Clinical Trial Protocol

Clinical Trial Protocol Number	MS200527_0086
Title	A Randomized, Double-Blind, Placebo-Controlled Phase II Study of M2951 with a Parallel, Open-Label, Active Control Group (Tecfidera), in Patients with Relapsing Multiple Sclerosis to Evaluate Efficacy, Safety, Tolerability, Pharmacokinetics, and Biological Activity.
Phase	II
IND Number	CCI
EudraCT Number	2016-001448-21
Coordinating Investigator	PPD
Sponsor	For all countries except the USA: Merck KGaA Frankfurter Str. 250, 64293 Darmstadt, Germany. For the USA only: EMD Serono Research and Development Institute, Inc. 45A Middlesex Turnpike Billerica, MA, 01821 USA Medical Responsible: PPD Merck Healthcare KGaA Frankfurter Str. 250 64293 Darmstadt Germany Telephone: PPD
Clinical Trial Protocol Version	06 July 2023/Version 8.0
Replaces Version	02 December 2022/Version 7.0

Protocol Amendment Summary of Changes

Protocol History

Version Number	Type	Version Date
1.0	Original Protocol	05-Jul-2016
1.1	Local Amendment 1	22-May-2017
2.0	Amendment 1	28-Nov-2017
3.0	Amendment 2	29-May-2018
4.0	Amendment 3	08-Aug-2018
5.0	Amendment 4	21-Nov-2018
6.0	Amendment 5	08-Nov-2019
6.1	Local Amendment 2	11-Jun-2020
7.0	Amendment 6	02-Dec-2022
8.0	Amendment 7	06-Jul-2023

Protocol Version 8.0 (06 July 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 the recent update to the risk profile of evobrutinib (i.e., important identified risk of drug-induced liver injury) by adapting monitoring and discontinuation criteria, as well as language on tolerability and safety of evobrutinib across the protocol.
- To extend the OLE period by up to one additional year to allow an opportunity for participants to transition into the long-term follow-up study under a new protocol.

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

Section # and Name	Description of Change	Brief Rationale
1 Synopsis including Table 3 (Schedule of Assessments – Optional OLE Period Week 108 up to 384)	• Duration of OLE Period was updated to include extension of 1 year; i.e., OLE Period duration was updated from 7 years to up to 8 years. Accordingly, study visits were added and duration of participation in the study was updated throughout the document. • Information on transitions into the long-term follow-up study under a new protocol was updated for clarity, including clarification for participants transitioning and not transitioning into the long-term follow-up study. Clarification that participants will complete the OLE according to study schedule under the current protocol was added in case the long-term follow-up study will not become available in their respective country. • Table 3 reflecting schedule of assessments in OLE Period Week 108 up to 384 was updated to include additional year in OLE Period (OLE Year 8), additional visits and corresponding assessments. MRI scan footnote was included for clarification and consistency. CCI CCI	• For consistency with the main protocol text.
2 Sponsor, Investigators and Trial Administrative Structure	• Description of HAC was added.	• To include involvement of newly formed HAC.
3 Background Information	• Text rephrased based on updated risk profile.	• To reflect recent update to risk profile of evobrutinib.

Section # and Name	Description of Change	Brief Rationale
3.2 Benefit-Risk	• Evobrutinib indications were updated to exclude SLE and RA, as studies were stopped for futility and no development is expected to occur. • Updated benefits to include data in primary analysis and more recent efficacy observations. • Updated important identified risks to include the asymptomatic DILI cases in Phase III studies. • Updated important potential risks: severe DILI and embryo-fetal toxicity including measures to mitigate these risks. Involvement of HAC in review of hepatic risk profile was added. • Updated benefit-risk conclusion to include recent data indicating benefits of evobrutinib,	• To outline more recent data including beneficial data related to evobrutinib efficacy and to reflect recent update to risk profile of evobrutinib.
5.1 Overall Trial Design and Plan	• Clarification was added to reflect that OLE Period is planned to have a duration of up to 384 weeks. Accordingly, extension of OLE was updated where applicable. • Information on transitions into the long-term follow-up study under a new protocol was updated, including clarification for participants transitioning and not transitioning into the long-term follow-up study. Clarification that participants will complete the OLE according to study schedule under the current protocol was added in case the long-term follow-up study will not become available in their respective country. • Previous Figure 2 and Figure 3 reflecting design of OLE Period were merged into one Figure for clarity and to address change in duration of OLE Period. Clarification in the footnote was added that time point of interim analysis will be planned around the time of the trigger for the primary analysis of the Phase III RMS studies.	• To extend the OLE period by up to one additional year to allow an opportunity for participants to transition into the long-term follow-up study under a new protocol. • To add supportive guidance for consistency and accuracy. • For consistency with the change in study design.
5.2.2 Justification for Dose	CCI	• To briefly describe rationale of Phase 3 dose selection.
5.8 Definition of End of Trial	• Updated information on study termination.	• For consistency with the change in study design.

Section # and Name	Description of Change	Brief Rationale
6.4.4 Special Precautions 6.4.4.1 For M2951 Only	• Liver function test-related monitoring and discontinuation further specified. • Liver function testing criteria updated. • Hepatic panel for participants for whom withdrawal criteria are met or who permanently/temporarily discontinue dosing because of elevated transaminases was updated. • Table 7 reflecting guidelines for withholding or permanent withdrawal of IMP was modified in according to updated specifications.	• To enhance safety monitoring of liver function.
7.1.6 Open-label Extension Period	• Clarification was added to reflect that OLE Period is planned to have a duration of up to 384 weeks. • Information on transitions into the long-term follow-up study under a new protocol was updated, including clarification for participants transitioning into the long-term follow-up study.	• To extend the OLE period by up to one additional year to allow an opportunity for participants to transition into the long-term follow-up study under a new protocol.
7.1.7 Open-label Extension End of Treatment Visit 7.1.8 4-week Safety Follow-up/End of Trial Visit	• Information on transitions into the long-term follow-up study under a new protocol was updated, including clarification for participants transitioning and not transitioning into the long-term follow-up study. Clarification that participants will complete the OLE according to study schedule under the current protocol was added in case the long-term follow-up study will not become available in their respective country.	• To add supportive guidance for consistency and accuracy. • For consistency with the change in study design.
7.1.8 4-week Safety Follow-up/End of Trial Visit CCI	CCI CCI	CCI
7.4.3 Clinical Laboratory Assessments	CCI	• To enhance safety monitoring of liver function.
8.6 Interim and Additional Planned Analyses	• Clarification was added that time point of interim analysis will be planned around the time of the trigger for the primary analysis of the Phase III RMS studies.	• For consistency with the change in study design.
11 References Cited in the Text	• Montalban et al 2023 reference was added. • Kuhle et al 2021, Arnold et al 2022, Piasecka-Stryczynska et al 2021, and Bar-Or et al., 2023 were added.	• To include published reference for recent data including OLE beneficial results related to evobrutinib.
Appendix II: Total Blood Volume	• Total blood volume was updated.	• To consider the extension for the OLE period.

Section # and Name	Description of Change	Brief Rationale
Throughout the document	• Minor editorial and document formatting revisions. • Extension of OLE was updated where applicable.	• Minor; therefore, have not been summarized. • For consistency with the change in study design.

Protocol Table of Contents

Table of In-Text Tables

Table of In-Text Figures

List of Abbreviations

AE	Adverse Event
ALT	Alanine aminotransferase
ARR	Annualized relapse rate
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
CCI	[redacted]
CI	Confidence Interval
CRO	Contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for AEs
CCI	[redacted]
CXR	Chest X-ray
DILI	Drug-induced liver injury
DMCs	Data Monitoring Committees
DMD	Disease-modifying drugs
EAE	Experimental autoimmune encephalomyelitis
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDSS	Expanded Disability Status Scale
EU	European Union
FDA	US Food and Drug Administration
FIM	First-in-man
FSH	Follicle-stimulating hormone
FWER	Family-wise Type I error rate
GCP	Good Clinical Practice
Gd+	Gadolinium-positive
eGFR	Estimated glomerular filtration rate
GI	Gastrointestinal
GMP	Good Manufacturing Practice
HAC	Hepatology Assessment Committee

HbsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
CCI	[redacted]
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
ITT	Intention To Treat
IV	intravenous
IWRS	Interactive Web Response System
LLN	Lower limit of normal
LLOQ	Lower limit of quantification
LTBI	Latent Tuberculosis Infection
MCS	Mental component summary
mITT	Modified ITT
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
NB	Negative binomial
CCI	[redacted]
OLE	Open-label extension
PCR	Polymerase chain reaction
PCS	Physical component summary
CCI	[redacted]
[redacted]	[redacted]
PML	Progressive multifocal leukoencephalopathy
RA	Rheumatoid arthritis
RMS	Relapsing multiple sclerosis

RoW	Rest of the world
SAE	Serious Adverse Event
SD	Standard deviation
CCI	[redacted]
SLE	Systemic lupus erythematosus
SMC	Safety Monitoring Committee
SPMS	Secondary progressive multiple sclerosis
TEAE(s)	Treatment-emergent Adverse Event(s)
TB	Tuberculosis
TLR	Toll like receptor
ULN	Upper Limit of Normal

1 Synopsis

Clinical Trial Protocol Number	MS200527_0086
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Trial Phase	II
IND Number	CCI
FDA covered trial	Yes
EudraCT Number	2016-001448-21
Coordinating Investigator	PPD
Sponsor	For all countries except the USA: Merck KGaA Frankfurter Str. 250, 64293 Darmstadt, Germany. For the USA only: EMD Serono Research and Development Institute, Inc. 45A Middlesex Turnpike Billerica, MA, 01821 USA
Trial centers/countries	This trial will be conducted at approximately 64 sites globally in Europe, USA, and in the rest of the world (RoW).
Planned trial period (first participant in-last participant out)	First participant in: Q2, 2017 Last participant out: Q1, 2026
Trial Registry	ClinicalTrials.Gov, EudraCT

Objectives:

Primary Objective

The primary objective is to evaluate the efficacy and dose-response of evobrutinib (also referred to as M2951) on the number of gadolinium-positive (Gd+) T1 magnetic resonance imaging (MRI) lesions versus placebo after 24 weeks of treatment.

Secondary Objectives

The key secondary objectives are as follows:

- To evaluate the efficacy and dose-response of M2951 on clinical endpoints over 24 weeks versus placebo.
- To evaluate the safety of M2951.

Additional secondary objectives are as follows:

- To evaluate the efficacy of M2951 on additional MRI parameters over 24 weeks versus placebo.
- To evaluate the efficacy of M2951 on clinical and MRI endpoints from Week 24 to 48.
- To evaluate the efficacy of Tecfidera on clinical and MRI endpoints over 24 weeks.
- To evaluate the efficacy of Tecfidera on clinical and MRI endpoints from Week 24 to 48.
- To evaluate the safety of Tecfidera.

CCI [redacted]

Open-label Long-Term Extension Period objective

The objective of the Open-Label Extension (OLE) Period is:

- To evaluate the long-term safety, efficacy, and CCI of M2951 for up to 8 additional years, at an initial dose of 75 mg once daily which is eventually switched to 75 mg twice daily.

Methodology: The study will be a randomized, double-blind, placebo-controlled study in participants with relapsing multiple sclerosis (RMS), with a parallel, open-label active control group (Tecfidera) involving 5 treatment groups with 3 doses of M2951 (administered in fasted conditions), placebo, and active control (Tecfidera).

The study will consist of 4 major periods: (i) a Screening period of 4 weeks, (ii) active treatment with 3 dose groups of M2951, active control (Tecfidera), or placebo for 24 weeks, (iii) a 24-week extension on active treatment with M2951 or active control (Tecfidera) for 24 weeks, where participants on placebo will be switched to M2951, and (iv) an optional OLE Period of a duration up to 384 weeks. At the end of the 48-week main study, participants will be in 1 of 4 treatment groups (M2951 25 mg daily, 75 mg once daily, or 75 mg twice daily or Tecfidera). Participants who entered the OLE Period initially received M2951 at 75 mg once daily. After review of the efficacy and safety data from the primary analysis at 24 weeks and the blinded extension analysis at 48 weeks, the optimal tested dose is 75 mg twice daily. Accordingly, once investigational medicinal product (IMP) for this dose is available at the study site, participants participating in the OLE Period will either enter the OLE Period on the 75 mg twice daily dose or will be switched to the 75 mg twice daily dose. For participants who received Tecfidera during the 48-week main study and choose to enter the OLE Period, there will be a minimum 4-week washout period before starting open-label M2951. Following completion or early termination of treatment, participants will return after 4 weeks for safety evaluation.

In Amendment 5 (08 November 2019), the duration of treatment in the OLE Period was extended from 96 by 240 weeks to 336 weeks. In some cases, due to Institutional Regulatory Board/Independent Ethics Committee approval, regulatory-specific, or other administrative delays, a participant may experience a treatment gap between the evobrutinib dose received in the first 96 weeks of the OLE Period and the first evobrutinib dose received in the 240-week extension of the OLE Period.

Upon Principal Investigator request, a participant in this circumstance at Week 96 of the OLE Period may still be able to continue into the 240-week extension of the OLE with approval from Merck/EMD Serono, on a case-by-case basis, provided that the treatment gap would not exceed 90 days from the last evobrutinib dose received in the first 96 weeks of OLE Period (OLE Week 96 Visit) to the first evobrutinib dose received in the 240-week extension of the OLE Period.

It is planned that placebo participants will be switched to the 25 mg M2951 once daily dose after Week 24.

Placebo, M2951, and Tecfidera will be administered orally daily. After Day 1, participants will return every 4 weeks for trial visits and will be assessed for safety and efficacy. CCI

CCI [redacted]

An independent data monitoring committee (IDMC) will be responsible for safety monitoring until the last randomized participant completes the blinded phase. The IDMC will consist of at least the following core members: 2 clinicians and 1 biostatistician. After the blinded phase, a switch to an internally convened Safety Monitoring Committee (SMC) will be considered. The SMC will consist of at least the following members: Sponsor and Contract research organization (CRO) medical advisor, Sponsor biostatistician, Sponsor Drug Safety Physician, Sponsor Clinical Pharmacology representative and Coordinating Investigator. Suspected cases of drug-induced liver injury (DILI) will also be reviewed by a Hepatology Assessment Committee (HAC) with appropriate expertise. HAC assessment will be shared with the Data Monitoring Committees (DMCs) (data review meetings of SMCs and IDMCs held in evobrutinib RMS development program) for consideration.

Planned number of participants: Approximately 50 participants will be enrolled in each treatment group, for a total of approximately 250 enrolled participants. Approximately 200 participants are expected to participate in the OLE.

Primary endpoint: Total number of gadolinium -enhancing T1 lesions at Week 12, 16, 20, and 24.

Secondary endpoints:

Key secondary endpoints to evaluate the efficacy and safety of M2951 compared to placebo:

- Annualized relapse rate (ARR), based on protocol-defined qualified relapses, at Week 24;
- Qualified relapse-free status at Week 24;
- Change from Baseline in Expanded Disability Status Scale (EDSS) at Week 24;
- Safety as assessed by the nature, severity, and occurrence of adverse events (AEs); vital signs; electrocardiograms (ECGs); absolute concentrations and change from Baseline in immunoglobulin (Ig) levels; absolute numbers and change from Baseline in B cells; and clinical laboratory safety parameters (duration of placebo treatment group is limited to 24 weeks).

Additional secondary endpoints:

To evaluate the efficacy of M2951 compared to placebo:

- Total number of new Gd+ T1 lesions at Week 12, 16, 20, and 24;
- Mean per-scan number of Gd+ T1 lesions at Week 12, 16, 20, and 24;
- Total number of new or enlarging T2 lesions at Week 12, 16, 20, and 24;
- Change from Baseline in the volume of Gd+ T1 lesions at Week 24;
- Change from Baseline in the volume of T2 lesions at Week 24;

To evaluate efficacy within M2951 dose groups:

- Number of Gd+ T1 lesions at Week 48;
- Number of new Gd+ T1 lesions at Week 48;
- Annualized relapse rate, based on protocol-defined qualified relapses, at Week 48;
- Qualified relapse-free status at Week 48;
- Change from Baseline in EDSS at Week 48;
- Number of new or enlarging T2 lesions at Week 48;
- Change from Baseline in the volume of Gd+ T1 lesions at Week 48;
- Change from Baseline in the volume of T2 lesions at Week 48.

To evaluate the efficacy and safety of Tecfidera:

- Total number of gadolinium-enhancing T1 lesions at Week 12, 16, 20, and 24;
- Annualized relapse rate, based on protocol-defined qualified relapses at Week 24;
- Qualified relapse-free status at Week 24;
- Change from Baseline in EDSS at Week 24;
- Safety as assessed by the nature, severity, and occurrence of AEs; vital signs; ECGs; absolute concentrations and change from Baseline in Ig levels; absolute numbers and change from Baseline in B cells; and clinical laboratory safety parameters;
- Total number of new Gd+ T1 lesions at Week 12, 16, 20, 24;
- Mean per-scan number of Gd+ T1 lesions at Week 12, 16, 20, and 24;
- Total number of new or enlarging T2 lesions at Week 12, 16, 20, and 24;
- Change from Baseline in the volume of Gd+ T1 lesions at Week 24;
- Change from Baseline in the volume of T2 lesions at Week 24;
- Number of Gd+ T1 lesions at Week 48;
- Number of new Gd+ T1 lesions at Week 48;
- Annualized relapse rate, based on protocol-defined qualified relapses, at Week 48;
- Qualified relapse-free status at Week 48;
- Change from Baseline in EDSS at Week 48;
- Number of new or enlarging T2 lesions at Week 48;
- Change from Baseline in the volume of Gd+ T1 lesions at Week 48;
- Change from Baseline in the volume of T2 lesions at Week 48.

CCI

Endpoints for OLE Period:

- Efficacy and CCI endpoints at Week 48, 96, 144, 192, 240, 288, 336 and 384.
  - Number of gadolinium-enhancing T1 lesions;
  - ARR, based on protocol-defined qualified relapses;
  - Qualified relapse-free status;
  - Change from baseline in disability score based on EDSS score;
  - CCI
- Safety as assessed by the nature, severity, and occurrence of AEs; vital signs; ECGs; absolute concentrations and change from Baseline in Ig levels; CCI ; and clinical laboratory safety parameters.

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Diagnosis and key inclusion and exclusion criteria: Male or female participants aged 18 to 65 years with RMS or secondary progressive MS (SPMS) with superimposed relapses. Participants should have 1 or more documented relapses within the 2 years before Screening, with either 1 relapse occurring within the year before randomization or the presence of at least 1 gadolinium-positive T1 lesion within 6 months prior to randomization. The participant should also have an EDSS score of 0 to 6.

Participants will be excluded if they are diagnosed with primary progressive MS or SPMS without evidence of relapse, if they have a disease duration > 15 years and an EDSS ≤ 2. Participants will be excluded if they have received treatment with: rituxumab, ocrelizumab, mitoxantrone, or lymphocyte-depleting therapies (e.g., alemtuzumab, cladribine, cyclophosphamide, total body irradiation, bone marrow transplantation) within 48 weeks prior to randomization; lymphocyte trafficking blockers within 24 weeks prior to randomization (e.g., natalizumab, fingolimod); intravenous (IV) Ig, plasmapheresis, and immunosuppressive treatments within the 4 weeks prior to randomization; glatiramer acetate and B-interferons within 4 weeks prior to randomization; systemic glucocorticoids within 4 weeks prior to randomization; treatment with teriflunomide or daclizumab within 12 weeks prior to randomization; had exposure to Tecfidera within 6 months prior to randomization; has any allergy, contraindication, or inability to tolerate Tecfidera; or has not been on a stable dose of dalfampridine for ≥ 30 days prior to Screening. Participants will also be excluded if they have a history of splenectomy; any major surgery within 2 months prior to Screening; history of myocardial infarction or cerebrovascular event within 6 months prior to Screening; current active angina pectoris, symptomatic heart failure, uncontrolled seizures, untreated hypertension, gastrointestinal (GI) bleeding; a history of attempted suicide within the last 6 months prior to Screening; an episode of major depression within the last 6 months prior to Screening; significant cytopenia; or any other significant active medical condition in the Investigator's opinion.
Investigational Medicinal Product: dose/mode of administration/ dosing schedule: M2951 (25 mg tablets) will be administered orally daily for 48 weeks as needed based on the dose (e.g., 3 × 25 mg tablets for a 75 mg dose). Dosing will be either 25 mg once daily, 75 mg once daily, or 75 mg twice daily. Matched placebo tablets will be provided. For participants who choose to enroll in the OLE, M2951 may be administered for a total of up to 432 weeks.
Reference therapy: dose/mode of administration/dosing schedule: Tecfidera (120 or 240 mg hard capsules) will be used as an active control. For the first 7 days, Tecfidera is administered orally at 120 mg twice daily. Following this and for the duration of treatment, Tecfidera is administered orally at 240 mg twice daily orally. Detailed recommendations for the use of this product are described in the summary of product characteristics or prescribing information.
Planned trial and treatment duration per participant: Total duration of participation is approximately 440 to 448 weeks for participants who choose to participate in the optional OLE Period and approximately 392 days (56 weeks) for participants who do not participate in the optional OLE Period. Total duration includes: • Screening: 28 days (4 weeks); • Treatment: 168 days (24 weeks); • Blinded treatment extension: 168 days (24 weeks); • Tecfidera Washout for participants who were in Tecfidera arm: 4 to 8 weeks; • Optional OLE Period (up to 384 weeks); • 4-week Safety Follow-Up/End of Trial Visit: 28 days (4 weeks).

After completing the 48-week main study, participants will be offered the opportunity to participate in an optional OLE Period with M2951 up to 384 weeks.

Once the long-term follow-up study is open for enrollment in their country (i.e., once the Sponsor, upon agreement with Health Authorities/Ethics Committees, will have notified sites), participants in the OLE Period will have the option to transition into the long-term follow-up study under a new protocol for continued treatment. Upon Sponsor site notification, all participants will be asked to return for an OLE End of Treatment Visit within 30 days.

- For participants entering the long-term follow-up study under a new protocol, their OLE End of Treatment Visit in the current study is also their first visit in the long-term follow-up study. Therefore, these participants are neither required to enter the 4-week Safety Follow-up Period nor to undergo a 4-week Safety Follow-up Visit/End of Trial Visit.
- Participants who do not wish to transition into the long-term follow-up study, will have the OLE End of Treatment Visit followed by a 4-week Safety Follow-up Visit/End of Trial Visit.

In case the long-term follow-up study will not become available in their respective country, participants will complete the OLE per study schedule and have the OLE End of Treatment Visit at Week 384 followed by a 4-week Safety Follow-up Visit/End of Trial Visit.

Statistical methods:

A per-group sample size of 44 evaluable participants provides 85% power to detect a decrease of 90% in the total number of gadolinium-enhancing T1 lesions, summed over scans at Week 12, 16, 20, and 24, between a given M2951 group versus placebo at the 2-sided 5% level, using the Wilcoxon rank-sum test, where the p-value is evaluated using a continuity-corrected normal approximation to the test statistic.

Eligible participants will be randomized 1:1:1:1:1 to treatment with placebo, low-dose M2951 (25 mg once daily), mid-dose M2951 (75 mg once daily), high-dose M2951 (75 mg twice daily), or Tecfidera (administered twice daily at a final dose of 240 mg), through a central randomization process by an Interactive Web Response System (IWRS), stratified according to region (USA or Western Europe, Eastern Europe and CCI , Eastern Europe and not CCI , Rest of World). Approximately 50 participants will be randomized per group to protect against a loss of information due to a 12% drop-out rate over 1 year.

There will be 5 analyses: (1) a primary analysis, triggered when 100% of participants enrolled reach Week 24 of treatment, or prematurely discontinue from treatment; (2) a blinded extension analysis, triggered when 100% of participants enrolled either reach Week 52 (4-week Safety Follow-up Visit) and complete the study, enroll in the OLE, or prematurely discontinue from study; (3) an OLE Week 60 interim analysis, triggered when 100% of OLE participants either reach Week 60 of the OLE, or prematurely discontinue from treatment; (4) an OLE interim analysis, planned at the appropriate time point considering the visits schedule around the time of the trigger for the primary analysis of the Phase III RMS studies; and (5) a final analysis, triggered when 100% of participants enrolled in the OLE complete the OLE (4-week Safety

Follow-up Visit for participants not transitioning into the long-term follow-up study under a new protocol and OLE End of Treatment Visit for transitioning participants) or discontinue from the OLE.

The Family-wise Type I error rate (FWER) at the primary analysis, due to multiple comparisons of M2951 dose to placebo based on the primary endpoint, will be controlled at the 2-sided 0.05 significance level using the Hochberg procedure.

Primary Endpoint

The primary analysis of total number of Gd+ T1 lesions, Week 12, 16, 20, and 24, will be an estimate of lesion rate ratio, together with associated 95% confidence interval (CI) and p-value, comparing each M2951 dose group to placebo, based on a negative binomial (NB) model, where the offset will be based on the log of number of scans, with M2951 dose or placebo group as a factor, and adjustment for covariates based on randomization strata and baseline MRI activity. Other covariates may be considered. Should the model fail to converge, the primary analysis will be an estimate of the shift in location of the distribution of total number of Gd+ T1 lesions via the Hodges-Lehman estimate, together with associated 95% CI and p-value based on the stratified Wilcoxon rank-sum test, comparing each M2951 dose group to placebo. Descriptive statistics for the total number of Gd+ T1 lesions, Week 12, 16, 20, and 24, will be provided for each treatment group. The primary analysis will be based on only the M2951 dose groups and placebo group.

Other Efficacy Endpoints, Baseline to 24 weeks:

The comparison of a M2951 treatment group to placebo group using ARR at Week 24 will be based on the rate ratio estimated from an NB model for qualified relapse count, with offset equal to the log of years on study, with M2951 dose group or placebo group as a factor, and adjustment for covariates based on randomization strata and prebaseline relapse activity. The comparison of a M2951 treatment group to placebo group using proportion qualified relapse-free at Week 24 will be based on the odds ratio estimated from a logistic model for the odds of a participant being qualified relapse-free, where participants who discontinue prior to Week 24 without having a qualified relapse are counted as not being qualified relapse-free at Week 24, with M2951 dose group or placebo group as a factor, and adjustment for covariates based on randomization strata and prebaseline relapse activity. The comparison of a M2951 treatment group to placebo group using change from Baseline in EDSS at Week 24 will be based on a stratified Wilcoxon rank-sum test, with strata defined by baseline EDSS and randomization strata.

