Clinical Study Protocol

Title Page

Clinical Study Protocol Title:	A Phase III, Multicenter, Randomized, Parallel Group, Double Blind, Double Dummy, Active Controlled Study of Evobrutinib Compared with Teriflunomide, in Participants with Relapsing Multiple Sclerosis to Evaluate Efficacy and Safety
Study Number:	MS200527_0082
Merck Compound Number:	M2951
Study Phase:	III
Short Title:	Phase III Study of Evobrutinib in RMS
Acronym:	Evolution RMS 2
Coordinating Investigator:	PPD
Sponsor Name and Legal Registered Address:	**Sponsor:** Affiliates of Merck KGaA, Darmstadt, Germany For all countries, except the US and Canada: Merck Healthcare KGaA an affiliate of Merck KGaA, Darmstadt, Germany Frankfurter Str. 250 Darmstadt, Germany In the US and Canada: EMD Serono Research & Development Institute, Inc. an affiliate of Merck KGaA, Darmstadt, Germany 45A Middlesex Turnpike Billerica, MA, 01821, USA **Medical Responsible:** Name: PPD Address: PPD EMD Serono Research & Development Institute Inc. 45A Middlesex Turnpike, Billerica, MA 01821, USA Phone: PPD Fax: Not Applicable E-mail: PPD

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Protocol Amendment Summary of Changes

Protocol History

Version Number	Type	Version Date
1.0	Original Protocol	13 February 2020
1.1-CAN	Local amendment Canada	03 July 2020
1.2-DEU	Local amendment Germany	04 August 2020
1.3-NOR	Local amendment Norway	25 August 2020
1.4-LTU	Local amendment Lithuania	16 September 2020
2.0	Amendment 1 - Global	09 December 2020
2.1-CAN	Local amendment Canada	09 December 2020
2.2-LTU	Local amendment Lithuania	09 December 2020
3.0	Amendment 2 - Global	19 May 2021
3.1-CAN	Local amendment Canada	26 May 2021
3.2-LTU	Local amendment Lithuania	26 May 2021
4.0	Amendment 3 – Global	03 April 2022
4.1-CAN	Local amendment Canada	20 April 2022
4.2-LTU	Local amendment Lithuania	26 April 2022
5.0	Amendment 4 – Global	08 December 2022
5.1-LTU	Local amendment Lithuania	18 December 2022
5.2-CZE	Local amendment Czech Republic	16 March 2023
6.0	Amendment 5 - Global	27 April 2023

Protocol Version 6.0 (27 April 2023)

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

The primary purpose of this amendment is:

- To reflect recent update to risk profile of evobrutinib (i.e., important identified risk of drug-induced liver injury) by adapting liver-related eligibility criteria, monitoring, and discontinuation criteria as well as language on tolerability and safety of evobrutinib across the protocol.

- To allow participants to stay on blinded IMP after DBTP in a DBE period to delay the switch of participants naïve to evobrutinib treatment to the OLE period. This will also allow to generate additional data on efficacy and safety over an extended period of time.

A high-level description of each change with rationale is summarized below.

Section # and Name	Description of Change and Brief Rationale if applicable	
1.1 Synopsis	• Updated to include relevant information for DBE period including DBE objectives and endpoints, information on transitions after the DBTP, and involvement of special committees	• To enable continuous treatment of participants with IMP • Generation of additional data on efficacy and safety
1.2 Schema	• Updated to include the optional DBE period	• To ensure continuous treatment of participants with IMP • Generation of additional data on efficacy and safety
1.3.1 Schedule of Activities – Double-blind Treatment Period	• Week 3, 5, 7, 9, and 11 have been added to allow weekly LFT monitoring until after Study Day 70	• To enhance liver function monitoring plan
1.3.2 Schedule of Activities – Double-blind Extension Period	• New SoA has been added for the DBE period	• To ensure participants' safety and continuous treatment of participants with IMP • Generation of additional data on efficacy and safety
1.3.3 Schedule of Activities – Open-label Extension Period	• SoA has been updated • Week 3, 5, 7, 9, and 11 have been added to allow weekly LFT monitoring until after Study Day 70	• To enhance liver function monitoring plan
2.2 Background	• Rephrased based on updated risk profile	• To reflect recent update to risk profile of evobrutinib
2.3 Benefit/Risk Assessment	• Updated Important Identified Risks to include the asymptomatic DILI cases. • Updated Important Potential Risks to include weekly monitoring of liver enzymes first 12 weeks of DBTP and OLE and Hepatology Assessment Committee (HAC) review	• To reflect recent update to risk profile of evobrutinib
3 Objectives and Estimands	• Added objectives and endpoints for the DBE period (primary, secondary, and tertiary/exploratory)	• To specify objectives and endpoints for the newly added DBE period
4.1 Study Design	• Updated description of transition into the DBE period; transition into OLE period; transition into the long-term follow-up study	• To ensure continuous treatment of participants with IMP
4.4 End of Study Definition	• Added definition of treatment completion for the DBE period • Added information on study termination	• To define treatment completion for newly added DBE period
5.3 Criteria for Entry into Open Label Extension Period	• Added criteria for entry into DBE period	• To specify inclusion and exclusion criteria for newly added DBE period

Section # and Name	Description of Change and Brief Rationale if applicable	
5.4.1 Inclusion Criteria for Open-label Extension Period 5.4.2 Exclusion Criteria for Open-label Extension Period	• OLE exclusion criteria have been updated for liver enzymes and to accommodate the new DBE period	• To ensure exclusion of participants with abnormal blood tests into OLE period • To ensure participants safety
5.5.2 Caffeine, Alcohol, and Tobacco	• Description specified for additive hepatotoxic effects associated with IMPs (teriflunomide and evobrutinib)	• To reflect risk of alcohol consumption associated with IMPs
6.3.2 Blinding	• Blinding during the DBE period specified	• Clarification of blinding in the newly added study period
6.5.3 Prohibited Medicines	• Clarification regarding use of CYP2C8 substrates	• Content related to the newly added DBE period was included
7.1 Discontinuation of Study Intervention	• Liver function test-related monitoring and discontinuation further specified • Liver function testing criteria updated • HCV RNA by PCR was added	• To enhance safety monitoring of liver function • For clarification
8 Study Assessments and Procedures	• Update with information regarding the addition of the DBE period • Updated requirements for AEP adapted to DBE period • AEP (at Screening Visit for OLE only) was updated	• Clarification added as related to the newly added DBE period
8.1.2 Brain Magnetic Resonance Imaging Scans	• Added clarification that the Investigator will have full access to the results of the MRI scans during the OLE period, starting with the first MRI assessment in the OLE period at Week 48	• Updated text to clarify that the Investigator will have access to the full MRI reports including MS pathology during the OLE period. As the End-of-DBE MRI is used as baseline for OLE period, this MRI will remain blinded to MS pathology to ensure the integrity of the blinded periods of the study.
8.2.8 Independent Data Monitoring Committee, Hepatology Assessment Committee, Endpoint Adjudication Committee, and Study Steering Committee	• Description of Hepatology Assessment Committee was added • DBE period added to Endpoint Adjudication Committee	• To include involvement of newly formed Hepatology Assessment Committee
8.5 Pharmacokinetics	• Description for DBE period added	• Content related to the newly added DBE period was included
8.8 Biomarkers	• Update on repurposing of blood samples and update of blood volumes	• Content related to the newly added DBE period was added
8.8.1 Biomarkers of Disease, Disease Activity and Progression, Drug-related Outcomes, and Treatment Response	• DBE added and OLE description updated	• Content related to the newly added DBE period was added

Section # and Name	Description of Change and Brief Rationale if applicable	
8.8.1.2 Novel Liver Function Biomarkers 8.8.2 OLE Blood Biomarker PD Substudy – Biomarkers of Disease Activity, Progression and Response to Drug 8.8.3 Gene Expression		
9.3 Populations for Analyses	• Analysis sets for the DBE Period were specified	Clarified that the subgroups were defined specifically for the PA
9.4.3.5 Analysis of Open Label Extension Period Endpoints	• New Section 9.4.3.5 added for Analysis of DBE period endpoints • Analysis of Open Label Extension Period Endpoints moved to Section 9.4.3.6	Content related to the newly added DBE period was added
9.4.4 Sequence of Analyses	• Additional analysis was added for DBE	Content related to the newly added DBE period was added
9.4.4.2 Primary Analysis	• Specified that all data until PA trigger will be analyzed	Specified that the PA will be performed on all data until the PA trigger date.
Appendix 2 Study Governance	• Hepatology Assessment Committee added to the list of committees	To include newly formed Hepatology Assessment Committee
Appendix 5	• Parameters added to Hepatic/Autoimmune Panel	Content related to the newly added DBE period, consistency and clarity.
Appendix 8 Procedure for Accelerated Elimination of Teriflunomide	• Updated text on mandatory AEP for OLE period	Content related to the newly added DBE period was added
Throughout the document	• Minor editorial and document formatting revisions • Minor changes to accommodate addition of DBE, e.g., addition of the word 'DBE' in the respective sections	Minor; therefore, have not been summarized. Content related to the newly added DBE period was added

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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 Teriflunomide, in Participants with Relapsing Multiple Sclerosis to Evaluate Efficacy and Safety.

Short Title: Phase III Study of Evobrutinib in RMS.

Rationale: The purpose of this study is to characterize the efficacy and safety of evobrutinib 45 mg administered orally twice daily versus teriflunomide (Aubagio®; 14 mg once a day orally) in participants with relapsing multiple sclerosis (RMS).

Objectives and Endpoints for the Double-blind Treatment Period:

Objectives	Estimand Attributes
Primary	
To demonstrate superior efficacy with evobrutinib compared to teriflunomide in terms of Annualized Relapse Rate (ARR)	Endpoint: ARR based on qualified relapses up to 156 weeks in participants with RMS Population: Patients with RMS as defined by inclusion/exclusion criteria Treatment: Evobrutinib versus teriflunomide Intercurrent Event Strategy: • Treatment discontinuation: Treatment policy • Death attributable to MS or treatment: Composite variable • Death unattributable to MS or treatment: While Alive • Ukraine crisis: Hypothetical Population-Level Summary: relapse rate ratio and confidence interval (CI) (negative binomial [NB] model), with test of treatment effect based on test of relapse rate ratio

Objectives	Estimand Attributes
Secondary	
To demonstrate the efficacy of evobrutinib relative to that of teriflunomide on disability progression	Endpoints: • Time to first occurrence of 12-week Confirmed Disability Progression (CDP) as measured by the Expanded Disability Status Scale (EDSS) up to 156 weeks • Time to first occurrence of 24-week CDP as measured by the EDSS up to 156 weeks Population: Patients with RMS as defined by inclusion/exclusion criteria Treatment: Evobrutinib versus teriflunomide Intercurrent Event Strategy: • Treatment discontinuation: Treatment policy • Death attributable to MS or treatment: Composite variable • Death unattributable to MS or treatment: While Alive • Ukraine crisis: Hypothetical Population-Level Summary: hazard ratio and CI (Cox model), with test of treatment effect based on logrank test
To demonstrate the efficacy of evobrutinib relative to that of teriflunomide on disability improvement	Endpoints: • Time to first occurrence of 24-week Confirmed Disability Improvement (CDI) as measured by the EDSS up to 156 weeks Population: Patients with RMS as defined by inclusion/ exclusion criteria and who have baseline EDSS ≥ 2.0 Treatment: Evobrutinib versus teriflunomide Intercurrent Event Strategy: • Treatment discontinuation: Treatment policy • Death (any cause): While Alive • Ukraine crisis: Hypothetical Population-Level Summary: hazard ratio and CI (Cox model), with test of treatment effect based on logrank test

Objectives	Estimand Attributes
To demonstrate the efficacy of evobrutinib relative to that of teriflunomide on patient reported symptoms and functional status	Endpoints: • Change from Baseline (CFB) in Patient Reported Outcomes Measurement Information System (PROMIS) Physical Function (PF) score over 96 weeks • CFB in PROMIS Fatigue score over 96 weeks Population: Patients with RMS as defined by inclusion/exclusion criteria Treatment: Evobrutinib versus teriflunomide Intercurrent Event Strategy: • Treatment discontinuation: Treatment policy • Death (any cause): While Alive • Ukraine crisis: Hypothetical Population-Level Summary: difference of average least-squares means of score CFB (average over Weeks 72, 84, and 96 for PROMIS PF and average over Weeks 48, 60, 72, 84, and 96 for PROMIS Fatigue) and CI (Mixed effect model for repeated measures [MMRM] model), with test of treatment effect based on difference of average least-squares means
To demonstrate the efficacy of evobrutinib relative to that of teriflunomide on magnetic resonance imaging (MRI) lesion parameters	Endpoints: • Total number of T1 Gd+ lesions based on all available MRI scans • Number of new or enlarging T2 lesions on the last available MRI scan relative to the baseline MRI scan Population: Patients with RMS as defined by inclusion/exclusion criteria Treatment: Evobrutinib versus teriflunomide Intercurrent Event Strategy: • Treatment discontinuation: Treatment policy • Death (any cause): While Alive • Ukraine crisis: Hypothetical Population-Level Summary: lesion rate ratio and CI (NB model), with test of treatment effect based on test of lesion rate ratio

Objectives	Estimand Attributes
To demonstrate the efficacy of evobrutinib relative to that of teriflunomide by evaluating response on Neurofilament light chain (NfL) concentrations in serum	Endpoint: • NfL concentration at 12 weeks Population: Patients with RMS as defined by inclusion/ exclusion criteria Treatment: Evobrutinib versus teriflunomide Intercurrent Event Strategy: • Treatment discontinuation: Treatment policy • Death (any cause): While Alive • Ukraine crisis: Hypothetical Population-Level Summary: difference of geometric means at 12 weeks and CI (MMRM model), with test of treatment effect based on difference of least-squares means
To characterize the safety and tolerability of evobrutinib	Endpoints: • 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 CFB in immunoglobulin (Ig) levels; and clinical laboratory safety parameters up to the end of the Safety Follow-up period Population: Patients with RMS as defined by inclusion/exclusion criteria Treatment: Evobrutinib versus teriflunomide Intercurrent Event Strategy: • Ukraine crisis: Hypothetical Population-Level Summary: Not applicable

Objectives and Endpoints for the Double-Blind Extension Period:

Objectives	Endpoints
Double-blind Extension (DBE) Period - Primary	
To further evaluate the efficacy with evobrutinib compared to teriflunomide in terms of Annualized Relapse Rate (ARR)	• ARR based on qualified relapses in participants with RMS
DBE Period - Secondary	
To further evaluate the efficacy of evobrutinib relative to that of	• Time to first occurrence of 12-week CDP as measured by EDSS • Time to first occurrence of 24-week CDP as measured by the EDSS

teriflunomide on disability progression	
To further evaluate the efficacy of evobrutinib relative to that of teriflunomide on disability improvement	• Time to first occurrence of 24-week CDI as measured by the EDSS
To further evaluate the efficacy of evobrutinib relative to that of teriflunomide on patient reported symptoms and functional status	• CFB in PROMIS PF score over time • CFB in PROMIS Fatigue score over time
To further evaluate the efficacy of evobrutinib relative to that of teriflunomide on magnetic resonance imaging (MRI) lesion parameters	• Total number of T1 Gd+ lesions based on all available MRI scans • Number of new or enlarging T2 lesions on the last available MRI scan relative to the baseline MRI scan
To further 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 CFB in immunoglobulin (Ig) levels; and clinical laboratory safety parameters up to the end of the Safety Follow-up period

Objectives and Endpoints for the Open Label Extension Period:

Objectives	Endpoints (Outcome Measures)
Open-label Extension (OLE) Period – Primary	
To evaluate the long-term safety and tolerability of evobrutinib 45 mg twice daily (BID) in participants with RMS over time	• Occurrence of AEs and serious AEs (SAEs)

Objectives	Endpoints (Outcome Measures)
OLE Period – Secondary	
To evaluate the long-term efficacy of evobrutinib 45 mg BID in participants with RMS	• ARR, based on protocol-defined qualified relapses • Time to first occurrence of 24-week CDP as measured by EDSS • Time to first occurrence of 24-week CDI as measured by EDSS • Symbol Digit Modalities Test (SDMT) over time
To evaluate the long-term effect of evobrutinib 45 mg BID in participants with RMS on patient reported symptoms and functional status	• PROMISnq PF (MS) 15a score change over time • PROMIS Fatigue (MS) 8a score change over time
To further evaluate the long-term safety and tolerability of evobrutinib 45 mg BID in participants with RMS over time	• Safety Laboratory Parameters including Blood Chemistry, Hematology, Coagulation, Vitals, ECGs
OLE Period - Secondary – MRI Substudy	
To evaluate the long-term efficacy of evobrutinib 45 mg BID in participants with RMS on MRI parameters	• Total number of new or enlarging T2 lesions (relative to Baseline) • Change from Baseline in T2 lesion volume over time

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

Eligible participants will be randomized 1:1 to treatment with evobrutinib 45 mg twice daily, or teriflunomide 14 mg once a day (oral), stratified by region and Baseline EDSS. Blinding will be accomplished using a double dummy design.

Number of Arms: 2

Blinding: Participant, Care Provider, Investigator, Outcomes Assessor

Number of Participants: The total sample size is calculated to be 898 participants with a randomization ratio of 1:1 (approximately 449 participants per treatment group), under the variable treatment duration (information driven) study design adopted in Protocol Version 4.0 and the ideal assumption that no data from randomized participants has been rendered unreliable due to an intercurrent event. This calculation is an underestimate of the enrollment required to fully power the study as the Ukraine crisis intercurrent event has impacted data reliability. Under the intermediate scenario where data from participants randomized in the crisis region are either included fully or censored due to unreliability, the final enrollment will be in the range of 1,041 to

1,294 participants for Study MS200527_0080 and 1,053 to 1,464 participants for Study MS200527_0082, where the lower limit of the range is the actual enrollment at the time of Clinical Study Protocol Version 4.0, and the upper limit is the expected enrollment under the worst-case scenario. The intermediate scenario assumes that the second phase of enrollment will be halted short of worst-case, based on an evaluation of information accrual within data assessed to be reliable.

Study Intervention Groups and Duration: The Treatment Period of up to 156 weeks (minimum 24 weeks) will be preceded by a 4-week Screening Period (may be extended after discussion with the Medical Monitor but cannot exceed 12 weeks) and followed by a 4-week Safety Follow-up after treatment completion or early discontinuation.

Transition Into the DBE Period

Participants who complete the DBTP period, or who are still under study treatment when the PA is triggered, will be considered completers and will be eligible to continue in the DBE period for continuation of treatment as assigned at randomization. Those participants who have not reached the Week 156 visit when the PA is triggered, need to undergo an End-of-DBTP Visit, which is also their first visit in the DBE. Participants who do not wish to enter the DBE period will have a Safety Follow-up Visit occurring after the End-of-DBTP visit.

Transition Into OLE Period

Participants who complete the DBE period, or who are still under study treatment once the Sponsor – upon agreement with Health Authorities / Ethics Committees – will have notified sites (i.e., the OLE is open for enrollment), will be eligible for transition into the OLE period. Participants entering the OLE period need to undergo an End-of-DBTP Visit, which is also their first visit in the OLE period. All participants previously treated with teriflunomide, or unknown exposure status, entering the OLE will be required to complete the AEP prior to dispensation of the IMP in the OLE period. Participants who do not wish to transition into OLE, will have a Safety Follow-up Visit after the End of the DBE period. The treating physician may consider conducting the AEP for participants coming off the IMP and prior to initiation of alternative DMTs.

Transition Into Long-term Follow-up Study (MS200527_0123, LONGEVO)

Once the long-term follow-up study (MS200527_0123, LONGEVO) is open for enrollment (i.e., once the sponsor – upon agreement with Health Authorities / Ethics Committees – will have notified sites), participants of the OLE will switch into the long-term follow-up study at the nearest transition visit (at Weeks 24, 48, 72, or 96 of the OLE period). Participants who do not wish to transition into the long-term follow-up study, will have a Safety Follow-up Visit after the End of Treatment visit in the OLE Period.

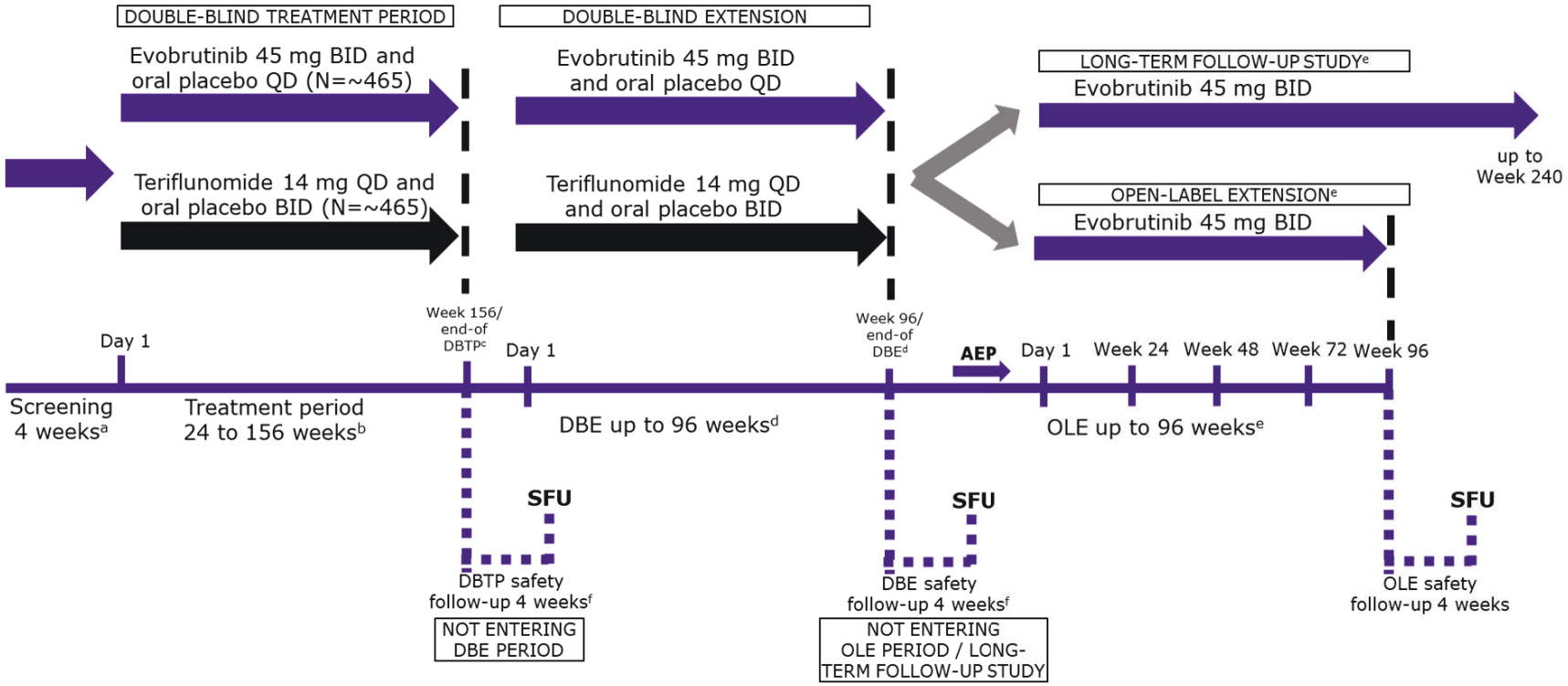
In case the long-term follow-up study is open for enrollment while participants are still under study treatment in the DBE period, they will be offered the possibility to transition into that study by default. For participants entering the long-term follow-up study, their last visit in the current study (i.e., End-of-DBE Visit) is also their first visit in the long-term follow-up study. Participants who

do not wish to transition into the long-term follow-up study will have a Safety Follow-up Visit after the End-of-DBE Visit.

Involvement of Special Committee(s): Yes. Independent Data Monitoring Committee, Hepatology Assessment Committee (HAC), Endpoint Adjudication Committee (for the DBTP and DBE period), and Study Steering Committee.

1.2 Schema

Figure 1 Study Schema



AEP = accelerated elimination procedure, BID = twice daily, DBE = Double-Blind Extension, DBTP = Double-Blind Treatment Period, OLE = Open-Label Extension, PA = primary analysis, QD = once daily, SFU = Safety Follow-up.

a Screening may be extended to 12 weeks after approval by the Medical Monitor (see Section 8).

b Treatment Period of up to 156 weeks with a minimum treatment duration of 24 weeks.

c Once PA is triggered, participants who have not reached Week 156 will undergo an End-of-DBTP visit

d Once the primary analysis is triggered, participants have the option to extend their treatment in the DBE for up to 96 weeks, until the Sponsor, upon agreement with Health Authorities/Ethics Committees, notifies sites that the OLE and/or the long-term follow-up study is open for enrollment. At that point, participants who have not reached Week 96, will need to undergo an End-of-DBE visit. The long-term follow-up study is covered by a separate study protocol.

e If the long-term follow-up study is not yet approved in their country participants have the option to enter an OLE period of up to 96 weeks, which is covered in the current protocol. If the long-term follow-up study is approved and open for enrollment after beginning the OLE, participants may transfer from the OLE to the long-term follow-up study at Weeks 24, 48, 72, or 96. The long-term follow-up study is covered by a separate study protocol.

f Participants not entering the DBE period, OLE period, or long-term follow-up study will have a Safety Follow-up visit 4 weeks after End-of-DBTP/End-of-DBE/End-of-OLE Visit, respectively.

1.3 Schedule of Activities

1.3.1 Schedule of Activities - Double-blind Treatment Period

Assessments & Procedures	Screening[a]	Intervention Period																																									Unscheduled Visit[d]	Safety Follow-up[e]	Notes
		D1 / Baseline	W2[b]	W3	W4	W5	W6[b]	W7	W8[b]	W9	W10[b]	W11	W12	W14[b]	W16[b]	W18[b]	W20[b]	W22[b]	W24	W28[b]	W32[b]	W36	W40[b]	W44[b]	W48	W60	W72	W84	W96	W108	W120	W132	W144	W156 / ED / EODBTP[c]			
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	28	29	-	30	a Screening period is 4 weeks and can be extended to 12 weeks after approval by the Medical Monitor (see Section 8). b Home visits (if available) may be provided as an option. c EODBTP Visit will be performed after trigger of the PA (within 28 days). d For unscheduled visits, assessments not marked below may be performed at the discretion of the Investigator. e Safety follow-up visit will be performed 28 + 3 days after the last study intervention administration.
Study Day	-28 to -1	1	15	-	29	-	43	-	57	-	71	-	85	99	113	127	141	155	169	197	225	253	281	309	337	421	505	589	673	757	841	925	1009	1093	-		• Visit window is ± 3 days for all visits from W2 to W44, inclusive. Visit window is± 7 days for all visits from W48 to W156, inclusive. • Exception: W4 has a visit window of ± 2 days • Visit window is + 3 days for SFU

Assessments & Procedures	Intervention Period																																		Unscheduled Visit[d]	Safety Follow-up[e]	Notes
	Screening[a]	D1 / Baseline	W2[b]	W3	W4	W5	W6[b]	W7	W8[b]	W9	W10[b]	W11	W12	W14[b]	W16[b]	W18[b]	W20[b]	W22[b]	W24	W28[b]	W32[b]	W36	W40[b]	W44[b]	W48	W60	W72	W84	W96	W108	W120	W132	W144	W156 / ED / EODBTP[c]			
Informed Consent	X																																			a Screening period is 4 weeks and can be extended to 12 weeks after approval by the Medical Monitor (see Section 8).
Inclusion and Exclusion Criteria	X	X																																			Review Inclusion and Exclusion Criteria before randomization and first dose of study intervention.
Demography	X																																				
Full Physical Examination	X	X																							X				X					X	X	X	Additional examinations may be completed at the discretion of the Investigator.
Medical History (includes substance usage)	X																																				Substances: drugs, alcohol, tobacco, and caffeine.
MS History	X																																				
Serum Pregnancy Test (WOCBP only)	X																																				

b Home visits (if available) may be provided as an option.
c EODBTP Visit will be performed after trigger of the PA (within 28 days).
d For unscheduled visits, assessments not marked below may be performed at the discretion of the Investigator.
e Safety follow-up visit will be performed 28 + 3 days after the last study intervention administration.

Assessments & Procedures	Intervention Period																																						Unscheduled Visit[d]	Safety Follow-up[e]	Notes
	Screening[a]	D1 / Baseline	W2[b]	W3	W4	W5	W6[b]	W7	W8[b]	W9	W10[b]	W11	W12	W14[b]	W16[b]	W18[b]	W20[b]	W22[b]	W24	W28[b]	W32[b]	W36	W40[b]	W44[b]	W48	W60	W72	W84	W96	W108	W120	W132	W144	W156 / ED / EODBTP[c]			
Highly sensitive urine pregnancy test		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	Monthly urine pregnancy tests to be performed for all WOCBP. In-between visits, urine pregnancy testing will be performed at home.
Telephone Contact									X[f]						X[f]		X[f]			X[f]	X[f]		X[f]	X[f,g]	[-------X[g]---------]														See Section 8 and Appendix 10. f For participants utilizing home visit option g Telephone contacts between W44 and W156 should occur every 4 weeks if a clinic visit is not scheduled.
QuantiFERON®-TB tuberculosis test	X																																						See Exclusion Criteria 7 and 8. Participants can be tested for TB at any time during the study at the discretion of the Investigator.

Assessments & Procedures	Intervention Period																																		Unscheduled Visit[d]	Safety Follow-up[e]	Notes
	Screening[a]	D1 / Baseline	W2[b]	W3	W4	W5	W6[b]	W7	W8[b]	W9	W10[b]	W11	W12	W14[b]	W16[b]	W18[b]	W20[b]	W22[b]	W24	W28[b]	W32[b]	W36	W40[b]	W44[b]	W48	W60	W72	W84	W96	W108	W120	W132	W144	W156 / ED / EODBTP[c]			
TB testing for high TB burden countries																									X				X					X			See Exclusion Criteria 7 and 8. TB testing to be repeated at the indicated visits (or more frequently at the discretion of the Investigator) using the assay that was negative at Screening or replacement (refer to Laboratory Manual).
Ferritin, and transferrin saturation	X																																				See Exclusion Criterion 10.

a Screening period is 4 weeks and can be extended to 12 weeks after approval by the Medical Monitor (see Section 8).
b Home visits (if available) may be provided as an option.
c EODBTP Visit will be performed after trigger of the PA (within 28 days).
d For unscheduled visits, assessments not marked below may be performed at the discretion of the Investigator.
e Safety follow-up visit will be performed 28 + 3 days after the last study intervention administration.

Assessments & Procedures	Intervention Period																																	Unscheduled Visit[d]	Safety Follow-up[e]	Notes
	Screening[a]	D1 / Baseline	W2[b]	W3	W4	W5	W6[b]	W7	W8[b]	W9	W10[b]	W11	W12	W14[b]	W16[b]	W18[b]	W20[b]	W22[b]	W24	W28[b]	W32[b]	W36	W40[b]	W44[b]	W48	W60	W72	W84	W96	W108	W120	W132	W144	W156 / ED / EODBTP[c]			
HIV, HBV, and HCV testing	X																																		HIV testing will be conducted centrally. Where required by local regulations, testing can be conducted and analyzed locally. HBV and HCV testing will be performed at the central laboratory. Participants positive for anti-HCV antibodies will have reflex testing performed for HCV RNA by PCR. See Exclusion Criterion 34.
Efficacy																																				
Neurological Evaluation EDSS, T25-FW, 9-HPT, and SDMT	X	X											X						X			X			X	X	X	X	X	X	X	X	X	X	X	Preferably done after PRO assessments. Completed by the Examining Investigator (assessor) (or Qualified Examining Designee for T25-FW, 9-HPT, and SDMT).

Assessments & Procedures	Intervention Period																																Unscheduled Visit[d]	Safety Follow-up[e]	Notes
	Screening[a]	D1 / Baseline	W2[b]	W3	W4	W5	W6[b]	W7	W8[b]	W9	W10[b]	W11	W12	W14[b]	W16[b]	W18[b]	W20[b]	W22[b]	W24	W28[b]	W32[b]	W36	W40[b]	W44[b]	W48	W60	W72	W84	W96	W108	W120	W132	W144	W156 / ED / EODBTP[c]			
Relapse assessment													X						X			X			X	X	X	X	X	X	X	X	X	X	X	During unscheduled visits for relapse, EDSS assessment is required within 7 days of relapse reporting.
MRI scan	X																		X						X				X					X			Participants should meet all non-imaging inclusion/exclusion criteria before the Screening (Baseline) MRI is performed. An MRI is mandatory at the EOT/ED Visit if the previous MRI was performed more than 4 weeks prior to the visit.
PRO assessments and health resource utilization																																				
PROMIS Fatigue and Physical Functioning, EQ-5D-5L		X											X						X			X			X	X	X	X	X	X	X	X	X	X	X	PROs should be completed prior to administration of study intervention and prior to any other study assessment(s).

Assessments & Procedures	Intervention Period																																			Unscheduled Visit[d]	Safety Follow-up[e]	Notes
	Screening[a]	D1 / Baseline	W2[b]	W3	W4	W5	W6[b]	W7	W8[b]	W9	W10[b]	W11	W12	W14[b]	W16[b]	W18[b]	W20[b]	W22[b]	W24	W28[b]	W32[b]	W36	W40[b]	W44[b]	W48	W60	W72	W84	W96	W108	W120	W132	W144	W156 / ED / EODBTP[c]			
SF-36v2		X																	X						X		X		X		X			X	X			
Health resource utilization		X											X						X			X			X	X	X	X	X	X	X	X	X	X			See Section 8.9.
Safety assessments																																						
C-SSRS	X	X											X						X			X			X	X	X	X	X	X	X	X	X	X		X	The Treating Investigator or designee will complete this at each assessment. See Section 8.2.7
Reflex testing for HBV DNA	X				X				X				X						X			X			X	X	X	X	X		X			X		X	For participants who are anti-hepatitis B surface antibody positive and/or anti-hepatitis B core antibody positive at Screening, reflex testing for HBV DNA by PCR will be performed. See Exclusion Criterion 34.

Assessments & Procedures	Intervention Period																																		Unscheduled Visit[d]	Safety Follow-up[e]	Notes
	Screening[a]	D1 / Baseline	W2[b]	W3	W4	W5	W6[b]	W7	W8[b]	W9	W10[b]	W11	W12	W14[b]	W16[b]	W18[b]	W20[b]	W22[b]	W24	W28[b]	W32[b]	W36	W40[b]	W44[b]	W48	W60	W72	W84	W96	W108	W120	W132	W144	W156 / ED / EODBTP[c]			
Evobrutinib concentration assessment			[----------X----------]																																	Analysis will only be conducted if elevated LFTs are observed.
Biochemistry and Hematology	X	X											X						X						X		X		X	X		X		X	X	X	See Section 7.1 and Appendix 5.
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	X	X		X		X			X		X			If elevated, LFTs will be repeated along with additional testing (see Section 7.1).
Hepatic/ Autoimmune Panel/focused genetic testing (e.g., HFE)			Sample collection and analysis will only be conducted if elevated LFTs are observed.																																	See Section 7.1 and Appendix 5.
Coagulation	X																																X			Coagulation tests will be performed in case of LFT elevation.

Assessments & Procedures	Screening[a]	Intervention Period																																			Unscheduled Visit[d]	Safety Follow-up[e]	Notes
		D1 / Baseline	W2[b]	W3	W4	W5	W6[b]	W7	W8[b]	W9	W10[b]	W11	W12	W14[b]	W16[b]	W18[b]	W20[b]	W22[b]	W24	W28[b]	W32[b]	W36	W40[b]	W44[b]	W48	W60	W72	W84	W96	W108	W120	W132	W144	W156 / ED / EODBTP[c]			
Urinalysis (local)	X	X																X						X		X		X					X	X	X	a Screening period is 4 weeks and can be extended to 12 weeks after approval by the Medical Monitor (see Section 8). b Home visits (if available) may be provided as an option. c EODBTP Visit will be performed after trigger of the PA (within 28 days). d For unscheduled visits, assessments not marked below may be performed at the discretion of the Investigator. e Safety follow-up visit will be performed 28 + 3 days after the last study intervention administration.
12-lead ECG	X	X			X													X										X					X			A Baseline ECG will be collected on Day 1 prior to dosing, in addition to the regular ECG required per visit (see bullet below). All other ECG assessments must be conducted approximately 45 to 60 minutes after study intervention administration at the site. See PK sampling row for timing of PK collection.

Assessments & Procedures	Intervention Period																																	Unscheduled Visit[d]	Safety Follow-up[e]	Notes
	Screening[a]	D1 / Baseline	W2[b]	W3	W4	W5	W6[b]	W7	W8[b]	W9	W10[b]	W11	W12	W14[b]	W16[b]	W18[b]	W20[b]	W22[b]	W24	W28[b]	W32[b]	W36	W40[b]	W44[b]	W48	W60	W72	W84	W96	W108	W120	W132	W144	W156 / ED / EODBTP[c]			a Screening period is 4 weeks and can be extended to 12 weeks after approval by the Medical Monitor (see Section 8). b Home visits (if available) may be provided as an option. c EODBTP Visit will be performed after trigger of the PA (within 28 days). d For unscheduled visits, assessments not marked below may be performed at the discretion of the Investigator. e Safety follow-up visit will be performed 28 + 3 days after the last study intervention administration.
																																				Additional ECGs can be done if there are concerns about cardiac signs or symptoms and at the Investigator's discretion, if clinically indicated.
Vital Signs, Height, and Weight	X	X											X						X			X			X	X	X	X	X				X	X	X	Collect Height at Screening only.
AE, SAE & AESI Review	[----------X----------]																																			AE review to be started after ICF is signed.
Concomitant Medication and Procedures Review	[----------X----------]																																			
Blinded Immuno-globulin levels		X											X						X						X		X		X		X		X	X		X	

Assessments & Procedures		**Intervention Period**																																**Unscheduled Visit[d]**	**Safety Follow-up[e]**	**Notes**
	Screening[a]	**D1 / Baseline**	**W2[b]**	**W3**	**W4**	**W5**	**W6[b]**	**W7**	**W8[b]**	**W9**	**W10[b]**	**W11**	**W12**	**W14[b]**	**W16[b]**	**W18[b]**	**W20[b]**	**W22[b]**	**W24**	**W28[b]**	**W32[b]**	**W36**	**W40[b]**	**W44[b]**	**W48**	**W60**	**W72**	**W84**	**W96**	**W108**	**W120**	**W132**	**W144**	**W156 / ED / EODBTP[c]**			
Study Intervention																																				
Randomization		X																																		Randomization occurs on Day 1, prior to start of study intervention and after participant has met all eligibility criteria and all assessments have been completed.
Dispense Study Intervention (s)		X			X								X						X			X			X	X	X	X	X	X	X	X	X			Dispense as needed per IWRS.
Study Intervention(s) Administration		Administration of study interventions																																		Study intervention must be taken in the fed state, see Section 6.1. Study intervention should be administered during the study visit on PK sampling days.

a Screening period is 4 weeks and can be extended to 12 weeks after approval by the Medical Monitor (see Section 8).

b Home visits (if available) may be provided as an option.

c EODBTP Visit will be performed after trigger of the PA (within 28 days).

d For unscheduled visits, assessments not marked below may be performed at the discretion of the Investigator.

e Safety follow-up visit will be performed 28 + 3 days after the last study intervention administration.

Assessments & Procedures		**Intervention Period**																																**Unscheduled Visit[d]**	**Safety Follow-up[e]**	**Notes**
	Screening[a]	**D1 / Baseline**	**W2[b]**	**W3**	**W4**	**W5**	**W6[b]**	**W7**	**W8[b]**	**W9**	**W10[b]**	**W11**	**W12**	**W14[b]**	**W16[b]**	**W18[b]**	**W20[b]**	**W22[b]**	**W24**	**W28[b]**	**W32[b]**	**W36**	**W40[b]**	**W44[b]**	**W48**	**W60**	**W72**	**W84**	**W96**	**W108**	**W120**	**W132**	**W144**	**W156 / ED / EODBTP[c]**			
Study Intervention(s) Compliance		[----------X----------]																																		Participant to complete diary after every study intervention administration. See Section 6.4. Diary to be reviewed during on-site visits
PK/PD, PGx, and Biomarker assessments																																				
PK sampling		X			X							X						X					X		X		X				X				Study visits containing PK sampling should be scheduled before first daily dose, and participants should be instructed to wait and take study interventions at the site (see Section 6.1).

Assessments & Procedures	Intervention Period																																							Unscheduled Visit[d]	Safety Follow-up[e]	Notes
	Screening[a]	D1 / Baseline	W2[b]	W3	W4	W5	W6[b]	W7	W8[b]	W9	W10[b]	W11	W12	W14[b]	W16[b]	W18[b]	W20[b]	W22[b]	W24	W28[b]	W32[b]	W36	W40[b]	W44[b]	W48	W60	W72	W84	W96	W108	W120	W132	W144	W156 / ED / EODBTP[c]			
																																								• Day 1 PK collected at 0 (predose), 0.5, 1, 2, and 4 hours postdose. Prior to the predose blood draw, the baseline ECG assessment should be taken. The postdose ECG assessment on Day 1 should be near the Cmax, or approximately 45-60 minutes after dosing, with PK sampling within 30 minutes AFTER the ECG assessment.

a Screening period is 4 weeks and can be extended to 12 weeks after approval by the Medical Monitor (see Section 8).

b Home visits (if available) may be provided as an option.

c EODBTP Visit will be performed after trigger of the PA (within 28 days).

d For unscheduled visits, assessments not marked below may be performed at the discretion of the Investigator.

e Safety follow-up visit will be performed 28 + 3 days after the last study intervention administration.

Assessments & Procedures	Intervention Period																																	Unscheduled Visit[d]	Safety Follow-up[e]	Notes
	Screening[a]	D1 / Baseline	W2[b]	W3	W4	W5	W6[b]	W7	W8[b]	W9	W10[b]	W11	W12	W14[b]	W16[b]	W18[b]	W20[b]	W22[b]	W24	W28[b]	W32[b]	W36	W40[b]	W44[b]	W48	W60	W72	W84	W96	W108	W120	W132	W144	W156 / ED / EODBTP[c]			a Screening period is 4 weeks and can be extended to 12 weeks after approval by the Medical Monitor (see Section 8). b Home visits (if available) may be provided as an option. c EODBTP Visit will be performed after trigger of the PA (within 28 days). d For unscheduled visits, assessments not marked below may be performed at the discretion of the Investigator. e Safety follow-up visit will be performed 28 + 3 days after the last study intervention administration.
																																				• W4, W24, and W96 PK collected at 0 hours (predose) and 1 sample within 30 minutes AFTER the ECG assessment. ECG assessment should be performed approximately 45-60 minutes postdose. • W156 / ED / EOT PK sample collected prior to dosing. • W12, W48, and W72 PK collected at 0 hours (predose) and 1 sample between 1 and 6 hours postdose.
Gene expression		X											X						X						X				X					X			To be collected prior to first daily dose.

Assessments & Procedures		**Intervention Period**																																**Unscheduled Visit[d]**	**Safety Follow-up[e]**	**Notes**
	Screening[a]	**D1 / Baseline**	**W2[b]**	**W3**	**W4**	**W5**	**W6[b]**	**W7**	**W8[b]**	**W9**	**W10[b]**	**W11**	**W12**	**W14[b]**	**W16[b]**	**W18[b]**	**W20[b]**	**W22[b]**	**W24**	**W28[b]**	**W32[b]**	**W36**	**W40[b]**	**W44[b]**	**W48**	**W60**	**W72**	**W84**	**W96**	**W108**	**W120**	**W132**	**W144**	**W156 / ED / EODBTP[c]**			
Pharmaco-genetics		X																																		Sample to be collected on Day 1 before study intervention starts (optional for participants who sign Pharmacogenetics ICF). If not collected on Day 1 or a redraw is needed, the sample may be obtained at any other point of time during the study.
Biomarkers of disease (including NfL)		X											X						X						X		X		X			X	X			To be collected prior to first daily dose. Samples may be repurposed to evaluate other biomarkers as outlined in Section 8.8.

a Screening period is 4 weeks and can be extended to 12 weeks after approval by the Medical Monitor (see Section 8).

b Home visits (if available) may be provided as an option.

c EODBTP Visit will be performed after trigger of the PA (within 28 days).

d For unscheduled visits, assessments not marked below may be performed at the discretion of the Investigator.

e Safety follow-up visit will be performed 28 + 3 days after the last study intervention administration.

Assessments & Procedures	Screening[a]	Intervention Period																																Unscheduled Visit[d]	Safety Follow-up[e]	Notes
		D1 / Baseline	W2[b]	W3	W4	W5	W6[b]	W7	W8[b]	W9	W10[b]	W11	W12	W14[b]	W16[b]	W18[b]	W20[b]	W22[b]	W24	W28[b]	W32[b]	W36	W40[b]	W44[b]	W48	W60	W72	W84	W96	W108	W120	W132	W144	W156 / ED / EODBTP[c]			
Novel liver function protein biomarkers in serum		[----------X----------]																																		Samples will be collected at each visit; however, analysis will only be conducted if elevated LFTs are observed or if the samples serve as an appropriate control sample (see Section 8.8. Samples may be repurposed to evaluate other biomarkers as outlined in Section 8.8.
Novel liver function genomic biomarkers in plasma		[----------X----------]																																		Samples will be collected at each visit; however, analysis will only be conducted if elevated LFTs are observed or if the samples serve as an appropriate control sample (see Section 8.8. Samples may be repurposed to evaluate other biomarkers as outlined in Section 8.8.

a Screening period is 4 weeks and can be extended to 12 weeks after approval by the Medical Monitor (see Section 8).
b Home visits (if available) may be provided as an option.
c EODBTP Visit will be performed after trigger of the PA (within 28 days).
d For unscheduled visits, assessments not marked below may be performed at the discretion of the Investigator.
e Safety follow-up visit will be performed 28 + 3 days after the last study intervention administration.

9-HPT = 9-Hole Peg Test, AE = adverse event, AESI = adverse event of special interest, ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, C_{max} = maximum evobrutinib concentration, COVID-19 = coronavirus disease 2019, C-SSRS = Columbia-Suicide Severity Rating Scale, D = Day, DNA = deoxyribonucleic acid, ECG = electrocardiogram, ED = Early Discontinuation, EDSS = Expanded Disability Status Scale, EODBTP = End-of-Double-Blind Treatment Period, EOT = End-of-Treatment; EQ-5D-5L = EuroQoL 5 Dimension 5 Level, GGT = γ-glutamyl-transferase, HBV = hepatitis B virus, HCV = hepatitis C virus, HFE = High Iron Fe (human hemochromatosis 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, NfL = Neurofilament Light Chain; PA = primary analysis, PCR = polymerase chain reaction, PGx = Pharmacogenetics, PK = Pharmacokinetic, PRO = Patient Reported Outcomes, PROMIS = Patient Reported Outcomes Measurement Information System, RNA = Ribonucleic acid, SAE = Serious Adverse Event, SDMT = Symbol Digit Modalities Test, SF-36v2 = 36-Item Short Form Survey Instrument Version 2, SFU = Safety Follow-up, TB = Tuberculosis, T25-FW = Timed 25-Foot Walk, W = Week, WOCBP = Women Of Childbearing Potential.

1.3.2 Schedule of Activities – Double-Blind Extension Period

Assessments & Procedures	Intervention Period														SFU[d]	Notes
	D1 / Baseline[a]	W4	W8[b]	W12	W16	W20	W24	W36	W48	W60	W72	W84	W96 / EODBE	Unscheduled[c]		a D1/Baseline can be performed on the same day as the EODBT visit but no later than 28 days. D1/Baseline assessments only need to be performed if the EODBT visit occurred at least 3 days ago. b Home visits (if available) may be provided as an option. c For unscheduled visits, assessments not marked below may be performed at the discretion of the Investigator. d SFU visit will be performed 28 + 3 days after the last study intervention administration.
Visit window (days)		± 3 from W4 to W20					± 7 from W24 to ~W96/ED/EODBE									
Path 1 Participants with at least 24 weeks (but less than 48 weeks) of blinded treatment in the DBTP at the time of PA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Path 2 Participants with at least 48 weeks of blinded treatment in the DBTP at the time of PA	X			X			X	X	X	X	X	X	X	X	X	
Informed Consent	X															Check if ICF has been signed at Week 156 or EODBTP visit before proceeding with the DBE period
Full Physical Examination									X				X		X	Additional examinations may be completed at discretion of Investigator.
Highly sensitive urine pregnancy test	[----------X----------]															Monthly urine pregnancy tests to be performed for all WOCBP.
Highly sensitive urine pregnancy test (home)	[----------X----------]															Monthly tests performed for all WOCBP. In-between visits testing performed at home. (Section 8.3.5).

Assessments & Procedures	**Intervention Period**														**SFU[d]**	**Notes**
	D1 / Baseline[a]	**W4**	**W8[b]**	**W12**	**W16**	**W20**	**W24**	**W36**	**W48**	**W60**	**W72**	**W84**	**W96 / EODBE**	**Unscheduled[c]**		a D1/Baseline can be performed on the same day as the EODBT visit but no later than 28 days. D1/Baseline assessments only need to be performed if the EODBT visit occurred at least 3 days ago. b Home visits (if available) may be provided as an option. c For unscheduled visits, assessments not marked below may be performed at the discretion of the Investigator. d SFU visit will be performed 28 + 3 days after the last study intervention administration.
TB testing for high TB burden countries									X				X			See Exclusion Criteria 7 and 8. TB testing to be repeated at the indicated visits, but at least annually (or more frequently at the discretion of the Investigator) using the assay that was negative at Screening or replacement (refer to Laboratory Manual). For TB burden countries as defined by WHO (World Health Organization 2022, WHO TB Burden Estimates). QuantiFERON test to be repeated annually at the indicated visits. No repeats if completed within 12 months before D1.
Efficacy																For all efficacy assessments, values collected at Week 156/EODBTP visit will serve as values for Day 1.
Neurological Evaluation EDSS, T25-FW, 9-HPT, and SDMT	X			X			X	X	X	X	X	X	X	X		Preferably done after PRO assessments. Completed by the Examining Investigator (assessor) (or Qualified Examining Designee for T25-FW, 9-HPT, and SDMT).
Relay assessment	[----------X----------]															During unscheduled visits for relapse, EDSS assessment is required within 7 days of relapse reporting.

Assessments & Procedures	**Intervention Period**														**SFU[d]**	**Notes**
	D1 / Baseline[a]	**W4**	**W8[b]**	**W12**	**W16**	**W20**	**W24**	**W36**	**W48**	**W60**	**W72**	**W84**	**W96 / EODBE**	**Unscheduled[c]**		a D1/Baseline can be performed on the same day as the EODBT visit but no later than 28 days. D1/Baseline assessments only need to be performed if the EODBT visit occurred at least 3 days ago. b Home visits (if available) may be provided as an option. c For unscheduled visits, assessments not marked below may be performed at the discretion of the Investigator. d SFU visit will be performed 28 + 3 days after the last study intervention administration.
MRI scan							X[e]		X				X			An MRI is mandatory at the EODBE/ED Visit if the previous MRI was performed more than 4 weeks prior to the visit. e Applicable to participants in Path A only
PRO assessments and health resource utilization																For all PRO assessments, values collected at Week 156/EODBTP visit will serve as values for Day 1.
PROMIS Fatigue and Physical Functioning, EQ-5D-5L				X			X	X	X	X	X	X	X			PROs should be completed prior to administration of study intervention and prior to any other study assessment(s).
SF-36v2							X		X		X		X			
Health Resource Utilization				X			X	X	X	X	X	X	X			See Section 8.9
C-SSRS	X			X			X	X	X	X	X	X	X		X	The Treating Investigator or designee will complete this at each assessment. See Section 8.2.7
Reflex testing for HBV DNA	X						X		X		X		X		X	For participants who are anti-hepatitis B surface antibody positive without history of vaccination for hepatitis B and/or anti-hepatitis B core antibody positive at DBTP Screening, reflex testing for HBV DNA by PCR will be performed.
Evobrutinib concentration assessment		[----------X----------]														Analysis will only be conducted if elevated LFTs are observed.

