Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Montalban X, Arnold DL, Weber MS, et al. Placebo-controlled trial of an oral BTK inhibitor in multiple sclerosis. N Engl J Med 2019;380:2406-17. DOI: 10.1056/NEJMoa1901981

This supplement contains the following materials:

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 [redacted]
EudraCT Number	2016-001448-21
Coordinating Investigator	PPD [redacted]
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 [redacted] Telephone: PPD [redacted]
Clinical Trial Protocol Version	31 May 2016/ Version 1.0
Replaces Version	Not applicable

- Confidential –

Protocol Table of Contents

Table of In-Text Tables

Table of In-Text Figures

List of Abbreviations

AE	Adverse Event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ARR	Annualized relapse rate
AST	Aspartate aminotransferase
BID	Twice daily
BTK	Bruton's Tyrosine Kinase
CI	Confidence Interval
C-SSRS	Columbia Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for AEs
CTR	Clinical trial report
CCI [redacted]	[redacted]
CXR	Chest X-ray
DMD	Disease-modifying drugs
EAE	Experimental autoimmune encephalomyelitis
ECG	Electrocardiogram
EDSS	Expanded Disability Status Scale
eCRF	Electronic Case Report Form
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
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus

HRQoL	Health-related quality of life
IA	Interim analysis
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
LTBI	Latent Tuberculosis Infection
MCS	Mental component summary
mITT	Modified ITT
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
NB	Negative binomial
CCI	[redacted]
PCS	Physical component summary
CCI	[redacted]
[redacted]	[redacted]
PML	Progressive multifocal leukoencephalopathy
QD	Once daily
RA	Rheumatoid arthritis
RMS	Relapsing multiple sclerosis
RoW	Rest of the world
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard deviation
SF-36v2	Short Form 36-item Health Status Survey version 2.0

SLE	Systemic lupus erythematosus
SPMS	Secondary progressive multiple sclerosis
TB	Tuberculosis
TLR	Toll-like receptor
ULN	Upper Limit of Normal

1 Synopsis

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.
Trial Phase	II
IND Number	129428
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 100 sites globally in Europe, USA, and in the rest of the world (RoW).
Planned trial period (first subject in-last subject out)	First subject in: Q3, 2016 Last subject out: Q4, 2018
Trial Registry	ClinicalTrials.gov, EudraCT

Objectives:

Primary Objective

The primary objective is to evaluate the efficacy and dose-response of 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 Weeks 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 Weeks 24 to 48
- To evaluate the safety of Tecfidera

Exploratory Objectives

The exploratory objectives are as follows:

[redacted]

- To explore the benefit of M2951 treatment on patient-reported health related quality of life (HRQoL) versus placebo, and to evaluate the effect of Tecfidera on HRQoL

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

The study will consist of 3 major periods; a Screening period of 4 weeks, active treatment with 3 dose groups of M2951, active control (Tecfidera), or placebo for 24 weeks, and a 24-week extension on active treatment with M2951 or active control (Tecfidera) for 24 weeks, where subjects on placebo will be switched to M2951. Following completion or early termination of treatment, subjects will return after 4 weeks for safety evaluation. A separate open-label extension protocol will be developed allowing continued dosing, provided that safety and tolerability are acceptable.

An interim analysis (IA) for futility may be conducted during the placebo-controlled portion of the treatment period when the first 50% of subjects enrolled out of the planned enrollment have reached the end of 24 weeks of treatment. If conducted, this analysis will evaluate overall futility for the highest dose of M2951 to determine whether or not to continue with the study.

It is planned that placebo subjects will be switched to the 25 mg M2951 once daily (QD) dose after Week 24; however, consideration will be given to changing this dose based on data from the IA. The Sponsor may decide not to perform the IA if the IA trigger date is sufficiently close (ie, within approximately 4 months) of the primary analysis trigger date.

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

An independent data monitoring committee (IDMC) will be responsible for both safety monitoring and futility analyses. The IDMC will consist of at least the following core members: 2 clinicians and 1 biostatistician.

Planned number of subjects: Approximately 50 subjects will be enrolled in each treatment group, for a total of approximately 250 enrolled subjects.

Primary endpoint: Total number of gadolinium-enhancing T1 lesions at Weeks 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
- Proportion of subjects who remain qualified relapse-free at Week 24
- Change from Baseline in Expanded Disability Status Scale (EDSS) at Week 24
- Safety as assessed by the nature, severity, and incidence 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 Weeks 12, 16, 20, and 24
- Mean per-scan number of Gd+ T1 lesions at Weeks 12, 16, 20, and 24
- Total number of new or enlarging T2 lesions at Weeks 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:

- Total number of Gd+ T1 lesions at Week 48
- Total number of new Gd+ T1 lesions at Week 48
- Annualized relapse rate, based on protocol-defined qualified relapses, at Week 48
- Proportion of subjects who remain qualified relapse-free at Week 48
- Change from Baseline in EDSS at Week 48
- Total 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 Weeks 12, 16, 20, and 24
- Annualized relapse rate, based on protocol-defined qualified relapses at Week 24
- Proportion of subjects who remain qualified relapse-free at Week 24
- Change from Baseline EDSS at Week 24
- Safety as assessed by the nature, severity, and incidence 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 Weeks 12, 16, 20, 24
- Mean per-scan number of Gd+ T1 lesions at Weeks 12, 16, 20, and 24
- Total number of new or enlarging T2 lesions at Weeks 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
- Total number of Gd+ T1 lesions at Week 48
- Total number of new Gd+ T1 lesions at Week 48
- Annualized relapse rate, based on protocol-defined qualified relapses, at Week 48
- Proportion of subjects who remain qualified relapse-free at Week 48
- Change from Baseline in EDSS at Week 48
- Total 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

Exploratory endpoints:

Exploratory endpoints are as follows:

[redacted]

- Change in HRQoL as measured with SF-36v2 (physical component summary [PCS]/mental component summary [MCS] and sub-domains) over time (area under the curve) in all subjects
- Change in HRQoL as measured with SF-36v2 (PCS/MCS and sub-domains) from Baseline to Week 24 and from Baseline to Week 48 in all subjects

[redacted]

Pharmacodynamics:

[redacted]

Diagnosis and key inclusion and exclusion criteria: Male or female subjects aged 18-65 years with relapsing MS or secondary progressive MS (SPMS) with superimposed relapses. Subjects 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 subject should also have an EDSS score of 0 to 6.

Subjects will be excluded if they are diagnosed with primary progressive MS or SPMS without evidence of relapse. Subjects who have a disease duration > 15 years and an EDSS ≤ 2. Subjects will be excluded if they have received treatment with: ritixumab, ocrelizumab, mitoxantrone, or lymphocyte-depleting therapies (eg, alemtuzumab, cladribine, cyclophosphamide, total body irradiation, bone marrow transplantation) within 48 weeks prior to randomization; lymphocyte trafficking blockers within 24 weeks prior to randomization (eg, natalziumb, 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 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. Subjects 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 (eg, 3 x 25 mg tablets for a 75 mg dose). Dosing will be either 25 mg QD, 75 mg QD, or 75 mg twice daily (BID). Matched placebo tablets will be provided.

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 BID. Following this and for the duration of treatment, Tecfidera is administered orally at 240 mg BID 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 subject: Total duration of subject participation is approximately 392 days (56 weeks), which includes:

- Screening: 28 days (4 weeks)
- Treatment: 168 days (24 weeks)
- Blinded treatment extension: 168 days (24 weeks)
- 4-week Safety Follow-Up/End of Trial Visit: 28 days (4 weeks).

Statistical methods:

A per-group sample size of 44 evaluable subjects provides 85% power to detect a decrease of 90% in the total number of gadolinium-enhancing T1 lesions, summed over scans at Weeks 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 subjects will be randomized 1:1:1:1:1 to treatment with placebo, low-dose M2951 (25 mg QD), mid-dose M2951 (75 mg QD), high-dose M2951 (75 mg BID), or Tecfidera (administered BID at a final dose of 240 mg), through a central randomization process by an Interactive Web Response System (IWRS), stratified according to region (US or Western Europe, Eastern Europe and CCI , Eastern Europe and CCI , Rest of World). Approximately 50 subjects will be randomized per group to protect against a loss of information due to a 12% drop-out rate over one year.

There will be 3 analyses: (1) an IA, triggered when the first 50% of subjects enrolled out of the planned enrollment reach Week 24 of treatment, or prematurely discontinue from treatment, and (2) a primary analysis, triggered when 100% of subjects enrolled reach Week 24 of treatment, or prematurely discontinue from treatment, and (3) a final analysis, triggered when 100% of subjects enrolled complete all study parts, or discontinue prematurely from study. The Sponsor may decide not to perform the IA if the IA trigger date is sufficiently close (ie, within approximately 4 months) of the primary analysis trigger date.

If performed, the IA for futility will be conducted during the placebo-controlled portion of the treatment period when the first 50% of subjects enrolled out of the planned enrollment have reached the end of 24 weeks of treatment. The IA will test for futility, not efficacy, so will not affect the 0.05 Type I error rate available at the primary analysis. 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, Weeks 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. Other covariates, such as baseline MRI activity, may be included in the model. 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 Wilcoxon rank sum test, comparing each M2951 dose group to placebo. Descriptive statistics for the total number of Gd+ T1 lesions, Weeks 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 a Poisson 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. The comparison of a M2951 treatment group to placebo group using proportion qualified relapse-free at Week 24 will be based on a logistic model for the odds of a subject being qualified relapse-free, where subjects 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. The comparison of a M2951 treatment group to placebo group using change from Baseline in EDSS at Week 24 will be based on a rank analysis of covariance (ANCOVA) model, with M2951 dose group or placebo group as a factor, and adjustment for Baseline, and covariates based on randomization strata. The analysis of mean per-scan number of Gd+ T1 lesions, at Weeks 12, 16, 20, and 24, 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 an ANCOVA model of the appropriately transformed variable. 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 Weeks 12, 16, 20, and 24, will be based on a NB model, similar to that used for the primary analysis. In the analysis of each secondary endpoint, other covariates, such as baseline MRI activity, 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 total number of Gd+ T1 lesions, total number of new Gd+ T1 lesions, total number of new and enlarging T2 lesions, the change from Baseline in Gd+ T1 lesion volume, and change from Baseline in T2 lesion volume, will be summarized by timepoint (Baseline and Weeks 12, 16, 20, 24, and 48) and treatment group (placebo, 3 M2951 dose groups, and Tecfidera).