The analysis of change from Baseline in volume of Gd+ T1 lesions at Week 24, and change from Baseline in volume of T2 lesions at Week 24, will be based on a Mixed-effect Model for Repeated Measures (MMRM) approach for the appropriately transformed variable, with M2951 dose group or placebo group as a factor, randomization strata as a factor and baseline MRI activity as a covariate. The comparison of a M2951 treatment group to placebo using total number of new Gd+ T1 lesions, or total number of new or enlarging T2 lesions, at Week 12, 16, 20, and 24, will be based on an NB model, similar to that used for the primary analysis. Estimation of mean per-scan number of Gd+ T1 lesions, at Weeks 12, 16, 20, and 24, for each

treatment group, will be based on the NB model. In the analysis of each secondary endpoint, other covariates may be included in the model.

Descriptive statistics for MRI and clinical endpoints, Baseline to Week 24, will be provided for the M2951 dose arms, the placebo arm, and the Tecfidera arm. No inferential analyses comparing the Tecfidera group to any other treatment group will be conducted.

Other Efficacy Endpoints, Baseline to 48 weeks:

Descriptive statistics for MRI and clinical endpoints, Baseline to Week 48, will be provided for the M2951 dose arms, the placebo/M2951 arm, and the Tecfidera arm.

The number of Gd+ T1 lesions, number of new Gd+ T1 lesions, number of new and enlarging T2 lesions, the observed and change from Baseline values of Gd+ T1 lesion volume, and observed and change from Baseline values of T2 lesion volume, will be summarized by treatment group (placebo, 3 M2951 dose groups, and Tecfidera) and time point over the treatment period.

Annualized relapse rate from Baseline to Week 24, from Week 24 to Week 48, and from Baseline to Week 48 will be summarized by treatment group. Qualifying relapse-free status at Week 24 and at Week 48 will be summarized by treatment group. Observed and change from Baseline values of EDSS will be summarized by treatment group and time point over the treatment period.

Safety

Safety data for all treatment groups (M2951 dose groups, placebo group, Tecfidera group) will be listed and summarized using descriptive statistics.

CCI [redacted]

[redacted]

OLE Period Endpoints

Safety, efficacy, and CCI [redacted] data collected during the OLE Period will be summarized.

CCI [redacted]

[redacted]

[redacted]

CCI [redacted]

Table 1 **Schedule of Assessments: Screening and Treatment period (All Participants), End of Trial (Participants Not Entering OLE Period)**

Activity/ Assessment	Screening	On Treatment Visits																				Unscheduled Visit	End of Treatment Visit	End of Trial Visit
Visit number	1	2	3	4	4.1	5	5.1	6	6.1	7	7.1	8	8.1	8.2	8.3	8.4	8.5	9	9.1	9.2	9.4		10	11
Study Week		D 1	W 4	W 8	W 10	W 12	W 14	W 16	W 18	W 20	W 22	W 24	W 26	W 28	W 30	W 32	W 34	W 36	W 38	W 40	W 44		W 48	W 52
Study Day ± Visit Window	-28 to -1	1	28 ±3	56 ±3	70 ±3	84 ±3	98 ±3	112 ±3	126 ±3	140 ±3	154 ±3	168 ±3	182 ±3	196 ±3	210 ±3	224 ±3	238 ±3	252 ±3	266 ±3	280 ±3	308 ±3		336 ±3	364 ±5
Obtain ICF[a]	X																						X[b]	
Inclusion / Exclusion criteria	X	X																						
Medical history /demographics	X																							
MS history	X																							
Physical examination	X				X[c]	X	X[c]		X[c]		X[c]	X	X[c]	X[c]	X[c]	X[c]	X[c]		X[c]	X[c]	X[c]	X		
Vital signs[d]	X	X	X	X		X		X		X		X						X				X	X	X
Neurological examination	X	X	X	X		X		X		X		X						X				X	X	X
Quantiferon tuberculosis test, viral serology testing[e]	X																							
Randomization[f]		X																						
Hematology[g]	X		X	X		X		X		X		X						X				X	X	X
Clinical chemistry[g]	X		X	X		X		X		X		X						X				X	X	X

Activity/ Assessment	Screening	On Treatment Visits																				Unscheduled Visit	End of Treatment Visit	End of Trial Visit
Visit number	1	2	3	4	4.1	5	5.1	6	6.1	7	7.1	8	8.1	8.2	8.3	8.4	8.5	9	9.1	9.2	9.4		10	11
Study Week		D 1	W 4	W 8	W 10	W 12	W 14	W 16	W 18	W 20	W 22	W 24	W 26	W 28	W 30	W 32	W 34	W 36	W 38	W 40	W 44		W 48	W 52
Study Day ± Visit Window	-28 to -1	1	28 ±3	56 ±3	70 ±3	84 ±3	98 ±3	112 ±3	126 ±3	140 ±3	154 ±3	168 ±3	182 ±3	196 ±3	210 ±3	224 ±3	238 ±3	252 ±3	266 ±3	280 ±3	308 ±3		336 ±3	364 ±5
Supplemental Safety Visits including LFTs [h]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Immunoglobulin levels[i]		X	X					X				X											X	
Urinalysis (microscopy, urine protein/ creatinine ratio)[j]	X					X						X										X	X	X
Coagulation (INR, PTT)	X																						X	
CCI [redacted]	[redacted]	[redacted]	[redacted]									[redacted]											[redacted]	[redacted]
Serum pregnancy test[l]	X																							
Urine pregnancy test (all countries)[l]		X	X	X		X		X		X		X		X^m		X^m		X		X^m	X^m		X	X
12-lead ECG[n]	X											X										X	X	
Chest X-ray[n]	X																							
EDSS	X	X				X						X						X				X	X	
Relapse assessment			X	X		X		X		X		X						X				X	X	X
MRI scan	X[o]					X		X		X		X											X	

Activity/ Assessment	Screening	On Treatment Visits																				Unscheduled Visit	End of Treatment Visit	End of Trial Visit
Visit number	1	2	3	4	4.1	5	5.1	6	6.1	7	7.1	8	8.1	8.2	8.3	8.4	8.5	9	9.1	9.2	9.4		10	11
Study Week		D 1	W 4	W 8	W 10	W 12	W 14	W 16	W 18	W 20	W 22	W 24	W 26	W 28	W 30	W 32	W 34	W 36	W 38	W 40	W 44		W 48	W 52
Study Day ± Visit Window	-28 to -1	1	28 ±3	56 ±3	70 ±3	84 ±3	98 ±3	112 ±3	126 ±3	140 ±3	154 ±3	168 ±3	182 ±3	196 ±3	210 ±3	224 ±3	238 ±3	252 ±3	266 ±3	280 ±3	308 ±3		336 ±3	364 ±5
Concomitant medications and procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE evaluation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense IMP[p]		X	X	X		X		X		X		X						X						
IMP Administration		Oral Administration																						
IMP compliance			X	X		X		X		X		X						X					X	
CCI [redacted]		[redacted]																						
CCI [redacted]		[redacted]																						
CCI [redacted]		[redacted]																						
CCI [redacted]		[redacted]																						
C-SSRS (Screening Scale)	X																							
CCI [redacted]		[redacted]																						
ESR, hsCRP, and fibrinogen[w]																		X						

AE=adverse event, CCI [redacted], CMV=cytomegalovirus, C-SSRS=Columbia-Suicide Severity Rating Scale, CXR=chest X-ray, ECG=electrocardiogram, eCRF=electronic case report form, EDSS=expanded disability status scale, ESR=erythrocyte sedimentation rate, FSH=follicle-stimulating hormone, HbsAg=hepatitis B surface antigen, HBV=hepatitis B virus, HCV=hepatitis C virus, HIV=human immunodeficiency virus, CCI [redacted], hsCRP=high sensitivity C-reactive protein, ICF=informed consent form, IDMC=independent data monitoring committee, Ig=immunoglobulin, IMP=investigational medicinal product, INR=international normalized ratio, MRI=magnetic resonance imaging, MS=multiple sclerosis, CCI [redacted], OLE=Open-label Extension, CCI [redacted], PTT=partial thromboplastin time, CCI [redacted]

a. Informed consent must be obtained at the Screening Visit prior to initiating any Screening procedures or collecting any data. An addendum ICF must be obtained following the IDMC recommendation (October 2017).
b. Informed consent for the OLE Period will be obtained at the End of Treatment Visit for all participants who received Tecfidera during the 48-week main study and who choose to enter the OLE Period.
c. An additional physical examination may be performed at the additional safety visits (e.g., 4.1, 5.1) at the Investigator's discretion.
d. Vital signs are assessed predose. Height is measured at Screening only.
e. Blood samples for tuberculosis (Quantiferon) testing will be obtained at Screening. Additional samples should be taken for viral serology testing at Screening: HBV antibodies, HbsAg, and HCV antibodies. HIV testing will be done at Screening only where required as per local regulations.
f. Randomization should occur on Day 1 after all Screening procedures have been completed; participant eligibility must be reviewed again and confirmed at the site on Day 1 prior to randomization.
g. Blood samples for hematology and chemistry (Table 8) to be obtained at Screening, predose at all Visits when collected except Day 1.
h. For participants in the placebo/M2951 arms, supplemental LFT monitoring (Table 8) will be conducted, and additional CCI [redacted] samples drawn.
i. Samples for total Ig levels (IgM, IgA, IgG) will be obtained predose (see Section 7.4.5).
j. Urine samples for urinalysis will be obtained at Screening, predose at Weeks 12, 24, 48, and 52. If local urinalysis by dipstick is abnormal, urine microscopy should be performed by a central laboratory. If at least 1+ protein is detected, urine protein/creatinine ratio should be determined.
k. Blood samples for CCI [redacted] CCI [redacted] CCI [redacted] CCI [redacted] will be obtained predose. An additional sample will be collected at the 4-week Safety Follow-up/End of Trial Visit (see Sections 7.4.6 and 7.6.3).
l. Serum pregnancy test collected at Screening, and urine tests collected predose at every monthly trial visit, for women of childbearing potential only. Urine pregnancy tests will also be performed at home/site at Weeks 28, 32, 40, and 44 for women of childbearing potential randomized to the M2951/placebo arm. If necessary to confirm postmenopausal status, FSH testing will be done at Screening in postmenopausal women.
m. Phone calls: To be done only if urine pregnancy test is completed at home. Participants will be supplied with at-home test kits. The Principal Investigator and/or delegated site staff will call participant at Weeks 28, 32, 40, and 44 to confirm completion of home pregnancy testing and discuss results.
n. ECG and posteroanterior CXR performed at Screening. Participants who have previously had a CXR for clinical reasons within 3 months prior to Day 1 do not need to have the CXR repeated if the results are available and show no sign of active infective process or any other clinically significant abnormalities. ECGs will also be conducted at Weeks 24 and 48.
o. The Screening MRI scan should be acquired before randomization and dosing to allow for the readouts to be read by the central MRI reader (approximately 7 days).
p. The IMP will be dispensed after randomization on Day 1 and at the indicated visits thereafter. All remaining IMP will be collected on Week 48.

CCI [redacted]

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u. To be completed before any other procedure takes place.

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w. All participants in the study, regardless of their liver function status, should have at least 1 test during the study period for ESR, hsCRP, and fibrinogen. This test may be conducted from a sample at any study visit.

Table 2 Schedule of Assessments – Optional OLE Period Week 0 to 96

Activity/ Assessment	OLE Day 1	On Treatment Visits: Week 0 to 96																													Unscheduled Visit
OLE Year	**OLE Year 1**																					**OLE Year 2**									
Visit number (for OLE)	1	1A	1.1	1B	2	2A	2.1	2B	3	3A	3.1	3B	4	4A	4.1	4B	4.2, 4.4	5	5.2, 5.4	6	6.2, 6.4	7	7.2, 7.4	8	8.2, 8.4	9	9.2, 9.4	10	10.2, 10.4	11[a]	
Additional Visits for Tecfidera participants ONLY[b]	X	X		X	X	X		X	X	X		X		X		X															
Study Week	W 0	W 1	W 2	W 3	W 4	W 5	W 6	W 7	W 8	W 9	W 10	W 11	W 12	W 13	W 14	W 15	W16, W20	W 24	W28, W32	W 36	W40, W44	W 48	W52, W56	W 60	W64, W68	W 72	W76, W80	W 84	W88, W92	W 96[c]	
Study Day ± Visit Window	1 ±3	±3	±3	±3	28 ±7	±3	±3	±3	56 ±7	±3	±3	±3	84 ±7	±3	±3	±3	±3	168 ±7	±3	252 ±7	±3	336 ±7	±3	420 ±7	±3	504 ±7	±3	588 ±7	±3	672 ±7	
Obtain ICF[d]	X																													X	
Physical examination[e]	X												X					X		X		X		X		X		X			X
Vital signs[f]	X				X				X				X					X		X		X		X		X		X		X	X
Neurological examination	X												X					X		X		X		X		X		X		X	X
Hematology[f]	X				X				X				X					X		X		X		X		X		X		X	X
Clinical chemistry[f]	X				X				X				X					X		X		X		X		X		X		X	X
Supplemental Safety Visits including LFTs[g]	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	
CCI																															
Immunoglobulin levels[f]	X																	X				X				X				X	
Urinalysis (microscopy, urine protein/ creatinine ratio)[i]	X																	X						X						X	X

Activity/ Assessment	OLE Day 1	On Treatment Visits: Week 0 to 96																													Unscheduled Visit
OLE Year	**OLE Year 1**																					**OLE Year 2**									
Visit number (for OLE)	1	1A	1.1	1B	2	2A	2.1	2B	3	3A	3.1	3B	4	4A	4.1	4B	4.2, 4.4	5	5.2, 5.4	6	6.2, 6.4	7	7.2, 7.4	8	8.2, 8.4	9	9.2, 9.4	10	10.2, 10.4	11[a]	
Additional Visits for Tecfidera participants ONLY[b]	X	X		X	X	X		X	X	X		X		X		X															
Study Week	W 0	W 1	W 2	W 3	W 4	W 5	W 6	W 7	W 8	W 9	W 10	W 11	W 12	W 13	W 14	W 15	W16, W20	W 24	W28, W32	W 36	W40, W44	W 48	W52, W56	W 60	W64, W68	W 72	W76, W80	W 84	W88, W92	W 96[c]	
Study Day ± Visit Window	1 ±3	±3	±3	±3	28 ±7	±3	±3	±3	56 ±7	±3	±3	±3	84 ±7	±3	±3	±3	±3	168 ±7	±3	252 ±7	±3	336 ±7	±3	420 ±7	±3	504 ±7	±3	588 ±7	±3	672 ±7	
CCI [redacted]	[redacted]																					[redacted]								X	
Urine pregnancy test (all countries)[k,l]	X				X				X				X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG	X																					X								X	X
Chest X-ray	X																														
EDSS	X																					X								X	X
Relapse assessment	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
MRI scan	X																					X								X	
Concomitant medications and procedures	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
AE evaluation	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
Dispense IMP[m]	X				X				X				X					X		X		X		X		X		X		X	
IMP compliance	X				X				X				X					X		X		X		X		X		X		X	
CCI [redacted]																															
C-SSRS (Since Last Visit Scale)	X																					X								X	

AE=adverse event, ALT=alanine aminotransferase, AST=aspartate aminotransferase, CCI , CMV=cytomegalovirus, C-SSRS=Columbia-Suicide Severity Rating Scale, EA=early antigen, EBNA=Epstein-Barr nuclear antigen, ECG=electrocardiogram, eCRF=electronic case report form, EDSS=expanded disability status scale, ESR=erythrocyte sedimentation rate, GGT=γ-glutamyl-transferase, HAV=hepatitis A virus, HBc=hepatitis B core antigen, HEV=hepatitis E virus, CCI , hsCRP=high sensitivity C-reactive protein, ICF=informed consent form, Ig=immunoglobulin, IMP=investigational medicinal product, INR=international normalized ratio, LFT=liver function test, MRI=magnetic resonance imaging, MS=multiple sclerosis, CCI , OLE=Open-label Extension, PTT=partial thromboplastin time, CCI , VCA=viral capsid antigen.

a. As described in Section 7.1.6, there may be a dosing delay between Visit 11 (Week 96) and Visit 12 (Week 108). In this circumstance, the participant should return to the study site when dosing resumes, and the procedures described in Section 7.1.6 should be performed.

b. Visits 2 (Week 4) and 3 (Week 8) are applicable only for participants who received Tecfidera, and for participants who received M2951/placebo these visits are only for LFTs (Section 7.1.6 and Section 7.1.3).

c. Between Week 96 and Week 108, the participant should be contacted for a Telephone Visit on Week 102 as described in Table 3 and Section 7.1.6.1.

d. Signed consent will be obtained prior to participation in the optional OLE Period. Participants entering from M2951 will sign the ICF at OLE Day 1, and participants entering from Tecfidera will sign at the Week 48 End of Treatment Visit. As the OLE Period was extended beyond Week 96 in Protocol amendment 5, consent will also be obtained at Week 96 to allow OLE Period treatment beyond this point.

e. A physical examination may be performed at additional chemistry visits at the Investigator's discretion.

f. The following will be obtained predose: vital signs (Section 7.4.4.1), hematology and chemistry (Table 8), and total Ig levels (IgM, IgA, IgG) (see Section 7.4.5).

g. Supplementary LFTs include AST, ALT, alkaline phosphatase, GGT, and bilirubin for participants.

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During Week 0 to 96 of the OLE, urine samples for urinalysis will be obtained predose on OLE Day 1 and at Weeks 24, 60, 96, and unscheduled visits. If local urinalysis by dipstick is abnormal, urine microscopy should be performed by a central laboratory. If at least 1+ protein is detected, urine protein/creatinine ratio should be determined.

j. During Week 0 to 96 of the OLE, blood samples for CCI CCI CCI CCI will be obtained predose on OLE Day 1, Week 48, and Week 96 visits (see Sections 7.4.6 and 7.6.3).

k. During Week 0 to 104 of the OLE, urine pregnancy tests will also be performed at home at Week 14, Week 16, Week 20, Week 28, Week 32, Week 40, Week 44, Week 52, Week 56, Week 64, Week 68, Week 76, Week 80, Week 88, Week 92, Week 96, Week 100, and Week 104 for women of childbearing potential. Participants will be supplied with at-home test kits.

l. Phone calls: during Week 0 to 104 of the OLE, to be done only if urine pregnancy test is completed at home: The Principal Investigator and/or delegated site staff will call participant at Week 14, Week 16, Week 20, Week 28, Week 32, Week 40, Week 44, Week 52, Week 56, Week 64, Week 68, Week 76, Week 80, Week 88, Week 92, Week 96, Week 100, and Week 104 to confirm completion of home pregnancy testing and discuss results.

m. The IMP will be dispensed on OLE Day 1 and at indicated visits thereafter.

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Table 3 Schedule of Assessments – Optional OLE Period Week 108 up to 384

Activity/ Assessment	On Treatment Visits: Week 108 to 384											Unscheduled Visit	OLE End of Treatment[m]	End of Trial Visit[m]
OLE Year	**OLE Year 3**		**OLE Year 4**		**OLE Year 5**		**OLE Year 6**		**OLE Year 7**		**OLE Year 8**		**OLE year 8**	
Visit number (for OLE)	12, 13, 14	15	16, 17, 18	19	20	21	22	23	24	25	26		27	28
Study Week	W 108, 120, 132	W 144	W 156, 168, 180	W 192	W 216	W 240	W 264	W 288	W 312	W 336	W 360		W 384	W 388
Study Day ± Visit Window	756, 840, 924 ±7	1008 ±7	1092, 1176, 1260 ±7	1344 ±7	1512 ±14	1680 ±14	1848 ±14	2016 ±14	2184 ±14	2352 ±14	2520 ±14		2688 ±14	2716 ±7
Physical examination[a]	X[a]	X	X[a]	X	X	X	X	X	X	X	X	X		
Vital signs[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Neurological examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical chemistry[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CCI [redacted]	[redacted]													
Immunoglobulin levels[b, d]	X[d]	X	X[d]	X	X	X	X	X	X	X	X		X	
Urinalysis (microscopy, urine protein/ creatinine ratio)[e]	X[e]	X	X[e]	X	X	X	X	X	X	X	X	X	X	X
CCI [redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]			[redacted]	[redacted]

Activity/ Assessment	On Treatment Visits: Week 108 to 384											Unscheduled Visit	OLE End of Treatment[m]	End of Trial Visit[m]
OLE Year	**OLE Year 3**		**OLE Year 4**		**OLE Year 5**		**OLE Year 6**		**OLE Year 7**		**OLE Year 8**		**OLE year 8**	
Visit number (for OLE)	12, 13, 14	15	16, 17, 18	19	20	21	22	23	24	25	26		27	28
Study Week	W 108, 120, 132	W 144	W 156, 168, 180	W 192	W 216	W 240	W 264	W 288	W 312	W 336	W 360		W 384	W 388
Study Day ± Visit Window	756, 840, 924 ±7	1008 ±7	1092, 1176, 1260 ±7	1344 ±7	1512 ±14	1680 ±14	1848 ±14	2016 ±14	2184 ±14	2352 ±14	2520 ±14		2688 ±14	2716 ±7
Telephone Visit[g]	Weeks 102, 114, 126, 138, 150		Weeks 162, 174, 186, 200, 208		Weeks 224, 232, 248, 256		Weeks 272, 280, 296, 304		Weeks 320, 328	Weeks 344, 352	Weeks 368, 376			
Urine pregnancy test (all countries)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
At-home pregnancy test and phone calls[h]	Monthly when no on-site visit scheduled[h]													
12-lead ECG		X		X		X		X		X		X	X	
EDSS		X		X		X		X		X		X	X	
Relapse assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MRI scan[i]		X		X		X		X		X			X	
Concomitant medications and procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE evaluation	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense IMP[j]	X	X	X	X	X	X	X	X	X	X	X			
IMP compliance	X	X	X	X	X	X	X	X	X	X	X		X	

CCI [redacted]

Activity/ Assessment	On Treatment Visits: Week 108 to 384											Unscheduled Visit	OLE End of Treatment[m]	End of Trial Visit[m]
OLE Year	OLE Year 3		OLE Year 4		OLE Year 5		OLE Year 6		OLE Year 7		OLE Year 8		OLE year 8	
Visit number (for OLE)	12, 13, 14	15	16, 17, 18	19	20	21	22	23	24	25	26		27	28
Study Week	W 108, 120, 132	W 144	W 156, 168, 180	W 192	W 216	W 240	W 264	W 288	W 312	W 336	W 360		W 384	W 388
Study Day ± Visit Window	756, 840, 924 ±7	1008 ±7	1092, 1176, 1260 ±7	1344 ±7	1512 ±14	1680 ±14	1848 ±14	2016 ±14	2184 ±14	2352 ±14	2520 ±14		2688 ±14	2716 ±7
C-SSRS (Since Last Visit Scale)		X		X		X		X		X			X	

AE=adverse event, C-SSRS=Columbia-Suicide Severity Rating Scale, ECG=electrocardiogram, eCRF=electronic Case Report Form; EDSS=expanded disability status scale, CCI , CCI , Ig=immunoglobulin, IMP=investigational medicinal product, LFT=liver function test, MRI=magnetic resonance imaging, CCI , OLE=Open-label Extension, CCI ; CCI , W=Week.

a. Physical exams will be performed every 24 weeks (Weeks 120, 144, 168, 192, 216, 240, 264, 288, 312, 336, and 360) and at unscheduled visits.

b. The following will be obtained predose: vital signs (Section 7.4.4.1), hematology and chemistry (Table 8), and total Ig levels (IgM, IgA, IgG) (see Section 7.4.5).

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d. Blood samples for Ig levels will be obtained predose every 24 weeks (Weeks 120, 144, 168, 192, 216, 240, 264, 288, 312, 336, 360, and OLE End of Treatment).

e. Urine samples for urinalysis will be obtained predose every 24 weeks (Weeks 120, 144, 168, 192, 216, 240, 264, 288, 312, 336, 360 and OLE End of Treatment), at the 4-week Safety Follow-up/End of Trial Visit, and at unscheduled visits. If local urinalysis by dipstick is abnormal, urine microscopy should be performed by a central laboratory. If at least 1+ protein is detected, urine protein/creatinine ratio should be determined.

f. Blood samples for CCI CCI CCI CCI will be obtained predose every 48 weeks, including the OLE End of Treatment Visit. An additional sample will be collected at the 4-week Safety Follow-up/End of Trial Visit (see Sections 7.4.6 and 7.6.3).

g. The participant will have Telephone Visits at regular intervals between on-site visits. For details of Telephone Visits, please see Section 7.1.6.1. The phone calls have a window of ± 1 week, and will occur at Week 102, Week 114, Week 126, Week 138, Week 150, Week 162, Week 174, Week 186, Week 200, Week 208, Week 224, Week 232, Week 248, Week 256, Week 272, Week 280, Week 296, Week 304, Week 320, Week 328, Week 344, Week 352, Week 368, Week 376. Confirmation of completion of monthly home pregnancy testing and discussion of results can be included in these calls if they are scheduled to occur during the same week.

h. Urine pregnancy tests will also be performed at home at Week 112, Week 116, Week 124, Week 128, Week 136, Week 140, Week 148, Week 152, Week 160, Week 164, Week 172, Week 176, Week 184, Week 188, Week 196, Week 200, Week 204, Week 208, Week 212, Week 220, Week 224, Week 228, Week 232, Week 236, Week 244, Week 248, Week 252, Week 256, Week 260, Week 268, Week 272, Week 276, Week 280, Week 284, Week 292, Week 296, Week 300, Week 304, Week 308, Week 316, Week 320, Week 324, Week 328, Week 332, Week 340, Week 344, Week 348, Week 352, Week 356, Week 364, Week 368, Week 372, Week 376 and Week 380 for women of childbearing potential. Participants will be supplied with at-home test kits. The Principal Investigator and/or delegated site staff will call participant to confirm completion of home pregnancy testing and discuss results. This call can be combined with the Telephone Visit described above in footnote g if they are scheduled to occur during the same week (women of childbearing potential only).

i. If a participant discontinues the study more than 4 weeks after his or her most recent MRI, an MRI may be obtained at the 4-week Safety Follow-up Visit.

j. All remaining IMP will be collected at the OLE End of Treatment Visit.

