MRI	Magnetic Resonance Imaging
MMRM	Mixed effect model for repeated measures
MS	Multiple sclerosis
NB	Negative binomial
NCI	National Cancer Institute
NYHA	New York Heart Association
OLE	Open Label Extension
PA	Primary Analysis
CCI	
PF	Physical function
CCI	
PML	Progressive multifocal leukoencephalopathy
PP	Per-Protocol
PRO	Patient Reported Outcomes
PROMIS	Patient Reported Outcomes Measurement Information System
QD	Once a day
QoL	Quality of Life
RA	Rheumatoid arthritis
RMS	Relapsing multiple sclerosis
RR	Rate ratio
SAE	Serious Adverse Event
SCR (or S)	Screening
SD	Standard deviation
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CCI	
SLE	Systemic lupus erythematosus
SoA	Schedule of activities
SOC	System Organ Class
SPMS	Secondary progressive multiple sclerosis
SSC	Study Steering Committee
SSR	Sample size re-estimation
SUSAR	Suspected Unexpected Serious Adverse Reaction
CCI	
TB	Tuberculosis
TEAE	Treatment emergent adverse event
ULN	Upper limit of normal
US	United States of America
WHO	World Health Organization
WOCBP	Woman of Childbearing Potential

## Appendix 2 Study Governance

### Financial Disclosure

Investigators and Sub-Investigators will provide the Sponsor with sufficient, accurate financial information, as requested, for the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. This information is required during the study and for 1 year after completion of the study.

### Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant and answer all questions on the study.
- Participants must be informed that their participation is voluntary.
- Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50; local regulations; International Council for Harmonisation (ICH) guidelines; Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable; and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- If the ICF is updated during their participation in the study, participants must be re-consented to the most current, approved version.
- A copy of the ICF(s) must be provided to the participant.
- The original signed and dated consent will remain at the Investigator's site and must be safely archived so that it can be retrieved at any time for monitoring, auditing and inspection purposes.
- As this study includes optional pharmacogenetic examinations, including collection and storage of biological samples, participants may consent to a separate pharmacogenetic analysis, the process of which will need to be documented in the participant's medical records.
- Participants who are rescreened are required to sign a new ICF.
- Consenting participant will enter the 4-week screening period to be evaluated for eligibility. Please see the SoA (Section 1.3.1) for details. Participants must fulfill all entry criteria for participation in the study.
- The screening period can be extended to a total period of 8 weeks. The following should be performed:
  - An Eligibility Screening Form [ESF] documenting the Investigator's assessment of each screened participant with regard to the protocol's inclusion and exclusion criteria is to be completed by the Investigator.

- Each participant screened must be registered in the IWRS by the Investigator or the Investigator's research staff at Screening. A screen failure record must be maintained by the Investigator, and reasons must be captured in the IWRS.
- It should be stated in the medical record that the participant is participating in this clinical study.
- Eligibility will be evaluated and confirmed by the study eligibility team. Sites will be required to submit an eligibility packet to the Medical Monitor (consisting of an eligibility checklist and appropriate documentation) for potential eligible participants.

### **Data Protection**

- The Sponsor will assign a unique identifier to participants after obtaining their informed consent. All participant records or datasets transferred to the Sponsor will contain the identifier only; participant names or any identifiable information will not be transferred.
- The Sponsor must inform participants that their personal study-related data will be used per local data protection and privacy laws. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other Sponsor-appointed, authorized personnel, by appropriate IRB/IEC members, and by regulatory authority inspectors. All such persons will strictly maintain participants' confidentiality.

### **Study Administrative**

This clinical study will be sponsored by Merck Healthcare KGaA Darmstadt, Germany for sites outside of the US and Canada and EMD Serono Research & Development Institute, Inc., Billerica, MA, US for sites in the US and Canada.

The study will be conducted at approximately 198 global sites anticipated from approximately 25 to 30 countries (approximately 30 sites in the US). Sites will be a mixture of academic centers and outpatient clinics.

The Coordinating Investigator listed on the title page represents all Investigators for decisions and discussions on this study, per ICH Good Clinical Practice (GCP). The Coordinating Investigator will provide expert medical input and advice on the study design and execution and is responsible for the review and signoff of the clinical study report.