Assessments & Procedures	Intervention Period														SFU[d]	Notes
	D1 / Baseline[a]	W4	W8[b]	W12	W16	W20	W24	W36	W48	W60	W72	W84	W96 / EODBE	Unscheduled[c]		a D1/Baseline can be performed on the same day as the EODBT visit but no later than 28 days. D1/Baseline assessments only need to be performed if the EODBT visit occurred at least 3 days ago. b Home visits (if available) may be provided as an option. c For unscheduled visits, assessments not marked below may be performed at the discretion of the Investigator. d SFU visit will be performed 28 + 3 days after the last study intervention administration.
Safety Assessments																
Biochemistry and Hematology	X			X			X		X		X		X	X	X	
LFT: ALP, AST, ALT, GGT, and Total Bilirubin		X[f]	X[g]		X[g]	X[g]		X[g]		X[g]		X[g]				f Applicable to participants in Path A only g Applicable to participants in Paths A and B
Hepatic/ Autoimmune panel/focused genetic testing	Sample collection and analysis will only be conducted if elevated LFTs are observed.															See Section 7.1 and Appendix 5.
Coagulation	X												X			Coagulation tests will be performed in case of LFT elevation.
Urinalysis (local)							X		X		X		X		X	Urine microscopy should be submitted for central evaluation if indicated (see Section 8 and Appendix 5).
12-lead ECG	X						X						X			• All ECG assessments must be conducted approximately 45 to 60 minutes after study intervention administration at the site. • Additional ECGs can be done if there are concerns about cardiac signs or symptoms and at the Investigator's discretion, if clinically indicated.
Vital Signs and Weight	X						X		X		X		X	X	X	
Blinded Immuno-globulin levels	X						X		X		X		X		X	
AE, SAE & AESI	[----------X----------]															

Assessments & Procedures	**Intervention Period**														**SFU[d]**	**Notes**
	D1 / Baseline[a]	**W4**	**W8[b]**	**W12**	**W16**	**W20**	**W24**	**W36**	**W48**	**W60**	**W72**	**W84**	**W96 / EODBE**	**Unscheduled[c]**		a D1/Baseline can be performed on the same day as the EODBT visit but no later than 28 days. D1/Baseline assessments only need to be performed if the EODBT visit occurred at least 3 days ago. b Home visits (if available) may be provided as an option. c For unscheduled visits, assessments not marked below may be performed at the discretion of the Investigator. d SFU visit will be performed 28 + 3 days after the last study intervention administration.
Concomitant Medication and Procedures Review	[----------X----------]															
Study Intervention																
Dispense Study Intervention(s)	X			X			X	X	X	X	X	X	X			
Study Intervention Administration	[----------X----------]															Study intervention must be taken in the fed state. see Section 6.1. Visits with biomarker collection, first daily dose administered during study visit (D1, W48, W96). Diary to be reviewed during on-site visits.
Study Intervention Compliance																
Biomarker assessments																
Biomarkers of disease (including NfL)	X						X		X		X		X			To be collected prior to first (morning) daily dose. Samples may be repurposed as outlined in Section 8.8.2.
Gene expression	X								X				X			To be collected prior to first daily dose.
Novel liver function protein biomarker in serum	[----------X----------]															Samples will be collected at each visit; however, analysis will only be conducted if elevated LFTs are observed or if the samples serve as an appropriate control sample (see Section 8.8). Samples may be repurposed to evaluate other biomarkers as outlined in Section 8.8.

Assessments & Procedures	**Intervention Period**														**SFU[d]**	**Notes**
	D1 / Baseline[a]	**W4**	**W8[b]**	**W12**	**W16**	**W20**	**W24**	**W36**	**W48**	**W60**	**W72**	**W84**	**W96 / EODBE**	**Unscheduled[c]**		a D1/Baseline can be performed on the same day as the EODBT visit but no later than 28 days. D1/Baseline assessments only need to be performed if the EODBT visit occurred at least 3 days ago. b Home visits (if available) may be provided as an option. c For unscheduled visits, assessments not marked below may be performed at the discretion of the Investigator. d SFU visit will be performed 28 + 3 days after the last study intervention administration.
Novel liver function genomic biomarkers in plasma	[----------X----------]															Samples will be collected at each visit; however, analysis will only be conducted if elevated LFTs are observed or if the samples serve as an appropriate control sample (see Section 8.8). Samples may be repurposed to evaluate other biomarkers as outlined in Section 8.8.

9-HPT = 9-Hole Peg Test, AE = adverse event, AESI = adverse event of special interest, ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BTK = Bruton's Tyrosine Kinase, C_{max} = maximum evobrutinib concentration, COVID-19 = coronavirus disease 2019, C-SSRS = Columbia-Suicide Severity Rating Scale, D = Day, DBE = Double-blind Extension, DBTP = Double-Blind Treatment Period, DNA = deoxyribonucleic acid, ECG = electrocardiogram, ED = Early Discontinuation, EDSS = Expanded Disability Status Scale, EODBE = End-of-Double-Blind Extension, EODBTP = End-of-Double-Blind Treatment Period, EQ-5D-5L = EuroQoL 5 Dimension 5 Level, GGT = γ-glutamyl-transferase, HBV = hepatitis B virus, HCV = hepatitis C virus, HIV = Human Immunodeficiency Virus, ICF = Informed Consent Form, IWRS = Interactive Web Response System, LFT = Liver Function Test, MRI = Magnetic Resonance Imaging, MS = multiple sclerosis, NfL = Neurofilament light chain; PA = primary analysis; PCR = polymerase chain reaction, PD = Pharmacodynamic, PGx = Pharmacogenetics, PK = Pharmacokinetic, PRO = Patient Reported Outcomes, PROMIS = Patient Reported Outcomes Measurement Information System, RNA = Ribonucleic acid, SAE = Serious Adverse Event, SDMT = Symbol Digit Modalities Test, SF-36v2 = 36-Item Short Form Survey Instrument Version 2, SFU = Safety Follow-up, TB = Tuberculosis, T25-FW = Timed 25-Foot Walk, W = Week, WOCBP = Women Of Childbearing Potential.

1.3.3 Schedule of Activities – Open-label Extension Period

Assessments & Procedures	Intervention Period																														Safety Follow-up[e]	Notes
	Screening[a]	D1/Baseline	W2[b]	W3[b]	W4[b]	W5[b]	W6[b]	W7[b]	W8[b]	W9[b]	W10[b]	W11[b]	W12	W14[b]	W16[b]	W18[b]	W20[b]	W22[b]	W24[c]	W28[b]	W32[b]	W36	W40[b]	W44[b]	W48[c]	W60	W72[c]	W84	W96/ED/EOT[c]	Unscheduled Visit[d]		a Screening assessments for the OLE will be performed during the last visit of the DBE period. b Home visits (if available) may be provided as an option. c Possible transfer points to the long-term follow-up study are Weeks 24, 48, 72, or 96. At the transfer point, assessments should be done as per W96/ED/EOT Visit schedule. d For unscheduled visits, assessments not marked below may be performed at the discretion of the Investigator. e SFU visit will be performed 28 + 3 days after the last study intervention administration.
Visit window (days)			±3 from W2 to W44																						±7 from W48 to W96/ED/EOT								
Path A: participants not previously exposed to evobrutinib or treatment arm in DBTP and DBE unknown	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	X	X	X	X	X	X	

Assessments & Procedures	Intervention Period																														Safety Follow-up[e]	Notes
	Screening[a]	D1/Baseline	W2[b]	W3[b]	W4[b]	W5[b]	W6[b]	W7[b]	W8[b]	W9[b]	W10[b]	W11[b]	W12	W14[b]	W16[b]	W18[b]	W20[b]	W22[b]	W24[c]	W28[b]	W32[b]	W36	W40[b]	W44[b]	W48[c]	W60	W72[c]	W84	W96/ED/EOT[c]	Unscheduled Visit[d]		a Screening assessments for the OLE will be performed during the last visit of the DBE period. b Home visits (if available) may be provided as an option. c Possible transfer points to the long-term follow-up study are Weeks 24, 48, 72, or 96. At the transfer point, assessments should be done as per W96/ED/EOT Visit schedule. d For unscheduled visits, assessments not marked below may be performed at the discretion of the Investigator. e SFU visit will be performed 28 + 3 days after the last study intervention administration.
Only applicable after unblinding of the study																																
Path B: participants previously exposed to evobrutinib for at least 24 week (but less than 48 weeks)	X	X			X				X				X		X		X		X			X			X	X	X	X	X	X	X	Paths B and C are only applicable once the study has been unblinded.
Path C: participants previously exposed to evobrutinib for at least 48 weeks	X	X											X						X			X			X	X	X	X	X	X	X	Paths B and C are only applicable once the study has been unblinded.
Informed Consent	X																															

Assessments & Procedures	**Intervention Period**																													**Safety Follow-up[e]**	**Notes**
	Screening[a]	**D1/Baseline**	**W2[b]**	**W3[b]**	**W4[b]**	**W5[b]**	**W6[b]**	**W7[b]**	**W8[b]**	**W9[b]**	**W10[b]**	**W11[b]**	**W12**	**W14[b]**	**W16[b]**	**W18[b]**	**W20[b]**	**W22[b]**	**W24[c]**	**W28[b]**	**W32[b]**	**W36**	**W40[b]**	**W44[b]**	**W48[c]**	**W60**	**W72[c]**	**W84**	**W96/ED/EOT[c]**	**Unscheduled Visit[d]**		
																															a Screening assessments for the OLE will be performed during the last visit of the DBE period. b Home visits (if available) may be provided as an option. c Possible transfer points to the long-term follow-up study are Weeks 24, 48, 72, or 96. At the transfer point, assessments should be done as per W96/ED/EOT Visit schedule. d For unscheduled visits, assessments not marked below may be performed at the discretion of the Investigator. e SFU visit will be performed 28 + 3 days after the last study intervention administration.
Inclusion and Exclusion Criteria	X	X																													Review before first dose of study intervention. f Confirm AEP was completed prior to D1
Full Physical Examination	X																							X				X		X	Additional examinations may be completed at discretion of Investigator.
Highly sensitive urine pregnancy test	X	X																						X				X		X	Required if last monthly urine test was ≥ 1 month; serum test must be performed if positive urine test pregnancy reported. (Section 8.3.5).
Highly sensitive urine pregnancy test (home)		[----------X----------]																													Monthly tests performed for all WOCBP. In-between visits testing performed at home. (Section 8.3.5).

Assessments & Procedures	**Intervention Period**																														**Safety Follow-up[e]**	**Notes**
	Screening[a]	**D1/Baseline**	**W2[b]**	**W3[b]**	**W4[b]**	**W5[b]**	**W6[b]**	**W7[b]**	**W8[b]**	**W9[b]**	**W10[b]**	**W11[b]**	**W12**	**W14[b]**	**W16[b]**	**W18[b]**	**W20[b]**	**W22[b]**	**W24[c]**	**W28[b]**	**W32[b]**	**W36**	**W40[b]**	**W44[b]**	**W48[c]**	**W60**	**W72[c]**	**W84**	**W96/ED/EOT[c]**	**Unscheduled Visit[d]**		a Screening assessments for the OLE will be performed during the last visit of the DBE period. b Home visits (if available) may be provided as an option. c Possible transfer points to the long-term follow-up study are Weeks 24, 48, 72, or 96. At the transfer point, assessments should be done as per W96/ED/EOT Visit schedule. d For unscheduled visits, assessments not marked below may be performed at the discretion of the Investigator. e SFU visit will be performed 28 + 3 days after the last study intervention administration.
TB testing for high TB burden countries	X	X																						X				X			For TB burden countries as defined by WHO (World Health Organization 2022, WHO TB Burden Estimates). QuantiFERON test to be repeated annually at the indicated visits. No repeats if completed within 12 months before D1.
Efficacy																																
Neurological examination/ EDSS	X	X											X						X					X		X		X	X[g]	X	g Neurological examinations are not needed if the unscheduled visit is for safety follow-up.
Relapse assessment		[----------X ----------]																													During unscheduled visits for relapse, EDSS assessment is required.

Assessments & Procedures	Intervention Period																														Safety Follow-up[e]	Notes
	Screening[a]	D1/Baseline	W2[b]	W3[b]	W4[b]	W5[b]	W6[b]	W7[b]	W8[b]	W9[b]	W10[b]	W11[b]	W12	W14[b]	W16[b]	W18[b]	W20[b]	W22[b]	W24[c]	W28[b]	W32[b]	W36	W40[b]	W44[b]	W48[c]	W60	W72[c]	W84	W96/ED/EOT[c]	Unscheduled Visit[d]		a Screening assessments for the OLE will be performed during the last visit of the DBE period. b Home visits (if available) may be provided as an option. c Possible transfer points to the long-term follow-up study are Weeks 24, 48, 72, or 96. At the transfer point, assessments should be done as per W96/ED/EOT Visit schedule. d For unscheduled visits, assessments not marked below may be performed at the discretion of the Investigator. e SFU visit will be performed 28 + 3 days after the last study intervention administration.
T25-FW, 9-HPT and SDMT	X	X																							X				X			
PRO assessments and health resource utilization																																
PROMISnq PF (MS) 15a and PROMIS Fatigue (MS) 8a	X	X																	X						X		X		X			PROs should be completed prior to administration of study intervention and prior to any other study assessment(s).
EQ-5D-5L	X	X																							X				X			
WPAI:MS v2.0		X																							X				X			
Health Resource Utilization	X	X																							X				X			
Safety assessments																																

Assessments & Procedures	**Intervention Period**																														**Safety Follow-up[e]**	**Notes**
	Screening[a]	**D1/Baseline**	**W2[b]**	**W3[b]**	**W4[b]**	**W5[b]**	**W6[b]**	**W7[b]**	**W8[b]**	**W9[b]**	**W10[b]**	**W11[b]**	**W12**	**W14[b]**	**W16[b]**	**W18[b]**	**W20[b]**	**W22[b]**	**W24[c]**	**W28[b]**	**W32[b]**	**W36**	**W40[b]**	**W44[b]**	**W48[c]**	**W60**	**W72[c]**	**W84**	**W96/ED/EOT[c]**	**Unscheduled Visit[d]**		
AE, SAE & AESI Review	[----------X ----------]																															AE review to be started after ICF is signed
AEP and Teriflunomide level	X																															Path A: All participants MUST undergo AEP. See Section 8.
C-SSRS	X	X																							X				X		X	The Treating Investigator or designee will complete this at each assessment. See Section 8.2.7
Reflex testing for HBV DNA	X	X																							X				X		X	For participants who are anti-hepatitis B surface antibody positive without history of vaccination for hepatitis B and/or anti-hepatitis B core antibody positive at DBTP Screening, reflex testing for HBV DNA by PCR will be performed.

Assessments & Procedures	Intervention Period																													Safety Follow-up[e]	Notes
	Screening[a]	D1/Baseline	W2[b]	W3[b]	W4[b]	W5[b]	W6[b]	W7[b]	W8[b]	W9[b]	W10[b]	W11[b]	W12	W14[b]	W16[b]	W18[b]	W20[b]	W22[b]	W24[c]	W28[b]	W32[b]	W36	W40[b]	W44[b]	W48[c]	W60	W72[c]	W84	W96/ED/EOT[c]	Unscheduled Visit[d]		a Screening assessments for the OLE will be performed during the last visit of the DBE period. b Home visits (if available) may be provided as an option. c Possible transfer points to the long-term follow-up study are Weeks 24, 48, 72, or 96. At the transfer point, assessments should be done as per W96/ED/EOT Visit schedule. d For unscheduled visits, assessments not marked below may be performed at the discretion of the Investigator. e SFU visit will be performed 28 + 3 days after the last study intervention administration.
Biochemistry and Hematology	X	X											X						X						X		X		X	X	X	Laboratory results from W156/EOT visit of DBE period to be used for OLE screening. See Section 7.1 and Appendix 5.
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	X	X		X		X				**Path A:** W1, W2, W3, W4, W5, W6, W7, W8, W9, W10, W11, W14, W16, W18, W20, W22, W28, W32, W36, W40, W44, W60, W84 **Path B:** W4, W8, W16, W20, W36, W60, W84, **Path C:** W36, W60, W84 If elevated, LFTs will be repeated along with additional testing (see Section 7.1).

Assessments & Procedures	Intervention Period																														Safety Follow-up[e]	Notes
	Screening[a]	D1/Baseline	W2[b]	W3[b]	W4[b]	W5[b]	W6[b]	W7[b]	W8[b]	W9[b]	W10[b]	W11[b]	W12	W14[b]	W16[b]	W18[b]	W20[b]	W22[b]	W24[c]	W28[b]	W32[b]	W36	W40[b]	W44[b]	W48[c]	W60	W72[c]	W84	W96/ED/EOT[c]	Unscheduled Visit[d]		
Hepatic/ Autoimmune panel/focused genetic testing (e.g., HFE)	Sample collection and analysis will only be conducted if elevated LFTs are observed.																															See Section 7.1 and Appendix 5.
Coagulation	X	X																							X				X			Coagulation tests will be performed in case of LFT elevation.
Urinalysis (local)	X																		X						X		X		X		X	Urine microscopy should be submitted for central evaluation if indicated (see Section 8 and Appendix 5).
Vital Signs and Weight	X																		X						X		X		X	X	X	
12-lead ECG	X																								X				X			

Assessments & Procedures	**Screening[a]**	**Intervention Period**																													**Safety Follow-up[e]**	**Notes**
		D1/Baseline	**W2[b]**	**W3[b]**	**W4[b]**	**W5[b]**	**W6[b]**	**W7[b]**	**W8[b]**	**W9[b]**	**W10[b]**	**W11[b]**	**W12**	**W14[b]**	**W16[b]**	**W18[b]**	**W20[b]**	**W22[b]**	**W24[c]**	**W28[b]**	**W32[b]**	**W36**	**W40[b]**	**W44[b]**	**W48[c]**	**W60**	**W72[c]**	**W84**	**W96/ED/EOT[c]**	**Unscheduled Visit[d]**		
																															a Screening assessments for the OLE will be performed during the last visit of the DBE period. b Home visits (if available) may be provided as an option. c Possible transfer points to the long-term follow-up study are Weeks 24, 48, 72, or 96. At the transfer point, assessments should be done as per W96/ED/EOT Visit schedule. d For unscheduled visits, assessments not marked below may be performed at the discretion of the Investigator. e SFU visit will be performed 28 + 3 days after the last study intervention administration.
Concomitant Medication and Procedures Review		[----------X----------]																													
Study Intervention																															
Dispense Study Intervention(s)		X											X						X			X				X					Dispense as needed per IWRS
Study Intervention Administration			[----------X----------]																												Study intervention must be taken in the fed state. see Section 6.1. Visits with biomarker collection, first daily dose administered during study visit (D1, W48, W96). Diary to be reviewed during on-site visits.
Optional OLE MRI and Blood Biomarker Sub-studies (selected participants/sites/countries) (See Sections 8.1.2 and 8.8)																															

Assessments & Procedures	Intervention Period																														Safety Follow-up[e]	Notes
	Screening[a]	D1/Baseline	W2[b]	W3[b]	W4[b]	W5[b]	W6[b]	W7[b]	W8[b]	W9[b]	W10[b]	W11[b]	W12	W14[b]	W16[b]	W18[b]	W20[b]	W22[b]	W24[c]	W28[b]	W32[b]	W36	W40[b]	W44[b]	W48[c]	W60	W72[c]	W84	W96/ED/EOT[c]	Unscheduled Visit[d]		a Screening assessments for the OLE will be performed during the last visit of the DBE period. b Home visits (if available) may be provided as an option. c Possible transfer points to the long-term follow-up study are Weeks 24, 48, 72, or 96. At the transfer point, assessments should be done as per W96/ED/EOT Visit schedule. d For unscheduled visits, assessments not marked below may be performed at the discretion of the Investigator. e SFU visit will be performed 28 + 3 days after the last study intervention administration.
MRI scan	X[h]																								X				X			h End-of-DBE MRI will serve as Baseline scans in OLE MRI substudy.
T, B, and NK cell count		X																	X						X		X		X		X	
Immuno-globulin levels	X	X																							X				X		X	
Biomarkers of disease (including NfL)	X	X																							X				X			To be collected prior to first (morning) daily dose. Samples may be repurposed as outlined in Section 8.8.2.

9-HPT = 9-Hole Peg Test, AE = adverse event; AEP = accelerated elimination procedure, AESI = adverse event of special interest, ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, C-SSRS = Columbia-Suicide Severity Rating Scale, D = Day, DBE = Double-blind Extension, DBTP = Double-Blind Treatment Period, DNA = deoxyribonucleic acid, ECG = electrocardiogram, ED = Early Discontinuation, EDSS = Expanded Disability Status Scale, EOT = End-of-Treatment, EQ-5D-5L = EuroQoL 5 Dimension 5 Level, GGT = γ-glutamyl-transferase, HBV = hepatitis B virus, HFE = High Iron Fe (human hemochromatosis protein), ICF = Informed Consent Form, Ig = Immunoglobulin, IWRS = Interactive Web Response System, LFT = Liver Function Test, MRI = Magnetic Resonance Imaging, MS = multiple sclerosis, NfL = Neurofilament light chain, OLE = Open-label Extension, PRO = Patient Reported Outcomes, PROMIS = Patient Reported Outcomes Measurement Information System, SAE = Serious Adverse Event, SDMT = Symbol Digit Modalities Test, SFU = Safety follow-up, TB = Tuberculosis, T25-FW = Timed 25-Foot Walk, W = Week, WOCBP = Women Of Childbearing Potential, WPAI:MS = Work Productivity and Activity Impairment Questionnaire: Multiple Sclerosis

2 Introduction

Evobrutinib is a potent, orally administered, highly selective, irreversible inhibitor of BTK that is being developed for the treatment of 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 45 mg administered orally twice daily versus teriflunomide (Aubagio®; 14 mg once a day orally) 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 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, PK, and biological activity (MS200527_0086) is completed; the OLE part of the study is ongoing. The study consisted of first a 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 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% 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 2020).

The first key secondary endpoint was 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. The results of the Phase II OLE (cutoff 26 September 2019) indicate that the participants from the evobrutinib 75 mg twice daily arm had an ARR of 0.11, consistent with what was observed at the end of the main study (Week 48, cutoff 13 July 2018).

Evobrutinib at 45 mg twice daily in the fed state is expected to be similar to the tested 75 mg twice daily dose in the fasted state based on the available exposure/response data (see Section 4.3).

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 (and SPMS) with subclinical CNS inflammation.

Reversible elevations in transaminases (ALT and 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 DMT 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 DMTs 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, DMTs perceived to be more efficacious have also been shown to be associated with more significant adverse effects, ranging from serious infections (i.e., PML) to autoimmunity and cancer. Switching among these DMTs occurs primarily due to perceived lack of efficacy or the occurrence of 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 disease-modifying therapies that address not only inflammation but also disability progression within the CNS for patients with MS at all stages

of the disease. Early treatment with a highly efficacious and safer DMT 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 grey 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 (Boschert 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 DMTs.

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 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 SLE/lupus nephritis, experimental autoimmune encephalomyelitis, 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 that 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 TLR activation (Block 2012, López-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

Benefit

In the PA of the MS200527_0086 study, evobrutinib significantly decreased the number of T1 Gd+ lesions at Weeks 12, 16, 20, and 24 in participants with RMS. 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. In the OLE, the ARR remained low and similar to those observed in the PA and BEA. These results show evobrutinib is efficacious in participants with RMS, and consequently warrant further investigation in Phase III clinical studies.

Important Identified Risks

As of July 2022, more than 2,490 participants in completed and ongoing clinical studies have been exposed to evobrutinib including healthy volunteers, participants with RMS, SLE, or RA, and participants with renal and hepatic impairment. The incidence of SAEs and TEAEs leading to withdrawal of study intervention was ≤ 10% in completed SLE, RA, or RMS studies.

Overall, evobrutinib demonstrated manageable tolerability based on the completed and ongoing clinical studies across various indications. Observed TEAEs resolved after treatment discontinuation and did not result in permanent disabilities. In the ongoing blinded Phase III studies, cases of DILI have been reported, which were typically asymptomatic and were resolving after drug discontinuation. The TEAEs have been primarily mild to moderate in severity.

Important Potential Risk

Important Potential Risk: Severe DILI, i.e., Requiring Transplant or Leading to Death

Based on the important identified risk DILI, there is a theoretical consideration that evobrutinib may have the potential to cause severe DILI defined as liver organ failure, i.e., requiring transplant or leading to death. Hence, severe DILI, i.e., requiring transplant or leading to death is considered an important potential risk for evobrutinib.

Important Potential Risk: Embryo-Fetal Toxicity

Embryo-fetal toxicity has been classified as an important potential risk based on nonclinical experience with evobrutinib (refer to the IB), as well as other drugs in the same class. Results of nonclinical studies carried out in experimental models show that there is a risk of harm, which could lead to increased rates of stillbirth, abortion, or cleft palate and limb deformities. While nonclinical data suggest no risk for male-mediated developmental effects, female participants of childbearing potential must use highly effective contraception and barrier method during the study and some period after the study is completed, as specified in the clinical study protocols.

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 > 1.5 × ULN values for ALT, AST, and total bilirubin, > 2 × ULN amylase, or lipase elevation at Screening. During the study, liver transaminase will be monitored weekly during the first 12 weeks of DBTP and OLE, and every 2 weeks thereafter, for the first 6 months of exposure to evobrutinib. The protocol has strict stopping criteria for liver transaminase and total bilirubin elevations leading to treatment discontinuation and timely medical management. Also, relevant data will be reviewed by a Hepatology Assessment Committee (HAC) with appropriate expertise, which will report findings to the IDMC for consideration with appropriate expertise.

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 investigations, 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 after the last dose, and should not donate eggs, as risk mitigation measures (for further details, see Section 5.1).

Adverse Events of Special Interest

Although no causal relationship has been established, AESIs 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 coadministration of evobrutinib with a moderate (e.g., fluconazole) or strong (e.g., itraconazole) CYP3A4 inhibitor resulted in a significant DDI. Evobrutinib peak and total exposures were increased by approximately 2.5- to 3.4-fold when evobrutinib was dosed concurrently with fluconazole or itraconazole. Based on these observations, the coadministration of medications that are moderate or strong inhibitors or inducers of CYP3A4/5 is not permitted during ongoing clinical studies.

No new potential risks emerged from the completed studies: EMR200527_001, MS200527_0019, MS200527_0017, MS200527_0022, EMR200527_002, MS200527_0081, MS200527_0060, MS200527_0018, MS200527_0073, and MS200527_0074.

Evobrutinib is a BTK inhibitor and, as such, works as an immunomodulator. There was some decrease in IgM, an increase in IgA, and IgG levels remained stable following treatment with evobrutinib. There was a decrease in CD19+ B cells and mature-naïve B cells, but no evidence

of a change in memory B cell levels. The changes in B cells, IgA and IgM levels do not appear to be associated with an enhanced risk of infections, but the significance of these changes is not known (Montalban 2020). BTK is not required to clear viral infections, apart from enteroviruses. There is currently no evidence that evobrutinib treatment leads to a higher risk of SARS-CoV-2 infection, or a more severe disease. While no data regarding evobrutinib and COVID-19 are available, published data on approved BTK inhibitors (e.g., ibrutinib, acalabrutinib) used in oncology suggest a protective effect of BTK inhibitors for severity and mortality of COVID-19 (Scarfò 2020, Thibaud 2020, Treon 2020).

The evobrutinib data suggest that the risk of infections, including severe and opportunistic infections, is not higher than that observed with other disease-modifying treatments in MS, and no side effects have been identified that could exacerbate SARS-CoV-2 infection or mask COVID-19 symptoms.

Similarly, while teriflunomide is, like evobrutinib, an immunomodulatory agent, published reports of patients with MS and COVID-19 while on treatment with teriflunomide do not suggest an increased risk to patients, but rather a milder course of disease while on treatment (Ciardi 2020, Bollo 2020, Maghzi 2020, Möhn 2020).

The recommendation by the Multiple Sclerosis International Federation is to continue disease-modifying treatment in MS to offset the risk of relapses, as the risk of disease rebound outweighs the risk of SARS-CoV-2 infection (MS International Federation 2020).

To mitigate the risk of contracting COVID-19 during the study, there is flexibility in the timing of MRI assessments postscreening on a case-by-case basis. Safety labs, including liver function monitoring, may be collected during home visits, if available, and if permitted per local laws and regulations.

In case a SARS-CoV-2 infection occurs during this study, interruption of the study treatment and treatment of COVID-19 are recommended as clinically indicated. After recovery, the continuation of the study will be at the Investigator's discretion and in agreement with the medical monitoring team.

The Sponsor will monitor the events related to any SARS-CoV-2 infection regularly. In addition, the IDMC will review the impact of any SARS-CoV-2 infection of a study participant as part of their activities and will provide recommendations, if required.

Following the review of the totality of the safety data from the concluded clinical studies with evobrutinib, overall, evobrutinib was reported as well tolerated in patients with MS up to 75 mg twice daily. 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. Furthermore, evobrutinib at 45 mg twice daily in the fed state is expected to be similar to the tested 75 mg twice daily dose in the fasted state based on the available exposure/response data (see Section 4.3).

Benefit-Risk Conclusion

Overall, considering the unmet medical need in MS patients, reduction of MS activities (decreased the number of T1 Gd+ lesions and lower ARR compared 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 45 mg twice daily fed supports continued clinical development of evobrutinib in this population.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of evobrutinib may be found in Section 4.2 and the Investigator's Brochure. More detailed information about the known risks and benefits of teriflunomide are provided in the locally approved product information (e.g., relevant SmPC or the USPI).

The anticipated benefit for participants with RMS outweighs the risks as described in the paragraphs above. 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 Estimands

Table 1 Primary and Secondary Objectives, Endpoints and Estimands for the Double-blind Treatment Period

Objectives	Estimand Attributes
Primary	
To demonstrate superior efficacy with evobrutinib compared to teriflunomide in terms of ARR	Endpoint: ARR based on qualified relapses up to 156 weeks in participants with RMS Population: Patients with RMS as defined by inclusion/exclusion criteria Treatment: Evobrutinib versus teriflunomide Intercurrent Event Strategy: • Treatment discontinuation: Treatment policy • Death attributable to MS or treatment: Composite variable • Death unattributable to MS or treatment: While Alive • Ukraine crisis: Hypothetical Population-Level Summary: relapse rate ratio and CI (NB model), with test of treatment effect based on test of relapse rate ratio
Secondary	
To demonstrate the efficacy of evobrutinib relative to that of teriflunomide on disability progression	Endpoints: • Time to first occurrence of 12-week CDP as measured by the EDSS up to 156 weeks • Time to first occurrence of 24-week CDP as measured by the EDSS up to 156 weeks Population: Patients with RMS as defined by inclusion/exclusion criteria Treatment: Evobrutinib versus teriflunomide Intercurrent Event Strategy: • Treatment discontinuation: Treatment policy • Death attributable to MS or treatment: Composite variable • Death unattributable to MS or treatment: While Alive • Ukraine crisis: Hypothetical Population-Level Summary: hazard ratio and CI (Cox model), with test of treatment effect based on logrank test

Objectives	Estimand Attributes
To demonstrate the efficacy of evobrutinib relative to that of teriflunomide on disability improvement	Endpoints: • Time to first occurrence of 24-week CDI as measured by the EDSS up to 156 weeks Population: Patients with RMS as defined by inclusion/exclusion criteria and who have baseline EDSS ≥ 2.0 Treatment: Evobrutinib versus teriflunomide Intercurrent Event Strategy: • Treatment discontinuation: Treatment policy • Death (any cause): While Alive • Ukraine crisis: Hypothetical Population-Level Summary: hazard ratio and CI (Cox model), with test of treatment effect based on logrank test
To demonstrate the efficacy of evobrutinib relative to that of teriflunomide on patient reported symptoms and functional status	Endpoints: • CFB in PROMIS PF score over 96 weeks • CFB in PROMIS Fatigue score over 96 weeks Population: Patients with RMS as defined by inclusion/exclusion criteria Treatment: Evobrutinib versus teriflunomide Intercurrent Event Strategy: • Treatment discontinuation: Treatment policy • Death (any cause): While Alive • Ukraine crisis: Hypothetical Population-Level Summary: difference of average least-squares means of score CFB (average over Weeks 72, 84, and 96 for PROMIS PF and average over Weeks 48, 60, 72, 84, and 96 for PROMIS Fatigue)and CI (MMRM model), with test of treatment effect based on difference of average least-squares means

Objectives	Estimand Attributes
To demonstrate the efficacy of evobrutinib relative to that of teriflunomide on MRI lesion parameters	Endpoints: • Total number of T1 Gd+ lesions based on all available MRI scans • Number of new or enlarging T2 lesions on the last available MRI scan relative to the baseline MRI scan Population: Patients with RMS as defined by inclusion/exclusion criteria Treatment: Evobrutinib versus teriflunomide Intercurrent Event Strategy: • Treatment discontinuation: Treatment policy • Death (any cause): While Alive • Ukraine crisis: Hypothetical Population-Level Summary: lesion rate ratio and CI (NB model), with test of treatment effect based on test of lesion rate ratio
To demonstrate the efficacy of evobrutinib relative to that of teriflunomide by evaluating response on NfL concentrations in serum	Endpoint: • NfL concentration at 12 weeks Population: Patients with RMS as defined by inclusion/exclusion criteria Treatment: Evobrutinib versus teriflunomide Intercurrent Event Strategy: • Treatment discontinuation: Treatment policy • Death (any cause): While Alive • Ukraine crisis: Hypothetical Population-Level Summary: difference of geometric means at 12 weeks and CI (MMRM model), with test of treatment effect based on difference of least-squares means
To characterize the safety and tolerability of evobrutinib.	Endpoints: • Safety as assessed by the nature, severity, and occurrence of AEs and AESIs; vital signs; ECGs; absolute concentrations and CFB in Ig levels; and clinical laboratory safety parameters up to the end of the Safety Follow-up period Population: Patients with RMS as defined by inclusion/exclusion criteria Treatment: Evobrutinib versus teriflunomide Intercurrent Event Strategy: • Ukraine crisis: Hypothetical Population-Level Summary: Not applicable

Table 2 Tertiary/Exploratory Objectives and Endpoints for the Double-blind Treatment Period

Objectives	Endpoints (Outcome Measures)
Tertiary/Exploratory	
To evaluate the effect of evobrutinib compared to teriflunomide on clinical parameters	• ARR based on qualified relapses at Weeks 48 and 96 • Time to first qualified relapse over 156 weeks • Qualifying relapse-free status at Week 96 • 12-week confirmed EDSS progression free status at Week 96 • 24-week confirmed EDSS progression free status at Week 96 • 12-week confirmed disability improvement status at Week 96 • 24-week confirmed disability improvement status at Week 96
To evaluate the efficacy of evobrutinib relative to that of teriflunomide on MRI parameters	• T1 Gd+ lesion free status at Week 96 based on assessments up to Week 96 • Change in volume of T1 Gd+ lesions from Baseline to Week 96 based on assessments up to Week 96 • New or enlarging T2 lesion free status at Week 96 based on assessments up to Week 96 • Change in volume of T2 lesions from Baseline to Week 96 based on assessments up to Week 96 • CUA lesion free status at Week 96 based on assessments up to Week 96 • Total number of CUA lesions based on all available MRI scans • Total number of new T1 hypo-intense lesions based on all available MRI scans • Percentage change in BV from Week 24 to Week 96 based on assessments up to Week 96 • Percentage change in thalamic volume from Week 24 to Week 96 based on assessments up to Week 96 • Percentage change in cortical grey matter volume from Week 24 to Week 96 based on assessments up to Week 96

Objectives	Endpoints (Outcome Measures)
	• Change in normalized T1 intensity within pre-existing nonenhancing T2 weighted lesion volume from Baseline to Week 96 based on assessments up to Week 96 • Volume of SELs based on scans at Weeks 24, 48, and 96 • Change in number of PRL at Weeks 24, 48, and 96 • Change in CBF in NAWM at Weeks 24, 48, and 96
To evaluate the effect of evobrutinib compared to teriflunomide on functional parameters	• Time to ≥ 20% increase (confirmed at 12 weeks) in T25-FW up to 156 weeks • Time to ≥ 20% increase (confirmed at 12 weeks) in 9-HPT up to 156 weeks
To evaluate the effect of evobrutinib compared to teriflunomide on composite parameters	• NEDA-3 at Week 48, Week 96 defined by: o Qualifying relapse-free status o T1 Gd+ lesions free status and new or enlarging T2 lesion free status o 12-week confirmed EDSS progression free status • Time to first occurrence of 12-week CDP up to 156 weeks based on a composite score defined by: o 12-week confirmed EDSS progression (at least 0.5- or 1.0- point change, depending on the Baseline EDSS) or; o 12-week confirmed worsening (≥ 20%) in T25-FW versus Baseline or; o 12-week confirmed worsening (≥ 20%) in 9-HPT versus Baseline • NEP at Week 48, Week 96 as defined by: o No 12-week CDP on EDSS o No 12-week confirmed worsening (≥ 20%) in 9-HPT score o No 12-week confirmed worsening (≥ 20%) in T25-FW time • NEPAD at Week 48, Week 96 as defined by: o No protocol-defined relapses on treatment o No 12-week CDP on EDSS o No 12-week confirmed worsening (≥ 20%) in 9-HPT score

Objectives	Endpoints (Outcome Measures)
	○ No 12-week confirmed worsening (≥ 20%) in T25-FW time ○ No new or enlarging T2 lesions and no T1 Gd+ lesions on MRI
To evaluate the efficacy of evobrutinib relative to that of teriflunomide on progression independent of relapse activity	• Time to PIRA, where disability progression is defined for each of 2 endpoints as follows: ○ 12-week CDP on EDSS ○ 12-week confirmed worsening as a composite of 3 endpoints (EDSS, 9HPT, T25-FW)
To evaluate the efficacy of evobrutinib relative to that of teriflunomide on progression independent of relapse and brain MRI activity	• Time to PIRMA, where disability progression is defined for each of 2 endpoints as follows: ○ 12-week CDP on EDSS ○ 12-week confirmed worsening as a composite of the 3 endpoints (EDSS, 9HPT, T25-FW)
To evaluate the efficacy of evobrutinib relative to that of teriflunomide on cognitive function	• Change from Baseline in SDMT score at Week 48, Week 96
To evaluate the efficacy of evobrutinib relative to that of teriflunomide on patient reported symptoms and functional status	• Change from Baseline in PROMIS PF score at Week 48, Week 96, and Week 144 • Change from Baseline in PROMIS Fatigue score at Week 48, Week 96, and Week 144 • Time to first occurrence of 12-week confirmed PF deterioration compared to Baseline (decrease of at least 2.7 points on PROMIS PF score) up to 156 weeks • Change from Baseline in Patient Reported Outcome scores at Week 48, Week 96, and Week 144: ○ Medical Outcomes SF-36v2 ○ EQ-5D-5L
To evaluate the effect of evobrutinib on HRU relative to that of teriflunomide up to 156 weeks	• Absolute values of HRU, including but not limited to doctor/home/emergency visits, hospitalizations, paid assistance, and missed work
To characterize the PK profile of evobrutinib in participants with MS and to describe the exposure-response relationship	• PK parameters: $CL_{/F}$, $V_{z/f}$, C_{max}, and AUC after a single dose (Day 1 data), and at steady state (Weeks 2, 4, 8, 12, 24, 48, 72, and 96 data)

Objectives	Endpoints (Outcome Measures)
between evobrutinib and efficacy endpoints and safety endpoints	
To assess relationship between candidate disease biomarker and disease activity or treatment response	• Level of biomarkers of disease with disease activity/treatment response at Baseline, Weeks 12, 24, 48, 72, 96; and upon relapse/disease progression (unscheduled) • NfL concentration at Weeks 24, 48, 72, and 96
To measure the antibody levels to SARS-CoV-2 vaccine administered in participants	• Level of anti-SARS-CoV-2 antibodies to vaccines pre- and post-vaccination in a subset of participants who have received anti-COVID vaccinations during the study.
To evaluate the relationship of the novel biomarkers of liver function e.g., protein miRNA, etc., compared to standard clinical chemistry endpoints (ALT)	• Levels of novel biomarkers of hepatic function compared to ALT at Baseline, and on treatment
To assess the effect of evobrutinib on gene expression in whole blood	• Gene expression at Baseline, Weeks 12, 24, 48, and 96

Table 3 Objectives and Endpoints for the Double-Blind Extension Period

Objectives	Endpoints
DBE Period - Primary	
To further evaluate the efficacy with evobrutinib compared to teriflunomide in terms of Annualized Relapse Rate (ARR)	• ARR based on qualified relapses in participants with RMS
DBE Period - Secondary	
To further evaluate the efficacy of evobrutinib relative to that of teriflunomide on disability progression	• Time to first occurrence of 12-week CDP as measured by EDSS Time to first occurrence of 24-week CDP as measured by EDSS
To further evaluate the efficacy of evobrutinib relative to that of teriflunomide on disability improvement	• Time to first occurrence of 24-week CDP as measured by the EDSS

To further evaluate the efficacy of evobrutinib relative to that of teriflunomide on patient reported symptoms and functional status	• CFB in PROMIS PF score over time • CFB in PROMIS Fatigue score over time
To further evaluate the efficacy of evobrutinib relative to that of teriflunomide on magnetic resonance imaging (MRI) lesion parameters	• Total number of T1 Gd+ lesions based on all available MRI scans • Number of new or enlarging T2 lesions on the last available MRI scan relative to the baseline MRI scan
To further characterize the safety and tolerability of evobrutinib	• Safety as assessed by the nature, severity, and occurrence of AEs and AESIs; vital signs; ECGs; absolute concentrations and CFB in Ig levels; and clinical laboratory safety parameters up to the end of the Safety Follow-up period
DBE Period – Tertiary / Exploratory	
DBE tertiary / exploratory objectives and endpoints will be analogous to the DBTP tertiary/exploratory objectives and endpoints.	

Table 4 Objectives and Endpoints for the Open Label Extension Period

Objectives	Endpoints (Outcome Measures)
OLE Period - Primary	
To evaluate the long-term safety and tolerability of evobrutinib 45 mg BID in participants with RMS over time	• Occurrence of AEs and SAEs
OLE Period - Secondary	
To evaluate the long-term efficacy of evobrutinib 45 mg BID in participants with RMS	• ARR based on protocol defined qualified relapses • Time to first occurrence of 24-week CDP as measured by EDSS • Time to first occurrence of 24-week CDI as measured by EDSS • SDMT over time
To evaluate the long-term effect of evobrutinib 45 mg BID in participants with RMS on patient reported symptoms and functional status	• PROMISnq PF (MS) 15a score change over time • PROMIS Fatigue (MS) 8a score change over time
To further evaluate the long-term safety and tolerability of evobrutinib 45 mg BID in participants with RMS over time	• Safety Laboratory Parameters including Blood Chemistry, Hematology, Coagulation, Vitals, ECGs
OLE Period - Secondary – MRI Substudy	
To evaluate the long-term efficacy of evobrutinib 45 mg BID in participants with RMS on MRI parameters	• Total number of new or enlarging T2 lesions (relative to Baseline) • Change from Baseline in T2 lesion volume over time
OLE Period - Exploratory	
To further explore the long-term efficacy of evobrutinib 45 mg BID in participants with RMS	• EQ-5D-5L over time • WPAI:MS v2.0 over time • T25-FW over time • 9-HPT over time • No evidence of disease activity as assessed by NEDA-3, NEP, and NEPAD over time
To further explore the long-term efficacy of evobrutinib 45 mg BID in participants with RMS in the absence of relapse	• Time to PIRA, where disability progression is defined as 24-week CDP based on EDSS

Objectives	Endpoints (Outcome Measures)
OLE Period – Exploratory: MRI Substudy	
To further explore the long-term efficacy of evobrutinib 45 mg BID in participants with RMS on MRI parameters	• Change from Baseline in T1 lesion volume over time • NBV at Baseline • PBVC over time • SEL volume in Baseline T2 lesion volume (based on scans at Day 1/Baseline, Week 48, Week 96) • SEL volume in Week 96 T2 lesion volume (based on scans at Week 96, Week 144, Week 192) • Total number of PRLs (from inactive lesions) • Number of Baseline unenhancing PRLs that resolve at Week 96, Week 192 • Number of PRLs, new relative to Baseline, that persist at Week 96 • Number of PRLs, new relative to Week 96, that persist at Week 192 • Number of PRLs from active lesions, new relative to Baseline, that persist at Week 96 • Number of PRLs from active lesions, new relative to Week 96, that persist at W192 • nT1 intensity evolution in Baseline T2 lesion volume at W96, W192 • nT1 intensity evolution in SEL volume at Week 96, Week 192 (where SELs are a subset of Baseline T2 lesions)
OLE Period – Exploratory: Biomarker Substudy	
To further explore the long-term efficacy of evobrutinib 45 mg BID in participants with RMS by evaluating responses to biomarkers of disease (e.g., NfL)	• Changes in the concentration of biomarkers of disease (e.g., NfL) over time
To further explore the long-term safety of evobrutinib 45 mg BID in participants with RMS over time	• Absolute concentrations and change from baseline in Ig levels, T, B and NK cell count

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 teriflunomide, in participants with RMS.

Eligible participants will be randomized 1:1 to treatment with evobrutinib 45 mg twice daily, or teriflunomide 14 mg once daily (oral), stratified by region and Baseline EDSS. Blinding will be accomplished using a double-dummy design. The total sample size is planned to be 898 participants (approximately 449 participants per treatment group).

The Treatment Period of up to 156 weeks (minimum 24 weeks) will be preceded by a 4-week Screening Period (may be extended after discussion with the Medical Monitor but cannot exceed 12 weeks) and followed by a 4-week Safety Follow-up after treatment completion or early discontinuation.

Transition Into the DBE Period

Participants who complete the DBTP, or who are still under study treatment when the PA is triggered, will be considered treatment completers and will be eligible to continue in the DBE period for continuation of treatment as assigned at randomization (Figure 2). Those participants who have not reached the Week 156 visit when the PA is triggered, need to undergo an End-of-DBTP Visit, which is also their first visit in the DBE. Participants who do not wish to enter the DBE period will have a Safety Follow-up Visit occurring after the End-of-DBTP visit.

Transition Into OLE Period

Participants who complete the DBE period, or who are still under study treatment once the Sponsor – upon agreement with Health Authorities / Ethics Committees – will have notified sites (i.e., the OLE is open for enrollment), will be eligible for transition into the OLE period. Participants entering the OLE period need to undergo an End-of-DBTP Visit which is also their first visit in the OLE period. All participants previously treated with teriflunomide, or unknown exposure status, entering the OLE will be required to complete the AEP prior to dispensation of the IMP in the OLE period. Participants who do not wish to transition into OLE, will have a Safety Follow-up Visit after the end of the DBE Period. The treating physician may consider conducting the AEP for participants coming off the IMP and prior to initiation of alternative DMTs.

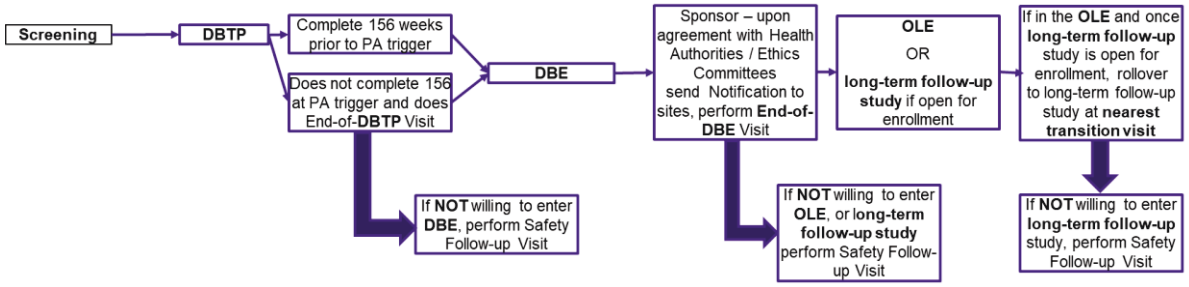
Transition Into Long-term Follow-up Study (MS200527_0123, LONGEVO)

Once the long-term follow-up study (MS200527_0123, LONGEVO) is open for enrollment (i.e., once the sponsor – upon agreement with Health Authorities / Ethics Committees – will have notified sites), participants of the OLE will switch into the long-term follow-up study at the nearest transition visit (at Weeks 24, 48, 72, or 96 of the OLE period). Participants who

do not wish to transition into the long-term follow-up study, will have a Safety Follow-up Visit after the End of Treatment visit in the OLE Period.

In case the long-term follow-up study is open for enrollment while participants are still under study treatment in the DBE period, they will be offered the possibility to transition into that study by default. For participants entering the long-term follow-up study, their last visit in the current study (i.e., End-of-DBE Visit) is also their first visit in the long-term follow-up study. Participants who do not wish to transition into the long-term follow-up study will have a Safety Follow-up Visit after the End-of-DBE Visit.

Figure 2 Participant Transition Schema



DBE = Double-blind Extension, DBTP = Double-blind Treatment Period, OLE = Open-label Extension, PA = primary analysis.

Per Protocol Version 3, prior to the completion of enrollment, an optional IA for BSSR, based on 12-week CDP (as measured by EDSS) data pooled from the present study and second Phase III study (MS200527_0080), was conducted. Based on this BSSR, in August 2021, it was decided that the number of participants to be enrolled would not be increased.

Initial enrollment was closed on 01 October 2021. The actual enrollment figures exceeded the original planned enrollment of 930 participants per study.

The currently escalating crisis that erupted in Ukraine in February 2022, and the countries sanctioned as a result, pose a challenge to the successful conduct of the MS200527_0080 and MS200527_0082 studies due to the large representation of these countries in the initial enrollment. In the worst-case scenario, all data from participants in the regions affected by the crisis (Ukraine, Russian Federation, and Belarus) will be unable to be queried for cleaning purposes and will be considered unreliable for inclusion in the PA. The impact on study power is discussed in Section 9.2.3.

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 teriflunomide in adult participants with RMS based on the ARR up to 156 weeks.

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. In the Phase II study of evobrutinib, the PA showed a clinically significant reduction in MRI activity in participants treated with evobrutinib compared to placebo. Furthermore, the results indicate that the ARR in the OLE remained low and similar to those observed in the PA and BEA.

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). Teriflunomide is an acknowledged therapy that has recently been used in pivotal studies as a comparator and is well-suited for the objectives of this study. It is currently widely used in the treatment of MS and has a well-established efficacy and safety profile. Teriflunomide is administered as a tablet once daily and eliminates the burden of injections specific to other standard of care therapies such as interferons. For further information on teriflunomide, refer to the locally approved product information (e.g., relevant SmPC or USPI).

The study will have a double dummy design, to minimize the potential for bias and maintain 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 and Baseline (Day 1) who had at least one or more documented relapses within the 2 years before Screening with either:

- one relapse which occurred within the last year prior to randomization, OR
- the presence of at least 1 T1 Gd+ 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 ≤ 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 up to 156 weeks, based on qualified relapses. Secondary efficacy endpoints will include time to 12- or 24-week CDP (as measured by EDSS), total number of new or enlarging T2 lesions based on all available MRI scans, and total number of T1 Gd+ lesions based on all available MRI scans. 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.

Time-to-24-week-CDI (as measured by EDSS) is a relatively new clinical endpoint complementary to the CDP endpoints. Week 12 NfL concentration is an emerging biomarker endpoint thought to reflect the early impact of treatment on reducing neuronal damage (Kuhle 2021; see Section 8.8.1.1 for details on NfL). The timepoint at Week 12 was chosen based on a post-hoc analysis of the data from a Phase II clinical study with evobrutinib.

Patient Reported Outcomes including those assessing fatigue and PF, are included as a secondary endpoint and several exploratory endpoints 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, Brañas 2000). In turn, these are associated with impairments in various functional areas, including 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 studies support positive treatment effects of currently available DMTs (including, teriflunomide, dimethyl fumarate, natalizumab, and ocrelizumab) on HRQoL, i.e., improving or preventing the worsening of HRQoL (Jongen 2017).

Exploratory research of biomarkers of evobrutinib treatment response in MS aims to define responders and non-responders to therapy and to better understand disease pathology. Exploratory biomarkers will help to define an optimal evobrutinib treatment response in MS and thus be of considerable value for taking treatment decisions and ensuring continued benefit from evobrutinib therapy. As genetic variation may impact a participant's response to therapy, susceptibility to disease, and severity and progression of disease, pharmacogenomic and pharmacogenetic biomarkers will be assessed to explore the long-term effect evobrutinib. In addition to this, blood sample assessments are included to test for biomarkers that are thought to play a key role in the disease pathology of MS and to be impacted by treatment with evobrutinib.

The DBE and OLE periods have been introduced for participants completing the DBTP to enable an option for treatment continuation and to investigate sustained or long-term efficacy and safety of evobrutinib prior to enrollment in the long-term follow-up study. 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 PD, efficacy, and safety data from the 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 the exposure-response relationship between PK and BTK occupancy (target engagement), ARR, number of T1 Gd+ lesions and number of new or enlarging (active) T2 lesions (efficacy endpoints) were used in the selection of the dose. The results of the modeling of evobrutinib concentrations, BTK occupancy, ARR, T1 Gd+ and active T2 lesions were used to select the dose of 45 mg twice daily (fed) that will deliver efficacy anticipated to be better than 75 mg once daily (fasted) or equal to 75 mg twice daily (fasted) observed in the RMS Phase IIb study.