Annualized relapse rate from Baseline to Week 24 and from Baseline to Week 48 will be summarized by treatment group. The proportion of subjects remaining qualifying relapse-free at Week 24 and at Week 48 will be summarized by treatment group. The change from Baseline in EDSS will be summarized by treatment group and timepoint (Weeks 4, 8, 12, 16, 20, 24, 36, 48, and the 4-week Safety Follow-up/End of Trial Visit).

Safety

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

Patient-reported Health Related Quality of Life (HRQoL)

HRQoL data for all treatment groups and timepoints will be summarized using descriptive statistics. Change in HRQoL for PCS/MCS and sub-domains over time (area under the curve) will be compared between M2951 treatment arms and placebo.

CCI [redacted]

[redacted]

[redacted]

Table 1 Schedule of Assessments

Activity/Assessment	Screening[a]	On Treatment Visits								Unscheduled Visit for Neurological Worsening and Relapse Assessment[b]	End of Treatment	4-week Safety Follow-up/ End of Trial Visit
Visit number	1	2	3	4	5	6	7	8	9		10	11
Study Week		D1	W4	W8	W12	W16	W20	W24	W36		W48	W52
Study Day ± Visit Window[c]	-28 to -1	1	28±3	56±3	84±3	112±3	140±3	168±3	252±3		336±3	364±5
Obtain ICF[d]	X											
Inclusion / Exclusion criteria	X	X										
Medical history[e] / demographics	X											
MS history	X											
Physical examination[e]	X				X			X		X		
Vital signs[f]	X	X	X	X	X	X	X	X	X	X	X	X
Neurological examination[g]	X	X	X	X	X	X	X	X	X	X	X	X
Quantiferon tuberculosis test, viral serology testing[h]	X											
Randomization[i]		X										
Hematology, chemistry[j]	X		X	X	X	X	X	X	X	X	X	X
Immunoglobulin levels[k]		X	X			X		X			X	
Urinalysis (microscopy, urine protein/creatinine ratio)[l]	X				X			X		X	X	X
Coagulation (INR, PTT)[m]	X											
B, CCI cell count[n]		X	X					X			X	X
Serum pregnancy test[o]	X											
Urine pregnancy test[o]		X	X	X	X	X	X	X	X		X	X
12-lead ECG[p]	X							X		X	X	
Chest X-ray[p]	X											

Activity/Assessment	Screening[a]	On Treatment Visits								Unscheduled Visit for Neurological Worsening and Relapse Assessment[b]	End of Treatment	4-week Safety Follow-up/ End of Trial Visit
Visit number	1	2	3	4	5	6	7	8	9		10	11
Study Week		D1	W4	W8	W12	W16	W20	W24	W36		W48	W52
Study Day ± Visit Window[c]	-28 to -1	1	28±3	56±3	84±3	112±3	140±3	168±3	252±3		336±3	364±5
EDSS[q]	X	X	X	X	X	X	X	X	X	X	X	X
Relapse assessment[r]			X	X	X	X	X	X	X	X	X	X
MRI scan[s]	X				X	X	X	X			X	
Concomitant medications and procedures[t]	X	X	X	X	X	X	X	X	X	X	X	X
AE evaluation[u]	X	X	X	X	X	X	X	X	X	X	X	X
Dispense IMP[v]		X	X	X	X	X	X	X	X			
IMP Administration		Oral Administration										
IMP compliance[w]			X	X	X	X	X	X	X		X	
CCI [redacted]												
HRQoL[aa]	X	X	X	X	X	X	X	X	X		X	
C-SSRS[bb]	X											
CCI [redacted]												

AE=adverse event, CCI [redacted], C-SSRS=Columbia-Suicide Severity Rating Scale, CCI [redacted], ECG=electrocardiogram, eCRF=electronic case report form, EDSS=expanded disability status scale, FSH=follicle stimulating hormone, HBsAg=hepatitis B surface antigen, HBV=hepatitis B virus, HCV=hepatitis C virus, HIV=human immunodeficiency virus, HRQoL=health-related quality of life, ICF=informed consent form, Ig=immunoglobulin, IMP=investigational medicinal product, INR=international normalized ratio, MRI=magnetic resonance imaging, MS=multiple sclerosis, CCI [redacted], CCI [redacted], PTT=partial thromboplastin time, SF-36v2=Short Form 36-item Health Status Survey version 2.0.

a. Screening procedures will be performed within 28 days prior to the first administration of placebo/M2951 or Tecfidera.

b. These unscheduled visits will occur if a subject relapses and it is not feasible to wait for an upcoming scheduled study visit.

c. Trial visits will occur within the range of days noted for each week on trial. The 4-week Safety Follow-up/End of Trial Visit will take place 28 days after the End of Treatment Visit.

d. Informed consent must be obtained at the Screening visit prior to initiating any Screening procedures or collecting any data.

e. Medical history includes both disease and medication history. Records from physical examinations will be retained at each site and will not be captured in the eCRF. Abnormal findings from the physical exam conducted before informed consent is obtained should be reported as medical history.

f. Vital signs, including oral temperature, seated blood pressure, pulse rate, and respiratory rate, and weight are assessed predose at every trial visit. Height is measured as Screening only.

g. Neurological examinations will be conducted at Screening, Day 1, and all subsequent trial visits. Records from physical examinations will be retained at each site and will not captured in the eCRF.

h. Blood samples for tuberculosis (Quantiferon) testing will be obtained at Screening. Additional samples should be taken for viral serology testing at Screening: HBV core antigen, HBV antibodies, HBsAg, and HCV antibodies. HIV testing will be done at Screening only where required as per local regulations (see Table 5).

i. Randomization should occur on Day 1 after all Screening procedures have been completed; subject eligibility must be reviewed again and confirmed at the site on Day 1 prior to randomization.

j. Blood samples for hematology and chemistry (Table 5) to be obtained at Screening, predose at all Visits except Day 1.

k. Samples for total Ig levels (IgM, IgA, IgG) will be obtained at Screening and predose on Days 1, 28, 112, 168, and 336 (see Section 7.4.5). 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.

l. Urine samples for urinalysis will be obtained at Screening, predose on Days, 84, 168, 336, and Day 364. 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.

m. Coagulation tests (INR and PTT) will be obtained at Screening only.

n. Blood samples for B, CCI cell numbers and B, CCI cell subclasses will be obtained predose on Days 1, 28, 168, and 336. 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).

o. Serum pregnancy test collected at Screening, and urine tests collected predose at every trial visit, women of childbearing potential only. If necessary to confirm postmenopausal status, FSH testing will be done at Screening in postmenopausal women.

p. ECG and posteroanterior chest X-ray performed at Screening. Subjects who have previously had a chest x-ray for clinical reasons within 3 months prior to Day 1 do not need to have the chest X-ray 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 Days 168 and 336.

q. EDSS will be assessed at Screening, Day 1, and all subsequent trial visits.

r. Relapse assessments will be conducted at Day 28 and all subsequent trial visits.

s. MRIs will be conducted at Screening and at Days 84, 112, 140, 168, and 336.

t. Concomitant medications and procedures will be recorded at Screening and Day 1, and any changes elicited/recorded at every trial visit.

u. Any AEs occurring during the Screening period will be recorded, and AEs will be elicited/recorded at every trial visit.

v. The IMP will be dispensed after randomization on Day 1 and at each visit thereafter. All remaining IMP will be collected on Day 336.

w. On trial visit days, the previous week's IMP adherence will be documented using pill counts.

x. [redacted]

CCI [redacted]

aa. HRQoL will be assessed with the SF-36v2 questionnaire at Screening, Day 1, and all subsequent trial visits except the 4-week Safety Follow-up/End of Trial Visit. Questionnaire to be completed before any other procedure takes place.

bb. The C-SSRS should be administered as part of the inclusion/exclusion criteria at Screening (see Section 5.3.2).

CCI [redacted]

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 100 sites in Western and Eastern Europe, in USA, and rest of the world (RoW).

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 contract research organization (CRO), to conduct the clinical part of the trial including trial set-up, operation of an Interactive Web Response System (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 independent data monitoring committee (IDMC) will be responsible for both safety monitoring and the futility analysis. 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.

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.

Investigational medicinal product (IMP) will be supplied by the Clinical Trial Supply Department at Merck, except Tecfidera for the US. In the US 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

Multiple sclerosis (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 relapsing MS (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 disease-modifying drugs (DMDs) with varying levels of efficacy, and distinct safety and tolerability profiles. Most active RMS patients initiate treatment with an interferon-beta or glatiramer acetate (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 (ie, progressive multifocal leukoencephalopathy [PML]) to autoimmunity and cancer. Switching among these DMDs occurs primarily due to perceived lack of efficacy or the occurrence of adverse events (AEs), as well as individual patient preferences.

Despite the recent approvals of newer therapies for the treatment of MS, there remains an unmet need for highly effective and well-tolerated therapies for patients with RMS at all stages of the disease. Early treatment with a highly efficacious, but safe 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 safe solution for the treatment of MS patients with high disease activity would be an attractive treatment choice for patients switching therapy. Using the US 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 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 Bruton's Tyrosine kinase (BTK) in development for the treatment of autoimmune and inflammatory diseases, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and MS. BTK mediates signaling through the B cell receptor and has been described downstream of several other receptors, including Fc receptor, Toll Like (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 rheumatoid arthritis (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 anti-CD20 therapies in Phase II and Phase III clinical trials in RMS and progressive MS (2-5). Ocrelizumab inhibited the formation of new inflammatory magnetic resonance imaging (MRI) lesions up to 90% (Hauser, 2008) in Phase II RMS trials and high efficacy on MRI (-94%), annualized relapse rate (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 anti-CD20 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 anti-CD20 in B cell antigen presentation, a recent publication of Li et al (7) describes a diminished proinflammatory myeloid cell response in Ocrelizumab-treated MS subjects. M2951 shows inhibition of myeloid cell activation by immune complexes.