An Independent Data Monitoring Committee (IDMC), Endpoint Adjudication Committee (EAC), and Study Steering Committee (SSC) will perform specific study related activities as detailed in each committee's charter (see Section 8.2.9).



The study will appear in the following clinical studies registries: ClinicalTrials.gov and EudraCT.

Details of structures and associated procedures will be defined in a separate Study Reference Manual.

### **Regulatory and Ethical Considerations**

- This study will be conducted in accordance with the protocol and the following:
  - Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The Investigator must submit the protocol, protocol amendments (if applicable), ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) to an IRB/IEC and the IRB/IEC must review and approve them before the study is initiated.
- Any protocol amendments (i.e., changes to the protocol) will be documented in writing and require IRB/IEC approval before implementation of changes, except for changes necessary to eliminate an immediate hazard to study participants. When applicable, amendments will be submitted to the appropriate Health Authorities.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently per the IRB's/IEC's requirements, policies, and procedures.
  - Notifying the IRB/IEC of SAEs or other significant safety findings, as required by IRB/IEC procedures
  - Providing oversight of the study conduct at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
- The protocol and any applicable documentation will be submitted or notified to the Health Authorities in accordance with all local and national regulations for each site.

### **Emergency Medical Support**

- The Sponsor or designee will provide Emergency Medical Support cards to participants for use during the study. These provide the means for participants to identify themselves as participating in a clinical study. Also, these give health care providers access to any information about this participation that may be needed to determine the course of medical treatment for the participant. The information on the

Emergency Medical Support card may include the process for emergency unblinding (if applicable).

- The first point of contact for all emergencies will be the clinical study Investigator caring for the participant. Consequently, the Investigator agrees to provide his or her emergency contact information on the card. If the Investigator is available when an event occurs, they will answer any questions. Any subsequent action (e.g., unblinding) will follow the standard process established for Investigators.

When the Investigator is not available, the Sponsor provides the appropriate means to contact a Sponsor (or designee) physician. This includes provision of a 24-hour contact number at a call center, whereby the health care providers will be given access to the appropriate Sponsor (or designee) physician to assist with the medical emergency and to provide support for the potential unblinding of the participant concerned.

### **Clinical Study Insurance and Compensation to Participants**

Insurance coverage will be provided for each country participating in the study. Insurance conditions shall meet good local standards, as applicable.

### **Clinical Study Report**

After study completion, the Sponsor will write a clinical study report in consultation with the Coordinating Investigator.

### **Publication**

- 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 Merck to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. Per standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by agreement.
- Authorship will be determined by agreement and in line with International Committee of Medical Journal Editors authorship requirements.

### **Dissemination of Clinical Study Data**

After completion of the study, a clinical study report will be written by the Sponsor in consultation with the Coordinating Investigator following the guidance in ICH Topic E3, and will be submitted in accordance with local regulations.

Any and all scientific, commercial, and technical information disclosed by the Sponsor in this protocol or elsewhere should be considered the confidential and proprietary property of the Sponsor. The Investigator shall hold such information in confidence and shall not disclose the

information to any third party except to such of the Investigator's employees and staff as have been made aware that the information is confidential and who are bound to treat it as such and to whom disclosure is necessary to evaluate that information. The Investigator shall not use such information for any purpose other than for determining mutual interest in performing the study and, if the parties decide to proceed with the study, for the purpose of conducting the study.

The Investigator understands that the information developed from this clinical study will be used by the Sponsor in connection with the development of the study drug and therefore may be disclosed as required to other clinical Investigators, to the US Food and Drug Administration, and to other government agencies. The Investigator also understands that, to allow for the use of the information derived from the clinical study, the Investigator has the obligation to provide the Sponsor with complete test results and all data developed in the study.

No publication or disclosure of study results will be permitted except under the terms and conditions of a separate written agreement.