In the exposure-response analysis of Study MS200527_0086 for participants with RMS, a steep exposure-response curve was observed with a threshold evobrutinib exposure ($AUC_{0\text{-}24,ss}$) of 355 ng•h/mL associated with the onset of a reduction in ARR, and a significant reduction in ARR observed at evobrutinib exposure of ≥ 400 ng•h/mL. Participants with

exposure ≤ 355 ng•h/mL had mean ARR values between 0.42 to 0.63, whereas participants with exposure > 355 ng•h/mL had mean ARR values between 0.00 to 0.14. The significant reduction in ARR was observed when trough BTK occupancy was > 95%, indicating high target engagement over the entire dosing interval. In addition, for the participants with RMS and > 0 T1 Gd+ lesions at Baseline or > 13 cc T2 lesion volume at Baseline, a significant reduction in the number of T1 Gd+ lesions, and the number of active T2 lesions was observed when evobrutinib exposure was greater than 468 ng•h/mL. This significant reduction in the number of active T2 lesions was observed when trough BTK occupancy was > 96%.

Thus, the criteria for selection of an efficacious dose to be used in Phase III is based on targeting exposure of ≥ 468 ng•h/mL and with a high percentage of participants expected to have > 95% trough BTK occupancy.

One dose of evobrutinib will be utilized in this study. A dose of 45 mg twice daily, when given with a meal, is expected to provide a (geometric) mean evobrutinib daily exposure ($AUC_{0\text{-}24,ss}$) of 840 ng•h/mL, with only 7.6% of the participants expected to have a daily exposure of < 400 ng•h/mL. The 45 mg twice daily dose will be administered to participants with a meal, where food (either a high-fat or low/moderate-fat meal) has been shown to increase evobrutinib exposure by 50%. Thus, the daily exposure with 45 mg twice daily fed is similar to the exposure observed in the Phase IIb study for 75 mg twice daily fasted (835 ng•h/mL), which provided a significant reduction in ARR (see Section 2.1). Mean $C_{max,ss}$ for 45 mg twice daily fed is expected to be 24% less (128 ng/mL) than the observed mean peak exposure (168 ng/mL) for 75 mg twice daily fasted.

In addition, high BTK occupancy (at least 95% occupancy in 93% of the participants) is expected at the end of a dosing interval; therefore, similar efficacy to that of 75 mg twice daily (BTK occupancy of at least 95% in 92% of the participants).

Teriflunomide will be administered orally at the highest approved dose of 14 mg once a day. Refer to the locally approved product information (e.g., relevant SmPC or USPI) 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 visits, including the last visit (as defined in the SoA in Section 1.3). A participant is considered a study completer if the participant has completed the Safety Follow-up Visit, even if the participant discontinued treatment prematurely. Treatment completers who do not require a Safety Follow-up Visit per protocol are also considered study completers (i.e., participants entering the long-term follow-up study at protocol-defined visits).

- **Treatment completion for the DBTP** is defined as completing treatment up until the time of the PA trigger or 156 weeks post randomization, whichever is earliest.

- **Treatment completion for the DBE period** is defined as completing treatment during the DBE at protocol-defined visits.
- **Treatment completion for the OLE period** is defined as completing treatment during the OLE at protocol-defined visits.

Refer to Section 9.4.4.2 for details on the PA.

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

The Sponsor may terminate the study at any time once access to the study intervention for participants still benefiting is provided via the long-term follow up study, expanded access, marketed product, or another mechanism of access, as appropriate.

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 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 (RRMS or 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 T1 Gd+ lesion within 6 months prior to randomization.
4. Have an EDSS score of 0 to 5.5 at Screening and Baseline (Day 1).
    a. Participants with an EDSS score ≤ 2 at Screening and Baseline (Day 1) 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 ≥ 30 days prior to both Screening and Baseline (i.e., no new signs or symptoms referable to the CNS for ≥ 30 days).

Sex

6. Are female or male
   a. Male Participants:

      Agree to the following during the study intervention period and for at least 2 years after study intervention due to the long elimination period for teriflunomide of 2 years, unless the participant undergoes an AEP (see Appendix 8) with a confirmed teriflunomide level of < 0.02 mg/L after the last dose of study intervention:

      • Refrain from donating sperm

      PLUS, either:

      • Abstain from intercourse with a woman of childbearing potential.

      OR

      - Use a male condom:
        - When having sexual intercourse with a woman of childbearing potential, who is **not** currently pregnant, and advise her to use a highly effective contraceptive method with a failure rate of < 1% per year, as described in Appendix 3, since a condom may break or leak.

   b. Female participants:

- Are **not** pregnant or breastfeeding, and at least one of the following conditions applies:
  - Not a woman of childbearing potential.

  OR

  - If a woman of childbearing 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.
    - 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.
    - During the Intervention Period

      For at least 2 years after study intervention due to the long elimination period for teriflunomide of (up to) 2 years, unless the participant undergoes an AEP (see Appendix 8) with a confirmed teriflunomide level of < 0.02 mg/L after the last dose of study intervention and agree not to donate eggs (ova, oocytes) for reproduction during this period (see Appendix 9). The Investigator evaluates the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

- Additional requirements for pregnancy testing during and after study intervention are in Sections 8.2.4 and 8.2.5.
- 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 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 SPMS without evidence of relapse.

2. Disease duration > 10 years in participants with an EDSS ≤ 2.0 at Screening and Baseline (Day 1).
3. Immunologic disorder other than MS or any other condition requiring oral, 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, cerebrovascular disorders, documented peripheral neuropathy (including polyneuropathy or mononeuropathy).
5. History or current diagnosis of PML. If a brain MRI has findings suggestive of PML, CSF JCV PCR should be performed to rule out PML (see Appendix 7).
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 before or during 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 TB.

OR

- Is currently undergoing treatment for 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 PPD with induration ≥ 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.

Study participants in high TB burden settings (> 100 cases/100,000 individuals [World Health Organization, 2019], based on WHO TB database [WHO TB Burden Estimates 2022]) must repeat TB testing at least annually at the visits indicated (see SoASection 1.3), using the assay that was negative at Screening or a replacement (see Laboratory Manual) (see Exclusion Criterion 8).

In addition, participants can be tested for TB at any time during the study, at the discretion of the Investigator.

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. Individuals with indeterminate or positive QuantiFERON test results felt to represent a false positive result by the Investigator, with no clinical features consistent with active TB, may 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 study eligibility team. Sites that are not able to process T-SPOT.TB please see Section 8 (Retesting before Baseline).
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:
    a Elevated transferrin saturation (> 50% transferrin saturation in males; and > 40% transferrin saturation in females) AND elevated ferritin levels > 500 µg/L will be excluded.
    b Highly elevated ferritin levels > 1,000 µg/L (independent of transferrin saturation) will also 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 Class III or Class IV, uncontrolled seizures (remote infantile febrile seizures are not exclusionary), prolonged untreated hypertension (systolic ≥ 160 mm Hg and/or diastolic ≥ 100 mm Hg), active gastrointestinal bleeding, or any other significant active medical condition in the Investigator's opinion or Sponsor's/designee's opinion.
14. Participants who have evidence of serious suicide risk including any history of suicidal behavior in the last 6 months and/or any suicidal ideation of type 4 or 5 on the C-SSRS in the 6 months prior to Screening.

    OR
    Are at significant suicide risk, as determined by the Treating Investigator.
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 nonmelanoma 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 atrioventricular conduction block, ventricular tachyarrhythmias) that in the Investigator's opinion may impact participation in the study.
18. Any other clinically significant abnormality per Investigator opinion.

Prior/Concomitant Therapy

19. Contraindication to teriflunomide or leflunomide or incompatibility with teriflunomide or leflunomide use, including:

    a. Hypersensitivity to teriflunomide, or to any excipients.

    b. Hypersensitivity to leflunomide, or to any excipients.

    c. Cessation of teriflunomide therapy due to poor tolerability or safety concerns, or suboptimal response.

20. Injectable (e.g., iv, intramuscular, intra-articular) or oral glucocorticoids, or ACTH (e.g., Acthar gel) within 4 weeks prior to randomization (inhaled and topical corticosteroids are allowed) (see Section 8).
21. Treatment with monthly iv methylprednisolone (see Section 6.5.1).
22. Prior treatment with beta-interferons or glatiramer acetate is not exclusionary, but these treatments must be discontinued at least 1 day prior to randomization.
23. Treatment with dimethyl fumarate, diroximel fumarate, or other approved fumaric acid esters within 4 weeks prior to randomization (see also Exclusion Criterion 37).
24. Treatment with teriflunomide within 4 weeks with an AEP or 14 weeks without the completion of an AEP prior to randomization (see Appendix 8 for AEP). Reason for switch from teriflunomide could not have been because of efficacy or safety related considerations. See also Exclusion Criterion 19.
25. Any of the following:

    a. Use of lymphocyte trafficking blockers (e.g., natalizumab) within 2 months prior to randomization. Patients whose last dose of natalizumab was within 6 months prior to randomization should be evaluated to rule out PML (see Appendix 7).

    b. Use of S1P inhibitors (e.g., fingolimod, ozanimod, ponesimod, siponimod) within 2 months prior to randomization.

    See also Exclusion Criterion 37.

26. Use of iv Ig or plasmapheresis within 8 weeks prior to randomization.

27. Treatment with rituximab, ofatumumab, or ocrelizumab. Participants who have received 1 dose of rituximab, ofatumumab, 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 of the following:
    a. Mildly to moderately immunosuppressive medications (e.g., azathioprine, methotrexate): within 6 months prior to randomization.
    b. Highly immunosuppressive medications (mitoxantrone, cyclophosphamide, cladribine): within 2 years prior to randomization.
    c. Alemtuzumab, lymphoid irradiation, bone marrow transplantation, or other strongly immunosuppressive treatments (with effects potentially lasting over 6 months): at any time.
    d. BTK inhibitors (including evobrutinib): at any time.
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. [Criterion removed by Amendment 1]
31. On anticoagulation, or antiplatelet therapy other than daily aspirin for cardioprotection. Fish oil supplements must be stopped prior to randomization (first dose).
32. Participants currently receiving (or unable to stop using prior to receiving the first dose of study intervention) potent (strong to moderate) inducers of 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). CYP2C8 substrates with a narrow therapeutic index must also be stopped at least 1 day prior to randomization.

    Note: CYP2B6 substrates with a narrow therapeutic index, as well as substrates of P-gp, BCRP, OCT1, MATE1 and/or MATE2K, while not exclusionary, should be administered with caution.

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 HIV at Screening.

    b. History of or positive for HCV antibody and/or HCV RNA by PCR at Screening. However, if a participant has a history of HCV infection and has completed and documented 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 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 HBV DNA by PCR will be performed:

       i. Hepatitis B antibody positive participants who have detectable HBV DNA $\geq$ 20 IU/mL are excluded.

       ii. Hepatitis B antibody positive participants who are HBV DNA negative or have detectable HBV DNA < 20 IU/mL are not excluded from the study. However, these participants will have HBV DNA monitoring by PCR at visits noted in the SoA (see Section 1.3).

35. eGFR < 60 mL/min/1.73 m^2 as calculated by the 4-variable Modification of Diet in Renal-Disease equation by the central laboratory or any renal condition that would preclude the administration of gadolinium (e.g., acute kidney injury).

36. ALT, AST and total bilirubin > 1.5 × ULN of laboratory reference range, amylase, or lipase > 2 × ULN, or any other clinically significant laboratory abnormality.

37. Significant cytopenia, including neutrophil count < 1,500 / mm^3, platelet count < 75,000 / mm^3, absolute lymphocyte count < 1,000 / mm^3, or a white blood cell count < 3,500 / mm^3.

Other Exclusions

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

    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 study intervention, 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 Double-Blind Extension Period

Participants need to be able and willing to provide written informed consent for the DBE before the first procedure in DBE.

Investigators need to ensure that participant does not fulfill any permanent discontinuation criteria (Section 7.1) based on Week 156/EODBTP assessments.

5.4 Criteria for Entry into Open Label Extension Period

5.4.1 Inclusion Criteria for Open Label Extension Period

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

1. Complete the DBE period or are still under study treatment when enrollment into OLE is opened - but not into the long-term follow-up study, 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 period (e.g., before the first OLE procedure on OLE Day 1) and to comply with the study protocol.
3. Have documentation of completed AEP (confirmed blood concentration level of < 0.02 µcg/mL of teriflunomide as per Appendix 8) before Day 1/Baseline visit (applicable to all participants previously treated with teriflunomide, or with an unknown exposure status during the DBTP and DBE period).
4. Women of childbearing potential are willing to continue to use the contraceptive methods as described in Section 5.1 (Inclusion Criterion 6) and Appendix 3.

5.4.2 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 intervention in DBE period.
2. Treatment with injectable (e.g., iv, intramuscular, intra-articular) or oral glucocorticoids, or ACTH (e.g., Acthar gel) within 30 days before OLE Day 1, with the exception of rescue treatment for MS relapse specified by the study protocol.
3. History of suicidal ideation or an episode of clinically severe depression (as determined by the Investigator) within 12 weeks prior to OLE Day 1.
4. 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.
5. Any of the following abnormal blood tests during the DBE period requiring discontinuation of study intervention, and/or at End-of-DBE visit, within a week before OLE Day 1:
    - ALT/serum glutamate pyruvate transaminase > 1.5 × ULN
    - AST/serum glutamic oxaloacetic transaminase> 1.5 × ULN
    - Total Bilirubin > 1.5 × ULN
    - Amylase > 2 × ULN
    - Lipase > 2 × ULN
6. eGFR < 60 mL/min/1.73 m^2 as calculated by the 4-variable Modification of Diet in Renal-Disease 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.

5.5 Lifestyle Considerations

5.5.1 Meals and Dietary Restrictions

Refrain from consumption of 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 (see Section 6.5.4).

5.5.2 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 PD sample. Due to a potential for

additive hepatotoxic effects associated with IMPs (teriflunomide and evobrutinib), alcohol consumption should be avoided during participation in the study.

There are no restrictions on caffeine or tobacco intake.

5.6 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. This Screening Period may be extended after approval by the Medical Monitor (but cannot exceed 12 weeks) for the reasons described in Section 8. 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

Study Intervention Name:	Evobrutinib	Teriflunomide
Dose Formulation:	Tablets	Tablets
Unit Dose Strength(s)/ Dosage Level(s):	45 mg (active or placebo)	14 mg (active or placebo)
Route of Administration:	Oral	Oral
Dosing Instructions:	Evobrutinib (or placebo) to be taken with a meal twice per day	Teriflunomide (or placebo) to be taken with a meal once per day
	Study intervention should be administered during the study visit on PK sampling days; otherwise, study intervention should be self-administered at home at a set time.	
Supplier/ Manufacturer:	Evobrutinib and placebo will be supplied by the Sponsor.	Teriflunomide and placebo will be supplied by the Sponsor.
Packaging and Labeling	• Evobrutinib active (45 mg): 1 blister contains 30 × 45 mg tablets. Two blisters to be packed in one wallet. One wallet is equivalent to a kit. **OR** • Matching placebo to Evobrutinib (45 mg): 1 blister contains 30 × matching Placebo to 45 mg tablets. Two blisters to be packed in one wallet. One wallet is equivalent to a kit. • Teriflunomide active (14 mg): 1 blister contains 30 × 14 mg tablets. One blister to be packed in one wallet. One wallet is equivalent to a kit. **OR** • Matching placebo to Teriflunomide (14 mg): 1 blister contains 30 × matching Placebo to 14 mg tablets. One blister to be packed in one wallet. One wallet is equivalent to a kit. Each kit will be packaged and labeled per all applicable regulatory requirements and Good Manufacturing Practice Guidelines.	

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 and safely. The storage facility at the study site must be locked and temperature controlled.

Evobrutinib and its placebo must be stored at no more than 30°C (86°F). For teriflunomide and its placebo storage conditions, refer to the teriflunomide approved product label.

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 teriflunomide are described in the locally approved product information (e.g., relevant SmPC or USPI), 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 Pharmacy 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 redispensed 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 Pharmacy 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 teriflunomide 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 (Day 1) EDSS (2 levels: < 4.0, ≥ 4.0). A unique participant identification number, assigned according to the Pharmacy Manual, will be used throughout the study.

Study using IWRS	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 teriflunomide in a 1:1 ratio using an IWRS and per a computer-generated randomization list. 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. 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.

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 tablet characteristics between the study intervention and the active control.
- Packaging and labeling will be prepared to protect the blinded nature of the study. Study interventions will be provided in a manner that participants or Investigator will not be able to distinguish active study intervention from placebo. Each kit will be labeled by the manufacturer with a unique kit number; labeling will not indicate whether the medication

is study intervention (evobrutinib/teriflunomide) or placebo. Blinded treatment kit numbers will be obtained through the IWRS.

- The Treating Investigator is a neurologist and will be the only one to discuss signs and symptoms with the participant to prevent unblinding of study personnel, based on associated clinical signs and symptoms related to study intervention. The Treating Investigator will be blinded to study intervention and will be responsible for:
  - Management of the routine neurological care of the participant, including the management of background treatment and associated safety monitoring
  - Assessment (including assignment of causality) and treatment of AEs and MS relapses
  - Review of hematology and blood chemistry results from the central laboratory to assess whether the participant's study intervention should be discontinued as per the criteria detailed in Section 7.1
  - If the Treating Investigator is not able to perform the C-SSRS and/or HRU tasks, they can assign these tasks to a non-neurologist delegate (Treating Investigator Designee), as long as the delegate is trained and qualified in performing these tasks.
- The independent Examining Investigator (assessor) (or their Qualified Examining Designee) will perform neurological assessments only, will remain blinded to all study interventions (evobrutinib and teriflunomide), all other study-related assessments, and to all laboratory results throughout the study.
- The central MRI reader will be blinded to all study interventions (evobrutinib and teriflunomide) throughout the study.
- The participants, site staff, and the Investigator will be blinded to all study interventions throughout the DBTP and the DBE period.
- The Contract Research Organization and Sponsor will be blinded to all study interventions until the database is locked for the PA (see Section 9.4).
- Importantly, the Treating Investigator (or designee) and the Examining Investigator (or designee) cannot perform the same tests. The Treating Investigator (or designee) performs the relapse assessments, AEs, monitors the participant, and performs C-SSRS and is not permitted to perform the EDSS, T25-FW, 9-HPT, and SDMT, and vice-versa, in order to maintain the blind. The Patient Reported Outcomes: PROMIS (physical function and fatigue), EQ-5D-5L and SF-36v2 can be administered by any site personnel.
- Study participants will be instructed to not discuss AEs, signs, and/or symptoms with the independent Examining Investigator (assessor) (or designee).
- The participants, site staff, and the Investigators will remain blinded to all study interventions during the Safety Follow-up.
- The IDMC and supporting independent statistician will be unblinded to treatment, as described in the IDMC charter.
- The bioanalytical monitors and other study team members responsible for analyses of PK will be blinded to study treatment codes prior to database lock for the PA. Analytical laboratories will be unblinded to study treatment codes to enable sample testing of study

intervention prior to database lock. The process by which masked participant identifiers will be used to prevent linking PK data with other clinical data will be documented.

- Subject matter experts and other study team members responsible for analyses of PGx will be blinded to study treatment codes prior to database lock for the PA. Analytical laboratories may be unblinded to study treatment codes to enable study-treatment-specific PGx testing prior to database lock for the PA. If study treatment specific PGx testing is performed, the process by which masked participant identifiers are used to maintain blinding will be documented.
- Study intervention information that would unblind the study participants will not be reported with participant identifiers to investigative sites or blinded personnel until the study has been unblinded.
- All other staff, other than those identified above, will remain blinded to the evobrutinib and teriflunomide study interventions.
- Only when the last participant completes study intervention up to the PA trigger or a maximum of 156 weeks, or discontinues study intervention prematurely, the protocol deviations are determined, and the database is locked for the PA will the drug codes be broken and made available for the data analysis. At that point, the Contract Research Organization and Sponsor study teams will be unblinded to study intervention, while the PI and study personnel remain blinded to the study intervention throughout the DBE.
- All breaks of the study blind must be adequately documented.

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 global patient 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 global patient safety department will submit any 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 study visit days as defined in the SoA (see 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 study. Participants or participant's caregiver will be asked to record the date and time of dosing and food intake around dosing (food intake to be recorded only on the day prior to PK sampling and the day

of PK sampling, and around the time of the last dose prior to evobrutinib concentration assessment sampling) in a participant diary.

Participants will be instructed to bring all study intervention, including the used packaging/empty boxes and all blisters, to each study visit during which IMP is dispensed as indicated in the SoA (see 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 during which IMP is dispensed as indicated in the SoA (see 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 IMP. 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 discretion of the Investigator, 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.

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 (or orally if high-dose oral formulation is locally available) 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 presteroid scan is within 1 week of the scheduled visit. In all instances, the treatment of the relapse per the Investigator's clinical judgment 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 (or equivalent, where approved), 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.

There are no restrictions on the use of marijuana, where and as permitted by 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. However, as this may impact continued participation in the study, the Medical Monitor must be informed that prohibited medication was used.

6.5.3 Prohibited Medicines

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

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

- Rituximab, ofatumumab, ocrelizumab, and any other B cell depleting therapy, BTK inhibitors (excluding evobrutinib), mitoxantrone, or lymphocyte-depleting therapies (e.g., alemtuzumab, anti-CD4, cladribine, cyclophosphamide, azathioprine, total body irradiation, bone marrow transplantation).
- Lymphocyte trafficking blockers (e.g., natalizumab, fingolimod, or siponimod).
- Intravenous Ig therapy and/or plasmapheresis and immunosuppressive treatments (e.g., azathioprine, methotrexate).
- Beta-interferons or glatiramer acetate.
- Dimethyl fumarate, diroximel fumarate, other approved fumaric acid esters, or leflunomide.

- 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 judgment in order to manage the participant's symptoms (see Section 6.5).
- Medications known to lower the seizure threshold should be avoided. If treatment with these medications is required, the Investigator must inform the Medical Monitor.
    - Dalfampridine (Ampyra) or fampridine are not permitted during the DBTP and the DBE unless 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.
    - During the OLE period of the study, initiation of therapy with dalfampridine (Ampyra) is allowed if (1) indicated by the Treating Investigator, (2) no contraindication as per local label is present and (3) participant has been exposed to evobrutinib for at least 3 months.
- Anticoagulation (e.g., warfarin), fish oil supplements, or antiplatelet therapy other than daily aspirin for cardioprotection.
- CYP2C8 substrates with a narrow therapeutic index must also be stopped at least 1 day prior to randomization in the DBTP and should not be administered throughout the DBTP as well as the DBE. Only during OLE period of the study, CYP2C8 substrates with a narrow therapeutic index are not prohibited if indicated by the Treating Investigator (see Appendix 11).
- 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. Medications known to be CYP2B6 substrates with a narrow therapeutic index, as well as substrates of P-gp, BCRP, OCT1, MATE1 and/or MATE2K, while not prohibited, should be administered with caution.
- Cholestyramine and activated charcoal, for use other than for AEP after discontinuation (see Appendix 8).
- Live or live-attenuated vaccines.
- Biologic therapies for MS are prohibited. Biologic therapies for other indications must be discussed with the Medical Monitor as their use may impact continued participation in the study, with the exception of insulin and antibodies used for bone density (e.g., denosumab), which are permitted.
- Systemic corticosteroids (oral, injected, iv) except as described in Section 6.5.1. Topical, intranasal, or inhaled corticosteroids are permitted.

For further information on teriflunomide-related DDI, see Appendix 9 and refer to the locally approved product information (e.g., relevant SmPC or USPI).

6.5.4 Other Interventions

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. As resveratrol supplements can significantly inhibit CYP3A, intake of resveratrol supplements must be limited to no more than 500 mg/day.

Teriflunomide has additional potential for drug interactions and due to the blinded treatment assignment, these should be considered when treating participants. See Appendix 9 for potential teriflunomide DDI, as defined in the locally approved product information (e.g., relevant SmPC or USPI).

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, CSF JCV PCR should be performed to rule out PML, see Appendix 7 for further details. See Section 7.1 for precautions related to suspected PML.

6.9 Management of Adverse Events of Interest

Adverse events of special interests 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 as specified in Appendix 4.

Liver adverse events

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

Evobrutinib liver AESIs will include transaminases (> 3 × ULN), bilirubin elevations (> 1.5 × ULN), 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 SOC Infection was one of the most reported SOCs (e.g., in the MS200527_0086 RMS study approximately 18% to 32% of participants treated with evobrutinib reported infection; a similar rate was reported in the placebo group in the 0 to 24 week period), the individual events were of low grade, mainly Grade 1, nonserious and did not lead to study intervention discontinuation. 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 ≥ 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. In RMS Study MS200527_0086, the incidence of TEAEs of lipase increased was slightly higher in evobrutinib 75 mg once daily and 75 mg twice daily arms (5 [9.4%] and 5 [9.3%], respectively) when compared to other arms (approximately between 4% to 6%). However, shifts from Baseline to highest grade on treatment were similar across all treatment arms for both amylase and lipase. In evobrutinib studies in other indications and in healthy participants the incidence of TEAEs of increased amylase or lipase, or both was infrequent and no clinically meaningful differences were observed across treatment arms. Any elevation of > 2 × ULN of lipase or amylase and any type of pancreatitis are classified as AESIs.

Seizures

Seizures are more common in patients with MS than in the general population, occurring in 2% to 3% of MS patients (Poser 2003). Convulsions were observed in early studies of evobrutinib in dogs, however the plasma concentration of evobrutinib was approximately 140-fold greater than it is predicted for the dose used in this study. One participant with RMS with significant brain lesion load reported seizure of unclear clinical picture. The PK data for this participant did not exceed the expected values and was similar to other participants in the study. Anticonvulsant therapy was started and the participant continued treatment with evobrutinib with no reoccurrence. The Investigator did not consider the event to be related to evobrutinib. No event of convulsion/seizure was reported in other indications. Evobrutinib has been administered to approximately 800 patients with MS, RA and SLE. Moreover, an electroencephalogram study in healthy volunteers did not show an epileptogenic potential for evobrutinib. Any type of seizures/epilepsy of any grade or its consequences are classified as AESIs.

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is definitively discontinued, the participant will remain in the study to be evaluated for the SFU visit. The SoA indicates data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

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. Due to the prolonged half-life of teriflunomide, and the possibility that the participant received teriflunomide, accelerated elimination with cholestyramine, activated charcoal, or as per local standard of care may be considered (for more details see Appendix 8). In cases for which permanent discontinuation of study intervention is required, no rechallenge will be allowed.

Liver function test-related monitoring and discontinuation criteria should be based on both central and local laboratory assessments depending on availability (i.e., participants should be discontinued if central or local laboratory result fulfills related criterion). The final decision should be based on the highest reported values (regardless of central or the local lab evaluation).

Criteria for Permanent Discontinuation of Study Intervention:

The Investigator should **permanently discontinue study intervention** upon confirmation of the criteria outlined below.

For laboratory or assessment related criteria:

- a neutrophil count < 500 / mm^3
- a neutrophil count 500–999 / mm^3 with fever
- platelet count < 25,000 / mm^3
- platelet count 25,000–49,999 / mm^3 with bleeding
- an increase in lipase to > 5 × ULN
- an increase in amylase to > 5 × ULN
- an increase in serum creatinine to > 3 × ULN
- any other laboratory abnormality of clinical significance, with the exception of lymphopenia (see below)
- QTcF > 500 msec OR an increase in QTcF > 60 msec relative to the participant's Baseline ECG (Day 1) is observed and confirmed (with a second ECG).
- Detectable HBV DNA ≥ 20 IU/mL. 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 [Section 1.3] and Exclusion Criterion 34).

- Confirmed increase of ALT/AST ≥ 5 ULN (without increased bilirubin values)
- Confirmed increase of total bilirubin > 2 ULN (without increased ALT/AST values)
- For an increase in AST and/or ALT to > 3 × ULN in combination with an increase in bilirubin to > 2 × ULN, the study intervention should be permanently discontinued and the Medical Monitor informed. In addition, a comprehensive hepatic/autoimmune panel is required (see below).

For other reasons:

- Pregnancy. As a pregnant participant may have received teriflunomide and due to the prolonged half-life of teriflunomide, an AEP should be performed and a teriflunomide level < 0.02 mg/L should be reached (for more details see Appendix 8).
- 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.
- Noncompliance regarding study intervention (see Section 6.4).
- Extended interruption of the study treatment for more than 30 days for any reason, except during AEP (between DBE period and OLE period) where a treatment gap over 30 days is acceptable if approved by the Medical Monitor.
- Use of prohibited medications, as defined in Section 6.5.3.
  - Note: Any medications that are considered necessary for the participant's well-being may be given at the discretion of the Investigator. However, as this may impact continued participation in the study, the Medical Monitor must be informed that prohibited medication was used, and a protocol deviation should be documented.
- Lack of efficacy and/or progression of MS as defined by Investigator judgment 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 (i.e., performed centrally or locally), the Investigator should follow instructions as outlined below, including **permanently discontinuing study intervention** when indicated.

For any study intervention 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 an acceptable value. 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 × to < 5× ULN, temporarily interrupt the study intervention and recheck the value within 72 hours to confirm the reported elevation.
- If AST and/or ALT > 3 × ULN to < 5 × ULN are confirmed within 72 hours and have increased by more than 50% (compared to latest confirmed value), continue interruption of the study intervention with an additional recheck in 72 hours later.
    - If rechecked value in the second recheck has decreased to < ULN or < participant's baseline, rechallenge can be considered in the absence of hyperbilirubinemia
    - In all other cases, permanently discontinue the study intervention and inform the Medical Monitor.
- If AST and/or ALT > 3 × ULN to < 5 × ULN are confirmed within 72 hours and have increased by **less than** 50% (compared to latest confirmed value), continue interruption of the study intervention with an addition recheck in 1 week.
    - If rechecked value in the second recheck has decreased to < ULN or < participant's baseline, rechallenge can be considered in the absence of hyperbilirubinemia
    - In all other cases, permanently discontinue the study intervention and inform the Medical Monitor.
- For an increase in bilirubin of > 1.5 × to ≤ 2 × ULN, temporarily interrupt the study intervention and recheck the value within 72 hours to confirm the reported elevation.
    - If the value is still > 1.5 × to ≤ 2 × ULN upon recheck, continue temporary interruption of the study intervention with an additional recheck in 1 week.
    - If the value is still > 1.5 × to ≤ 2 × ULN upon 2nd recheck, the study intervention should be permanently discontinued and the Medical Monitor informed.
    - If the value has decreased to ≤ 1.5 × ULN, the Investigator may reinitiate study intervention (see Section 7.1).

Any re-challenge associated with LFT elevations should follow the weekly monitoring for 12 weeks.

For participants who temporarily or permanently discontinue study intervention because of abnormal liver function or detection of HBV DNA (see Exclusion Criterion 34), consultations with specialists, such as a hepatologist and liver imaging such as ultrasound are encouraged to exclude potential alternative causes of liver injury. In addition, a comprehensive hepatic/autoimmune panel is required, including the following (performed by central laboratory, unless otherwise stated):

- International normalized ratio (INR), partial thromboplastin time, fibrinogen, high sensitivity C reactive protein
- Anti-Hepatitis A Virus (anti-HAV) IgM, HBsAg, anti-Hepatitis B Core Antigen (antiHBc) IgM, anti-HBsAg, anti-HCV (6 weeks or later post initial LFTs elevation), anti-Hepatitis E Virus (anti-HEV) IgG and IgM, antiviral capsid antigen (anti-VCA) IgG and IgM, anti- early antigen (anti-EA) IgG, antiEpstein-Barr Nuclear Antigen (anti-EBNA) IgG, anti- cytomegalovirus (CMV) IgG and IgM, Epstein-Barr virus (EBV) PCR, and CMV PCR
- HCV RNA by PCR
- Antinuclear antibody, antismooth muscle antibody, antibody to liver-kidney microsomes
- Albumin
- Alkaline phosphatase
- Ferritin and transferrin saturation
- 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 High Iron Fe (human hemochromatosis protein) (HFE) gene (C282Y, H63D) in the setting of abnormal ferritin/transferrin saturation values as defined in Exclusion Criterion 10.

Other Laboratory Criteria:

- For a decrease in neutrophil count to 500 to 999 / mm^3 without fever, temporarily discontinue study intervention and recheck the value within 1 week.
    - **If the value is still < 1,000 / mm^3 upon retest, permanently discontinue study intervention.**
    - For an improvement to 1,000 to 1,499 / mm^3 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**.
        - If no further downward trend is observed, the Investigator may reinitiate study intervention.
    - If the neutrophil count returns to ≥ 1,500 / mm^3 upon retest, the Investigator may reinitiate study intervention.
- For a decrease in neutrophil count to 1,000 to 1,499 / mm^3, temporarily discontinue study intervention and recheck the value within 1 week.
    - If a downward trend is observed upon retest, **permanently discontinue study intervention**.
    - If no downward trend is observed, the Investigator may reinitiate study intervention.
- For a decrease in platelet count to 25,000 to 49,999 / mm^3 without bleeding, temporarily discontinue study intervention and recheck the value within 1 week.

- **If the value is still < 50,000 / mm^3 upon retest, permanently discontinue study intervention.**
- For an improvement to 50,000 to 74,999 / mm^3 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**.
  - If no further downward trend is observed, the Investigator may reinitiate study intervention.
- If the platelet count returns to ≥ 75,000 / mm^3 upon retest, the Investigator may reinitiate study intervention.

- For a decrease in platelet count to 50,000 to 74,999 / mm^3, temporarily discontinue study intervention and recheck the value within 1 week.
  - If a downward trend is observed upon retest, **permanently discontinue study intervention**.
  - If no downward trend is observed upon retest, the Investigator may reinitiate study intervention.
- For an increase in amylase to > 2 to 5 × ULN, temporarily discontinue study intervention and recheck the value within 72 hours of receipt in fasting state (and no later than 1 week).
  - If the value is still > 2 × ULN or higher upon retest, **permanently discontinue study intervention.**
  - If the amylase returns to ≤ 2 × ULN upon retest, the Investigator may reinitiate study intervention.
- For an increase in lipase to > 2 to 5 × ULN, temporarily discontinue study intervention and recheck the value within 72 hours of receipt in fasting state (and no later than 1 week).
  - If the value is still > 2 × ULN or higher upon retest, **permanently discontinue study intervention.**
  - If the lipase returns to ≤ 2 × ULN upon retest, the Investigator may reinitiate study intervention.
- For any increase in serum creatinine > 1.5 × ULN but ≤ 3 × ULN, 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**
  - If a downward trend is observed, the Investigator may reinitiate study intervention.
- For an absolute lymphocyte count < 200 / mm^3, study intervention should be temporarily discontinued, and follow-up testing should be conducted as clinically indicated

  - If the absolute lymphocyte count returns to $\geq 500 / mm^3$, the Investigator may reinitiate study intervention.
  - If there is persistent lymphopenia $< 200 / mm^3$, **permanently discontinue study intervention**.
- 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 reinitiate 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 (performed by central laboratory). If positive, permanently withdraw the study intervention (see Appendix 7).

  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.

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.
  - 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.

- 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.
- 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; see Section 7.1) will not be replaced. 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, if reviewed and approved by the Sponsor.

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.
- Participants will be asked to record the following information daily in a paper participant diary:
    - dosing date and time
    - food intake around time of dosing (only on the day prior to PK sampling and the day of PK sampling, and around the time of the last dose prior to evobrutinib concentration assessment sampling).

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

- Urine testing for β-human chorionic gonadotropin will be conducted at the local laboratories.
- Urine dipstick results will be interpreted locally. Urine microscopic examination will be conducted centrally. Please see the SoA (see Section 1.3) and Appendix 5 for information regarding abnormal dipstick results.
- PK and biomarker samples will be analyzed by the analytical laboratories specified by the Sponsor.
- HIV testing should be conducted centrally. Where required by local regulations, can be conducted, and analyzed locally.
- T-SPOT test will be conducted at the local laboratories after an indeterminate or positive QuantiFERON test.
- A standard 12-lead ECG will be performed (see Section 8.2.3).

Screening

See the SoA (see Section 1.3) 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 after approval by the Medical Monitor (but cannot exceed 12 weeks) when a laboratory test must be repeated or reflex testing must be performed, an unanticipated event occurs, or 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.

Accelerated Elimination Procedure (At Screening Visit for OLE only)

All participants previously treated with teriflunomide, or unknown exposure status during the DBTP and DBE period, entering the OLE must undergo an AEP for teriflunomide. The AEP is to be initiated at the Screening visit upon signing of ICF and initial screening and completed during 11 consecutive days preferably within a 30-day period before Day 1 of the OLE (refer to Appendix 8). If justified for clinical or logistical reasons, an extension of the 30-day period for the AEP procedure is possible upon approval by the Medical Monitor. The Investigator should dispense cholestyramine or activated charcoal and to instruct participant about proper intake. The blood concentration of teriflunomide has to be verified upon completion of the AEP via blood sample collection between Day 12 to Day 30 at the central laboratory. The Investigator will remain blinded to the teriflunomide levels. Please refer to the study-specific central laboratory manual for detailed information on the sampling procedures. The Investigator is responsible to ensure proper and timely completion of the AEP and will document completion at the Day 1 visit prior to the IWRS call and dispensation of the IMP.

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 after approval by the Medical Monitor but should not exceed 12 weeks.

In the event that an initial ferritin and/or transferrin saturation is abnormal and needs to be repeated, consider having participants abstain from iron supplements and vitamin C for 1 week prior to retest, and perform the retest as a fasting collection.

For screen failures, see Section 5.6.

Rescreening

Participants who are considered screen failures after a first Screening Period may undergo rescreening once, after approval by the Medical Monitor. For those participants, the Screening Period for rescreening may be extended after approval by the Medical Monitor (but cannot

exceed 12 weeks) for the reasons described above. If a participant is rescreened, all Screening tests will need to be repeated except as follows:

a. Documented 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 study, 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 Treating Investigator and if appropriate, the Examining Investigator (assessor), 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 (EDSS) should be performed during the same visit. 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. Once the assessments by the Treating Investigator and the Examining Investigator (assessor) are completed, the reported relapse will be adjudicated by the EAC. During the OLE, the full assessments of relapse should be completed by Treating Investigator also at the same visit (neurological exams and EDSS).

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 and biochemistry).
- Urine collection for urinalysis, and, if necessary, microscopy.
- Additional assessments can be performed at the discretion of the Investigator.

Telephone Contact

If a clinic visit is not scheduled, Telephone Contacts will be scheduled with participants as indicated in the SoA (Section 1.3). During the Telephone Contacts, the following should be discussed with the participant:

- Structured Interview (see Appendix 10)

- Pregnancy, if applicable, including confirm completion of home pregnancy testing and discuss results

Telephone contacts between D1 and W44 are not expected to occur every 4 weeks, since participants are scheduled to be on site at least every 4 weeks. However, if a participant is utilizing the home visit option, telephone contacts should occur as indicated in the SoA.

Telephone contacts between Week 44 and Week 156 should occur every 4 weeks if a clinic visit is not scheduled.

Participants experiencing new or worsening neurological symptoms, including possible relapse, should be evaluated by the Investigator, if necessary, at an Unscheduled Visit.

Double-Blind Extension Period

After completing the DBTP (flexible duration up to 156 weeks) or at the time of PA trigger, all participants will be considered treatment completers and offered the opportunity to continue treatment assigned at randomization in the DBE. Signed consent will also be obtained prior to participation in the DBE period.

Scheduled assessments will be performed according to the SoA (see Section 1.3.2) before administration of study intervention. All scheduled visits during the DBE period may take place within the visit windows specified in the SoA. Participants who discontinue early must return for the EODBE visit (Week 96/ED/EODBE). For further details see Sections 1.3.2 and 4.

Open Label Extension Period

After completing the DBE period (up to 96 weeks) and if the long-term follow-up study is not yet open for enrollment, participants will be considered treatment completers and offered the opportunity to continue the treatment with evobrutinib in an OLE period under the current protocol. Signed consent will also be obtained prior to participation in the OLE period.

Scheduled assessments will be performed according to the SoA (see Section 1.3.3) 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 96/ED/EOT). For further details see Sections 1.3.3 and 4.

8.1 Efficacy Assessments and Procedures

8.1.1 Neurological Assessment

The Examining Investigator should ideally be a neurologist. However, if a neurologist is not available to perform the scope of the Examining Investigator's tasks, other raters can be considered for the study as delegates; the delegate assigned for EDSS must be approved on a case-by-case basis by the Sponsor.

The Examining Investigator (assessor) or Qualified Examining Designee will perform the neurological examination, document the FSS, and assess EDSS scores. The Examining Investigator (assessor) or Qualified Examining Designee will be also responsible for performing and documenting results from: T25-FW, 9-HPT, and the SDMT. He or she will have access only to data from assessments listed above. The Examining Investigator (assessor) or Qualified Examining Designee 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 Investigator (assessor) or Qualified Examining Designee throughout the course of the study for any individual participant. The Examining Investigator (assessor) or Qualified Examining Designee will be trained and instructed not to discuss what adverse effects (if any) the participant is experiencing from their medication. The Examining Investigator (assessor) or Qualified Examining Designee 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, achieving Level C qualification, within 24 months of participation. All Examining Investigators (assessors) and Qualified Examining Designees will maintain ongoing training on performance of the Neurostatus EDSS examination and must maintain Level C qualification throughout the course of the study.

Prior to being examined by the Examining Investigator (assessor), Treating Investigator 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.

During the OLE period, the Investigator or Qualified Examining designee will perform neurological examination and assess EDSS scores. The Investigator or Qualified Examining designee will be also responsible for performing and documenting results from: T25-FW, 9-HPT and the SDMT. The assessor should ideally be a neurologist. However, if a neurologist is not available to perform the task, other site personnel can be considered for the study as Qualified Examining designee.

The Investigator or Qualified Examining Designee must have successfully passed an examination on performance of the Neurostatus EDSS examination, achieving Level C qualification, within 24 months of participation. All assessors and Qualified Examining Designees will maintain ongoing training on performance of the Neurostatus EDSS examination and must maintain Level C qualification throughout the course of the study.

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 ≥ 30 days). The relapse should be accompanied by an increase of ≥ 0.5 EDSS, or 2 points increase on 1 of the FSS, or 1-point increase on ≥ 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, cerebellar, brainstem, sensory, or visual, excluding cerebral, bladder or bowel).

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

Adjudication of qualified relapses during the DBTP and DBE period (regardless of whether they are identified during a scheduled or unscheduled visit) will be performed by the EAC based on prespecified criteria, applied to data collected by the Treating and Examining Investigator, in a blinded fashion. During the OLE period, relapses will be evaluated, reported, and qualified by the Investigator only and no further adjudication via EAC will be performed. Any assessments needed to confirm the relapse should be performed, and details of the relapse should be documented within the relevant section(s) of the eCRF. The criteria for a qualified relapse should be clear and there should be documentation of how each potential relapse did or did not meet the criteria. Participants who have a documented relapse during treatment are not required to discontinue study intervention unless they meet any of the criteria for discontinuation from the study intervention (see Section 7). Relapse assessments may be conducted as phone assessments between study site visits. If neurological signs and symptoms are identified that are consistent with relapse, the participant should be evaluated on site.

The annualized relapse rates up to 156 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 ≥ 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 ≥ 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.

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

8.1.1.3 Confirmed Disability Improvement

Disability improvement will be analyzed only for the subgroup of participants with a Baseline EDSS score ≥ 2.0 to ensure relevant baseline disability that is potentially amenable to improvement. Disability improvement is defined as a reduction of 1 point from Baseline EDSS score when the Baseline score is ≥ 2 and≤ 6 and a reduction of 0.5 point from Baseline EDSS score when the Baseline score is ≥ 6.5 and ≤ 9.5. Disability improvement is considered sustained when the initial reduction in the EDSS score is confirmed at a regularly scheduled visit at least 24 weeks after the initial reduction.

CDI, sustained for 24 weeks after the initial documentation of neurological improvement, will be analyzed as a secondary endpoint.

8.1.1.4 Timed Twenty-Five Foot Walk

The T25-FW is a quantitative mobility and leg function performance test based on a timed 25-foot walk. The participant is directed to one end of a clearly marked 25-foot course and is instructed to walk 25 feet as quickly as possible, but safely. The time is calculated from the initiation of the instruction to start and ends when the participant has reached the 25-foot mark. The task is immediately administered again by having the participant walk back the same distance. Participants may use assistive devices when doing this task. T25-FW will be administered by the Examining Investigator (assessor) or Qualified Examining Designee in DBTP/DBE period and by qualified non-blinded site personnel during the OLE period.

A worsening of ≥ 20% is considered to have occurred in this task, when the time it takes to complete the task is longer by equal to or more than 20% than the time it took at Baseline. The worsening is considered confirmed at 12 weeks if the following assessment (at a scheduled visit of 12 weeks or more after the initial observed worsening) confirms it.

8.1.1.5 Nine Hole Peg Test

The 9-HPT is a brief, standardized, quantitative test of upper extremity function. Both the dominant and nondominant hands are tested twice. The participant is seated at a table with a small, shallow container holding nine pegs and a wood or plastic block containing nine empty holes. On a start command when a stopwatch is started, the participant picks up the nine pegs one at a time as quickly as possible, puts them in the nine holes, and, once they are in the holes, removes them again as quickly as possible one at a time, replacing them into the shallow container. The total time to complete the task is recorded. Two consecutive studies with the dominant hand are immediately followed by two consecutive studies with the nondominant hand. 9-HPT will be administered by the Examining Investigator (assessor) or Qualified Examining Designee in DBTP/DBE period and by qualified non-blinded site personnel during the OLE period.

A worsening of > 20% (either hand) is considered to have occurred in this task, when the time it takes to complete the task is longer by equal to or more than 20% than the time it took at Baseline. The worsening is considered confirmed at 12 weeks if the following assessment (at a scheduled visit of 12 weeks or more after the initial observed worsening) confirms it.

8.1.1.6 Symbol Digit Modalities Test

The SDMT has demonstrated sensitivity in detecting not only the presence of cognitive impairment, but also changes in cognitive functioning over time and in response to treatment. The SDMT is brief, easy to administer, and involves a simple substitution task that normal children and adults can easily perform. Using a reference key, the examinee has 90 seconds to pair specific numbers with given geometric figures. Responses will be written and administration time is just 5 minutes. SDMT will be administered by the Examining Investigator (assessor) or Qualified Examining Designee in DBTP/DBE period and by qualified non-blinded site personnel during the OLE period.

Two different SDMT forms will be used, administered at alternating visits, to overcome learning effects.

8.1.2 Brain Magnetic Resonance Imaging Scans

If a participant discontinues the study more than 4 weeks after his or her most recent MRI, during the double-blind, double-dummy phase of the Treatment Period, an MRI may be obtained at the Discontinuation Visit. The Screening MRI scan should be acquired before randomization and dosing to allow baseline evaluation by the central MRI reader (before randomization).

Magnetic resonance imaging is a useful tool for monitoring CNS lesions in MS. Various MRI derived parameters have been related to disease activity, including T1 weighted gadolinium-enhancing (T1 Gd+) lesions and new or enlarging hyperintense T2 (active T2) lesions. Other MRI readouts such as chronic T1 hypo-intense lesions are reflective of long-term brain damage (black holes). Combined unique active lesions are defined as the sum of new T1 Gd+ lesions and active T2 lesions (without double counting). It is hypothesized that changes in brain volume may reflect brain atrophy as a result of MS-related tissue loss and may thereby correlate with long-term clinical outcome in these participants (De Stefano 2002).

Brain MRI scans will be performed according to a standardized imaging protocol before and after the administration of single-dose gadolinium. Further details, including the scans required and the optimal MRI workflow, will be provided in a separate Imaging Manual that will be provided to each study site.

Images will be assessed by an independent, blinded, centralized MRI reading service, provided by NeuroRx Research. The assessment will be performed in the absence of clinical information. At the site level, the local radiologist assigned to this study will have access to the MRI scans and produces the local reports to inform the Treating Investigator of any noted safety issues. The Treating Investigator has access to the Screening (baseline) MRI scan in order to evaluate eligibility (see Section 5.1, inclusion criterion 3b) and, during the DBTP and DBE period of the study, to local MRI reports only in case of safety-related issues (e.g., non-MS pathologies) to preserve the blinding of the data. When assessment of the local MRI report is required for safety concerns, a blinded report will be provided to the Treating Investigator by the local radiologist containing only non-MS pathology information. In addition, the Treating Investigator may inquire about an overall increase in new lesions observed, but this information must not be shared proactively or in detail by the local radiologist (such as number, type, or location of MS lesions). This inquiry should only occur annually and not more frequently. Overall, the Treating Investigator should never have access to the detailed MRI report to preserve the integrity of the study data.

Independent safety-reads of all MRI scans can be obtained from the local radiology centers.

In addition, if a scheduled MRI scan is delayed or an unscheduled MRI scan is indicated, 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 per schedule). For example, if the next

scheduled visit is the Week 96, the Week 96 MRI scan should be performed as soon as the 4-week period since previous exposure to gadolinium has elapsed.

Gadolinium will be used to enhance T1-weighted lesions and to optimize clarity and accuracy of reporting. As gadolinium is excreted renally, participants with acute renal insufficiency (eGFR < 60 mL/min/1.73 m^2) will be excluded from the study (see Section 5.2).

In the OLE period, only those participants who have completed Week 96 and DBTP as well as DBE End-of-Treatment MRI assessments will be offered participation in a respective OLE MRI substudy. The End-of-DBE MRI will also serve as baseline MRI of the OLE and will require to preserve the blinding outlined for the DBTP and DBE period as described in the paragraphs above. During the OLE period, the Treating Investigator will have access to the full MRI reports including MS pathology (starting with the first MRI assessment in the OLE period at Week 48). Irrespective of the MRI substudy, all participants in the OLE period will have access to MRI evaluations for safety reasons if indicated by the Investigator.

8.1.3 Patient Reported Outcomes

PRO data will be collected at the study visit with an electronic tablet device at specified study visits (see the SoA for details, Section 1.3). The tablet with the PRO instruments will be distributed by the Investigator staff and completed in their entirety by the participant. In the event of a tablet device not being available, an alternative method of data collection may be used.

PROs should be completed 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 meets requirements of the Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims (Food and Drug Administration [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 Section 8.1.3. Please note that the methods for collecting and analyzing PRO data are different from those for the ascertainment of observed or volunteered AEs. Due to these differences, PRO data will not be reported as AEs 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 study, 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 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 PF (Cella 2007).

The PROMIS 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 PF 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 was developed with input from MS patients (n = 57) and validated in 2 observational studies. Measures from the PF item bank are scored on a T-score metric (higher scores = higher PF). An MID estimate of 2.7 is proposed for worsening PF for the PROMISnq PF(MS)15a (Kamudoni 2022).

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 was further validated. Measures from the fatigue item bank are scored on a T-score metric (higher scores = higher fatigue).An MID estimate of 4 is proposed for minimal improvement and minimal worsening in the PROMIS Fatigue (MS) 8a scores (Kamudoni 2021).

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 DDT in MS (MS Working Group, 2018; DDT COA, 2018).

Physical function deterioration is defined as a reduction in PROMIS PF T-score ≥ 2.7 compared to Baseline PROMIS PF T-score sustained for at least 12 weeks.

8.1.3.2 Medical Outcomes Study 36-Item Short Form Survey Instrument

The Medical Outcomes SF-36v2 is a 36-item questionnaire that measures 8 areas of participant reported health rated from 0 to 100 (McHorney 1992, Ware 1992, McHorney 1993, McHorney 1994, and Freeman 2000). The areas are:

- Physical function
- Role limitations due to health problems
- Bodily pain
- Social functioning
- General mental health
- Role limitations due to emotional problems
- Energy/fatigue
- General health perceptions

The instrument will be used to calculate a normalized score for each of the 8 health domain scales, a PCS score, and a MSC score, with higher scores indicating better health.

8.1.3.3 EuroQoL 5 Dimension 5 Levels

The EQ-5D is a standardized instrument developed as a measure of health-related quality of life that can be used in a wide range of health conditions and treatments. The EQ-5D-5L was introduced in 2009 to improve the instrument's sensitivity and to reduce ceiling effects, as compared to the EQ-5D-3L. The EQ-5D-5L essentially consists of 2 pages: the EQ-5D descriptive system and the EQ VAS.

The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The levels of the five dimensions can be combined into a 5-digit number that describes the patient's health state.

EQ-5D-5L health states, defined by the EQ-5D-5L descriptive system, may be converted into a single health utility index value using country specific value sets. Health utility values facilitate the calculation of quality-adjusted life years that are used to inform pharmacoeconomic evaluations of health care interventions.

The EQ VAS records the respondent's self-rated health on a 20 cm vertical, visual analogue scale with endpoints labeled 'the best health you can imagine' and 'the worst health you can imagine'. This information can be used as a quantitative measure of health as judged by the individual respondents.

Higher scores on both EQ-5D-5L health utility values and EQ VAS represent a better HRQoL.