Anti-CD20 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, experimental autoimmune encephalomyelitis (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 anti-CD20 therapies, should the need to interrupt or stop therapy arise. This suggests a more favorable benefit to risk profile for M2951 vs. anti-CD20 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 anti-CD20 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 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 non-depleting B cell therapies may deliver a more favorable benefit risk profile than current B cell-directed therapeutic approaches.

CCI [redacted]

CCI [redacted]

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

3.2 Benefit-Risk

M2951 is being considered for the treatment of autoimmune diseases, including RA and SLE as well as MS. To date, no efficacy data are available. However, M2951 is the first agent with a mechanism of action that directly targets both B cells and myeloid cells, and it is reasonable to anticipate that M2951 may represent a significant advance in the treatment of MS and other autoimmune diseases.

No identified risks or new potential risks emerged from the FIM trial, Trial EMR200527-001. M2951 was well tolerated at single doses up to 500 mg and at multiple doses up to 200 mg for 14 days.

Important potential risks to subjects are based on nonclinical safety data of M2951 and clinical data on adverse drug effects associated with compounds of a similar pharmacological class. They include infection, leukopenia, thrombocytopenia, hemorrhage, gastrointestinal (GI) intolerance, renal toxicity, hepatocellular injury, atrial fibrillation, drug-drug interactions, and embryofetal toxicity.

Risk minimization measures inherent to early phase clinical trials are considered adequate for the proposed clinical trial in patients with MS. An IDMC will be set up to continually review available safety and tolerability data and will be mandated to make immediate decisions regarding the conduct of the trial; no additional risk minimization measures are proposed.

The doses of M2951 (up to 75 mg BID) selected for the proposed trial are within the dose ranges studied in Trial EMR200527-001 and were associated with high levels of target occupancy in healthy volunteers.

This clinical trial will be conducted in compliance with the clinical trial protocol, ICH GCP, and any additional applicable regulatory requirements.

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 Objectives

The primary objective is to evaluate the efficacy and dose-response of M2951 on the number of gadolinium-positive (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 Weeks 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 Weeks 24 to 48
- To evaluate the safety of Tecfidera

4.3 Exploratory Objectives

The exploratory objectives are as follows:

CCI [redacted]

- To explore the benefit of M2951 treatment on patient-reported health-related quality of life (HRQoL) versus placebo, and to evaluate the effect of Tecfidera on HRQoL

5 Investigational Plan

5.1 Overall Trial Design and Plan

This will be a randomized, double-blind, placebo-controlled study in subjects with relapsing multiple sclerosis, 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 radiologist will be treatment blinded.

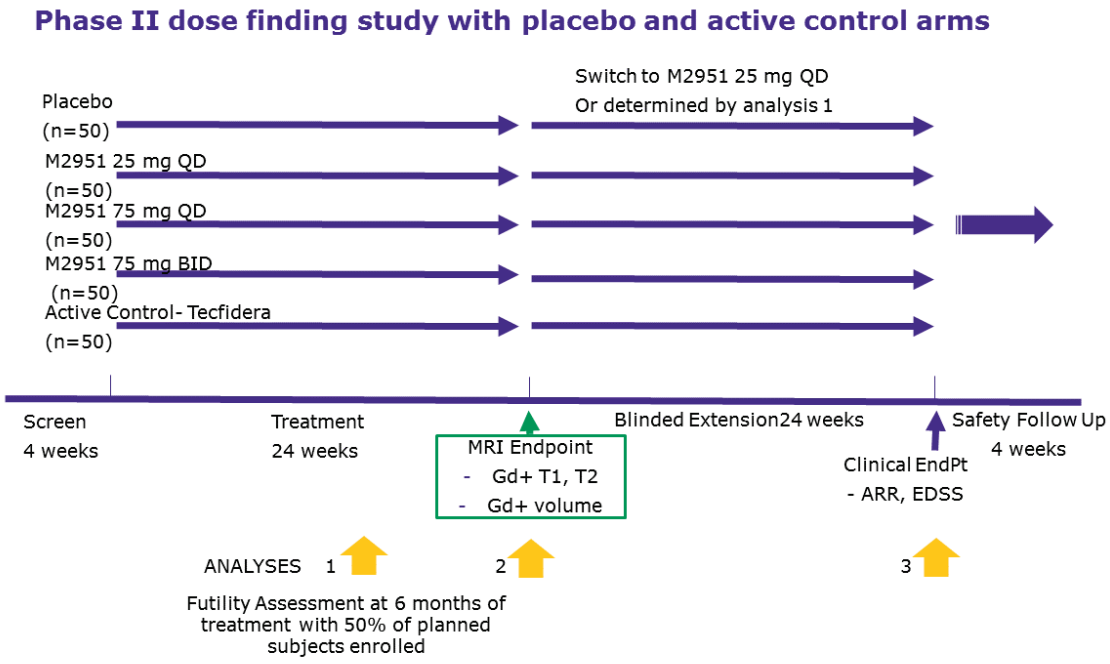
The study will consist of 3 major periods; a Screening period of 4 weeks, active treatment with 3 dose groups of M2951, active control (Tecfidera), or placebo for 24 weeks, and a 24 week

extension on M2951 or active control (Tecfidera) for 24 weeks, where subjects on placebo will be switched to M2951. Following completion or early termination of treatment, subjects will return after 4 weeks for safety evaluation. A separate open-label extension protocol will be developed allowing continued dosing, provided that safety and tolerability are acceptable.

An interim analysis (IA) for futility may be conducted during the placebo-controlled portion of the treatment period when the first 50% of subjects enrolled out of the planned enrollment have reached the end of 24 weeks of treatment. If conducted, this analysis will evaluate overall futility for the highest dose of M2951 to determine whether or not to continue with the study. It is planned that placebo subjects will be switched to the 25 mg once daily (QD) dose after Week 24; however, consideration will be given to changing this dose based on data from the IA. The Sponsor may decide not to perform this IA if the IA trigger date is sufficiently close (i.e., within approximately 4 months) of the primary analysis trigger date.

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

Figure 1 Trial Design



ARR=annualized relapse rate; EDSS=expanded disability status scale; Gd+=gadolinium-positive; MRI=magnetic resonance imaging.

A detailed schedule of study procedures is provided in Table 1.

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 subjects exposed to placebo (up to 50) and short duration (24 weeks) is acceptable. Furthermore, all placebo subjects will be switched to M2951 during the blinded treatment extension phase. A futility analysis may be carried out when 50% of the subjects planned to be enrolled have completed 24 weeks of treatment to aid in making a go-no-go decision.

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 Weeks 24 to 48, will be continued in a blinded fashion.

5.2.2 Justification for Dose

CCI [redacted]

[redacted]

M2951, at a dose of 75 mg QD, is being 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]

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 QD, 75 mg QD, 75 mg BID) 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 QD during the second part of the study from Weeks 24 to 48; however, flexibility will be maintained in deciding to use this dose or an alternative dose, based on data from the interim and/or primary analyses.

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 Weeks 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 measures. 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 Expanded Disability Status Scale (EDSS), proportion of subjects who remain qualifying relapse-free, and patient-reported outcome measures.

The SF-36v2 is one of the most widely used generic patient-reported HRQoL instruments and has been applied in a number of MS studies. The SF-36v2 is an essential part of a number of other more comprehensive MS instruments like the MSQoL-54 or the MSQLI. The SF-36v2 is a multi-purpose, short-form health survey with only 36 questions. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary (13).

5.2.4 Inclusion of Special Populations

Not applicable.

5.3 Selection of Trial Population

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

Subjects 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 subject will receive a new identification number. All other testing is required to be redone at rescreening.

5.3.1 Inclusion Criteria

1. Subjects with a diagnosis of relapsing multiple sclerosis (may include subjects with Secondary PMS [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. Expanded Disability Status Scale 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 follicle-stimulating hormone [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 (subject must be able to understand the informed consent) indicating that the subject 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 (subject reported adequate in absence of written medical record) in subjects with EDSS of 2 or less
3. Treatment with rituximab, ocrelizumab, mitoxantrone, or lymphocyte-depleting therapies (eg, alemtuzumab, anti-CD4, 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 (eg, natalizumab, fingolimod) within 24 weeks prior to randomization
5. Use of intravenous (IV) immunoglobulins (Ig), 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. Exposure to Tecfidera within 6 months prior to randomization
10. Any allergy, contraindication, or inability to tolerate Tecfidera
11. Treatment with dalfampridine (fampridine, Ampyra) unless on a stable dose for ≥ 30 days prior to randomization
12. 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
13. 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
14. Vaccination with live or live-attenuated virus vaccine within 1 month prior to Screening
15. Severe drug allergy or history of anaphylaxis, or allergy to the IMP or any of its incipients
16. 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 (ie, 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.
17. History of or positive testing for human immunodeficiency virus (HIV), hepatitis C (HCV) antibody and/or polymerase chain reaction, hepatitis B surface antigen (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.
18. The subject:

    - Has a history of or current diagnosis of active tuberculosis (TB)

    or

    - Is currently undergoing treatment for latent TB infection (LTBI)

    or

    - Has an untreated LTBI as determined by documented results within 3 months of the Screening visit of a positive TB skin test with purified protein derivative with induration ≥ 5 mm

    or

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

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

19. Indeterminate **QuantiFERON®**-TB tests may be repeated once, and will be considered positive if retest results are positive or indeterminate.
20. Subjects with current household contacts with active TB will also be excluded
21. History of splenectomy at any time, or any major surgery within 2 months prior to Screening
22. 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
23. A history of attempted suicide within 6 months prior to Screening or a positive response to items 4 or 5 of Columbia-Suicide Severity Rating Scale (C-SSRS)
24. An episode of major depression within the last 6 months prior to Screening (clinically stable minor depression is not exclusionary)
25. On anticoagulation, fish oil supplements, or antiplatelet therapy other than daily aspirin for cardioprotection and treatment of Tecfidera induced flushing
26. 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
27. Breastfeeding/lactating or pregnant women
28. Participation in any investigational drug trial within 1 month or 5 half-lives of the investigational drug, whichever is longest, prior to Screening
29. Subjects 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 cytochrome P450 3A (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).
30. 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
31. Clinically significant abnormality on electrocardiogram (ECG), or an active infective process or any other clinically significant abnormality on Screening chest X-ray (CXR) taken within 4 weeks of the first dose, per Investigator opinion. If a CXR has been taken within the previous 3 months and results are available and normal, the CXR does not need to be carried out

32. Estimated glomerular filtration rate (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 (eg, acute renal insufficiency)
33. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), amylase, or lipase > 2X above upper limit of normal (ULN) of laboratory reference range, total bilirubin > 1.5X ULN, any other clinically significant laboratory abnormality
34. B cell (CD19) count < 50% of the lower limit of normal at Screening
35. 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

5.4 Criteria for Randomization and Initiation of Trial Treatment

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

Eligible subjects will be randomized to treatment with M2951 (25 mg QD, 75 mg QD, or 75 mg BID), Tecfidera, or placebo through a central randomization process by an IWRS. Stratification will occur by region (US or Western Europe, Eastern Europe and CCI [redacted], Eastern Europe and CCI [redacted], RoW).

5.5 Criteria for Subject Withdrawal

Subjects 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 electronic case report form (eCRF) and source documents, and should be followed up by the Investigator.

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

5.5.1 Withdrawal from Trial Therapy

Subjects who withdraw from therapy must immediately return for an End of Treatment Visit followed by the 4-week Safety Follow-Up/End of Trial visit 4 weeks later (see Section 7.1.4 and 7.1.5). A subject must be withdrawn if any of the following occur:

- Withdrawn from study (see Section 5.5.2)
- Adverse events, if discontinuation of IMP is desired or considered necessary by the Investigator and/or subject
- Use of prohibited medications, as defined in Section 6.4.2. However, any medications that are considered necessary for the subject's well-being may be given at the discretion of the

Investigator. Use of a prohibited medication may be cause for a subject 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
  - Disability progression, which does not apply in cases of relapse, is defined as an increase of ≥ 1.0 points from the Baseline EDSS score (see Section 7.3.2) that is not attributable to another etiology (eg, fever, concurrent illness, or concomitant medication) when the Baseline score is ≤ 5.5. When the Baseline EDSS is > 5.5, an increase of ≥ 0.5 points is considered disease progression. Disability progression is considered sustained when the increase in EDSS is confirmed at a regularly scheduled visit at least 12 or 24 weeks after the initial documentation of neurological worsening.
- Any events that unacceptably endanger the safety of the subject.
- If any of the following occur while a subject 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.

5.5.2 Withdrawal from the Trial

Subjects may withdraw from the trial at any time without giving a reason. Withdrawal of consent will be considered withdrawal from the trial. Subjects 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. Subjects 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 7.1.5.

A subject 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)
- Subject withdrew consent
- Participation in another clinical trial
- Lost to follow-up
- Any events that endanger the safety of the subject.
- Sponsor decision to end clinical trial

If a subject fails to return for the post-treatment safety visit, all attempts should be made to contact the subject to ensure the reason for not returning is not an AE. Likewise, if a subject wishes to discontinue from the trial (eg, for personal reasons), attempts should be made to establish the true reason is not an AE (bearing in mind the subject 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 subject'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 subject has failed to attend scheduled trial assessments, the Investigator must determine the reasons and the circumstances as completely and accurately as possible.

Subjects who are withdrawn after randomization (eg, due to AEs or lack of efficacy) will not be replaced. Subjects 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 will not be allowed.

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

5.6 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 IA indicates that the trial is unlikely to achieve the primary endpoint at the time of the primary analysis, 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 Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) will be informed about the discontinuation of the trial in accordance with applicable regulations.

5.7 Definition of End of Trial

The end of the trial is defined as the last contact date with the last subject who participates in this trial (last subject’s last visit).

A clinical trial protocol may not be considered closed as long as:

- Any subject 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 subject
- 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 subject

6 Investigational Medicinal Product and Other Drugs Used in the Trial

The term "Investigational Medicinal Product" refers to the investigational drug undergoing study (ie, 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 Good Manufacturing Practice (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 BID orally. Following this, and for the duration of treatment, it is given 240 mg BID orally. For sites in the European Union (EU), Tecfidera will be centrally sourced and provided by the Sponsor. For sites in the US, 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

Subjects will receive 25 mg QD, 75 mg QD, or 75 mg BID M2951 or placebo administered as tablets for 168 days. To maintain blinding for placebo and M2951 (see Section 6.9), subjects will self-administer study medication at a schedule similar to the 75 mg M2951 BID dosing schedule (ie, 3 tablets BID). 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 QD; however, flexibility will be maintained to allow adjusting this dose based on data from the IA or primary analysis.

Subjects will self-administer the IMP at a set time each day (every 12 hours ± 2 hours). Subjects 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 [redacted]) are completed.

If a dose is missed, the subject 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 subject 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 subject should refrain from taking their scheduled morning dose and take their dose of IMP when instructed at the visit.

Subjects will be asked to record the date and time of dosing and food intake around dosing in a subject diary.

Subjects who develop GI or flushing disturbances while receiving Tecfidera may reduce their study treatment dose by taking 120 mg BID for 1 month. After 1 month at the reduced dose, subjects will resume the 240 mg BID dosing. If the subject is still unable to tolerate the study treatment, the subject must permanently discontinue study treatment as described in Section 6.4.4.2.

6.3 Assignment to Treatment Groups

Eligible subjects will be randomized 1:1:1:1:1 to treatment with placebo, low-dose M2951 (25 mg QD), mid-dose M2951 (75 mg QD), high-dose M2951 (75 mg BID), or Tecfidera (administered BID 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 (US or Western Europe, Eastern Europe and CCI, Eastern Europe and CCI, RoW). For the first 7 days, Tecfidera is administered orally at 120 mg BID. Following this and for the duration of treatment, Tecfidera is administered orally at 240 mg BID.

6.4 Concomitant Medications and Therapies

All concomitant medications taken by the subject 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.

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 subject's previous treatment and will therefore not be provided by the Sponsor. Any such medications prescribed or used should be recorded in the eCRF.

Subjects who experience an MS relapse (see Section 7.3.3) during treatment may receive rescue medication subject 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.

Subjects 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 5.5).

Note: Where possible, the use of high dose corticosteroids should be avoided in the 2 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 subjects' 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 subject from the IMP (see Section 5.5.1).
- Oral or parenteral steroids, except rescue medication to treat a relapse of MS, or adrenocorticotropic hormone.
- Biologic therapies
- Intravenous Ig therapy and/or plasmapheresis
- Treatment with teriflunomide
- Live and live-attenuated vaccines
- Changes in dalfampridine dose (subject 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 3 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.
- Any investigational drug or experimental procedure for MS.

Table 3 Examples of Inhibitors or Inducers of CYP3A Enzymes or Substrates with Narrow Therapeutic Range

Inhibitors		
Strong	**Moderate**	**Weak**
Boceprevir, clarithromycin, conivaptan, grapefruit juice,[a] indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, and voriconazole	Amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice,[a] imatinib, and verapamil	Alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, ginkgo, goldenseal, isoniazid, nilotinib, oral contraceptives, ranitidine, ranolazine, tipranavir/ritonavir, and zileuton
Inducers		
Strong	**Moderate**	**Weak**
Avasimibe, carbamazepine, phenytoin, rifampin, and St. John's wort	Bosentan, efavirenz, etravirine, modafinil, and nafcillin	Amprenavir, aprepitant, armodafinil, echinacea, pioglitazone, prednisone, and rufinamide
Substrates With a Narrow Therapeutic Range		
Alfentanil, astemizole,[b] cisapride,[b] cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine[b]		

CYP=cytochrome P450
[a] The effect of grapefruit juice varies widely among brands and is concentration, dose, and preparation dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation is used (eg, high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation is used (eg, low dose, single strength).
[b] Withdrawn from the US and certain other markets because of safety reasons.
Note: This is not an exhaustive list. For an updated list, see Tables 5, 6, and 7 in the following link: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm
Note: A strong inhibitor is defined as an inhibitor that increases the AUC of a substrate sensitive for that CYP ≥ 5-fold or decreases clearance by > 80%, and a strong inducer decreases AUC of a substrate by ≥ 80%.
Note: A moderate inhibitor is defined as an inhibitor that increases the AUC of a substrate sensitive for that CYP ≥ 2 fold but < 5-fold or decreases clearance by 50%-80%, and a strong inducer decreases AUC by 50%-80%.
Note: A weak inhibitor is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP < 2-fold or decreases clearance 20%-50%, and a weak inducer decreases AUC by 20%-50%.
Note: CYP substrates with narrow therapeutic range refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns (eg, Torsades de pointes).