#### **Data Quality Assurance**

- All participant study data will be recorded on printed or electronic CRFs or transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are complete, accurate, legible, and timely by physically or electronically signing the CRF. Details for managing CRFs are in the Study Reference Manual.
- For PRO data (e.g., QoL and pain assessments), ePRO will be used.
- The Investigator must maintain accurate documentation (source data) that supports the information in the CRF.
- The Investigator must permit study-related monitoring, quality assurance audits, IRB/IEC review, and regulatory agency inspections and provide direct access to the study file and source data.
- 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 noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are in the Monitoring Plan.
- The Sponsor or designee is responsible for data management of this study, including quality checking of the data and maintaining a validated database. Database lock will occur once quality control and quality assurance procedures have been completed. PDF files of the CRFs will be provided to the Investigators at study completion.
- Study monitors will perform ongoing source data verification to confirm that data in the CRF are accurate, complete, and verifiable; that the safety and rights of participants are being protected; and that the study is being conducted per the

currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

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

### **Source Documents**

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected.
- The Investigator must keep a paper or electronic file (medical file and original medical records) at the site for each study participant. The file must identify each participant, contain the following demographic and medical information for the participant, and should be as complete as possible:
  - Participant's full name, date of birth, sex, height, and weight
  - Medical history and concomitant diseases
  - Prior and concomitant therapies (including changes during the study)
  - Study identifier (i.e., the Sponsor's study number) and participant's study number.
  - Dates of entry into the study (i.e., signature date on the informed consent) and each visit to the site
  - Any medical examinations and clinical findings predefined in the protocol
  - All AEs
  - Date that the participant left the study, including any reason for early withdrawal from the study or study intervention, if applicable.
- All source data must be filed (e.g., CT or MRI scan images, ECG recordings, and laboratory results). Each document must have the participant number and the procedure date; ideally, printed by the instrument used for the procedure. As necessary, medical evaluation of these records should be performed, documented, signed and dated by the Investigator.
- Data recorded on printed or electronic CRFs 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.

- The study monitors will use printouts of electronic files for source data verification. These printouts must be signed and dated by the Investigator and kept in the study file.
- Source documents are stored at the site for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. The Investigator ensures that no destruction of medical records is performed without the Sponsor's written approval.
- Definition of what constitutes source data is found in the eCRF guidelines.

### **Study and Site Closure**

- The Sponsor reserves the right to close the study site or terminate the study at any time and for any reason. 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 completed.
- 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:
  - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
  - Inadequate recruitment of participants by the Investigator
  - Discontinuation of further development of the Sponsor's compound

## Appendix 3 Contraception

### Definitions:

#### Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile, as specified below.

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, consider additional evaluation.

A WOCBP is **not**:

1. Premenarchal
2. A premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Documentation can come from the site personnel's review of the female's medical records, medical examination, or medical history interview.

For a female with permanent infertility due to an alternate medical cause other than the above, (e.g., Müllerian agenesis, androgen insensitivity), investigator discretion applies to determine study entry.

3. A postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in a female not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, more than 1 FSH measurement is required in the postmenopausal range.
  - A female on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if she wishes to continue her HRT during the study. Otherwise, she must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

## Contraception Guidance:

### CONTRACEPTIVES ALLOWED DURING THE STUDY INCLUDE:

#### Highly Effective Methods That Have Low User Dependency

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation<sup>a</sup>
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)<sup>a</sup>
- Bilateral tubal occlusion
- Vasectomized partner: a highly effective contraceptive method provided that the partner is the sole sexual partner of a WOCBP and the absence of sperm has been confirmed. Otherwise, use an additional highly effective method of contraception. The spermatogenesis cycle is approximately 90 days.

#### Highly Effective Methods That Are User Dependent

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation<sup>a</sup>
  - Oral
  - Intravaginal
  - Transdermal
  - Injectable
- Progestogen-only hormone contraception associated with inhibition of ovulation<sup>a</sup>
  - Oral
  - Injectable
- Sexual abstinence: a highly effective method only if defined as refraining from intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study. Abstinence is only acceptable as a contraceptive method for study purposes if it is in line with the preferred and usual lifestyle of the participant as evaluated by the Investigator.

#### Barrier Methods

- Male or female condom with or without spermicide
- Cap, diaphragm, or sponge with spermicide

#### Notes:

Contraceptive use by men or women is consistent with local regulations on the use of contraceptive methods for clinical study participants.

Highly effective methods are those with a failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Evobrutinib has been characterized as both an inducer and a time-dependent inhibitor of CYP3A4/5 in vitro, an enzyme involved in the metabolism of estrogen and progestin. Although it is a low risk, it is possible that co-administration with evobrutinib results in increased metabolism of estrogen, progestin, and other hormones used for contraception, increasing the likelihood that hormonal contraception methods, marked above with <sup>a</sup>, might fail. However, all participants that are WOCBP are required to use a barrier method as backup (see Inclusion Criterion 6) in part to mitigate this potential risk.

Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are **not** acceptable methods of contraception for this study. Male condom and female condom cannot be used together (due to risk of failure with friction).



## Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

### Definitions

#### Adverse Event

An AE is any untoward medical occurrence in a participant administered a pharmaceutical product, regardless of causal relationship with this treatment. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, regardless if it is considered related to the medicinal product.

For surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

The Investigator is required to grade the severity or toxicity of each AE.

Investigators will reference the National Cancer Institute - Common Terminology Criteria for AEs (CTCAE), version 4.03 (publication date: 14 June 2010), a descriptive terminology that can be used for AE reporting.

A general grading (severity/intensity; hereafter referred to as severity) scale is provided at the beginning of the above referenced document, and specific event grades are also provided.

If the severity for an AE is not specifically graded by NCI-CTCAE, the Investigator is to use the general NCI-CTCAE definitions of Grade 1 through Grade 5, using his or her best medical judgment.

The 5 general grades are:

Grade 1 or Mild

Grade 2 or Moderate

Grade 3 or Severe

Grade 4 or Life-threatening

Grade 5 or Death

Any clinical AE with severity of Grade 4 or 5 must also be reported as an SAE. However, a laboratory abnormality of Grade 4, such as anemia or neutropenia, is considered serious only if the condition meets one of the serious criteria specified below.

If death occurs, the primary cause of death or event leading to death should be recorded and reported as an SAE. "Fatal" will be recorded as the outcome of this specific event and death



will not be recorded as separate event. Only, if no cause of death can be reported (e.g., sudden death, unexplained death), the death per se might then be reported as an SAE.

Investigators must also systematically assess the causal relationship of AEs to study intervention (including any other non-study interventions, radiation therapy, etc.) using the following definitions. Decisive factors for the assessment of causal relationship of an AE to the study interventions (evobrutinib and Avonex) include, but may not be limited to, temporal relationship between the AE and the study interventions, known side effects of study interventions, medical history, concomitant medication, course of the underlying disease, and study procedures.

**Unrelated:** Not reasonably related to the study intervention. AE could not medically (pharmacologically/clinically) be attributed to the study intervention under study in this clinical study protocol. A reasonable alternative explanation must be available.

**Related:** Reasonably related to the study intervention. AE could medically (pharmacologically/clinically) be attributed to the study intervention under study in this clinical study protocol.

### **Abnormal Laboratory Findings and Other Abnormal Investigational Findings**

Abnormal laboratory findings and other abnormal investigational findings (e.g., on an ECG trace) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to study intervention discontinuation or are considered otherwise medically important by the Investigator. If a laboratory abnormality fulfills these criteria, the identified medical condition (e.g., anemia or increased ALT) must be reported as the AE rather than the abnormal value itself.

### **Serious Adverse Events**

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening. Life-threatening refers to an event in which the participant is at risk of death at the time of the event, not an event that hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongs an existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is otherwise considered to be medically important. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the participant or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood

dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For the purposes of reporting, any suspected transmission of an infectious agent via a study intervention is also considered an SAE, as specified below for reporting SAEs and AESIs.

### **Events that Do Not Meet the Definition of an SAE**

Elective hospitalizations to administer, or to simplify study intervention or procedures (e.g., an overnight stay to facilitate intravenous therapy) are not considered SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (i.e., undesirable effects of any administered treatment) must be documented and reported as SAEs.

### **Events Not to Be Considered as AEs/SAEs**

Medical conditions present at the initial study visit that do not worsen in severity or frequency during the study are defined as Baseline Medical Conditions, and are not to be considered AEs.

### **Other Adverse Events to be Reported Following a Specialized Procedure**

The following procedures should be followed for reporting overdoses (see eCRF guidelines for further details):

- Overdoses without an AE should be reported using the paper SAE form only, stating if the overdose was accidental or intentional.
- Overdoses associated with a nonserious AE should be recorded on the AE eCRF and also the paper SAE form.
- Overdoses associated with an SAE should be recorded on the AE eCRF and the SAE reporting procedure outlined below should be followed.