CCI [redacted]

m. Once the long-term follow-up study is open for enrollment in their country (i.e. once the Sponsor – upon agreement with Health Authorities/Ethics Committees – will have notified sites), participants in the OLE Period will have the option to transition into the long-term follow-up study under a new protocol for continued treatment. Upon Sponsor site notification, all participants will be asked to return for an OLE End of Treatment Visit within 30 days. Participants who do not wish to transition into the long-term follow-up study, will have the OLE End of Treatment Visit followed by a 4-week Safety Follow-up Visit/End of Trial Visit. For participants entering the long-term follow-up study under a new protocol, their OLE End of Treatment Visit in the current study is also their first visit in the long-term follow-up study. Therefore, these participants are neither required to enter the 4-week Safety Follow-up Period nor to undergo a 4-week Safety Follow-up Visit/End of Trial Visit. In case the long-term follow-up study will not become available in their respective country, participants will complete the OLE per study schedule and have the OLE End of Treatment Visit at Week 384 followed by a 4-week Safety Follow-up Visit/End of Trial Visit.

2 Sponsor, Investigators and Trial Administrative Structure

This clinical trial will be sponsored by:

- EMD Serono Research & Development Institute, Inc., Billerica, Massachusetts, USA.
- Merck KGaA, Darmstadt, Germany in countries outside the USA.

The trial will be conducted at approximately 64 sites in Western and Eastern Europe, in USA, and RoW. For the OLE Period, enrollment will continue at the sites used during the Screening and Treatment periods.

The Coordinating Investigator, PPD , represents all Investigators for decisions and discussions regarding this trial, consistent with the International Council for Harmonisation (ICH) Topic E6 Good Clinical Practice (GCP; hereafter referred to as ICH GCP). The Coordinating Investigator will provide expert medical input and advice relating to trial design and execution and is responsible for the review and signoff of the clinical trial report.

Signature pages for the Protocol Lead and the Coordinating Investigator as well as a list of Sponsor responsible persons are in Appendix I.

The trial will appear in the following clinical trial registries: ClinicalTrials.Gov and EUDRACT.

The Sponsor will enlist the support of a CRO, to conduct the clinical part of the trial including trial set-up, operation of an IWRS for randomization, coordination, monitoring, medical oversight, data capture, data management, statistical analysis, and clinical trial reporting. The Sponsor will also make use of the CRO's central laboratory for sample analyses, storage, and shipment to specialized bioanalytical laboratories. The Sponsor will supervise all outsourced activities.

An IDMC will be responsible for safety monitoring until the last randomized participant completes the blinded phase. The IDMC will consist of at least the following core members: 2 clinicians and 1 biostatistician. The full list of IDMC members and responsibilities will be included in the IDMC charter. After the blinded phase, a switch to an internally convened SMC will be considered. The SMC will consist of at least the following members: Sponsor and CRO medical advisor, Sponsor biostatistician, Sponsor Drug Safety Physician, Sponsor Clinical Pharmacology representative and Coordinating Investigator. An SMC charter will be provided once the transition from the IDMC has been completed.

HAC will review suspected cases of drug-induced liver injury (DILI). The HAC is composed of external, independent hepatologists with the requisite scientific, and medical experience in review of suspected DILI cases and in provision of an expert recommendation on the hepatic risk profile. Details regarding HAC roles, responsibilities, activities, and possible recommendations are provided in a separate HAC charter. HAC assessment will be shared with the Data Monitoring Committees (DMCs) (data review meetings of SMCs and IDMCs held in evobrutinib RMS development program) for consideration.

The CRO will also provide a qualified neurologist who will adjudicate the relapses (to confirm qualified relapse) and systematically review the EDSS to determine if there is lack of efficacy/disease progression. The scope of this review will be described in detail in the Medical Monitoring Plan.

IMP will be supplied by the Clinical Trial Supply Department at Merck, except Tecfidera for the USA. In the USA Tecfidera will be sourced locally by the clinical trial sites. IMP supplied by the Clinical Trial Supply Department at Merck will be packaged and labeled by a designated contract manufacturing organization.

Details of structures and associated procedures will be defined in a separate Manual of Operations, which will be prepared under the supervision of the clinical trial leader.

3 Background Information

MS is a chronic, inflammatory, demyelinating disease of the central nervous system and the most common cause of serious neurological disability in young adults. Approximately 85% of patients with MS initially present with RMS, which is characterized by periodic acute exacerbations of disease activity (multifocal inflammatory lesion, relapses) and periods of remission, consisting of partial or complete recovery. With recurring relapses, disability tends to accumulate (1).

Currently there is no cure for MS, but the course of the disease can be altered favorably with DMDs with varying levels of efficacy, and distinct safety and tolerability profiles. Most active RMS patients initiate treatment with an interferon-beta or glatiramer acetate (Copaxone®) therapy. Tecfidera has recently been added as a first-line therapy and is the most prescribed first-line therapy in an oral formulation. If responding suboptimally, patients can be treated with an alternative, second-line therapy such as fingolimod (Gilenya®) or natalizumab (Tysabri®). Generally, DMDs perceived to be more efficacious have also been shown to be associated with more significant adverse effects, ranging from serious infections (i.e., PML) to autoimmunity and cancer. Switching among these DMDs 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 DMDs that address not only inflammation but also disability progression within the CNS for patients with RMS at all stages of the disease. Early treatment with a highly efficacious, but safer DMD could be extremely advantageous for long-term quality of life for MS patients and might slow the process of brain atrophy, which accompanies axonal damage and loss in grey and white matter. An oral and safer solution for the treatment of MS patients with high disease activity would be an attractive treatment choice for patients switching therapy. Using the USA as an example, we assume that there are approximately 20,000 new MS patients (naïve= 8%) per year, and 60,000 patients (24%) that are switching therapy per year. If the efficacy and safety profile for evobrutinib (also referred to as M2951) are as predicted with a favorable benefit to risk profile, it could be utilized throughout the course of the disease (early, mid and late stage) – capturing naïve and early switch patients.

M2951 is an oral, highly selective, irreversible inhibitor of BTK in development for the treatment of autoimmune and inflammatory diseases, including RA, SLE and MS. BTK mediates signaling

through the B cell receptor and has been described downstream of several other receptors, including Fc receptor, TLR and Integrin receptors, expressed in innate immune cells. Inhibition of BTK blocks both B cell function and innate immune activation and may therefore offer advantages over B cell-only directed therapies.

BTK is a clinically validated target in oncology and although BTKi competitor companies are planning for point-of-care in several inflammatory indications including pemphigus/bullous pemphigoid and RA, none of them is currently preparing for the MS indication. M2951 has a superior kinase selectivity profile vs. ibrutinib and spebrutinib which may translate into a clinically relevant safety advantage.

Robust, high-efficacy clinical proof of concept was recently demonstrated with B cell depleting antiCD20 therapies in Phase II and Phase III clinical trials in RMS and progressive MS (2-5). Ocrelizumab inhibited the formation of new inflammatory MRI lesions up to 90% (2) in Phase II RMS trials and high efficacy on MRI (-94%), ARR (-46%) and 6-month disease progression (-40%) was also reached in ORACLE Phase I, II, and III trials against interferon-β. Translational mechanism of action studies in antiCD20 treated RMS patients show diminished proliferation and proinflammatory differentiation of T cells (6), pointing towards abrogation of antigen presenting cell function as the primary mechanism. In addition to the role of antiCD20 in B cell antigen presentation, a recent publication of Li et al (7) describes a diminished proinflammatory myeloid cell response in Ocrelizumab-treated MS participants. M2951 shows inhibition of myeloid cell activation by immune complexes.

AntiCD20 like efficacy is anticipated with BTK inhibition given the overlap on B cell-related activities of BTKi molecules in key in vitro assays targeting B cell antigen presentation, proliferation/differentiation, and cytokine production. Preclinical proof of concept with M2951 has been demonstrated for systemic lupus erythematous/lupus nephritis, EAE, RA and passive cutaneous anaphylaxis. Oral M2951 does not deplete B cells in the studies carried out to date and, upon withdrawal, restoration of immune function can be obtained in days vs. months with antiCD20 therapies, should the need to interrupt or stop therapy arise. This suggests a more favorable benefit to risk profile for M2951 vs. antiCD20 therapies. In addition, BTKi might have broader efficacy than B cell depletion alone, due to the importance of BTK activation downstream of various receptors expressed in myeloid cells, suggesting a direct effect of M2951 on innate immune cell activation induced by immune complexes, cytokines/chemokines, or TLR activation (8-10). A direct myeloid silencing activity also best explains the significant reduction of clinical score, relapse rate, and time to first relapse in T cell-dependent EAE models, in which antiCD20 antibodies do not work.

3.1 Trial Rationale

This study is designed to determine efficacy and safety of M2951 in patients with RMS, and to determine a dose to take forward into Phase III development. The OLE Period will allow for assessment of long-term safety and efficacy of M2951.

The findings in Section 3 clearly support the pathogenic contribution of B cells to MS damage. In contrast, a failed clinical trial with another B cell targeting agent, atacicept, supports the notion

that certain B cell subtypes may mediate beneficial anti-inflammatory effects (11). Novel nondepleting B cell therapies may deliver a more favorable benefit-risk profile than current B cell-directed therapeutic approaches.

CCI [redacted].

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

3.2 Benefit-Risk

Benefit

M2951 is the first agent with a mechanism of action that directly targets both B cells and myeloid cells. In the primary analysis of this study (MS200527_0086), 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 was associated with a lower ARR compared to placebo. During the OLE period, the efficacy was maintained and similar to that observed in the primary analysis (26). Post-hoc analyses show that evobrutinib significantly reduced blood levels of neurofilament light chain and slowly expanding lesion volume, markers of ongoing CNS-compartmentalized inflammation and neurodegeneration that predict long-term disability (27, 28). This coupled with the detection of evobrutinib in the cerebrospinal fluid of participants with RMS (29) support the potential for evobrutinib to have biologically relevant effects directly within the CNS by acting on mechanisms of progression. Though data suggests evobrutinib inhibits immune inflammation association with progression, participants treated with evobrutinib successfully develop humoral responses to COVID-19 vaccines (30). It is reasonable to anticipate that M2951 may represent a significant advance in the treatment of MS.

Important Identified Risk

- *Important Identified Risk: Drug-Induced Liver Injury*
    - As of July 2022, more than 2,490 participants have been exposed to evobrutinib in completed and ongoing clinical studies including healthy volunteers, participants with RMS, SLE, or RA, and participants with renal and hepatic impairment. The incidence of SAEs and treatment-emergent adverse events (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 drug-induced liver injury (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 Risks

Important potential risks to participants are based on nonclinical safety data of M2951, clinical data on adverse drug effects associated with compounds of a similar pharmacological class, and clinical data on adverse drug effects observed in ongoing studies of M2951 including this Phase II study and Phase III RMS studies.

- *Important Potential Risk: Severe DILI, i.e., Requiring Transplant or Leading to Death*
  - Based on the important identified risk of 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 Investigator's Brochure), as well as other drugs in the same class. 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.
  - These results 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 not be pregnant, must have a negative pregnancy test at the time of enrollment, 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 protocol.

In view of the observation of asymptomatic elevated transaminases in a number of participants randomized to M2951 or placebo in this study and ongoing Phase III RMS study, the frequency of monitoring has been adapted to optimize timely implementation of the IMP withdrawal or holding criteria.

With the above modification to monitoring, risk minimization measures inherent to early phase clinical trials are considered adequate for the proposed clinical trial. The IDMC/SMC/HAC continually reviews available safety and tolerability data and is mandated to make immediate decisions regarding the conduct of the trial.

Noting the finding of asymptomatic increases in transaminases in participants across completed and ongoing clinical studies of various indications, evobrutinib has demonstrated manageable tolerability.

Other Potential Risks

Although no causal relationship has been established, other potential risks including infections (serious and opportunistic infections), lipase and amylase elevation (including pancreatitis), and seizure, are under Sponsor's close monitoring (refer to Investigator's Brochure section 5.3.6.1) and will be evaluated.

Benefit-Risk Conclusion

Overall, considering the unmet medical need in patients with MS, reduction of MS activities (decreased the number of T1 Gd+ lesions and lower ARR compared with placebo), effect on makers of CNS inflammation and neurodegeneration, development of humoral response, convenience of an oral therapy with a short half-life and the measures put in place to mitigate the important identified and important potential risks, the benefit-risk of evobrutinib 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 the Investigator's Brochure.

This clinical trial will be conducted in compliance with the clinical trial protocol, ICH GCP, and any additional applicable regulatory requirements. 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 and benefit-risk considerations, the conduct of the trial specified in this protocol is considered justifiable.

4 Trial Objectives

4.1 Primary Objective

The primary objective is to evaluate the efficacy and dose-response of M2951 on the number of Gd+ T1 MRI lesions versus placebo after 24 weeks of treatment.

4.2 Secondary Objectives

The key secondary objectives are as follows:

- To evaluate the efficacy and dose-response of M2951 on clinical endpoints over 24 weeks versus placebo;
- To evaluate the safety of M2951.

Additional secondary objectives are as follows:

- To evaluate the efficacy of M2951 on additional MRI parameters over 24 weeks versus placebo;
- To evaluate the efficacy of M2951 on clinical and MRI endpoints from Week 24 to 48;
- To evaluate the efficacy of Tecfidera on clinical and MRI endpoints over 24 weeks;
- To evaluate the efficacy of Tecfidera on clinical and MRI endpoints from Week 24 to 48;
- To evaluate the safety of Tecfidera.

CCI [redacted]

4.4 Open-label Extension Period Objective

The objective of the OLE Period is:

- To evaluate the long-term safety, efficacy, and CCI of M2951 for up to 8 additional years, at an initial dose of 75 mg once daily which is eventually switched to 75 mg twice daily.

5 Investigational Plan

5.1 Overall Trial Design and Plan

This will be a randomized, double-blind, placebo-controlled study in participants with RMS, with a parallel, open-label active control group (Tecfidera) involving 5 treatment groups with 3 doses of M2951, placebo, and active control (Tecfidera). The assessing Investigator and central MRI reader will be treatment blinded.

The study will consist of 4 major periods: (i) a Screening period of 4 weeks, (ii) active treatment with 3 dose groups of M2951, active control (Tecfidera), or placebo for 24 weeks, (iii) a 24-week extension on active treatment with M2951 or active control (Tecfidera) for 24 weeks, where participants on placebo will be switched to M2951 (Figure 1), and (iv) an optional OLE Period of a duration up to 384 weeks. At the end of the 48-week main study, participants will be in 1 of 4 treatment groups (M2951 25 mg daily, 75 mg once daily, or 75 mg twice daily or Tecfidera). Participants who entered the OLE Period initially received M2951 at 75 mg once daily. After review of the efficacy and safety data from the primary analysis at 24 weeks and the blinded extension analysis at 48 weeks, the optimal tested dose is 75 mg twice daily. Accordingly, once IMP for this dose is available at the study site, participants in the OLE Period will either enter the OLE Period on the 75 mg twice daily dose or will be switched to the 75 mg twice daily dose (Figure 2). Participants transitioning from Tecfidera will complete a washout period of at least 4 weeks prior to initiating M2951 treatment in the OLE Period (see Section 5.5.1 and (Figure 2). Following completion or early termination of treatment, participants will return after 4 weeks for safety evaluation. It is planned that placebo participants will be switched to the 25 mg M2951 once daily dose after Week 24.

Approximately 50 participants will be enrolled in each treatment group to obtain 44 evaluable participants per group (total = approximately 250), assuming a 12% drop-out rate per year, and to compile an adequate safety database. Approximately 200 participants are expected to be enrolled in the OLE.

In Amendment 5 (08 November 2019), the duration of treatment in the OLE Period was extended by 240 weeks from 96 to 336 weeks. In some cases, due to IRB/IEC approval, regulatory-specific, or other administrative delays, a participant may experience a treatment gap between the evobrutinib dose received in the first 96 weeks of the OLE Period and the first evobrutinib dose received in the 240-week extension of the OLE Period.

Upon Principal Investigator request, a participant in this circumstance at Week 96 of the OLE Period may still be able to continue into the 240-week extension of the OLE with approval from Merck/EMD Serono, on a case-by-case basis, provided that the treatment gap would not exceed 90 days from the last evobrutinib dose received in the first 96 weeks of OLE Period (OLE Week 96 Visit) to the first evobrutinib dose received in the 240-week extension of the OLE Period. See Section 7.1.6 for further details.

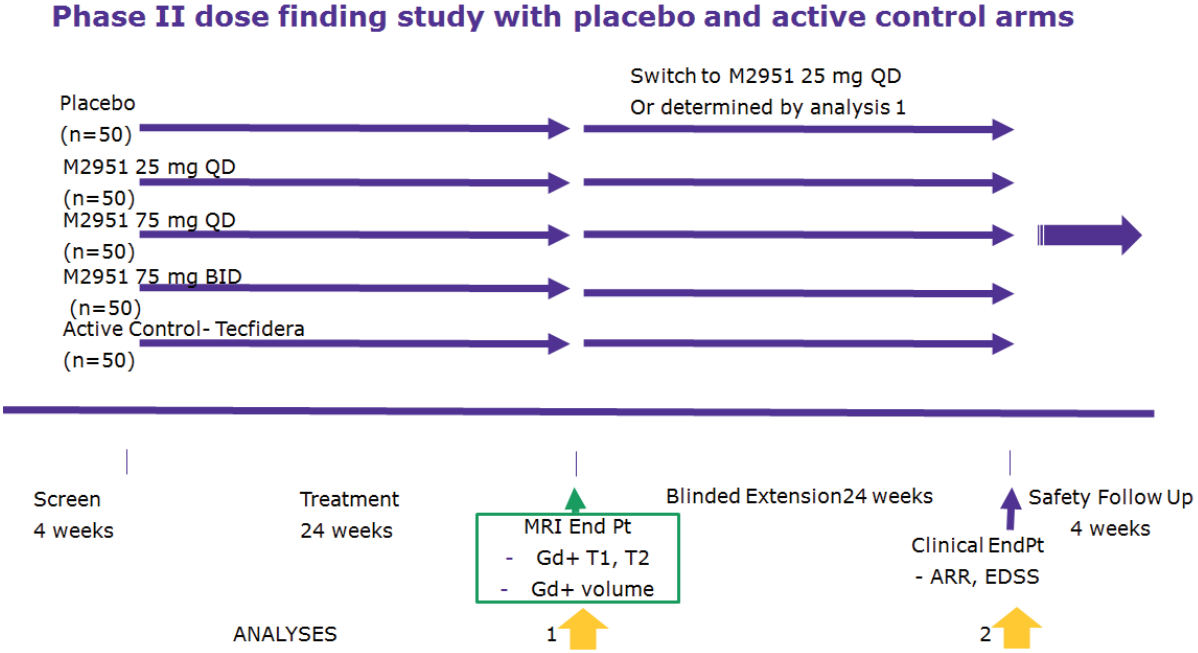
Once the long-term follow-up study is open for enrollment in their country (i.e., once the Sponsor – upon agreement with Health Authorities/Ethics Committees – will have notified sites),

participants in the OLE Period will have the option to transition into the long-term follow-up study under a new protocol for continued treatment. Upon Sponsor site notification, all participants will be asked to return for an OLE End of Treatment visit within 30 days.

- For participants entering the long-term follow-up study under a new protocol, their OLE End of Treatment Visit in the current study is also their first visit in the long-term follow-up study. Therefore, these participants are neither required to enter the 4-week Safety Follow-up Period nor to undergo a 4-week Safety Follow-up Visit/End of Trial Visit.
- Participants who do not wish to transition into the long-term follow-up study, will have the OLE End of Treatment Visit followed by a 4-week Safety Follow-up Visit/End of Trial Visit.

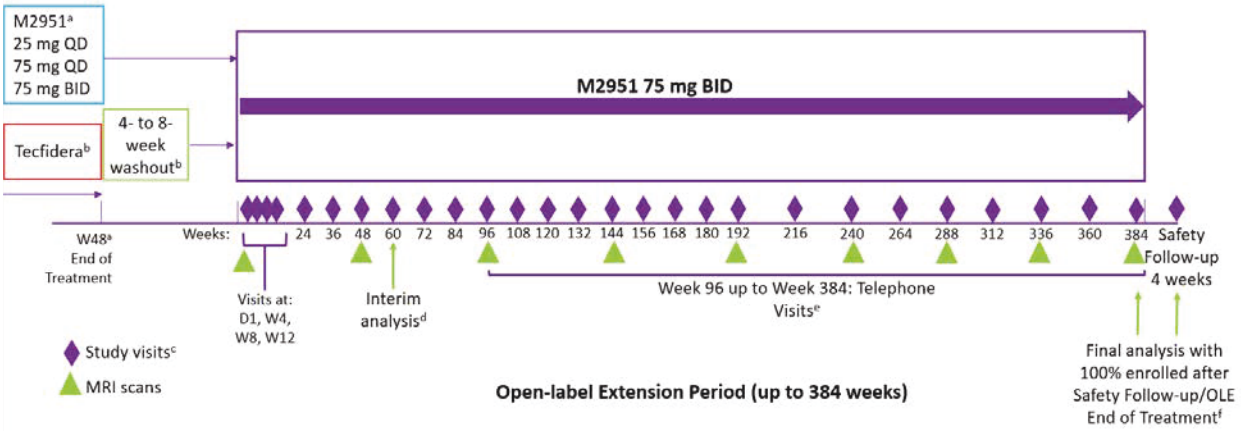
In case the long-term follow-up study will not become available in their respective country, participants will complete the OLE per study schedule and have the OLE End of Treatment Visit at Week 384 followed by a 4-week Safety Follow-up Visit/End of Trial Visit.

Figure 1 Trial Design – Main Study



ARR=annualized relapse rate; BID=twice a day; EDSS=expanded disability status scale; EndPt=endpoint; Gd+=gadolinium-positive; MRI=magnetic resonance imaging; QD=once a day.

Figure 2 Trial Design – Optional OLE Period



BID=twice a day; D=Day; IMP= investigational medicinal product; MRI=magnetic resonance imaging; OLE=Open-label Extension; QD=once a day.

a Participants who entered the OLE Period initially received M2951 at 75 mg once daily. After review of the efficacy and safety data from the primary analysis at 24 weeks and the blinded extension analysis at 48 weeks, the optimal tested dose is 75 mg twice daily. Accordingly, once IMP for this dose is available at the study site, participants participating in the OLE Period will either enter the OLE Period on the 75 mg twice daily dose or will be switched to the 75 mg twice daily dose.

For participants entering the OLE after receiving M2951 during the 48-week main study, the Week 48 Visit is considered the Day 1 Visit for the OLE period.

b For participants entering from Tecfidera treatment arm, treatment with M2951 will only commence if a participant who received Tecfidera during the 48-week main study has an absolute lymphocyte count ≥ 800/mm^3 following 4 weeks of washout. If the participant does not have an absolute lymphocyte count ≥ 800/mm^3 following 8 weeks of washout, he or she will be discontinued from the study.

c Denotes efficacy visits only. Safety visits will be conducted every 2 weeks during the first 16 weeks of treatment, then monthly during the OLE period until Week 96, then 3-monthly until Week 192, then 6-monthly until Week 384.

d An interim analysis will be performed at Week 60 of the OLE period. A further interim analysis will be planned at the appropriate time point considering the visits schedule around the time of the trigger for the primary analysis of the Phase III RMS studies.

e Between Week 96 and Week 384 regular Telephone Visits will occur. See Table 3 for the schedule and Section 7.1.6.1 for details of the Telephone Visits.

f Once the long-term follow-up study is open for enrollment in their country (i.e., once the Sponsor – upon agreement with Health Authorities / Ethics Committees – will have notified sites), participants will have the option to transition into the long-term follow-up study for continued treatment. All participants will be asked to return for an OLE End of Treatment Visit within 30 days of Sponsor notification. Participants who do not wish to transition into the long-term follow-up study, will have the OLE End of Treatment Visit followed by a 4-week Safety Follow-up Visit/End of Trial Visit. For participants entering the long-term follow-up study under a new protocol, their OLE End of Treatment Visit in the current study is also their first visit in the long-term follow-up study. Therefore, these participants are neither required to enter the 4-week Safety Follow-up Period nor to undergo a 4-week Safety Follow-up Visit/End of Trial Visit. The final analysis will occur only when the last participant in the OLE Period completes the OLE (4-week Safety Follow-up Visit for participant not transitioning and OLE End of Treatment Visit for transitioning participant) or discontinues (see Section 5.8).

Detailed schedules of study procedures are provided in Table 1, Table 2, and Table 3. The Tecfidera washout period is described in Table 5.

5.2 Discussion of Trial Design

5.2.1 Scientific Rationale for Trial Design

This trial is modeled after the ocrelizumab Phase II trial design (12). The first part of the study will compare M2951 versus placebo for the main study objective of evaluating M2951 efficacy and dose-response. It is becoming more difficult to perform placebo-controlled trials in MS due to the wide range of efficacious therapies. It is still however necessary to have placebo-controlled data to accurately measure the size of the treatment effect and assess safety. The number of participants exposed to placebo (up to 50) and short duration (24 weeks) is acceptable. Furthermore, all placebo participants will be switched to M2951 during the blinded treatment extension phase.

An active control group will also be enrolled. Tecfidera has been chosen as the control as it is the oral first-line therapy for RMS and has significant efficacy on early MRI endpoints. As it is very difficult to blind Tecfidera due to its specific safety profile, it will be administered in an open-label fashion.

The second phase of the study, from Week 24 to 48, will be continued in a blinded fashion. Participants who choose to enter the OLE Period will receive open-label M2951 for up to 8 years (up to 384 weeks).

5.2.2 Justification for Dose

CCI [redacted]

[redacted]

M2951, at a dose of 75 mg once daily, was used in the 4-week SLE study (Trial EMR200527_002: A Phase Ib Double-blind, Randomized, Placebo-controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Biological Effect of MSC2364447C in Systemic Lupus Erythematosus). CCI [redacted] Refer to the current Investigator's Brochure for more detailed results from the completed clinical studies.

CCI [redacted]

Finally, 1 lower dose (expected suboptimal therapeutic dose) should be chosen. CCI [redacted]

From a safety perspective, the doses of M2951 (25 mg once daily, 75 mg once daily, 75 mg twice daily) selected for this trial are within the dose ranges studied in clinical trial EMR200527_001. Single doses up to CCI [redacted] were well tolerated in healthy volunteers and no safety signals were identified.