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 re-occur, as relevant, and re-initiation following temporarily withholding of IMP should be discussed with the Medical Monitor:

- For a neutrophil count < 500/mm^3 or platelet count < 25,000/mm^3 (Grade 4) or neutrophil count 500 to 999/mm^3 (Grade 3) with fever 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 decrease to Grade 2, temporarily hold the IMP and recheck the value. Re-initiate the IMP after discussion with the Medical Monitor if no further downward trend is observed
- For an increase in AST or ALT to > 3X ULN and increase in bilirubin to > 1.5X ULN (Grade 2 or higher), the IMP should be permanently withdrawn. The subject should be followed with additional testing as needed until a return to ULN. Consultations with specialists, such as a hepatologist, can be considered at the discretion of the Investigator and in conjunction with the Medical Monitor
    - For an increase in AST or ALT to > 5X ULN without bilirubin elevation, the IMP should be permanently withdrawn. The subject should be followed with additional testing as needed until a return to ULN. Consultations with specialists, such as a hepatologist, can be considered at the discretion of the Investigator and in conjunction with the Medical Monitor
    - For any other increase in AST ALT or bilirubin to Grade 2, temporarily hold the IMP and recheck the value. Re-initiate the IMP after discussion with the Medical Monitor if no further upward trend is observed
- For an increase in amylase or lipase to > 5X ULN (Grade 4), the IMP should be permanently withdrawn
    - For an increase in amylase or lipase to > 2 to 5X 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 to 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 re-initiate the IMP after discussion with the Medical Monitor if a downward trend is observed
- For an increase in serum creatinine to > 3X from Baseline (Grade 3 or higher), the IMP should be permanently withdrawn
    - For any other increase in serum creatinine > 1.5X from Baseline, temporarily hold the IMP and recheck the value within 24 hours of receipt. Discontinue the IMP if the value does not decrease, or re-initiate 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 (ie, returns to grade 2), IMP can be resumed.

6.4.4.2 For Tecfidera Only

- For a lymphocyte count < 500/mm^3 for > 24 weeks, Tecfidera should be temporarily withheld and the subject monitored until lymphocyte counts are back to the lower limit of normal (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 subject 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.
- For a flushing reaction (eg, 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

Laboratory values corresponding to Common Terminology Criteria for AEs (CTCAE) Grades 1 to 4 are presented for selected laboratory parameters in Table 4. For all other laboratory abnormalities, refer to the CTCAE, version 4.03.

Table 4 CTCAE Grades for Relevant Laboratory Parameters

Laboratory Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Neutrophil (/mm^3)	< LLN to 1,500	< 1,500 to 1,000	< 1,000 to 500	< 500
Absolute lymphocyte count (/mm^3)	< LLN to 800	< 800 to 500	< 500 to 200	< 200
WBC count (/mm^3)	< LLN to 3000	< 3000 to 2000	< 2000 to 1000	< 1000
Platelets (/mm^3)	< LLN to 75,000	< 75,000 to 50,000	< 50,000 to 25,000	< 25,000
AST and ALT	< ULN to 3X ULN	> 3 to 5X ULN	> 5 to 20X ULN	> 20X ULN
Bilirubin	< ULN to 1.5X ULN	> 1.5 to 3X ULN	> 3 to 10X ULN	> 10X ULN
Amylase and lipase	< ULN to 1.5X ULN	> 1.5 to 2X ULN	> 2 to 5X ULN	> 5X ULN
Creatinine	> Baseline to ≤ 1.5X Baseline, or > ULN to 1.5X ULN	> 1.5 to 3X Baseline or > 1.5 to 3X ULN	> 3X Baseline, or > 3 to 6X ULN	> 6X ULN

ALT=alanine aminotransferase, AST=aspartate aminotransferase, CTCAE=Common Terminology Criteria for AEs, LLN=lower limit of normal, ULN=upper limit of normal; WBC=white blood cell.

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 30°C. 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 subject 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 subject trial numbers

The Investigator site should maintain records, which adequately document that subjects 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 subject may be redispensed to a different subject.

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 subject(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. All other dosing will be done by the subject or subject's caregiver at home throughout the rest of the trial. Subjects or subject's caregiver will be asked to record the date and time of dosing and food intake around dosing in a subject diary.

Subjects will be instructed to bring all IMP, including the used packaging, to each trial visit to allow for the assessment of compliance with trial treatment. Prior to discharge from each scheduled visit, subjects will be given sufficient IMP for at-home dosing until the next scheduled visit during the treatment period.

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 radiologist will be blinded to all treatments (placebo, M2951, and Tecfidera) throughout the study. The subjects, 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.

A team from the Sponsor, independent of the CRO and Sponsor study teams, will be tasked with review of the unblinded IA data as described in the firewall charter and analysis plan. IA results will be presented on a limited set of endpoints when the first 50% of subjects enrolled out of the planned enrollment have reached Week 24 or prematurely discontinued treatment. The IDMC will also be unblinded to treatment, as described in the IDMC charter.

The bioanalytical laboratory(ies) responsible for the analysis of the CCI and CCI samples will be allowed to be partially unblinded during study conduct using masked subject identifiers, to support association of CCI data with M2951 dose and placebo treatment codes for timely decision making, but prevent association of treatment codes with any other clinical data, such as efficacy or safety data.

All other staff other than those identified above will remain blinded to the placebo and M2951 treatments. IA results from the independent team will not be communicated back to the sites, the CRO study team, or the Sponsor study team.

Only when the last subject reaches 24 weeks of treatment or discontinues from treatment prematurely, the protocol violations are determined, the database is partially locked for the primary analysis, and the data file verified, 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 with subjects, site staff, and the Investigator blinded to M2951 dose group, and with assessing neurologist and central radiologist blinded to all treatments. The final analysis will occur only when the last subject

completes all study parts or discontinues from the study prematurely, protocol violations are determined, the database is locked for the final analysis, and the data file verified.

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 subject. 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 subject emergency card provided to each subject (see Section 9.4).

Under certain circumstances, the IDMC or Drug Safety may be required to unblind the treatment assignment for an individual subject following a serious adverse event (SAE) or other serious event; eg, 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 subject 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 Subjects after End of Trial

After a subject has completed the trial or has withdrawn early, the subject is free to access further treatment as deemed appropriate by the Treating Investigator. The Sponsor will not provide any additional care to subjects after they leave the trial because such care should not differ from what is normally expected for subjects 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 subject, the Investigator will obtain written informed consent as described in Section 9.2.

Throughout the trial, subjects will undergo the assessments detailed in Table 1, including collection of patient-reported HRQoL data and blood sampling. Completion of the HRQoL instrument SF-36v2 shall always be done before any other procedure or Investigator interaction of the visit takes place. 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, footnote l for information regarding abnormal dipstick results.
- CCI [redacted]
- ECGs results will be interpreted locally.
- HIV testing, when required by local regulation, should be conducted and analyzed locally.

The Treating Investigator will be the physician responsible for subject 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 subject's clinical response and laboratory findings. The Treating Investigator will also be responsible for the treatment of relapses and determining if non-MS-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 subject's treatment, laboratory data, adverse event 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 subject's neurological state, where possible. Both the Treating Investigator and the subject will be informed of the importance of not discussing these issues with the Assessing Neurologist to prevent unblinding.

The Assessing Radiologist will be an independent, blinded, central radiologist provided by PPD. A local radiologist will also review all MRI scans for safety and provide a report to the Treating Investigator, containing only non-MS 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 subject's eligibility will be assessed at the Screening visit that will occur between Day -28 to Day -1. See Table 1 for a list of assessments done at Screening to determine the eligibility of the subject to participate in the trial. If a subject does not meet eligibility criteria, the subject can be retested and rescreened once at the Investigator's discretion.

If there are no clinically significant findings and the subject meets all protocol-defined inclusion criteria and none of the exclusion, the subject will be considered as eligible to be enrolled in the trial. Subjects 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 subjects who failed Screening: informed consent, demographics, reason for screen failure, AEs from the date of informed consent until the subject 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 SF-36v2 HRQoL questionnaire, 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.
- 12-lead ECG and chest x-ray
- Blood sample collection for Quantiferon TB test, viral serology testing, HIV testing if required, safety assessments (hematology, 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 (eg, CCI [redacted] occupancy 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. Subjects who discontinue early must immediately return for the 4-week Safety Follow-up/End of Trial visit (see Section 7.1.5).

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
- SF-36v2 HRQoL questionnaire
- 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, B, CCI cell counts; CCI
- CCI
- Urine collection for a urine pregnancy test (women only)
- IMP dispensation

The following will be performed on Days 28, 56, 84, 112, 140, 168, and 252:

- SF-36v2 HRQoL questionnaire
- Review of concomitant medications and procedures; evaluation of AEs; disease activity assessment (relapse assessment, EDSS); a complete physical examination (Days 84 and 168 only); vital sign assessment; and a neurologic exam
- IMP compliance
- 12-lead ECG (Day 168 only)
- Blood sample collection for safety assessments (hematology, chemistry); Ig levels (Days 28, 112, and 168 only); B, CCI cell count and CCI (Days 28 and 168 only); CCI
- Urine collection for urine pregnancy testing (women only); urinalysis and, if necessary, microscopy and protein:creatinine ratio (Days 84 and 168 only).
- MRI assessment (Days 84, 112, 140, and 168 only)
- IMP dispensation

7.1.3 Unscheduled Visit for Neurological Worsening and Relapse Assessment

Subjects 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 subject 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 non-qualifying 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 subject being exposed to gadolinium more than once in a 4-week period, ie, 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

7.1.4 End of Treatment Visit

The following will be performed on Day 336 ± 3 days/End of Treatment visit:

- SF-36v2 HRQoL questionnaire
- 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); Ig levels; B, CCI and CCI cell and CCI
- CCI Urine collection for urinalysis and, if necessary, microscopy and protein:creatinine ratio; urine pregnancy testing (women only).
- MRI assessment

7.1.5 4-week Safety Follow-up/End of Trial Visit

The Safety Follow-up/End of Trial Visit will be performed on Day 364 ± 5 days.

See Table 1 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, EDSS), vital signs, and a neurologic exam
- Blood sample collection for safety assessments (hematology, chemistry); B, CCI and CCI cell counts CCI

- 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 subject, 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. Vital signs, including oral temperature, heart rate, respiratory rate, blood pressure, weight, and height will be obtained. All other Baseline measures, such as safety laboratory parameters, Quantiferon TB test, ECG, and chest x-ray will be assessed. Baseline disease will be assessed by EDSS and MRI. Baseline QoL using the SF-36v2 questionnaire will also be assessed.

7.3 Efficacy Assessments

The following efficacy assessments will be undertaken, as outlined in the Schedule of Assessments (Table 1). During treatment, ie, Day 1 to Week 48, 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 Weeks 12 to 24, and at the End of Treatment Visit at Week 48.