### **Recording and Follow-up of AE and/or SAE**

It is important that each AE report include a description of the event, its duration (onset and resolution dates and also onset and resolution times, when it is important to assess the time of AE onset relative to the recorded study intervention administration time), its severity, its causal relationship with the study intervention, any other potential causal factors, any treatment given or other action taken, including dose modification or discontinuation of the study intervention, and its outcome. In addition, serious cases should be identified and the appropriate seriousness criteria documented.

Specific guidance is in the CRF Completion and Monitoring Conventions provided by the Sponsor.

## Reporting Serious Adverse Events and Adverse Events of Special Interest

### Serious Adverse Events

In the event of any new SAE occurring during the reporting period, the Investigator must immediately (within a maximum of 24 HOURS after becoming aware of the event) inform the Sponsor or its designee using the electronic SAE report form in the Electronic Data Capture (EDC) system.

Reporting of SAEs using a paper report form is required as a back-up method only for an EDC system failure. Names, addresses, and telephone and fax numbers will be included on the paper form. All information from the paper form must be transcribed into the electronic form as soon as the system becomes available.

In exceptional circumstances, an SAE (or follow-up information) may be reported by telephone; in these cases, an electronic SAE report form must be completed immediately thereafter.

Relevant pages from the CRF may be provided in parallel (e.g., medical history, concomitant drugs). Additional documents may be provided by the Investigator, if available (e.g., laboratory results, hospital report, autopsy report).

The Investigator must respond to any request for follow-up information (e.g., additional information, outcome, final evaluation, other records where needed) or to any question the Sponsor/designee may have on the AE within the same timelines as those noted above for initial reports. This is necessary to ensure prompt assessment of the event by the Sponsor or designee and (as applicable) to allow the Sponsor to meet strict regulatory timelines associated with expedited safety reporting obligations.

Requests for follow-up will usually be made via the study monitor, although in exceptional circumstances the drug safety department may contact the Investigator directly to obtain further information or to discuss the event.

### Adverse Events of Special Interest

In the event of a nonserious AESI, the Investigator will complete the AESI Report Form and send it to the Sponsor/designee within 7 days (nonserious AESIs), or 24 hours (AESIs classified as serious). Names, addresses, and telephone and fax numbers for AESI reporting will be included on the Report Form. Serious AESIs must be reported in an expedited manner as SAEs as outlined above.

## Appendix 5 Clinical Laboratory Tests

**Table 1 Protocol-Required Clinical Laboratory Assessments**

Laboratory Assessments	Parameters			
Hematology	Platelet count		Mean Corpuscular Volume (MCV)	White Blood Cell (WBC) Count with Differential: <ul style="list-style-type: none"> <li>• Neutrophils</li> <li>• Lymphocytes</li> <li>• Monocytes</li> <li>• Eosinophils</li> <li>• Basophils</li> </ul>
	Reticulocytes			
	Hemoglobin			
	Hematocrit			
Coagulation	International normalized ratio	Partial thromboplastin time		
Supplementary LFT visits	Aspartate aminotransferase		γ-Glutamyl-transferase	Total Bilirubin
	Alanine aminotransferase		Alkaline phosphatase	
Biochemistry	Blood Urea Nitrogen	Potassium	Aspartate Aminotransferase	Bilirubin
	Creatinine and eGFR calculation	Sodium	Alanine Aminotransferase	Protein
	Glucose	Calcium	Alkaline phosphatase	Albumin
	Chloride	Lactate dehydrogenase	Lipase	Amylase
		Magnesium	Total carbon dioxide	Phosphate
		γ-Glutamyl-transferase	Immunoglobulin and subclass concentrations (as specified in the SoA, Section 1.3) <sup>a</sup>	
Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1.				
CCI				
Routine Urinalysis	<ul style="list-style-type: none"> <li>• Specific gravity</li> <li>• pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick</li> <li>• Microscopic examination (if blood or protein is abnormal).</li> <li>• βhCG (women only)</li> </ul>			