CCI [redacted]

The placebo group will be switched to M2951 25 mg once daily during the second part of the study from Week 24 to 48; however, flexibility will be maintained in deciding to use this dose or an alternative dose, based on data from the primary analyses. Participants who entered the OLE Period initially received M2951 at 75 mg once daily. After review of the efficacy and safety data from the primary analysis at 24 weeks and the blinded extension analysis at 48 weeks, the optimal tested dose is 75 mg twice daily. Accordingly, once IMP for this dose is available at the study site, participants participating in the OLE Period will either enter the OLE Period on the 75 mg twice daily dose or will be switched to the 75 mg twice daily dose.

Exposure-response analyses were conducted for key efficacy endpoints. These analyses clearly demonstrated significant relationships between evobrutinib exposure (steady state AUC) and the following efficacy endpoints: ARR, total number of T1 Gd+ lesions in participants with > 0 lesions at baseline, and new/enlarging T2 lesions with lesion volume > 13 cc.

In particular for ARR, a steep exposure-response relationship was identified between it and evobrutinib steady state AUC. The model predicted a significant and sustained reduction in ARR at evobrutinib $AUC_{0\text{-}24,ss} \geq 400$ ng × h/mL. CCI [redacted] predicted that the exposures in a majority (> 90%) of participants with the 45 mg twice daily regimen administered with a meal were expected to be greater than this threshold.

CCI [redacted]

CCI [redacted]

5.2.3 Rationale for Endpoints

The primary endpoint chosen is a standard one for RMS Phase II studies. For early treatment effects to be seen, MRI endpoints are used. The most sensitive is the total number of Gd+ T1 lesions on MRI summed over scans at Weeks 12, 16, 20, and 24. MRIs will be carried out at Screening and every 4 weeks from Week 12 to 24. MRIs will also be carried out at Week 48 in the blinded treatment extension phase.

Other MRI measures will be used as secondary endpoints. These include the total number of new Gd+ T1 lesions, total number of new or enlarging T2 lesions, mean per-scan number of Gd+ T1 lesions, Gd+ T1 lesion volume change from Baseline, and T2 lesion volume change from Baseline.

MRI measures alone may not predict final clinical outcome. Therefore, ARR will be assessed at Week 24 and Week 48 in the blinded treatment extension phase.

Other clinical endpoints will be measured including change from Baseline in EDSS, qualifying relapse-free status, and patient-reported outcome measures.

CCI [redacted]

5.2.4 Inclusion of Special Populations

Not applicable.

5.3 Selection of Trial Population

Only participants meeting all inclusion criteria and no exclusion criteria may be enrolled into the trial as participants. Prior to performing any trial assessments not part of the participant's routine medical care, the Investigator will ensure that the participant or the participant's legal representative has provided written informed consent following the procedure described in Section 9.2.

Participants who do not meet the inclusion/exclusion criteria within the first Screening period and are considered screen failures may undergo rescreening once after approval by the Medical Monitor. The second Screening period is a new 28-day Screening period, and the participant will receive a new identification number. All other testing is required to be redone at rescreening.

5.3.1 Inclusion Criteria

1. Participants with a diagnosis of RMS (may include participants with SPMS with superimposed relapses provided they meet the other criteria) in accordance with revised McDonald criteria for MS (14, 15) and Lublin and Reingold (16).
2. Male or female aged 18 to 65 years.
3. One or more documented relapses within the 2 years before Screening with either:
   a) One relapse which occurred within the last year prior to randomization
   or
   b) the presence of at least 1 Gd+ T1 lesion within 6 months prior to randomization would make the patient eligible.
4. EDSS score of 0 to 6 at Baseline.
5. Women of childbearing potential must use a supplementary barrier method together with a highly effective method of contraception (according to ICH guidance M3[R2]) for 4 weeks prior to randomization, throughout the trial, and for 90 days after the last dose of IMP. For the purposes of this trial:
   - Women are considered of childbearing potential unless they are postmenopausal. Females who are postmenopausal (age-related amenorrhea ≥ 12 consecutive months and increased FSH > 40 mIU/mL) or who have undergone hysterectomy or bilateral oophorectomy are exempt from pregnancy testing. If necessary to confirm postmenopausal status, an FSH will be drawn at Screening.
   - Highly effective contraception includes:
     - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation; oral, intravaginal or transdermal;
     - Progestogen-only hormonal contraception associated with inhibition of ovulation; oral, injectable or implantable;
     - Intrauterine device (IUD);
     - Intrauterine hormone-releasing system (IUS);
     - Bilateral tubal occlusion;
     - Vasectomized partner;
     - Sexual abstinence.
   - Supplementary barrier methods include:
     - Male or female condom with or without spermicide;
     - Cap, diaphragm or sponge with spermicide.
   - Men must agree to use and have their female partners use a supplementary barrier method together with a highly effective contraceptive method as defined above for at least 90 days after the last IMP administration.

- Women of childbearing potential must have a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test at randomization on Day 1 before dosing.

6. Signed and dated informed consent (participant must be able to understand the informed consent) indicating that the participant has been informed of all the pertinent aspects of the trial prior to enrollment and will comply with the requirements of the protocol.

5.3.2 Exclusion Criteria

1. Progressive MS either Primary or Secondary if Secondary is without evidence of relapse.
2. Disease duration > 15 years (participant reported adequate in absence of written medical record) in participants with EDSS of 2 or less.
3. Treatment with rituximab, ocrelizumab, mitoxantrone, or lymphocyte-depleting therapies (e.g., alemtuzumab, antiCD4, cladribine, cyclophosphamide, total body irradiation, bone marrow transplantation) which should not be used within 48 weeks prior to randomization.
4. Use of lymphocyte trafficking blockers (e.g., natalizumab, fingolimod) within 24 weeks prior to randomization.
5. Use of IV Igs, plasmapheresis, and immunosuppressive treatments within 4 weeks prior to randomization.
6. Treatment with B-interferons or glatiramer acetate within 4 weeks prior to randomization.
7. Systemic glucocorticoids within 4 weeks prior to randomization.
8. Treatment with teriflunomide within 12 weeks prior to randomization.
9. Treatment with daclizumab within 12 weeks prior to randomization.
10. Exposure to Tecfidera within 6 months prior to randomization.
11. Any allergy, contraindication, or inability to tolerate Tecfidera.
12. Treatment with dalfampridine (fampridine, Ampyra) unless on a stable dose for ≥ 30 days prior to randomization
13. Inability to comply with MRI scanning, including contra-indications to MRI such as known allergy to gadolinium contrast media, claustrophobia, presence of a pacemaker, cochlear implants, ferromagnetic devices or clips, intracranial vascular clips, insulin pumps, nerve stimulators.
14. Immunologic disorder other than MS, with the exception of secondary well-controlled diabetes or thyroid disorder, or any other condition requiring oral, IV, intramuscular, or intra-articular corticosteroid therapy.
15. Vaccination with live or live-attenuated virus vaccine within 1 month prior to Screening.
16. Severe drug allergy or history of anaphylaxis, or allergy to the IMP or any of its incipients.
17. Active, clinically significant viral, bacterial, or fungal infection, or any major episode of infection requiring hospitalization or treatment with parenteral anti-infectives within 4 weeks of Screening, or completion of oral anti-infectives within 2 weeks before or during

Screening, or a history of recurrent infections (i.e., 3 or more of the same type of infection in a 12-month rolling period). Vaginal candidiasis, onychomycosis, and genital or oral herpes simplex virus considered by the Investigator to be sufficiently controlled would not be exclusionary.

18. History of or positive testing for HIV, HCV antibody and/or polymerase chain reaction, HbsAg (+) and/or hepatitis B core total, and/or IgM antibody (+) at Screening. Testing for HIV will only be conducted where required as per local regulation.
19. 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 purified protein derivative with induration ≥ 5 mm;

    or

    - Has a positive **QuantiFERON®**-TB test at Screening.

    Participants with documented completed appropriate LTBI treatment would not be excluded and are not required to be tested.
20. Indeterminate **QuantiFERON**-TB tests may be repeated once, and will be considered positive if retest results are positive or indeterminate.
21. Participants with current household contacts with active TB will also be excluded.
22. History of splenectomy at any time, or any major surgery within 2 months prior to Screening.
23. History of myocardial infarction or cerebrovascular event within 6 months prior to Screening, or current active angina pectoris, symptomatic heart failure, uncontrolled seizures, untreated hypertension, GI bleeding, or any other significant active medical condition in the Investigator's opinion.
24. A history of attempted suicide within 6 months prior to Screening or a positive response to items 4 or 5 of C-SSRS.
25. An episode of major depression within the last 6 months prior to Screening (clinically stable minor depression is not exclusionary).
26. On anticoagulation, fish oil supplements, or antiplatelet therapy other than daily aspirin for cardioprotection and treatment of Tecfidera induced flushing.
27. History of cancer, except adequately treated basal cell or squamous cell carcinoma of the skin (no more than 3 lesions requiring treatment in lifetime) or carcinoma in situ/cervical intraepithelial neoplasia of the uterine cervix, unless considered cured ≥ 5 years.

28. Breastfeeding/lactating or pregnant women.
29. Participation in any investigational drug trial within 1 month or 5 half-lives of the investigational drug, whichever is longest, prior to Screening.
30. Participants currently receiving (or unable to stop using prior to receiving the first dose of IMP) medications or herbal supplements known to be potent inhibitors of CYP3A (must stop at least 1 week prior), potent inducers of CYP3A (must stop at least 3 weeks prior), or drugs mainly metabolized by CYP3A with a narrow therapeutic index (must stop at least 1 day prior).
31. History of or current alcohol or substance abuse
    - Excessive alcohol use is defined as alcohol and/or substance abuse or dependence (as defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th edition) in the past year or a history of alcohol or substance abuse, as determined by the Investigator.
32. Clinically significant abnormality on ECG, or an active infective process or any other clinically significant abnormality on Screening CXR taken within 4 weeks of the first dose, per Investigator opinion. If a CXR has been taken within the previous 3 months and results are available and normal, the CXR does not need to be carried out.
33. eGFR by the 4-variable Modification of Diet in Renal Disease equation of < 45 mL/min/1.73 m^2 or any renal condition that would preclude the administration of gadolinium (e.g., acute renal insufficiency).
34. ALT, AST, amylase, or lipase $> 2\times$ above ULN of laboratory reference range, total bilirubin $> 1.5\times$ ULN, any other clinically significant laboratory abnormality.
35. B cell (CD19) count $< 50\%$ of the LLN at Screening.
36. Significant cytopenia, including neutrophil count $< 1{,}500/mm^3$, platelet count $< 75{,}000/mm^3$, absolute lymphocyte count $< 800/mm^3$, or a white blood cell count $< 3500/mm^3$

    Note: for participants participating in the OLE Period after receiving Tecfidera during the 48-week main study, absolute lymphocyte count $< 800/mm^3$ is considered an exclusion criterion.

5.4 Criteria for Randomization and Initiation of Trial Treatment

Randomization should occur on Day 1 after all Screening procedures have been completed; participant eligibility must be reviewed again and confirmed at the site on Day 1 prior to randomization. If a participant does not meet eligibility criteria, the participant can be retested and rescreened once after the approval of the Medical Monitor as described in Section 5.3.

Eligible participants will be randomized to treatment with M2951 (25 mg once daily, 75 mg once daily, or 75 mg twice daily), Tecfidera, or placebo through a central randomization process by an IWRS. Stratification will occur by region (USA or Western Europe, Eastern Europe and CCI [redacted], Eastern Europe and not CCI [redacted], and RoW).

5.5 Criteria for Entry into OLE Period

Participants who have withdrawn after randomization (e.g., due to AEs or lack of efficacy) will not be replaced and will not be eligible to participate in the OLE Period. Only participants who have completed the 48-week main study are eligible to participate in the OLE Period. Participants who entered the OLE Period initially received M2951 at 75 mg once daily. After review of the efficacy and safety data from the primary analysis at 24 weeks and the blinded extension analysis at 48 weeks, the optimal tested dose is 75 mg twice daily. Accordingly, once IMP for this dose is available at the study site, participants participating in the OLE Period will either enter the OLE Period on the 75 mg twice daily dose or will be switched to the 75 mg twice daily dose.

5.5.1 Participants Entering OLE Period after Receiving Tecfidera

For participants who received Tecfidera during the 48-week main study and choose to enter the OLE Period, there should be a minimum 4-week washout period before starting open-label M2951 (Table 5). If a participant who received Tecfidera has an absolute lymphocyte count < 800/mm^3 4 weeks after discontinuing Tecfidera, M2951 treatment should not be initiated. If the participant's absolute lymphocyte value reaches ≥ 800/mm^3 after 8 weeks of discontinuing Tecfidera, he or she may begin M2951 treatment in the OLE Period, and the OLE Day 1 Visit should be scheduled within 1 week. During this washout period, a participant may continue to be monitored for absolute lymphocyte count values (at Tecfidera Washout Visit 1 or 2) or may discontinue the study and begin a different treatment regimen in agreement with the Investigator. If a participant is not eligible to enter the OLE Period by Tecfidera Washout Visit 2, he or she will need to return for the End of Trial Visit described in Section 7.1.8. This End of Trial Visit should be completed within 14 days ± 7 days from the time the decision is reached that the participant is not eligible to enter the OLE Period.

Table 5 Washout Period for Participants on Tecfidera Treatment Arm before Entering OLE Period

Activity/Assessment	Tecfidera Washout Visit(s)	
Visit number (for Washout Period)	Tecfidera WO 1	Tecfidera WO 2[a,b]
Tecfidera Washout Week	W4	W8
Tecfidera Washout Day ± Visit Window[c]	28 ± 7	56 ± 7
Absolute lymphocyte count[d]	X	X
Relapse assessment	X	X

OLE=Open-label Extension, WO=washout.

a. Tecfidera Washout Visit 2 will occur only if the participant has an absolute lymphocyte count < 800/mm^3 at Tecfidera Washout Visit 1.

b. If a participant is not eligible to enter the OLE Period by Tecfidera Washout Visit 2, he or she will need to return for the End of Trial Visit described in Table 1. This End of Trial Visit should be completed within 14 days ± 7 days from the time the decision is reached that the participant is not eligible to enter the OLE Period.

c. Tecfidera washout visits will occur within the range of days noted for each week following end of treatment with Tecfidera.

d. Treatment with M2951 will only commence if a participant who received Tecfidera during the 48-week main study has an absolute lymphocyte count ≥ 800/mm^3 following 4 weeks of washout. If the participant does not have an absolute lymphocyte count ≥ 800/mm^3 at Tecfidera Washout Visit 2, he or she will be excluded from the OLE

Period. At any time during the washout period, the participant may choose to discontinue from the study and begin a different treatment regimen in agreement with the Investigator.

5.6 Criteria for Participant Withdrawal

Participants will be informed that they have the right to withdraw from the trial at any time, without prejudice to their medical care, and they are not obliged to state a reason for withdrawing. Any withdrawal must be fully documented in the eCRF and source documents, and should be followed up by the Investigator.

The Investigator may withdraw a participant at any time if this is considered to be in the participant's best interest.

5.6.1 Withdrawal from Trial Therapy

Participants who withdraw from therapy (during the 48-week main study or OLE Period) must immediately return for an End of Treatment Visit or an OLE End of Treatment Visit followed by the 4-week Safety Follow-Up/End of Trial Visit 4 weeks later (see Section 7.1.5 and 7.1.6). A participant must be withdrawn if any of the following occur:

- Withdrawn from study (see Section 5.6.2);
- AEs, if discontinuation of IMP is desired or considered necessary by the Investigator and/or participant;
- Use of prohibited medications, as defined in Section 6.4.2. However, any medications that are considered necessary for the participant's well-being may be given at the discretion of the Investigator. Use of a prohibited medication may be cause for a participant to withdraw, however each incident should be discussed on a case-by-case basis with the study and Medical Monitor;
- Pregnancy;
- Lack of efficacy and/or progression of MS as defined by Investigator judgment or when a medication other than protocol-allowed medications is needed for treatment;
- Any events that unacceptably endanger the safety of the participant;
- IMP will be discontinued in case of elevated liver tests as defined in protocol Section 6.4.4.
- If any of the following occur while a participant is receiving Tecfidera (17, 18):
  - Any instance of lymphocyte counts < 200/mm^3 or < 500/mm^3 for > 24 weeks
  - In the event of serious infection, Tecfidera should be withheld until the infection is resolved
  - At the first sign or symptom suggestive of PML
  - More than 1 instance of dose reduction due to a flushing reaction (see Section 6.4.4 or the local label [17, 18]) and GI disturbances.

Withdrawal due to special precautions is described in Section 6.4.4.

5.6.2 Withdrawal from the Trial

Participants may withdraw from the trial at any time without giving a reason. Withdrawal of consent will be considered withdrawal from the trial. Participants who withdraw from the trial while still on the IMP should return immediately for an End of Treatment Visit upon discontinuation of the IMP and a Safety Follow-Up/End of Trial Visit 4 weeks after the last administered dose of IMP. Participants who withdraw and are no longer on the IMP must complete the 4-week Safety Follow-up/End of Trial Visit assessments described in Section 7.1.8.

A participant must be withdrawn if any of the following occur during the trial:

- Pregnancy (for further details in case of pregnancy, see Section 7.4.2);
- Participant withdrew consent;
- Participation in another clinical trial;
- Lost to follow-up;
- Any events that endanger the safety of the participant;
- Sponsor decision to end clinical trial.

If a participant fails to return for the post-treatment safety visit, all attempts should be made to contact the participant to ensure the reason for not returning is not an AE. Likewise, if a participant wishes to discontinue from the trial (e.g., for personal reasons), attempts should be made to establish the true reason is not an AE (bearing in mind the participant is not obliged to state the reasons).

If IMP is prematurely discontinued, the primary reason for discontinuation must be recorded in the appropriate section of the eCRF, and all efforts will be made to complete and report the observations as thoroughly as possible. A complete final evaluation at the time of the participant's withdrawal should be made and any AEs followed up until resolution or a period of 30 days after the last Safety Visit (or withdrawal from the trial).

If a participant has failed to attend scheduled trial assessments, the Investigator must determine the reasons and the circumstances as completely and accurately as possible.

Participants who have withdrawn after randomization (e.g., due to AEs or lack of efficacy) will not be replaced and will not be eligible to participate in the OLE Period. Only participants who have completed the 48-week main study are eligible to participate in the OLE Period. Participants who are withdrawn from the trial will not be allowed to re-enroll in the trial.

Participation in any other trial during the duration of this trial (including the OLE Period) will not be allowed.

At least 3 attempts to contact lost to follow-up participants should be made and documented (2 phone calls and 1 acknowledgement of receipt letter).

The Investigator should permanently discontinue study treatment upon confirmation of noncompliance regarding study treatment (see Section 6.8) or extended interruption of the study treatment for more than 30 days.

5.7 Premature Termination of the Trial

The clinical trial may be terminated prematurely or suspended at the request of Health Authorities or if new safety or efficacy information leads to an unfavorable risk benefit judgment for any IMP. The Sponsor may discontinue the trial if the trial becomes unjustifiable for medical or ethical reasons, the trial experiences poor enrollment, or due to discontinuation of clinical development of an IMP or withdrawal of an IMP or comparator from the market for safety reasons.

Health Authorities and IECs/IRBs will be informed about the discontinuation of the trial in accordance with applicable regulations.

5.8 Definition of End of Trial

A participant is considered a study completer if one of the following conditions applies:

- The participant has completed the 4-week Safety Follow-up Visit/End of Trial Visit (main or OLE study), even if the participant discontinued treatment prematurely.

  OR

- The participant has completed the OLE End of Treatment Visit and is entering the long-term follow-up study under a new protocol.

Participants who are not continuing the treatment in the long-term follow-up study under a new protocol, must attend an OLE End of Treatment Visit followed by a 4-week Safety Follow-up Visit/End of Trial Visit of the OLE Period to complete the study under the current protocol. Participants who are entering the long-term follow-up study under a new protocol, are neither required to enter the 4-week Safety Follow-up Period nor to undergo a 4-week Safety Follow-up Visit/End of Trial Visit to complete the study under the current protocol. These participants must attend the OLE End of Treatment Visit to be considered study completers.

The end of the study is defined as the last contact date with the last participant who participates in this trial (last participant's last visit). A clinical trial protocol may not be considered closed as long as:

- Any participant is still receiving any IMP;
- Visits specified by the protocol are still taking place;
- Procedures or interventions according to the protocol are still being undertaken in any participant;
- The post-treatment follow-up period, defined in the clinical trial protocol as being part of the trial, has not yet been completed for any participant.

6 Investigational Medicinal Product and Other Drugs Used in the Trial

The term "Investigational Medicinal Product" refers to the investigational drug undergoing study (i.e., M2951), the placebo and the reference therapy, Tecfidera.

6.1 Description of the Investigational Medicinal Product

Investigational Medicinal Product M2951 and placebo: dose/mode of administration/ dosing schedule:

The drug substance M2951, chemical name 1-(4-{[6-Amino-5-(4-phenoxy-phenyl)-pyrimidin-4-ylamino]-methyl}-piperidin-1-yl)-propenone, is a white to yellow powder.

M2951 will be administered as white tablets ready for oral administration containing 25 mg of drug substance formulated with excipients. The placebo will be administered as white tablets ready for oral administration matching the active both in color and in size.

The Sponsor will provide M2951 and placebo to the trial site, manufactured and tested according to applicable current GMP requirements for clinical trial supplies and a confirmation of release for human use in clinical trials.

Reference therapy Tecfidera: dose/mode of administration/dosing schedule (17, 18):

The active control group will receive Tecfidera. For the first 7 days, Tecfidera is given 120 mg twice daily orally. Following this, and for the duration of treatment, it is given 240 mg twice daily orally. For sites in the EU, Tecfidera will be centrally sourced and provided by the Sponsor. For sites in the USA, Tecfidera will be locally sourced at each trial site according to local regulations. Tecfidera should be administered according to the local label and applicable regulations.

6.2 Dosage and Administration

Participants will receive 25 mg once daily, 75 mg once daily, or 75 mg twice daily M2951 or placebo administered as tablets for 168 days. To maintain blinding for placebo and M2951 (see Section 6.9), participants will self-administer study medication at a schedule similar to the 75 mg M2951 twice daily dosing schedule (i.e., 3 tablets twice daily). At the end of the 24-week treatment period, it is intended to switch the placebo group to M2951 at a dose of 25 mg once daily; however, flexibility will be maintained to allow adjusting this dose based on data from the primary analysis.

Participants who entered the OLE Period initially received M2951 at 75 mg once daily. After review of the efficacy and safety data from the primary analysis at 24 weeks and the blinded extension analysis at 48 weeks, the optimal tested dose is 75 mg twice daily. Accordingly, once IMP for this dose is available at the study site, participants participating in the OLE Period will either enter the OLE Period on the 75 mg twice daily dose or will be switched to the 75 mg twice daily dose. Participants who do not participate in the OLE Period will no longer receive M2951 or Tecfidera.

If a dose is missed, the participant can take the missed dose up to 6 hours after the scheduled time. If more than 6 hours have elapsed since the dose was missed, the participant should skip the dose for that period, make note of the missed dose, and take the next dose at the regularly scheduled time.

When CCI visits are scheduled to occur (see Section 7.5) the participant should refrain from taking their scheduled morning dose and take their dose of IMP when instructed at the visit.

Participants will be asked to record the date and time of dosing and food intake around dosing in a participant diary. Participants will self-administer the IMP at a set time each day (every 12 hours ± 2 hours). Participants must take their daily dose more than 1 hour prior to a meal or snack and more than 2 hours after a meal or snack. Clear fluids are allowed at any time. On trial visit days, the IMP will be administered during the trial visit after the scheduled trial visit procedures (other than post-treatment CCI) are completed.

Participants who develop GI or flushing disturbances while receiving Tecfidera may reduce their study treatment dose by taking 120 mg twice daily for 1 month at the Investigator's discretion. After 1 month at the reduced dose, participants will resume the 240 mg twice daily dosing. If the participant is still unable to tolerate the study treatment, the participant must permanently discontinue study treatment as described in Section 6.4.4.2.

6.3 Assignment to Treatment Groups

Eligible participants will be randomized 1:1:1:1:1 to treatment with placebo, low-dose M2951 (25 mg once daily), mid-dose M2951 (75 mg once daily), high-dose M2951 (75 mg twice daily), or Tecfidera (administered twice daily at a final dose of 240 mg), through a central randomization process by an IWRS prior to dosing on Day 1. Stratification will occur by region (USA or Western Europe, Eastern Europe and CCI , Eastern Europe and not CCI , and RoW). For the first 7 days, Tecfidera is administered orally at 120 mg twice daily. Following this and for the duration of treatment, Tecfidera is administered orally at 240 mg twice daily. Participants who entered the OLE Period initially received M2951 at 75 mg once daily. After review of the efficacy and safety data from the primary analysis at 24 weeks and the blinded extension analysis at 48 weeks, the optimal tested dose is 75 mg twice daily. Accordingly, once IMP for this dose is available at the study site, participants participating in the OLE Period will either enter the OLE Period on the 75 mg twice daily dose or will be switched to the 75 mg twice daily dose.

6.4 Concomitant Medications and Therapies

All concomitant medications taken by the participant during the trial, from the date of signature of informed consent are to be recorded in the appropriate section of the eCRF, noting the name, dose, duration, regimen, and indication of each drug. Nondrug interventions and any changes to a concomitant medication or other intervention should also be recorded in the eCRF. Concomitant medications and procedures will be recorded at Screening and Day 1, and any changes elicited/recorded at every trial visit.

6.4.1 Permitted Medicines

Permitted medications are any medications required per the medical history and not specifically prohibited by the protocol during the trial. These standard of care medications are part of the participant's previous treatment and will therefore not be provided by the Sponsor. Any such medications prescribed or used should be recorded in the eCRF.

Participants who experience an MS relapse (see Section 7.3.3) during treatment may receive rescue medication participant to the following restrictions:

- Up to 1 g daily of methylprednisolone administered IV for up to 5 consecutive days.

Oral tapering of corticosteroid rescue medication is permitted, with a maximum of 15 days of tapering allowed.

Participants should not be withdrawn from treatment with trial medication solely because of the occurrence of a relapse unless they meet the criteria for withdrawal (see Section 5.6).

Note: Where possible, the use of high dose corticosteroids should be avoided in the 3 weeks prior to a scheduled MRI scan.

Any medications (other than those excluded as per exclusion criteria in Section 5.3.2 or prohibited as per Section 6.4.2) that are considered necessary for the participants' welfare and will not interfere with the trial medication may be given at the Investigator's discretion.