Gadolinium will be used to enhance T1-weighted lesions and to optimize clarity and accuracy of reporting. As gadolinium is excreted renally, subjects with acute renal insufficiency (eGFR < 45 mL/min/1.73m^2) will be excluded from the trial (see Section 5.3.2, exclusion criterion 32).

Brain 1.5T 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 non-MS pathology and will be provided to the Treating Investigator.

Note: Where possible, the use of high dose corticosteroids should be avoided in the 2-week period prior to a scheduled MRI scan. In subjects 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 subject being exposed to gadolinium more than once in a 4-week period, ie, 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

At Screening and all subsequent study visits, a standard neurological examination will be performed by an Assessing Neurologist and the subject's level of disability will be assessed using the EDSS.

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 subject 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

Subjects will be assessed for MS relapse at each visit beginning at Week 4. Relapse will also be assessed at any Unscheduled Visit for Neurological Worsening and Relapse Assessment (see Section 7.1.3). 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 (ie, 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. Subjects 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 5.5.1) or withdrawal from the trial, including the need for treatment with a non-permitted medication (see Section 5.5.2).

A non-qualifying 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 B, CCI [redacted] cell counts).

Comprehensive assessment of any apparent toxicity experienced by each subject 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 subject (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 subject or clinical investigation subject 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 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 (eg, 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 (eg, 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 (eg, 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 subject 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 subject 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 (eg, an overnight stay to facilitate intravenous therapy) are not considered SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (eg, 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 subject will be queried on changes in his or her condition. During the reporting period, any unfavorable changes in the subject's condition will be recorded as AEs, whether reported by the subject 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 subject 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.

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 (eg, medical history, concomitant drugs). Additional documents may be provided by the Investigator, if available (eg, 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 (eg, 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 subjects 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 subjects, 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 Subjects with Adverse Events

Adverse events 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. All SAEs ongoing at the 4-week Safety Follow-up/End of Trial Visit must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the subject 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 (eg, 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 subjects and to pregnancies in female partners of male subjects. 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 subjects 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 subject 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 subject occurring during the course of the trial, the subject must be discontinued from trial medication immediately. The Sponsor/designee must be notified without delay and the subject 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). All samples should be clearly identified. Sample collection, preparation, and handling/shipment procedures are described in the Laboratory Manual.

Table 5 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
Hematology	• Hematocrit • Hemoglobin • Red blood cell count • Mean corpuscular volume • Mean corpuscular hemoglobin • Mean corpuscular hemoglobin concentration • Reticulocyte count	• Platelet count • White blood cell count • B, 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[b] 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]	• HBV core antigen • HCV antibodies • Serum βhCG (women only)	• HBV IgM antibodies • HIV[f] • FSH	• HBsAg • Quantiferon tuberculosis test

βhCG=β-human chorionic gonadotropin, eGFR=estimated glomerular filtration rate, FSH=follicle stimulating hormone, HBsAg=hepatitis B surface antigen, HBV=hepatitis B virus, HCV=hepatitis C virus, HIV=human immunodeficiency virus, IgM=immunoglobulin M, CCI .

a. To be done only when specified in Table 1 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.

7.4.4 Vital Signs, Physical Examinations, and Other Assessments

7.4.4.1 Vital Signs

Vital signs, including seated blood pressure, pulse rate, respiratory rate, weight, and oral temperature will be assessed predose at all trial visits (Table 1). 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 subject's arm unconstrained by clothing or other material. The blood pressure should be assessed on the same arm for each subject throughout the trial.

7.4.4.2 Physical Examinations

Physical examinations will be assessed at each site as indicated in Table 1. 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.

7.4.4.3 12-Lead ECG and Chest X-ray

A 12-lead ECG will be performed during Screening. 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).

Posterioanterior CXRs will be performed during Screening according to local standard practice. Subjects 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 obtained at predose on Days 1, 28, 112, 168, and 336.

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.

7.4.6 B Cell Counts

Blood samples for B, CCI cell counts will be obtained predose on Days 1, 28, 168, and 336. An additional sample will be collected at the 4-week Safety Follow-up/End of Trial Visit.

The actual date and time of each sample will be recorded. Samples will be analyzed by the central laboratory selected by the Sponsor using an appropriately validated bioanalytical method. Samples will be collected, labeled, processed, stored, and shipped according to the instructions in the Laboratory Manual.

7.5 CCI

CCI [redacted]

7.6 CCI [redacted]

[redacted]

7.6.1 CCI [redacted]

[redacted]

[redacted]

[redacted]

7.6.2 CCI [redacted]

[redacted]

CCI [redacted]

7.6.3 CCI [redacted]

[redacted]

[redacted]

7.6.4 CCI [redacted]

[redacted]

[redacted]

7.7 Health Related Quality of Life Assessments

7.7.1 Short Form 36-item Health Status Survey

The SF-36v2 is a 36-item questionnaire that measures 8 areas of subject reported health rated from 0 to 100 for a total score ranging from 0 to 800 (21-25). The areas are:

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

- General health perceptions

The SF-36v2 will be measured in all subjects as indicated in Table 1. Completion of the SF-36v2 shall be done before any other procedure or Investigator interaction takes place. The English version of the instrument can be found in Appendix III.

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 subjects. 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 at. 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 subjects provides 85% power to detect a decrease of 90% in the total number of gadolinium-enhancing T1 lesions, summed over scans at Weeks 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 negative binomial (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 subjects will be randomized per group to protect against a loss of information due to a 12% drop-out rate over one 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.)

The IA, if conducted, will test for futility, not efficacy, so will not affect the 0.05 Type I error rate available at the primary analysis. The Family-wise Type I error rate (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 subjects will be randomized 1:1:1:1:1 to treatment with placebo, low-dose M2951 (25mg QD), mid-dose M2951 (75mg QD), high-dose M2951 (75mg BID), or Tecfidera (administered BID at a final dose of 240 mg), through a central randomization process by an

IWRS, stratified according to region (US or Western Europe, Eastern Europe and CCI [redacted], Eastern Europe and CCI [redacted], RoW).

8.3 Endpoints

8.3.1 Primary Endpoints

The primary endpoint is the total number of gadolinium-enhancing T1 lesions at Weeks 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:

- Annualized relapse rate (ARR), based on protocol-defined qualified relapses, at Week 24
- Proportion of subjects who remain qualified relapse-free at Week 24
- Change from Baseline in EDSS at Week 24
- Safety as assessed by the nature, severity, and incidence 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 Weeks 12, 16, 20, and 24
- Mean per-scan number of Gd+ T1 lesions at Weeks 12, 16, 20, and 24
- Total number of new or enlarging T2 lesions at Weeks 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:

- Total number of Gd+ T1 lesions at Week 48
- Total number of new Gd+ T1 lesions at Week 48
- Annualized relapse rate, based on protocol-defined qualified relapses, at Week 48
- Proportion of subjects who remain qualified relapse-free at Week 48
- Change from Baseline in EDSS at Week 48
- Total 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 Weeks 12, 16, 20, and 24
- Annualized relapse rate, based on protocol-defined qualified relapses, at Week 24
- Proportion of subjects who remain qualified relapse-free at Week 24
- Change from Baseline EDSS at Week 24
- Safety as assessed by the nature, severity, and incidence 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 Weeks 12, 16, 20, and 24
- Mean per-scan number of Gd+ T1 lesions at Weeks 12, 16, 20, and 24
- Total number of new or enlarging T2 lesions at Weeks 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
- Total number of Gd+ T1 lesions at Week 48
- Total number of new Gd+ T1 lesions at Week 48
- Annualized relapse rate, based on protocol-defined qualified relapses, by Week 48
- Proportion of subjects who remain qualified relapse-free at Week 48
- Change from Baseline in EDSS at Week 48
- Total 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

8.3.3 Exploratory Endpoints

Exploratory endpoints are as follows:

CCI [redacted]

- Change in HRQoL as measured with SF-36v2 (physical component summary [PCS]/mental component summary [MCS] and sub-domains) over time (area under the curve) in all subjects
- Change in HRQoL as measured with SF-36v2 (PCS/MCS and sub-domains) from Baseline to Week 24 and from Baseline to Week 48 in all subjects

CCI [redacted]

CCI [redacted]

8.3.4 CCI [redacted]

[redacted]

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 subjects who receive at least one dose of trial treatment. Subjects 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 subjects randomly allocated to a treatment, based on the intention to treat "as randomized" principle (ie, the planned treatment regimen rather than the actual treatment given in case of any difference).

Modified Intent-To-Treat Analysis Set

The modified ITT (mITT) Analysis Set consists of all subjects who belong to both the ITT and Safety Analysis Sets, and who have at least one baseline and one post-baseline MRI assessment.

Per-Protocol (PP) Analysis Set

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

CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

CCI [redacted]

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 Statistical Analysis Plan (SAP) will be developed.

Continuous variables will be summarized descriptively using the number of observations, mean, standard deviation (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 subjects 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 subjects 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% confidence intervals (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 SAP.

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 SAP. The SAP will provide the definition(s) of Baseline measurement as required.

All subjects will be included in individual subject 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 SAP and the Clinical Trial Report (CTR). Additional exploratory analyses will be conducted as deemed appropriate.

8.5.2 Analysis of Primary Endpoint

Primary Efficacy Endpoint

The primary analysis of total number of Gd+ T1 lesions, at Weeks 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 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. Other covariates, such as baseline MRI activity, may be included in the model. 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 Wilcoxon rank sum test, comparing each M2951 dose group to placebo. Descriptive statistics for the total number of Gd+ T1 lesions, at Weeks 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 negative binomial 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 non-convergence, the computed p-value testing the null hypothesis H_0: $P(X < Y) + 0.5*P(X = Y) = 0.5$, via the Wilcoxon rank sum test, for each M2951 treatment group will be reported, where X denotes the primary endpoint evaluated for a subject in a given M2951 treatment group, and Y denotes the primary endpoint evaluated for a subject in the placebo group. The FWER, ie, 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 Gd+ T1 lesion rate ratio relative to placebo, 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 subject-years of observation.