**Evobrutinib Phase III Study of Evobrutinib in RMS (EVOLUTION MS2)**  
**MS200527\_0074**

Laboratory Assessments	Parameters
Reflex Testing for HBV DNA	<ul style="list-style-type: none"> <li>• HBV DNA PCR</li> </ul>
Other Screening Tests	<ul style="list-style-type: none"> <li>• Serology (HCV antibodies, HBV antibodies, HIV testing<sup>b</sup>, HBsAg, HCV RNA PCR, QuantiFERON tuberculosis test)</li> <li>• FSH and estradiol (as needed if <b>not</b> a WOCBP <b>only</b>)</li> <li>• Serum or highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test (as needed for a WOCBP). Note: Local urine testing will be standard for the protocol unless serum testing is required by local regulation or the IRB/IEC.</li> <li>• Ferritin and transferrin saturation</li> <li>• All study-required laboratory assessments will be performed by a central laboratory, except for urine dipstick, urine pregnancy, ESR, PPD, and T-SPOT.</li> </ul>

βhCG = β-Human Chorionic Gonadotropin, CMV = Cytomegalovirus, DNA = deoxyribonucleic acid, EA = Early Antigen, EBNA = Epstein-Barr Nuclear Antigen, eGFR = Estimated Glomerular Filtration Rate, ESR = Erythrocyte Sedimentation Rate, FSH = Follicle Stimulating Hormone, HAV = Hepatitis A Virus, HBc = Hepatitis B Core Antigen, HBsAg = Hepatitis B Surface Antigen, HBV = Hepatitis B Virus, HCV = Hepatitis C Virus, HEV = Hepatitis E Virus, HFE = High Iron Fe (human hemochromatosis protein), HIV = Human Immunodeficiency Virus, hsCRP = High Sensitivity C Reactive Protein, IDMC = Independent Data Monitoring Committee, IEC = Independent Ethics Committee, IRB = Institutional Review Board, Ig = Immunoglobulin, PCR = polymerase chain reaction, VCA = Viral Capsid Antigen, MCH = mean corpuscular hemoglobin, MCHC = mean corpuscular hemoglobin concentration; PPD = purified protein derivative, WBC = White Blood Cell, WOCBP = Women of Childbearing Potential.

a Results will not be disclosed to the sites, Sponsor, or representative, to avoid unblinding. However, the IDMC will have access to these data as applicable.

b HIV testing will be done at Screening and will be analyzed locally.

c Focused genetic testing for variants that confer risk for liver diseases and/or drug-related liver injury, including but not limited to testing for variants in the HFE gene (C282Y, H63D) in the setting of abnormal ferritin/transferrin saturation values as defined in Exclusion Criterion 10.

## Appendix 6 Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

### Definitions of a Medical Device Incident

The detection and documentation procedures specified in this protocol apply to all Sponsor medical devices provided for use in the study. See Section 6.1.1 for the list of Sponsor medical devices.

#### Medical Device Incident Definition

- A medical device incident is any malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a participant/user/other person or to a serious deterioration in his/her state of health.
- Not all incidents lead to death or serious deterioration in health. The nonoccurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

#### It is sufficient that:

- An incident associated with a device happened.

AND

- The incident was such that, if it occurred again, might lead to death or a serious deterioration in health.

A serious deterioration in state of health can include any of the following:

- Life-threatening illness
- Permanent impairment of body function or permanent damage to body structure
- Condition necessitating medical or surgical intervention to prevent one of the above
- Fetal distress, fetal death, or any congenital abnormality or birth defects

#### Examples of Incidents

- A participant, user, caregiver, or healthcare professional is injured as a result of a medical device failure or its misuse.
- A participant's study intervention is interrupted or compromised by a medical device failure.
- A misdiagnosis due to medical device failure leads to inappropriate treatment.
- A participant's health deteriorates due to medical device failure.

## Documenting Medical Device Incidents

### Medical Device Incident Documenting

- Any medical device incident occurring during the study will be documented in the participant's medical records, in accordance with the Investigator's normal clinical practice, and on the appropriate form of the CRF.
- For incidents fulfilling the definition of an AE or an SAE, the appropriate AE/SAE CRF page will be completed as specified in [Appendix 4](#).
- The CRF will be completed as thoroughly as possible and signed by the Investigator before transmittal to the Sponsor or designee.
- It is very important that the Investigator provides his/her assessment of causality (relationship to the medical device provided by the Sponsor) at the time of the initial AE or SAE report and specify any corrective or remedial actions taken to prevent recurrence of the incident.
- A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of an incident. This includes any amendment to the device design to prevent recurrence.