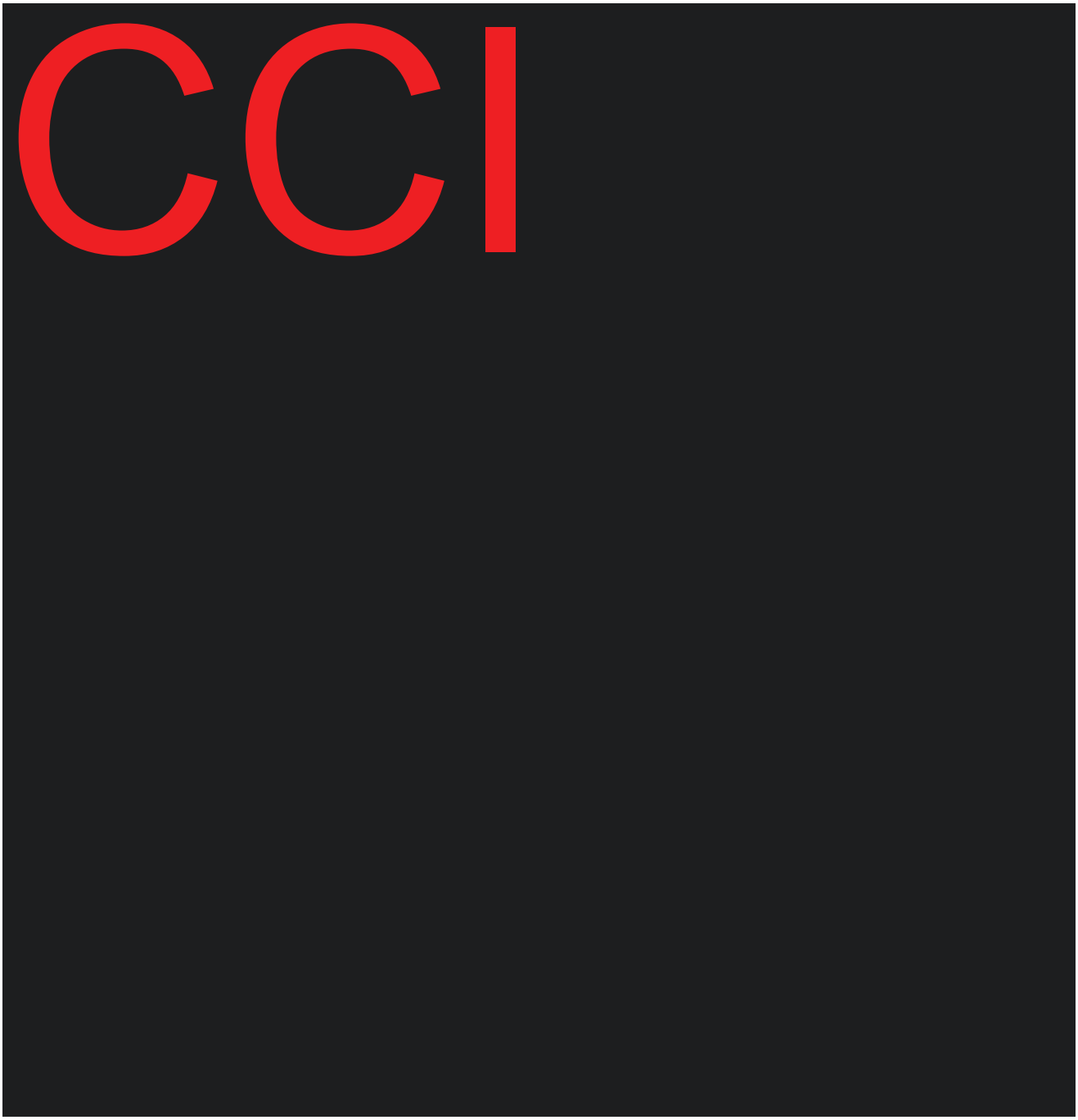
6.4.2 Prohibited Medicines

Medications prohibited before the trial are listed in the exclusion criteria (Section 5.3.2).

The following medications and therapies are not permitted during the trial and would require discontinuation of the trial treatment:

- Initiation of an immunosuppressant or immunomodulator, such as cladribine, cyclophosphamide, azathioprine.
- New therapies for MS should not be initiated during the trial. Initiation of any new immunosuppressant or immunomodulatory therapy would be considered a treatment failure and should result in withdrawal of the participant from the IMP (see Section 5.6.1).

- Oral or parenteral steroids, except rescue medication to treat a relapse of MS, or adrenocorticotropic hormone. For participants experiencing a treatment gap (as described in Section 7.1.6), these medications can be administered only during that gap period if medically indicated, and must be discontinued prior to restarting study treatment.
- Biologic therapies.
- IV Ig therapy and/or plasmapheresis.
- Treatment with teriflunomide.
- Daclizumab.
- Live and live-attenuated vaccines.
- Medications known to lower the seizure threshold should be avoided. If treatment with these medications is required, the Investigator must inform the Medical Monitor.
- Initiation or dose changes of dalfampridine (Ampyra) or fampridine during OLE Period is permitted only in case the participant has been on a stable dose of evobrutinib for at least 3 months prior to initiation or dose change.
- Changes in dalfampridine dose (participant must be on a stable dose).
- Herbal supplements including, but not limited to, St. John's wort, grapefruit, Seville oranges, cranberries, or juices of these fruits.
- Any investigational drug within 1 month or 5 half-lives of the investigational drug, whichever is longest, prior to Screening.
- Moderate or strong inhibitors or inducers of CYP3A or drugs mainly metabolized by CYP3A with a narrow therapeutic index. The list in Table 6 is not meant to be a complete list of all CYP3A inhibitors, inducers, or substrates with a narrow therapeutic range. Study sites should consider each medication on a case-by-case basis and discuss with the Medical Monitor. The additive effects of weak inhibitors taken in combination must also be taken into account. For participants experiencing a treatment gap (as described in Section 7.1.6), these medications can be administered only during that gap period if medically indicated, and must be discontinued prior to restarting study treatment.
- Any investigational drug or experimental procedure for MS.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6.4.2.1 Use of Prohibited Medications in the Treatment Gap

A gap in study drug treatment during the OLE Period after Week 96 may occur as described in Section 7.1.6.

If the Investigator considers alternate RMS treatment appropriate during the treatment gap, and the participant opts to resume study drug after the treatment gap the following guidelines should be applied:

- Study drug can be resumed after β-interferon or glatiramer acetate treatment discontinuation with no washout period;
- Study drug can be resumed 4 weeks after tecfidera treatment discontinuation;
- Study drug can be resumed 12 days after teriflunomide treatment discontinuation **only** if an accelerated elimination procedure is followed prior to resumption of study drug;
- If an RMS treatment other than those above is preferred, the participant will not be able to restart the study drug and should instead enter the 4-week Safety Follow-up Period.

Any alternate RMS treatment administered during a treatment gap should be used according to the local label and local guidelines.

Participants still on the study should at no point be receiving study drug and an alternate RMS treatment at the same time.

6.4.3 Other Interventions

Not applicable.

6.4.4 Special Precautions

6.4.4.1 For M2951 Only

The IMP should be temporarily withheld or permanently withdrawn if the following abnormalities occur or reoccur (also see Table 7), as relevant, and reinitiation following temporarily withholding of IMP should be discussed with the Medical Monitor. If a participant's OLE predose or OLE baseline value is abnormal and/or falls within any of the below criteria, consult with the Medical Monitor regarding potential withdrawal, continued participation in study, and additional monitoring if needed. Retesting should be completed within 1 week:

- For a neutrophil count < 500/mm^3 or platelet count < 25,000/mm^3 (Grade 4) or neutrophil count 500 to 999/mm^3 with fever (Grade 3) or platelet count 25,000 to 49,999/mm^3 (Grade 3) with bleeding, the IMP should be permanently withdrawn.
- For a Grade 3 decrease in neutrophil count without fever or Grade 3 decrease in platelet count without bleeding, temporarily hold the IMP and recheck the value. If the value is still Grade 3, permanently discontinue the IMP.
- For a Grade 2 decrease in neutrophil count (1,000 to 1,499/mm^3) or Grade 2 decrease in platelets counts (50,000 to 74,999/mm^3), temporarily hold the IMP and recheck the value. Reinitiate the IMP after discussion with the Medical Monitor if no further downward trend is observed.

The Investigator is required to discontinue the study treatment for abnormal liver function when a participant meets one of the conditions outlined below or if the Investigator believes that it is in best interest of the participant. 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 laboratory evaluation).

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

Decision about discontinuation of the study treatment due to elevated LFTs after 24 weeks of exposure to evobrutinib may be taken on a case-by-case basis in consultation with the Medical Monitor.

For any study treatment discontinuation related to laboratory or assessment results, the participant should be followed with additional testing as needed until a return to within normal limits or an acceptable value. In cases for which permanent discontinuation of study treatment 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 additional 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 second 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.

Any rechallenge associated with LFT elevations should follow a weekly monitoring for 12 weeks.

For participants who temporarily or permanently discontinue study treatment because of abnormal liver function consultations with specialists, such as a hepatologist and liver imaging such as ultrasound are encouraged to exclude potential alternative causes of liver injury.

A comprehensive hepatic panel is requested for participants for whom withdrawal criteria (see Section 5.6.1) are met or who permanently or temporarily discontinue dosing because of elevated transaminases. Testing should include screening for the following:

- International normalized ratio (INR), partial thromboplastin time, fibrinogen, high sensitivity C reactive protein
- Anti-Hepatitis A Virus (anti-HAV) IgG and IgM, HBsAg, anti-Hepatitis B Core Antigen (anti-HBc) 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) polymerase chain reaction (PCR), and CMV PCR

- HCV RNA by PCR
- Antinuclear antibody, antismooth muscle antibody, antibody to liver-kidney microsomes
- Alkaline phosphatase, albumin, ALT, AST, GGT, and total bilirubin
- Ferritin and transferrin saturation

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- For an increase in amylase or lipase to > 5× ULN (Grade 4), the IMP should be permanently withdrawn.
  - For an increase in amylase or lipase to > 2 to 5× ULN (Grade 3), temporarily hold the IMP and recheck the value within 24 hours of receipt. If the value is still Grade 3, permanently discontinue the IMP.
  - For an increase in amylase or lipase to Grade 2 (> 1.5 - 2× ULN), temporarily hold the IMP and recheck the value within 24 hours of receipt. Discontinue the IMP if the value does not decrease or reinitiate the IMP after discussion with the Medical Monitor if a downward trend is observed.
- For an increase in serum creatinine to > 3× from Baseline (Grade 3 or higher), the IMP should be permanently withdrawn.
  - For any other increase in serum creatinine > 1.5 – 3.0× from Baseline (Grade 2), temporarily hold the IMP and recheck the value within 24 hours of receipt. Discontinue the IMP if the value does not decrease, or reinitiate the IMP after discussion with the Medical Monitor if a downward trend is observed.
- For any other laboratory abnormality of Grade 4 severity, the IMP should be permanently withdrawn.
  - For any other laboratory increase/decrease (as relevant) from Baseline to a clinically significant higher severity grade, temporarily hold the IMP and recheck the value within 24 hours of receipt. Discuss restarting the IMP with the Medical Monitor if an improving trend is observed.
  - For an absolute lymphocyte count < 200/mm^3 (Grade 4), should be temporarily withdrawn and follow-up testing should be conducted. When the absolute lymphocyte count returns to ≥ 800/mm^3 (i.e., returns to Grade 1), IMP can be resumed.

Table 7 Guidelines for Withholding or Permanent Withdrawal of IMP

Parameters	Grade 1	Grade 2	Grade 3	Grade 4
Neutrophil count decrease	-	1,000 - 1,499/mm^3 [b] < 1.5 - 1.0× 10^9/L [b]	500 - 999/mm^3 [a] < 1.0 - 0.5× 10^9/L [a]	< 500/mm^3 < 0.5× 10^9/L
Neutrophil count decrease with fever	-	-	500 - 999/mm^3 < 1.0 - 0.5× 10^9/L	< 500/mm^3 < 0.5× 10^9/L
Platelet count decrease	-	50,000 - 74,999/mm^3 [b] < 75.0 - 50.0× 10^9/L [b]	25,000 - 49,999/mm^3 [a] < 50.0 - 25.0× 10^9/L [a]	< 25,000/mm^3 < 25.0× 10^9/L
Platelet count decrease with bleeding	-	-	25,000 - 49,999/mm^3 < 50.0 - 25.0× 10^9/L	< 25,000/mm^3 < 25.0× 10^9/L
Amylase or lipase increase	-	> 1.5 - 2.0× ULN [c]	> 2.0 - 5.0× ULN [a]	> 5.0× ULN
Serum creatinine increase	-	> 1.5 - 3.0× baseline [c]	> 3.0× baseline	> 6.0× ULN
Absolute lymphocyte count decrease	< LLN - 800/mm^3 < LLN - 0.8× 10^9/L	500 - 799/mm^3 < 0.8 - 0.5× 10^9/L	200 - 499/mm^3 < 0.5 - 0.2× 10^9/L	< 200/mm^3 [d] < 0.2× 10^9/L [d]
ALT, AST and Bilirubin Increase				
AST or ALT increase	>3.0 - < 5.0× ULN [e]		≥ 5.0× ULN	
AST or ALT with bilirubin increased > 2× ULN	> 3.0x ULN			
Bilirubin increase	>1.5 - ≤2× ULN [e]		> 2× ULN	

ALT=alkaline aminotransferase, AST=aspartate aminotransferase, IMP=investigational medicinal product, LLN=lower limit of normal, ULN=upper limit of normal.

IMP should be permanently withdrawn.

a. Temporarily withhold and recheck value. If the value is still Grade 3, permanently discontinue the IMP.

b. Temporarily withhold IMP and recheck the value. Reinitiate the IMP after discussion with the Medical Monitor if no further downward trend is observed.

c. Temporarily withhold IMP and recheck the value. Reinitiate the IMP after discussion with the Medical Monitor if a downward trend is observed.

d. Temporarily withhold IMP and follow-up testing should be conducted. When the absolute lymphocyte count returns to Grade 1, IMP can be resumed.

e. Temporarily withhold IMP and recheck value per Liver Function Testing criteria above. For participants who temporarily or permanently discontinue study treatment because of abnormal liver function consultations with specialists, such as a hepatologist and liver imaging such as ultrasound are encouraged to exclude potential alternative causes of liver injury and the Medical Monitor should be informed.

6.4.4.2 For Tecfidera Only

- For a lymphocyte count < 500/mm^3 for > 24 weeks, Tecfidera should be temporarily withheld and the participant monitored until lymphocyte counts are back to the LLN. Once lymphocyte counts are back to LLN, the IMP can be restarted with additional follow-up monitoring of lymphocyte counts.
  - For an absolute lymphocyte count < 200/mm^3 (Grade 4), Tecfidera should be permanently withdrawn and the lymphocyte count of the participant monitored.
- For a serious infection, after discussion with the Medical Monitor, consideration should be given to temporarily withholding Tecfidera until resolution of the infection.
- At the first sign or symptom suggestive of PML, Tecfidera should be withheld and an appropriate diagnostic evaluation conducted. MRI findings may be apparent before clinical signs or symptoms. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes.
- Discontinue Tecfidera if clinically significant liver injury induced by Tecfidera is suspected.
- Patients should be instructed to discontinue Tecfidera and seek immediate medical care should they experience signs and symptoms of anaphylaxis or angioedema.
- For a flushing reaction (e.g., warmth, redness, itching, and/or burning sensation), Tecfidera should be temporarily withheld until symptoms have resolved. After the flushing reaction has resolved, Tecfidera should be restarted at a reduced dose (see Section 6.2).
  - Should a flushing reaction occur again, Tecfidera should be permanently discontinued.

6.4.4.3 Grading Adverse Events for Investigational Medicinal Products

For all laboratory abnormalities that correspond to CTCAE Grades 1 to 4, refer to the CTCAE, Version 4.03.

The reason for IMP withdrawal and the nature, duration, and results of any planned follow-up observations should be recorded in the appropriate section of the eCRF.

6.4.5 Management of Specific Adverse Events or Adverse Drug Reactions

No specific measures are proposed at this stage. Standard medical care will be provided at the trial site for all AEs occurring during the trial.

6.5 Packaging and Labeling of the Investigational Medicinal Product

All IMPs will be supplied in accordance with all applicable regulatory requirements and GMP Guidelines.

M2951 and placebo tablets will be packaged as alu/alu blister wallets.

6.6 Preparation, Handling, and Storage of the Investigational Medicinal Product

IMP must be carefully stored at the trial site in a closed room or cabinet with restricted access and separately from other drugs.

M2951 should be stored below CCI. Any deviations from the recommended storage conditions should be immediately reported to the Sponsor, and the medication should not be used until authorization has been received from the Sponsor.

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

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

The IMP may not be used for any purpose other than the trial in question. It must be ensured at the trial site that IMP is not used after the use-by date. This is to be closely monitored by the responsible monitor.

6.7 Investigational Medicinal Product Accountability

The Investigator or designee is responsible for ensuring IMP accountability, including reconciliation of drugs and maintenance of records.

- Upon receipt of IMP, the responsible person will check for accurate delivery and acknowledge receipt in the IWRS and by signing or initialing and dating the appropriate documentation and returning it to the location specified. The original or a copy will be archived for the Investigator Site File.
- IMP dispensing will be recorded on the appropriate drug accountability forms so that accurate records will be available for verification at each monitoring visit.
- Trial site IMP accountability records will include the following:
  - Confirmation of IMP receipt, in good condition and in the defined temperature range;
  - The inventory of IMP provided for the clinical trial and prepared at the site;
  - The use of each dose by each participant in case of Tecfidera;
  - The disposition (including return, if applicable) of any unused IMP;

- Dates, quantities, batch numbers, kit numbers, expiry dates, and the individual participant trial numbers.

The Investigator site should maintain records, which adequately document that participants were provided the doses specified in this protocol, and all IMPs provided were fully reconciled.

Unused IMP must not be discarded or used for any purpose other than the present trial. No IMP that is dispensed to a participant may be redispensed to a different participant.

A Trial Monitor will verify and periodically collect the IMP accountability forms.

After completion of the study, any IMP distributed to the site but not administered, dispensed to or taken by the participant(s) will be destroyed at the trial site. Details will be agreed upon between the Sponsor and the Investigator. All unused medications will be carefully recorded and documented before destruction.

6.8 Assessment of Investigational Medicinal Product Compliance

The IMP will be administered at the site on trial visit days as defined in Table 1, Table 2, and Table 3. All other dosing will be done by the participant or participant's caregiver at home throughout the rest of the trial. Participants or participant's caregiver will be asked to record the date and time of dosing and food intake around dosing in a participant diary.

Participants will be instructed to bring all IMP, including the used packaging and all blisters, to each trial visit indicated in Table 1, Table 2, and Table 3, and to allow for the assessment of compliance with trial treatment. Prior to discharge from each scheduled visit, participants will be given sufficient IMP for at-home dosing until the next scheduled visit during the treatment period. On trial visit days indicated in Table 1, Table 2, and Table 3, the previous week's IMP adherence will be documented using pill counts.

Insufficient compliance with the protocol-specified dosing regimen is defined as receiving < 80% of the required number of scheduled doses of trial medication.

6.9 Blinding

Treatment with M2951 and placebo will be double-blinded but the Tecfidera group will be open label. Tecfidera comes in 2 different colors of capsule (120 mg and 240 mg) with the lower dose being used during the initial 7 days of administration.

The Assessing Neurologist and central MRI reader will be blinded to all treatments (placebo, M2951, and Tecfidera) throughout the study. The participants, site staff, and the Investigator will be blinded to placebo and M2951 throughout the study, but not Tecfidera. The CRO study team and Sponsor study team will be blinded to placebo and M2951 until the database is partially locked for the primary analysis.

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CCI [redacted]

The IDMC will also be unblinded to treatment, as described in the IDMC charter.

All other staff other than those identified above will remain blinded to the placebo and M2951 treatments.

Only when the last participant reaches 24 weeks of treatment or discontinues from treatment prematurely, the protocol violations are determined, and the database is partially locked for the primary analysis will the drug codes be broken and made available for the primary data analysis. At that point, the CRO and Sponsor study teams will be unblinded to treatment. Dissemination of results from the primary analysis will be limited to senior management. There will be no communication of primary analysis results to the sites.

After the primary analysis, the study will continue as a blinded extension until the Week 52 Analysis occurs, with participants, site staff, and the Investigator blinded to M2951 dose group, and with the Assessing Neurologist and central MRI reader blinded to all treatments. For participants entering the OLE Period at the End of Treatment Visit (Week 48), the data will no longer be blinded.

All breaks of the trial blind must be adequately documented.

6.10 Emergency Unblinding

The trial blind may be broken for an individual only if knowledge of the IMP is essential for clinical management of the participant. The Investigator must promptly explain the reason for any unblinding of an IMP to the Sponsor without revealing the result to any Sponsor employee except the designated Drug Safety representative (using the Emergency Unblinding Notification Form). The Investigator must record the date of unblinding and the reason in the eCRF. Contact information for breaking the blind in an emergency is given on the participant emergency card provided to each participant (see Section 9.4).

Under certain circumstances, the IDMC or Drug Safety may be required to unblind the treatment assignment for an individual participant following a SAE or other serious event; e.g., if an expedited regulatory report is required. See Section 7.4.1.4 for further details on expedited reporting and SAEs.

6.11 Treatment of Overdose

An overdose is defined as any dose greater than the highest daily dose included in a clinical trial protocol or planned for an individual participant enrolled in the trial. Even if it does not meet other criteria for an SAE, any overdose must be recorded in the trial medication section of the eCRF and reported to Drug Safety in an expedited manner using the SAE Report Form, and following the procedure in Section 7.4. No specific treatments for overdose are available.

6.12 Medical Care of Participants after End of Trial

After a participant has completed the trial or has withdrawn early, the participant is free to access further treatment as deemed appropriate by the Treating Investigator. The Sponsor will not provide any additional care to participants after they leave the trial because such care should not differ from what is normally expected for participants with relapsing-remitting MS or SPMS with superimposed relapses.

7 Trial Procedures and Assessments

During the Screening Visit, prior to performing any trial assessments that are not part of routine medical care for the participant, the Investigator will obtain written informed consent as described in Section 9.2.

CCI [redacted] The maximum amount of blood to be obtained during the trial is within the commonly accepted maximum of 275 mL over 4 weeks and 550 mL over 8 weeks. Details of the blood volumes to be collected for each sample/visit will be detailed in the Laboratory Manual and an estimate is provided in Appendix II. Instructions on how samples will be collected, labeled, processed, stored, and shipped as well as specification on bioanalytical methods will be detailed in the Laboratory Manual.

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. Please see Table 1 for information regarding abnormal dipstick results.

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- HIV testing, when required by local regulation, should be conducted and analyzed locally.
- In addition, ECGs results will be interpreted locally.
- Additional safety monitoring as noted in Section 7.1.3.

The Treating Investigator will be the physician responsible for participant care and should be a neurologist experienced in the care of MS patients. The Treating Investigator will have access to safety and blinded efficacy data and will make treatment decisions based on the participant's clinical response and laboratory findings. The Treating Investigator will also be responsible for the treatment of relapses and determining if nonMS-related factors could account for neurological worsening. The Treating Investigator will determine if a relapse has occurred.

The Assessing Neurologist will be a neurologist or other health care practitioner and must be trained and certified in administering the Neurostatus Functional System Scores and EDSS

examination prior to study start. The Assessing Neurologist is responsible for all EDSS assessments beginning at Screening and including all unscheduled visits initiated by a new or changing symptom potentially related to MS, as requested by the Treating Investigator. Throughout the trial, the Assessing Neurologist will be blinded to the participant's treatment, laboratory data, AE profile, any changes in safety assessments, and prior EDSS scores. The Assessing Neurologist must complete the EDSS prior to any treatment with steroids or other therapeutics intervention(s) that may alter the participant's neurological state, where possible. Both the Treating Investigator and the participant will be informed of the importance of not discussing these issues with the Assessing Neurologist to prevent unblinding.

The Assessing MRI reader will be an independent, blinded, central MRI reader provided by PPD. A local radiologist will also review all MRI scans for safety and provide a report to the Treating Investigator, containing only nonMS pathology information.

The CRO will also provide a qualified neurologist who will adjudicate whether relapses meet the definition of a qualifying relapse (see Section 7.3.3) and review systematically the EDSS to determine if there is a lack of efficacy/disease progression. The scope of this review will be described in detail in the Medical Monitoring Plan.

7.1 Schedule of Assessments

7.1.1 Screening

The participant's eligibility will be assessed at the Screening Visit that will occur between Day -28 to Day -1 (within 28 days prior to the first administration of placebo/M2951 or Tecfidera). See Table 1 for a list of assessments done at Screening to determine the eligibility of the participant to participate in the trial. If a participant does not meet eligibility criteria, the participant can be retested and rescreened once at the Investigator's discretion.

If there are no clinically significant findings and the participant meets all protocol-defined inclusion criteria and none of the exclusion, the participant will be considered as eligible to be enrolled in the trial. Participants who fail to meet the protocol-specified criteria or who withdraw their consent will be considered screen failures. The following information, as a minimum, should be collected for participants who failed Screening: informed consent, demographics, reason for screen failure, AEs from the date of informed consent until the participant is considered to have failed Screening by the Investigator, and the Investigator's signature.

The following should be performed at the Screening Visit:

- Signing of informed consent before any study procedures;
- Review of inclusion/exclusion criteria, including administration of the C-SSRS;
- The CCI, collection of demographic and other Baseline characteristics (MS history and other medical history, including medication history), review of concomitant medications and procedures, evaluation of AEs, a physical examination, vital signs, a neurological examination, MRI, EDSS. The MRI scan should be acquired before

randomization and dosing to allow for the readouts to be read by the central MRI reader (approximately 7 days);

- 12-lead ECG and CXR;
- Blood sample collection for Quantiferon-TB test, viral serology testing, HIV testing if required, safety assessments (hematology, clinical chemistry, coagulation), and serum pregnancy testing with FSH (women only);
- Urine collection for urinalysis and, if necessary, microscopy and protein/creatinine ratio.