The multiple-comparison procedure for testing the key secondary efficacy endpoints will be provided in the SAP. Other secondary efficacy endpoints will be analyzed for exploratory purposes. 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 a Poisson 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. The comparison of a M2951 treatment group to the placebo group using proportion qualified relapse-free at Week 24, will be based on a logistic model for the odds of a

subject being qualified relapse-free at Week 24, where subjects 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 rank analysis of covariance (ANCOVA) model, with M2951 dose group or placebo group as a factor, and adjustment for Baseline and covariates based on randomization strata. The analysis of mean per-scan number of Gd+ T1 lesions at Weeks 12, 16, 20, and 24, 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 an ANCOVA model of the appropriately transformed variable. 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 Weeks 12, 16, 20, and 24, will be based on a NB model, similar to that used for the primary analysis. In the analysis of each secondary endpoint, other covariates, such as baseline MRI activity, 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 total number of Gd+ T1 lesions, total number of new Gd+ T1 lesions, total number of new and enlarging T2 lesions, the change from Baseline in Gd+ T1 lesion volume, and change from Baseline in T2 lesion volume, will be summarized by timepoint (Baseline and Weeks 12, 16, 20, 24, and 48) and treatment group (placebo, 3 M2951 dose groups, and Tecfidera).

Annualized relapse rate from Baseline to Week 24, and from Baseline to Week 48 will be summarized by treatment group. The proportion of subjects remaining qualifying relapse-free at Week 24 and at Week 48 will be summarized by treatment group. The change from Baseline in EDSS will be summarized by treatment group and timepoint (Weeks 4, 8, 12, 16, 20, 24, 36, and 48, and the 4-week Safety Follow-up/End of Trial Visit).

8.5.4 Analysis of Safety and Other Endpoints

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

8.5.4.1 Safety

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

Serious AEs, 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.

Adverse events 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 subjects experiencing 1 or more treatment-emergent AEs (TEAEs) 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 subject and time point.

8.5.4.2 Patient-reported Health Related Quality of Life (HRQoL)

Descriptive statistics for each time point and change from baseline will be provided for each health domain score and the physical and mental component summary scores (PCS/MCS) for each assessment time point.

In addition, change in HRQoL for PCS/MCS and sub-domains over time (area under the curve) will be compared between different M2951 treatment arms and placebo.

Further details on psychometric analyses will be presented in the SAP that will be finalized before database lock.

8.5.4.3 CCI [redacted]

[redacted]

8.5.4.4 CCI [redacted]

[redacted]

8.5.4.5 CCI [redacted]

[redacted]

8.6 Interim and Additional Planned Analyses

There will be three analyses: (1) an IA, triggered when the first 50% of subjects enrolled out of the planned enrollment reach Week 24 of treatment, or prematurely discontinue from treatment, (2) a primary analysis, triggered when 100% of subjects enrolled reach Week 24 of treatment, or prematurely discontinue from treatment, and (3) a final analysis, triggered when 100% of subjects enrolled complete all study parts, or discontinue prematurely from study. The Sponsor may decide not to perform the IA if the IA trigger date is sufficiently close (i.e., within approximately 4 months) of the primary analysis trigger date.

Interim Analysis

If performed, the aim of the IA will be to evaluate overall futility based on the highest dose of M2951 to determine whether or not to continue the study. It is planned that placebo subjects will be continued at the 25 mg QD dose after Week 24, however consideration will be given to changing this dose based on data from the IA. Pharmacokinetic analysis will not be included in the IA.

The conditional power of a test based on the rate ratio parameter of a NB model, comparing the primary efficacy endpoint (total number of Gd^+ T1 lesions at Weeks 12, 16, 20, and 24) for the highest M2951 group versus the placebo group, will be evaluated, under the assumption that the unevaluable subjects will have lesion data for Weeks 12, 16, 20, and 24 following the same distribution as that observed among subjects evaluated at the time of the IA. If conditional power is sufficiently low, as defined in the SAP, consideration will be given to termination of the study, in which case all subjects will be discontinued from IMP and scheduled for a 4-week Safety Follow-up Visit/End of Trial Visit.

If conditional power cannot be ascertained via a NB model, then conditional power will be ascertained via a nonparametric analysis, based on the Wilcoxon rank sum test.

Descriptive statistics for the primary efficacy endpoint will be presented by treatment group. A point estimate (rate ratio or Hodges-Lehmann estimate) of the effect of treatment on total number of Gd^+ T1 lesions at Weeks 12, 16, 20, and 24), comparing each M2951 dose group to the placebo group, will be provided, together with a 2-sided 95% CI. A test for a monotonic relationship, between ordered M2951 dose (low, mid, high) and Gd+ T1 lesion rate ratio relative to placebo, will be performed as a supportive analysis.

Primary Analysis

When the last subject reaches 24 weeks of treatment or discontinues from treatment prematurely, the protocol violations are determined, the database is partially locked for the primary analysis, and the data file verified, 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 SAP.

Final Analysis

The final analysis will occur only when the last subject completes all study parts, the protocol violations are determined, the database is locked for the final analysis, and the data file verified. All endpoints based on Baseline to Week 48 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 subjects 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 US Food and Drug Administration (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 Sub-investigators 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 Subject Information Sheet and Informed Consent

An unconditional prerequisite for each subject 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 subject by the Investigator or an appropriate designee (if local regulations permit) before informed consent is obtained.

A Subject 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 subject, the Investigator or a designate will inform the subject verbally of all pertinent aspects of the trial, using language chosen so that the information can be fully and readily understood by laypersons. The subject 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 subject about the trial and sign the Informed Consent Form (ICF), as above.

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

A separate ICF will be needed for the subset of subjects consenting to CCI [redacted].

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 subject prior to participation.

Whenever important new information becomes available that may be relevant to informed consent, the Investigator will revise the Subject Information Sheet and any other written information to be provided to the subjects and submit them to the IRB for review and opinion. Using the approved revised Subject Information Sheet and other written information, the Investigator will explain the changes to the previous version to each trial subject and obtain new written consent for continued participation in the trial. The subject 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 Subject Identification and Privacy

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

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing subject data. Subjects 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 Subject Card

Subjects will be provided with Emergency Medical Support cards supplied by the Sponsor for use during trial participation in order to provide clinical trial subjects 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 subject. 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 subject. 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 (eg, 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 subject concerned.

9.5 Clinical Trial Insurance and Compensation to Subjects

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 Subject 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 (eg, IMP Dossier, Subject 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 subject names.

For patient-reported outcomes, these will be collected either on paper or by means of ePRO.

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 Subject Files

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

- Subject'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, ie, the Sponsor trial number for this clinical trial, and subject 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 subject 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 subject 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 subject 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 subject data in the eCRF to be considered source data.

Electronic subject 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 Subject Identification List and the signed subject ICFs. If archiving of the Investigator Site File is no longer possible at the site, the Investigator must notify the Sponsor/designee.

All original subject 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 subject.

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 subject'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 trial, 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.

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 subject 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:	129428
EudraCT Number:	2016-001448-21
Clinical Trial Protocol Date / Version:	31 May 2016/ Version 1.0

Protocol Lead responsible for designing the clinical trial:

I approve the design of the clinical trial:

PPD _____ PPD

Signature Date of Signature

Name, academic degree: PPD

Function / Title: PPD

Institution: EMD Serono Research & Development Institute, Inc.

Address: PPD

Telephone number: PPD

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	129428
EudraCT Number	2016-001448-21
Clinical Trial Protocol Date / Version	31 May 2016/ Version 1.0

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

Signature

PPD

Date of Signature

PPD

Name, academic degree:

PPD

Function / Title:

Institution:

Address:

Telephone number:

Fax number:

E-mail address:

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	129428
EudraCT Number	2016-001448-21
Clinical Trial Protocol Date / Version	31 May 2016/ Version 1.0
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:

Sponsor Responsible Persons not Named on the Cover Page

Name, academic degree:	PPD
Function / Title:	Clinical Trial Leader
Institution:	Merck KGaA
Address:	PPD
Telephone number:	PPD
Fax number:	PPD
E-mail address:	PPD

Name, academic degree:	PPD
Function / Title:	Biostatistician
Institution:	EMD Serono Research & Development Institute, Inc.
Address:	PPD
Telephone number:	PPD
Fax number:	PPD
E-mail address:	PPD

Appendix II: Total Blood Volume

Blood will be drawn on at least 11 separate days/visits. Additional samples may be drawn if unscheduled visits occur. CCI [redacted] The planned maximum volume of blood to be drawn in this trial is approximately 327 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).

Assay	Approximate Sample Volume(mL)	Number of Samples	Approximate Subtotal Volume (mL)
Screening tests: hematology, chemistry, coagulation, FSH, viral serology testing (HBsAg, Anti-HCV, HIV[a])	19.5	1	19.5
Hematology, chemistry[b]	12.5	10	125
Immunoglobulins	4	5	20
QuantiFERON-TB test	4.5	1	4.5
B, CCI cell count	10	5	50
CCI [redacted]			
Total			**337**

ALP=alkaline phosphatase, ALT=Alanine aminotransferase, AST= Aspartate aminotransferase, CCI [redacted], CYP=cytochrome P450, FSH=follicle stimulating hormone, GGT=gamma-glutamyl transferase, HBsAg= hepatitis B surface antigen, HCV=hepatitis C virus, HIV=human immunodeficiency virus, LDH=lactate dehydrogenase, CCI [redacted], 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 CO_2, blood urea nitrogen, glucose, sodium, potassium, chloride, calcium, magnesium, phosphate as shown in Table 5.

CCI [redacted]

Appendix III: SF-36v2 Instrument

The questions contained in the SF-36v2 are detailed below.