8.1.3.4 WPAI: MS v2.0 (for OLE Period Only)

Change in disability, fatigue, cognition, and health related quality of life are known to impact physical absence from work (i.e., absenteeism) and reduced productivity while working (i.e., presenteeism) and by that cause substantial costs. Work productivity and absenteeism is assessed to characterize the associations with disability, fatigue, cognition, and health-related quality of life.

The Work Productivity and Activity Impairment Questionnaire: Multiple Sclerosis, Version 2.0 (WPAI: MS v2.0) is a validated and reliable 6-item questionnaire developed to measure the effect of multiple sclerosis on the ability to work and perform regular activities during the last 7 days. The instrument yields 4 types of scores:

- Absenteeism (work time missed)
- Presenteeism (impairment at work / reduced on-the-job effectiveness)
- Work productivity loss (overall work impairment / absenteeism plus presenteeism)
- Activity Impairment

WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity, i.e. worse outcomes.

WPAI:MS v2.0 will be assessed in a subset of participants based on questionnaire availability for individual countries and languages.

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, AEs, physical examination findings, vital signs, ECGs, 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.
- 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 be measured and recorded. Weight will be measured and recorded at each visit where vital signs are recorded as noted in the SoA.
- Temperature (should be measured at the same location throughout the study), 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 will 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

- Single 12-lead ECG will be obtained as outlined in the SoA using an ECG machine that automatically calculates the HR and measures PR, QRS, and QT intervals and RR duration.
- The 12-lead ECG recordings will be obtained after 10 minutes of rest in a semi-supine position.
- ECG results will be reviewed 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 judgment (including but not limited to repeat ECGs, echocardiography, evaluation by a cardiologist). The printout of the ECG is to be signed, dated, and filed in the Investigator's Site File along with a signed and dated copy (if the printouts are not on archive-quality paper). ECG tracings will be sent to the central reader electronically for processing. Final interpretation of ECGs may be made by the central ECG vendor. In addition, ECGs will also be stored digitally by the Sponsor.
- In the OLE period, no ECG evaluation by central reader is required; however, ECGs will also be transmitted and stored digitally at the central location.

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 will 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. Immunoglobulin levels should not be done locally unless clinically indicated, as these results may lead to unblinding (see Section 8.2.6).
- The Sponsor will receive a list of the local laboratory normal ranges before shipment of study intervention(s). Any changes to the ranges during the study will be forwarded to the Sponsor or designated organization.
- The Investigator will 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 will 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.
- Reflex analysis testing for HBV DNA by PCR will be conducted for participants who are anti-hepatitis B surface antibody positive and/or anti-hepatitis B core antibody positive at Screening (see Exclusion Criterion 34). Whole blood samples of approximately 4 mL will be collected at the times specified in SoA.

8.2.5 Pregnancy

Pregnancy testing (urine or serum as required by local regulations) should be conducted as summarized in the SoA (see 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 (see 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 relative to the PA to avoid unblinding. However, the IDMC will have access to these data as applicable.

8.2.7 Columbia-Suicide Severity Rating Scale

The 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 Investigator (or designee) at the timepoints indicated in the SoA (see 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.

Participants 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. The decision to discontinue the participant from the study should be taken by the Investigator in conjunction with the mental health provider. Any mental health issues considered to be life threatening should be recorded as appropriate.

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.

8.2.8 Independent Data Monitoring Committee, Hepatology Assessment 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. 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.

Hepatology Assessment Committee

A HAC will be formed to evaluate cases of possible DILI and to render ongoing opinion on overall DILI risk for evobrutinib. The DILI cases are to be suspected if at least one of the following criteria are met:

a.) ALT or/and AST elevations > 8 × ULN;

b.) ALT or/and AST elevations between > 5 × ULN and ≤ 8 × ULN;

c.) Total bilirubin > 2 × ULN;

d.) Total bilirubin > 2 × ULN with ALT or AST > 3 × ULN;

e.) Acute or chronic hepatic failure, fibrosis, cirrhosis, and other liver damage-related conditions;

f.) Any other case that might point to suspected DILI, based on Investigator assessment.

HAC members will review case summaries including but not limited to clinician assessment, IMP exposure, laboratory assessments, hepatologist reports, medical history, and prior and concomitant medication to evaluate cases of suspected DILI. HAC will make recommendation to escalate cases to inform the IDMC and will advise IDMC on whether benefit/risk profile of evobrutinib requires changes based on their review. The HAC is composed of external hepatologists with the requisite scientific and medical experience in review of suspected DILI cases. HAC members are independent from the Clinical Study Team and the development program team and are blinded to treatment assignments. Details regarding HAC roles, responsibilities, activities, and possible recommendations will be provided in a separate HAC charter.

Endpoint Adjudication Committee

An EAC will be formed for centralized, blinded review and determination of qualified relapses during the DBTP and DBE (see Section 8.1.1.1). The EAC will be comprised of subject matter experts convened for the purpose of ensuring consistency across study sites and to allow for an unbiased endpoint assessment. Sponsor representatives and study Investigators are not eligible for membership on the EAC. The EAC will be managed by a central vendor; the vendor will be under contract to the Sponsor. Specific membership, roles, and responsibilities, required source documentation, data format, details about review process, and procedures and timing of meetings will be addressed in a separate EAC charter.

No EAC will be maintained after the DBTP and DBE have ended as relapses will be qualified by Treating Investigators in the OLE period.

Study Steering Committee

An 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 study may serve on this committee.

8.3 Adverse Events and Serious Adverse Events

The definitions of an AE and a SAE are in Appendix 4.

The Investigator and any qualified designees (e.g., Sub-Investigators) are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. The Investigator remains responsible for following up AEs that are serious or that caused the participant to discontinue study intervention, as specified in Section 8.3.3.

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

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.

Individual Case Safety Reports will be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators within 15 days.

An Investigator or sub-investigator who receives an Individual Case Safety Report describing a SUSAR or other specific safety information (e.g., Emerging Safety Issue Report, summary or listing of SAEs/SUSARs) from the Sponsor will review the safety reports and confirm completion of this review. This information will be filed it in the Investigator's Site File, and the IRB/IEC will be notified, if appropriate, according to applicable local laws/regulations and site Standard Operating Procedures.

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

Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and until the Safety Follow-up Visit.

If a pregnancy is reported, the Investigator will inform the Sponsor within 24 hours of learning of the pregnancy and will follow the procedures specified below for collection of pregnancy information.

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

Collection of Pregnancy Information

Male participants with partners who become pregnant:

- The Investigator will attempt to collect pregnancy information on any male participant's female partner, who becomes pregnant while the participant is in this study. This applies only to participants who receive study intervention.
- After obtaining signed consent from the pregnant female partner directly, the Investigator will record the pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Participants who become pregnant:

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while she is in the study. The initial information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of the pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

- A spontaneous abortion (occurring at < 22 weeks gestational age) or stillbirth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as specified in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention. Participants who intend to become pregnant during the study will also discontinue study intervention. As a pregnant participant may have received teriflunomide and due to the prolonged half-life of teriflunomide, an AEP should be performed and a teriflunomide level < 0.02 mg/L has to be reached (for more details see Appendix 8).

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 - 6 hours will be considered an overdose.

The Sponsor does not recommend specific treatment for an overdose if not associated with any clinical signs/symptoms, but assistive/supportive measures, as necessary, should be provided. However, if there are clinical signs/symptoms then AEP should be performed as described in Appendix 8.

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.

8.5 Pharmacokinetics

- The following PK parameters will be calculated, when appropriate:

Symbol	Definition
AUC	Area under the plasma concentration-time curve
$CL_{/f}$	The apparent total body clearance of study intervention following extravascular administration
C_{max}	Maximum evobrutinib concentration
$Vz_{/f}$	The apparent volume of distribution during the terminal phase following extravascular administration

DBTP

- Whole blood samples of approximately 2 mL will be collected for measurement of plasma concentrations of evobrutinib, as specified in the SoA. The actual date and time (24-hour

clock time) of each sample will be recorded to calculate actual time elapsed since the prior dose administration. The sampling timing may be altered during the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

- The exact date/time of sample collection and drug administration must be recorded in the eCRF and will be used in the calculation of PK parameters. Time deviations from planned PK sampling times will not be considered a protocol deviation provided the exact date/time of sample collection and drug administration are recorded in the eCRF.
- The quantification of evobrutinib in plasma will be performed using a validated assay method. Concentrations will be used to evaluate the PK of evobrutinib.
- Remaining samples collected for analyses of evobrutinib concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Details on processes for collection and shipment of these samples are in the Laboratory Manual. Retention time and possible analyses of samples after the end of study are specified in the respective ICF.
- Evobrutinib concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded. As samples from participants randomized to teriflunomide will not be analyzed for plasma concentrations of evobrutinib, measurements of evobrutinib concentration will be performed by unblinded analysts as detailed in Section 6.3.2.
- All samples collected for PK, as noted in the SoA, still within the known stability of the evobrutinib at the time of receipt by the bioanalytical laboratory will be analyzed.

DBE and OLE periods

- No blood samples for PK analysis will be collected from participants enrolled in the DBE and OLE periods.

See Section 9.4.3.1 for further details of the PK analysis.

8.6 Pharmacodynamics

Not applicable.

8.7 Pharmacogenetics

- Where local regulations and IRB/IEC allow, approximately 4 mL blood (total) sample will be collected for DNA analysis from consenting participants. Participation in pharmacogenetic research is optional. Participants who do not wish to participate in the pharmacogenetic research may still participate in the study.
- If not collected on Day 1 or a redraw is needed, the pharmacogenetic sample may be obtained at any other point of time during the study.

- In the event of DNA extraction failure, a replacement sample for pharmacogenetic testing may be requested from the participant. Additional informed consent will not be required to obtain a replacement sample.
- Appendix 6 provides further information on pharmacogenetic research.

8.8 Biomarkers

- Collection of participant samples for biomarker research is also part of this study and is governed by the appropriate ICF.
- **DBTP and DBE**: The following participant samples for biomarker research are required and will be collected from all participants enrolled in the DBTP and DBE. Collection times are specified in the SoA:
  - Blood samples may be tested for biomarkers of disease to evaluate disease activity or treatment response.
  - Blood samples will be tested for biomarkers of disease to evaluate the exposure-response relationship between PD biomarkers.
  - Blood samples may be tested for novel liver function biomarkers (e.g., protein, miRNA, etc.) to evaluate their activity with respect to predictivity and sensitivity of the novel biomarkers of hepatic function compared to traditional clinical chemistry endpoints.
  - Blood samples may be tested for gene expression/gene products to evaluate disease activity or treatment response.
  - Blood samples may be tested for impact on vaccinal responses.
  - In addition, participant samples (i.e., blood and PGx) collected may be analyzed for biomarkers thought to play a role in pharmacokinetics, safety endpoints, MS disease progression, drug response, and treatment efficacy including, specific candidate genes/genome-wide analysis for genetic variations. Also, samples may be re-purposed or used for future research studies.
- **OLE**:
  - Blood Biomarker Substudy:
    - Blood samples for biomarker analyses will be collected in the Blood Biomarker Substudy (see Section 8.8.2).
- Participants' blood samples collected during the DBTP, DBE and OLE, may be repurposed to evaluate safety endpoints, MS disease progression, drug response, treatment efficacy, response to prophylactic vaccines, and/or future research, as specified in the ICF.
- Up to approximately 840 mL total blood will be collected during the DBTP. For participants in the DBE period, up to approximately 420 mL of blood will be collected. For participants in the OLE period, up to approximately 220 mL of blood will be collected, with an additional approximately 80 mL collected from participants in the OLE biomarker substudy. Further details are provided in the ICF and Laboratory Manual.

- Details on processes for collection and shipment of DBTP, DBE, and OLE samples are in the Laboratory Manual. The Sponsor will store the samples in a secure storage space with adequate measures to protect confidentiality. Retention time and possible analyses of samples after the end of study are specified in the respective ICF.

8.8.1 Biomarkers of Disease, Disease Activity and Progression, Drug-related Outcomes, and Treatment Response

DBTP, DBE and OLE Blood Biomarker Substudy - Blood samples will be collected from all participants to assess the relationship between candidate disease biomarkers (e.g., cytokines, etc.) and disease activity and progression (e.g., NfL), drug-related outcomes (e.g., impact on vaccinal responses), and/or treatment response. Samples will be obtained predose as noted in the SoA. Biomarkers of disease may be measured at the analytical laboratory selected by the Sponsor using an appropriately validated bioanalytical method.

8.8.1.1 Neurofilament Light Chain

Recently, NfL, a critical component of neurons, has been established as a marker of neuronal damage and has become a potential biomarker for treatment monitoring in MS. As 1 of 5 neurofilament proteins, NfL contributes to the structural support of axons, and the maintenance of their size, shape, and integrity. Following axonal damage, NfL is released into the CSF and blood. In patients with MS, serum NfL concentrations correlate with relapses, disability worsening, MRI disease activity and brain volume loss (Kuhle 2016, Kuhle 2017, Disanto 2017, Piehl 2018, Novakova 2017, Barro 2018). Recently, the International Progressive MS Alliance received a Letter of Support from the US FDA encouraging additional studies evaluating NfL as a pharmacodynamic and/or response biomarker in early clinical trials involving patients with progressive MS. Consequently, serum NfL concentrations will be assessed in all participants enrolled in this study.

8.8.1.2 Novel Liver Function Biomarkers

DBTP and DBE

Blood samples will be collected from all study participants enrolled in the DBTP to evaluate the relationship of novel biomarkers (e.g., protein, miRNA, etc.) of hepatic function levels compared to standard clinical chemistry endpoints during the DBTP. Levels of novel biomarkers of hepatic function may be measured using various methods in samples collected from participants at time points noted in the SoA.

Sampling for novel liver function biomarkers is performed in parallel with LFT clinical chemistry monitoring. To enable analysis of a variety of biomarkers, samples are needed both prior as well as during the occurrence of elevated liver enzymes. Samples will be collected from all participants, stored, and a subset may be analyzed retrospectively, as appropriate. In addition, samples (both plasma and serum) may be repurposed to evaluate disease activity and progression (e.g., NfL), drug-related outcomes (e.g., impact on vaccinal responses), treatment responses, role of EBV in MS and/or future research studies.

8.8.2 OLE Blood Biomarker PD Substudy – Biomarkers of Disease Activity, Progression and Response to Drug

OLE - Blood samples will be collected from a subset of participants to evaluate the effect of extended evobrutinib treatment on biomarkers associated with disease progression (e.g., NfL), disease activity, drug-related outcomes (e.g., immune cell frequencies [TBNK assay] and Ig levels), candidate disease biomarkers (e.g., cytokines), and/or treatment responses. Samples will be obtained from participants (N = ~750; ~50% anticipated to be treated with evobrutinib and ~50% with teriflunomide throughout the DBE) at selected sites and participants will be selected in a blinded fashion. Due to the limited stability windows of the TBNK and Ig assays, the samples analyses will be performed before the study is unblinded. However, study team members will remain blinded to any results and not view the data until the study is unblinded. Assays involving biomarkers of disease will only be performed after the study is unblinded.

Participation in the OLE Blood Biomarker Substudy for biomarker research is optional. Participants who do not wish to participate in the biomarker research portion (i.e., blood sample collection) of the study may still participate in the MRI substudy.

The following samples for biomarker research will be collected from a subset of participants. Collection timepoints are specified in the SoA:

- Blood samples will be tested for biomarkers of disease to evaluate disease activity or treatment response. (e.g., NfL).
- Blood samples will be tested for immune cell frequencies (e.g., T cells, B cells and NK cells).
- Blood samples will be tested for Ig levels (IgM, IgA, IgG, and IgE).
- In addition, participants' samples may be repurposed to evaluate drug-related outcomes, treatment responses, role of EBV in MS, and/or for future research, as specified in the ICF.

Samples (predose) will be collected as noted on the SoA (see Section 1.3.3).

Samples will be analyzed by an analytical laboratory selected by the Sponsor using an appropriately validated bioanalytical method.

For details describing the MRI substudy, please refer to Section 8.1.2.

8.8.3 Gene Expression

DBTP and DBE

Blood samples for gene expression analysis will be collected, except from participants in countries where collection of samples is not allowed, predose at time points noted in the SoA from all participants enrolled in the DBTP. These samples should be obtained after the assessment of vital signs in all participants (where allowed by local regulations). The actual date and time of each sample will be recorded. Samples may be analyzed by an analytical laboratory selected by the Sponsor using an appropriately validated bioanalytical method. The

purpose of this analysis is to test whether potential differences in expression of specific genes may be linked to PK, safety endpoints, drug response, and treatment efficacy.

OLE

For participants enrolled in the OLE, blood samples for gene expression analysis will not be collected.

8.9 Health Resource Utilization

Health resource utilization data, associated with medical encounters, will be collected by the Treating Investigator and study-site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

The data collected may be used to conduct exploratory economic analyses and will include: number of unplanned doctor/home/emergency visits, number of hospitalizations, paid assistance, and number of missed work days.

8.10 Immunogenicity Assessments

Not applicable.

9 Statistical Considerations

9.1 Statistical Hypotheses

9.1.1 Statistical Hypotheses Related to Primary Objective

The primary endpoint, ARR based on up to 156 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 teriflunomide. The alternative hypothesis is H_1: rRR < 1. The rRR effect measure will be estimated from a 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 6 efficacy secondary endpoints and 2 HRQoL secondary endpoints:

- time to first occurrence of 12-week CDP based on up to 156 weeks of follow-up (pooled)
- time to first occurrence of 24-week CDP based on up to 156 weeks of follow-up (pooled)
- time to first occurrence of 24-week CDI based on up to 156 weeks of follow-up (pooled)
- CFB in PROMIS PF score over 96 weeks (pooled)
- CFB in PROMIS Fatigue score over 96 weeks (pooled)
- total number of T1 Gd+ lesions based on all available MRI scans

- number of new or enlarging T2 lesions on the last available MRI scan relative to the baseline MRI scan
- NfL concentration level at Week 12.

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) group, $S_c(t)$ denotes the survival function for time to 12-week CDP in the control (teriflunomide) group, 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, time to 24-week CDI (pooled), will be assessed for superiority via a 1-sided stratified log rank test of the null hypothesis H_0: $S_e(t) \geq S_c(t)$, evaluated for the participants with baseline EDSS ≥ 2.0, where $S_e(t)$ denotes the survival function for time to 24-week CDI in the experimental (evobrutinib) group, $S_c(t)$ denotes the survival function for time to 24-week CDI in the control (teriflunomide) group, 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, CFB in PROMIS PF score over 96 weeks (pooled), will be assessed for superiority via a 1-sided test of the null hypothesis H_0: $\Delta_{PF} \leq 0$, where Δ_{PF} denotes difference in average PROMIS PF score CFB least-squares means, comparing evobrutinib to teriflunomide, with average taken over Weeks 72, 84, and 96, 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 over 96 weeks (pooled) will be analyzed similarly, based on the null hypothesis H_0: $\Delta_{Fatigue} \geq 0$ (higher score corresponds to more fatigue), with the exception that the average will be taken over Weeks 48, 60, 72, 84, and 96.

The secondary endpoint, total number of T1 Gd+ lesions based on all available MRI scans, from participants enrolled in the present study, will be assessed for superiority via a 1-sided test of the null hypothesis H_0: lRR ≥ 1, where lRR denotes lesion rate ratio comparing evobrutinib to teriflunomide. The alternative hypothesis is H_1: lRR < 1. The lRR effect measure will be estimated from a NB model for total number of T1 Gd+ lesions that adjusts for covariates based on stratification factors, with offset based on number of available scans.

The secondary endpoint number of active T2 lesions on the last available MRI scan relative to the baseline scan, will be analyzed similarly, with a similar null hypothesis tested, with the exception that the offset will be based on the time (in years) between the last available scan and the baseline scan.

The secondary endpoint, NfL concentrations at 12 weeks, will be assessed for superiority via a 1-sided test of the null hypothesis H_0: $GM_e \leq GM_c$, where GM_e denotes the Geometric Mean estimate at 12 weeks in the experimental (evobrutinib) group, and GM_c denotes the Geometric

Mean estimate at 12 weeks in in the control (teriflunomide) group. The alternative hypothesis is H_1: $GM_e > GM_c$.

9.2 Sample Size Determination

9.2.1 Sample Size for Primary Endpoint: ARR

The sample size is estimated based on the primary endpoint, ARR up to 156 weeks, under the assumption that participants are followed for an average of 102 weeks. The ARR at 102 weeks among participants receiving evobrutinib is estimated to be 0.13 (NB dispersion parameter ≈ 2.5), as compared with 0.23 (NB dispersion parameter ≈ 2.5) among participants receiving the control treatment, teriflunomide. This represents a reduction in qualified relapse rate of 43% due to evobrutinib relative to teriflunomide. A 1-sided test of superiority based on the qualified relapse rate ratio from a NB model for qualified relapse count, H_0: rRR ≥ 1.0, H_1: rRR < 1.0, requires an evaluable sample size of 359 participants per group, followed for 102 weeks, to provide 90% power, assuming a 1-sided significance level of 0.025 for the evobrutinib versus teriflunomide comparison. To account for a drop-out rate of 20% over 2 years (i.e., normal drop-out expected in an MS trial in the absence of the escalating crisis in Eastern Europe), the enrollment per group is targeted to be 449 participants, resulting in a targeted enrollment of 898 participants.

The assumption for evobrutinib ARR is based on 48-week data from the Phase II study of evobrutinib in RMS, in which the highest dose, 75 mg twice daily administered under fasted conditions, resulted in an ARR of 0.11 (95% CI: 0.04, 0.25). Due to the wide CI, an estimate of 0.13 is assumed for evobrutinib in Phase III study powering. The assumption of 0.23 for teriflunomide ARR is based on recent Phase III studies (ASCLEPIOS I and II), wherein ARR ranged from 0.22 to 0.25 (Hauser 2020). The assumption of 2.5 for the dispersion parameter is derived from point and CI estimates for ARR from active treatment groups of recent Phase III studies and modeling of relapse data from the Phase II study of evobrutinib. If the distribution of relapse count is more disperse than assumed (i.e., dispersion ≈ 3.0 in both groups), the power provided by an enrolled sample size of 449 participants per group will be reduced from 90% to 87.4%.

The PA is to be triggered when the primary endpoint (ARR) in the first Phase III study (i.e., MS200527_0080), the primary endpoint in the present study (i.e., MS200527_0082), and the important secondary endpoint (12-week CDP pooled) are adequately powered. The power associated with the ARR endpoint depends on the information collected, defined as the reciprocal of the variance of the qualified relapse ratio estimate (evobrutinib versus teriflunomide), as in a group sequential design. The information for the qualified relapse rate ratio based on a negative binomial model (as per Appendix 5 of the ASCLEPIOS I/II protocol, available as Supplementary Material to Hauser 2020) is given by:

Equation 9.2.1: Information $I = [1/n \{1/(\lambda_1 T) + 1/(\lambda_2 T) + 2\gamma\}]^{-1}$

where n = evaluable sample size per group, T is the common follow-up time, λ_1 is ARR for evobrutinib, λ_2 is ARR for teriflunomide, and γ is the dispersion parameter ($\gamma > 0$). The assumptions for this study are n = 359, T = 1.97 years (i.e., average follow-up time of

102 weeks), $\lambda_1 = 0.13$, $\lambda_2 = 0.23$, and $\gamma = 2.5$. When the study has accrued Information I=32.3, the test of the qualified relapse rate ratio, comparing evobrutinib to teriflunomide at the 1-sided 0.025 alpha level, is powered at 90%.

9.2.2 Sample Size for Secondary Endpoint: 12-week CDP

A total of 149 events (defined as 12-week CDP) from the pooled studies is required to provide 71.5% power to detect hazard ratio = 0.66 at the 1-sided significance level of $0.025\text{-}0.025^2 = 0.024375$ (see Section 9.4.4.3). It is expected that these events will be achieved by following the 1796 participants for up to 156 weeks, assuming a logrank test, 2-year CDP rate in the teriflunomide group of 15% (i.e., teriflunomide hazard rate of 0.0813), and 2-year drop-out rate of 20%.

The treatment effect of HR = 0.66 is justified by the assumption that evobrutinib has an impact on time to 12-week CDP similar to that of anti-CD20 therapies, and thus the HR reported in Hauser 2020, comparing ofatumumab to teriflunomide, applies to the treatment effect of evobrutinib relative to teriflunomide. The 2-year CDP rate in the teriflunomide group is also based on results reported in Hauser 2020.

When the pooled studies have accrued 149 12-week CDP events, the test of the hazard ratio, comparing evobrutinib to teriflunomide at the 1-sided 0.024375 alpha level, is powered at 71.5%.

The trial-wise and family-wise type-1 error will be preserved at the 0.025 1-sided level in the presence of multiple testing due to multiple endpoints (primary and secondary), as described in Section 9.4.4.3.

Sample size and power calculations for the ARR and 12-week CDP endpoints were performed using the East v6.5 package and via simulation in R v6.3.

9.2.3 Sample Size Considerations due to the Currently Escalating Crisis in Eastern Europe

Initial enrollment was closed on 01 October 2021 with 1041 participants enrolled in Study MS200527_0080 and 1053 participants enrolled in Study MS200527_0082. These enrollment figures exceeded the original planned enrollment of 930 participants per study.

The currently escalating crisis in Eastern Europe poses a challenge to the successful conduct of the MS200527_0080 and MS200527_0082 studies due to the large representation of this region in the initial enrollment. In the worst-case scenario, all data from participants in the region affected by the crisis (Ukraine, Russian Federation, and Belarus) will be unable to be queried for cleaning purposes and will be considered unreliable. In that scenario, only 645 participants from MS200527_0080 and 487 participants from MS200527_0082 will be included in the PA, reducing ARR power from 90% to 77.1% and 65.1%, respectively.

The study design introduced in Protocol Version 4.0 (i.e., variable treatment duration) decreased the required participants per study from 930 to 898. To ensure preservation of 90%

power for the ARR per study, such that up to 898 participants per study have data sufficiently robust for the PA, enrollment will be re-opened. Up to 253 participants for MS200527_0080 and up to 411 participants for MS200527_0082 will be recruited due to the impact on data quality of participants in the above mentioned regions. Participants that are in screening at the time when sufficient participant numbers have already been reached will still be allowed to be enrolled in the study. As eligibility criteria are identical between initial and reopened enrollment periods, the newly enrolled participants are not expected to significantly impact key baseline and disease characteristics of the overall study population.

Based on simulations that take a more precise approach to modeling dropout, the ARR for each study will be powered at 90% for a sample size of 887-909. Thus, under the worst-case scenario, the number of participants recruited to Studies MS200527_0080 and 0082 in the second phase of enrollment is expected to be 242 to 264 and 400 to 422, respectively.

Throughout the currently escalating crisis in Eastern Europe, the Sponsor will assess the reliability and usability of efficacy and safety data from the affected regions, to determine what fraction, if any, of the participants' data from these countries can robustly contribute to the study objectives evaluation and be accepted by Health Authorities. This will determine the extent of additional participants to be recruited in each study (i.e., up to 253 participants for Study MS200527_0080 and up to 411 participants for MS200527_0082). Under the intermediate scenario where data from participants randomized in the crisis region are either included fully or censored due to unreliability, the final enrollment will be in the range of 1,041 to 1,294 participants for Study MS200527_0080 and 1,053 to 1,464 participants for Study MS200527_0082, where the lower limit of the range is the actual enrollment at the time of Clinical Study Protocol Version 4.0, and the upper limit is the expected enrollment under the worst-case scenario. The intermediate scenario assumes that the second phase of enrollment will be halted short of worst-case, based on an evaluation of information accrual within data assessed to be reliable. The decision to stop additional recruitment prior to reaching the pre-defined cap will be based solely on this assessment, in consultation with the study IDMC and Steering Committees. The Sponsor will work closely with the IDMC to safeguard the study integrity and the ability to reliably deliver on study objectives.

9.3 Populations for Analyses

The analysis sets for the primary analysis of the DBTP 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 for the PA 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). This analysis set will be used for sensitivity analyses of efficacy.
Modified FAS (mFAS)	All participants in FAS except those participants from Ukraine, Russian Federation, and Belarus lacking data robustness. This analysis set will be specified in the IAP prior to unblinding and will be used for the PA of efficacy.
Safety (SAF)	All participants, who were administered any dose of any study intervention. Participants will be analyzed per the actual study intervention they received. This analysis set will be used for sensitivity analyses of safety.
Modified SAF (mSAF)	All participants in SAF except those participants from Ukraine, Russian Federation, and Belarus lacking data robustness. This analysis set will be specified in the IAP prior to unblinding and will be used for the PA of safety.
PK	All participants who receive at least 1 dose of evobrutinib and have at least 1 quantifiable evobrutinib plasma concentration at a scheduled PK time point postdose without any important deviations or events that may impact the quality of the data or alter the evaluation of PK. Participants who receive active control will not be included.

Analysis sets for the DBE Period are specified below.

Analysis Set	Description
FAS for DBE	All participants who enter the DBE period. Participants will be analyzed per the intervention group to which they are randomized.
SAF for DBE	All participants who enter the DBE period. Participants will be analyzed per the actual study intervention they received.

Analysis sets for the OLE Period are specified below:

Analysis Set	Description
FAS for OLE	All participants who were administered any dose of any study intervention during the OLE period. Analyses will consider participants as treated
SAF for OLE	Same as FAS for OLE

The following subgroups of the mFAS will be considered for efficacy analyses at PA:

- 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, membership in initial or second recruitment cohort.

9.4 Statistical Analyses

This section provides a description of the statistical methods to be used to analyze efficacy, safety, and other endpoints for the PA. Prior to locking the database, a detailed IAP will be finalized. Analyses of DBE and OLE endpoints will be described in separate IAPs.

Unless otherwise specified, for the PA, the mFAS will be used for all efficacy analyses, PRO analyses, and reporting of demographic and Baseline characteristics and the mSAF will be used for all safety data reporting.

For the PA, secondary objectives based on disability progression, disability improvement, 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_0080).

The PA will be performed on all data until the PA trigger date.

9.4.1 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	
ARR up to 156 weeks	Primary analysis based on NB model of qualified relapse count over 156 weeks, with terms for intervention group and 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 PA of ARR, missing data assumed to be missing at random, with missing data status noninformative for qualified relapse.
Secondary efficacy and HRQoL	
Time to first occurrence of 12-week CDP, Time to first occurrence of 24-week CDP	Analyzed for participants pooled from both Phase III studies. Primary analysis based on stratified logrank test of distribution of time to 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 CDP hazard rate, with terms for intervention group, and strata defined by randomization strata and study ID. Cumulative distribution function for time to CDP will be estimated via Kaplan-Meier method by intervention group. In the PA of time to CDP, censoring assumed to be noninformative for CDP.
Time to first occurrence of 24-week CDI	Analyzed for participants pooled from both Phase III studies who have baseline EDSS ≥ 2.0. Primary analysis based on stratified logrank test of distribution of time to CDI 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 CDI hazard rate, with terms for intervention group, and strata defined by randomization strata and study ID. Cumulative distribution function for time to CDI will be estimated via Kaplan-Meier method by intervention group. In the PA of time to CDI, censoring assumed to be noninformative for CDI.
CFB in PROMIS PF score over 96 weeks, CFB in PROMIS Fatigue score over 96 weeks	Analyzed for participants pooled from both Phase III studies. Primary analysis based on MMRM where score CFB is modeled, with terms for intervention group, visit, intervention group by visit interaction, Baseline score, randomization strata, and study ID. Test and treatment effect estimator (with 95% 2-sided CI) based on difference (evobrutinib versus comparator) in average least-squares means of CFB from the model. Average is taken over Weeks 72, 84, 96 for PROMIS PF. Average is taken over Weeks 48, 60, 72, 84, 96 for PROMIS Fatigue. Cumulative distribution function for average CFB will be estimated by intervention group. In the PA of CFB, missing data assumed to be MAR, with missing data status noninformative for CFB.

Endpoint	Statistical Analysis Methods
Total number of T1 Gd+ lesions based on all available MRI scans; Number of new or enlarging T2 lesions on the last available MRI scan relative to the baseline MRI scan	Primary analysis based on NB model of total lesion count, with terms for intervention group, Baseline lesion activity, and randomization strata. For T1 Gd+ lesions, offset is log number of total available scans. For new/enlarging T2 lesions, offset is log of the time between baseline scan and last available scan in years. Test and treatment effect estimator (with 95% 2-sided CI) based on adjusted lesion rate ratio (evobrutinib versus comparator) from model. In the PA of lesion rate, missing data assumed to be MAR, with missing data status noninformative for lesion count.
Week 12 NfL concentration	Primary analysis based on MMRM where the log(NfL concentration) will be modeled, with terms for intervention group, visit, intervention group by visit interaction, Baseline concentration and randomization strata. Test and treatment effect estimator (with 95% 2-sided CI) based on difference (evobrutinib versus comparator) in least-squares means of Week 12 from the model. In the PA, missing data assumed to be MAR, with missing data status noninformative for NfL concentrations.
Tertiary/Exploratory	
ARR at 48 weeks, ARR at 96 weeks	Analysis follows that of ARR up to 156 weeks, with only follow-up and events up to 48 weeks, or up to 96 weeks, considered.
Time to first qualified relapse	Stratified logrank test of distribution of time to event with strata defined by randomization strata. Estimation of treatment effect (and 95% 2-sided CI) based on hazard ratio from stratified Cox model of event hazard rate. Cumulative distribution function will be estimated via Kaplan-Meier method by intervention group. Censoring assumed to be noninformative for qualified relapse.
Time to 12-week confirmed disability based on composite score; Time to ≥ 20% increase (confirmed at 12 weeks) in T25-FW; Time to ≥ 20% increase (confirmed at 12 weeks) in 9-HPT. Time to first occurrence of 12 week confirmed PF deterioration	Analyzed for participants pooled from both Phase III studies. Primary analysis based on stratified logrank test of distribution of time to event 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 12-week CDP hazard rate, with terms for intervention group and strata defined by randomization strata and study ID. Cumulative distribution function will be estimated via Kaplan-Meier method by intervention group. Censoring assumed to be noninformative for event of interest.
NfL concentration at Weeks 24, 48, and 72	Analysis follows that of NfL concentration at Week 12
Relapse-free status at Week 96; NEDA-3 at Week 48 or Week 96; NEP at Week 48 or Week 96; NEPAD at Week 48 or Week 96; T1 Gd+ lesion free status at Week 96; new or enlarging T2 lesion free status at Week 96; CUA lesion free status at Week 96	Proportions within intervention groups compared using CMH $\chi 2$ test stratified by randomization strata.
12-week (or 24-week) confirmed EDSS progression free status at Week 96	Analyzed for participants pooled from both Phase III studies. Proportions within intervention groups compared using CMH $\chi 2$ test stratified by randomization strata and study ID.
Time to PIRA, Time to PIRMA	The statistical analysis methods for these exploratory endpoints will be specified in the IAP.

Endpoint	Statistical Analysis Methods
Total number of new T1 hypo-intense lesions based on all available MRI scans; Total number of CUA lesions based on all available MRI scans	NB model of total lesion count, with terms for intervention group, Baseline lesion activity, and randomization strata. Offset is log number of total available scans. Estimation of treatment effect (and 95% 2-sided CI) based on adjusted lesion rate ratio from NB model. Missing data assumed to be MAR, with missing data status noninformative for lesion count.
Change in volume of T1 Gd+ lesions from Baseline to Week 96; Change in volume of T2 lesions from Baseline to Week 96	MMRM analysis where CFB in cube-rooted volume is modeled, with terms for intervention group, visit, intervention group by visit interaction, randomization strata, and Baseline value of cube-rooted volume. Estimation of treatment effect (and 95% 2-sided CI) based on adjusted difference in least-squares means from the model. Missing data assumed to be MAR, with missing data status noninformative for CFB.
Change in normalized T1 intensity within pre-existing nonenhancing T2 weighted lesion volume from Baseline to Week 96	Hodges-Lehman estimate (and 95% 2-sided CI) of shift in distribution of Week 96 normalized T1 intensity CFB between intervention groups and Wilcoxon rank sum test, stratified according to randomization strata and Baseline T2 lesion volume category (based on tertiles).
Volume of SELs based on scans at Weeks 24, 48, and 96	Hodges-Lehman estimate (and 95% 2-sided CI) of shift in distribution of SEL Volume (detected from Baseline to Week 96) between intervention groups and Wilcoxon rank sum test, stratified according to randomization strata and Baseline T2 lesion volume category (based on tertiles).
Percentage change in BV from Week 24 to Week 96; Percentage change in Thalamic volume from Week 24 to Week 96; Percentage change in cortical grey matter volume from Week 24 to Week 96.	MMRM analysis where percentage change from Week 24 is modeled, with terms for intervention group, visit, intervention group by visit interaction, Week 24 value of volume, and randomization strata. Estimation of treatment effect (and 95% 2-sided CI) based on adjusted difference in least-squares means from the model. Missing data assumed to be MAR, with missing data status noninformative for percentage change from Week 24.
Change in number of PRL at Weeks 24, 48, and 96	The statistical analysis methods for this exploratory endpoint will be specified in the IAP
Change in CBF in NAWM at Weeks 24, 48, and 96	The statistical analysis methods for this exploratory endpoint will be specified in a separate Statistical Analysis Plan
CFB in PROMIS PF score at Week 48, Week 96, and Week 144; CFB in PROMIS Fatigue score at Week 48, Week 96, and Week 144	Analyzed for participants pooled from both Phase III studies. MMRM analysis of CFB at a specific timepoint uses same model as described for secondary PROMIS PRO endpoints, with inclusion of terms for additional timepoints as needed
CFB in SDMT score at Week 48 and Week 96; CFB in SF-36v2 score at Week 48, Week 96, and Week 144; CFB in EQ-5D-5L score at Week 48, Week 96, and Week 144	Analyzed for participants pooled from both Phase III studies. MMRM analysis where CFB is modeled, with terms for intervention group, visit, intervention group by visit interaction, Baseline value of endpoint, randomization strata, and study ID. Estimation of treatment effect (and 95% 2-sided CI) based on adjusted difference in least-squares means from the model. Missing data assumed to be MAR, with missing data status noninformative for CFB.
12-week and 24-week confirmed disability improvement status	Analyzed for the subgroup of participants from the pooled Phase III studies with Baseline EDSS score ≥ 2.0. Participants without confirmed disability improvement counted as not improved, independent of follow-up time. CMH test stratified according to randomization strata and study ID.

Endpoint	Statistical Analysis Methods
Absolute values of HRU endpoints at study visit up to 156 weeks, including but not limited to doctor/home/ emergency visits, hospitalizations, paid assistance, and missed work days	Analyzed for participants pooled from both Phase III studies. Descriptive statistics (mean, SD, median, minimum/maximum, 25th and 75th percentile; 95% CI) at the various time points.
anti-SARS-CoV-2 antibody levels	Descriptive statistics for anti-SARS-CoV-2 titers.

9-HPT = 9-Hole Peg Test, ARR = Annualized Relapse Rate, BV = brain volume, CBF = cerebral blood flow, CDP = Confirmed disability progression, CFB = change from Baseline, CMH = Cochran-Mantel-Haenszel, 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, HRU = Health Resource Utilization, MAR = Missing at Random, MMRM = Mixed Effect model for repeated measures, NB = negative binomial, NEDA = No Evidence of Disease Activity; NEPAD = No evidence of progression or active disease, NfL = neurofilament light chain, PIRA = Progression independent of Relapse Activity, PIRMA = Progression Independent of Relapse and brain MRI activities, PROMIS = Patient Reported Outcomes Measurement Information System, SD = standard deviation, SDMT = Symbol Digit Modalities Test, SEL = slowly expanding lesions, SF-36v2 = 36-Item Short Form Survey Instrument Version 2, T25-FW = Timed 25-Foot Walk.

9.4.1.1 Efficacy Analyses Related to Primary Objective

Per ICH E9(R1), Addendum on Estimands and Sensitivity Analysis in Clinical Trials (November 2019), the primary estimand targeting the primary objective in this study is defined by the following attributes:

- **Variable (endpoint):** The primary endpoint is ARR up to 156 weeks. Measurements on the participant-level are number of qualified relapses experienced by the participant and follow-up time over which those relapses occurred (potentially less than 156 weeks).
- **Treatment:** The intervention of interest is evobrutinib 45 mg twice daily for up to 156 weeks and the alternative intervention is teriflunomide 14 mg once daily for up to 156 weeks.
- **Population:** The population of participants targeted by the clinical question is defined by the inclusion/exclusion criteria.
- **Strategies for handling intercurrent events:** In the absence of the currently escalating crisis in Eastern Europe, the main intercurrent event envisaged is discontinuation of assigned treatment. The strategy for dealing with this is Treatment Policy, which requires that the qualified relapse count up to 156 weeks post randomization be used, if available, regardless of treatment discontinuation. The Compositive Variable strategy is used to handle the intercurrent event of death attributable to MS or treatment. The While Alive strategy is used to handle the intercurrent event of death unattributable to MS or treatment. The intercurrent event of the crisis in Eastern Europe ("Ukraine crisis") will be handled via the Hypothetical strategy; strategy details will be specified in the IAP prior to unblinding and after a careful evaluation of data robustness for participants from sites in the region affected by the crisis (Ukraine, Russian Federation, and Belarus).
- **Population-level summary:** The population-level summary comparing the intervention groups is relapse rate ratio, based on an NB model for qualified relapse count, with terms

for intervention group and randomization strata, with offset equal to log follow-up time (in years) over which the qualified relapses experienced by a participant are observed.

In accordance with Treatment Policy strategy, for participants discontinuing treatment, any qualified relapses occurring through Safety Follow-up will be included in the analysis up to 156 weeks post randomization. For participants who have not been followed to 156 weeks post randomization, the missing data will be assumed to be MAR; treatment discontinuers will be assumed to experience relapse through 156 weeks post randomization at the same rate as treatment completers within the same intervention group and stratum. This is the assumption underlying the rate ratio estimator implemented by the NB model that uses observed relapse events and observed follow-up time for each participant, regardless of treatment completer/discontinuer status.

In accordance with the Composite Variable strategy, for participants experiencing death attributable to MS or treatment, the death will be counted as a qualified relapse. In accordance with the While Alive strategy, for participants experiencing death unattributable to MS or treatment, the death will not be counted as a qualified relapse.

In accordance with the Hypothetical strategy, for participants from sites in Ukraine, Russian Federation, and Belarus, the "Ukraine crisis" intercurrent event will lead to exclusion from the mFAS (i.e., hypothetical scenario in which participant was not recruited), or inclusion in the mFAS with censoring at the start of the crisis (i.e., hypothetical scenario in which crisis would not occur), or inclusion in the mFAS without censoring at the start of crisis, depending on the assessment of data robustness. Details of the Hypothetical strategy for handling the intercurrent event of the "Ukraine crisis" will be specified in the IAP prior to unblinding.

The adjusted relapse rate ratio comparing evobrutinib to teriflunomide will be estimated from the NB model. The adjusted rate ratio, 95% 2-sided CI, and 1-sided p-value will be reported, together with adjusted ARR (and 95% CI) for each intervention group from the model, and unadjusted ARR (and 95% CI) for each intervention group estimated nonparametrically. The analysis of ARR will be based on data from this study alone.

Unadjusted ARR up to 156 weeks is calculated by dividing the total number of qualified relapse events experienced by all participants in a given group through Week 156 by the person-time (in years) observed for those participants through Week 156.

The covariates defined by randomization strata are region (4 levels: North America, Western Europe, Eastern Europe, Rest of World) and Baseline (Day 1) EDSS (2 levels: < 4.0, ≥ 4.0). The NB model assumes a common dispersion parameter for all participants, independent of intervention group 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 PA, only observed events and observation time will be included in the analysis; there will be no imputation of events for participants discontinuing study early.

Sensitivity analyses of the primary estimand for the primary endpoint are specified in Section 9.4.1.3.

The IAP will further specify rates, timings, and potential roles of intercurrent events, strategies for handling them, and potential consequences on the analyses and results.

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 9.4.4.3.

The primary estimands targeting the secondary objectives in this study share some of the attributes of the primary estimand in Section 9.4.1.1, such as the treatment comparison attribute, the population attribute, and the strategy for dealing with the intercurrent events of treatment discontinuation and "Ukraine crisis." Distinctive attributes of each estimand are described below for each secondary endpoint.

Time to 12-week CDP, Time to 24-week CDP

For the secondary efficacy endpoint, time to 12-week CDP (CDP based on EDSS), the Treatment Policy strategy requires that all EDSS data, up to 156 weeks post randomization, will be used if available, regardless of treatment discontinuation. In accordance with Treatment Policy strategy, for participants discontinuing treatment, all EDSS data through Safety Follow-up will be included in the analysis up to 156 weeks post randomization. The population-level summary comparing the intervention groups is 12-week CDP hazard ratio, based on a stratified Cox model for 12-week CDP hazard rate, with terms for intervention group, strata defined by randomization strata and study ID, and where the data are pooled from the mFAS of the present study and the mFAS of the second Phase III study.

Participants who did not experience 12-week CDP by 156 weeks post randomization, by time of PA trigger, by time of early study discontinuation, or before being lost to follow-up, will be censored at the date of the last EDSS assessment during the 156 weeks post randomization. Censoring will be assumed to be noninformative for 12-week CDP, conditional on intervention group, randomization stratum, and study ID. This is the assumption underlying the hazard ratio estimator implemented by the stratified Cox model that uses observed follow-up time for each participant, regardless of treatment completer/discontinuer status, where participants are censored for 12-week CDP at the latest EDSS assessment.

In accordance with the Composite Variable strategy, for participants experiencing death attributable to MS or treatment, the death will be counted as 12-week CDP. In accordance with the While Alive strategy, for participants experiencing death unattributable to MS or treatment, the death will not be counted as 12-week CDP. Details of the Hypothetical strategy for handling the intercurrent event of the "Ukraine crisis" will be specified in the IAP prior to unblinding.

Per Protocol Version 3, prior to the completion of enrollment, an optional IA for BSSR was performed based on the secondary efficacy endpoint, time to 12-week CDP, with data pooled across the present study and the second Phase III study (see Section 9.4.4.1). Performed in August 2021, the outcome of this IA for BSSR was a decision to not increase sample size.

The PA of time to 12-week CDP will report the hazard ratio comparing evobrutinib to teriflunomide estimated via a stratified Cox model, 95% 2-sided CI, and 1-sided p-value for the stratified logrank test, together with a Kaplan-Meier estimate of cumulative probability of experiencing 12-week CDP over time for each intervention group. Prior to pooling, the validity of pooling data across the present study and the second Phase III study will be assessed by reviewing consistency of demographics, Baseline characteristics, ARR and 12-week CDP results.

The secondary endpoint, time to 24-week CDP, will be analyzed in the same manner as that of the 12-week CDP endpoint. The primary estimand attributes for the time to 24-week CDP endpoint are the same as the primary estimand attributes for the time to 12-week CDP endpoint.

Time to 24-week CDI

For the secondary efficacy endpoint, time to 24-week CDI (CDI based on EDSS), the Treatment Policy strategy requires that all EDSS data, up to 156 weeks post randomization, will be used if available, regardless of treatment discontinuation. In accordance with Treatment Policy strategy, for participants discontinuing treatment, all EDSS data through Safety Follow-up will be included in the analysis up to 156 weeks post randomization. The population-level summary comparing the intervention groups is 24-week CDI hazard ratio, based on a stratified Cox model for 24-week CDI hazard rate, with terms for intervention group, strata defined by randomization strata and study ID, and where the data are pooled from participants in the mFAS of the present study and the mFAS of the second Phase III study who have baseline EDSS $\geq$ 2.0.

Participants who did not experience 24-week CDI by 156 weeks post randomization, by time of PA trigger, by time of early study discontinuation, or before being lost to follow-up, will be censored at the date of the last EDSS assessment during the 156 weeks post randomization. Censoring will be assumed to be noninformative for 24-week CDI, conditional on intervention group, randomization stratum, and study ID. This is the assumption underlying the hazard ratio estimator implemented by the stratified Cox model that uses observed follow-up time for each participant, regardless of treatment completer/discontinuer status, where participants are censored for 24-week CDI at the latest EDSS assessment.

In accordance with the While Alive strategy, for participants experiencing death (any cause), participants will be censored at time of death. Details of the Hypothetical strategy for handling the intercurrent event of the “Ukraine crisis” will be specified in the IAP prior to unblinding.

The PA of time to 24-week CDI will report the hazard ratio comparing evobrutinib to teriflunomide estimated via a stratified Cox model, 95% 2-sided CI, and 1-sided p-value for the stratified logrank test, together with a Kaplan-Meier estimate of cumulative probability of experiencing 24-week CDI over time for each intervention group.

CFB in PROMIS PF score over 96 weeks, CFB in PROMIS Fatigue score over 96 weeks

For the secondary efficacy endpoint, CFB in PROMIS PF score over 96 weeks, the Treatment Policy strategy requires that the CFB in PROMIS PF score over 96 weeks post randomization

be used if available, regardless of treatment discontinuation. The population-level summary comparing the intervention groups is difference in average least-squares means, based on a MMRM for CFB, with average taken over Weeks 72, 84, and 96, where the model includes terms for intervention group, visit, intervention group by visit interaction, Baseline score, randomization strata, and study ID, and where the data are pooled from the mFAS of the present study and the mFAS of the second Phase III study.

For participants with missing PROMIS PF data, the missing data will be assumed to be MAR; such participants will be assumed to have the same mean PROMIS PF score CFB trajectory through 96 weeks as participants with available data within the same intervention group and stratum, and having the same Baseline score and study ID. This is the assumption underlying the estimator of difference of average least-squares means implemented by the MMRM that uses observed score CFB data from each participant, regardless of treatment completer/discontinuer status.

In accordance with the While Alive strategy, for participants experiencing death, all PROMIS PF data up to the time of death will be used in the analysis. Details of the Hypothetical strategy for handling the intercurrent event of the "Ukraine crisis" will be specified in the IAP prior to unblinding.

The difference (comparing evobrutinib and teriflunomide) in average least-squares mean CFB, 95% 2-sided CI, and 1-sided p-value will be reported. For each intervention group, the average adjusted least-squares mean score CFB and associated 95% 2-sided CI will be reported, as will the estimated cumulative distribution function for average score CFB.

The secondary endpoint, CFB in PROMIS Fatigue score over 96 weeks, will be analyzed in the same manner as CFB in PROMIS PF score over 96 weeks, except that the average will be taken over Weeks 48, 60, 72, 84, and 96. The primary estimand attributes for these 2 endpoints are the same.

Total number of T1 Gd+ lesions based on all available MRI scans, Number of new or enlarging T2 lesions on the last available MRI scan relative to the baseline MRI scan

For the secondary efficacy endpoint, total number of T1 Gd+ lesions based on all available MRI scans, the Treatment Policy strategy requires that the lesion count over all available scans post randomization be used, if available, regardless of treatment discontinuation. Offset will be log total number of available scans. The population-level summary comparing the intervention groups is total lesion rate ratio, based on a NB model for total lesion count, with terms for intervention group, randomization strata, and Baseline lesion activity, with offset equal to log number of total available scans over which the lesions experienced by a participant are observed.

For participants missing one or more scans, the missing data will be assumed to be MAR; such participants will be assumed to experience lesions through planned end of treatment (i.e., PA trigger or 156 weeks, whichever occurs first) at the same rate as participants with available data within the same intervention group and stratum, and having the same Baseline lesion activity. This is the assumption underlying the rate ratio estimator implemented by the NB

model that uses observed lesion count and number of scans giving rise to that count for each participant, regardless of treatment completer/discontinuer status.

In accordance with the While Alive strategy, for participants experiencing death, all T1 Gd+ lesion data up to the time of death will be used in the analysis. Details of the Hypothetical strategy for handling the intercurrent event of the "Ukraine crisis" will be specified in the IAP prior to unblinding.

The adjusted lesion rate ratio comparing evobrutinib to teriflunomide estimated from the NB model, 95% 2-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.

The secondary endpoint, number of new or enlarging T2 lesions on the last available MRI scan relative to the baseline MRI scan, will be analyzed in the same manner as total number of T1 Gd+ lesions based on all available MRI scans, except that the offset will be log of time between the baseline scan and last available scan (in years). The primary estimand attributes for these two endpoints are the same.

Sensitivity analyses of the primary estimands of the secondary endpoints are specified in Section 9.4.1.3.

Week 12 NfL Concentration

For the secondary efficacy endpoint, Week 12 NfL concentration, the Treatment Policy strategy requires that all values of NfL concentrations be used if available, regardless of treatment discontinuation. The population-level summary comparing the intervention groups is difference in least-squares means, based on a MMRM for log(NfL concentration), where the model includes terms for intervention group, visit, intervention group by visit interaction, Baseline concentration and randomization strata.

For participants with missing NfL concentration data, the missing data will be assumed to be MAR; such participants will be assumed to have the same mean NfL concentration trajectory through planned end of treatment (i.e., PA trigger or 156 weeks, whichever occurs first) as participants with available data within the same intervention group and stratum, and having the same Baseline concentration. This is the assumption underlying the estimator of difference of least-squares means through Week 12 implemented by the MMRM that uses observed NfL concentration data from each participant, regardless of treatment completer/discontinuer status.