7.1.2 Treatment Visits, Including Blinded Treatment Extension Phase

At all trial visits, scheduled assessments will be performed before administration of the trial medication, with the exception of relevant blood draws (e.g., CCI as noted in Table 1). After Day 1, all scheduled visits during the treatment period may take place within ± 3 days of the protocol-specified day. Participants who discontinue early must immediately return for the 4-week Safety Follow-up/End of Trial Visit (see Section 7.1.8).

See Table 1 for specific assessments to be done during treatment periods.

The following will be performed on Day 1:

- Review of inclusion/exclusion criteria;
- Randomization;
- CCI ;
- Review of concomitant medications and procedures, evaluation of AEs, disease activity assessment (EDSS), vital signs, and a neurologic exam;
- Blood sample collection for Ig levels, CCI cell counts; CCI
- CCI
- Urine collection for a urine pregnancy test (women only);
- IMP dispensation;

The following will be performed at Week 4, 8, 12, 16, 20, 24, and 36:

- CCI ;
- Review of concomitant medications and procedures; evaluation of AEs; disease activity assessment (relapse assessment, EDSS [Week 12, 24, and 36 only]); a complete physical examination (Week 12 and 24 only); vital sign assessment; and a neurologic exam;
- IMP compliance;

- 12-lead ECG (Week 24 only);
- Blood sample collection for safety assessments (hematology, chemistry); Ig levels (Week 4, 16, and 24 only); CCI cell count and CCI [redacted];
- Blood tests (ESR, hsCRP, and fibrinogen) at Week 36;
- Urine collection for urine pregnancy testing (women only); urinalysis and, if necessary, microscopy and protein:creatinine ratio (Weeks 12 and 24 only);

  The following will be performed at Weeks 28, 32, 40, and 44 for women of childbearing potential: urine pregnancy testing will be performed at home or at the site. Urine pregnancy test kits will be provided to the participant at Week 24 (for testing at Weeks 28 and 32) and at Week 36 (for testing at Weeks 40 and 44). At and/or prior to the Week 24 Visit, the Principal 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 at Week 28 (± 3 days), 32 (± 3 days), 40 (± 3 days), and 44 (± 3 days) to confirm completion of urine pregnancy testing and discuss results.
- MRI assessment (Weeks 12, 16, 20, and 24 only);
- IMP dispensation.

7.1.3 Supplemental Safety Visits

Additional chemistry monitoring (including ALT, AST, alkaline phosphatase, γ-glutamyl-transferase, and bilirubin) will be conducted every 2 weeks until 16 weeks of treatment with evobrutinib (or an increase in the dose of evobrutinib). Subsequently, this will be conducted monthly (every 4 weeks). In the OLE, participants crossing over from the Tecfidera arm to M2951 will have additional safety monitoring conducted as described below.

- In the main study, for all participants in the placebo/M2951 arm, safety visits will be conducted every 2 weeks until Week 40, then monthly at Weeks 44 and 48 (see Table 1).
- During the first 2 years of the OLE period, safety visits will be conducted every 2 weeks until Week 16, then monthly at Weeks 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92, and 96 (see Table 2). Subsequently, participants will attend the study site or have a Telephone Visit at least every 6 weeks (see Table 3).
- During the OLE period, additional safety visits will be conducted for participants crossing over from the Tecfidera arm at Weeks 1, 3, 5, 7, 9, 11, 13, and 15.

Safety visits will be conducted after obtaining participant's informed consent. These safety evaluations have been implemented by a letter to Investigators as an urgent safety measure. Given the current status of most participants, these evaluations will start after Week 1 of OLE. It is preferable for chemistry monitoring to be performed at the Investigator's site. CCI [redacted] An

additional physical examination may be performed at the Investigator's discretion based on the participant's history at the time of the visit. Any new or change in AEs and concomitant medications should be documented. Patient compliance to additional safety monitoring will be overseen to evaluate continuation in the trial.

These visits should be done at the Investigator's site and blood samples sent to Central Laboratory. In the event that the participant cannot return to the site for the additional blood draws, chemistry monitoring should be done locally; any participants completing a supplemental safety visit locally will not have CCI collected at that visit.

7.1.4 Unscheduled Visit for Neurological Worsening and Relapse Assessment

Participants should be instructed that if, at any point during the trial, they suspect that they are experiencing new or worsening neurological symptoms, including possible relapse, they should contact the Investigator as soon as possible after the onset of symptoms. If necessary, the participant should be evaluated by the Investigator within the clinic and every effort should be made to complete this evaluation within 1 week after the start of symptoms. Any assessments needed to confirm the relapse should be performed at the discretion of the Investigator. Details should be documented within the relevant section(s) of the eCRF. The definition of a qualifying and nonqualifying relapse is provided in Section 7.3.3.

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).

The following will be performed at an Unscheduled Visit for Neurological Worsening and Relapse Assessment:

- Review of concomitant medications and procedures, evaluation of AEs, disease activity assessment (relapse assessment, EDSS), complete physical examination, vital signs, and a neurologic exam;
- 12-lead ECG;
- Blood sample collection for safety assessments (hematology, chemistry);
- Urine collection for urinalysis, and, if necessary, microscopy and protein:creatinine ratio.

7.1.5 End of Treatment Visit

The following will be performed at Week 48 ± 3 days/End of Treatment Visit (for participants who do not continue in the OLE or participants who received Tecfidera during the 48-week main study and choose to participate in the OLE):

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- Review of concomitant medications and procedures, evaluation of AEs, disease activity assessment (relapse assessment, EDSS), vital signs, and a neurologic exam;
- IMP compliance;
- 12-lead ECG;
- Blood sample collection for safety assessments (hematology, chemistry, coagulation); Ig levels; CCI and CCI ;
- Urine collection for urinalysis and, if necessary, microscopy and protein:creatinine ratio; urine pregnancy testing (women only);
- MRI assessment.

Participants who complete 48 weeks of treatment with M2951 or Tecfidera (and do not withdraw early) will be given the opportunity to participate in the OLE Period. Participants who enter the OLE from Tecfidera will sign the OLE ICF at this visit.

7.1.6 Open-label Extension Period

After completing the Treatment Period (Weeks 1 through 24) and Blinded Extension Period (Weeks 25 through 48), participants will be offered the opportunity to participate in an OLE Period, where all participants will receive M2951. Signed consent will also be obtained prior to participation in the optional OLE Period. Participants who enter the OLE Period after receiving M2951 during the main study will not complete the End of Treatment Visit at Week 48 but will complete the OLE Day 1 visit at Week 0 of the OLE (Table 2). Participants who received Tecfidera and participate in the OLE Period will complete the End of Treatment Visit at Week 48 (at which visit they will sign the OLE ICF) and will have a washout period for a minimum of 4 weeks prior to receiving M2951 at Day 1 visit (Visit 1/Week 0) of the OLE (see Section 5.5.1 and Table 5).

The OLE Visits 2 (Week 4) and 3 (Week 8) are only applicable for participants who received Tecfidera in the 48-week main study. All participants participating in the OLE (including participants who received Tecfidera during the 48-week main study) will complete the supplemental safety visits described in Section 7.1.3.

Scheduled assessments will be performed according to Table 2 (Weeks 0 to 96 of the OLE period) and Table 3 (Weeks 108 to up to 384 of the OLE period) before administration of the IMP. All scheduled visits during the OLE Period may take place within the visit windows specified in Table 2 and Table 3. Participants who discontinue early must return for the OLE End of Treatment Visit (Visit 27).

After Week 96 of the OLE Period, regular contact will be made with the participant during Telephone Visits; the schedule of these is shown in Table 3, and details of the phone calls are in Section 7.1.6.1. As the OLE Period was extended beyond Week 96 in Protocol amendment 5 (08 November 2019), consent will be obtained at Week 96 to allow OLE Period treatment beyond this point.

In Amendment 5 (08 November 2019), the duration of treatment in the OLE Period was extended by 240 weeks from 96 to 336 weeks. In some cases, due to IRB/IEC approval, regulatory-specific, or other administrative delays, a participant may experience a treatment gap between the evobrutinib dose received in the first 96 weeks of the OLE Period and the first evobrutinib dose received in the 240-week extension of the OLE Period.

Upon Principal Investigator request, a participant in this circumstance at Week 96 of the OLE Period may still be able to continue into the 240-week extension of the OLE with approval from Merck/EMD Serono, on a case-by-case basis, provided that the treatment gap would not exceed 90 days from the last evobrutinib dose received in the first 96 weeks of OLE Period (OLE Week 96 Visit) to the first evobrutinib dose received in the 240-week extension of the OLE Period.

Participants with a treatment gap should attend the study site upon resumption of treatment. Unless otherwise clinically indicated, only the following procedures should be performed at this visit:

- Review concomitant medications and AEs;
- Allow the Investigator to ensure that the participant remains eligible for the study (see Section 5.4), including urine pregnancy test if applicable;
- Dispensing evobrutinib;
- EDSS (only if the treatment gap is ≥ 4 weeks).

See Section 6.4.2.1 for details of whether alternate treatment for RMS should be administered during a treatment gap that results from pending regulatory approval for the extension of the OLE Period.

Participants with a treatment gap following Week 96 of the OLE Period who restart study drug should attend any scheduled telephone visits and the Week 108 Visit (Visit 12) as scheduled.

Once the long-term follow-up study is open for enrollment in their country (i.e., once the Sponsor, upon agreement with Health Authorities/Ethics Committees, will have notified sites), participants in the OLE period will have the option to transition into the long-term follow-up study under a new protocol within 30 days of Sponsor notification, allowing continued access to study treatment (refer to Sections 7.7.1 and 7.1.8).

7.1.6.1 Telephone Visits

After Week 96 of the OLE Period, on-site visits become less frequent. During this period, regular Telephone Visits with participants are scheduled, as per Table 3.

During the Telephone Visits, the following should be discussed with the participant:

- Any AEs or SAEs that may have occurred since the last on-site visit/phone call;
- Any changes in concomitant medications that may have occurred since the last on-site visit/phone call;
- Occurrence of MS relapses since the last on-site visit/phone call;
- Overall well-being;
- Pregnancy, if applicable;
- Occurrence of other notable medical events (e.g., surgeries, injuries, laboratory tests performed outside the study);
- Details of any overdose with the study drug that may have occurred since the last on-site visit/phone call.

In addition, if a participant is due to be contacted to confirm and discuss at-home pregnancy testing, this can be covered in the same phone call (women of childbearing potential only).

7.1.7 Open-label Extension End of Treatment Visit

Once the long-term follow-up study is open for enrollment in their country (i.e., once the Sponsor, upon agreement with Health Authorities/Ethics Committees, will have notified sites), participants in the OLE Period will have the option to transition into the long-term follow-up study under a new protocol for continued treatment. Upon Sponsor site notification, all participants will be asked to return for an OLE End of Treatment visit within 30 days.

- For participants entering the long-term follow-up study under a new protocol, their OLE End of Treatment Visit in the current study is also their first visit in the long-term follow-up study. Therefore, these participants are neither required to enter the 4-week Safety Follow-up Period nor to undergo a 4-week Safety Follow-up Visit/End of Trial Visit.
- Participants who do not wish to transition into the long-term follow-up study, will have the OLE End of Treatment Visit followed by a 4-week Safety Follow-up Visit/End of Trial Visit.

In case the long-term follow-up study will not become available in their respective country, participants will complete the OLE per study schedule and have the OLE End of Treatment Visit at Week 384 followed by a 4-week Safety Follow-up Visit/End of Trial Visit.

Thus, the OLE End of Treatment Visit will be performed at Week 384 (± 14 days) or earlier, if the long-term follow-up study is open for enrollment. Participants will undergo assessments as described in Table 3.

7.1.8 4-week Safety Follow-up/End of Trial Visit

The Safety Follow-up/End of Trial Visit will be performed at Week 52 ± 5 days for participants who do not participate in the OLE Period or 28 days (± 7-day window) after the OLE End of Treatment Visit for participants who participate in the OLE Period. There will be only one 4-week Safety Follow-up/End of Trial Visit per participant, and the assessments performed will be the

same if this visit occurs at the end of the main study or the end of the OLE Period CCI [redacted] Participants who are entering the long-term follow-up study under a new protocol, are neither required to enter the 4-week Safety Follow-up Period nor to undergo a 4-week Safety Follow-up Visit/End of Trial Visit (see Section 5.8).

If a participant is not eligible to enter the OLE Period by Tecfidera Washout Visit 2, he or she will need to return for the End of Trial Visit. This End of Trial Visit should be completed within 14 days ± 7 days from the time the decision is reached that the participant is not eligible to enter the OLE Period. See Table 1 and Table 3 for specific assessments to be done. The following assessments will be performed:

- Review of concomitant medications and procedures, evaluation of AEs, disease activity assessment (relapse assessment), vital signs, and a neurologic exam;
- Blood sample collection for safety assessments (hematology, chemistry); CCI [redacted] cell counts and CCI [redacted]

Urine collection for urinalysis and, if necessary, microscopy and protein:creatinine ratio; urine pregnancy testing (women only). Prior to performing any trial assessments that are not part of routine medical care for the participant, the Investigator will obtain written informed consent as described in Section 9.2.

7.2 Demographic and Other Baseline Characteristics

At Screening, the following demographic data will be collected: date of birth, sex (gender), race, and ethnicity. Information about previous and concomitant medications taken within 4 weeks prior to randomization and the number of documented relapses within 1 year of randomization will be collected.

Medical history data (including diagnosis and duration of MS) will be recorded and a complete physical exam, will be performed. Medical history includes both disease and medication history. Vital signs, including oral temperature, heart rate, respiratory rate, semisupine blood pressure, weight, and height will be obtained. All other Baseline measures, such as safety laboratory parameters, Quantiferon-TB test, ECG, and CXR will be assessed. Baseline disease will be assessed by EDSS and MRI. CCI [redacted]

7.3 Efficacy Assessments

The following efficacy assessments will be undertaken, as outlined in the Schedule of Assessments (Table 1, Table 2, and Table 3). During treatment, i.e., Day 1 to Week 48 (or up to Week 384 for the OLE Period), all assessments should be completed prior to the administration of study medication.

7.3.1 Brain Magnetic Resonance Imaging Scans

MRI scans will be performed at Screening, at 4-week intervals from Week 12 to 24, and at the End of Treatment Visit at Week 48 (including for participants receiving Tecfidera who choose to enter

the OLE Period). For participants in the OLE Period, an MRI will also be performed at Day 1 (except for participants who received Tecfidera during the 48-week parent study and had an MRI at the End of Treatment Visit at Week 48), Week 48, and then every 48 weeks up to and including the OLE End of Treatment Visit. If a participant discontinues the study more than 4 weeks after his or her most recent MRI, an MRI may be obtained at the 4-week Safety Follow-up Visit. The Screening MRI scan should be acquired before randomization and dosing to allow for the readouts to be read by the central MRI reader (approximately 7 days).

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 < 45 mL/min/1.73 m^2) will be excluded from the trial (see Section 5.3.2, exclusion criterion 33).

Brain MRI scans will be performed according to a standardized imaging protocol before and after the administration of single-dose gadolinium.

Images will be assessed and reported by an independent, blinded, centralized MRI reading service, provided by PPD. The assessment will be performed in the absence of clinical information. 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 trial site by PPD. All MRI images will be reviewed and reported locally by a radiologist for safety. The local report will contain only nonMS pathology and will be provided to the Treating Investigator.

Note: Where possible, the use of high dose corticosteroids should be avoided in the 3-week period prior to a scheduled MRI scan. In participants receiving corticosteroids for an MS relapse, there must be a 3-week interval between the last dose of corticosteroids and the scheduled MRI scan.

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 normal). If the next scheduled visit is the End of Treatment Visit (Week 48), the Week 48 MRI scan should be performed as soon as the 4-week period since previous exposure to gadolinium has elapsed. See also Section 7.1.3.

7.3.2 Expanded Disability Status Scale

A standard neurological examination will be performed by an Assessing Neurologist and the participant's level of disability will be assessed using the EDSS as outlined in Table 1, Table 2, and Table 3.

The EDSS is an ordinal clinical rating scale ranging from 0 (normal neurological examination) to 10 (death due to MS) in half-point increments and should be administered in person by a neurologist trained in its use (19).

The EDSS score is calculated after neurologic testing and examination of the following eight functional systems, areas of the central nervous system that control bodily functions:

- Pyramidal (ability to walk);

- Cerebellar (coordination);
- Brain stem (speech and swallowing);
- Sensory (touch and pain);
- Bowel and bladder functions;
- Visual;
- Mental;
- Other (includes any other neurological findings due to MS).

Steps will be taken to eliminate inter- and intra-rater variability in the administration and assessment of the EDSS in the trial. The EDSS should be administered by an Assessing Neurologist who has undergone trial-specific EDSS training prior to the start of the trial and the same individual should evaluate a given participant throughout the course of the trial. The EDSS assessment should take place at approximately the same time of day and a standardized protocol should be followed for the neurologic examination.

Further information regarding the EDSS assessment will be provided in the Laboratory Manual.

7.3.3 Relapse Assessment

Participants will be assessed for MS relapse at visits as outlined in Table 1, Table 2, and Table 3, beginning at Week 4. Relapse will also be assessed at any Unscheduled Visit for Neurological Worsening and Relapse Assessment (see Section 7.1.4). For participants in the OLE Period, MS relapse will be assessed at all visits. A qualifying relapse is defined as new, worsening or recurrent neurological symptoms attributed to MS that last for at least 24 hours without fever or infection, or adverse reaction to prescribed medication, preceded by a stable or improving neurological status of at least 30 days. This relapse must be accompanied by new clinical signs (i.e., changes in the neurological examination or an increase in EDSS score).

All cases of potential relapse should be objectively confirmed by the Investigator regardless of whether they are identified during a scheduled or unscheduled visit. 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 protocol-defined 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 treatment unless they meet any of the criteria for withdrawal from the trial therapy (see Section 5.6.1) or withdrawal from the trial, including the need for treatment with a nonpermitted medication (see Section 5.6.2).

A nonqualifying relapse is any other relapse as defined by the Investigator that does not meet the qualifying relapse definition.

7.4 Assessment of Safety

The safety profile of the IMP will be assessed through the recording, reporting and analysis of baseline medical conditions; AEs; physical examination findings including vital signs, ECGs, and laboratory tests (including Ig and subclass concentration and CCI cell counts).

Comprehensive assessment of any apparent toxicity experienced by each participant will be performed from the time of giving informed consent and throughout the trial. The Investigator will report any AEs, whether observed by the Investigator or reported by the participant (see Section 7.4.1.2). The reporting period for AEs is described in Section 7.4.1.3.

7.4.1 Adverse Events

7.4.1.1 Adverse Event Definitions

Adverse Event

An AE is any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product, regardless of causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

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

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

Investigators will reference the National Cancer Institute-Common Terminology Criteria for AEs (NCI-CTCAE), Version 4.03 (publication date: 14 June 2010) (20), a descriptive terminology that will be provided in the Manual of Procedures 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.

Only if a particular AE's severity is not specifically graded by the guidance document, the Investigator is to use the general NCI-CTCAE definitions of Grade 1 through Grade 5 following 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.

According to Sponsor convention, any clinical AE with severity of Grade 4 or Grade 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 1 of the serious criteria described 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 a 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 IMP using the following definitions. Decisive factors for the assessment of causal relationship of an AE to the IMP include, but may not be limited to, temporal relationship between the AE and the IMP, known side effects of IMP, medical history, concomitant medication, course of the underlying disease, trial procedures.

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

Related: Reasonably related to the IMP. AE could medically (pharmacologically/clinically) be attributed to the IMP under study in this clinical trial 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 treatment discontinuation or are considered otherwise medically important by the Investigator. If a laboratory abnormality fulfills these criteria, the identified medical condition (e.g., anemia, 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. (Note: The term "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, except in the case of hospitalizations due to protocol-defined relapses;
- Results in persistent or significant disability or incapacity;
- Is a congenital anomaly or birth defect;

- Is otherwise considered to be medically important. (Note: 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 1 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 an IMP is also considered an SAE, as described in 7.4.1.4.

Events that Do Not Meet the Definition of an SAE

Elective hospitalizations to administer, or to simplify trial treatment or trial procedures (e.g., an overnight stay to facilitate IV therapy) are not considered SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (e.g., undesirable effects of any administered treatment) must be documented and reported as SAEs, except for unplanned hospitalizations due to relapse of MS.

Events Not to Be Considered as AEs/SAEs

Medical conditions present at the initial trial visit that do not worsen in severity or frequency during the trial 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.

7.4.1.2 Methods of Recording and Assessing Adverse Events

At each trial 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, whether 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 eCRF. All SAEs must be additionally documented and reported using the appropriate Report Form as described in Section 7.4.1.4.

It is important that each AE report include a description of the event, its duration (onset and resolution dates and times when it is important to assess the time of AE onset relative to the recorded treatment administration time), its severity, its causal relationship with the trial treatment, any other potential causal factors, any treatment given or other action taken, including dose

modification or discontinuation of the IMP, and its outcome. In addition, serious cases should be identified and the appropriate seriousness criteria documented.

Specific guidance can be found in the eCRF Completion and Monitoring Conventions provided by the Sponsor.

7.4.1.3 Definition of the Adverse Event Reporting Period

The AE reporting period for safety surveillance begins when the participant is initially included in the trial (date of first signature of informed consent/date of first signature of first informed consent) and continues until the 4-week Safety Follow-up/End of Trial Visit for participants who are not transitioning into the long-term follow-up study under a new protocol or until OLE End of Treatment Visit for participants transitioning into the long-term follow-up study under a new protocol.

Any SAE assessed as related to IMP must be reported whenever it occurs, irrespective of the time elapsed since the last administration of IMP.

7.4.1.4 Procedure for Reporting Serious Adverse Events

Serious Adverse Events

In the event of any new SAE occurring during the reporting period, the Investigator must immediately (within a maximum of 24 hours after becoming aware of the event) inform the Sponsor or its designee using the SAE Report Form, which must be completed by the Investigator following specific completion instructions.

For names, addresses, telephone and fax numbers for SAE reporting, see information included in the Adverse Event Safety Report Form.

In exceptional circumstances, an SAE (or follow-up information) may be reported by telephone; in these cases, the eCRF must be completed.

Relevant pages from the eCRF 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). In all cases, the information provided on the SAE Report Form must be consistent with the data about the event recorded in the eCRF.

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 responsible Medical Monitor, although in exceptional circumstances the Global Drug Safety department may contact the Investigator directly to obtain further information or to discuss the event.

7.4.1.5 Safety Reporting to Health Authorities, Independent Ethics Committees/ Institutional Review Boards and Investigators

The Sponsor or designee 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 trial participants to the IEC/IRB that approved the trial.

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 trial or alter the IEC's/IRB's approval/favorable opinion to continue the trial." In particular and in line with respective regulations, the Sponsor/designee will inform the Investigator of AEs that are both serious and unexpected and are 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 with regard to Safety Report notifications to Investigators will be taken into account.

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 trials 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.

7.4.1.6 Monitoring of Participants with Adverse Events

AEs are recorded and assessed continuously throughout the trial (see Section 7.4.1.3) and are assessed for final outcome at the 4-week Safety Follow-up/End of Trial Visit for participants who are not transitioning into the long-term follow-up study under a new protocol. For participants transitioning into the long-term follow-up study under a new protocol, AEs are assessed for final outcome at the OLE End of Treatment Visit.

All SAEs ongoing at the 4-week Safety Follow-up/End of Trial Visit for participants who are not transitioning into the long-term follow-up study under a new protocol and at the OLE End of Treatment Visit for participants transitioning into the long-term follow-up study under a new protocol 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.

7.4.2 Pregnancy and In Utero Drug Exposure

Only pregnancies considered by the Investigator to be related to trial treatment (e.g., resulting from a drug interaction with a contraceptive medication) are considered to be AEs. However, all pregnancies with an estimated conception date during the period defined in Section 7.4.1.3 must be recorded by convention in the AE page/section of the eCRF. The same rule applies to pregnancies in female participants and to pregnancies in female partners of male participants. The Investigator must notify the Sponsor/designee in an expedited manner of any pregnancy using the Pregnancy Report Form, which must be transmitted according to the same timeline as described for SAE reporting in Section 7.4.1.4.

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

The Investigator must notify the Sponsor/designee of these outcomes using the Pregnancy Report Form. If an abnormal outcome occurs, the SAE Report Form will be used if the participant sustains an event and the Parent-Child/Fetus Adverse Event Report Form if the child/fetus sustains an event.

Any abnormal outcome must be reported in an expedited manner as described in Section 7.4.1.4, while normal outcomes must be reported within 45 days after delivery.

In the event of a pregnancy in a participant occurring during the course of the trial, the participant must be discontinued from trial medication immediately. The Sponsor/designee must be notified without delay and the participant must be followed as mentioned above.

7.4.3 Clinical Laboratory Assessments

Blood and urine samples will be collected for the following clinical laboratory tests, following the timing noted in the Schedule of Assessments (Table 1, Table 2, and Table 3). All samples should be clearly identified. Sample collection, preparation, and handling/shipment procedures are described in the Laboratory Manual.

Table 8 Clinical Safety Laboratory Evaluations

Type of Evaluation	Tests		
Biochemistry	• Albumin • Aspartate aminotransferase • Alanine aminotransferase • Alkaline phosphatase • γ-Glutamyl-transferase • Lactate dehydrogenase	• Bilirubin (total) • Protein (total) • Creatinine and eGFR calculation • Amylase • Lipase • Total carbon dioxide • Blood urea nitrogen • Glucose	• Sodium • Potassium • Chloride • Calcium • Magnesium • Phosphate
LFT visits	• Aspartate aminotransferase • Alanine aminotransferase • Alkaline phosphatase • γ-Glutamyl-transferase	• Bilirubin (total)	
CCI			
Hematology	• Hematocrit • Hemoglobin • Red blood cell count • ESR • Mean corpuscular volume • Mean corpuscular hemoglobin • Mean corpuscular hemoglobin concentration • Reticulocyte count	• Platelet count • White blood cell count • CCI cell count[a] • Immunoglobulin and subclass concentrations[a,b]	• White blood cell differentials and absolute counts: ○ Basophils ○ Eosinophils ○ Lymphocytes ○ Monocytes ○ Neutrophils
Coagulation[a]	• International normalized ratio • Partial thromboplastin time		
Urinalysis/ microscopy[c] and urine chemistry	• pH • Nitrite • Urobilinogen • Bilirubin	• Glucose • Ketone bodies • Protein	• βhCG (women only)[a] • Microscopy[c] (white blood cells, red blood cells, casts) • Protein/creatinine ratio[d]

Additional urine testing	• βhCG (women only)[a]		
Other Screening tests[e]	• HCV antibodies • Serum βhCG (women only)	• HBV IgM antibodies • HIV[f] • FSH	• HBsAg • Quantiferon tuberculosis test

ALT=Alanine aminotransferase, AST=Aspartate aminotransferase, βhCG=β-human chorionic gonadotropin, CMV=cytomegalovirus, EA=early antigen, EBNA=Epstein-Barr nuclear antigen, EBV= Epstein-Barr virus, eGFR=estimated glomerular filtration rate, ESR=erythrocyte sedimentation rate, FSH=follicle-stimulating hormone, GGT=γ-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, HIV=human immunodeficiency virus, hsCRP=high sensitivity C-reactive protein, IDMC=independent data monitoring committee, Ig=immunoglobulin, LFT=liver function test, CCI , PCR=polymerase chain reaction, ViRNA=virus RNA, VCA=viral capsid antigen.

a. To be done only when specified in Table 1, Table 2, and Table 3, and not as a standard laboratory evaluation.
b. 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.
c. Microscopy will be performed only if urine dipstick is abnormal.
d. Protein/creatinine ratio will only be determined at the central laboratory if urine dipstick is abnormal
e. Performed only at Screening.
f. HIV testing will be done at Screening only where required as per local regulation.