## Appendix 8 Guidance for Diagnosis of PML

The safety monitoring algorithm presented in [Figure 3](#) will be implemented in this study.

Comprehensive neurological assessments will be performed every 12 weeks at the regular study visits. Additionally, telephone interviews will be conducted to assess for new or worsening neurological symptoms and a neurological evaluation will be conducted if clinically indicated. This neurological exam will include calculation of an Expanded Disability Status Scale (EDSS) score at the scheduled 12-week visit or in the event of new/worsening symptoms. This exam requires that Functional System Score (FSS) also be determined. The examination to calculate the FSS includes cognitive, visual and motor assessments, as well as assessments of other neurological systems. These neurological systems are often affected by PML, and by MS as well.

Should a non-MS etiology, such as PML, be considered as a differential etiology for any change in the clinical picture (neurological symptoms and/or exam), further assessments should be done. The evaluation of PML may include a brain MRI scan and CSF analysis per the proposed treatment algorithm ([Figure 3](#)).

### Action Steps if PML is suspected:

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 a lumbar puncture with evaluation of the cerebrospinal fluid (CSF) for the detection of JCV DNA 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.

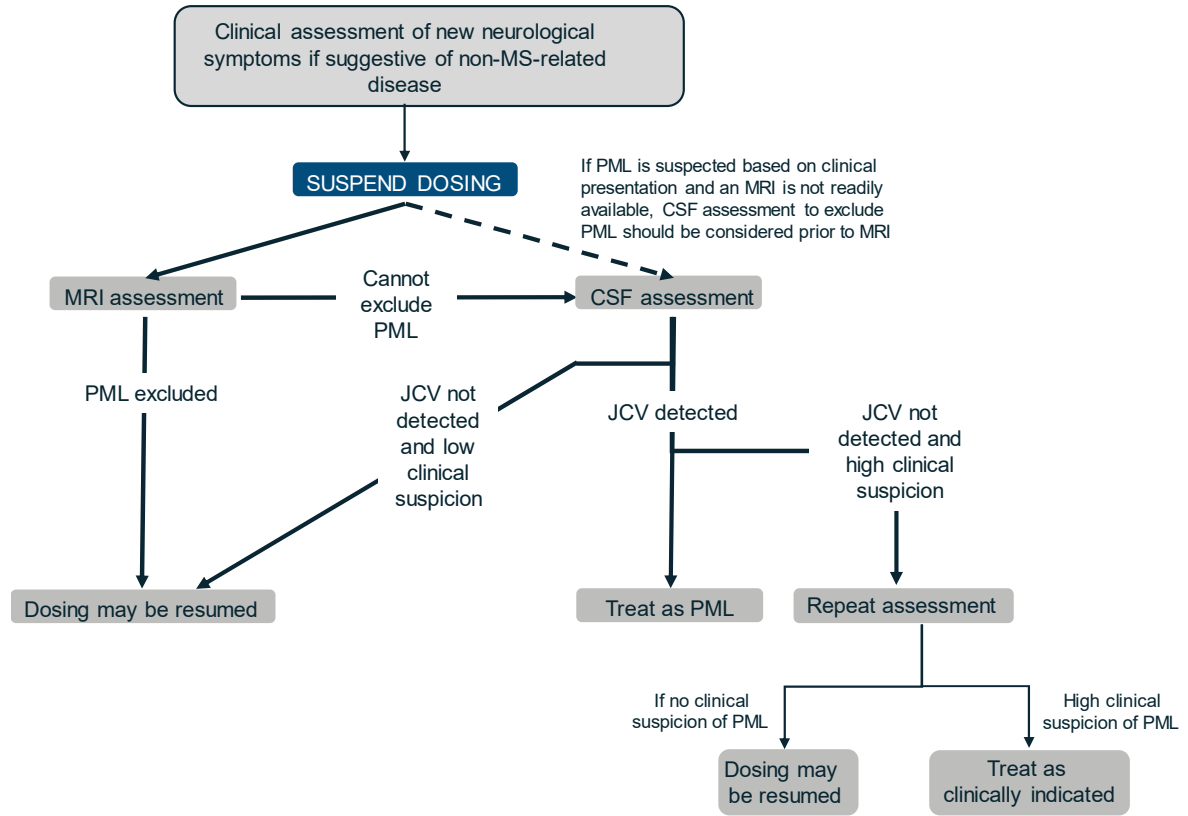
### MRI Assessments

Although there are no pathognomonic findings that differentiate PML from 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 patients with neurological changes suggestive of PML.