In accordance with the While Alive strategy, for participants experiencing death, all NfL concentration data up to the time of death will be used in the analysis. Details of the Hypothetical strategy for handling the intercurrent event of the "Ukraine crisis" will be specified in the IAP prior to unblinding.

The difference (comparing evobrutinib and teriflunomide) in least-squares mean, 95% 2-sided CI, and 1-sided p-value will be reported. For each intervention group, the adjusted least-squares mean at Week 12 and associated 95% 2-sided CI will be reported.

9.4.1.3 Sensitivity Analyses

The following sensitivity analyses for the primary endpoint ARR up to 156 weeks will be detailed in the IAP:

1. Analysis to evaluate the potential influence of informative treatment discontinuation according to discontinuation reason. If a participant's discontinuation is unrelated to treatment (i.e., unrelated to efficacy or safety issues), the participant's relapse count will be multiply imputed using ARR in the comparator group, for the interval between discontinuation and planned end of treatment (i.e., PA trigger or 156 weeks post randomization, whichever occurs first). If a participant's discontinuation is related to treatment, relapse count will be multiply imputed at a rate higher than ARR in comparator group, for the interval between discontinuation and planned end of treatment.

2. Analysis in which participants who discontinued treatment early during the 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 in which additional covariates are included 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, to evaluate the potential impact of model misspecification.

4. Analysis to evaluate the impact of the currently escalating crisis in Eastern Europe. All participants in the FAS will be included, with consideration given to including a time-dependent covariate indicating whether the participant is under the stress of the crisis, which may be associated with increased frequency of relapses.

For the primary estimand of the secondary endpoint, time to 12-week CDP, it is important to assess the sensitivity of results to the assumption that censoring is noninformative for 12-week CDP, conditional on intervention group, study ID, and stratum. The following sensitivity analyses for the secondary efficacy endpoint time to 12-week CDP will be detailed in the IAP:

1. Analysis to evaluate the potential influence of informative treatment discontinuation, according to discontinuation reason or occurrence of initial progression event at last assessment. If a participant's discontinuation is unrelated to treatment (i.e., unrelated to efficacy or safety issues) and no initial progression event occurred, the participant's time to CDP will be multiply imputed using hazard rate in comparator group, for the interval between discontinuation and planned end of treatment (i.e., PA trigger or 156 weeks post randomization, whichever occurs first). If a participant's discontinuation is related to treatment or an initial unconfirmed progression event occurred, the participant's time to CDP will be multiply imputed using hazard rate higher than that in comparator group, for the interval between discontinuation and planned end of treatment.

2. Analysis in which participants who discontinued treatment early during the 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 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.

4. Analysis to evaluate the impact of the currently escalating crisis in Eastern Europe. All participants in the FAS will be included, with consideration given to including a time-dependent covariate in the model.

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

Sensitivity analyses for the secondary endpoint time to 24-week CDI will be specified in the IAP.

For the primary estimand of the secondary endpoint, PROMIS PF CFB, it is important to assess the sensitivity of results to the MAR assumption that participants with missing data have the same mean CFB trajectory through 96 weeks or PA trigger, whichever occurs first, as participants with complete data, conditional on intervention group, Baseline score, study ID, and stratum. The following sensitivity analysis for the secondary endpoint PROMIS PF score CFB over 96 weeks will be detailed in the IAP:

1. Analysis to evaluate the potential influence of informative treatment discontinuation according to discontinuation reason. If a participant's discontinuation is unrelated to treatment (i.e., unrelated to efficacy or safety issues), the participant's score CFB at each timepoint will be multiply imputed using CFB distribution at that timepoint in comparator group, for the interval between discontinuation and 96 weeks post randomization, or PA trigger, whichever occurs first. If a participant's discontinuation is related to treatment, the participant's score CFB at each timepoint will be multiply imputed using a worse CFB distribution at that timepoint than that in comparator group, for the interval between discontinuation and 96 weeks post randomization or PA trigger, whichever occurs first.

2. Analysis to evaluate the impact of the currently escalating crisis in Eastern Europe. All participants in the FAS will be included, with consideration given to including a time-dependent covariate in the model.

Sensitivity analyses for PROMIS Fatigue score CFB over 96 weeks will be similar.

For the primary estimand of the secondary endpoint, total number of T1 Gd+ lesions based on all available MRI scans, it is important to assess the sensitivity of results to the MAR assumption that participants with missing data experience lesions until planned end of treatment at the same rate as participants with complete data, conditional on intervention group, Baseline lesion activity, and stratum. The following sensitivity analysis for the secondary efficacy endpoint total T1 Gd+ lesions will be detailed in the IAP:

1. Analysis to evaluate the potential influence of informative treatment discontinuation according to discontinuation reason. If a participant's discontinuation is unrelated to treatment (i.e., unrelated to efficacy or safety issues), the participant's lesion count will be multiply imputed using rate in comparator group, for the interval between discontinuation and planned end of treatment (i.e., PA trigger or 156 weeks post

randomization, whichever occurs first). If a participant's discontinuation is related to treatment, lesion count will be multiply imputed at a rate higher than that in comparator group, for the interval between discontinuation and planned end of treatment.

2. Analysis to evaluate the impact of the currently escalating crisis in Eastern Europe. All participants in FAS will be included, with consideration given to including a time-dependent covariate in the model.

The following supplemental analyses for the secondary efficacy endpoint total number of T1 Gd+ lesions based on all available MRI scans will be detailed in the IAP:

1. Analysis wherein lesion count at a single scan is modeled as Poisson-distributed, with a random effect for participant, and terms for intervention group, randomization strata, and Baseline lesion activity. This model will compare treatment on the basis of conditional adjusted lesion rate ratio, where conditioning is on the random effect.

Sensitivity and supplemental analyses for number of new/enlarging T2 lesions on the last available MRI scan relative to the baseline MRI scan, except that the offset in the model will be log time from baseline scan to last available scan (in years) in place of log number of scans.

Sensitivity analyses for the secondary endpoint, NfL concentration at 12 weeks, will be specified in the IAP.

Further details on sensitivity analyses of ARR, 12-week CDP, and other secondary efficacy endpoints, which incorporate available data from participants enrolled at sites in the currently escalating crisis regions in Eastern Europe, will be described in the IAP.

9.4.2 Safety Analyses

All safety analyses will be performed on the mSAF.

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
ECG Parameters	Descriptive statistics
Vital Signs	Descriptive statistics
Immunoglobulin Levels	Descriptive statistics
Tertiary/Exploratory	Not applicable

9.4.2.1 Adverse Events

Adverse events will be coded using the MedDRA. All TEAEs will be summarized by intervention group. TEAEs 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. TEAEs 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 predefined 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 postbaseline 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 NCI-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 postbaseline 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 CFB to Week 96 in ECG parameters (e.g., PR, HR, QRS, RR, QT, and QTcF) will be summarized by intervention group using descriptive statistics. QTc will be reported based on Fridericia's method. Percentage and counts of participants with 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 (predose Day 1):

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 > 30 msec

QRS:

- Absolute > 110 msec

QTcF:

- 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 QTcF intervals, and frequency counts and percentages for categorical variables.

9.4.2.5 Immunoglobulin Levels

Data on Ig levels (observed values, change, and percent CFB, with Baseline defined as the Day 1 sample) will be descriptively summarized in tabular and/or graphic format, as appropriate.

Correlative analyses may be explored and reported separately.

9.4.2.6 Concomitant Medication and Procedures

Prior and concomitant medications will each be categorized by therapeutic class and preferred term using 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 categorized by SOC and preferred term using MedDRA. The number of and percent of participants experiencing each prior and concomitant procedure will be summarized by type of procedure for each intervention group.

9.4.2.7 Columbia-Suicide Severity Rating Scale

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

9.4.2.8 Sensitivity Analyses

Sensitivity analyses of important safety endpoints, which incorporate available data from participants enrolled at sites in the currently escalating crisis regions in Eastern Europe, will be described in the IAP.

9.4.3 Other Analyses

9.4.3.1 Pharmacokinetic Parameters and Biomarkers

PK and biomarker exploratory analyses will be specified in the IAP finalized before database lock. Integrated analyses across studies, such as the population PK analysis will be presented separately from the main CSR.

In general, biomarkers assessed at planned visits and premature early discontinuation from treatment will be summarized in a manner similar to safety laboratory parameters.

The PK data of the current study will be used for the development of population PK models (possibly in combination with the corresponding data of earlier studies, e.g., MS200527_0019, MS200527_0017, MS200527_0086, and/or others), to describe the concentration-time profiles for the participants in the study. Population PK model-based exposure metrics such as C_{max} and AUC (from 0 to 24 hour) at steady state will be derived.

The derived PK profiles and exposure metrics will be used to develop exposure-response models (longitudinal or cross-sectional) for MRI, efficacy, and safety endpoints. In particular, a cross-sectional model of ARR as a function of steady state AUC, a longitudinal repeated time to event (qualified relapse) model, a longitudinal model for EDSS, cross-sectional or longitudinal exposure-response models for MRI lesions (T1 Gd+ lesion and new or enlarging T2 lesion count), and a longitudinal (if possible) exposure-response model for ALT elevations, will be developed.

Other endpoints of interest depending on the signals that will be detected based on the exploratory/inferential statistical analysis of the study data may also be included in the exposure-response analyses.

Full details of the planned population PK modeling and other exposure-related modeling will be described in the study IAP. The results of the corresponding analyses will be reported separately from the study CSR.

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 analysis of PROMIS PRO secondary endpoints is described in Section 9.4.1.2. A similar analysis will be performed for exploratory PRO score CFB endpoints. The exploratory endpoint, time to deterioration in PROMIS PF score confirmed at 12 weeks will be analyzed in a manner similar to that of time to 24-week CDP.

9.4.3.4 Health Resource Utilization

For the exploratory endpoint HRU observed values at each visit and CFB to each postbaseline visit in HRU (doctor/home/emergency visits, hospitalizations, paid assistance, and missed work) will be summarized by time point and intervention group using descriptive statistics (mean, standard deviation, median, minimum/maximum, 25th and 75th percentile; 95% CI).

9.4.3.5 Analysis of Double-Blind Extension Period Endpoints

Efficacy and HRQoL data collected during the DBE period will be analyzed as additional data to DBTP (i.e., baseline will be baseline of DBTP). Details will be provided in the IAP.

Safety data collected during the DBE Period will be analyzed as described in Section 9.4.2.

9.4.3.6 Analysis of Open Label Extension Period Endpoints

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

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

9.4.4 Sequence of Analyses

4 analyses are planned for the study: (1) an optional IA for BSSR based on the secondary endpoint 12-week CDP, with data pooled across the present study and the second Phase III study, performed by the Sponsor, triggered when enrollment is nearing completion, (2) a PA, performed by the Sponsor after the PA database lock, with timing and endpoint evaluation as described in Section 9.4.4.2, (3) an analysis of all data from blinded periods at the end of DBE, performed by the Sponsor after the corresponding DBE database lock, (4) a final analysis, performed by the Sponsor after the final database lock, triggered when 100% of

participants enrolled in the OLE Period complete the OLE, or discontinue prematurely from the OLE.

The PA of the first Phase III study (i.e., MS200527_0080) and the present study (i.e., MS200527_0082) will be triggered as described in Section 9.4.4.2.

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

9.4.4.1 Optional Interim Analysis for Blinded Sample Size Re-estimation

Per Protocol Version 3, when enrollment was nearing completion, an optional IA for BSSR based on the secondary endpoint 12-week CDP may be performed by the Sponsor, using data pooled across studies. Only data relevant to 12-week CDP needed to be cleaned for the IA.

Parametric distributions for time to 12-week CDP and time to censoring were fitted using blinded data pooled across studies. The resulting parameter estimates were used to estimate expected number of events given the originally planned sample size. If the expected number of events was less than the number required to power the 12-week CDP endpoint at 80%, consideration was to be given to increasing the sample size up to 25% so that the required number of events was achieved (Friede 2019). Performed in August 2021, the outcome of this IA for BSSR was a decision to not increase sample size. In the setting of superiority trials, an IA for BSSR has a minimal or non-existent effect on type-1 error inflation (Friede 2019).

9.4.4.2 Primary Analysis

Based on an analysis of accumulating blinded data, the PA will be triggered for both studies simultaneously when all of the following conditions are met.

- This study and the second Phase III study have individually collected ≥ 32.3 units of information for the primary ARR endpoint, where "Information" is defined below. At this timepoint both studies will provide ≥ 90% power for the detection of a 43.5% relative treatment effect on ARR in the primary statistical test at a 1-sided alpha level of 0.025.

- In data pooled from the 2 studies, ≥ 149 12-week CDP events have been observed. At this timepoint, the combined studies have collected sufficient information to provide ≥ 71.5% power for the detection of 34% (hazard ratio = 0.66) relative reduction in risk of 12-week CDP in a logrank test at a 1-sided alpha-level of $0.025\text{-}0.025^2 = 0.024375$.

- All participants have been treated for 24 weeks or discontinued prematurely.

The default is that the PA will be triggered when all participants have been treated for 156 weeks or discontinued prematurely, if this occurs before the information for ARR and 12-week CDP event criteria are met.

After protocol deviations are determined, and the database is locked for the PA, the drug codes will be broken and made available for the primary data analysis. All endpoints based on data from the DBTP until PA trigger date will be evaluated. This implies that the data related to End-of-DBTP visits occurring after the PA trigger date or any other data post PA trigger date will not be part of the PA.

Blinded review of Information for ARR

Based on blinded data, the information associated with the ARR endpoint will be monitored to determine when the PA can be triggered.

Fitting an NB model to the aggregate data (i.e., the qualified relapse data of all participants in a given study combined) provides an estimate of the overall ARR λ and the dispersion parameter γ. For an assumed rate ratio of 0.565 = 0.13/0.23, comparing evobrutinib to teriflunomide, an ARR estimate can be obtained for each group, denoted by λ_1 for evobrutinib and λ_2 for teriflunomide.

Since the treatment allocation of the participants is unknown, but randomization was done in a 1:1 ratio, it is assumed that the follow-up times in the 2 groups (j = 1,2, denoting evobrutinib and teriflunomide, respectively) are the same, i.e., $T_{\cdot 1} = T_{\cdot 2} = T_{total}/2$, where T_{total} is the total of the follow-up times at the review time. It is further assumed that the sum of the squared follow-up times is the same in both groups, i.e., that $\Sigma_i T_{i1}^2 = \Sigma_i T_{i2}^2 = \Sigma_j \Sigma_i T_{ij}^2/2 = \tau_{total}/2$. The information for ARR (as per Appendix 5 of the ASCLEPIOS I/II protocol, available as Supplementary Material to Hauser 2020) based on blinded data is given by:

Equation 9.4.4: Information $I = [2/(\lambda_1 T_{total}) + 2/(\lambda_2 T_{total}) + 4 \gamma \tau_{total}/T_{total}^2]^{-1}$

where λ_1, λ_2, and γ are the re-estimated values based on fitting a NB model to the aggregate data, and T_{total} and τ_{total} are as defined above.

Information for ARR will be monitored in a blinded fashion throughout the study. The first criterion of the PA trigger is met when ≥ 32.3 units of information (Section 9.2.1) have been collected in the first evobrutinib Phase III study (i.e., MS200527_0080) and in the present study (i.e., MS200527_0082, indicating that that the ARR endpoint is powered at ≥ 90% for the detection of a 43.5% reduction in ARR at the 1-sided alpha level of 0.025.

Blinded monitoring of 12-week CDP events

Pooled CDP events will be monitored in a blinded fashion throughout the studies. The second criterion of the PA trigger is met when ≥ 149 pooled 12-week CDP events have been observed, indicating that the 12-week CDP endpoint is powered at ≥ 71.1% for the detection of a 34% reduction in HR at the 1-sided alpha level of 0.024375.

9.4.4.3 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, Bretz 2019). 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 teriflunomide in Study 1

H_{012}: $rRR_2 \geq 1$, where rRR_2 denotes qualified relapse rate ratio comparing evobrutinib to teriflunomide 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) group based on pooled data, $S_{12c}(t)$ denotes the survival function for time to 12-week CDP in the comparator (teriflunomide) group 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 $S_{24c}(t)$ denotes the survival functions for time to 24-week CDP based on pooled data

H_{04}: $S_{24e}(t) \geq S_{24c}(t)$, where $S_{24e}(t)$ denotes the survival function for time to 24-week CDI in the experimental (evobrutinib) group based on pooled data from participants with baseline EDSS ≥ 2.0, $S_{24c}(t)$ denotes the survival function for time to 24-week CDI in the comparator (teriflunomide) group based on pooled data from participants with baseline EDSS ≥ 2.0, and the variable t denotes time since randomization.

H_{05}: $\Delta_{PF} \leq 0$, where Δ_{PF} denotes difference in PROMIS Physical Function score CFB over 96 weeks least-squares mean, comparing evobrutinib to teriflunomide, based on pooled data (higher score corresponds to improved physical function).

H_{06}: $\Delta_{Fatigue} \geq 0$, where $\Delta_{Fatigue}$ denotes difference in PROMIS Fatigue score CFB over 96 weeks least-squares mean, comparing evobrutinib to teriflunomide, based on pooled data (higher score corresponds to more fatigue).

H_{021}: $lRR_{21} \geq 1$, where lRR_{21} denotes T1 Gd+ lesion rate ratio comparing evobrutinib to teriflunomide in Study 1

H_{022}: $lRR_{22} \geq 1$, where lRR_{22} denotes T1 Gd+ lesion rate ratio comparing evobrutinib to teriflunomide in Study 2

H_{031}: $lRR_{31} \geq 1$, where lRR_{31} denotes new or enlarging T2 lesion rate ratio comparing evobrutinib to teriflunomide in Study 1

H_{032}: $lRR_{32} \geq 1$, where lRR_{32} denotes new or enlarging T2 lesion rate ratio comparing evobrutinib to teriflunomide in Study 2

H_{041}: $\Delta_{NfL1} \geq 0$, where Δ_{NfL1} denotes a difference in NfL Concentration at 12 weeks comparing evobrutinib to teriflunomide in Study 1

H_{042}: $\Delta_{NfL2} \geq 0$, where Δ_{NfL2} denotes a difference in NfL Concentration at 12 weeks comparing evobrutinib to teriflunomide in Study 2

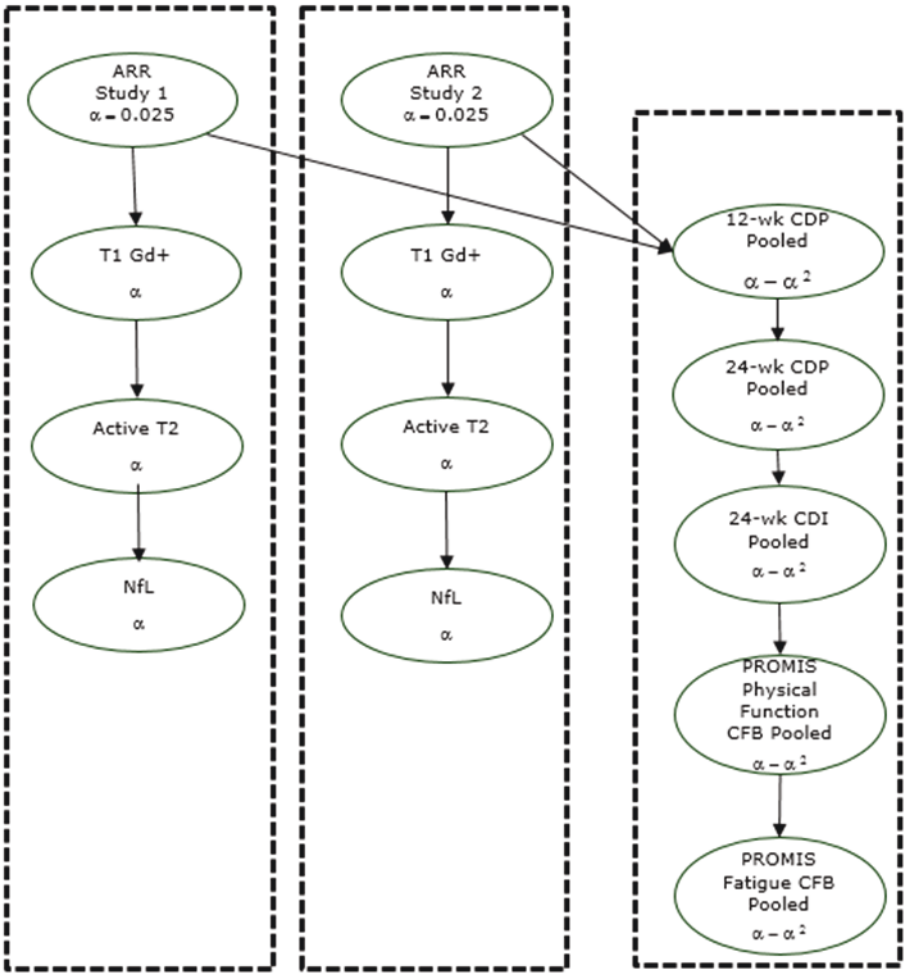
At the PA, the primary efficacy endpoint, ARR, will be tested at the 0.025 (1-sided) level in each study. Figure 3 shows the multiple testing procedure involving study-specific endpoints and pooled endpoints.

At the PA, the 12-week CDP pooled endpoint will be tested at the $0.025\text{-}0.025^2 = 0.024375$ level, 1-sided, only if ARR is significant in both studies at the 0.025 level, 1-sided.

If the 12-week CDP pooled endpoint is significant at the 0.024375 level, 1-sided, the subsequent pooled endpoints (24-week CDP, 24-week CDI, PROMIS PF CFB over 96 weeks, PROMIS Fatigue CFB over 96 weeks) will be tested in a hierarchical order at 0.024375 level, 1-sided.

If the primary efficacy endpoint, ARR up to 156 weeks, is significant within a study at the 0.025 level, 1-sided, the subsequent single-study endpoints (total number of T1 Gd+ lesions based on all available MRI scans, number of new/enlarging T2 lesions on the last available MRI scan relative to the baseline scan, Week 12 NfL concentration) will be tested in a hierarchical order at the 0.025 level, 1-sided.

Figure 3 Multiplicity Graph



ARR = Annualized Relapse Rate, CDI = Confirmed Disability Improvement, CDP = Confirmed Disability Progression, CFB = change from Baseline, Gd^{+} = gadolinium positive, NfL = neurofilament light chain, PROMIS = Patient Reported Outcomes Measurement Information System, T1 and T2 = type of Magnetic Resonance Image, Wk = Week.

10 References

Alankus YB, Grenningloh R, Haselmayer P, et al. BTK Inhibition Prevents Inflammatory Macrophage Differentiation: A Potential Role in MS. EMD Serono, Global Clinical Development Center, Billerica, Massachusetts, USA. 2018 P557.

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.

Barro C, Benkert P, Disanto G, et al. Serum neurofilament light chain as a predictor of disease worsening and brain and spinal cord atrophy in multiple sclerosis. Brain Epub. 2018 May 30.

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.

Bollo L, Guerra T, Bavaro DF, et al. Seroconversion and indolent course of COVID-19 in patients with multiple sclerosis treated with fingolimod and teriflunomide. J Neurol Sci. 2020;416:117011.

Boschert 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.

Bretz F, Maurer W, Xi D. Replicability, Reproducibility, and Multiplicity in Drug Development, CHANCE, 2019;32(4), 4-11.

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.

Ciardi MR, Zingaropoli MA, Pasculli P, et al. The peripheral blood immune cell profile in a teriflunomide-treated multiple sclerosis patient with COVID-19 pneumonia. J Neuroimmunol. 2020;346:577323.

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.

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.

Disanto G, Barro C, Benkert P, et al. Serum neurofilament light: a biomarker of neuronal damage in multiple sclerosis. Ann Neurol. 2017;81:857–70.

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.

Freeman JA, Hobart JC, Langdon DW, et al. Clinical appropriateness: a key factor in outcome measure selection: the 36-item short-form health survey in multiple sclerosis. J Neurol Neurosurg Psychiatry. 2000;68(2):150-6.

Friede T, Pohlmann H, Schmidli H. Blinded sample size restimation in event-driven clinical trials: Methods and an application in multiple sclerosis. Pharm Stat. 2019;18:351-65.

Haselmayer P, Camps M, Liu-Bujalski L, et al. Pharmacodynamic Modeling of BTK Occupancy Versus Efficacy in Ra and SLE Models Using the Novel Specific BTK Inhibitor Evobrutinib. ACR/ARHP Annual Meeting; 2017: Abstract number:2565.

Hauser SL, Bar-Or A, Cohen J, et al. Ofatumumab versus Teriflunomide in Multiple Sclerosis. N Engl J Med. 2020;383:546-57.

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(3):420-9.

Jelcic I, Nimer FA, Wang J, et al. Memory B cells Activate Brain-Homing, Autoreactive CD4+ T Cells in Multiple Sclerosis. Cell. 2018;175(1):85-100 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, Johns J, Cook KF, et al. Standardizing fatigue measurement in multiple sclerosis: the validity, responsiveness and score interpretation of the PROMIS SF v1.0 - Fatigue (MS) 8a. Mult Scler Relat Disord. 2021;54.

Kamudoni P, Amtmann D, Johns J, et al. The validity, responsiveness, and score interpretation of the PROMISnq Physical Function - Multiple Sclerosis 15a short form in multiple sclerosis. Mult Scler Relat Disord. 2022;62.

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

Kuhle J, Barro C, Disanto G, et al. Serum neurofilament light chain in early relapsing remitting MS is increased and correlates with CSF levels and with MRI measures of disease severity. Mult Scler. 2016;22:1550–9.

Kuhle J, Kappos L, Montalban X, et al. The Effect of Evobrutinib, a BTK Inhibitor, on Blood Neurofilament Light Chain Levels in Relapsing Multiple Sclerosis. AAN 2021.Neurology. 2021;96(22):e2785.

Kuhle J, Nourbakhsh B, Grant D, et al. Serum neurofilament is associated with progression of brain atrophy and disability in early MS. Neurology. 2017;88:826–31.

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):189-201.

Lechner-Scott J, Kappos L, Hofman M, et al. Can the Expanded Disability Status Scale be assessed by telephone? Mult Scler. 2003 Mar;9(2):154-9.

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. J. Leukoc Biol. 2014;95:243-50.

Maghzi AH, Houtchens MK, Preziosa P, et al. COVID-19 in teriflunomide-treated patients with multiple sclerosis. J Neurol. 2020;267(10):2790-6.

Martin SA, Olayinka-Amao OC, Henke C, et al. Conceptual Model and Instrument Review in Multiple Sclerosis. Value Health 2017;20(9):A726-7.

McHorney CA, Ware JE Jr, Rachel Lu JF, et al. The MOS 36-item short-form health survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. Med Care. 1994;32(1):40-66.

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(5):MS253-65.

McHorney CA, Ware JE, Raczek AE. The MOS 36-item short-form health survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care. 1993;31(3):247-63.

Möhn N, Saker F, Bonda V, et al. Mild COVID-19 symptoms despite treatment with teriflunomide and high-dose methylprednisolone due to multiple sclerosis relapse. J Neurol. 2020; Oct;267(10):2803-5.

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.

Montalban X, Shaw J, Dangond F, et al. Effect of evobrutinib, a BTK inhibitor, on immune cell and immunoglobulin levels in relapsing MS: an open-label extension to a phase II study. Presented at MS Virtual 2020: 8th Joint ACTRIMS-ECTRIMS Meeting, 9—12 September.

MS International Federation available at http://www.msif.org/wp-content/uploads/2020/06/MSIF-Global-advice-on-COVID-19-for-people-with-MS-_-updated17June2020.pdf.

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. Accessed 11 April 2019.

Novakova L, Zetterberg H, Sundström P, et al. Monitoring disease activity in multiple sclerosis using serum neurofilament light protein. Neurology. 2017;89:2230–7.

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.

Piehl F, Kockum I, Khademi M, et al. Plasma neurofilament light chain levels in patients with MS switching from injectable therapies to fingolimod. Mult Scler. 2018; 24:1046–54.

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 VV. 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.

Scarfò L, Chatzikonstantinou T, Rigolin GM, et al. COVID-19 severity and mortality in patients with chronic lymphocytic leukemia: a joint study by ERIC, the European Research Initiative on CLL, and CLL Campus. Leukemia. 2020; 34(9):2354-63.

Teriflunomide (Aubagio®) SmPC. https://www.ema.europa.eu/en/medicines/human/EPAR/aubagio. Last accessed on 25 November, 2019.

Teriflunomide (Aubagio®) USPI. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=202992. Last accessed on 25 November, 2019.

Thibaud S, Tremblay D, Bhalla S, et al. Protective role of Bruton tyrosine kinase inhibitors in patients with chronic lymphocytic leukaemia and COVID-19. Br J Haematol. 2020; Jul;190(2):e73-6.

Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018;17(2):162-73.

Torke S, Grenningloh R, Boschert U, et al. Inhibition of Bruton's tyrosine kinase selectively prevents antigen-activation of B cells and ameliorates B cell-mediated experimental autoimmune encephalomyelitis. University Medical Center, Gottingen, Germany. 2018 P575.

Treon SP, Castillo JJ, Skarbnik AP, et al. The BTK inhibitor ibrutinib may protect against pulmonary injury in COVID-19-infected patients. Blood. 2020;135(21):1912-15. doi:10.1182/blood.2020006288.

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

Ware JE, Sherbourne CD. The MOS 36-ltem Short-Form Health Survey (SF-36) I. Conceptual Framework and Item Selection. Med Care. 1992;30(6):473-83.

Whang JA, Chang BY. Brutons tyrosine kinase inhibitors for the treatment of rheumatoid arthritis. Drug Discovery Today. 2014, doi:10.1016/j.drudis.

WHO Guidelines on Tuberculosis Infection Prevention and Control. 2019 Update. Geneva. World Health Organization. 2019.

WHO TB Burden Estimates. https://extranet.who.int/tme/generateCSV.asp?ds=estimates. Last accessed on 07 October 2022.

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.

11 Appendices

Appendix 1 Abbreviations

9-HPT	9 Hole Peg Test
ACTH	Adrenocorticotropic hormone
AE	Adverse Event
AEP	Accelerated elimination procedure
AESI	Adverse Event of Special Interest
ALT	Alanine aminotransferase
ARR	Annualized Relapse Rate
AST	Aspartate aminotransferase
AUC	Area under the curve
BEA	Blinded Extension Analysis
BSSR	Blinded Sample Size Re-estimation
BTK	Bruton's Tyrosine Kinase
BV	Brain volume
CBF	Cerebral blood flow
CDI	Confirmed disability improvement
CDP	Confirmed disability progression
CFB	Change from Baseline
CI	Confidence interval
CL/f	The apparent total body clearance of study intervention following extravascular administration
C_{max}	Maximum evobrutinib concentration
CMV	Cytomegalovirus
CNS	Central nervous system
COVID	Coronavirus disease
CRF	Case Report Form
CSF	Cerebrospinal fluid
CSF JCV PCR	Cerebrospinal fluid JC virus polymerase chain reaction
CSR	Clinical study report

C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CUA	Combined unique active
CYP3A	Cytochrome P450 3A
DBE	Double-blind extension
DBTP	Double-blind Treatment Period
DDI	Drug-drug interactions
DILI	Drug induced liver injury
DMT	Disease-modifying therapy
EA	Early antigen
EAC	Endpoint Adjudication Committee
EBNA	Epstein-Barr Nuclear Antigen
EBV	Epstein-Barr virus
ECG	Electrocardiogram
EDC	Electronic Data Capture
EDSS	Expanded Disability Status Scale
EODBTP	End-of-DBTP
EODBE	End-of-DBE
eGFR	Estimated glomerular filtration rate
EQ-5D-5L	EuroQoL 5 Dimension 5 Levels
FAS	Full Analysis Set
FDA	Food and Drug Administration
FLAIR	Fluid-attenuated inversion recovery
FSH	Follicle-stimulating hormone
FSS	Functional system scores
GCP	Good Clinical Practice
Gd	Gadolinium
HAC	Hepatology Assessment Committee
HAV	Hepatitis A Virus
HBc	Hepatitis B Core Antigen
HBV	Hepatitis B Virus

HCV	Hepatitis C virus
HEV	Hepatitis E Virus
HFE	High Iron Fe (human hemochromatosis protein)
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life
HRT	Hormonal replacement therapy
HRU	Health Resource Utilization
IA	Interim analysis
IAP	Integrated Analysis Plan
ICF	Informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IMP	Investigational medicinal product
IRB	Institutional Review Board
IWRS	Interactive Web Response System
JCV	John Cunningham virus
LFT	Liver function test
LTBI	Latent TB infection
MAR	Missing at random
MedDRA	Medical Dictionary of Regulatory Activities
MMRM	Mixed effect model for repeated measures
MRI	Magnetic Resonance Imaging
MS	Multiple sclerosis
nT1	Normalized T1
NAWM	Normal appearing white matter
NB	Negative binomial
NBV	Normalized brain volume
NCI	National Cancer Institute
NEDA	No evidence of disease activity

NEP	No evidence of progression
NEPAD	No evidence of progression or active disease
NfL	Neurofilament light chain
NK	Natural killer
OLE	Open Label Extension
PA	Primary Analysis
PBVC	Percent brain volume change
PCR	Polymerase chain reaction
PF	Physical function
PIRA	Progression Independent of Relapse Activity
PIRMA	Progression Independent of Relapse and Brain Magnetic Resonance Imaging Activities
PK	Pharmacokinetics
PML	Progressive multifocal leukoencephalopathy
PPD	Purified protein derivative
PRL	Phase rim lesions
PRO	Patient Reported Outcomes
PROMIS	Patient Reported Outcomes Measurement Information System
QoL	Quality of Life
QTL	Quality tolerance limits
RA	Rheumatoid arthritis
RMS	Relapsing multiple sclerosis
SAE	Serious Adverse Event
SARS-CoV-2	Severe acute respiratory syndrome-coronavirus-2
SCR	Screening
SDMT	Symbol Digit Modalities Test
SEL	Slowly expanding lesions
SF-36v2	36-Item Short Form Survey Instrument Version 2
SLE	Systemic lupus erythematosus
SmPC	Summary of Product Characteristics
SoA	Schedule of activities
SOC	System Organ Class

SPMS	Secondary progressive multiple sclerosis
SSC	Study Steering Committee
SUSAR	Suspected Unexpected Serious Adverse Reaction
T25-FW	Timed 25-Foot Walk
TB	Tuberculosis
TEAE	Treatment emergent adverse event
ULN	Upper limit of normal
USPI	United States Prescribing Information
USSR	Unblinded Sample Size Re-estimation
VCA	Viral capsid antigen
$V_{z/f}$	The apparent volume of distribution during the terminal phase following extravascular administration
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; 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 reconsented 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 (see Section 1.3) for details. Participants must fulfill all entry criteria for participation in the study.
- The screening period may be extended to a total period of 12 weeks after approval by the Medical Monitor (see Section 8). The following should be performed:
  - An Eligibility Review Form [ERF] 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 and pregnant partners (if applicable), who will be required to give consent for their data to be used, as specified in the informed consent.
- 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 200 global sites anticipated from approximately 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 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 IDMC, HAC, EAC, and SSC will perform specific study-related activities as detailed in each committee's charter (see Section 8.2.8).

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 Pharmacy 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 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 Pharmacy 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.
- QTLs will be predefined and documented in the applicable project management database to help support the identification of systematic issues that could potentially impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study and important deviations from the QTL thresholds and remedial actions taken will be summarized in the clinical study report.
- 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, including but not limited to new or emerging safety information that negatively affects the benefit/risk assessment of the clinical study. 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.
- If the study is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator will promptly inform the participants and assure appropriate participant therapy and/or follow-up.

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 nonestrogen 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[a]
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)[a]
- Bilateral tubal occlusion
- Vasectomized partner[b]: 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[a]
  - Oral
  - Intravaginal
  - Transdermal
  - Injectable
- Progestogen-only hormone contraception associated with inhibition of ovulation[a]
  - 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

a 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 coadministration 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 [a], 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.

Teriflunomide may increase the systemic exposures of ethinylestradiol and levonorgestrel. Consideration should be given to the type or dose of contraceptives used in combination with teriflunomide (see Appendix 9 and refer to the locally approved product information [e.g., relevant SmPC or USPI]). There was an increase in mean ethinylestradiol C_{max} and AUC_{0-24} (1.58- and 1.54-fold, respectively) and levonorgestrel C_{max} and AUC_{0-24} (1.33- and 1.41-fold, respectively) following repeated doses of teriflunomide.

b If a WOCBP participant is using a highly effective method other than sexual abstinence or vasectomized partner, AND ALSO has a vasectomized partner, the vasectomized partner will be considered the “barrier method” for study purposes.

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.

Periodic abstinence (calendar, symptothermal, postovulation 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 NCI-CTCAE, version 5.0 (publication date: 27 November 2017), 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 nonstudy 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 teriflunomide) 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. Worsening of the underlying disease is not routinely to be considered an AE or SAE, but is rather an efficacy endpoint, unless deemed to be causally related to the IMP. However, if significant adverse signs or symptoms occur in association with complications or a prolonging of a hospitalization originally due to relapse or disease progression, then these specific complications or hospital prolongation events should be recorded as AEs.

Adverse Events of Special Interest

Adverse events of special interest are liver AEs (possible drug-induced, non-infectious, non-alcoholic, and immune-mediated), infections (serious and opportunistic infections), lipase and amylase elevation, and seizure, as described in Section 6.9.

Other Adverse Events to be Reported Following a Specialized Procedure

The following procedures should be followed for reporting overdoses (refer to 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.
- 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 inform the Sponsor or its designee using the electronic SAE report form in the Electronic Data Capture (EDC) system. The site will enter into the electronic system the SAE data within 24 hours after becoming aware of the event. It is expected that the investigator/sub-investigator signs off this data in the system and any relevant associated data (e.g., additional laboratory tests, medical records, diagnostic reports, histopathological examinations, or consultation with other health care professionals) will be entered as soon as it becomes available.

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 global patient safety department may contact the Investigator directly to obtain further information or to discuss the event.

Adverse Events of Special Interest

For a non-serious AESI, the site will complete the specific AESI report form and notify the Sponsor immediately (within 24 hours), using the same process for reporting SAEs, as specified above.

For a serious AESI, the site will complete an SAE report form, using the SAE reporting process, specified above.

Suspected Unexpected Serious Adverse Reactions (SUSARs)

Individual Case Safety Reports will be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators within 15 days.

An Investigator or sub-investigator who receives an Individual Case Safety Report describing a SUSAR or other specific safety information (e.g., Emerging Safety Issue Report, summary or listing of SAEs/SUSARs) from the Sponsor will review the safety reports and confirm completion of this review. This information will be filed it in the Investigator's Site File, and the IRB/IEC will be notified, if appropriate, according to applicable local laws/regulations and site SOPs.

Appendix 5 Clinical Laboratory Tests

Table 5 Protocol-Required Clinical Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet count		Mean Corpuscular Volume (MCV)	White Blood Cell (WBC) Count with Differential: • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils
	Reticulocytes			
	Hemoglobin		Mean corpuscular hemoglobin (MCH)	
	Hematocrit		Mean corpuscular hemoglobin concentration (MCHC)	
	Erythrocytes			
LFT visits	Aspartate aminotransferase		γ-Glutamyl-transferase	Bilirubin, total
	Alanine aminotransferase		Alkaline phosphatase	
Biochemistry	Blood Urea Nitrogen	Potassium	Aspartate Aminotransferase	Bilirubin, total
	Creatinine and eGFR calculation	Sodium	Alanine Aminotransferase	Protein, total
	Glucose	Calcium	Alkaline phosphatase	Albumin
	Chloride	Lactate dehydrogenase	Lipase	Amylase
		Magnesium	Total carbon dioxide	Phosphate
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.				
Hepatic/Autoimmune Panel (to be performed in the event of elevated LFTs, see Section 7.1)	Antinuclear antibody, antismooth muscle antibody, antibody to liver kidney microsomes	Alkaline phosphatase, Albumin, ALT, AST, GGT, and total bilirubin	Anti-HAV IgM, HBsAg, anti-HBc IgM, anti- HBsAg, anti-HCV, anti-HEV IgG and IgM, anti-VCA IgG and IgM, anti-EA IgG, anti-EBNA IgG, anti-CMV IgG and IgM, EBV PCR, and CMV PCR	
	Ferritin/ Transferrin saturation[b]	Fibrinogen, hsCRP	Focused Genetic Testing[b]	
	Hepatitis C ViRNA PCR			
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, by dipstick • Microscopic examination (if blood or protein is abnormal)			
Reflex Testing for HBV DNA	• Hepatitis B Virus DNA PCR			
Other Tests	• QuantiFERON TB testing for high TB burden countries			

Laboratory Assessments	Parameters
	• 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. • Teriflunomide levels[c] • B, T and NK cell absolute count[f] • Immunoglobulin (IgM, IgA, IgG, and IgE)[f] • Teriflunomide plasma concentration related to AEP[f]
Other Screening Tests	• Serology (hepatitis C virus antibodies, hepatitis B virus antibodies, HIV testing[d], hepatitis B surface antigen, hepatitis C virus RNA PCR, QuantiFERON TB test) • FSH (as needed if **not** a WOCBP **only**)[e] • Serum pregnancy test (as needed for a WOCBP) • Ferritin and transferrin saturation • JC virus DNA PCR to be performed if MRI has findings suggestive of progressive multifocal leukoencephalopathy • All study-required laboratory assessments will be performed by a central laboratory, except for urine dipstick (microscopic examination done centrally), urine pregnancy, and T-SPOT

AEP = accelerated elimination procedure, ALT = alanine transaminase, AST = aspartate aminotransferase, βhCG = β-Human Chorionic Gonadotropin, CMV = Cytomegalovirus, DNA = deoxyribonucleic acid, EA = Early Antigen, EBV = Epstein–Barr virus, EBNA = Epstein-Barr Nuclear Antigen, eGFR = Estimated Glomerular Filtration Rate, FSH = Follicle Stimulating Hormone, GGT = gamma-glutamyl transferase, 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, MCH = mean corpuscular hemoglobin, MCHC = mean corpuscular hemoglobin concentration, PCR = polymerase chain reaction, TB = tuberculosis, VCA = Viral Capsid Antigen, 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 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.

c During the DBTP, teriflunomide level determination might be completed for safety reasons only. Teriflunomide levels will be determined in all participants planning to enter the OLE.

d HIV testing will be done at Screening centrally, unless indicated otherwise by local regulations.

e Exam not applicable to participants in the OLE Period.

f Only applicable to participants in the OLE Period.

Appendix 6 Pharmacogenetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to therapy, susceptibility to, and severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact study intervention absorption, distribution, metabolism, and excretion; mechanism of action of the study intervention; disease etiology; and/or molecular subtype of the disease being treated.
- DNA samples may be used for research related to pharmacokinetics, safety endpoints, drug response, and treatment efficacy of evobrutinib or MS and related diseases. They may also be used to develop tests or assays, including diagnostic tests related to pharmacokinetics, safety endpoints, drug response, and treatment efficacy of evobrutinib and MS. Pharmacogenetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- The results of pharmacogenetic analyses may be reported in the CSR or in a separate study summary.
- Details on processes for collection and shipment of these samples can be found in the Laboratory Manual. The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- Retention time and possible analysis of DNA sample after the study ends are specified in the respective ICF.

Appendix 7 Guidance for Diagnosis of PML

The safety monitoring algorithm presented in Figure 4 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 EDSS score at the scheduled 12-week visit or in the event of new/worsening symptoms. This exam requires that 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 4).

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 CSF for the detection of JCV DNA should be undertaken (performed by central laboratory). A diagnosis of PML can potentially be made by evaluating clinical and MRI findings plus the identification of JCV in the CSF.

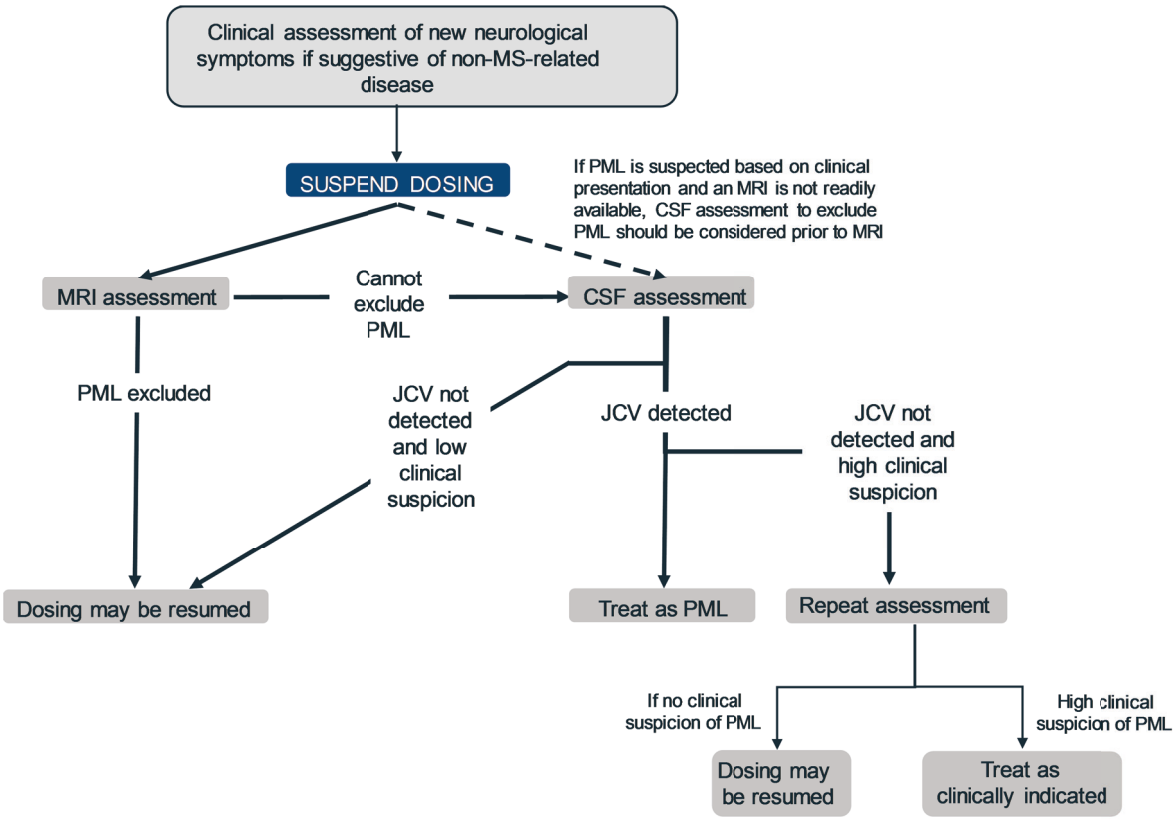
MRI Assessments

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 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.
- CSF will be analyzed centrally.

Figure 4 Diagnostic Algorithm for PML – Suggested Diagnostic Algorithm



CSF = cerebrospinal fluid, JCV = JC virus, MRI = Magnetic Resonance Imaging, MS = multiple sclerosis, PML = progressive multifocal leukoencephalopathy.

Appendix 8 Procedure for Accelerated Elimination of Teriflunomide

Teriflunomide is eliminated slowly from the plasma based on the teriflunomide SmPC and teriflunomide USPI. Without an accelerated elimination procedure (AEP), it takes on average 8 months to reach plasma concentrations < 0.02 mg/L, although because of individual variations in drug clearance it may take as long as 2 years. An AEP could be used at any time after discontinuation of teriflunomide. Elimination can be accelerated by either of the following procedures, or as per local standard of care:

- Administration of cholestyramine 8 g every 8 hours for 11 days. If cholestyramine 8 g three times a day is not well tolerated, cholestyramine 4 g three times a day can be used.
- Administration of 50 g oral activated charcoal powder every 12 hours for 11 days.

If either elimination procedure is poorly tolerated, treatment days do not need to be consecutive unless there is a need to lower teriflunomide plasma concentration rapidly. At the end of 11 days, both regimens successfully accelerated teriflunomide elimination, leading to more than 98% decrease in teriflunomide plasma concentrations. Use of the AEP may potentially result in return of disease activity if the participant had been responding to treatment with teriflunomide.

In accordance with the teriflunomide prescribing information, it is recommended to confirm a teriflunomide level of < 0.02 mg/L after the AEP if the AEP is being done for pregnancy-related considerations. All participants previously treated with teriflunomide, or with an unknown exposure status during the DBTP and DBE period entering the OLE, should undergo mandatory AEP (all genders) upon completion of the DBE period. The Investigator should dispense cholestyramine or activated charcoal and to instruct participant about proper intake. The blood concentration of teriflunomide has to be verified upon completion of the AEP via blood sample collection between Day 12 to Day 30 at the central laboratory. The Investigator will remain blinded to the teriflunomide levels. Please refer to the study-specific central laboratory manual for detailed information on the teriflunomide blood level testing. If the AEP is being done for any other safety reason (e.g., elevated LFTs), a level can be obtained after the AEP, but is not required.

Appendix 9 Teriflunomide Drug-Drug Interactions

Teriflunomide has the potential for drug interactions and due to the blinded treatment assignment, these should be considered when treating participants. The following are the potential drug interactions as defined in the teriflunomide USPI (teriflunomide USPI).

DRUG INTERACTIONS

Effect of AUBAGIO on CYP2C8 Substrates

- Teriflunomide is an inhibitor of CYP2C8 in vivo. In patients taking AUBAGIO, exposure of drugs metabolized by CYP2C8 (e.g., paclitaxel, pioglitazone, repaglinide, rosiglitazone) may be increased. Monitor these patients and adjust the dose of the concomitant drug(s) metabolized by CYP2C8 as required.

Effect of AUBAGIO on Warfarin

- Coadministration of AUBAGIO with warfarin requires close monitoring of the INR because AUBAGIO may decrease peak INR by approximately 25%.

Effect of AUBAGIO on Oral Contraceptives

- AUBAGIO may increase the systemic exposures of ethinylestradiol and levonorgestrel. Consideration should be given to the type or dose of contraceptives used in combination with AUBAGIO.

Effect of AUBAGIO on CYP1A2 Substrates

- Teriflunomide may be a weak inducer of CYP1A2 in vivo. In patients taking AUBAGIO, exposure of drugs metabolized by CYP1A2 (e.g., alosetron, duloxetine, theophylline, tizanidine) may be reduced. Monitor these patients and adjust the dose of the concomitant drug(s) metabolized by CYP1A2 as required.

Effect of AUBAGIO on Organic Anion Transporter 3 (OAT3) Substrates

- Teriflunomide inhibits the activity of OAT3 in vivo. In patients taking AUBAGIO, exposure of drugs which are OAT3 substrates (e.g., cefaclor, cimetidine, ciprofloxacin, penicillin G, ketoprofen, furosemide, methotrexate, zidovudine) may be increased. Monitor these patients and adjust the dose of the concomitant drug(s) which are OAT3 substrates as required.

Effect of AUBAGIO on BCRP and Organic Anion Transporting Polypeptide B1 and B3 (OATP1B1/1B3) Substrates

- Teriflunomide inhibits the activity of BCRP and OATP1B1/1B3 in vivo. For a patient taking AUBAGIO, the dose of rosuvastatin should not exceed 10 mg once daily. For other substrates of BCRP (e.g., mitoxantrone) and drugs in the OATP family (e.g., methotrexate, rifampin), especially HMG-Co reductase inhibitors (e.g., atorvastatin, nateglinide, pravastatin, repaglinide, and simvastatin), consider reducing the dose of these drugs and monitor patients closely for signs and symptoms of increased exposures to the drugs while patients are taking AUBAGIO.

DRUG INTERACTION STUDIES

- Teriflunomide is not metabolized by Cytochrome P450 or flavin monoamine oxidase enzymes.

The potential effect of AUBAGIO on other drugs:

- CYP2C8 substrates
    - There was an increase in mean repaglinide C_{max} and AUC (1.7- and 2.4-fold, respectively) following repeated doses of teriflunomide and a single dose of 0.25 mg repaglinide, suggesting that teriflunomide is an inhibitor of CYP2C8 in vivo. The magnitude of interaction could be higher at the recommended repaglinide dose.
- CYP1A2 substrates
    - Repeated doses of teriflunomide decreased mean C_{max} and AUC of caffeine by 18% and 55%, respectively, suggesting that teriflunomide may be a weak inducer of CYP1A2 in vivo.
- OAT3 substrates
    - There was an increase in mean cefaclor C_{max} and AUC (1.43- and 1.54-fold, respectively), following repeated doses of teriflunomide, suggesting that teriflunomide is an inhibitor of organic anion transporter 3 (OAT3) in vivo.
- BCRP and OATP1B1/1B3 substrates
    - There was an increase in mean rosuvastatin C_{max} and AUC (2.65- and 2.51-fold, respectively) following repeated doses of teriflunomide, suggesting that teriflunomide is an inhibitor of BCRP transporter and organic anion transporting polypeptide 1B1 and 1B3 (OATP1B1/1B3).
- Oral contraceptives
    - There was an increase in mean ethinylestradiol C_{max} and AUC0-24 (1.58- and 1.54-fold, respectively) and levonorgestrel C_{max} and AUC0-24 (1.33- and 1.41-fold, respectively) following repeated doses of teriflunomide.
- Teriflunomide did not affect the pharmacokinetics of bupropion (a CYP2B6 substrate), midazolam (a CYP3A4 substrate), S-warfarin (a CYP2C9 substrate), omeprazole (a CYP2C19 substrate), and metoprolol (a CYP2D6 substrate).