CCI

7.4.4 Vital Signs, Physical Examinations, and Other Assessments

7.4.4.1 Vital Signs

Vital signs, including semisupine blood pressure, pulse rate, respiratory rate, weight, and oral temperature will be assessed predose at all specified trial visits (Table 1, Table 2, and Table 3). Height will be measured at Screening only.

A semiautomated pulse rate and blood pressure recording device with an appropriate cuff size will be utilized. Pulse rate and blood pressure will be measured after 10 minutes rest in the semisupine position with the participant's arm unconstrained by clothing or other material. The blood pressure should be assessed on the same arm for each participant throughout the trial.

7.4.4.2 Physical Examinations

Physical examinations will be assessed at each site as indicated in Table 1, Table 2, and Table 3. Physical examination includes assessment of the following: general appearance, skin, head and neck, mouth, lymph nodes, thyroid, abdomen, and musculoskeletal, cardiovascular, and respiratory systems. Physical examination findings during Screening before obtaining informed consent will be recorded as medical history events and new findings or worsening during the trial as AEs. Records from physical examinations will be retained at each site and will not be captured in the eCRF.

7.4.4.3 12-Lead ECG and Chest X-ray

A 12-lead ECG will be performed during Screening. For participants in the OLE Period, a 12-lead ECG will also be conducted at OLE Day 1, unscheduled visits, Week 48, and then every 48 weeks

up to and including the OLE End of Treatment Visit. The 12-lead ECG recordings will be obtained after 10 minutes of rest in a semisupine position.

The following ECG parameters will be obtained directly from the computerized 12-lead ECG recordings: rhythm, ventricular rate, PR interval, QRS duration, and QT interval. The corrected QT interval will be calculated using Fridericia's formula. The overall evaluation (normal/abnormal) will be recorded on the eCRF, and if abnormal, the specific abnormality will be recorded. Abnormal evaluations will be judged as clinically significant or not clinically significant by the Investigator.

The 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).

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

The 12-lead ECG and CXR will be performed and read locally.

7.4.5 Total Immunoglobulin Assessments

Blood samples for Ig levels (IgM, IgA, and IgG) will be collected as noted in Table 1, Table 2, and Table 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, to avoid unblinding. However, the IDMC will have access to these data as applicable.

CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7.8 Columbia-Suicide Severity Rating Scale

The C-SSRS will be used for prospective suicidality assessment. The C-SSRS will be a tool used at Screening to identify eligible participants. The C-SSRS will be measured in all participants as indicated in Table 1, Table 2, and Table 3. The C-SSRS Screening Scale will be used in the main study and C-SSRS Since Last Visit Scale will be used in the OLE. 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 a qualified designee. Please note that assessing the risk of suicide is a difficult and complex task when applied to the individual patient. 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 Statistics

8.1 Sample Size

A per-group sample size of 44 evaluable participants provides 85% power to detect a decrease of 90% in the total number of gadolinium-enhancing T1 lesions, summed over scans at Week 12, 16, 20, and 24, between each M2951 group versus placebo at the 2-sided 5% level, using the Wilcoxon rank-sum test, where the p-value is evaluated using a continuity-corrected normal approximation to the test statistic. Power was evaluated via simulation in R of the Wilcoxon test (wilcox.test) applied to lesion count data generated according to a NB distribution, with mean $\lambda_t = 0.55$ and shape parameter $\Upsilon_t = 14.0$ for a given M2951 group (Υ_t based on rituximab data) (2), and mean $\lambda_c = 5.5$ and shape parameter $\Upsilon_c = 7.256$ for the placebo group (λ_c and Υ_c based on placebo data) (2), yielding a lesion rate ratio of $\lambda_t/\lambda_c = 0.10$. Approximately 50 participants will be randomized per group to protect against a loss of information due to a 12% drop-out rate over 1 year, and to provide for an adequate assessment of safety. (Note that the NB distribution parameterization assumed here implies lesion count variance equals $\lambda + \lambda^2 \Upsilon$ for a given treatment group.)

Approximately 250 participants will enter the main study. Assuming an 80% rate of continuation to OLE, approximately 200 participants are expected to enter the OLE Period.

FWER at the primary analysis will be controlled at the 2-sided 0.05 significance level for the 3 comparisons of M2951 dose group versus placebo using the Hochberg procedure.

8.2 Randomization

Eligible participants will be randomized 1:1:1:1:1 to treatment with placebo, low-dose M2951 (25 mg once daily), mid-dose M2951 (75 mg once daily), high-dose M2951 (75 mg twice daily), or Tecfidera (administered twice daily at a final dose of 240 mg), through a central randomization process by an IWRS, stratified according to region (USA or Western Europe, Eastern Europe and CCI , Eastern Europe and not CCI , and RoW).

8.3 Endpoints

8.3.1 Primary Endpoints

The primary endpoint is the total number of gadolinium-enhancing T1 lesions at Week 12, 16, 20, and 24. The primary analysis is a comparison of each M2951 dose arm versus placebo based on this endpoint, with a supportive test for dose-response.

8.3.2 Secondary Endpoints

Key secondary endpoints to evaluate the efficacy and safety of M2951 compared to placebo:

- ARR, based on protocol-defined qualified relapses, at Week 24;
- Qualified relapse-free status at Week 24;
- Change from Baseline in EDSS at Week 24;
- Safety as assessed by the nature, severity, and occurrence of AEs; vital signs; ECGs; absolute concentrations and change from Baseline in Ig levels; absolute numbers and change from Baseline in B cells; and clinical laboratory safety parameters (duration of placebo treatment group limited to 24 weeks).

Additional secondary endpoints:

To evaluate the efficacy of M2951 compared to placebo:

- Total number of new Gd+ T1 lesions at Week 12, 16, 20, and 24;
- Mean per-scan number of Gd+ T1 lesions at Week 12, 16, 20, and 24;
- Total number of new or enlarging T2 lesions at Week 12, 16, 20, and 24;
- Change from Baseline in the volume of Gd+ T1 lesions at Week 24;
- Change from Baseline in the volume of T2 lesions at Week 24.

To evaluate efficacy within M2951 dose groups:

- Number of Gd+ T1 lesions at Week 48;
- Number of new Gd+ T1 lesions at Week 48;
- ARR, based on protocol-defined qualified relapses, at Week 48;
- Qualified relapse-free status at Week 48;
- Change from Baseline in EDSS at Week 48;
- Number of new or enlarging T2 lesions at Week 48;
- Change from Baseline in the volume of Gd+ T1 lesions at Week 48;
- Change from Baseline in the volume of T2 lesions at Week 48.

To evaluate the efficacy and safety of Tecfidera:

- Total number of gadolinium-enhancing T1 lesions at Week 12, 16, 20, and 24;
- ARR, based on protocol-defined qualified relapses, at Week 24;
- Qualified relapse-free status at Week 24;
- Change from Baseline in EDSS at Week 24;

- Safety as assessed by the nature, severity, and occurrence of AEs; vital signs; ECGs; absolute concentrations and change from Baseline in Ig levels; absolute numbers and change from Baseline in B cells; and clinical laboratory safety parameters;
- Total number of new Gd+ T1 lesions at Week 12, 16, 20, and 24;
- Mean per-scan number of Gd+ T1 lesions at Week 12, 16, 20, and 24;
- Total number of new or enlarging T2 lesions at Week 12, 16, 20, and 24;
- Change from Baseline in the volume of Gd+ T1 lesions at Week 24;
- Change from Baseline in the volume of T2 lesions at Week 24;
- Number of Gd+ T1 lesions at Week 48;
- Number of new Gd+ T1 lesions at Week 48;
- ARR, based on protocol-defined qualified relapses, by Week 48;
- Qualified relapse-free status at Week 48;
- Change from Baseline in EDSS at Week 48;
- Number of new or enlarging T2 lesions at Week 48;
- Change from Baseline in the volume of Gd+ T1 lesions at Week 48;
- Change from Baseline in the volume of T2 lesions at Week 48.

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8.3.4 Endpoints for Open-label Extension Period

The endpoints for the OLE Period are as follows:

- Efficacy and CCI endpoints at Week 48, 96, 144, 192, 240, 288, 336, and 384.
    - Number of gadolinium-enhancing T1 lesions;
    - ARR, based on protocol-defined qualified relapses;
    - Qualified relapse-free status;
    - Change from baseline in disability score based on EDSS score;

    CCI
- Safety as assessed by the nature, severity, and occurrence of AEs; vital signs; ECGs; absolute concentrations and change from Baseline in Ig levels; CCI ; and clinical laboratory safety parameters.

CCI

8.4 Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

Safety Analysis Set

The Safety Analysis Set consists of all participants who receive at least 1 dose of trial treatment. Participants will be analyzed according to the actual treatment they receive.

Intent-To-Treat Analysis Set

The Intent-To-Treat ITT Analysis Set consists of all participants randomly allocated to a treatment, based on the intention to treat "as randomized" principle (i.e., the planned treatment regimen rather than the actual treatment given in case of any difference).

Modified Intent-To-Treat Analysis Set

The mITT Analysis Set consists of all participants who belong to both the ITT and Safety Analysis Sets, and who have at least one baseline and one postbaseline MRI assessment.

Per-Protocol (PP) Analysis Set

The PP Analysis Set consists of all participants who belong to the mITT Analysis Set, complete 24 weeks of treatment, and do not have any important protocol deviations.

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CCI [redacted]

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CCI [redacted]

Open-Label Extension Analysis Set

The OLE Analysis Set consists of all participants who receive at least 1 dose of M2951 during the OLE.

8.5 Description of Statistical Analyses

8.5.1 General Considerations

A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Prior to partial locking the database for the primary analysis, a detailed IAP will be developed.

Continuous variables will be summarized descriptively using the number of observations, mean, SD, median, first quartile (Q1), third quartile (Q3), minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages. The denominator for the percentages will be the total number of participants in the treatment group and analysis set being presented, unless otherwise specified (e.g., on some occasions, percentages may be calculated out of the total number of participants with available data at a particular time point).

All tests of treatment effects will be conducted at a 2-sided α-level of 0.05. P-values and the 95% CIs will be presented where applicable. Actual p-values will be interpreted based on the multiple testing strategy. Treatment comparisons for each data type are described in later sections. Alternative or additional statistical methods may be used as appropriate as outlined in the IAP.

Data from all investigative sites will be pooled for all planned analyses. Analysis of individual site findings or country findings will be considered if necessary. For those measures that are analyzed using change from baseline scores, observed scores may also be presented descriptively.

The procedures to be followed in relation to handling missing, unused, or spurious data will be described in the IAP. The IAP will provide the definition(s) of Baseline measurement as required.

All participants will be included in individual participant data listings.

Any changes to the data analysis methods described in the protocol will require an amendment only if a principal feature of the protocol is affected. Any other changes to the planned data analysis that does not require a protocol amendment will be described in the IAP and the CSR. CCI [redacted]

8.5.2 Analysis of Primary Endpoint

Primary Efficacy Endpoint

The primary analysis of total number of Gd+ T1 lesions, at Week 12, 16, 20, and 24, will be an estimate of lesion rate ratio, together with associated 95% CI and p-value, comparing each M2951 dose group to placebo, based on a NB model, where the offset will be based on the log of number of scans, with M2951 dose or placebo group as a factor and adjustment for covariates based on randomization strata and baseline MRI activity. Other covariates may be considered. Should the model fail to converge, the primary analysis will be an estimate of the shift in location of the distribution of the Gd+T1 lesion count via the Hodges-Lehman estimate, together with associated 95% CI and p-value based on the stratified Wilcoxon rank-sum test, comparing each M2951 dose group to placebo. Descriptive statistics for the total number of Gd+ T1 lesions, at Week 12, 16, 20, and 24, will be provided for each treatment group.

The primary analysis of the primary endpoint will be based on the mITT analysis set, with supportive analyses based on the ITT and PP analysis sets. If the primary analysis is comprised of NB modeling, the computed p-value testing the null hypothesis H_0: RR = 1.0 for each M2951 dose group will be reported, where RR denotes lesion rate ratio comparing a given M2951 dose group to placebo. If the primary analysis must be nonparametric due to model nonconvergence, the computed p-value testing the null hypothesis H_0: $P(X < Y) + 0.5 \times P(X = Y) = 0.5$, via the stratified Wilcoxon rank-sum test, for each M2951 treatment group will be reported, where X denotes the primary endpoint evaluated for a participant in a given M2951 treatment group, and Y denotes the primary endpoint evaluated for a participant in the placebo group. The FWER, i.e., overall type I error rate for the primary analysis, will be controlled at the 0.05 level by testing the 3 M2951 hypotheses for the low, mid, and high dose groups using the Hochberg procedure. A test for a monotonic dose-response relationship, between ordered M2951 dose (low, mid, high) and the primary efficacy endpoint, will be performed as a supportive analysis.

No formal comparisons between the Tecfidera arm and any other treatment group will be performed for the primary endpoint.

8.5.3 Analysis of Secondary Endpoints

The analysis of secondary endpoints will be based on the mITT analysis set.

Descriptive statistics for MRI and clinical secondary endpoints, will be provided for the M2951 dose arms, the placebo arm (limited to 24 week endpoints), and the Tecfidera arm. For 48 week endpoints, descriptive statistics will be provided for the placebo/M2951 arm. Descriptive statistics for ARR will be calculated for each treatment group as the total number of qualified relapses divided by the number of participant-years of observation.

The multiple-comparison procedure for testing the key secondary efficacy endpoints will be provided in the IAP. CCI [redacted].
No formal comparisons between the Tecfidera arm and any other treatment group will be performed for the secondary efficacy endpoints.

Secondary Efficacy Endpoints: Baseline to 24 weeks

The comparison of a M2951 treatment group to the placebo group using ARR at Week 24 will be based on the rate ratio estimated from an NB model for qualified relapse count, with offset equal to the log of years on study, with M2951 dose group or placebo group as a factor and adjustment for covariates based on randomization strata and prebaseline relapse activity. The comparison of a M2951 treatment group to the placebo group using proportion qualified relapse-free at Week 24, will be based on the odds ratio estimated from a logistic model for the odds of a participant being qualified relapse-free at Week 24, where participants who discontinue study prior to Week 24 without having a qualified relapse are counted as not being qualified relapse-free at Week 24, with M2951 dose group or placebo group as a factor and adjustment for covariates based on randomization strata. The comparison of a M2951 treatment group to placebo group using change from Baseline in EDSS at Week 24 will be based on a stratified Wilcoxon rank-sum test, with strata defined by baseline EDSS and randomization strata and prebaseline relapse activity. The analysis of change from Baseline in volume of Gd+ T1 lesions at Week 24, and change from Baseline in volume of T2 lesions at Week 24, will be based on a Mixed-effect Model for Repeated Measures (MMRM) approach for the appropriately transformed variable, with M2951 dose group or placebo group as a factor, randomization strata as a factor and baseline MRI activity as a covariate. The comparison of a M2951 treatment group to placebo using total number of new Gd+ T1 lesions, or total number of new or enlarging T2 lesions, at Week 12, 16, 20, and 24, will be based on an NB model, similar to that used for the primary analysis. Estimation of mean per-scan number of Gd+ T1 lesions at Weeks 12, 16, 20, and 24, for each treatment group, will be based on the NB model. In the analysis of each secondary endpoint, other covariates may be included in the model.

A test for a monotonic dose-response relationship, between ordered M2951 dose (low, mid, high) and each of the key secondary efficacy endpoints, will be performed as supportive analyses.

Secondary Efficacy Endpoints: Baseline to 48 weeks

Descriptive statistics for MRI and clinical endpoints, Baseline to Week 48, will be provided for the M2951 dose arms, the placebo/M2951 arm, and the Tecfidera arm.

The number of Gd+ T1 lesions, number of new Gd+ T1 lesions, number of new and enlarging T2 lesions, the observed and change from Baseline values of Gd+ T1 lesion volume, and observed and change from Baseline values of T2 lesion volume, will be summarized by treatment group (placebo, 3 M2951 dose groups, and Tecfidera) and time point over the treatment period.

ARR from Baseline to Week 24, from Week 24 to Week 48, and from Baseline to Week 48 will be summarized by treatment group. Qualifying relapse-free status at Week 24 and at Week 48 will be summarized by treatment group. Observed and change from Baseline values of EDSS will be summarized by treatment group and time point over the treatment period.

8.5.4 Analysis of Safety and CCI Endpoints

No formal comparisons between the Tecfidera arm and any other treatment group will be performed for the safety, CCI [redacted] endpoints.

8.5.4.1 Safety

AEs will be summarized by treatment group, by severity, and by relationship to IMP.

SAEs, AEs leading to treatment discontinuation, and AEs leading to treatment interruption, will be summarized by treatment group.

Summary statistics will be used to present observed values and changes from baseline in continuous laboratory, vital sign, and ECG data. Shift tables will be used to present changes in categorical laboratory parameters. Figures may be generated to assist safety evaluation.

AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). The severity of AEs will be graded using NCI-CTCAE v4.03 toxicity grades (20).

The number and percentage of participants experiencing 1 or more treatment-emergent AEs will be summarized according to the MedDRA system organ classes and preferred terms by treatment group, relationship to IMP, and severity.

Values for all safety variables will be listed by participant and time point.

CCI [redacted]

CCI [redacted]

[redacted]

8.5.4.3 Analysis of Open-label Extension Period Endpoints

Efficacy and CCI [redacted] 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 8.5.4.1.

CCI [redacted]

[redacted]

[redacted]

[redacted]

CCI [redacted]

[redacted]

[redacted]

[redacted]

8.6 Interim and Additional Planned Analyses

There will be 5 analyses: (1) a primary analysis, triggered when 100% of participants enrolled reach Week 24 of treatment, or prematurely discontinue from treatment; (2) a blinded extension analysis, triggered when 100% of participants enrolled either reach Week 52 (4-week Safety Follow-up Visit) and complete the study, enroll in the OLE, or prematurely discontinue from study; (3) an OLE Week 60 interim analysis, triggered when 100% of OLE participants either reach Week 60 of the OLE, or prematurely discontinue from treatment; (4) an OLE interim analysis, planned at the appropriate time point considering the visits schedule around the time of the trigger for the primary analysis of the Phase III RMS studies; and (5) a final analysis, triggered when 100% of participants enrolled in the OLE complete the OLE (4-week Safety Follow-up Visit for participants not transitioning into the long-term follow-up study under a new protocol and OLE End of Treatment Visit for transitioning participants) or discontinue from the OLE.

Primary Analysis

When the last participant reaches 24 weeks of treatment or discontinues from treatment prematurely, the protocol violations are determined, and the database is partially locked for the

primary analysis, the drug codes will be broken and made available for the primary data analysis. All endpoints based on Baseline to Week 24 data will be evaluated. The FWER associated with the multiple comparisons of M2951 dose to placebo based on the primary endpoint will be controlled via the Hochberg procedure. The multiple-comparison procedure for testing the key secondary endpoints will be provided in the IAP.

Blinded Extension (Week 52) Analysis

The Blinded Extension (Week 52) analysis will occur when the last participant completes 48 weeks of treatment (either completing the 4-week Safety Follow-up Visit at Week 52, or enrolling in the OLE), or discontinues from the study prematurely. Protocol violations will be determined and the database partially locked prior to the Week 52 analysis. All endpoints based on Baseline to Week 52 data will be evaluated.

OLE Week 60 Interim Analysis

The OLE Week 60 interim analysis will occur when the last OLE participant completes 60 weeks of treatment, or discontinues from the study prematurely. Protocol violations will be determined and the database partially locked prior to the OLE Week 60 analysis. Selected safety endpoints based on OLE Day 1 to Week 60 data will be evaluated.

OLE Interim Analysis in support of Phase III

The OLE interim analysis will be planned at the appropriate time point considering the visits schedule around the time of the trigger for the primary analysis of the Phase III RMS studies. Protocol violations will be determined and the database partially locked prior to the interim analysis. Selected safety and efficacy endpoints based on data from OLE Day 1 to the data cutoff will be evaluated.

Final Analysis

The final analysis will occur only when the last participant enrolled in the OLE completes the OLE (4-week Safety Follow-up Visit for participants not transitioning and OLE End of Treatment Visit for participants transitioning into the long-term follow-up study under a new protocol) or discontinues prematurely, the protocol violations are determined, and the database is locked for the final analysis. All endpoints based on OLE data will be evaluated.

9 Ethical and Regulatory Aspects

9.1 Responsibilities of the Investigator

The Investigator is responsible for the conduct of the trial at the site and will ensure that the trial is performed in accordance with this protocol, the ethical principles outlined in the Declaration of Helsinki, ICH GCP, and any other applicable regulations. The Investigator must ensure that only participants who have given informed consent are included in the trial.

According to United States Code of Federal Regulations Part 54.2 (e), for trials conducted in any country that could result in a product submission to the FDA for marketing approval and could contribute significantly to the demonstration of efficacy and safety of an IMP (which are considered "covered clinical trials" by the FDA), the Investigator and all Subinvestigators are obliged to disclose any financial interest which they, their spouses or their dependent children may have in the Sponsor or the Sponsor's product under study. This information is required during the trial and for 12 months following completion of the trial. The financial aspects are documented in the Clinical Trial Agreement between the Sponsor and the Investigator/institution.

9.2 Participant Information Sheet and Informed Consent

An unconditional prerequisite for each participant prior to participation in the trial is written informed consent, which must be given before any trial-related activities are carried out. Adequate information must therefore be given to the participant by the Investigator or an appropriate designee (if local regulations permit) before informed consent is obtained.

A Participant Information Sheet must be prepared in the local language in accordance with ICH GCP and will be provided by the Sponsor for the purpose of obtaining informed consent. In addition to providing this written information to a potential participant, the Investigator or a designate will inform the participant verbally of all pertinent aspects of the trial, using language chosen so that the information can be fully and readily understood by laypersons. The participant will be given sufficient time to read the information and the opportunity to ask questions and to request additional information and clarification.

If permitted by national regulations, a person other than the Investigator may inform the participant about the trial and sign the ICF, as above.

After the information is provided by the Investigator, the ICF must be signed and dated by the participant and the Investigator. CCI [redacted]

A separate ICF will be needed for the subset of participants consenting CCI [redacted]

A separate ICF will be needed for volunteers prior to performing the MRI dummy run.

Signed consent will be obtained prior to participation in the optional OLE Period.

The signed and dated declaration of informed consent will remain at the Investigator's site, and must be safely archived so that the forms can be retrieved at any time for monitoring, auditing, and inspection purposes. A copy of the signed and dated information and ICF should be provided to the participant prior to participation.

Whenever important new information becomes available that may be relevant to informed consent, the Investigator will revise the Participant Information Sheet and any other written information to be provided to the participants and submit them to the IRB for review and opinion. Using the approved revised Participant Information Sheet and other written information, the Investigator will explain the changes to the previous version to each trial participant and obtain new written consent for continued participation in the trial. The participant will be given sufficient time to read the information and the opportunity to ask questions and to request additional information and clarification about the changes.

9.3 Participant Identification and Privacy

A unique number will be assigned to each participant, immediately after informed consent has been obtained. This number will serve as the participant's identifier in the trial as well as in the clinical trial database. All participant data collected in the trial will be stored under the appropriate participant number. Only the Investigator will be able to link trial data to an individual participant via an identification list kept at the site. For each participant, original medical data will be accessible for the purposes of source data verification by the Medical Monitor, audits and regulatory inspections, but participant confidentiality will be strictly maintained.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing participant data. Participants will be informed accordingly, and will be requested to give their consent on data handling procedures in accordance with national regulations.

9.4 Emergency Medical Support and Participant Card

Participants will be provided with Emergency Medical Support cards supplied by the Sponsor for use during trial participation in order to provide clinical trial participants with a way of identifying themselves as participating in a clinical trial and to 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 provided 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 trial Investigator caring for the affected participant. The Investigator agrees to provide his or her emergency contact information on the card for this purpose. 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.

In cases where the Investigator is not available, the Sponsor provides the appropriate means to contact a Sponsor physician. This includes the provision of a 24-hour contact number at a call center, whereby the health care providers will be given access to the appropriate Sponsor physician

to assist with the medical emergency and to provide support for the potential unblinding of the participant concerned.

9.5 Clinical Trial Insurance and Compensation to Participants

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

9.6 Independent Ethics Committee or Institutional Review Board

Prior to commencement of the trial at a given site, this clinical trial protocol will be submitted together with its associated documents to the responsible IEC or IRB for its favorable opinion or approval, which will be filed in the Investigator Site File. A copy will be filed in the Sponsor Trial Master File at the Sponsor or designee organization.

The IEC or IRB will be asked to document the date of the meeting at which the favorable opinion or approval was given and the members and voting members present. Written evidence of favorable opinion or approval that clearly identifies the trial, the clinical trial protocol version and the Participant Information Sheet and ICF version reviewed should be provided. Where possible, copies of the meeting minutes should be obtained.

Amendments to this clinical trial protocol will also be submitted to the concerned IEC or IRB, before implementation of substantial changes (see Section 10.5). Relevant safety information will be submitted to the IEC or IRB during the course of the trial in accordance with national regulations and requirements.

9.7 Health Authorities

The clinical trial protocol and any applicable documentation (e.g., IMP Dossier, Participant Information Sheet and ICF) will be submitted or notified to the Health Authorities in accordance with all local and national regulations for each site.