### CSF Assessment

- The detection of JCV DNA in the CSF of a participant 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 3 Diagnostic Algorithm for PML – Suggested Diagnostic Algorithm



## **Appendix 9 Protocol Amendment History**

The information for the current amendment is on the title page.

Appendix 10 Sponsor Signature Page

<b>Study Title:</b>	A Phase III, Multicenter, Randomized, Parallel Group, Double Blind, Double Dummy, Active Controlled Study of Evobrutinib Compared with an Interferon Beta 1a (Avonex®), in Participants with Relapsing Multiple Sclerosis to Evaluate Efficacy and Safety.
<b>Regulatory Agency Identifying Numbers:</b>	EudraCT: 2018-004700-19 CCI [REDACTED]
<b>Clinical Study Protocol Version:</b>	Version 2.0 / 05 Sep 2019

I approve the design of the clinical study:

PPD  
Signature

PPD  
Date of Signature

<b>Name, academic degree:</b>	PPD [REDACTED]
<b>Function/Title:</b>	PPD [REDACTED]
<b>Institution:</b>	EMD Serono Research & Development Institute, Inc
<b>Address:</b>	PPD [REDACTED] EMD Serono Research & Development Institute, Inc 45A Middlesex Turnpike, Billerica, MA 01821, USA
<b>Telephone number:</b>	PPD [REDACTED]
<b>Fax number:</b>	Not Applicable
<b>E-mail address:</b>	PPD [REDACTED]

**Appendix 11 Coordinating Investigator Signature Page**

<b>Study Title:</b>	A Phase III, Multicenter, Randomized, Parallel Group, Double Blind, Double Dummy, Active Controlled Study of Evobrutinib Compared with an Interferon Beta 1a (Avonex®), in Participants with Relapsing Multiple Sclerosis to Evaluate Efficacy and Safety.
<b>Regulatory Agency Identifying Numbers:</b>	EudraCT: 2018-004700-19 CCI [REDACTED]
<b>Clinical Study Protocol Version:</b>	Version 2.0 / 05 Sep 2019
<b>Site Number:</b>	

I approve the design of the clinical study, am responsible for the conduct of the study at this site, and understand and will conduct it per the clinical study protocol, any approved protocol amendments, International Council on Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

PPD

Signature

PPD

Date of Signature

<b>Name, academic degree:</b>	Professor. PPD [REDACTED]
<b>Function/Title:</b>	Professor
<b>Institution:</b>	PPD
<b>Address:</b>	
<b>Telephone number:</b>	
<b>Fax number:</b>	
<b>E-mail address:</b>	

## Appendix 12 Principal Investigator Signature Page

<b>Study Title:</b>	A Phase III, Multicenter, Randomized, Parallel Group, Double Blind, Double Dummy, Active Controlled Study of Evobrutinib Compared with an Interferon Beta 1a (Avonex®), in Participants with Relapsing Multiple Sclerosis to Evaluate Efficacy and Safety.
<b>Regulatory Agency Identifying Numbers:</b>	EudraCT: 2018-004700-19 CCI
<b>Clinical Study Protocol Version:</b>	Version 2.0 / 05 Sep 2019
<b>Site Number:</b>	

I am responsible for the conduct of the study at this site, and understand and will conduct it per the clinical study protocol, any approved protocol amendments, International Council on Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

I also understand that Health Authorities may require the Sponsors of clinical studies to obtain and supply details about ownership interests in the Sponsor or Investigational Medicinal Product and any other financial ties with the Sponsor. The Sponsor will use any such information solely for complying with the regulatory requirements. Therefore, I agree to supply the Sponsor with any necessary information regarding ownership interest and financial ties including those of my spouse and dependent children, and to provide updates as necessary to meet Health Authority requirements.

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date of Signature

<b>Name, academic degree:</b>	
<b>Function/Title:</b>	
<b>Institution:</b>	
<b>Address:</b>	
<b>Telephone number:</b>	
<b>Fax number:</b>	
<b>E-mail address:</b>	