The potential effect of other drugs on AUBAGIO

- Potent CYP and transporter inducers: Rifampin did not affect the pharmacokinetics of teriflunomide.

Appendix 10 Structured Interview at Telephone Contact

The primary purpose of this interview is to identify any new or worsening neurological symptoms that warrant evaluation at an unscheduled visit. Structured interviews should be performed by study personnel between clinic visits – see also Section 1.3 and Section 8.

Telephone contacts between D1 and W44 are not expected to occur every 4 weeks, since participants are scheduled to be on site at least every 4 weeks. However, if a participant is utilizing the home visit option, telephone contacts should occur as indicated in the SoA. Telephone contacts between W44 and W156 should occur every 4 weeks if a clinic visit is not scheduled.

If the participant is a woman of childbearing potential, please remember to confirm completion of home pregnancy testing and discuss results.

Please ask the following questions and record participant's answers during the Structured Interview:

#	Question:	No	Yes
1	Since your last visit or structured interview, have you had any new or worsening medical problems (such as sudden changes in your thinking, alterations in your behavior, visual disturbances, extremity weakness, limb coordination problems, or gait abnormalities) that have persisted over several days?		
2	Since your last visit or structured interview, have you taken any new medicines or had any changes in your medicines?		
3	Since your last visit or structured interview, have you had any notable medical events (e.g. new or changed signs or symptoms, procedures, injuries, or laboratory tests/imaging outside of the study)		

If the participant answered YES to any question, the interviewer should contact the Treating Investigator and review the participant's answers. The Treating Investigator should determine if an unscheduled visit is required.

Record any pertinent comments made by the participant during the interview:

_____

_____

_____

NAME:_____ Date:_____

Name of individual completing the structured interview

Appendix 11 Guidance on Clinically Relevant CYP Inducers, Inhibitors, and Substrates

For further information and examples of clinically relevant CYP inducers, inhibitors, and substrates, please refer to the applicable tables from the FDA's *Drug Development and Drug Interactions*.

Clinically relevant inducers:

https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-3

Clinically relevant inhibitors:

https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-2

Clinically relevant sensitive substrates:

https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-1

Appendix 12 Protocol Amendment History

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

Protocol Version 5.2-CZE (16 March 2023)

This amendment is non-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

The primary purpose of this amendment is:

- Clarification of language regarding Investigator access to MRI scans during the OLE period

A high-level description of each change is summarized below, along with its rationale.

Section # and Name	Description of Change	Brief Rationale
8.1.2 Brain Magnetic Resonance Imaging Scans	• Added clarification that the Investigator will have full access to the results of the MRI scans during the OLE period, starting with the first MRI assessment in the OLE period at Week 48	Updated text to clarify that the Investigator will have access to the full MRI reports during the OLE period including MS-related pathology. As the EOT MRI of the DBTP is used as baseline for OLE period, this MRI will remain blinded to MS pathology to ensure the integrity of the DBTP.

Protocol Version 5.1-LTU (18 December 2022)

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

The primary purpose of this amendment is to align the Lithuania-specific protocol with Version 5.0 (global Protocol Version 5.0; 08 December 2022), in which the following key changes were implemented:

- Introduction of an OLE period for participants completing the DBTP prior to approval of the long-term follow-up study in their country to enable an option for evobrutinib treatment continuation
- Addition of the following exploratory endpoints:
  - Time to PIRA and time to PIRMA (to evaluate the effect of treatment on progression not driven by relapse events or MRI activity)
  - NEP at Weeks 48, 96
  - Level of anti-SARS-CoV-2 antibodies

A high-level description of each change is summarized below, along with its rationale.

1.1 Synopsis	• Changes as per the main protocol text	For consistency with the main protocol text.
1.2 Schema	• Updated to include OLE period and information about transfer points to long-term follow-up study	Introduction of OLE period to allow participants to continue evobrutinib treatment if separate long-term follow-up study is not approved in their country. To provide further clarity of transitioning into the long-term follow-up study.
1.3.1 Schedule of Activities – Double-blind Treatment Period	• Clarification that no telephone visits are to be performed in the study, but rather telephone contacts • Clarification that telephone contacts should occur every 4 weeks through Week 156	The term “telephone visit” was replaced with “telephone contact”, to clarify that a phone call is not replacing an on-site visit, because only limited topics are to be addressed during those calls. To clarify study procedures.
	• Urine pregnancy tests every 4 weeks from Week 108 to Week 156 were added • Notes for coagulation tests were added • Urinalysis (local) and vital signs were added at Week 156	To clarify study procedures.
	• Clarification that the hepatic/autoimmune panel includes focused genetic testing (e.g., HFE) and that samples will only be collected and analyzed if elevated LFTs are observed	To clarify that the hepatic/autoimmune panel performed in case of elevated LFTs contains a component of focused genetic testing. To clarify sample collection.
	• Removal of IP dispensation at Week 156	To clarify study procedures.
	• Clarification that ECG is to be performed at Week 96	Assessment at Week 96 was inadvertently omitted from previous protocol version (4.0); therefore, has been added to correct this inconsistency in study procedures.
	• Included detailed description of sample collection and use of novel liver function protein biomarkers	To clarify sample collection.
	• Included information that during unscheduled visits for relapse, EDSS assessment is required	To clarify study procedures.
	• Included specification that novel liver function protein biomarkers were analyzed from serum, whereas novel liver function genomic biomarkers were analyzed from plasma	To clarify distinction between samples.
1.3.2 Schedule of Activities – Open-label Extension Period	• Schedule of Activities for OLE period added	To define study procedures to be conducted during the OLE period.
2.3 Benefit/Risk Assessment	• Updated number of participants in ongoing and completed clinical studies with evobrutinib	For consistency with the most recent IB and DSUR.

3 Objectives and Estimands	• Addition of exploratory endpoints: NEP at Weeks 48 or 96, Time to PIRA and PIRMA, level of anti-SARS-CoV-2 antibodies	NEP at Weeks 48 or 96 added to exploratory endpoints to further evaluate the effect of treatment on disease activity. Time to PIRA and time to PIRMA added to exploratory endpoints to evaluate the effect of treatment on progression not driven by relapse events or MRI activity. Level of anti-SARS-CoV-2 antibodies added to evaluate the impact of evobrutinib on COVID-19 vaccinations.
	• Updated the PF deterioration definition to a reduction of at least 2.7 points on PROMIS PF score	For consistency with the most recent IAP (version 2) and latest publication as 5 points was provisional.
	• Addition of Objectives and Endpoints table for the OLE Period	For consistency with the changes implemented in Section 1.2.
4.1 Study Design	• Text revised to include OLE period and AEP	Introduction of OLE for participants completing the DBTP prior to approval of the long-term follow-up study in their country to enable an option for evobrutinib treatment continuation.
4.2 Scientific Rationale for Study Design	• Text revised to include rationale for inclusion of OLE period.	To define the rationale for the OLE period.
4.4 End of Study Definition	• Included End of Study Definition to OLE Period	To define treatment completion for OLE period.
5.3 Criteria for Entry into Open-label Extension Period 5.3.1 Inclusion Criteria for Open-label Extension Period 5.3.2 Exclusion Criteria for Open-label Extension Period	• Added inclusion and exclusion criteria for entering into the OLE Period	For consistency with the changes implemented in Section 1.2 and Section 4.1.
5.4.2 Caffeine, Alcohol, and Tobacco	• Text added to clarify alcohol consumption should be avoided during the study	To clarify study procedures.
6.3.2 Blinding	• Clarification on blinding procedures for the bioanalytical laboratory	To clarify study procedures.
	• Removal of Assignment Method Retention	To clarify study procedures.
6.5.3 Prohibited Medicines	• Clarification for administration of prohibited medications (dalfampridine and CYP2C8 substrates) during the OLE Period of the study	To specify changes in prohibited medications during OLE period of the study.
7.1 Discontinuation of Study Intervention	• Modification of criteria leading to permanent IMP discontinuation after extended interruption beyond 30 days	To control the duration of IMP interruption to ensure an adequate safety monitoring as well as the data integrity impacted by the external uncontrolled situation (e.g., military, geopolitical conflicts)

	• Addition of 2 new bullet points to include individual ALT/AST and individual total bilirubin elevation as criteria for permanent discontinuation of study treatment	To further clarify that elevated levels of ALT/AST and bilirubin may not need to occur simultaneously to trigger permanent discontinuation of study treatment.
	• Text added to clarify liver function testing criteria	To further clarify that confirmatory laboratory testing will be needed after initial elevation of ALT/AST levels before interruption of study intervention.
8 Study Assessments and Procedures	• Addition of assessments in the OLE Period • Addition of text describing AEP procedure • Included information that during unscheduled visits for relapse, EDSS assessment is required • Clarification that no telephone visits are to be performed in the study, but rather telephone contacts	For consistency with changes implemented in the Section 1.2 and Section 4.1. To provide guidance on the AEP procedure required for the OLE period. To clarify study procedures. The term “telephone visit” was replaced with “telephone contact”, to clarify that a phone call is not replacing an on-site visit, because only limited topics are to be addressed during those calls.
8.1.1 Neurological Assessment	• Addition of details for neurological assessments performed in the OLE Period	For consistency with changes implemented in Section 1.2 and Section 4.1.
8.1.1.1. Qualified Relapse	• Addition of further clarification on qualification of relapses	For consistency with changes implemented in Section 1.2 and Section 4.1.
8.1.1.4 Timed Twenty-Five Foot Walk 8.1.1.5 Nine Hole Peg Test 8.1.1.6 Symbol Digit Modalities Test	• Added clarification that these assessments will be administered by qualified non-blinded site personnel during OLE period	For consistency with changes implemented in Section 1.2 and Section 4.1.
8.1.2 Brain Magnetic Resonance Imaging Scans	• Correction of Screening MRI instructions and clarification on the blinding of MRI reports to the Treating Investigator • Added details regarding MRI assessments in a respective OLE MRI substudy	Correction of erroneous text. Updated text to clarify that the study-related local radiologist’s MRI reports should not include details on MS-related pathology findings. MRI assessments in OLE Period were introduced according to changes made in Section 1.2 and Section 4.1.
8.1.3.1 Patient Reported Outcomes Measurement Information System	• Updated the PF deterioration definition to a reduction of at least 2.7 points on PROMIS PF score	For consistency with the most recent IAP (version 2) and latest publication as 5 points was provisional.
8.1.3.4 WPAI: MS v2.0 (for OLE period only)	• Added Work Productivity and Activity Impairment Questionnaire for assessment in the OLE Period	To characterize the associations of work productivity and absenteeism with disability, fatigue, cognition, and health-related quality of life.
8.2.3 Electrocardiograms	• Added clarification to reflect that no central ECG evaluation by central reader is required in the OLE period	According to changes introduced in Section 1.2 and Section 4.1.
8.2.4 Clinical Safety Laboratory Assessments	• The volume of whole blood collected for HBV DNA was increased to 4 mL	To correct details of blood volume collection.

8.2.8 Independent Data Monitoring Committee, Endpoint Adjudication Committee, and Study Steering Committee	• Added clarification that the EAC will be disbanded after the DBTP has ended as relapses will be qualified by the treating investigators in the OLE period	According to changes introduced in Section 1.2 and Section 4.1.
8.3.5 Pregnancy	• Added clarification that participants who intend to become pregnant during the study will be discontinued study intervention	To clarify study procedures.
8.5 Pharmacokinetics	• Added clarification that no blood samples for PK analysis will be collected from participants enrolled in the OLE	According to changes introduced in Section 1.2 and Section 4.1.
8.8 Biomarkers 8.8.1 Biomarkers of Disease, Disease Activity and Progression, Drug-related Outcomes, and Treatment Response 8.8.1.2 Novel Liver Function Biomarkers 8.8.2 OLE Blood Biomarker PD Substudy – Biomarkers of Disease Activity, Progression and Response to Drug 8.8.3 Gene Expression	• Include the option to repurpose biomarker-of-disease-samples or NfL-biomarker samples for vaccination testing • Specification for collection of samples in OLE Period and OLE PD Substudy was added • Collection and analysis of samples for assessment of Novel Liver Function Protein Biomarkers and for gene expression analysis during OLE Period was added	Evaluating the impact of disease-modifying MS therapies on vaccinations has taken on greater importance during the COVID-19 pandemic. To reflect assessment in OLE Period and to clarify that blood samples for gene expression will not be collected on OLE Period.
9.2.3 Sample Size Considerations due to the Currently Escalating Crisis in Eastern Europe	• Text was added to clarify enrollment numbers in the crisis region	To clarify sample size considerations.
9.3 Populations for Analyses	• Added population for analysis during OLE Period	According to changes introduced in Section 1.2 and Section 4.1.
9.4.1 Efficacy Analyses	• Added description of analyses of tertiary/exploratory endpoints NEP, Time to PIRA, Time to PIRMA, level of anti-SARS-CoV-2 antibodies, and NfL concentrations at additional timepoints	For consistency with tertiary/exploratory objectives in Section 3.
9.4.3.5 Analysis of Open-label Extension Period Endpoints	• Added specification of OLE Endpoints	According to changes introduced in Section 1.2 and Section 4.1.
9.4.4 Sequence of Analyses	• Final analysis was added according to added OLE Period	According to changes introduced in Section 1.2 and Section 4.1.
Appendix 5 Clinical Laboratory Tests	• Added tests that will be only applicable to participants in the OLE Period, and indicated the tests that will not be applicable to those participants • Changes made to align with long-term follow-up protocol language	According to changes introduced in Section 1.2.
Appendix 8 Procedure for Accelerated Elimination of Teriflunomide	• Clarification added to specify mandatory AEP procedure for participants entering OLE Period	According to changes introduced in Section 1.2 and Section 4.1.

Appendix 10 Structured Interview at Telephone Contacts	• Clarification that no telephone visits are to be performed in the study, but rather telephone contacts • Clarification that telephone contacts should occur every 4 weeks through Week 156	The term "telephone visit" was replaced with "telephone contact", to clarify that a phone call is not replacing an on-site visit, because only limited topics are to be addressed during those calls.
Appendix 11 Guidance on Clinically Relevant CYP Inducers, Inhibitors, and Substrates	• Added reference information for CYP inducers, inhibitors, and substrates	Appendix added to provide guidance to Investigators.
Throughout the document	• Changes made to align with updated protocol template • Minor editorial and document formatting revisions	Minor; therefore, have not been summarized.

Protocol Version 5.0 (08 December 2022)

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

The primary purpose of this amendment is:

- Introduction of an OLE period for participants completing the DBTP prior to approval of the long-term follow-up study in their country to enable an option for evobrutinib treatment continuation
- Addition of the following exploratory endpoints:
  - Time to PIRA and time to PIRMA (to evaluate the effect of treatment on progression not driven by relapse events or MRI activity)
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	• Clarification that the hepatic/autoimmune panel includes focused genetic testing (e.g., HFE) and that samples will only be collected and analyzed if elevated LFTs are observed	To clarify that the hepatic/autoimmune panel performed in case of elevated LFTs contains a component of focused genetic testing. To clarify sample collection.
	• Removal of IP dispensation at Week 156	To clarify study procedures.
	• Clarification that ECG is to be performed at Week 96	Assessment at Week 96 was inadvertently omitted from previous protocol version (4.0); therefore, has been added to correct this inconsistency in study procedures.
	• Included detailed description of sample collection and use of novel liver function protein biomarkers	To clarify sample collection.
	• Included information that during unscheduled visits for relapse, EDSS assessment is required.	To clarify study procedures.
	• Included specification that novel liver function protein biomarkers were analyzed from serum, whereas novel liver function genomic biomarkers were analyzed from plasma	To clarify distinction between samples.
1.3.2 Schedule of Activities – Open-label Extension Period	• Schedule of Activities for OLE period added	To define study procedures to be conducted during the OLE period

Section # and Name	Description of Change	Brief Rationale
2.3 Benefit/Risk Assessment	• Updated number of participants in completed and ongoing clinical studies with evobrutinib	For consistency with the most recent IB and DSUR.
3 Objectives and Estimands	• Addition of exploratory endpoints: NEP at Weeks 48 or 96, Time to PIRA and PIRMA, and level of anti-SARS-CoV-2 antibodies	NEP at Weeks 48 or 96 added to exploratory endpoints to further evaluate the effect of treatment on disease activity. Time to PIRA and time to PIRMA added to exploratory endpoints to evaluate the effect of treatment on progression not driven by relapse events or MRI activity. Level of anti-SARS-CoV-2 antibodies added to evaluate the impact of evobrutinib on COVID-19 vaccinations.
	• Updated the PF deterioration definition to a reduction of at least 2.7 points on PROMIS PF score	For consistency with the most recent IAP (Version 2) and latest publication as 5 points was provisional.
	• Addition of Objectives and Endpoints table for the OLE Period	For consistency with the changes implemented in Section 1.2.
4.1 Study Design	• Text revised to include OLE period and AEP	Introduction of OLE for participants completing the DBTP prior to approval of the long-term follow-up study in their country to enable an option for evobrutinib treatment continuation
4.2 Scientific Rationale for Study Design	• Text revised to include rationale for inclusion of OLE period.	To define the rationale for the OLE period.
4.4 End of Study Definition	• Included End of Study Definition to OLE Period	To define treatment completion for OLE period
5.3 Criteria for Entry into Open Label Extension Period 5.3.1 Inclusion Criteria for Open Label Extension Period 5.3.2 Exclusion Criteria for Open Label Extension Period	• Added inclusion and exclusion criteria for entering into the OLE Period	For consistency with the changes implemented in Section 1.2 and Section 4.1.
5.4.2 Caffeine, Alcohol, and Tobacco	• Text added to clarify alcohol consumption should be avoided during the study	To clarify study procedures.
6.3.2 Blinding	• Clarification on blinding procedures for the bioanalytical laboratory	To clarify study procedures.
	• Removal of Assignment Method Retention	To clarify study procedures.
6.5.3 Prohibited Medicines	• Clarification for administration of prohibited medications (dalfampridine, fampridine, and CYP2C8 substrates) during the OLE Period of the study	To specify changes in prohibited medications during OLE period of the study.

Section # and Name	Description of Change	Brief Rationale
7.1 Discontinuation of Study Intervention	• Modification of criteria leading to permanent IMP discontinuation after extended interruption beyond 30 days	To control the duration of IMP interruption to ensure an adequate safety monitoring as well as the data integrity impacted by the external uncontrolled situation (e.g., military, geopolitical conflicts)
	• Addition of 2 new bullet points to include individual ALT/AST and individual total bilirubin elevation as criteria for permanent discontinuation of study treatment	To further clarify that elevated levels of ALT/AST and bilirubin may not need to occur simultaneously to trigger permanent discontinuation of study treatment.
	• Text added to clarify liver function testing criteria	To further clarify that confirmatory laboratory testing will be needed after initial elevation of ALT/AST levels before interruption of study intervention
8 Study Assessments and Procedures	• Addition of assessments in the OLE Period • Addition of text describing AEP procedure • Included information that during unscheduled visits for relapse, EDSS assessment is required • Clarification that no telephone visits are to be performed in the study, but rather telephone contacts	For consistency with changes implemented in the Section 1.2 and Section 4.1. To provide guidance on the AEP procedure required for the OLE period To clarify study procedures The term “telephone visit” was replaced with “telephone contact”, to clarify that a phone call is not replacing an on-site visit, because only limited topics are to be addressed during those calls
8.1.1 Neurological Assessment	• Addition of details for neurological assessments performed in the OLE Period	For consistency with changes implemented in Section 1.2 and Section 4.1.
8.1.1.1. Qualified Relapse	• Addition of further clarification on qualification of relapses.	For consistency with changes implemented in Section 1.2 and Section 4.1.
8.1.1.4 Timed Twenty-Five Foot Walk 8.1.1.5 Nine Hole Peg Test 8.1.1.6 Symbol Digit Modalities Test	• Added clarification that these assessments will be administered by qualified non-blinded site personnel during OLE period	For consistency with changes implemented in Section 1.2 and Section 4.1.
8.1.2 Brain Magnetic Resonance Imaging Scans	• Correction of Screening MRI instructions and clarification on the blinding of MRI reports to the Treating Investigator • Added details regarding MRI assessments in a respective OLE MRI substudy	Correction of erroneous text. Updated text to clarify that the study-related local radiologist’s MRI reports should not include details on MS-related pathology findings. MRI assessments in OLE Period were introduced according to changes made in Section 1.2 and Section 4.1.

Section # and Name	Description of Change	Brief Rationale
8.1.3.1 Patient Reported Outcomes Measurement Information System	• Updated the PF deterioration definition to a reduction of at least 2.7 points on PROMIS PF score	For consistency with the most recent IAP (version 2) and latest publication as 5 points was provisional.
8.1.3.4 WPAI: MS v2.0 (for OLE period only)	• Added Work Productivity and Activity Impairment Questionnaire for assessment in the OLE Period	To characterize the associations of work productivity and absenteeism with disability, fatigue, cognition, and health-related quality of life.
8.2.3 Electrocardiograms	• Added clarification to reflect that no central ECG evaluation by central reader is required in the OLE period	According to changes introduced in Section 1.2 and Section 4.1.
8.2.4 Clinical Safety Laboratory Assessments	• The volume of whole blood collected for HBV DNA was increased to 4 mL	To correct details of blood volume collection
8.2.8 Independent Data Monitoring Committee, Endpoint Adjudication Committee, and Study Steering Committee	• Added clarification that the EAC will be disbanded after the DBTP has ended as relapses will be qualified by the Treating Investigators in the OLE period.	According to changes introduced in Section 1.2 and Section 4.1.
8.3.5 Pregnancy	• Added clarification that participants who intend to become pregnant during the study will be discontinued study intervention	To clarify study procedures
8.5 Pharmacokinetics	• Added clarification that no blood samples for PK analysis will be collected from participants enrolled in the OLE.	According to changes introduced in Section 1.2 and Section 4.1.
8.8 Biomarkers 8.8.1 Biomarkers of Disease, Disease Activity and Progression, Drug-related Outcomes, and Treatment Response 8.8.1.2 Novel Liver Function Biomarkers 8.8.2 OLE Blood Biomarker PD Substudy – Biomarkers of Disease Activity, Progression and Response to Drug 8.8.3 Gene Expression	• Include the option to repurpose biomarker-of-disease-samples or NfL-biomarker samples for vaccination testing • Specification for collection of samples in OLE Period and OLE PD Substudy was added • Collection and analysis of samples for assessment of Novel Liver Function Protein Biomarkers and for gene expression analysis during OLE Period was added	Evaluating the impact of disease-modifying MS therapies on vaccinations has taken on greater importance during the COVID-19 pandemic. To reflect assessment in OLE Period and to clarify that blood samples for gene expression will not be collected on OLE Period.
9.2.3 Sample Size Considerations due to the Currently Escalating Crisis in Eastern Europe	• Text was added to clarify enrollment numbers in the crisis region.	To clarify sample size considerations.
9.3 Populations for Analyses	• Added population for analysis during OLE Period	According to changes introduced in Section 1.2 and Section 4.1.

Section # and Name	Description of Change	Brief Rationale
9.4.1 Efficacy Analyses	• Added description of analyses of tertiary/exploratory endpoints NEP, Time to PIRA, Time to PIRMA, level of anti-SARS-CoV-2 antibodies, and NfL concentrations at additional timepoints	For consistency with tertiary/exploratory objectives in Section 3
9.4.3.5 Analysis of Open Label Extension Period Endpoints	• Added specification of OLE Endpoints	According to changes introduced in Section 1.2 and Section 4.1.
9.4.4 Sequence of Analyses	• Final analysis was added according to added OLE Period	According to changes introduced in Section 1.2 and Section 4.1.
Appendix 5 Clinical Laboratory Tests	• Added tests that will be only applicable to participants in the OLE Period and indicated the tests that will not be applicable to those participants. • Changes made to align with long-term follow-up protocol language	According to changes introduced in Section 1.2.
Appendix 8 Procedure for Accelerated Elimination of Teriflunomide	• Clarification added to specify mandatory AEP procedure for participants entering OLE Period	According to changes introduced in Section 1.2 and Section 4.1.
Appendix 10 Structured Interview at Telephone Contacts	• Clarification that no telephone visits are to be performed in the study, but rather telephone contacts. • Clarification that telephone contacts should occur every 4 weeks through Week 156	The term “telephone visit” was replaced with “telephone contact”, to clarify that a phone call is not replacing an on-site visit, because only limited topics are to be addressed during those calls.
Appendix 11 Guidance on Clinically Relevant CYP Inducers, Inhibitors, and Substrates	• Added reference information for CYP inducers, inhibitors, and substrates	Appendix added to provide guidance to Investigators
Throughout the document	• Changes made to align with updated protocol template. • Minor editorial and document formatting revisions.	Minor; therefore, have not been summarized.

Protocol Version 4.2-LTU (26 April 2022)

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

The primary purpose of this amendment is to align the Lithuania-specific protocol with Version 4.0 (global Protocol Version 4.0; 03 April 2022), in which required changes to the study design, duration, and statistical analyses were implemented as critical measures to ensure that the validity of the study data and the integrity of the study results are preserved despite the foreseen impact of the currently escalating crisis in Eastern Europe.

A high-level description of each change is summarized below, along with its rationale.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	• Revision of treatment duration and corresponding update of endpoints as applicable. • Addition of secondary endpoints: Time to first occurrence of 24-week CDI and Week 12 NfL concentration. • Modification of secondary PROMIS endpoints from CFB “at” 96 weeks to CFB “over” 96 weeks. Modification of population-level summary from difference of least-squares means at 96 weeks to difference of average least-squares means, with average taken over a set of timepoints ending with Week 96. • Modification of secondary MRI endpoint from “total number of T1 Gd+ lesions based on assessments at Week 24, Week 48, and Week 96” to “total number of T1 Gd+ lesions based on all available MRI scans.” • Modification of secondary MRI endpoint from “total number of new or enlarging T2 lesions based on assessments at Week 24, Week 48, and Week 96” to “number of new or enlarging T2 lesions on the last available MRI scan relative to the baseline MRI scan.” • Inclusion of intercurrent event “Ukraine crisis” and strategy for handling. • Removal of endpoints in the OLE Period. • Inclusion of opportunity to enter a long-term follow-up study under a new protocol for participants after completion of evobrutinib treatment under the current protocol. • Update to sample size.	For consistency with the main protocol text.
1.2 Schema	Revision of the treatment duration from fixed 96 weeks to variable duration up to 156 weeks.	To ensure primary and important secondary endpoints are adequately powered despite loss of data from participants at sites in Ukraine, Russian Federation, and Belarus.
	Removal of OLE Period.	Due to the extended study duration and the planned transition of all eligible study completers to the long-term follow-up study under a new protocol, the OLE Period is no longer needed.

Section # and Name	Description of Change	Brief Rationale
	Removal of the mandatory AEP for male participants prior to entry into the OLE Period in line with removal of the OLE Period.	To ensure consistency after removal of the OLE Period, and to ensure consistency in evaluation of safety and efficacy for all participants entering the long-term follow-up study. Furthermore, removal of the OLE Period and the mandatory AEP related to teriflunomide reduces the risk of unblinding due to the variable AEP duration.
1.3 Schedule of Activities	• Inclusion of regular study visits up to Week 156. • Section renumbered from 1.3.1 Schedule of Activities: Screening and Treatment Period (All Participants), End of Study (Participants Not Entering Open Label Extension Period) to 1.3 Schedule of Activities.	• For alignment with the revised study duration from 96 weeks to 156 weeks. • For consistency with the removal of the Schedule of Activities for the OLE Period.
1.3.2 Schedule of Activities - Optional Open Label Extension Period	Removal of the Schedule of Activities for the OLE Period.	For consistency with the changes in study design, including the removal of the OLE Period.
3 Objectives and Estimands	Revision of treatment duration and corresponding update of endpoints as applicable.	For consistency with the study design change from fixed treatment duration to variable treatment duration.
	Addition of secondary endpoints: Time to first occurrence of 24-week CDI and Week 12 NfL concentration.	CDI endpoint added to secondary endpoints to explore treatment effect on additional clinically relevant endpoint for disability. Week 12 NfL concentration added to investigate early impact of treatment on reducing neuronal damage.
	Modification of secondary PROMIS endpoints from CFB “at” 96 weeks to CFB “over” 96 weeks. Modification of population-level summary from difference of least-squares means at 96 weeks to difference of average least-squares means, with average taken over a set of timepoints ending with Week 96.	For consistency with the study design change from fixed treatment duration to variable treatment duration.
	• Modification of secondary MRI endpoint from “total number of T1 Gd+ lesions based on assessments at Week 24, Week 48, and Week 96” to “total number of T1 Gd+ lesions based on all available MRI scans.” • Modification of secondary MRI endpoint from “total number of new or enlarging T2 lesions based on assessments at Week 24, Week 48, and Week 96” to “number of new or	For consistency with the study design change from fixed treatment duration to variable treatment duration.

Section # and Name	Description of Change	Brief Rationale
	enlarging T2 lesions on the last available MRI scan relative to the baseline scan."	
	Inclusion of intercurrent event "Ukraine crisis" and strategy for handling.	To reflect intercurrent event leading to study design change.
	Modification of tertiary MRI endpoint from "total number of CUA lesions based on assessments up to Week 96" to "total number of CUA lesions based on all available MRI scans." Modification of tertiary MRI endpoint from "total number of new T1 hypo-intense lesions based on assessments up to Week 96" to "total number of new T1 hypo-intense lesions based on all available MRI scans."	For consistency with the study design change from fixed treatment duration to variable treatment duration.
	Removal of Objectives and Endpoints for the OLE Period.	For consistency with the changes in study design, including the removal of the OLE Period.
4.1 Overall Design	Inclusion of opportunity to enter a long-term follow-up study under a new protocol for participants after completion of evobrutinib treatment under the current protocol.	A new study will allow participants who completed the double-blind treatment period in the current protocol to enroll in a new, single-arm long-term follow-up study, which will also include participants who completed other RMS studies with evobrutinib. The text of the protocol has been amended to describe a transition opportunity to this long-term follow-up study.
	Revised planned number of participants.	For consistency with changes in Section 9.2
4.4 End of Study Definition	Added clarification that treatment completers who enter the long-term follow-up study and do not require a Safety Follow-up Visit are also considered study completers.	For consistency with the change in study design.
5.3 Criteria for Entry into Open Label Extension Period	Removal of separate criteria for entry into OLE Period.	For consistency with the changes in study design, including the removal of the OLE Period.
6.3.2 Blinding	Time point of unblinding was updated to after having reached the primary analysis trigger.	For consistency with the increased study duration, updated statistical analyses, and removal of the OLE Period.
6.5.3 Prohibited Medicines	• Correction from "(including evobrutinib)" to "(excluding evobrutinib)". • Removal of prohibited medicines specific for the OLE Period.	• Correction of typographical error. • For consistency with the removal of the OLE Period.

Section # and Name	Description of Change	Brief Rationale
8.1.1.3 Confirmed Disability Improvement	Addition of definitions for CDI.	For clarification.
8.3.4 Regulatory Reporting Requirements for Serious Adverse Events	Text on SUSAR reporting was updated in line with the latest protocol template.	To comply with changes to the protocol template, which includes a clarified text on the SUSAR reporting process.
8.8 Biomarkers	Approximate blood volume planned to be collected during the study was updated.	To reflect the increased duration including additional visits and associated sampling.
8.8.1.1 Neurofilament Light Chain	• Added detailed information on NfL as biomarker of disease, corresponding to the inclusion of NfL as a new secondary endpoint.	• NfL has emerged as a potential biomarker for disease activity and treatment monitoring of patients with MS. Additional information added to support the inclusion of NfL as secondary endpoint.
9.1.2 Statistical Hypotheses Related to Secondary Objectives	• Added description of hypotheses regarding secondary endpoints. Time to 24-Week CDI and Week 12 NfL concentration.	• To pre-specify hypotheses regarding all secondary endpoints in protocol.
9.2.1 Sample Size for Primary Endpoint: ARR	• Added equation 9.2.1 for the information for ARR provided by a given sample size, followed for a common follow-up time.	• The target information required to adequately power the ARR endpoint should be pre-specified, as the primary analysis will be triggered by achieving the target information in both studies, plus target CDP events pooled.
9.2.2 Sample Size for Secondary Endpoint: 12-week CDP	• Revised the assumption on treatment effect on 12-week CDP endpoint from HR = 0.7 to HR = 0.66. • Summarized the outcome of the optional IA for BSSR.	• Evobrutinib is considered to have efficacy similar to that of anti-CD20 therapies. Therefore, recent reporting of HR = 0.66 (Hauser et al 2020), comparing hazard of first 12-week CDP event between ofatumumab and teriflunomide, is used to revise the assumption of the 12-week CDP treatment effect. • To clarify action taken previously (when IA for BSSR was conducted in August 2021) to ensure adequate power for 12-week CDP.
9.2.3 Sample Size Considerations due to the Currently Escalating Crisis in Eastern Europe	Added description of re-opening of enrollment driven by loss of data due to the currently escalating crisis in Eastern Europe.	To ensure primary and important secondary endpoints are adequately powered despite loss of data from participants at sites in

Section # and Name	Description of Change	Brief Rationale
		Ukraine, Russian Federation, and Belarus.
9.3 Population for Analyses	• Inclusion of modified analysis sets (mFAS and mSAF). • Removal of analysis set specific for the OLE Period.	• To address potential lack of data robustness for data from participants and sites in Ukraine, Russian Federation, and Belarus. • For consistency with the removal of the OLE Period.
9.4.1 Efficacy Analyses	• Updated ARR endpoint to indicate “up to 156 weeks”. • Modification of secondary PROMIS and MRI endpoints. • Added description of analyses of secondary endpoints Time to 24-Week CDI and Week 12 NfL concentration.	• For consistency with change to study from fixed to variable treatment duration. • For consistency with the secondary PROMIS and MRI objective in Section 3. • To pre-specify analyses of all secondary endpoints and most exploratory endpoints in the protocol.
9.4.1.1 Efficacy Analyses Related to Primary Objective	• Updated ARR endpoint to indicate “up to 156 weeks”. • Updated intercurrent event strategy to include “Ukraine crisis” as intercurrent event.	• For consistency with change to study from fixed to variable treatment duration. • To reflect intercurrent event leading to study design change.
9.4.1.2 Efficacy Analyses Related to Secondary Objectives	• Updated intercurrent event strategy to include “Ukraine crisis” as intercurrent event. • Modification of secondary PROMIS and MRI endpoints. • Added description of analyses of secondary endpoints Time-to-24-Week CDI and Week 12 NfL concentration, including estimand framework details.	• To reflect intercurrent event leading to study design change. • For consistency with the secondary PROMIS and MRI objective in Section 3. • To pre-specify analyses of all secondary endpoints in the protocol, including estimand framework details.
9.4.1.3 Sensitivity Analyses	Updated sensitivity analyses.	For consistency with change to study from fixed to variable treatment duration and to evaluate the impact of the currently escalating crisis in Eastern Europe.
9.4.4 Sequence of Analyses	Removal of Final Analysis at the end of OLE.	For consistency with removal of OLE Period.
9.4.4.1 Optional Interim Analysis for Blinded Sample Size Re-estimation	Summarized the outcome of the optional IA for BSSR.	To clarify action taken previously (when IA for BSSR was conducted in August 2021) to ensure adequate power for 12-week CDP.
9.4.4.2 Primary Analysis	• Described trigger for primary analysis based on achieving sufficient information for ARR in each study and	• For consistency with change to study from fixed to variable treatment

Section # and Name	Description of Change	Brief Rationale
	sufficient 12-week CDP events from pooled studies. • Added Equation 9.4.4 for blinded monitoring of information for ARR provided by a study.	duration, where primary analysis is information driven. • The information should be monitored for each study, as the target information needs to be met for each study before the primary analysis can be triggered.
9.4.4.3 Multiplicity	Updated multiple testing strategy to incorporate addition of 2 secondary endpoints, minor change to testing order (CDI endpoint tested prior to PRO endpoints), and minor correction to alpha level for pooled tests. Multiplicity graph updated to depict the strategy update.	To ensure that the multiple testing strategy provides a more complete picture of treatment effect on EDSS and NfL levels. Alpha level at which pooled tests are to be conducted was corrected from 0.025 to 0.024375 based on Bretz 2019.
10 References	• Addition of Bretz 2019. • Addition of Kuhle 2016, Kuhle 2017, Kuhle 2021, Disanto 2017, Piehl 2018, Novakova 2017, Barro 2018. • Update of Hauser 2019 to Hauser 2020.	• Addition in line with changes in Section 9.4.4.3. • Addition in line with changes in Section 8.8.1.1. • Full publication has become available.
Appendix 4 Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	• Updated serious adverse event reporting requirements • Text on SUSAR reporting was updated in line with the latest protocol template.	To comply with changes to protocol template, which clarifies the SAE and SUSAR reporting process.
Appendix 8 Procedure for Accelerated Elimination of Teriflunomide	Removal of the mandatory AEP for male participants prior to entry into the OLE Period.	To ensure consistency after removal of the OLE Period, to avoid potential unblinding due to variability in duration of AEP; and in evaluation of safety and efficacy for all participants entering the long-term follow-up study.
Throughout the document	Changes made to align with updated protocol template. Minor editorial and document formatting revisions.	Minor; therefore, have not been summarized.

Protocol Version 4.1-CAN (20 April 2022)

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

The primary purpose of this amendment is to align the Canada-specific protocol with Version 4.0 (global Protocol Version 4.0; 03 April 2022), in which required changes to the study design, duration, and statistical analyses were implemented as critical measures to ensure that the validity

of the study data and the integrity of the study results are preserved despite the foreseen impact of the currently escalating crisis in Eastern Europe.

A high-level description of each change is summarized below, along with its rationale.

Section # and Name	Description of Change	Brief Rationale
Synopsis	• Revision of treatment duration and corresponding update of endpoints as applicable. • Addition of secondary endpoints: Time to first occurrence of 24-week CDI and Week 12 NfL concentration. • Modification of secondary PROMIS endpoints from CFB "at" 96 weeks to CFB "over" 96 weeks. Modification of population-level summary from difference of least-squares means at 96 weeks to difference of average least-squares means, with average taken over a set of timepoints ending with Week 96. • Modification of secondary MRI endpoint from "total number of T1 Gd+ lesions based on assessments at Week 24, Week 48, and Week 96" to "total number of T1 Gd+ lesions based on all available MRI scans." • Modification of secondary MRI endpoint from "total number of new or enlarging T2 lesions based on assessments at Week 24, Week 48, and Week 96" to "number of new or enlarging T2 lesions on the last available MRI scan relative to the baseline MRI scan." • Inclusion of intercurrent event "Ukraine crisis" and strategy for handling. • Removal of endpoints in the OLE Period. • Inclusion of opportunity to enter a long-term follow-up study under a new protocol for participants after completion of evobrutinib treatment under the current protocol. • Update to sample size	For consistency with the main protocol text.
1.2 Schema	Revision of the treatment duration from fixed 96 weeks to variable duration up to 156 weeks.	To ensure primary and important secondary endpoints are adequately powered despite loss of data from participants at sites in Ukraine, Russian Federation, and Belarus.
	Removal of OLE Period.	Due to the extended study duration and the planned transition of all eligible study completers to the long-term follow-up study under a new

Section # and Name	Description of Change	Brief Rationale
		protocol, the OLE Period is no longer needed.
	Removal of the mandatory AEP for male participants prior to entry into the OLE Period in line with removal of the OLE Period.	To ensure consistency after removal of the OLE Period, and to ensure consistency in evaluation of safety and efficacy for all participants entering the long-term follow-up study. Furthermore, removal of the OLE Period and the mandatory AEP related to teriflunomide reduces the risk of unblinding due to the variable AEP duration.
1.3 Schedule of Activities	• Inclusion of regular study visits up to Week 156. • Section renumbered from 1.3.1 Schedule of Activities: Screening and Treatment Period (All Participants), End of Study (Participants Not Entering Open Label Extension Period) to 1.3 Schedule of Activities.	• For alignment with the revised study duration from 96 weeks to 156 weeks. • For consistency with the removal of the Schedule of Activities for the OLE Period.
1.3.2 Schedule of Activities - Optional Open Label Extension Period	Removal of the Schedule of Activities for the OLE Period.	For consistency with the changes in study design, including the removal of the OLE Period.
3 Objectives and Estimands	Revision of treatment duration and corresponding update of endpoints as applicable.	For consistency with the study design change from fixed treatment duration to variable treatment duration.
	Addition of secondary endpoints: Time to first occurrence of 24-week CDI and Week 12 NfL concentration.	CDI endpoint added to secondary endpoints to explore treatment effect on additional clinically relevant endpoint for disability. Week 12 NfL concentration added to investigate early impact of treatment on reducing neuronal damage.
	Modification of secondary PROMIS endpoints from CFB “at” 96 weeks to CFB “over” 96 weeks. Modification of population-level summary from difference of least-squares means at 96 weeks to difference of average least-squares means, with average taken over a set of timepoints ending with Week 96.	For consistency with the study design change from fixed treatment duration to variable treatment duration.
	• Modification of secondary MRI endpoint from “total number of T1 Gd+ lesions based on assessments at Week 24, Week 48, and Week 96” to “total number of T1 Gd+ lesions based on all available MRI scans.” • Modification of secondary MRI endpoint from “total number of new or enlarging T2 lesions based on assessments at Week	For consistency with the study design change from fixed treatment duration to variable treatment duration.

Section # and Name	Description of Change	Brief Rationale
	24, Week 48, and Week 96" to "number of new or enlarging T2 lesions on the last available MRI scan relative to the baseline scan."	
	Inclusion of intercurrent event "Ukraine crisis" and strategy for handling	To reflect intercurrent event leading to study design change.
	Modification of tertiary MRI endpoint from "total number of CUA lesions based on assessments up to Week 96" to "total number of CUA lesions based on all available MRI scans." Modification of tertiary MRI endpoint from "total number of new T1 hypo-intense lesions based on assessments up to Week 96" to "total number of new T1 hypo-intense lesions based on all available MRI scans."	For consistency with the study design change from fixed treatment duration to variable treatment duration.
	Removal of Objectives and Endpoints for the OLE Period.	For consistency with the changes in study design, including the removal of the OLE Period.
4.1 Overall Design	Inclusion of opportunity to enter a long-term follow-up study under a new protocol for participants after completion of evobrutinib treatment under the current protocol.	A new study will allow participants who completed the double-blind treatment period in the current protocol to enroll in a new, single-arm long-term follow-up study, which will also include participants who completed other RMS studies with evobrutinib. The text of the protocol has been amended to describe a transition opportunity to this long-term follow-up study.
	Revised planned number of participants	For consistency with changes in Section 9.2
4.4 End of Study Definition	Added clarification that treatment completers who enter the long-term follow-up study and do not require a Safety Follow-up Visit are also considered study completers.	For consistency with the change in study design.
5.3 Criteria for Entry into Open Label Extension Period	Removal of separate criteria for entry into OLE Period.	For consistency with the changes in study design, including the removal of the OLE Period.
6.3.2 Blinding	Time point of unblinding was updated to after having reached the primary analysis trigger.	For consistency with the increased study duration, updated statistical analyses, and removal of the OLE Period.
6.5.3 Prohibited Medicines	• Correction from "(including evobrutinib)" to "(excluding evobrutinib)". • Removal of prohibited medicines specific for the OLE Period.	• Correction of typographical error. • For consistency with the removal of the OLE Period.

Section # and Name	Description of Change	Brief Rationale
8.1.1.3 Confirmed Disability Improvement	Addition of definitions for CDI.	For clarification.
8.3.4 Regulatory Reporting Requirements for Serious Adverse Events	Text on SUSAR reporting was updated in line with the latest protocol template.	To comply with changes to the protocol template, which includes a clarified text on the SUSAR reporting process.
8.8 Biomarkers	Approximate blood volume planned to be collected during the study was updated.	To reflect the increased duration including additional visits and associated sampling.
8.8.1.1 Neurofilament Light Chain	• Added detailed information on NfL as biomarker of disease, corresponding to the inclusion of NfL as a new secondary endpoint.	• NfL has emerged as a potential biomarker for disease activity and treatment monitoring of patients with MS. Additional information added to support the inclusion of NfL as secondary endpoint.
9.1.2 Statistical Hypotheses Related to Secondary Objectives	• Added description of hypotheses regarding secondary endpoints Time to 24-Week CDI and Week 12 NfL concentration	• To pre-specify hypotheses regarding all secondary endpoints in protocol.
9.2.1 Sample Size for Primary Endpoint: ARR	• Added equation 9.2.1 for the information for ARR provided by a given sample size, followed for a common follow-up time.	• The target information required to adequately power the ARR endpoint should be pre-specified, as the primary analysis will be triggered by achieving the target information in both studies, plus target CDP events pooled.
9.2.2 Sample Size for Secondary Endpoint: 12-week CDP	• Revised the assumption on treatment effect on 12-week CDP endpoint from HR = 0.7 to HR = 0.66. • Summarized the outcome of the optional IA for BSSR.	• Evobrutinib is considered to have efficacy similar to that of anti-CD20 therapies. Therefore, recent reporting of HR = 0.66 (Hauser et al 2020), comparing hazard of first 12-week CDP event between ofatumumab and teriflunomide, is used to revise the assumption of the 12-week CDP treatment effect. • To clarify action taken previously (when IA for BSSR was conducted in August 2021) to ensure adequate power for 12-week CDP.
9.2.3 Sample Size Considerations due to the Currently Escalating Crisis in Eastern Europe	Added description of re-opening of enrollment driven by loss of data due to the currently escalating crisis in Eastern Europe.	To ensure primary and important secondary endpoints are adequately powered despite loss of data from participants at sites in

Section # and Name	Description of Change	Brief Rationale
		Ukraine, Russian Federation, and Belarus.
9.3 Population for Analyses	• Inclusion of modified analysis sets (mFAS and mSAF) • Removal of analysis set specific for the OLE Period.	• To address potential lack of data robustness for data from participants and sites in Ukraine, Russian Federation, and Belarus. • For consistency with the removal of the OLE Period.
9.4.1 Efficacy Analyses	• Updated ARR endpoint to indicate “up to 156 weeks”. • Modification of secondary PROMIS and MRI endpoints. • Added description of analyses of secondary endpoints Time to 24-Week CDI and Week 12 NfL concentration.	• For consistency with change to study from fixed to variable treatment duration. • For consistency with the secondary PROMIS and MRI objective in Section 3. • To pre-specify analyses of all secondary endpoints and most exploratory endpoints in the protocol.
9.4.1.1 Efficacy Analyses Related to Primary Objective	• Updated ARR endpoint to indicate “up to 156 weeks”. • Updated intercurrent event strategy to include “Ukraine crisis” as intercurrent event.	• For consistency with change to study from fixed to variable treatment duration. • To reflect intercurrent event leading to study design change.
9.4.1.2 Efficacy Analyses Related to Secondary Objectives	• Updated intercurrent event strategy to include “Ukraine crisis” as intercurrent event. • Modification of secondary PROMIS and MRI endpoints. • Added description of analyses of secondary endpoints Time-to-24-Week CDI and Week 12 NfL concentration, including estimand framework details.	• To reflect intercurrent event leading to study design change. • For consistency with the secondary PROMIS and MRI objective in Section 3. • To pre-specify analyses of all secondary endpoints in the protocol, including estimand framework details.
9.4.1.3 Sensitivity Analyses	Updated sensitivity analyses	For consistency with change to study from fixed to variable treatment duration and to evaluate the impact of the currently escalating crisis in Eastern Europe.
9.4.2.8 Sensitivity Analyses	Updated sensitivity analyses	For consistency with change to study from fixed to variable treatment duration and to evaluate the impact of the currently escalating crisis in Eastern Europe.
9.4.4 Sequence of Analyses	Removal of Final Analysis at the end of OLE.	For consistency with removal of OLE Period.

Section # and Name	Description of Change	Brief Rationale
9.4.4.1 Optional Interim Analysis for Blinded Sample Size Re-estimation	Summarized the outcome of the optional IA for BSSR.	To clarify action taken previously (when IA for BSSR was conducted in August 2021) to ensure adequate power for 12-week CDP.
9.4.4.2 Primary Analysis	• Described trigger for primary analysis based on achieving sufficient information for ARR in each study and sufficient 12-week CDP events from pooled studies. • Added Equation 9.4.4 for blinded monitoring of information for ARR provided by a study.	• For consistency with change to study from fixed to variable treatment duration, where primary analysis is information driven. • The information should be monitored for each study, as the target information needs to be met for each study before the primary analysis can be triggered.
9.4.4.3 Multiplicity	Updated multiple testing strategy to incorporate addition of 2 secondary endpoints, minor change to testing order (CDI endpoint tested prior to PRO endpoints), and minor correction to alpha level for pooled tests. Multiplicity graph updated to depict the strategy update.	To ensure that the multiple testing strategy provides a more complete picture of treatment effect on EDSS and NfL levels. Alpha level at which pooled tests are to be conducted was corrected from 0.025 to 0.024375 based on Bretz 2019.
10 References	• Addition of Bretz 2019. • Addition of Kuhle 2016, Kuhle 2017, Disanto 2017, Piehl 2018, Novakova 2017, Barro 2018. • Update of Hauser 2019 to Hauser 2020.	• Addition in line with changes in Section 9.4.4.3. • Addition in line with changes in Section 8.8.1.1. • Full publication has become available.
Appendix 4	• Updated serious adverse event reporting requirements. Text on SUSAR reporting was updated in line with the latest protocol template.	To comply with changes to protocol template, which clarifies the SAE and SUSAR reporting process.
Appendix 8 Procedure for Accelerated Elimination of Teriflunomide	Removal of the mandatory AEP for male participants prior to entry into the OLE Period	To ensure consistency after removal of the OLE Period, to avoid potential unblinding due to variability in duration of AEP; and in evaluation of safety and efficacy for all participants entering the long-term follow-up study.
Throughout the document	Changes made to align with updated protocol template. Minor editorial and document formatting revisions.	Minor; therefore, have not been summarized.

Protocol Version 4.0 (03 April 2022)

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

The primary purpose of this amendment is the implementation of required changes to the study design, duration, and statistical analyses as critical measures to ensure that the validity of the study data and the integrity of the study results are preserved despite the foreseen impact of the currently escalating crisis in Eastern Europe.

A high-level description of each change is summarized below, along with its rationale.

Section # and Name	Description of Change	Brief Rationale
Synopsis	• Revision of treatment duration and corresponding update of endpoints as applicable. • Addition of secondary endpoints: Time to first occurrence of 24-week CDI and Week 12 NfL concentration. • Modification of secondary PROMIS endpoints from CFB "at" 96 weeks to CFB "over" 96 weeks. Modification of population-level summary from difference of least-squares means at 96 weeks to difference of average least-squares means, with average taken over a set of timepoints ending with Week 96. • Modification of secondary MRI endpoint from "total number of T1 Gd+ lesions based on assessments at Week 24, Week 48, and Week 96" to "total number of T1 Gd+ lesions based on all available MRI scans." • Modification of secondary MRI endpoint from "total number of new or enlarging T2 lesions based on assessments at Week 24, Week 48, and Week 96" to "number of new or enlarging T2 lesions on the last available MRI scan relative to the baseline MRI scan." • Inclusion of intercurrent event "Ukraine crisis" and strategy for handling. • Removal of endpoints in the OLE Period. • Inclusion of opportunity to enter a long-term follow-up study under a new protocol for participants after completion of evobrutinib treatment under the current protocol.	For consistency with the main protocol text.
1.2 Schema	Revision of the treatment duration from fixed 96 weeks to variable duration up to 156 weeks.	To ensure primary and important secondary endpoints are adequately powered despite loss of data from

Section # and Name	Description of Change	Brief Rationale
		participants at sites in Ukraine, Russian Federation, and Belarus.
	Removal of OLE Period	Due to the extended study duration and the planned transition of all eligible study completers to the long-term follow-up study under a new protocol, the OLE Period is no longer needed.
	Removal of the mandatory AEP for male participants prior to entry into the OLE Period in line with removal of the OLE Period.	To ensure consistency after removal of the OLE Period, and to ensure consistency in evaluation of safety and efficacy for all participants entering the long-term follow-up study. Furthermore, removal of the OLE Period and the mandatory AEP related to teriflunomide reduces the risk of unblinding due to the variable AEP duration.
1.3 Schedule of Activities	• Inclusion of regular study visits up to Week 156. • Section renumbered from 1.3.1 Schedule of Activities: Screening and Treatment Period (All Participants), End of Study (Participants Not Entering Open Label Extension Period) to 1.3 Schedule of Activities.	• For alignment with the revised study duration from 96 weeks to 156 weeks. • For consistency with the removal of the Schedule of Activities for the OLE Period.
1.3.2 Schedule of Activities - Optional Open Label Extension Period	Removal of the Schedule of Activities for the OLE Period.	For consistency with the changes in study design, including the removal of the OLE Period.
3 Objectives and Estimands	Revision of treatment duration and corresponding update of endpoints as applicable.	For consistency with the study design change from fixed treatment duration to variable treatment duration.
	Addition of secondary endpoints: Time to first occurrence of 24-week CDI and Week 12 NfL concentration.	CDI endpoint added to secondary endpoints to explore treatment effect on additional clinically relevant endpoint for disability. Week 12 NfL concentration added to investigate early impact of treatment on reducing neuronal damage.
	Modification of secondary PROMIS endpoints from CFB “at” 96 weeks to CFB “over” 96 weeks. Modification of population-level summary from difference of least-squares means at 96 weeks to difference of average least-squares means, with average taken over a set of timepoints ending with Week 96.	For consistency with the study design change from fixed treatment duration to variable treatment duration.
	• Modification of secondary MRI endpoint from “total number of T1 Gd+ lesions based on assessments at Week 24, Week 48, and Week 96” to “total number of T1 Gd+ lesions based on all available MRI scans.”	For consistency with the study design change from fixed treatment duration to variable treatment duration.