10 Trial Management

10.1 Case Report Form Handling

Refer to the Manual of Operations for eCRF handling guidelines.

The main purpose of the eCRF is to obtain data required by the clinical trial protocol in a complete, accurate, legible, and timely manner. The data in the eCRF should be consistent with the relevant source documents.

The Investigator or designee is responsible for ensuring that the data collected in the course of this trial is accurate and documented appropriately on all applicable forms. They will then be processed, evaluated, and stored in anonymous form in accordance with applicable data protection regulations. The Investigator must ensure that the eCRFs and any other associated documents forwarded to Sponsor or its designated organization contain no mention of any participant names.

For patient-reported outcomes, these will be collected on paper.

The data will be entered into a validated database. The Sponsor or its designee will be responsible for data processing, in accordance with the Sponsor's data management procedures. Database lock will occur once quality control and quality assurance procedures have been completed. Electronic PDF files of the eCRFs will be provided to the Investigators at the completion of the trial.

10.2 Source Data and Participant Files

The Investigator must keep a file (medical file, original medical records) on paper or electronically for every participant in the trial. It must be possible to identify each participant by using this participant file. This file will contain the demographic and medical information for the participant listed below and should be as complete as possible:

- Participant's full name, date of birth, sex, height, weight;
- Medical history and concomitant diseases;
- Prior and concomitant therapies (including changes during the trial) ;
- Trial identification, i.e., the Sponsor trial number for this clinical trial, and participant number;
- Dates for entry into the trial (informed consent) and visits to the site;
- Any medical examinations and clinical findings predefined in this clinical trial protocol;
- All AEs;
- Date that the participant left the trial including any reason for early withdrawal from the trial or IMP (if applicable).

All documents containing source data must be filed, including, but not limited to, computerized tomography or MRI scan images, ECG recordings, CXRs, and laboratory results. Such documents must bear the participant number and the date of the procedure. If possible, this information should be printed by the instrument used to perform the assessment or measurement. As necessary, medical evaluation of such records should be performed; all evaluations should be documented, signed, and dated by the Investigator.

For data that may be recorded directly in the eCRF such as a questionnaire or diary, there will be no record in the original participant file and therefore the data entered in the eCRF will be considered source data. The clinical trial protocol or the Manual of Operations should clearly and completely specify all participant data in the eCRF to be considered source data.

Electronic participant files will be printed whenever the Medical Monitor performs source data verification. Printouts must be signed and dated by the Investigator, countersigned by the Medical Monitor and kept in a safe place at the site.

10.3 Investigator Site File and Archiving

Upon initiation of the trial, the Investigator will be provided with an Investigator Site File containing all necessary trial documents, which will be completed throughout the trial and updated as necessary. The file must be available for review by the Medical Monitor, during Sponsor audits and for inspection by Health Authorities during and after the trial, and must be safely archived for at least 15 years (or longer, per local requirements or as otherwise notified by the Sponsor) after the end of the trial. The documents to be archived include the Participant Identification List and the signed participant ICFs. If archiving of the Investigator Site File is no longer possible at the site, the Investigator must notify the Sponsor/designee.

All original participant files (medical records) must be stored at the site (hospital, research institute, or practice) for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. In any case, the Investigator should ensure that no destruction of medical records is performed without the written approval of the Sponsor.

10.4 Monitoring, Quality Assurance and Inspection by Health Authorities

This trial will be monitored in accordance with the ICH GCP and any other applicable regulations. The site Medical Monitor will perform visits to the trial site at regular intervals.

The clinical trial protocol, each step of the data capture procedure, and the handling of the data, including the final clinical trial report, will be subjected to independent Quality Assurance activities. Audits may be conducted at any time during or after the trial to ensure the validity and integrity of the trial data. Representatives of the Quality Assurance unit from the Sponsor or a designated organization, as well as Health Authorities, must be permitted to access all trial documents and other materials at the site, including the Investigator Site File, the completed eCRFs, all IMP and IMP accountability records, and the original medical records or files for each participant.

10.5 Changes to the Clinical Trial Protocol

Changes to the clinical trial protocol will be documented in writing. Substantive amendments will usually require submission to the Health Authorities and to the relevant IEC/IRB for approval or favorable opinion. In such cases, the amendment will be implemented only after approval or favorable opinion has been obtained.

Minor (nonsubstantial) protocol amendments, including administrative changes, will be filed by the Sponsor and at the site. They will be submitted to the relevant IEC/IRB or to Health Authorities only where requested by pertinent regulations. Any amendment that could affect the participant's agreement to participate in the trial requires additional informed consent prior to implementation following the process as described in Section 9.2.

10.6 Clinical Trial Report and Publication Policy

10.6.1 Clinical Trial Report

After completion of the 48-week main study, a clinical trial report will be written by the Sponsor in consultation with the Coordinating Investigator following the guidance in ICH Topic E3 within the legally required period for participating countries. After completion of the OLE Period, an additional clinical trial report will be written by the Sponsor in consultation with the Coordinating Investigator following the guidance in ICH Topic E3 within the legally required period for participating countries.

10.6.2 Publication

An Investigator will inform the Sponsor in advance about any plans to publish or present data from the trial. Any publications and presentations of the results (abstracts in journals or newspapers, oral presentations, etc.), either in whole or in part, by Investigators or their representatives will require review by the Sponsor before submission. The Sponsor will not suppress publication, but maintains the right to delay publication in order to protect intellectual property rights.

Posting of data on clinicaltrials.gov is planned and will occur 12 months after the last clinic visit of the final trial participant or another appropriate date to meet applicable requirements.

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Appendix I: Signature Pages and Responsible Persons for the Trial

Signature Page – Protocol Lead

Trial Title:	A Randomized, Double-Blind, Placebo-Controlled Phase II Study of M2951 with a Parallel, Open-Label, Active Control Group (Tecfidera), in Patients with Relapsing Multiple Sclerosis to Evaluate Efficacy, Safety, Tolerability, Pharmacokinetics, and Biological Activity.
IND Number:	CCI
EudraCT Number:	2016-001448-21
Clinical Trial Protocol Date / Version:	06 July 2023 / Version 8.0

Protocol Lead responsible for designing the clinical trial:

I approve the design of the clinical trial:

PPD (on behalf of PPD) 10.07.2023

Signature Date of Signature

Name, academic degree:	PPD
Function / Title:	Medical Director, Global Clinical Development Center
Institution:	Merck Healthcare KGaA
Address:	Frankfurter Str. 250, 64293 Darmstadt, Germany
Telephone number:	PPD
Fax number:	Not applicable
E-mail address	PPD

Signature Page – Coordinating Investigator

Trial Title	A Randomized, Double-Blind, Placebo-Controlled Phase II Study of M2951 with a Parallel, Open-Label, Active Control Group (Tecfidera), in Patients with Relapsing Multiple Sclerosis to Evaluate Efficacy, Safety, Tolerability, Pharmacokinetics, and Biological Activity.
IND Number	CCI [redacted]
EudraCT Number	2016-001448-21
Clinical Trial Protocol Date / Version	06 July 2023 / Version 8.0

I approve the design of the clinical trial and I understand and will conduct the trial according to the clinical trial protocol, any approved protocol amendments, International Council for Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

PPD

Signatu

PPD

Date of Signature

Name, academic degree:

Function / Title:

Institution:

Address:

PPD

Telephone number:

Fax number:

E-mail address:

PPD PPD

Global Version ID: CCI [redacted]

Signature Page – Principal Investigator

Trial Title	A Randomized, Double-Blind, Placebo-Controlled Phase II Study of M2951 with a Parallel, Open-Label, Active Control Group (Tecfidera), in Patients with Relapsing Multiple Sclerosis to Evaluate Efficacy, Safety, Tolerability, Pharmacokinetics, and Biological Activity.
IND Number	CCI
EudraCT Number	2016-001448-21
Clinical Trial Protocol Date / Version	06 July 2023 / Version 8.0
Center Number	
Principal Investigator	

I, the undersigned, am responsible for the conduct of the trial at this site and affirm that I understand and will conduct the trial according to the clinical trial protocol, any approved protocol amendments, International Council for Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

I also affirm that I understand that Health Authorities may require the Sponsors of clinical trials 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 the purpose of complying with the regulatory requirements. I therefore 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:

Appendix II: Total Blood Volume

Blood will be drawn on at least 23 separate days/visits. Additional samples may be drawn if unscheduled visits occur. On the day of CCI sampling, participants will have an IV catheter inserted to facilitate obtaining the multiple samples required. The planned maximum volume of blood to be drawn in this trial is approximately 604 mL over the 4-week Screening Period, 24-week Treatment Period, 24-week Treatment Extension Period, and 4-week Safety Follow-Up Period (56 weeks total). For participants participating in the optional Open-label Long-Term Extension Period, up to additional 532.5 mL of blood (approximately) will be collected over the 388 weeks of participation.

Total Blood Volume during Main Study

Assay	Approximate Sample Volume (mL)	Number of Samples	Approximate Subtotal Volume (mL)
Screening tests: hematology, chemistry, coagulation, FSH, viral serology testing (HBsAg, AntiHCV, HIV[a])	19.5	1	19.5
Hematology, chemistry[b,c]	12.5	24	300
Immunoglobulins	4	5	20
QuantiFERON-TB test	4.5	1	4.5
CCI			
CCI			
Total			**604**

ALP=alkaline phosphatase, ALT=Alanine aminotransferase, AST=Aspartate aminotransferase, CCI, FSH=follicle-stimulating hormone, GGT=γ-glutamyl-transferase, HBsAg=hepatitis B surface antigen, HCV=hepatitis C virus, HIV=human immunodeficiency virus, LDH=lactate dehydrogenase, CCI, CCI, TB=tuberculosis.

[a] HIV testing will be done at Screening only where required as per local regulations.

[b] Chemistry will include: albumin, AST, ALT, ALP, GGT, LDH, total bilirubin, total protein, creatinine, amylase, lipase, total CO2, blood urea nitrogen, glucose, sodium, potassium, chloride, calcium, magnesium, phosphate as shown in Table 8.

[c] Supplemental LFTs are included in this row as shown in Table 8.

CCI

Total Blood Volume during Open-label Extension Period

Assay	Approximate Sample Volume(mL)	Number of Samples	Approximate Subtotal Volume (mL)
Hematology	2	26	52
Chemistry[a, b]	3.5	45	157.5
Immunoglobulins	5	17	85
CCI			
			82
CCI			
CCI			
Total			**532.5**

ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, GGT=γ-glutamyl-transferase, LDH=lactate dehydrogenase, CCI , CCI .

[a] Chemistry will include: albumin, AST, ALT, ALP, GGT, LDH, total bilirubin, total protein, creatinine, amylase, lipase, total CO_2, blood urea nitrogen, glucose, sodium, potassium, chloride, calcium, magnesium, phosphate as shown in Table 8.

[b] Supplemental LFTs are included in this row as shown in Table 8.

CCI

Appendix III: Protocol Amendments and List of Changes

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

Protocol Version 1.0 (05 July 2016) was the original protocol. The following global amended protocols were issued:

- Version 2.0 (Amendment # 1) was issued on 28 November 2017.
- Version 3.0 (Amendment # 2) was issued on 29 May 2018.
- Version 4.0 (Amendment # 3) was issued on 08 August 2018.
- Version 5.0 (Amendment # 4) was issued on 21 November 2018.
- Version 6.0 (Amendment # 5) was issued on 08 November 2019.
- Version 7.0 (Amendment # 6) was issued on 02 December 2022.

Amendment # 6

For Poland only, a local amendment (Version 6.1) was created to give the provision to conduct a local sub-study at approximately 3 study centers in Poland. The aim of this sub-study is to investigate evobrutinib concentrations and oligoclonal bands in blood and cerebrospinal fluid of subjects with RMS.

Rationale for Global Amendment 6, Protocol Version 7.0

The main purpose of this amendment is to include an opportunity for participants who completed their treatment under the current protocol to transition into the long-term follow-up study under a new protocol allowing continued access to study treatment. Additionally, the prohibited medicines section was revised to include an additional concomitant therapeutic option, as well as other prohibited medications. A high-level description of each change is summarized below, along with its rationale

Major Scientific Changes for Global Amendment 6, Protocol Version 7.0

Section # and Name	Description of Change	Brief Rationale
Section 1 Synopsis (Planned trial and treatment duration per participant and Table 3; Statistical methods; Methodology)	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. Added clarification that treatment completers who enter the long-term follow-up study are also considered study completers. Clarification was added in Statistical methods that these participants will be included in the final analysis as study completers. Table 3 (open-label extension [OLE] period Week 108 to 336 schedule of assessments) was updated accordingly. Clarification was added in Methodology that study treatments are administered in fasted conditions.	For consistency with the main protocol text.
Section 1 Synopsis (Endpoints for OLE Period)	The endpoint for OLE period “24-week confirmed disability-free status” was changed to “Change from baseline in disability score based on Expanded Disability Status Scale (EDSS) score” to correct previously inaccurately defined endpoint. The EDSS is collected on a yearly basis and therefore, confirmed disability free status based on 24 weeks confirmed disability progression is not feasible.	For consistency with the main protocol text.
Section 5.1 Overall Trial Design and Plan	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. Added clarification that treatment completers who enter the long-term follow-up study under a new protocol are also considered study completers. Please also see the Section 7.1.7 in this table. Clarification that these participants will be included in the final analysis as study completers was added in Figure 2 and 3 presenting Trial Design – Optional OLE Period.	A new study will allow participants who completed their treatment under the current protocol to enroll in the new, single-arm long-term follow-up study. The text of the protocol has been amended to describe a transition opportunity to this long-term follow-up study and continued access to the treatment.
Section 5.6.2 Withdrawal from the Trial	Added clarification that the Investigator should permanently discontinue study treatment upon confirmation of noncompliance regarding study treatment or extended interruption of the study treatment for more than 30 days.	To add supportive guidance for consistency and accuracy.
Section 5.8 Definition of End of Trial	Added clarification that treatment completers who enter the long-term follow-up study under a new protocol are also considered study completers.	For consistency with the change in study design.

Section # and Name	Description of Change	Brief Rationale
Section 6.4.2 Prohibited Medicines	Prohibited medications were revised and recommendation to avoid medications known to lower seizure threshold was added. The clarification was added regarding initiation or dose changes of dalfampridine (Ampyra) or fampridine therapy during OLE Period.	To allow participants to have additional therapeutic options during OLE Period only if they have been receiving a stable dose of evobrutinib for at least 3 months prior to initiation or dose change.
Section 6.4.4.1 Special Precautions (For M2951 Only)	Previous inconsistencies between wording and the Table 7 were corrected. Abnormal laboratory ranges values requiring withdrawn of treatment were specified in the section in addition to the previously stated severity grading; Table 7 was updated to further clarify required actions to the investigator in case of abnormal laboratory tests. Added further guidance on discontinuation of study treatment and confirmatory investigations due to abnormal liver function tests. Liver function testing criteria, confirmatory laboratory investigations, and conditions for treatment rechallenge were further specified.	To provide the Investigator with detailed guidance for withdrawn of study treatment and confirmatory laboratory investigations in case of abnormal laboratory tests.
Section 7.1.7 Open-label Extension End of Treatment Visit	Added clarification that treatment completers who enter the long-term follow-up study under a new protocol do not require a 4-week Safety Follow-up Visit to complete the study.	To allow participants who completed their treatment under the current protocol to enroll in the new long-term follow-up study without 4 weeks of treatment gap during 4-week Safety Follow-up Period.
Section 7.1.8 4-week Safety Follow-up/End of Trial Visit	Added clarification that treatment completers who enter the long-term follow-up study under a new protocol do not require a 4-week Safety Follow-up Visit to complete the study.	To allow participants who completed their treatment under the current protocol to enroll in the new long-term follow-up study without 4 weeks of treatment gap during 4-week Safety Follow-up Period.
Section 7.4.1.3 Definition of the Adverse Event Reporting Period	Added clarification that adverse event reporting period is until Week 336/OLE End of Treatment Visit for participants transitioning into the long-term follow-up study under a new protocol.	For consistency with the change in study design.

Section # and Name	Description of Change	Brief Rationale
Section 7.4.1.6 Monitoring of Participants with Adverse Events	Added clarification that adverse events are assessed for final outcome at Week 336/OLE End of Treatment Visit for participants transitioning into the long-term follow-up study under a new protocol. Added clarification that all serious adverse events ongoing at Week 336/OLE End of Treatment Visit for participants transitioning into the long-term follow-up study under a new protocol will be monitored until stabilization or until the outcome is known, unless participant is lost to follow-up.	For consistency with the change in study design.
CCI [redacted]	[redacted]	[redacted]
Section 8.3.4 Endpoints for Open-label Extension Period	The endpoint for OLE period "24-week confirmed disability-free status" was changed to "Change from baseline in disability score based on EDSS score".	To correct previously inaccurately defined endpoint. The EDSS is collected on a yearly basis and therefore, confirmed disability free status based on 24 weeks confirmed disability progression is not feasible.
Section 8.6 Interim and Additional Planned Analyses	Added clarification that treatment completers who enter the long-term follow-up study under a new protocol are also considered study completers. Clarification was added that these participants will be included in the final analysis as study completers. Text was updated to clarify the updated definition of participants who complete the OLE.	For consistency with the change in study design.
Throughout the document	Changes made to align with updated protocol template. Minor editorial and document formatting revisions.	Minor; therefore, have not been summarized.
Appendix I	Protocol Lead was updated. Information regarding Sponsor Responsible Persons not Named on the Cover Page was deleted.	Update was due to the personnel change, whereas deletion was the alignment with current practices and procedures.

Amendment # 5

Rationale

The protocol was amended to extend the optional open-label extension period of the study by 5 years (60 months), to allow patients continued access to study treatment and long-term characterization of the study drug in patients with relapsing multiple sclerosis. The Sponsor evaluated the duration of the extension on an annual basis.

Major Scientific Changes

Section # and Name	Description of Change	Brief Rationale
Throughout protocol	The open-label extension period has been extended from 2 years to 7 years.	To allow patients continued access to study treatment and long-term characterization of the study drug in patients with relapsing multiple sclerosis.
Section 1 Synopsis; Table 2	Table 2 (open-label extension period schedule of assessments) was updated.	For consistency with the extension of the open-label extension period.
Section 1 Synopsis, Section 8.3.4 Endpoints for Open-label Extension Period	The timing of endpoint assessments in the open-label extension has been modified to include timepoints beyond Week 96.	To reflect the extended duration of the open-label extension period.
Section 1 Synopsis, Section 8.3.4 Endpoints for Open-label Extension Period	The open-label extension period endpoint “change from Baseline in EDSS” has been updated to 24-week confirmed disability-free status.	For consistency with guidelines on clinical trials in multiple sclerosis.
Section 1 Synopsis, Section 5.1 Overall Trial Design, Section 8.6 Interim and Additional Planned Analyses	Addition of 2 interim analyses in the open-label extension period.	To support open-label extension period safety data publication at an upcoming conference, and to support anticipated Phase III submission.
Section 1 Synopsis, Section 8.5.3 Analysis of Secondary Endpoints	The analysis of other endpoints assessing efficacy from Baseline to 24 weeks was changed from an analysis of covariance to a mixed-effect model for repeated measures (MMRM).	For consistency with changes already described in the Integrated Analysis Plan.
CCI		
Section 6.4.2 Prohibited Medicines	Details were added regarding administration of prohibited medicines during the possible treatment gap in the open-label extension period.	To allow participants to receive specific treatments during the possible treatment gap.
Appendix II Total Blood Volume	The blood volume table for the open-label extension period was updated.	To reflect the longer duration of the open-label extension period.

Amendment # 4

Rationale

The protocol was amended to update the stopping rules for participants with increased liver enzymes following an urgent safety measure. The protocol amendment included the change in dose for the OLE based on the efficacy and safety data from the primary analysis at 24 weeks and the blinded extension analysis at 48 weeks. As the 75 mg twice daily dose was most efficacious during the blinded portion of the study, with an acceptable safety profile, the dose in the OLE was changed to 75 mg twice daily.

Major Scientific Changes

Section # and Name	Description of Change	Brief Rationale
Synopsis – Open-label Long Term Extension Period objective	Change in dose of Open-label Long Term Extension (OLE) Period dose from 75 mg once daily to 75 mg twice daily.	Based on the efficacy and safety data from the primary analysis at 24 weeks and the blinded extension analysis at 48 weeks, the optimal tested dose is 75 mg twice daily.
Synopsis – Methodology 4.4 Open-label Extension Period Objective 5.1 Overall Trial Design and Plan 5.1 Overall Trial Design and Plan Figure 2 Trial Design – Optional OLE Period (for Participants Entering from M2951 Treatment Arm) 5.1 Overall Trial Design and Plan Figure 3 Trial Design – Optional OLE Period (for Participants Entering from Tecfidera Treatment Arm 5.2.2 Justification of Dose 5.5 Criteria for Entry into OLE Period 6.2 Dosage and Administration 6.3 Assignment to Treatment Groups	Change in dose of Open-label Long Term Extension (OLE) Period dose from 75 mg once daily to 75 mg twice daily. Change in the dose for OLE period to 75 mg twice daily. Participants participating in the OLE Period will either enter the OLE Period on the 75 mg twice daily dose, or will be switched to the 75 mg twice daily dose	Based on the efficacy and safety data from the primary analysis at 24 weeks and the blinded extension analysis at 48 weeks, the optimal tested dose is 75 mg twice daily.
Table 2 Schedule of Assessments – Optional OLE Period	Revisions were made to clarify additional supplemental safety visits added for participants switching from Tecfidera. CCI concomitant medications, AEs, and relapse assessments were added for additional visits.	Increased liver monitoring was added following an urgent safety measure.
6.4.4.1 For M2951	Text was added to direct sites to consult with Medical Monitor if participants OLE predose or OLE baseline value is abnormal and/or below criteria	Provide direction to sites to consult with Medical Monitor regarding potential withdrawal, continued participation in study, additional monitoring, and retesting
6.4.4.1 For M2951 Only	The stopping criteria was adjusted for AST, ALT and bilirubin.	Updated liver enzyme stopping criteria to ensure the safety of the patients within the study.
Protocol History	Amendment 3 date updated.	To correct for consistency and accuracy.
7.1.3 Supplemental Safety Visits	Text was aligned to Table 2 for the additional visits for liver enzyme monitoring.	Increased liver monitoring was added following an urgent safety measure.
7.4.3	Added ESR to hematology evaluations	Correct omission
Sponsor Responsible Persons not Named on the Cover Page	Clinical trial leader was updated.	Personnel change.

Section # and Name	Description of Change	Brief Rationale
Appendix II: Total Blood Volume	Blood volume for the Open-label Extension Period was updated.	Blood volume was recalculated due to addition of assessments for the additional visits.

Amendment # 3

Rationale

The protocol was revised to include recommendations from the Czech Republic Regulatory Authority on reinitiating IMP following increase in AST, ALT, or bilirubin to Grade 2.

Major Scientific Changes

The key reasons for Amendment 3 was to include recommendations from the Czech Republic Regulatory Authority on reinitiating IMP following increase in AST, ALT, or bilirubin to Grade 2.

Section # and Name	Description of Change	Brief Rationale
6.4.4.1 For M2951 Only	Amended instructions for reinitiating IMP following increase in AST, ALT, or bilirubin to Grade 2.	To include the recommendations from the Czech Republic Regulatory Authority

Amendment # 2

Rationale

The protocol was revised to include the recommendations from the Czech Republic Regulatory Authority to provide clarification to guidelines on withholding or permanent withdrawal of IMP, remove interim/futility analyses since primary analyses could be reached earlier due to fast recruitment, update the visit schedule according to the Modification of Visit Schedule for Monitoring of Liver Function Tests based on IDMC recommendations (16 April 2018), clarify that monthly urine pregnancy testing would occur at all sites in all countries, as well as other administrative changes.

Major Scientific Changes

Changes to the protocol were made to include the recommendations from the Czech Republic Regulatory Authority, include clarification on urine pregnancy testing for all sites, modify the supplemental safety visit schedule in the Schedules of Assessment based on the visit schedule memo issued to sites (16 April 2018), include a table on withholding and permanent withdrawal of IMP.

The key reasons for Global Amendment 2, Protocol Version 3.0, are summarized below:

CCI [redacted]

- Remove Futility analyses (also referred to as interim analyses) ;

- Remove 2-week additional safety visits after Week 16 and update to a monthly (4-week) schedule;
- Clarify that phone calls for confirmation of home pregnancy testing is required only if urine pregnancy tests are completed at home;
- Include monthly urine pregnancy tests for all sites in all countries during the main study and OLE period;

CCI

- Update Section 5.6.1 to reference to Section 6.4.4 and add a table (in Section 6.4.4.1) with guidelines on withholding and withdrawal of IMP;
- Add sub bullets to Section 6.4.4.1 and 6.4.4.2 for increased clarity on management of laboratory evaluation abnormalities;
- Update Section 6.4.4.2 to match SmPC for Tecfidera;
- Include a new Table 6 to provide guidelines for withholding and modification of IMP;
- Update Table 7 (previously Table 6) to include a superscript to the footnote on urine microscopy.

Amendment # 1

Rationale

For Poland only, a local amendment (Version 1.1) was created to provide additional at-home pregnancy testing at the request of the Polish Health Authority. The protocol was further revised to include the changes from the local Poland amendment, recommendations from the IDMC meeting on 05 October 2017, and to add an optional Long Term Open-label Extension Period.

Major Scientific Changes

The key reasons for Global Amendment 1, Protocol Version 2.0, are summarized below:

- Addition of 2-week safety visits for chemistry monitoring (including ALT, AST, alkaline phosphatase, GGT, and bilirubin) until the IDMC determines the optimum monitoring interval for participant randomized to the M2951/placebo arm;
- Addition of a comprehensive hepatic panel for participants randomized to the M2951/placebo arm for whom withdrawal criteria are met or who permanently discontinue dosing because of elevated transaminases;
- Addition of blood tests (ESR, hsCRP, and fibrinogen) for all participants at any 1 point during the trial;

- Addition of Open-label extension period, with modifications to planned trial period, addition of objective and endpoints, addition of statistical analyses and analysis set, addition of informed consent prior to participation, and clarification that there will be a second clinical trial report;

- Addition of CCI endpoints and statistical analyses;

CCI

- Clarification that separate informed consent will be collected for the MRI dummy run;

CCI

- Clarification that blood pressure will be collected in a semisupine position;