Section # and Name	Description of Change	Brief Rationale
	• Modification of secondary MRI endpoint from “total number of new or enlarging T2 lesions based on assessments at Week 24, Week 48, and Week 96” to “number of new or enlarging T2 lesions on the last available MRI scan relative to the baseline scan.”	
	Inclusion of intercurrent event “Ukraine crisis” and strategy for handling	To reflect intercurrent event leading to study design change.
	Modification of tertiary MRI endpoint from “total number of CUA lesions based on assessments up to Week 96” to “total number of CUA lesions based on all available MRI scans.” Modification of tertiary MRI endpoint from “total number of new T1 hypo-intense lesions based on assessments up to Week 96” to “total number of new T1 hypo-intense lesions based on all available MRI scans.”	For consistency with the study design change from fixed treatment duration to variable treatment duration.
	Removal of Objectives and Endpoints for the OLE Period.	For consistency with the changes in study design, including the removal of the OLE Period.
4.1 Overall Design	Inclusion of opportunity to enter a long-term follow-up study under a new protocol for participants after completion of evobrutinib treatment under the current protocol.	A new study will allow participants who completed the double-blind treatment period in the current protocol to enroll in a new, single-arm long-term follow-up study, which will also include participants who completed other RMS studies with evobrutinib. The text of the protocol has been amended to describe a transition opportunity to this long-term follow-up study.
4.4 End of Study Definition	Added clarification that treatment completers who enter the long-term follow-up study and do not require a Safety Follow-up Visit are also considered study completers.	For consistency with the change in study design.
5.3 Criteria for Entry into Open Label Extension Period	Removal of separate criteria for entry into OLE Period.	For consistency with the changes in study design, including the removal of the OLE Period.
6.3.2 Blinding	Time point of unblinding was updated to after having reached the primary analysis trigger.	For consistency with the increased study duration, updated statistical analyses, and removal of the OLE Period.
6.5.3 Prohibited Medicines	• Correction from "(including evobrutinib)" to "(excluding evobrutinib)". • Removal of prohibited medicines specific for the OLE Period.	• Correction of typographical error. • For consistency with the removal of the OLE Period.
8.1.1.3 Confirmed Disability Improvement	Addition of definitions for CDI.	For clarification.

Section # and Name	Description of Change	Brief Rationale
8.3.4 Regulatory Reporting Requirements for Serious Adverse Events	Text on SUSAR reporting was updated in line with the latest protocol template.	To comply with changes to the protocol template, which includes a clarified text on the SUSAR reporting process.
8.8 Biomarkers	Approximate blood volume planned to be collected during the study was updated.	To reflect the increased duration including additional visits and associated sampling.
8.8.1.1 Neurofilament Light Chain	• Added detailed information on NfL as biomarker of disease, corresponding to the inclusion of NfL as a new secondary endpoint.	• NfL has emerged as a potential biomarker for disease activity and treatment monitoring of patients with MS. Additional information added to support the inclusion of NfL as secondary endpoint.
9.1.2 Statistical Hypotheses Related to Secondary Objectives	• Added description of hypotheses regarding secondary endpoints Time to 24-Week CDI and Week 12 NfL concentration	• To pre-specify hypotheses regarding all secondary endpoints in protocol.
9.2.1 Sample Size for Primary Endpoint: ARR	• Added equation 9.2.1 for the information for ARR provided by a given sample size, followed for a common follow-up time.	• The target information required to adequately power the ARR endpoint should be pre-specified, as the primary analysis will be triggered by achieving the target information in both studies, plus target CDP events pooled.
9.2.2 Sample Size for Secondary Endpoint: 12-week CDP	• Revised the assumption on treatment effect on 12-week CDP endpoint from HR = 0.7 to HR = 0.66. • Summarized the outcome of the optional IA for BSSR.	• Evobrutinib is considered to have efficacy similar to that of anti-CD20 therapies. Therefore, recent reporting of HR = 0.66 (Hauser et al 2020), comparing hazard of first 12-week CDP event between ofatumumab and teriflunomide, is used to revise the assumption of the 12-week CDP treatment effect. • To clarify action taken previously (when IA for BSSR was conducted in August 2021) to ensure adequate power for 12-week CDP.
9.2.3 Sample Size Considerations due to the Currently Escalating Crisis in Eastern Europe	Added description of re-opening of enrollment driven by loss of data due to the currently escalating crisis in Eastern Europe.	To ensure primary and important secondary endpoints are adequately powered despite loss of data from participants at sites in Ukraine, Russian Federation, and Belarus.
9.3 Population for Analyses	• Inclusion of modified analysis sets (mFAS and mSAF) • Removal of analysis set specific for the OLE Period.	• To address potential lack of data robustness for data from participants and sites in Ukraine, Russian Federation, and Belarus. • For consistency with the removal of the OLE Period.
9.4.1 Efficacy Analyses	• Updated ARR endpoint to indicate “up to 156 weeks”. • Modification of secondary PROMIS and MRI endpoints. • Added description of analyses of secondary endpoints Time to 24-Week CDI and Week 12 NfL concentration.	• For consistency with change to study from fixed to variable treatment duration. • For consistency with the secondary PROMIS and MRI objective in Section 3. • To pre-specify analyses of all secondary endpoints and most

Section # and Name	Description of Change	Brief Rationale
		exploratory endpoints in the protocol.
9.4.1.1 Efficacy Analyses Related to Primary Objective	• Updated ARR endpoint to indicate "up to 156 weeks". • Updated intercurrent event strategy to include "Ukraine crisis" as intercurrent event.	• For consistency with change to study from fixed to variable treatment duration. • To reflect intercurrent event leading to study design change.
9.4.1.2 Efficacy Analyses Related to Secondary Objectives	• Updated intercurrent event strategy to include "Ukraine crisis" as intercurrent event. • Modification of secondary PROMIS and MRI endpoints. • Added description of analyses of secondary endpoints Time-to-24-Week CDI and Week 12 NfL concentration, including estimand framework details.	• To reflect intercurrent event leading to study design change. • For consistency with the secondary PROMIS and MRI objective in Section 3. • To pre-specify analyses of all secondary endpoints in the protocol, including estimand framework details.
9.4.1.3 Sensitivity Analyses	Updated sensitivity analyses	For consistency with change to study from fixed to variable treatment duration and to evaluate the impact of the currently escalating crisis in Eastern Europe.
9.4.4 Sequence of Analyses	Removal of Final Analysis at the end of OLE.	For consistency with removal of OLE Period.
9.4.4.1 Optional Interim Analysis for Blinded Sample Size Re-estimation	Summarized the outcome of the optional IA for BSSR.	To clarify action taken previously (when IA for BSSR was conducted in August 2021) to ensure adequate power for 12-week CDP.
9.4.4.2 Primary Analysis	• Described trigger for primary analysis based on achieving sufficient information for ARR in each study and sufficient 12-week CDP events from pooled studies. • Added Equation 9.4.4 for blinded monitoring of information for ARR provided by a study.	• For consistency with change to study from fixed to variable treatment duration, where primary analysis is information driven. • The information should be monitored for each study, as the target information needs to be met for each study before the primary analysis can be triggered.
9.4.4.3 Multiplicity	Updated multiple testing strategy to incorporate addition of 2 secondary endpoints, minor change to testing order (CDI endpoint tested prior to PRO endpoints), and minor correction to alpha level for pooled tests. Multiplicity graph updated to depict the strategy update.	To ensure that the multiple testing strategy provides a more complete picture of treatment effect on EDSS and NfL levels. Alpha level at which pooled tests are to be conducted was corrected from 0.025 to 0.02475 based on Bretz 2019.
10 References	• Addition of Bretz 2019. • Addition of Kuhle 2016, Kuhle 2017, Disanto 2017, Piehl 2018, Novakova 2017, Barro 2018. • Update of Hauser 2019 to Hauser 2020.	• Addition in line with changes in Section 9.4.4.3. • Addition in line with changes in Section 8.8.1.1. • Full publication has become available.
Appendix 4	Text on SUSAR reporting was updated in line with the latest protocol template.	To comply with changes to protocol template, which clarifies the SUSAR reporting process.

Section # and Name	Description of Change	Brief Rationale
Appendix 8 Procedure for Accelerated Elimination of Teriflunomide	Removal of the mandatory AEP for male participants prior to entry into the OLE Period	To ensure consistency after removal of the OLE Period, to avoid potential unblinding due to variability in duration of AEP; and in evaluation of safety and efficacy for all participants entering the long-term follow-up study.
Throughout the document	Changes made to align with updated protocol template. Minor editorial and document formatting revisions.	Minor; therefore, have not been summarized.

Protocol Version 3.2-LTU (26 May 2021)

Overall Rationale for the Amendment

The purpose of this amendment is to align the Lithuania-specific protocol with Version 3.0 (global protocol amendment; 19 May 2021), in which changes and clarifications were made to remove the interim analysis (IA) for unblinded sample size re-estimation (USSR) and include an optional IA for blinded sample size re-estimation (BSSR). A high-level description of each change is summarized below, along with its rationale.

Section # and Name	Description of Change	Brief Rationale
Title page	PPD replaces PPD as Medical Monitor. PPD is Medical Responsible.	Change in personnel.
1.1 Synopsis	- Updated this section to reflect the inclusion of an optional IA for BSSR which are detailed below. - Included clarification that enrollment in the Open Label Extension (OLE) can comprise participants who are still under study treatment when an event-driven primary analysis (PA) is triggered.	For consistency and clarification.
1.2 Study Schema	Updated the footnote to remove details of treatment period for participants entering the OLE period.	To be aligned with the inclusion of an optional IA for BSSR.
4.1 Overall Design	- Included clarification that enrollment in the OLE can comprise participants who are still under study treatment when an event-driven PA is triggered. - Included an optional IA for BSSR and the information that the number of participants to be enrolled may be increased to approximately 1162 randomized participants. - Removed the IA for USSR triggered when approximately 35% to 45% of planned 12-week CDP events have been observed. - Included clarification that enrollment in the OLE will be offered to participants who have their blinded Treatment Period interrupted	Due to unexpectedly rapid enrollment, the trigger for the IA for USSR is projected to occur months after the completion of enrollment, considered too late to implement changes following outcome of IA from an operational perspective. The optional IA for BSSR, triggered prior to completion of enrollment, does not have this disadvantage.

Section # and Name	Description of Change	Brief Rationale
	due to PA trigger as they will be considered as study completers.	
5.3.1 Inclusion Criteria for Open Label Extension Period 5.3.2 Exclusion Criteria for Open Label Extension Period	- Included clarification that inclusion in the OLE can comprise participants who are still under study treatment when an event-driven PA is triggered. - Included clarification that exclusion in the OLE can happen for participants who had discontinued blinded treatment prior to the PA trigger (in the case of an event-driven PA).	For clarification.
6.3.2 Blinding	Minor update to consider current changes related to PA trigger.	For consistency.
7.1 Discontinuation of Study Intervention	Criteria for Temporary Discontinuation of Study Intervention: Amylase and lipase retest criteria amended to include the fasting state.	For clarification.
8 Study Assessments and Procedures	Included the information that T-SPOT test will be conducted at the local laboratories after positive QuantiFERON test.	To correct error as the requirement was included in Protocol Version 2.0.
8 Study Assessments and Procedures	Sentence was rephrased to clarify that reported relapse will be adjudicated by the Endpoint Adjudication Committee.	For clarification.
8 Study Assessments and Procedures	Removed coagulation.	To correct error as the requirement was removed in Protocol Version 2.0.
8 Study Assessments and Procedures	Included clarification that enrollment in the OLE will be offered to participants who have their blinded Treatment Period interrupted due to PA trigger as they will be considered as study completers.	For clarification.
8 Study Assessments and Procedures 8.2.3 Electrocardiograms 9.4.2.4 Electrocardiogram Parameters	Sections were rephrased to consider central ECG reading.	To avoid variability in interpretation of ECGs by non-cardiologists and in reports obtained from the locally sourced ECG machines.
8.2.8 Independent Data Monitoring Committee, Endpoint Adjudication Committee, and Study Steering Committee	Removed the information that IDMC will review unblinded interim data.	Due to the removal of the IA for USSR, the role played by the IDMC in making the sample size increase recommendation is no longer required.
9.2 Sample Size Determination	Removed the IA for USSR and included an optional IA for BSSR and the information that a minimal or non-existent effect on type-1 error inflation is expected.	Rationale same as for change to Section 4.1.
9.4.1 Efficacy Analyses	Clarified that Time to 24-week confirmed disability progression (CDP) will be analyzed in the same manner as the Time to 12-week CDP.	Due to removing the IA for USSR, there is no need to control type-1 error in the 12-week CDP analysis using the Cui, Hung, Wang method. Thus, 12-week CDP and 24-week CDP will be analyzed in the same manner.
9.4.1.1 Efficacy Analyses Related to Primary Objective	Updated the treatment duration to consider the participants who have their blinded	To be aligned with the inclusion of an optional IA for BSSR.

Section # and Name	Description of Change	Brief Rationale
	Treatment Period interrupted due to PA trigger.	
9.4.1.2 Efficacy Analyses Related to Secondary Objectives	- Removed the IA for USSR and included an optional IA for BSSR with details regarding methodology. - Changed the statistical test for the secondary endpoint Time to 12-week CDP from Cui, Hung, Wang to stratified logrank and clarified that Time to 24-week CDP will be analyzed in the same manner.	Rationale same as for change to Section 9.4.1.
9.4.4 Sequence of Analyses	- Removed the IA for USSR and included an optional IA for BSSR. - Clarified how the PA is triggered if the sample size is increased.	Rationale for replacing IA for USSR with optional IA for BSSR same as that for change to Section 4.1. Clarification.
9.4.4.1 Optional Interim Analysis for Blinded Sample Size Re-estimation	Removed the IA for USSR and included an optional IA for BSSR with details regarding methodology.	Rationale same as for change to Section 4.1.
9.4.4.2 Primary Analysis	- Clarified how the PA is triggered if the sample size is increased. - Clarified that the PA is based on data from the blinded Treatment Period.	Clarification.
9.4.4.4 Multiplicity	Removed the multiplicity approach for controlling family wise type I error at the 1 sided 0.025 level in the presence of USSR based on pooled 12-week CDP.	Rationale same as for change to Section 9.4.1.
10 References	Removed Cui, Hung, Wang reference that is no longer applicable and included new reference applicable to BSSR (Friede et al., 2019).	Rationale same as for change to Section 4.1 and Section 9.4.1.
Throughout the document	Changes made to align with updated protocol template. Minor editorial and document formatting revisions.	Minor; therefore, have not been summarized.

Protocol Version 3.1-CAN (26 May 2021)

Overall Rationale for the Amendment

The purpose of this amendment is to align the Canada-specific protocol with Version 3.0 (global protocol amendment; 19 May 2021), in which changes and clarifications were made to remove the interim analysis (IA) for unblinded sample size re-estimation (USSR) and include an optional IA for blinded sample size re-estimation (BSSR). A high-level description of each change is summarized below, along with its rationale.

Section # and Name	Description of Change	Brief Rationale
Title page	PPD replaces PPD as Medical Monitor. PPD is Medical Responsible.	Change in personnel.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	- Updated this section to reflect the inclusion of an optional IA for BSSR which are detailed below. - Included clarification that enrollment in the Open Label Extension (OLE) can comprise participants who are still under study treatment when an event-driven primary analysis (PA) is triggered.	For consistency and clarification.
1.2 Study Schema	Updated the footnote to remove details of treatment period for participants entering the OLE period.	To be aligned with the inclusion of an optional IA for BSSR.
4.1 Overall Design	- Included clarification that enrollment in the OLE can comprise participants who are still under study treatment when an event-driven PA is triggered. - Included an optional IA for BSSR and the information that the number of participants to be enrolled may be increased to approximately 1162 randomized participants. - Removed the IA for USSR triggered when approximately 35% to 45% of planned 12-week CDP events have been observed. - Included clarification that enrollment in the OLE will be offered to participants who have their blinded Treatment Period interrupted due to PA trigger as they will be considered as study completers.	Due to unexpectedly rapid enrollment, the trigger for the IA for USSR is projected to occur months after the completion of enrollment, considered too late to implement changes following outcome of IA from an operational perspective. The optional IA for BSSR, triggered prior to completion of enrollment, does not have this disadvantage.
5.3.1 Inclusion Criteria for Open Label Extension Period 5.3.2 Exclusion Criteria for Open Label Extension Period	- Included clarification that inclusion in the OLE can comprise participants who are still under study treatment when an event-driven PA is triggered. - Included clarification that exclusion in the OLE can happen for participants who had discontinued blinded treatment prior to the PA trigger (in the case of an event-driven PA).	For clarification.
6.3.2 Blinding	Minor update to consider current changes related to PA trigger.	For consistency.
7.1 Discontinuation of Study Intervention	Criteria for Temporary Discontinuation of Study Intervention: Amylase and lipase retest criteria amended to include the fasting state.	For clarification.
8 Study Assessments and Procedures	Included the information that T-SPOT test will be conducted at the local laboratories after positive QuantiFERON test.	To correct error as the requirement was included in Protocol Version 2.0.
8 Study Assessments and Procedures	Sentence was rephrased to clarify that reported relapse will be adjudicated by the Endpoint Adjudication Committee.	For clarification.
8 Study Assessments and Procedures	Removed coagulation.	To correct error as the requirement was removed in Protocol Version 2.0.

Section # and Name	Description of Change	Brief Rationale
8 Study Assessments and Procedures	Included clarification that enrollment in the OLE will be offered to participants who have their blinded Treatment Period interrupted due to PA trigger as they will be considered as study completers.	For clarification.
8 Study Assessments and Procedures 8.2.3 Electrocardiograms 9.4.2.4 Electrocardiogram Parameters	Sections were rephrased to consider central ECG reading.	To avoid variability in interpretation of ECGs by non-cardiologists and in reports obtained from the locally sourced ECG machines.
8.2.8 Independent Data Monitoring Committee, Endpoint Adjudication Committee, and Study Steering Committee	Removed the information that IDMC will review unblinded interim data.	Due to the removal of the IA for USSR, the role played by the IDMC in making the sample size increase recommendation is no longer required.
9.2 Sample Size Determination	Removed the IA for USSR and included an optional IA for BSSR and the information that a minimal or non-existent effect on type-1 error inflation is expected.	Rationale same as for change to Section 4.1.
9.4.1 Efficacy Analyses	Clarified that Time to 24-week confirmed disability progression (CDP) will be analyzed in the same manner as the Time to 12-week CDP.	Due to removing the IA for USSR, there is no need to control type-1 error in the 12-week CDP analysis using the Cui, Hung, Wang method. Thus, 12-week CDP and 24-week CDP will be analyzed in the same manner.
9.4.1.1 Efficacy Analyses Related to Primary Objective	Updated the treatment duration to consider the participants who have their blinded Treatment Period interrupted due to PA trigger.	To be aligned with the inclusion of an optional IA for BSSR.
9.4.1.2 Efficacy Analyses Related to Secondary Objectives	- Removed the IA for USSR and included an optional IA for BSSR with details regarding methodology. - Changed the statistical test for the secondary endpoint Time to 12-week CDP from Cui, Hung, Wang to stratified logrank and clarified that Time to 24-week CDP will be analyzed in the same manner.	Rationale same as for change to Section 9.4.1.
9.4.4 Sequence of Analyses	- Removed the IA for USSR and included an optional IA for BSSR. - Clarified how the PA is triggered if the sample size is increased.	Rationale for replacing IA for USSR with optional IA for BSSR same as that for change to Section 4.1. Clarification.
9.4.4.1 Optional Interim Analysis for Blinded Sample Size Re-estimation	Removed the IA for USSR and included an optional IA for BSSR with details regarding methodology.	Rationale same as for change to Section 4.1.
9.4.4.2 Primary Analysis	- Clarified how the PA is triggered if the sample size is increased. - Clarified that the PA is based on data from the blinded Treatment Period.	Clarification.
9.4.4.4 Multiplicity	Removed the multiplicity approach for controlling family wise type I error at the	Rationale same as for change to Section 9.4.1.

Section # and Name	Description of Change	Brief Rationale
	1 sided 0.025 level in the presence of USSR based on pooled 12-week CDP.	
10 References	Removed Cui, Hung, Wang reference that is no longer applicable and included new reference applicable to BSSR (Friede et al., 2019).	Rationale same as for change to Section 4.1 and Section 9.4.1.
Throughout the document	Changes made to align with updated protocol template. Minor editorial and document formatting revisions.	Minor; therefore, have not been summarized.

Protocol Version 3.0 (19 May 2021)

Overall Rationale for the Amendment

The primary purpose of this amendment is to remove the interim analysis (IA) for unblinded sample size re-estimation (USSR) and include an optional IA for blinded sample size re-estimation (BSSR). A high-level description of each change is summarized below, along with its rationale.

Section # and Name	Description of Change	Brief Rationale
Title page	PPD replaces PPD as Medical Monitor. PPD is Medical Responsible.	Change in personnel.
1.1 Synopsis	- Updated this section to reflect the inclusion of an optional IA for BSSR which are detailed below. - Included clarification that enrollment in the Open Label Extension (OLE) can comprise participants who are still under study treatment when an event-driven primary analysis (PA) is triggered.	For consistency and clarification.
1.2 Study Schema	Updated the footnote to remove details of treatment period for participants entering the OLE period.	To be aligned with the inclusion of an optional IA for BSSR.
4.1 Overall Design	- Included clarification that enrollment in the OLE can comprise participants who are still under study treatment when an event-driven PA is triggered. - Included an optional IA for BSSR and the information that the number of participants to be enrolled may be increased to approximately 1162 randomized participants. - Removed the IA for USSR triggered when approximately 35% to 45% of planned 12-week CDP events have been observed. - Included clarification that enrollment in the OLE will be offered to participants who	Due to unexpectedly rapid enrollment, the trigger for the IA for USSR is projected to occur months after the completion of enrollment, considered too late to implement changes following outcome of IA from an operational perspective. The optional IA for BSSR, triggered prior to completion of enrollment, does not have this disadvantage.

Section # and Name	Description of Change	Brief Rationale
	have their blinded Treatment Period interrupted due to PA trigger as they will be considered as study completers.	
5.3.1 Inclusion Criteria for Open Label Extension Period 5.3.2 Exclusion Criteria for Open Label Extension Period	- Included clarification that inclusion in the OLE can comprise participants who are still under study treatment when an event-driven PA is triggered. - Included clarification that exclusion in the OLE can happen for participants who had discontinued blinded treatment prior to the PA trigger (in the case of an event-driven PA).	For clarification.
6.3.2 Blinding	Minor update to consider current changes related to PA trigger.	For consistency.
7.1 Discontinuation of Study Intervention	Criteria for Temporary Discontinuation of Study Intervention: Amylase and lipase retest criteria amended to include the fasting state.	For clarification.
8 Study Assessments and Procedures	Included the information that T-SPOT test will be conducted at the local laboratories after positive QuantiFERON test.	To correct error as the requirement was included in Protocol Version 2.0.
8 Study Assessments and Procedures	Sentence was rephrased to clarify that reported relapse will be adjudicated by the Endpoint Adjudication Committee.	For clarification.
8 Study Assessments and Procedures	Removed coagulation.	To correct error as the requirement was removed in Protocol Version 2.0.
8 Study Assessments and Procedures	Included clarification that enrollment in the OLE will be offered to participants who have their blinded Treatment Period interrupted due to PA trigger as they will be considered as study completers.	For clarification.
8 Study Assessments and Procedures 8.2.3 Electrocardiograms 9.4.2.4 Electrocardiogram Parameters	Sections were rephrased to consider central ECG reading.	To avoid variability in interpretation of ECGs by non-cardiologists and in reports obtained from the locally sourced ECG machines.
8.2.8 Independent Data Monitoring Committee, Endpoint Adjudication Committee, and Study Steering Committee	Removed the information that IDMC will review unblinded interim data.	Due to the removal of the IA for USSR, the role played by the IDMC in making the sample size increase recommendation is no longer required.
9.2 Sample Size Determination	Removed the IA for USSR and included an optional IA for BSSR and the information that a minimal or non-existent effect on type-1 error inflation is expected.	Rationale same as for change to Section 4.1.
9.4.1 Efficacy Analyses	Clarified that Time to 24-week confirmed disability progression (CDP) will be analyzed in the same manner as the Time to 12-week CDP.	Due to removing the IA for USSR, there is no need to control type-1 error in the 12-week CDP analysis using the Cui, Hung, Wang method. Thus, 12-week CDP and

Section # and Name	Description of Change	Brief Rationale
		24-week CDP will be analyzed in the same manner.
9.4.1.1 Efficacy Analyses Related to Primary Objective	Updated the treatment duration to consider the participants who have their blinded Treatment Period interrupted due to PA trigger.	To be aligned with the inclusion of an optional IA for BSSR.
9.4.1.2 Efficacy Analyses Related to Secondary Objectives	- Removed the IA for USSR and included an optional IA for BSSR with details regarding methodology. - Changed the statistical test for the secondary endpoint Time to 12-week CDP from Cui, Hung, Wang to stratified logrank and clarified that Time to 24-week CDP will be analyzed in the same manner.	Rationale same as for change to Section 9.4.1.
9.4.4 Sequence of Analyses	- Removed the IA for USSR and included an optional IA for BSSR. - Clarified how the PA is triggered if the sample size is increased.	Rationale for replacing IA for USSR with optional IA for BSSR same as that for change to Section 4.1. Clarification.
9.4.4.1 Optional Interim Analysis for Blinded Sample Size Re-estimation	Removed the IA for USSR and included an optional IA for BSSR with details regarding methodology.	Rationale same as for change to Section 4.1.
9.4.4.2 Primary Analysis	- Clarified how the PA is triggered if the sample size is increased. - Clarified that the PA is based on data from the blinded Treatment Period.	Clarification.
9.4.4.4 Multiplicity	Removed the multiplicity approach for controlling family wise type I error at the 1 sided 0.025 level in the presence of USSR based on pooled 12-week CDP.	Rationale same as for change to Section 9.4.1.
10 References	Removed Cui, Hung, Wang reference that is no longer applicable and included new refence applicable to BSSR (Friede et al., 2019).	Rationale same as for change to Section 4.1 and Section 9.4.1.
Throughout the document	Changes made to align with updated protocol template. Minor editorial and document formatting revisions.	Minor; therefore, have not been summarized.

Protocol Version 2.2_LTU (09 December 2020)

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

The purpose of this amendment is to align the Lithuania-specific protocol with Version 2.0 (global protocol amendment; 09 December 2020), in which changes and clarifications were made based on feedback from early enrolling investigational sites, and newly available data from studies of other agents in multiple sclerosis, and to clarify COVID mitigation procedures. A high-level description of each change is summarized below, along with its rationale.

Section # and Name	Description of Change	Brief Rationale
Title page Appendix 12 Sponsor Signature Page	PPD replaces PPD as Medical Monitor PPD is Medical Responsible	Changes in personnel
1.1 Synopsis, Study Intervention Groups and Duration 1.2 Schema 4.1 Overall Design	Additional text included, and minor rewording, to clarify the follow-up window for 'confirmation' of disability progression as measured by the EDSS	For additional clarification
1.1 Synopsis 1.2 Schema 4.1 Overall Design 5.5 Screen Failures Appendix 2 Study Governance	With approval from the Medical Monitor, the Screening period may be extended to 12 weeks maximum (increased from 8 weeks maximum). See Section 8 Study Assessments and Procedures	To allow sufficient time for repeat laboratory results and other unanticipated events prior to randomization
1.1 Synopsis 1.2 Schema 4.1 Overall Design 1.3 Schedule of Activities	Added that female participants may undergo AEP at the Investigator's discretion, and that the same AEP process should be followed as for male participants	To clarify the process in the event of a female participant undergoing AEP
1.3 Schedule of Activities (Main Study)	'F/D' changed to SFU (Safety Follow-up) F/D visit window changed from ± 3 days to + 3 days Added note that visit window for Week 4 is ± 2 days	To clarify that this is a safety visit SFU visit must be ≥ 28 days after last study intervention Clarification
1.3 Schedule of Activities (Main Study and OLE)	Telephone Visit: Simplified notes and referred to Structured Interview Clarified individual visits	Clarification/simplification of protocol. Structured interview put into place. Telephone Visit not required when participants attend clinic
1.3 Schedule of Activities (Main Study)	QuantiFERON testing removed from W48 and W96 visits Separate row added for TB testing for high TB burden countries	TB testing is only required at Screening if the participant resides in a country that has a high TB burden Separated testing in high TB burden countries to avoid confusion. Clarified that the assay used to confirm eligibility should be used for monitoring during the study
1.3 Schedule of Activities Efficacy (Main Study and OLE)	Added note that neurological evaluation EDSS, T25-FW, 9-HPT, and SDMT should preferably be done after the PRO assessments EDSS evaluation: added note that this can be done by phone, if available, if the participant is unable to attend scheduled visit	To clarify that these should preferably be completed before other assessments, but PROs are done first Mitigation in light of the COVID-19 pandemic, if the participant is unable to attend scheduled visit Lechner-Scott 2003)
1.3 Schedule of Activities PRO Assessments (Main Study)	SF-36 v2 assessment added at Week 108	Assessment required at Week 108 for participants for whom this is also D1 of the OLE
1.3 Schedule of Activities PRO Assessments (Main Study and OLE)	PROs: Removed reference to the use of a tablet	For flexibility in method of collection

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities Safety Assessments (Main Study and OLE)	C-SSRS: Removed reference to the use of a tablet	For flexibility in method of collection
1.3 Schedule of Activities Safety Assessments (Main Study and OLE)	Coagulation test will be done at Screening, W96, OLE D1 and W144 only	No exposure-related abnormalities in PT or PTT have been identified in prior studies of evobrutinib.
1.3 Schedule of Activities Safety Assessments (Main Study and OLE)	Text amended to indicate that urinalysis will be assessed locally and microscopy will be submitted for central evaluation only if indicated	Clarification
1.3 Schedule of Activities Safety Assessments (Main Study)	Noted that a second ECG will be collected postdose on Day 1, and that additional ECGs can be done at the Investigator's discretion	To clarify that there are 2 ECGs on Day 1 and to allow additional ECGs if required
1.3 Schedule of Activities Safety Assessments (Main Study and OLE)	Removed notes regarding telephone visits from 'AE, SAE & AESI Review' and 'Concomitant Medication and Procedures Review' rows	Clarification/simplification of protocol. Structured interview put into place
1.3 Schedule of Activities Study Intervention (Main Study)	Added dispensing of study intervention at Week 4	Requested by the study team
1.3 Schedule of Activities Study Intervention (Main Study and OLE)	Text amended to state when study intervention should be administered on site: PK sampling days (Main Study) and biomarker sample collection days (OLE) Removed detail about self-administration at home	To clarify when study intervention should be administered in the clinic To avoid confusion; detail is in Section 6.1
1.3 Schedule of Activities Study Intervention (Main Study and OLE)	Compliance: Clarified that participant should complete the Participant diary. Note added that the diary should be reviewed during on-site visits	Clarification
1.3 Schedule of Activities Biomarkers (Main study and OLE) 8.8.2 Novel Liver Function Protein Biomarkers and Novel Liver Function Genomic Biomarkers	Removed requirement for novel liver function protein and genomic biomarkers to be collected prior to first daily dose	Dosing time is not relevant to sample collection time
1.3 Schedule of Activities (OLE)	Note 'd': Added 'unless they are undergoing AEP'	The last visit in the main study will not be the first visit in the OLE for female participants undergoing AEP
1.3 Schedule of Activities (OLE)	Informed consent: Removed reference to 'male' and added reference to notes on AEP Added text so that consent to the OLE Period can be given before Day 1	To clarify that the consent procedure for participants undergoing AEP also applies to females Clarification
1.3 Schedule of Activities (OLE)	Blinded Teriflunomide Levels: note amended to refer to all participants undergoing AEP rather than male participants only Sample moved from D1 to AEP period	Teriflunomide should also be measured for females undergoing AEP To correct error

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (OLE)	Medical history was removed from the OLE	Medical history is collected at Screening; any changes thereafter are recorded as AEs
1.3 Schedule of Activities (OLE)	Added text to state that a serum pregnancy test is only required on Day 1 of the OLE if the last monthly urine pregnancy test was ≥ 1 month ago	A urine pregnancy test is sufficient at this visit unless there has been a gap of ≥ 1 month since the last test
1.3 Schedule of Activities (OLE)	'QuantiFERON testing' replaced with 'TB testing' in high TB burden countries and notes aligned with Main Study SoA TB test removed from Week 108	TB testing is only required in the OLE if the participant resides in a country that has a high TB burden Test at Week 108 is unnecessary
1.3 Schedule of Activities Study Intervention (OLE)	Study Intervention(s) Administration: Dosing will only occur on site at visits when biomarkers are collected	Dosing does not need to be on site for all visits
1.3 Schedule of Activities Safety Assessments (OLE)	Added reference to Section 7.1 in the notes section of the OLE Biochemistry and Hematology assessments	To clarify that the criteria for discontinuation of study intervention apply in the OLE
2.3 Benefit/Risk Assessment	Updated list of completed studies with no new potential risks emerging	To provide updated information
2.3 Benefit/Risk Assessment	Added text to address potential risk and mitigation to decrease risk of severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) infection	To address new risks associated with the emergence of the COVID-19 pandemic
3 Objectives and Endpoints 1.1 Synopsis	Header changed to 'Objectives and Estimands', and Table 1 changed to a 2-column format with estimand details added	To comply with change to protocol template which clarifies estimand strategy
3 Objectives and Estimands: Table 2 Tertiary/Exploratory Objectives and Endpoints 9.4.1 Efficacy Analyses	Two more endpoints added for the evaluation of the efficacy of evobrutinib relative to that of teriflunomide on MRI parameters	Previously missing
3 Objectives and Estimands Table 2 Tertiary/Exploratory Objectives and Endpoints 9.4.1 Efficacy Analyses	'New T1 Gd+ lesions' changed to 'T1 Gd+ lesions' Changes to wording of endpoints measured to evaluate the effect on composite parameters to use the term 'confirmed worsening' rather than CDP in relation to the 9-HPT score and T25-FW times Clarification that progression or worsening should be confirmed	To align with the correct definition for NEDA Clarification
3 Objectives and Estimands: Table 2 Tertiary/Exploratory Objectives and Endpoints	T_{max} removed from list of PK parameters for evaluation	T_{max} is not needed for any analyses and will not be calculated
3 Objectives and Estimands Table 3 Objectives and Endpoints for the Open Label Extension Period 1.1 Synopsis	Objectives and endpoints added for biomarkers collected during the OLE	Previously missing
4.2 Scientific Rationale for Study Design	Rationale for biomarkers added	Previously missing
4.4 End of Study Definition	Expanded definition of study completer	Clarification

Section # and Name	Description of Change	Brief Rationale
5 Study Population; Appendix 2 Study Governance, Informed Consent Process	Removed reference to 'legal representative' throughout document	Regulatory authority request (to clarify that legal representative will not be allowed in the study)
5.1 Inclusion Criteria	Inclusion 5: Added text to clarify definition of neurologically stable	Clarification
5.2 Exclusion Criteria	Exclusion 6: Wording changed from 'within 4 weeks of Screening' to 'within 4 weeks before or during Screening'	Clarification in the event of extension of the Screening period
5.2 Exclusion Criteria	Exclusion 7: 'QuantiFERON testing' replaced with 'TB testing' in high TB burden countries. Text added to allow use of an alternative test to the assay used at Screening per protocol	Separated testing in high TB burden countries to avoid confusion. To clarify when an orthogonal Interferon Gamma Release Assay should be used to assess TB status, and that for monitoring, the assay used to confirm eligibility should be used for monitoring during the study
5.2 Exclusion Criteria	Exclusion 8: Amended to include reevaluation of false positive QuantiFERON results Removed text stating that individuals should be excluded if T-SPOT.TB is not available	False positive results were not addressed in the original protocol To enable sites to do another QuantiFERON if a local T-SPOT.TB is not available
5.2 Exclusion Criteria	Exclusion 10: reworded to exclude participants with highly elevated ferritin levels independent of transferrin saturation	Revised after review of current guidelines for evaluation of hemochromatosis and expert consultation.
5.2 Exclusion Criteria	Exclusion 14: Amended language regarding suicidal behavior and C-SSRS scores	To ensure exclusion of individuals considered a significant suicide risk and to clarify a time period for the assessment
5.2 Exclusion Criteria	Exclusion 22: amended time frame for discontinuation of treatment with beta-interferons or glatiramer acetate prior to randomization to 1 day	This does not need to be discontinued as early as 4 weeks before randomization
5.2 Exclusion Criteria	Exclusion 23: Removed reference to lymphocyte count as this is in a separate criterion	Clarification
5.2 Exclusion Criteria	Exclusion 24: Added that reason for switch to teriflunomide must not have been because of efficacy or safety related considerations	Clarification regarding study population, changes made to ensure teriflunomide is an appropriate therapeutic option for individuals entering the study
5.2 Exclusion Criteria	Exclusion 25: Amended wording and timing regarding use of lymphocyte trafficking blockers Added use of S1P inhibitors as an exclusion	Reflects recently published clinical trials in RMS indicating that the revised exclusion periods are safe and appropriate
5.2 Exclusion Criteria	Exclusion 26: Time frame for use of IV Ig or plasmapheresis prior to randomization changed from 12 to 8 weeks	Reflects recently published clinical trials in RMS indicating that the revised exclusion periods are safe and appropriate

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria	Exclusion 27: ofatumumab added to list of exclusionary treatments	Clarification. Ofatumumab is a B-cell depleting therapy; added to avoid confusion as it is now an approved agent in some countries
5.2 Exclusion Criteria	Exclusion 28: amended to provide timings and clarification of immunosuppressive medications	Reflects recently published clinical trials in RMS indicating that the revised exclusion periods are safe and appropriate. Provides more complete guidance to sites regarding prior treatments.
5.2 Exclusion Criteria	Exclusion 30: Removed this exclusion criterion (treatment with medical marijuana)	Removed given the complex nature of marijuana regulation in different countries and lack of anticipated impact on patient safety.
5.2 Exclusion Criteria	Exclusion 31: Changed the time for stopping fish oil supplements from 4 weeks prior to randomization to just prior to randomization (first dose)	Given size and durability of effects of fish oil supplements on coagulation, a 4 week period off fish oil supplements is not required.
5.2 Exclusion Criteria 6.5.3 Prohibited Medicines	Exclusion 32: Removed text “Diabetes medications such as tolbutamide, and pioglitazone, repaglinide and rosiglitazone or other CYP2C8 substrates are also exclusionary” and replaced with “CYP2C8 substrates with a narrow therapeutic index must also be stopped at least 1 day prior to randomization” Added clarification that CYP2B6 substrates with a narrow therapeutic index, as well as substrates of P-gp, BCRP, OCT1, MATE1 and/or MATE2K should be used with caution	 To correct an error Clarification on medicines to be used with caution.
5.2 Exclusion Criteria 7.1 Discontinuation of Study Intervention	Exclusion 34: Amended to permit inclusion of participants with HBV DNA detectable at levels below 20 IU/mL Clarified level of detectable HBV DNA for study intervention discontinuation	In prior studies of evobrutinib, evobrutinib was given to individuals with HBV DNA < 20 IU/mL, and HBV reactivation was not observed. To align with change to Exclusion Criterion 34
5.3.2 Exclusion Criteria for Open Label Extension Period	Exclusion 6: Gamma glutamyl transferase removed from list of abnormal blood tests requiring discontinuation	Correction aligns OLE exclusion criterion with main study stopping rules. GGT was included unintentionally.
5.4.1 Meals and Dietary Restrictions	Red wine removed from restrictions	No clinically relevant interaction between red wine and either study medication is anticipated. Red wine was not prohibited from prior studies of evobrutinib and no interactions were observed
6.1 Study Intervention(s) Administration	Dosing Instructions amended Packaging and Labeling information expanded	To align with elsewhere in the protocol Clarification

Section # and Name	Description of Change	Brief Rationale
6.2 Study Intervention(s) Preparation, Handling, Storage, and Accountability	Details of storage conditions for teriflunomide and its placebo were replaced with a reference to the teriflunomide product label	Clarification
6.3.2 Blinding	Clarified the wording regarding the assignment of a Treating Investigator Designee Moved the Treating Investigator text before the Examining Investigator text Added bullet to state that the Treating Investigator (or designee) and the Examining Investigator (or designee) cannot perform the same tests	Clarification Logical flow For additional clarity
6.4 Study Intervention Compliance 8 Study Assessments and Procedures	Clarified that food intake only needs to be recorded in the Participant diary around the time of dosing on the day prior to PK sampling and the day of PK sampling, and around the time of the last dose prior to evobrutinib concentration assessment sampling	Clarification
6.4 Study Intervention Compliance	Added text to indicate that participants only need to bring in study intervention at study visits 'during which IMP is dispensed'	To relieve burden on participants
6.5 Concomitant Therapy 6.5.3 Prohibited Medicines	"During the OLE, initiation of therapy with dalfampridine (Ampyra®) is allowed, if indicated by the Treating Investigator": text moved from Section 6.5 Concomitant Therapy to Section 6.5.3 Prohibited Medicines	Incorrect location
6.5.1 Rescue Medicine	Text added to allow use of methylprednisolone as an oral formulation Text added to allow use of an approved equivalent of Acthar gel	To provide flexibility (particularly in light of the Covid-19 pandemic) To allow use of an approved equivalent of Acthar gel
6.5.2 Permitted Medicines	Amended restrictions on use of marijuana	To align with removal of marijuana exclusion criterion
6.5.3 Prohibited Medicines	Ofatumumab added to list of medicines prohibited during the study Added azathioprine and methotrexate as examples of prohibited immunosuppressive treatments Live-attenuated vaccines added to list of medicines prohibited during the study Systemic corticosteroids (oral, injected, IV) added to list of medicines prohibited during the study (topical, intranasal, or inhaled corticosteroids are permitted)	Ofatumumab is a B-cell depleting therapy; added to avoid confusion as it is now an approved agent in some countries To align with the updated exclusion criterion #28 Omitted in error Omitted in error
6.5.4 Other Interventions	Resveratrol > 500 mg/day added to list of herbal and nutritional supplements that must be stopped at least 1 week prior to randomization	Resveratrol supplements of > 500 mg/day may result in clinically significant inhibition of CYP3A

Section # and Name	Description of Change	Brief Rationale
6.9 Management of Adverse Events of Interest	Liver adverse events: Level of increase clarified for transaminases and bilirubin elevations to be considered AESIs	Clarification
	Amylase and Lipase Elevations: CTCAE Grade ≥ 3 elevation changed to > 2 × ULN for AESI classification	To clarify a discrepancy between CTCAE Version 4.03 and Version 5.0
7.1 Discontinuation of Study Intervention	Added template mandatory text regarding permanent discontinuation (at start of section)	Previously missing
	Added text to indicate that the criteria for discontinuation of study intervention apply during both the main study and the OLE Period	Clarification
	Added local standard of care option for accelerated elimination of teriflunomide	To allow investigators to manage participants in accordance with local standard of care
7.1 Discontinuation of Study Intervention, Criteria for Permanent Discontinuation of Study Intervention	Text added to clarify that the lab criteria should be confirmed before study intervention is discontinued	Clarification
	For pregnancy reasons: changed the requirement that AEP 'must' be performed to 'should' be performed, and teriflunomide level < 0.02 mg/L 'has to' be reached to 'should' be reached	This is a decision for the Investigator and the participant; it is not absolutely mandatory
	Added text that a protocol deviation should be documented if prohibited medication is used	Clarification
7.1 Discontinuation of Study Intervention 8 Study Assessments and Procedures Appendix 5 Clinical Laboratory Tests	Erythrocyte sedimentation rate removed from list of hepatic assessments	Erythrocyte sedimentation rate via on-site/local laboratory was included in error as hsCRP is already collected and processed via central laboratory
7.1 Discontinuation of Study Intervention	Criteria for Temporary Discontinuation of Study Intervention: Amylase retest criteria amended and simplified to allow reinitiation of study intervention if value decreases to ≤ 2 × ULN upon retest Lipase retest criteria amended and simplified to allow reinitiation of study intervention if value decreases to ≤ 2 × ULN upon retest	To clarify a discrepancy between CTCAE Version 4.03 and Version 5.0
7.1 Discontinuation of Study Intervention	Criteria for Temporary Discontinuation of Study Intervention: Serum creatinine criteria changed to "For any increase in serum creatinine > 1.5 × ULN but ≤ 3 × ULN…"	Criteria did not cover an exact 3 × ULN and required clarification
7.1 Discontinuation of Study Intervention 8.3.5 Pregnancy	Changed requirement for AEP in pregnant participant from 'must' to 'should' be performed	To align with the AEP
8 Study Assessments and Procedures	Date of last menstrual period will not be collected	Not required

Section # and Name	Description of Change	Brief Rationale
8 Study Assessments and Procedures	Additional criteria added for extending the Screening Period, and permitted extension increased to a maximum of 12 weeks Instructions added for repeating ferritin or transferrin saturation tests	To provide guidance for retesting of ferritin or transferring saturation tests and allow sufficient time for repeat laboratory results and other unanticipated events prior to randomization
8 Study Assessments and Procedures	Telephone Visit: Replaced bulleted list of discussion items with a reference to the Structured Interview in Appendix 10	Clarification/simplification of protocol. Structured interview put into place.
8.1.1 Neurological Assessment	Added text to clarify the assignment of a Qualified Examining Designee	Clarification
8.1.1.1 Qualified Relapse	Added that if neurological signs and symptoms are identified that are consistent with relapse, the participant should be evaluated on site	Clarification; relapse cannot be confirmed over the phone
8.1.1.6 Symbol Digit Modalities Test	Text added to clarify that two different SDMT forms will be used, administered at alternating visits	Clarification
8.1.2 Brain Magnetic Resonance Imaging Scans	Amended text to state that images will be assessed (not assessed and reported) Added that the Treating Investigator can have access to the Screening (baseline) MRI scan in order to evaluate eligibility	To correct an error Access to the Screening (baseline) MRI scan is needed to evaluate eligibility
8.1.2 Brain Magnetic Resonance Imaging Scans 1.3 Schedule of Activities (Main Study)	Changed 'Screening/Baseline MRI' to 'Screening (Baseline) MRI'	To clarify that the MRI done at screening is the baseline MRI, rather than suggesting that an MRI might be done at the Baseline visit.
8.1.3 Patient Reported Outcomes 1.3 Schedule of Activities	Added text to allow an alternative method of PRO data collection Removed reference to the use of a tablet for PRO assessments	To allow an alternative method of collection in the event that a tablet cannot be used
8.2.2 Vital Signs	Text added to indicate that temperature should be measured at the same location throughout the study	To avoid variation in results if different methods were used
8.2.3 Electrocardiograms	Text amended to indicate that QTcF will be automatically calculated in the eCRF; it is not obtained from the ECG	Clarification
8.2.7 Columbia-Suicide Severity Rating Scale 1.3 Schedule of Activities (Main Study and OLE)	Text added to state that the C-SSRS may be administered by an assigned designee of the Treating Investigator	To clarify that the C-SSRS may be delegated per Section 6.3.2
8.3.5 Pregnancy	Amended all text regarding collection and reporting of pregnancy information Added that information on pregnant partners only needs to be collected in the Main Study	Text updated in accordance with new protocol template Once a male participant switches to evobrutinib in the OLE, it is not necessary to collect information on pregnancies in their partners
8.4 Treatment of Overdose	Definition of overdose amended to: "…within a 24-hour time period – [minus] 6 hours…"	To prevent erroneous reports of overdose
8.5 Pharmacokinetics	T_{max} removed from list of PK parameters for evaluation Revisions to definitions of PK parameters	T_{max} is not needed for any analyses and will not be calculated Correction

Section # and Name	Description of Change	Brief Rationale
9.1.2 Statistical Hypotheses Related to Secondary Objectives	Change to null hypothesis for the secondary endpoint CFB in PROMIS Fatigue score at 96 weeks	Correction
9.4.1 Efficacy Analyses Secondary efficacy endpoints: Time to 12-week CDP Time to 24-week CDP 9.4.1.2 Efficacy Analyses Related to Secondary Objectives	Statistical Analysis Methods: Cox model made consistent with Log-rank test which has strata defined by randomization strata and study ID	Correction
9.4.1 Efficacy Analyses Tertiary/Exploratory endpoints	Statistical Analysis Methods: Correction to test regarding stratified Cox model strata Minor edits to text	 Correction Clarification of statistical methods
9.4.1 Efficacy Analyses Tertiary/Exploratory endpoints	'Change in normalized T1 intensity…' endpoint moved to a new row New text for statistical method for the 'Volume of SELs…' endpoint	Correction of statistical method based on information from NeuroRx indicating one postbaseline value per participant
9.4.4.4 Multiplicity	Secondary Endpoint Null Hypotheses for H_{05}: '$\Delta_{Fatigue} \leq 0$' changed to '$\Delta_{Fatigue} \geq 0$', and 'higher score corresponds to reduced fatigue' changed to 'higher score corresponds to more fatigue'	Correction
10 References	Additional references added	In line with changes to text
Appendix 2 Study Governance	Study and Site Closure: Text added to indicate that new or emerging safety information that negatively affects the benefit/risk assessment of the clinical study may be a reason for closing study sites or terminating the study	Health Authority Request
Appendix 3 Contraception	Added missing footnote label 'a' Added footnote 'b' to indicate that if a WOCBP is using a highly effective method other than sexual abstinence or vasectomized partner, AND ALSO has a vasectomized partner, the vasectomized partner will be considered the "barrier method" for study purposes	Label was missing in footnotes Clarification
Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Events Not to Be Considered as AEs/SAEs: Text added to state that worsening of the underlying disease is not routinely considered an AE or SAE Text on reporting of AESIs was updated in line with the latest protocol template	Alignment with template wording For clarification and so that EDC can be used
Appendix 5 Clinical Laboratory Tests	Moved some assessments listed in 'Other screening tests' into new row 'Other tests' JCV DNA PCR added to list of 'Other screening tests' Estradiol removed from list of 'Other screening tests' βhCG removed from routine urinalysis	Clarification; not all tests listed were Screening only To include missing information Estradiol not used to determine postmenopausal status in this study This is a serum test; now listed under other tests

Section # and Name	Description of Change	Brief Rationale
	Teriflunomide footnote amended to include all participants undergoing AEP	To include females undergoing AEP
Appendix 8 Procedure for Accelerated Elimination of Teriflunomide	Text added to allow accelerated elimination of teriflunomide in accordance with standard of care Text added to note that it is only required to confirm a level of < 0.02 mg/L after the AEP if the AEP is being done for pregnancy-related considerations	To allow accelerated elimination of teriflunomide in accordance with local guidance For clarification
Appendix 10 Structured Interview at Telephone Visit	New appendix added: 'Structured Interview at Telephone Visit'	Clarification/simplification of protocol. Structured interview put into place to identify any new or worsening neurological symptoms that warrant evaluation at an unscheduled visit
Throughout the document	Changes made to align with updated protocol template Minor editorial and document formatting revisions	Minor; therefore, have not been summarized

Protocol Version 2.1-CAN (09 December 2020)

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

The purpose of this amendment is to align the Canada-specific protocol with Version 2.0 (global protocol amendment; 09 December 2020), in which changes and clarifications were made based on feedback from early enrolling investigational sites, and newly available data from studies of other agents in multiple sclerosis, and to clarify COVID mitigation procedures. A high-level description of each change is summarized below, along with its rationale.

Section # and Name	Description of Change	Brief Rationale
Title page Appendix 12 Sponsor Signature Page	PPD replaces PPD as Medical Monitor PPD is Medical Responsible	Changes in personnel
1.1 Synopsis, Study Intervention Groups and Duration 1.2 Schema 4.1 Overall Design	Additional text included, and minor rewording, to clarify the follow-up window for 'confirmation' of disability progression as measured by the EDSS	For additional clarification
1.1 Synopsis 1.2 Schema 4.1 Overall Design 5.5 Screen Failures Appendix 2 Study Governance	With approval from the Medical Monitor, the Screening period may be extended to 12 weeks maximum (increased from 8 weeks maximum). See Section 8 Study Assessments and Procedures	To allow sufficient time for repeat laboratory results and other unanticipated events prior to randomization

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.2 Schema 4.1 Overall Design 1.3 Schedule of Activities	Added that female participants may undergo AEP at the Investigator's discretion, and that the same AEP process should be followed as for male participants	To clarify the process in the event of a female participant undergoing AEP
1.3 Schedule of Activities (Main Study)	'F/D' changed to SFU (Safety Follow-up) F/D visit window changed from ± 3 days to + 3 days Added note that visit window for Week 4 is ± 2 days	To clarify that this is a safety visit SFU visit must be ≥ 28 days after last study intervention Clarification
1.3 Schedule of Activities (Main Study and OLE)	Telephone Visit: Simplified notes and referred to Structured Interview Clarified individual visits	Clarification/simplification of protocol. Structured interview put into place. Telephone Visit not required when participants attend clinic
1.3 Schedule of Activities (Main Study)	QuantiFERON testing removed from W48 and W96 visits Separate row added for TB testing for high TB burden countries	TB testing is only required at Screening if the participant resides in a country that has a high TB burden Separated testing in high TB burden countries to avoid confusion. Clarified that the assay used to confirm eligibility should be used for monitoring during the study
1.3 Schedule of Activities Efficacy (Main Study and OLE)	Added note that neurological evaluation EDSS, T25-FW, 9-HPT, and SDMT should preferably be done after the PRO assessments EDSS evaluation: added note that this can be done by phone, if available, if the participant is unable to attend scheduled visit	To clarify that these should preferably be completed before other assessments, but PROs are done first Mitigation in light of the COVID-19 pandemic, if the participant is unable to attend scheduled visit Lechner-Scott 2003)
1.3 Schedule of Activities PRO Assessments (Main Study)	SF-36 v2 assessment added at Week 108	Assessment required at Week 108 for participants for whom this is also D1 of the OLE
1.3 Schedule of Activities PRO Assessments (Main Study and OLE)	PROs: Removed reference to the use of a tablet	For flexibility in method of collection
1.3 Schedule of Activities Safety Assessments (Main Study and OLE)	C-SSRS: Removed reference to the use of a tablet	For flexibility in method of collection
1.3 Schedule of Activities Safety Assessments (Main Study and OLE)	Coagulation test will be done at Screening, W96, OLE D1 and W144 only	No exposure-related abnormalities in PT or PTT have been identified in prior studies of evobrutinib.
1.3 Schedule of Activities Safety Assessments (Main Study and OLE)	Text amended to indicate that urinalysis will be assessed locally and microscopy will be submitted for central evaluation only if indicated	Clarification
1.3 Schedule of Activities Safety Assessments (Main Study)	Noted that a second ECG will be collected postdose on Day 1, and that additional ECGs can be done at the Investigator's discretion	To clarify that there are 2 ECGs on Day 1 and to allow additional ECGs if required
1.3 Schedule of Activities	Removed notes regarding telephone	Clarification/simplification of

Section # and Name	Description of Change	Brief Rationale
Safety Assessments (Main Study and OLE)	visits from 'AE, SAE & AESI Review' and 'Concomitant Medication and Procedures Review' rows	protocol. Structured interview put into place
1.3 Schedule of Activities Study Intervention (Main Study)	Added dispensing of study intervention at Week 4	Requested by the study team
1.3 Schedule of Activities Study Intervention (Main Study and OLE)	Text amended to state when study intervention should be administered on site: PK sampling days (Main Study) and biomarker sample collection days (OLE) Removed detail about self-administration at home	To clarify when study intervention should be administered in the clinic To avoid confusion; detail is in Section 6.1
1.3 Schedule of Activities Study Intervention (Main Study and OLE)	Compliance: Clarified that participant should complete the Participant diary. Note added that the diary should be reviewed during on-site visits	Clarification
1.3 Schedule of Activities Biomarkers (Main study and OLE) 8.8.2 Novel Liver Function Protein Biomarkers and Novel Liver Function Genomic Biomarkers	Removed requirement for novel liver function protein and genomic biomarkers to be collected prior to first daily dose	Dosing time is not relevant to sample collection time
1.3 Schedule of Activities (OLE)	Note 'd': Added 'unless they are undergoing AEP'	The last visit in the main study will not be the first visit in the OLE for female participants undergoing AEP
1.3 Schedule of Activities (OLE)	Informed consent: Removed reference to 'male' and added reference to notes on AEP Added text so that consent to the OLE Period can be given before Day 1	To clarify that the consent procedure for participants undergoing AEP also applies to females Clarification
1.3 Schedule of Activities (OLE)	Blinded Teriflunomide Levels: note amended to refer to all participants undergoing AEP rather than male participants only Sample moved from D1 to AEP period	Teriflunomide should also be measured for females undergoing AEP To correct error
1.3 Schedule of Activities (OLE)	Medical history was removed from the OLE	Medical history is collected at Screening; any changes thereafter are recorded as AEs
1.3 Schedule of Activities (OLE)	Added text to state that a serum pregnancy test is only required on Day 1 of the OLE if the last monthly urine pregnancy test was ≥ 1 month ago	A urine pregnancy test is sufficient at this visit unless there has been a gap of ≥ 1 month since the last test
1.3 Schedule of Activities (OLE)	'QuantiFERON testing' replaced with 'TB testing' in high TB burden countries and notes aligned with Main Study SoA TB test removed from Week 108	TB testing is only required in the OLE if the participant resides in a country that has a high TB burden Test at Week 108 is unnecessary
1.3 Schedule of Activities Study Intervention (OLE)	Study Intervention(s) Administration: Dosing will only occur on site at visits when biomarkers are collected	Dosing does not need to be on site for all visits

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities Safety Assessments (OLE)	Added reference to Section 7.1 in the notes section of the OLE Biochemistry and Hematology assessments	To clarify that the criteria for discontinuation of study intervention apply in the OLE
2.3 Benefit/Risk Assessment	Updated list of completed studies with no new potential risks emerging	To provide updated information
2.3 Benefit/Risk Assessment	Added text to address potential risk and mitigation to decrease risk of severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) infection	To address new risks associated with the emergence of the COVID-19 pandemic
3 Objectives and Endpoints 1.1 Synopsis	Header changed to 'Objectives and Estimands', and Table 1 changed to a 2-column format with estimand details added	To comply with change to protocol template which clarifies estimand strategy
3 Objectives and Estimands: Table 2 Tertiary/Exploratory Objectives and Endpoints 9.4.1 Efficacy Analyses	Two more endpoints added for the evaluation of the efficacy of evobrutinib relative to that of teriflunomide on MRI parameters	Previously missing
3 Objectives and Estimands Table 2 Tertiary/Exploratory Objectives and Endpoints 9.4.1 Efficacy Analyses	'New T1 Gd+ lesions' changed to 'T1 Gd+ lesions' Changes to wording of endpoints measured to evaluate the effect on composite parameters to use the term 'confirmed worsening' rather than CDP in relation to the 9-HPT score and T25-FW times Clarification that progression or worsening should be confirmed	To align with the correct definition for NEDA Clarification
3 Objectives and Estimands: Table 2 Tertiary/Exploratory Objectives and Endpoints	T_{max} removed from list of PK parameters for evaluation	T_{max} is not needed for any analyses and will not be calculated
3 Objectives and Estimands Table 3 Objectives and Endpoints for the Open Label Extension Period 1.1 Synopsis	Objectives and endpoints added for biomarkers collected during the OLE	Previously missing
4.2 Scientific Rationale for Study Design	Rationale for biomarkers added	Previously missing
4.4 End of Study Definition	Expanded definition of study completer	Clarification
5 Study Population; Appendix 2 Study Governance, Informed Consent Process	Removed reference to 'legal representative' throughout document	Regulatory authority request (to clarify that legal representative will not be allowed in the study)
5.1 Inclusion Criteria	Inclusion 5: Added text to clarify definition of neurologically stable	Clarification
5.2 Exclusion Criteria	Exclusion 6: Wording changed from 'within 4 weeks of Screening' to 'within 4 weeks before or during Screening'	Clarification in the event of extension of the Screening period

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria	Exclusion 7: 'QuantiFERON testing' replaced with 'TB testing' in high TB burden countries. Text added to allow use of an alternative test to the assay used at Screening per protocol	Separated testing in high TB burden countries to avoid confusion. To clarify when an orthogonal Interferon Gamma Release Assay should be used to assess TB status, and that for monitoring, the assay used to confirm eligibility should be used for monitoring during the study
5.2 Exclusion Criteria	Exclusion 8: Amended to include reevaluation of false positive QuantiFERON results Removed text stating that individuals should be excluded if T-SPOT.TB is not available	False positive results were not addressed in the original protocol To enable sites to do another QuantiFERON if a local T-SPOT.TB is not available
5.2 Exclusion Criteria	Exclusion 10: reworded to exclude participants with highly elevated ferritin levels independent of transferrin saturation	Revised after review of current guidelines for evaluation of hemochromatosis and expert consultation.
5.2 Exclusion Criteria	Exclusion 14: Amended language regarding suicidal behavior and C-SSRS scores	To ensure exclusion of individuals considered a significant suicide risk and to clarify a time period for the assessment
5.2 Exclusion Criteria	Exclusion 22: amended time frame for discontinuation of treatment with beta-interferons or glatiramer acetate prior to randomization to 1 day	This does not need to be discontinued as early as 4 weeks before randomization
5.2 Exclusion Criteria	Exclusion 23: Removed reference to lymphocyte count as this is in a separate criterion	Clarification
5.2 Exclusion Criteria	Exclusion 24: Added that reason for switch to teriflunomide must not have been because of efficacy or safety related considerations	Clarification regarding study population, changes made to ensure teriflunomide is an appropriate therapeutic option for individuals entering the study
5.2 Exclusion Criteria	Exclusion 25: Amended wording and timing regarding use of lymphocyte trafficking blockers Added use of S1P inhibitors as an exclusion	Reflects recently published clinical trials in RMS indicating that the revised exclusion periods are safe and appropriate
5.2 Exclusion Criteria	Exclusion 26: Time frame for use of IV Ig or plasmapheresis prior to randomization changed from 12 to 8 weeks	Reflects recently published clinical trials in RMS indicating that the revised exclusion periods are safe and appropriate
5.2 Exclusion Criteria	Exclusion 27: ofatumumab added to list of exclusionary treatments	Clarification. Ofatumumab is a B-cell depleting therapy; added to avoid confusion as it is now an approved agent in some countries
5.2 Exclusion Criteria	Exclusion 28: amended to provide timings and clarification of immunosuppressive medications	Reflects recently published clinical trials in RMS indicating that the revised exclusion periods are safe and appropriate. Provides more complete guidance to sites regarding prior treatments.

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria	Exclusion 30: Removed this exclusion criterion (treatment with medical marijuana)	Removed given the complex nature of marijuana regulation in different countries and lack of anticipated impact on patient safety.
5.2 Exclusion Criteria	Exclusion 31: Changed the time for stopping fish oil supplements from 4 weeks prior to randomization to just prior to randomization (first dose)	Given size and durability of effects of fish oil supplements on coagulation, a 4 week period off fish oil supplements is not required.
5.2 Exclusion Criteria 6.5.3 Prohibited Medicines	Exclusion 32: Removed text "Diabetes medications such as tolbutamide, and pioglitazone, repaglinide and rosiglitazone or other CYP2C8 substrates are also exclusionary" and replaced with "CYP2C8 substrates with a narrow therapeutic index must also be stopped at least 1 day prior to randomization" Added clarification that CYP2B6 substrates with a narrow therapeutic index, as well as substrates of P-gp, BCRP, OCT1, MATE1 and/or MATE2K should be used with caution	 To correct an error Clarification on medicines to be used with caution.
5.2 Exclusion Criteria 7.1 Discontinuation of Study Intervention	Exclusion 34: Amended to permit inclusion of participants with HBV DNA detectable at levels below 20 IU/mL Clarified level of detectable HBV DNA for study intervention discontinuation	In prior studies of evobrutinib, evobrutinib was given to individuals with HBV DNA < 20 IU/mL, and HBV reactivation was not observed. To align with change to Exclusion Criterion 34
5.3.2 Exclusion Criteria for Open Label Extension Period	Exclusion 6: Gamma glutamyl transferase removed from list of abnormal blood tests requiring discontinuation	Correction aligns OLE exclusion criterion with main study stopping rules. GGT was included unintentionally.
5.4.1 Meals and Dietary Restrictions	Red wine removed from restrictions	No clinically relevant interaction between red wine and either study medication is anticipated. Red wine was not prohibited from prior studies of evobrutinib and no interactions were observed
6.1 Study Intervention(s) Administration	Dosing Instructions amended Packaging and Labeling information expanded	To align with elsewhere in the protocol Clarification
6.2 Study Intervention(s) Preparation, Handling, Storage, and Accountability	Details of storage conditions for teriflunomide and its placebo were replaced with a reference to the teriflunomide product label	Clarification
6.3.2 Blinding	Clarified the wording regarding the assignment of a Treating Investigator Designee Moved the Treating Investigator text before the Examining Investigator text	Clarification Logical flow For additional clarity

Section # and Name	Description of Change	Brief Rationale
	Added bullet to state that the Treating Investigator (or designee) and the Examining Investigator (or designee) cannot perform the same tests	
6.4 Study Intervention Compliance 8 Study Assessments and Procedures	Clarified that food intake only needs to be recorded in the Participant diary around the time of dosing on the day prior to PK sampling and the day of PK sampling, and around the time of the last dose prior to evobrutinib concentration assessment sampling	Clarification
6.4 Study Intervention Compliance	Added text to indicate that participants only need to bring in study intervention at study visits 'during which IMP is dispensed'	To relieve burden on participants
6.5 Concomitant Therapy 6.5.3 Prohibited Medicines	"During the OLE, initiation of therapy with dalfampridine (Ampyra®) is allowed, if indicated by the Treating Investigator": text moved from Section 6.5 Concomitant Therapy to Section 6.5.3 Prohibited Medicines	Incorrect location
6.5.1 Rescue Medicine	Text added to allow use of methylprednisolone as an oral formulation Text added to allow use of an approved equivalent of Acthar gel	To provide flexibility (particularly in light of the Covid-19 pandemic) To allow use of an approved equivalent of Acthar gel
6.5.2 Permitted Medicines	Amended restrictions on use of marijuana	To align with removal of marijuana exclusion criterion
6.5.3 Prohibited Medicines	Ofatumumab added to list of medicines prohibited during the study Added azathioprine and methotrexate as examples of prohibited immunosuppressive treatments Live-attenuated vaccines added to list of medicines prohibited during the study Systemic corticosteroids (oral, injected, IV) added to list of medicines prohibited during the study (topical, intranasal, or inhaled corticosteroids are permitted)	Ofatumumab is a B-cell depleting therapy; added to avoid confusion as it is now an approved agent in some countries To align with the updated exclusion criterion #28 Omitted in error Omitted in error
6.5.4 Other Interventions	Resveratrol > 500 mg/day added to list of herbal and nutritional supplements that must be stopped at least 1 week prior to randomization	Resveratrol supplements of > 500 mg/day may result in clinically significant inhibition of CYP3A
6.9 Management of Adverse Events of Interest	Liver adverse events: Level of increase clarified for transaminases and bilirubin elevations to be considered AESIs Amylase and Lipase Elevations: CTCAE Grade ≥ 3 elevation changed to > 2 × ULN for AESI classification	Clarification To clarify a discrepancy between CTCAE Version 4.03 and Version 5.0
7.1 Discontinuation of Study Intervention	Added template mandatory text regarding permanent discontinuation (at start of section)	Previously missing

Section # and Name	Description of Change	Brief Rationale
	Added text to indicate that the criteria for discontinuation of study intervention apply during both the main study and the OLE Period	Clarification
	Added local standard of care option for accelerated elimination of teriflunomide	To allow investigators to manage participants in accordance with local standard of care
7.1 Discontinuation of Study Intervention, Criteria for Permanent Discontinuation of Study Intervention	Text added to clarify that the lab criteria should be confirmed before study intervention is discontinued	Clarification
	For pregnancy reasons: changed the requirement that AEP 'must' be performed to 'should' be performed, and teriflunomide level < 0.02 mg/L 'has to' be reached to 'should' be reached	This is a decision for the Investigator and the participant; it is not absolutely mandatory
	Added text that a protocol deviation should be documented if prohibited medication is used	Clarification
7.1 Discontinuation of Study Intervention 8 Study Assessments and Procedures Appendix 5 Clinical Laboratory Tests	Erythrocyte sedimentation rate removed from list of hepatic assessments	Erythrocyte sedimentation rate via on-site/local laboratory was included in error as hsCRP is already collected and processed via central laboratory
7.1 Discontinuation of Study Intervention	Criteria for Temporary Discontinuation of Study Intervention: Amylase retest criteria amended and simplified to allow reinitiation of study intervention if value decreases to ≤ 2 × ULN upon retest Lipase retest criteria amended and simplified to allow reinitiation of study intervention if value decreases to ≤ 2 × ULN upon retest	To clarify a discrepancy between CTCAE Version 4.03 and Version 5.0
7.1 Discontinuation of Study Intervention	Criteria for Temporary Discontinuation of Study Intervention: Serum creatinine criteria changed to "For any increase in serum creatinine > 1.5 × ULN but ≤ 3 × ULN…"	Criteria did not cover an exact 3 × ULN and required clarification
7.1 Discontinuation of Study Intervention 8.3.5 Pregnancy	Changed requirement for AEP in pregnant participant from 'must' to 'should' be performed	To align with the AEP
8 Study Assessments and Procedures	Date of last menstrual period will not be collected	Not required
8 Study Assessments and Procedures	Additional criteria added for extending the Screening Period, and permitted extension increased to a maximum of 12 weeks Instructions added for repeating ferritin or transferrin saturation tests	To provide guidance for retesting of ferritin or transferring saturation tests and allow sufficient time for repeat laboratory results and other unanticipated events prior to randomization
8 Study Assessments and Procedures	Telephone Visit: Replaced bulleted list of discussion items with a reference to the Structured Interview in Appendix 10	Clarification/simplification of protocol. Structured interview put into place.
8.1.1 Neurological Assessment	Added text to clarify the assignment of a Qualified Examining Designee	Clarification

Section # and Name	Description of Change	Brief Rationale
8.1.1.1 Qualified Relapse	Added that if neurological signs and symptoms are identified that are consistent with relapse, the participant should be evaluated on site	Clarification; relapse cannot be confirmed over the phone
8.1.1.6 Symbol Digit Modalities Test	Text added to clarify that two different SDMT forms will be used, administered at alternating visits	Clarification
8.1.2 Brain Magnetic Resonance Imaging Scans	Amended text to state that images will be assessed (not assessed and reported) Added that the Treating Investigator can have access to the Screening (baseline) MRI scan in order to evaluate eligibility	To correct an error Access to the Screening (baseline) MRI scan is needed to evaluate eligibility
8.1.2 Brain Magnetic Resonance Imaging Scans 1.3 Schedule of Activities (Main Study)	Changed 'Screening/Baseline MRI' to 'Screening (Baseline) MRI'	To clarify that the MRI done at screening is the baseline MRI, rather than suggesting that an MRI might be done at the Baseline visit.
8.1.3 Patient Reported Outcomes 1.3 Schedule of Activities	Added text to allow an alternative method of PRO data collection Removed reference to the use of a tablet for PRO assessments	To allow an alternative method of collection in the event that a tablet cannot be used
8.2.2 Vital Signs	Text added to indicate that temperature should be measured at the same location throughout the study	To avoid variation in results if different methods were used
8.2.3 Electrocardiograms	Text amended to indicate that QTcF will be automatically calculated in the eCRF; it is not obtained from the ECG	Clarification
8.2.7 Columbia-Suicide Severity Rating Scale 1.3 Schedule of Activities (Main Study and OLE)	Text added to state that the C-SSRS may be administered by an assigned designee of the Treating Investigator	To clarify that the C-SSRS may be delegated per Section 6.3.2
8.3.5 Pregnancy	Amended all text regarding collection and reporting of pregnancy information Added that information on pregnant partners only needs to be collected in the Main Study	Text updated in accordance with new protocol template Once a male participant switches to evobrutinib in the OLE, it is not necessary to collect information on pregnancies in their partners
8.4 Treatment of Overdose	Definition of overdose amended to: "…within a 24-hour time period – [minus] 6 hours…"	To prevent erroneous reports of overdose
8.5 Pharmacokinetics	T_{max} removed from list of PK parameters for evaluation Revisions to definitions of PK parameters	T_{max} is not needed for any analyses and will not be calculated Correction
9.1.2 Statistical Hypotheses Related to Secondary Objectives	Change to null hypothesis for the secondary endpoint CFB in PROMIS Fatigue score at 96 weeks	Correction
9.4.1 Efficacy Analyses Secondary efficacy endpoints: Time to 12-week CDP Time to 24-week CDP 9.4.1.2 Efficacy Analyses Related to Secondary Objectives	Statistical Analysis Methods: Cox model made consistent with Log-rank test which has strata defined by randomization strata and study ID	Correction
9.4.1 Efficacy Analyses Tertiary/Exploratory endpoints	Statistical Analysis Methods:	

Section # and Name	Description of Change	Brief Rationale
	Correction to test regarding stratified Cox model strata Minor edits to text	Correction Clarification of statistical methods
9.4.1 Efficacy Analyses Tertiary/Exploratory endpoints	'Change in normalized T1 intensity…' endpoint moved to a new row New text for statistical method for the 'Volume of SELs…' endpoint	Correction of statistical method based on information from NeuroRx indicating one postbaseline value per participant
9.4.4.4 Multiplicity	Secondary Endpoint Null Hypotheses for H_{05}: '$\Delta_{Fatigue} \leq 0$' changed to '$\Delta_{Fatigue} \geq 0$', and 'higher score corresponds to reduced fatigue' changed to 'higher score corresponds to more fatigue'	Correction
10 References	Additional references added	In line with changes to text
Appendix 2 Study Governance	Study and Site Closure: Text added to indicate that new or emerging safety information that negatively affects the benefit/risk assessment of the clinical study may be a reason for closing study sites or terminating the study	Health Authority Request
Appendix 3 Contraception	Added missing footnote label 'a' Added footnote 'b' to indicate that if a WOCBP is using a highly effective method other than sexual abstinence or vasectomized partner, AND ALSO has a vasectomized partner, the vasectomized partner will be considered the "barrier method" for study purposes	Label was missing in footnotes Clarification
Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Events Not to Be Considered as AEs/SAEs: Text added to state that worsening of the underlying disease is not routinely considered an AE or SAE Text on reporting of AESIs was updated in line with the latest protocol template	Alignment with template wording For clarification and so that EDC can be used
Appendix 5 Clinical Laboratory Tests	Moved some assessments listed in 'Other screening tests' into new row 'Other tests' JCV DNA PCR added to list of 'Other screening tests' Estradiol removed from list of 'Other screening tests' βhCG removed from routine urinalysis Teriflunomide footnote amended to include all participants undergoing AEP	Clarification; not all tests listed were Screening only To include missing information Estradiol not used to determine postmenopausal status in this study This is a serum test; now listed under other tests To include females undergoing AEP
Appendix 8 Procedure for Accelerated Elimination of Teriflunomide	Text added to allow accelerated elimination of teriflunomide in accordance with standard of care Text added to note that it is only required to confirm a level of < 0.02 mg/L after the AEP if the AEP is being done for pregnancy-related considerations	To allow accelerated elimination of teriflunomide in accordance with local guidance For clarification

Section # and Name	Description of Change	Brief Rationale
Appendix 10 Structured Interview at Telephone Visit	New appendix added: 'Structured Interview at Telephone Visit'	Clarification/simplification of protocol. Structured interview put into place to identify any new or worsening neurological symptoms that warrant evaluation at an unscheduled visit
Throughout the document	Changes made to align with updated protocol template Minor editorial and document formatting revisions	Minor; therefore, have not been summarized

Protocol Version 2.0 (09 December 2020)

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

The primary purpose of this amendment is to make changes and clarifications based on feedback from early enrolling investigational sites, and newly available data from studies of other agents in multiple sclerosis, and to clarify COVID mitigation procedures. A high-level description of each change is summarized below, along with its rationale.

Section # and Name	Description of Change	Brief Rationale
Title page Appendix 12 Sponsor Signature Page	PPD replaces Kristen PPD as Medical Monitor PPD is Medical Responsible	Changes in personnel
1.1 Synopsis, Study Intervention Groups and Duration 1.2 Schema 4.1 Overall Design	Additional text included, and minor rewording, to clarify the follow-up window for 'confirmation' of disability progression as measured by the EDSS	For additional clarification
1.1 Synopsis 1.2 Schema 4.1 Overall Design 5.5 Screen Failures Appendix 2 Study Governance	With approval from the Medical Monitor, the Screening period may be extended to 12 weeks maximum (increased from 8 weeks maximum). See Section 8 Study Assessments and Procedures	To allow sufficient time for repeat laboratory results and other unanticipated events prior to randomization
1.1 Synopsis 1.2 Schema 4.1 Overall Design 1.3 Schedule of Activities	Added that female participants may undergo AEP at the Investigator's discretion, and that the same AEP process should be followed as for male participants	To clarify the process in the event of a female participant undergoing AEP
1.3 Schedule of Activities (Main Study)	'F/D' changed to SFU (Safety Follow-up) F/D visit window changed from ± 3 days to + 3 days Added note that visit window for Week 4 is ± 2 days	To clarify that this is a safety visit SFU visit must be ≥ 28 days after last study intervention Clarification

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (Main Study and OLE)	Telephone Visit: Simplified notes and referred to Structured Interview Clarified individual visits	Clarification/simplification of protocol. Structured interview put into place. Telephone Visit not required when participants attend clinic
1.3 Schedule of Activities (Main Study)	QuantiFERON testing removed from W48 and W96 visits Separate row added for TB testing for high TB burden countries	TB testing is only required at Screening if the participant resides in a country that has a high TB burden Separated testing in high TB burden countries to avoid confusion. Clarified that the assay used to confirm eligibility should be used for monitoring during the study
1.3 Schedule of Activities Efficacy (Main Study and OLE)	Added note that neurological evaluation EDSS, T25-FW, 9-HPT, and SDMT should preferably be done after the PRO assessments EDSS evaluation: added note that this can be done by phone, if available, if the participant is unable to attend scheduled visit	To clarify that these should preferably be completed before other assessments, but PROs are done first Mitigation in light of the COVID-19 pandemic, if the participant is unable to attend scheduled visit Lechner-Scott 2003)
1.3 Schedule of Activities PRO Assessments (Main Study)	SF-36 v2 assessment added at Week 108	Assessment required at Week 108 for participants for whom this is also D1 of the OLE
1.3 Schedule of Activities PRO Assessments (Main Study and OLE)	PROs: Removed reference to the use of a tablet	For flexibility in method of collection
1.3 Schedule of Activities Safety Assessments (Main Study and OLE)	C-SSRS: Removed reference to the use of a tablet	For flexibility in method of collection
1.3 Schedule of Activities Safety Assessments (Main Study and OLE)	Coagulation test will be done at Screening, W96, OLE D1 and W144 only	No exposure-related abnormalities in PT or PTT have been identified in prior studies of evobrutinib.
1.3 Schedule of Activities Safety Assessments (Main Study and OLE)	Text amended to indicate that urinalysis will be assessed locally and microscopy will be submitted for central evaluation only if indicated	Clarification
1.3 Schedule of Activities Safety Assessments (Main Study)	Noted that a second ECG will be collected postdose on Day 1, and that additional ECGs can be done at the Investigator's discretion	To clarify that there are 2 ECGs on Day 1 and to allow additional ECGs if required
1.3 Schedule of Activities Safety Assessments (Main Study and OLE)	Removed notes regarding telephone visits from 'AE, SAE & AESI Review' and 'Concomitant Medication and Procedures Review' rows	Clarification/simplification of protocol. Structured interview put into place
1.3 Schedule of Activities Study Intervention (Main Study)	Added dispensing of study intervention at Week 4	Requested by the study team
1.3 Schedule of Activities Study Intervention (Main Study and OLE)	Text amended to state when study intervention should be administered on site: PK sampling days (Main Study) and biomarker sample collection days (OLE)	To clarify when study intervention should be administered in the clinic

Section # and Name	Description of Change	Brief Rationale
	Removed detail about self-administration at home	To avoid confusion; detail is in Section 6.1
1.3 Schedule of Activities Study Intervention (Main Study and OLE)	Compliance: Clarified that participant should complete the Participant diary. Note added that the diary should be reviewed during on-site visits	Clarification
1.3 Schedule of Activities Biomarkers (Main study and OLE) 8.8.2 Novel Liver Function Protein Biomarkers and Novel Liver Function Genomic Biomarkers	Removed requirement for novel liver function protein and genomic biomarkers to be collected prior to first daily dose	Dosing time is not relevant to sample collection time
1.3 Schedule of Activities (OLE)	Note 'd': Added 'unless they are undergoing AEP'	The last visit in the main study will not be the first visit in the OLE for female participants undergoing AEP
1.3 Schedule of Activities (OLE)	Informed consent: Removed reference to 'male' and added reference to notes on AEP Added text so that consent to the OLE Period can be given before Day 1	To clarify that the consent procedure for participants undergoing AEP also applies to females Clarification
1.3 Schedule of Activities (OLE)	Blinded Teriflunomide Levels: note amended to refer to all participants undergoing AEP rather than male participants only Sample moved from D1 to AEP period	Teriflunomide should also be measured for females undergoing AEP To correct error
1.3 Schedule of Activities (OLE)	Medical history was removed from the OLE	Medical history is collected at Screening; any changes thereafter are recorded as AEs
1.3 Schedule of Activities (OLE)	Added text to state that a serum pregnancy test is only required on Day 1 of the OLE if the last monthly urine pregnancy test was ≥ 1 month ago	A urine pregnancy test is sufficient at this visit unless there has been a gap of ≥ 1 month since the last test
1.3 Schedule of Activities (OLE)	'QuantiFERON testing' replaced with 'TB testing' in high TB burden countries and notes aligned with Main Study SoA TB test removed from Week 108	TB testing is only required in the OLE if the participant resides in a country that has a high TB burden Test at Week 108 is unnecessary
1.3 Schedule of Activities Study Intervention (OLE)	Study Intervention(s) Administration: Dosing will only occur on site at visits when biomarkers are collected	Dosing does not need to be on site for all visits
1.3 Schedule of Activities Safety Assessments (OLE)	Added reference to Section 7.1 in the notes section of the OLE Biochemistry and Hematology assessments	To clarify that the criteria for discontinuation of study intervention apply in the OLE
2.3 Benefit/Risk Assessment	Updated list of completed studies with no new potential risks emerging	To provide updated information
2.3 Benefit/Risk Assessment	Added text to address potential risk and mitigation to decrease risk of severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) infection	To address new risks associated with the emergence of the COVID-19 pandemic

Section # and Name	Description of Change	Brief Rationale
3 Objectives and Endpoints 1.1 Synopsis	Header changed to 'Objectives and Estimands', and Table 1 changed to a 2-column format with estimand details added	To comply with change to protocol template which clarifies estimand strategy
3 Objectives and Estimands: Table 2 Tertiary/Exploratory Objectives and Endpoints 9.4.1 Efficacy Analyses	Two more endpoints added for the evaluation of the efficacy of evobrutinib relative to that of teriflunomide on MRI parameters	Previously missing
3 Objectives and Estimands Table 2 Tertiary/Exploratory Objectives and Endpoints 9.4.1 Efficacy Analyses	'New T1 Gd+ lesions' changed to 'T1 Gd+ lesions' Changes to wording of endpoints measured to evaluate the effect on composite parameters to use the term 'confirmed worsening' rather than CDP in relation to the 9-HPT score and T25-FW times Clarification that progression or worsening should be confirmed	To align with the correct definition for NEDA Clarification
3 Objectives and Estimands: Table 2 Tertiary/Exploratory Objectives and Endpoints	T_{max} removed from list of PK parameters for evaluation	T_{max} is not needed for any analyses and will not be calculated
3 Objectives and Estimands Table 3 Objectives and Endpoints for the Open Label Extension Period 1.1 Synopsis	Objectives and endpoints added for biomarkers collected during the OLE	Previously missing
4.2 Scientific Rationale for Study Design	Rationale for biomarkers added	Previously missing
4.4 End of Study Definition	Expanded definition of study completer	Clarification
5 Study Population; Appendix 2 Study Governance, Informed Consent Process	Removed reference to 'legal representative' throughout document	Regulatory authority request (to clarify that legal representative will not be allowed in the study)
5.1 Inclusion Criteria	Inclusion 5: Added text to clarify definition of neurologically stable	Clarification
5.2 Exclusion Criteria	Exclusion 6: Wording changed from 'within 4 weeks of Screening' to 'within 4 weeks before or during Screening'	Clarification in the event of extension of the Screening period
5.2 Exclusion Criteria	Exclusion 7: 'QuantiFERON testing' replaced with 'TB testing' in high TB burden countries. Text added to allow use of an alternative test to the assay used at Screening per protocol	Separated testing in high TB burden countries to avoid confusion. To clarify when an orthogonal Interferon Gamma Release Assay should be used to assess TB status, and that for monitoring, the assay used to confirm eligibility should be used for monitoring during the study

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria	Exclusion 8: Amended to include reevaluation of false positive QuantiFERON results Removed text stating that individuals should be excluded if T-SPOT.TB is not available	False positive results were not addressed in the original protocol To enable sites to do another QuantiFERON if a local T-SPOT.TB is not available
5.2 Exclusion Criteria	Exclusion 10: reworded to exclude participants with highly elevated ferritin levels independent of transferrin saturation	Revised after review of current guidelines for evaluation of hemochromatosis and expert consultation.
5.2 Exclusion Criteria	Exclusion 14: Amended language regarding suicidal behavior and C-SSRS scores	To ensure exclusion of individuals considered a significant suicide risk and to clarify a time period for the assessment
5.2 Exclusion Criteria	Exclusion 22: amended time frame for discontinuation of treatment with beta-interferons or glatiramer acetate prior to randomization to 1 day	This does not need to be discontinued as early as 4 weeks before randomization
5.2 Exclusion Criteria	Exclusion 23: Removed reference to lymphocyte count as this is in a separate criterion	Clarification
5.2 Exclusion Criteria	Exclusion 24: Added that reason for switch to teriflunomide must not have been because of efficacy or safety related considerations	Clarification regarding study population, changes made to ensure teriflunomide is an appropriate therapeutic option for individuals entering the study
5.2 Exclusion Criteria	Exclusion 25: Amended wording and timing regarding use of lymphocyte trafficking blockers Added use of S1P inhibitors as an exclusion	Reflects recently published clinical trials in RMS indicating that the revised exclusion periods are safe and appropriate
5.2 Exclusion Criteria	Exclusion 26: Time frame for use of IV Ig or plasmapheresis prior to randomization changed from 12 to 8 weeks	Reflects recently published clinical trials in RMS indicating that the revised exclusion periods are safe and appropriate
5.2 Exclusion Criteria	Exclusion 27: ofatumumab added to list of exclusionary treatments	Clarification. Ofatumumab is a B-cell depleting therapy; added to avoid confusion as it is now an approved agent in some countries
5.2 Exclusion Criteria	Exclusion 28: amended to provide timings and clarification of immunosuppressive medications	Reflects recently published clinical trials in RMS indicating that the revised exclusion periods are safe and appropriate. Provides more complete guidance to sites regarding prior treatments.
5.2 Exclusion Criteria	Exclusion 30: Removed this exclusion criterion (treatment with medical marijuana)	Removed given the complex nature of marijuana regulation in different countries and lack of anticipated impact on patient safety.
5.2 Exclusion Criteria	Exclusion 31: Changed the time for stopping fish oil supplements from 4 weeks prior to randomization to just prior to randomization (first dose)	Given size and durability of effects of fish oil supplements on coagulation, a 4 week period off fish oil supplements is not required.

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria 6.5.3 Prohibited Medicines	Exclusion 32: Removed text “Diabetes medications such as tolbutamide, and pioglitazone, repaglinide and rosiglitazone or other CYP2C8 substrates are also exclusionary” and replaced with “CYP2C8 substrates with a narrow therapeutic index must also be stopped at least 1 day prior to randomization” Added clarification that CYP2B6 substrates with a narrow therapeutic index, as well as substrates of P-gp, BCRP, OCT1, MATE1 and/or MATE2K should be used with caution	To correct an error Clarification on medicines to be used with caution.
5.2 Exclusion Criteria 7.1 Discontinuation of Study Intervention	Exclusion 34: Amended to permit inclusion of participants with HBV DNA detectable at levels below 20 IU/mL Clarified level of detectable HBV DNA for study intervention discontinuation	In prior studies of evobrutinib, evobrutinib was given to individuals with HBV DNA < 20 IU/mL, and HBV reactivation was not observed. To align with change to Exclusion Criterion 34
5.3.2 Exclusion Criteria for Open Label Extension Period	Exclusion 6: Gamma glutamyl transferase removed from list of abnormal blood tests requiring discontinuation	Correction aligns OLE exclusion criterion with main study stopping rules. GGT was included unintentionally.
5.4.1 Meals and Dietary Restrictions	Red wine removed from restrictions	No clinically relevant interaction between red wine and either study medication is anticipated. Red wine was not prohibited from prior studies of evobrutinib and no interactions were observed
6.1 Study Intervention(s) Administration	Dosing Instructions amended Packaging and Labeling information expanded	To align with elsewhere in the protocol Clarification
6.2 Study Intervention(s) Preparation, Handling, Storage, and Accountability	Details of storage conditions for teriflunomide and its placebo were replaced with a reference to the teriflunomide product label	Clarification
6.3.2 Blinding	Clarified the wording regarding the assignment of a Treating Investigator Designee Moved the Treating Investigator text before the Examining Investigator text Added bullet to state that the Treating Investigator (or designee) and the Examining Investigator (or designee) cannot perform the same tests	Clarification Logical flow For additional clarity
6.4 Study Intervention Compliance 8 Study Assessments and Procedures	Clarified that food intake only needs to be recorded in the Participant diary around the time of dosing on the day prior to PK sampling and the day of PK sampling, and around the time of the last dose prior to evobrutinib concentration assessment sampling	Clarification

Section # and Name	Description of Change	Brief Rationale
6.4 Study Intervention Compliance	Added text to indicate that participants only need to bring in study intervention at study visits 'during which IMP is dispensed'	To relieve burden on participants
6.5 Concomitant Therapy 6.5.3 Prohibited Medicines	"During the OLE, initiation of therapy with dalfampridine (Ampyra®) is allowed, if indicated by the Treating Investigator": text moved from Section 6.5 Concomitant Therapy to Section 6.5.3 Prohibited Medicines	Incorrect location
6.5.1 Rescue Medicine	Text added to allow use of methylprednisolone as an oral formulation Text added to allow use of an approved equivalent of Acthar gel	To provide flexibility (particularly in light of the Covid-19 pandemic) To allow use of an approved equivalent of Acthar gel
6.5.2 Permitted Medicines	Amended restrictions on use of marijuana	To align with removal of marijuana exclusion criterion
6.5.3 Prohibited Medicines	Ofatumumab added to list of medicines prohibited during the study Added azathioprine and methotrexate as examples of prohibited immunosuppressive treatments Live-attenuated vaccines added to list of medicines prohibited during the study Systemic corticosteroids (oral, injected, IV) added to list of medicines prohibited during the study (topical, intranasal, or inhaled corticosteroids are permitted)	Ofatumumab is a B-cell depleting therapy; added to avoid confusion as it is now an approved agent in some countries To align with the updated exclusion criterion #28 Omitted in error Omitted in error
6.5.4 Other Interventions	Resveratrol > 500 mg/day added to list of herbal and nutritional supplements that must be stopped at least 1 week prior to randomization	Resveratrol supplements of > 500 mg/day may result in clinically significant inhibition of CYP3A
6.9 Management of Adverse Events of Interest	Liver adverse events: Level of increase clarified for transaminases and bilirubin elevations to be considered AESIs Amylase and Lipase Elevations: CTCAE Grade ≥ 3 elevation changed to > 2 × ULN for AESI classification	Clarification To clarify a discrepancy between CTCAE Version 4.03 and Version 5.0
7.1 Discontinuation of Study Intervention	Added template mandatory text regarding permanent discontinuation (at start of section) Added text to indicate that the criteria for discontinuation of study intervention apply during both the main study and the OLE Period Added local standard of care option for accelerated elimination of teriflunomide	Previously missing Clarification To allow investigators to manage participants in accordance with local standard of care

Section # and Name	Description of Change	Brief Rationale
7.1 Discontinuation of Study Intervention, Criteria for Permanent Discontinuation of Study Intervention	Text added to clarify that the lab criteria should be confirmed before study intervention is discontinued For pregnancy reasons: changed the requirement that AEP 'must' be performed to 'should' be performed, and teriflunomide level < 0.02 mg/L 'has to' be reached to 'should' be reached Added text that a protocol deviation should be documented if prohibited medication is used	Clarification This is a decision for the Investigator and the participant; it is not absolutely mandatory Clarification
7.1 Discontinuation of Study Intervention 8 Study Assessments and Procedures Appendix 5 Clinical Laboratory Tests	Erythrocyte sedimentation rate removed from list of hepatic assessments	Erythrocyte sedimentation rate via on-site/local laboratory was included in error as hsCRP is already collected and processed via central laboratory
7.1 Discontinuation of Study Intervention	Criteria for Temporary Discontinuation of Study Intervention: Amylase retest criteria amended and simplified to allow reinitiation of study intervention if value decreases to ≤ 2 × ULN upon retest Lipase retest criteria amended and simplified to allow reinitiation of study intervention if value decreases to ≤ 2 × ULN upon retest	To clarify a discrepancy between CTCAE Version 4.03 and Version 5.0
7.1 Discontinuation of Study Intervention	Criteria for Temporary Discontinuation of Study Intervention: Serum creatinine criteria changed to "For any increase in serum creatinine > 1.5 × ULN but ≤ 3 × ULN…"	Criteria did not cover an exact 3 × ULN and required clarification
7.1 Discontinuation of Study Intervention 8.3.5 Pregnancy	Changed requirement for AEP in pregnant participant from 'must' to 'should' be performed	To align with the AEP
8 Study Assessments and Procedures	Date of last menstrual period will not be collected	Not required
8 Study Assessments and Procedures	Additional criteria added for extending the Screening Period, and permitted extension increased to a maximum of 12 weeks Instructions added for repeating ferritin or transferrin saturation tests	To provide guidance for retesting of ferritin or transferring saturation tests and allow sufficient time for repeat laboratory results and other unanticipated events prior to randomization
8 Study Assessments and Procedures	Telephone Visit: Replaced bulleted list of discussion items with a reference to the Structured Interview in Appendix 10	Clarification/simplification of protocol. Structured interview put into place.
8.1.1 Neurological Assessment	Added text to clarify the assignment of a Qualified Examining Designee	Clarification
8.1.1.1 Qualified Relapse	Added that if neurological signs and symptoms are identified that are consistent with relapse, the participant should be evaluated on site	Clarification; relapse cannot be confirmed over the phone

Section # and Name	Description of Change	Brief Rationale
8.1.1.6 Symbol Digit Modalities Test	Text added to clarify that two different SDMT forms will be used, administered at alternating visits	Clarification
8.1.2 Brain Magnetic Resonance Imaging Scans	Amended text to state that images will be assessed (not assessed and reported) Added that the Treating Investigator can have access to the Screening (baseline) MRI scan in order to evaluate eligibility	To correct an error Access to the Screening (baseline) MRI scan is needed to evaluate eligibility
8.1.2 Brain Magnetic Resonance Imaging Scans 1.3 Schedule of Activities (Main Study)	Changed 'Screening/Baseline MRI' to 'Screening (Baseline) MRI'	To clarify that the MRI done at screening is the baseline MRI, rather than suggesting that an MRI might be done at the Baseline visit.
8.1.3 Patient Reported Outcomes 1.3 Schedule of Activities	Added text to allow an alternative method of PRO data collection Removed reference to the use of a tablet for PRO assessments	To allow an alternative method of collection in the event that a tablet cannot be used
8.2.2 Vital Signs	Text added to indicate that temperature should be measured at the same location throughout the study	To avoid variation in results if different methods were used
8.2.3 Electrocardiograms	Text amended to indicate that QTcF will be automatically calculated in the eCRF; it is not obtained from the ECG	Clarification
8.2.7 Columbia-Suicide Severity Rating Scale 1.3 Schedule of Activities (Main Study and OLE)	Text added to state that the C-SSRS may be administered by an assigned designee of the Treating Investigator	To clarify that the C-SSRS may be delegated per Section 6.3.2
8.3.5 Pregnancy	Amended all text regarding collection and reporting of pregnancy information Added that information on pregnant partners only needs to be collected in the Main Study	Text updated in accordance with new protocol template Once a male participant switches to evobrutinib in the OLE, it is not necessary to collect information on pregnancies in their partners
8.4 Treatment of Overdose	Definition of overdose amended to: "…within a 24-hour time period – [minus] 6 hours…"	To prevent erroneous reports of overdose
8.5 Pharmacokinetics	T_{max} removed from list of PK parameters for evaluation Revisions to definitions of PK parameters	T_{max} is not needed for any analyses and will not be calculated Correction
9.1.2 Statistical Hypotheses Related to Secondary Objectives	Change to null hypothesis for the secondary endpoint CFB in PROMIS Fatigue score at 96 weeks	Correction
9.4.1 Efficacy Analyses Secondary efficacy endpoints: Time to 12-week CDP Time to 24-week CDP 9.4.1.2 Efficacy Analyses Related to Secondary Objectives	Statistical Analysis Methods: Cox model made consistent with Log-rank test which has strata defined by randomization strata and study ID	Correction
9.4.1 Efficacy Analyses Tertiary/Exploratory endpoints	Statistical Analysis Methods: Correction to test regarding stratified Cox model strata Minor edits to text	 Correction Clarification of statistical methods

Section # and Name	Description of Change	Brief Rationale
9.4.1 Efficacy Analyses Tertiary/Exploratory endpoints	'Change in normalized T1 intensity…' endpoint moved to a new row New text for statistical method for the 'Volume of SELs…' endpoint	Correction of statistical method based on information from NeuroRx indicating one postbaseline value per participant
9.4.4.4 Multiplicity	Secondary Endpoint Null Hypotheses for H_{05}: '$\Delta_{Fatigue} \leq 0$' changed to '$\Delta_{Fatigue} \geq 0$', and 'higher score corresponds to reduced fatigue' changed to 'higher score corresponds to more fatigue'	Correction
10 References	Additional references added	In line with changes to text
Appendix 2 Study Governance	Study and Site Closure: Text added to indicate that new or emerging safety information that negatively affects the benefit/risk assessment of the clinical study may be a reason for closing study sites or terminating the study	Health Authority Request
Appendix 3 Contraception	Added missing footnote label 'a' Added footnote 'b' to indicate that if a WOCBP is using a highly effective method other than sexual abstinence or vasectomized partner, AND ALSO has a vasectomized partner, the vasectomized partner will be considered the "barrier method" for study purposes	Label was missing in footnotes Clarification
Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Events Not to Be Considered as AEs/SAEs: Text added to state that worsening of the underlying disease is not routinely considered an AE or SAE Text on reporting of AESIs was updated in line with the latest protocol template	Alignment with template wording For clarification and so that EDC can be used
Appendix 5 Clinical Laboratory Tests	Moved some assessments listed in 'Other screening tests' into new row 'Other tests' JCV DNA PCR added to list of 'Other screening tests' Estradiol removed from list of 'Other screening tests' βhCG removed from routine urinalysis Teriflunomide footnote amended to include all participants undergoing AEP	Clarification; not all tests listed were Screening only To include missing information Estradiol not used to determine postmenopausal status in this study This is a serum test; now listed under other tests To include females undergoing AEP
Appendix 8 Procedure for Accelerated Elimination of Teriflunomide	Text added to allow accelerated elimination of teriflunomide in accordance with standard of care Text added to note that it is only required to confirm a level of < 0.02 mg/L after the AEP if the AEP is being done for pregnancy-related considerations	To allow accelerated elimination of teriflunomide in accordance with local guidance For clarification
Appendix 10 Structured Interview at Telephone Visit	New appendix added: 'Structured Interview at Telephone Visit'	Clarification/simplification of protocol. Structured interview put into place to identify any new or worsening neurological symptoms that warrant evaluation at an unscheduled visit

Section # and Name	Description of Change	Brief Rationale
Throughout the document	Changes made to align with updated protocol template Minor editorial and document formatting revisions	Minor; therefore, have not been summarized

Protocol Version 1.4-LTU (16-September-2020)

This amendment is nonsubstantial based on the criteria in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment

This local amendment increases the number of physical examinations that are performed during the study (both Treatment Period and the Open Label Extension Period).

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities	The frequency of full physical examinations has been increased to every 3 months (12 weeks) during the Treatment Phase and the Open Label Extension Phase	The frequency of physical examinations has been increased to every 3 months to align with local requirements

Protocol Version 1.3-NOR (25-August-2020)

This amendment is nonsubstantial based on the criteria in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment

This local amendment updates the protocol to add a definition of the criteria used for study termination.

Section # and Name	Description of Change	Brief Rationale
Appendix 2 Study Governance	Added text under Study and Site Closure section	A definition for the criteria for study termination has been added

Protocol Version 1.2-DEU (04 August 2020)

This amendment is nonsubstantial based on the criteria in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment

This local amendment updates the Medical Responsible, deletes language referring to the participant's legal representative and updates the benefit/risk assessment to account for the Caronavirus disease 2019 (COVID-19) pandemic.

Section # and Name	Description of Change	Brief Rationale
Title page; Appendix 11, Sponsor Signature Page	Updated with new Medical Responsible	Change in personnel
2.3 Benefit/Risk Assessment	Added text to address potential risk and mitigation to decrease risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection	To address new risks associated with the emergence of the COVID-19 pandemic
5.0, Study Population; Appendix 2 Study Governance	Deleted reference to participant's legal representative	Removal of template language not applicable for the trial

Protocol Version 1.1-CAN (03 July 2020)

This amendment is nonsubstantial based on the criteria in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment

This local amendment has been created to align the Clinical Study Protocol with the Canadian Product Monograph for Aubagio® (teriflunomide).

Section # and Name	Description of Change	Brief Rationale
5.4.2 – Caffeine, Alcohol and Tobacco	Section has been rephrased	Alignment with the Canadian Product Monograph for teriflunomide

Appendix 13 Sponsor Signature Page

Study Title:	A Phase III, Multicenter, Randomized, Parallel Group, Double Blind, Double Dummy, Active Controlled Study of Evobrutinib Compared with Teriflunomide, in Participants with Relapsing Multiple Sclerosis to Evaluate Efficacy and Safety.
Regulatory Agency Identifying Numbers:	EudraCT: 2019-004980-36 US IND: 129428
Clinical Study Protocol Version:	Version 6.0 / 27 April 2023

I approve the design of the clinical study:

PPD

Signature

PPD

Date of Signature

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

Appendix 13 Coordinating Investigator Signature Page

Study Title:	A Phase III, Multicenter, Randomized, Parallel Group, Double Blind, Double Dummy, Active Controlled Study of Evobrutinib Compared with Teriflunomide, in Participants with Relapsing Multiple Sclerosis to Evaluate Efficacy and Safety.
Regulatory Agency Identifying Numbers:	EudraCT: 2019-004980-36 US IND: 129428
Clinical Study Protocol Version:	Version 6.0 / 27 April 2023
Site Number:	

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 Heal PPD ority requirements and national laws.

PPD

Signa PPD

April 28, 2023

Date of Signature

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

Appendix 14 Principal Investigator Signature Page

Study Title:	A Phase III, Multicenter, Randomized, Parallel Group, Double Blind, Double Dummy, Active Controlled Study of Evobrutinib Compared with Teriflunomide, in Participants with Relapsing Multiple Sclerosis to Evaluate Efficacy and Safety.
Regulatory Agency Identifying Numbers:	EudraCT: 2019-004980-36 US IND: 129428
Clinical Study Protocol Version:	Version 6.0 / 27 April 2023
Site Number:	

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

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