Item	Answer category
In general, would you say your health is:	1) Excellent 2) Very good 3) Good 4) Fair 5) Poor
COMPARED TO 1 YEAR AGO, how would you rate your health in general NOW?	1) Much better now than 1 year ago 2) Somewhat better now than 1 year ago 3) About the same as 1 year ago 4) Somewhat worse now than 1 year ago 5) Much worse now than 1 year ago
The following questions are about activities you might do during a typical day. Does YOUR HEALTH NOW LIMIT YOU in these activities? If so, how much?	1) Yes, limited a lot 2) Yes, limited a little 3) No, not limited at all
a) VIGOROUS ACTIVITIES, such as running, lifting heavy objects, participating in strenuous sports b) MODERATE ACTIVITIES, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf c) Lifting or carrying groceries d) Climbing SEVERAL flights of stairs e) Climbing ONE flight of stairs f) Bending, kneeling, or stooping g) Walking MORE THAN A MILE h) Walking SEVERAL HUNDRED YARDS i) Walking ONE HUNDRED YARDS j) Bathing or dressing yourself	
During the PAST 4 WEEKS, how much of the time have you had any of the following problems with your work or other regular daily activities AS A RESULT OF YOUR PHYSICAL HEALTH?	1) All of the time 2) Most of the time 3) Some of the time 4) A little of the time 5) None of the time
a) Cut down on the AMOUNT OF TIME you spent on work or other activities b) ACCOMPLISHED LESS than you would like c) Were limited in the KIND of work or other activities d) Had DIFFICULTY performing the work or other activities (for example, it took extra effort)	
During the PAST 4 WEEKS, how much of the time have you had any of the following problems with your work or other regular daily activities AS A RESULT OF ANY EMOTIONAL PROBLEMS (such as feeling depressed or anxious)?	1) All of the time 2) Most of the time 3) Some of the time 4) A little of the time 5) None of the time
a) Cut down on the AMOUNT OF TIME you spent on work or other activities b) ACCOMPLISHED LESS than you would like c) Did work or other activities LESS CAREFULLY THAN USUAL	
During the PAST 4 WEEKS, to what extent has your PHYSICAL HEALTH OR EMOTIONAL PROBLEMS interfered with your normal social activities with family, friends, neighbors, or groups?	1) Not at all 2) Slightly 3) Moderately

	4) Quite a bit 5) Extremely
How much BODILY pain have you had during the PAST 4 WEEKS?	1) None 2) Very mild 3) Mild 4) Moderate 5) Severe 6) Very Severe
During the PAST 4 WEEKS, how much did PAIN interfere with your normal work (including both work outside the home and housework)?	1) Not at all 2) A little bit 3) Moderately 4) Quite a bit 5) Extremely
These questions are about how you feel and how things have been with you DURING THE PAST 4 WEEKS. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the PAST 4 WEEKS…	1) All of the time 2) Most of the time 3) Some of the time 4) A little of the time 5) None of the time
a) Did you feel full of life? b) Have you been very nervous? c) Have you felt so down in the dumps that nothing could cheer you up? d) Have you felt calm and peaceful? e) Did you have a lot of energy? f) Have you felt downhearted and depressed? g) Did you feel worn out? h) Have you been happy? i) Did you feel tired?	
During the PAST 4 WEEKS, how much of the time has your PHYSICAL HEALTH OR EMOTIONAL PROBLEMS interfered with your social activities (like visiting with friends, relatives, etc.)?	1) All of the time 2) Most of the time 3) Some of the time 4) A little of the time 5) None of the time
How TRUE OR FALSE is EACH of the following statements for you?	1) Definitely true 2) Mostly true 3) Don't know 4) Mostly false 5) Definitely false
a) I seem to get sick a little easier than other people b) I am as healthy as anybody I know. c) I expect my health to get worse. d) My health is excellent.	

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	129428
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 Telephone: PPD
Clinical Trial Protocol Version	08 August 2018 / Version 4.0
Replaces Version	29 May 2018 / Version 3.0

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	09-August-2018

Protocol Version [4.0] (09-August-2018)

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

Overall Rationale for the Amendment

Following a request from the Czech Republic Regulatory Authority, instructions for re-initiating IMP following increase in AST, ALT, or bilirubin to Grade 2 were amended.

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

[redacted]

Protocol Table of Contents

Table of In-Text Tables

Table of In-Text Figures

List of Abbreviations

AE	Adverse Event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ARR	Annualized relapse rate
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
BTK	Bruton's Tyrosine Kinase
CI	Confidence Interval
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for AEs
CTR	Clinical trial report
CCI	[redacted]
CXR	Chest X-ray
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
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus

HRQoL	Health-related quality of life
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
PCS	Physical component summary
CCI	[redacted]
CCI	[redacted]
PML	Progressive multifocal leukoencephalopathy
RA	Rheumatoid arthritis
RMS	Relapsing multiple sclerosis
RoW	Rest of the world
SAE	Serious Adverse Event
SD	Standard deviation
SF-36v2	Short Form 36-item Health Status Survey version 2.0

SLE	Systemic lupus erythematosus
SMC	Safety Monitoring Committee
SPMS	Secondary progressive multiple sclerosis
TB	Tuberculosis
TLR	Toll like receptor
ULN	Upper Limit of Normal

1 Synopsis

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.
Trial Phase	II
IND Number	129428
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 subject in-last subject out)	First subject in: Q2, 2017 Last subject out: Q3, 2020
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.

Exploratory Objectives

The exploratory objectives are as follows:

- CCI [redacted]
- [redacted]
- To explore the benefit of M2951 treatment on patient-reported health-related quality of life (HRQoL) versus placebo, and to evaluate the effect of Tecfidera on HRQoL.

CCI [redacted]

Methodology: The study will be a randomized, double-blind, placebo-controlled study in subjects with relapsing multiple sclerosis (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 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 subjects on placebo will be switched to M2951, and (iv) an optional Open-Label Extension (OLE) Period. At the end of the 48-week main study, subjects will be in 1 of 4 treatment groups (M2951 25 mg daily, 75 mg once daily, or 75 mg twice daily or Tecfidera). All subjects who choose to enter the OLE Period will be switched to active treatment with M2951 at a dose of 75 mg once daily or to the eventual Phase III dose when decided. CCI [redacted]

Following completion or early termination of treatment, subjects will return after 4 weeks for safety evaluation.

It is planned that placebo subjects 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, subjects will return every 4 weeks for trial visits and will be assessed for safety and efficacy. CCI [redacted]

An independent data monitoring committee (IDMC) will be responsible for safety monitoring until the last randomized subject 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 CRO medical advisor, Sponsor biostatistician, Sponsor Drug Safety Physician, Sponsor Clinical Pharmacology representative and Coordinating Investigator.

Planned number of subjects: Approximately 50 subjects will be enrolled in each treatment group, for a total of approximately 250 enrolled subjects. CCI [redacted]

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.

Exploratory endpoints:

- CCI [redacted]
- [redacted]
- [redacted]
- [redacted]
- Change in HRQoL as measured with SF-36v2 (physical component summary [PCS]/mental component summary [MCS] and sub-domains) over time (area under the curve) in all subjects
- Change in HRQoL as measured with SF-36v2 (PCS/MCS and sub-domains) from Baseline to Week 24 and from Baseline to Week 48 in all subjects
- CCI [redacted]

CCI [redacted]

[redacted]

- CCI [redacted]

CCI [redacted]

Diagnosis and key inclusion and exclusion criteria: Male or female subjects aged 18 to 65 years with RMS or secondary progressive MS (SPMS) with superimposed relapses. Subjects 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 subject should also have an EDSS score of 0 to 6.

Subjects will be excluded if they are diagnosed with primary progressive MS or SPMS without evidence of relapse. Subjects who have a disease duration > 15 years and an EDSS ≤ 2. Subjects will be excluded if they have received treatment with: ritixumab, ocrelizumab, mitoxantrone, or lymphocyte-depleting therapies (eg, alemtuzumab, cladribine, cyclophosphamide, total body irradiation, bone marrow transplantation) within 48 weeks prior to randomization; lymphocyte trafficking blockers within 24 weeks prior to randomization (eg, 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. Subjects 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 (eg, 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. CCI [redacted]

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 subject: Total duration of subject participation is CCI [redacted] approximately 392 days (56 weeks) for subjects 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 subjects who were in Tecfidera arm: 4 to 8 weeks
- CCI [redacted]
- 4-week Safety Follow-Up/End of Trial Visit: 28 days (4 weeks).

CCI [redacted].

Statistical methods:

A per-group sample size of 44 evaluable subjects 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 subjects 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 [redacted], Eastern Europe and not CCI [redacted], Rest of World). Approximately 50 subjects 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 3 analyses: (1) a primary analysis, triggered when 100% of subjects enrolled reach Week 24 of treatment, or prematurely discontinue from treatment; (2) a Week 52 analysis, triggered when 100% of subjects enrolled either reach Week 52 (4-week Safety Follow-up Visit) and complete the study, enroll in the OLE, or prematurely discontinue from study; and [redacted]

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 pre-baseline 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 subject being qualified relapse-free, where subjects 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 pre-baseline 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 an analysis of covariance (ANCOVA) model of 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.

Patient-reported HRQoL

HRQoL data for all treatment groups and time points will be summarized using descriptive statistics. Change in HRQoL for PCS/MCS and sub-domains over time (area under the curve) will be compared between M2951 treatment arms and placebo.

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

[redacted]

Table 1 Schedule of Assessments: Screening and Treatment period (All Subjects), End of Trial (Subjects 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	
B, CCI cell count[k]	X	X	X									X											X	X
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	
PK sampling[q]		X	X	X	X[r]	X	X[r]	X	X[r]		X[r]	X	X[r]	X[r]	X[r]	X[r]	X[r]		X[r]	X[r]	X[r]	X[r]		
BTK occupancy sampling[s]		X	X			X						X												
Gene expression analysis[t]		X	X									X											X	X
HRQoL[u]	X	X	X	X		X		X		X		X						X					X	
C-SSRS (Screening Scale)	X																							
CCI																								
ESR, hsCRP, and fibrinogen[w]																		X						

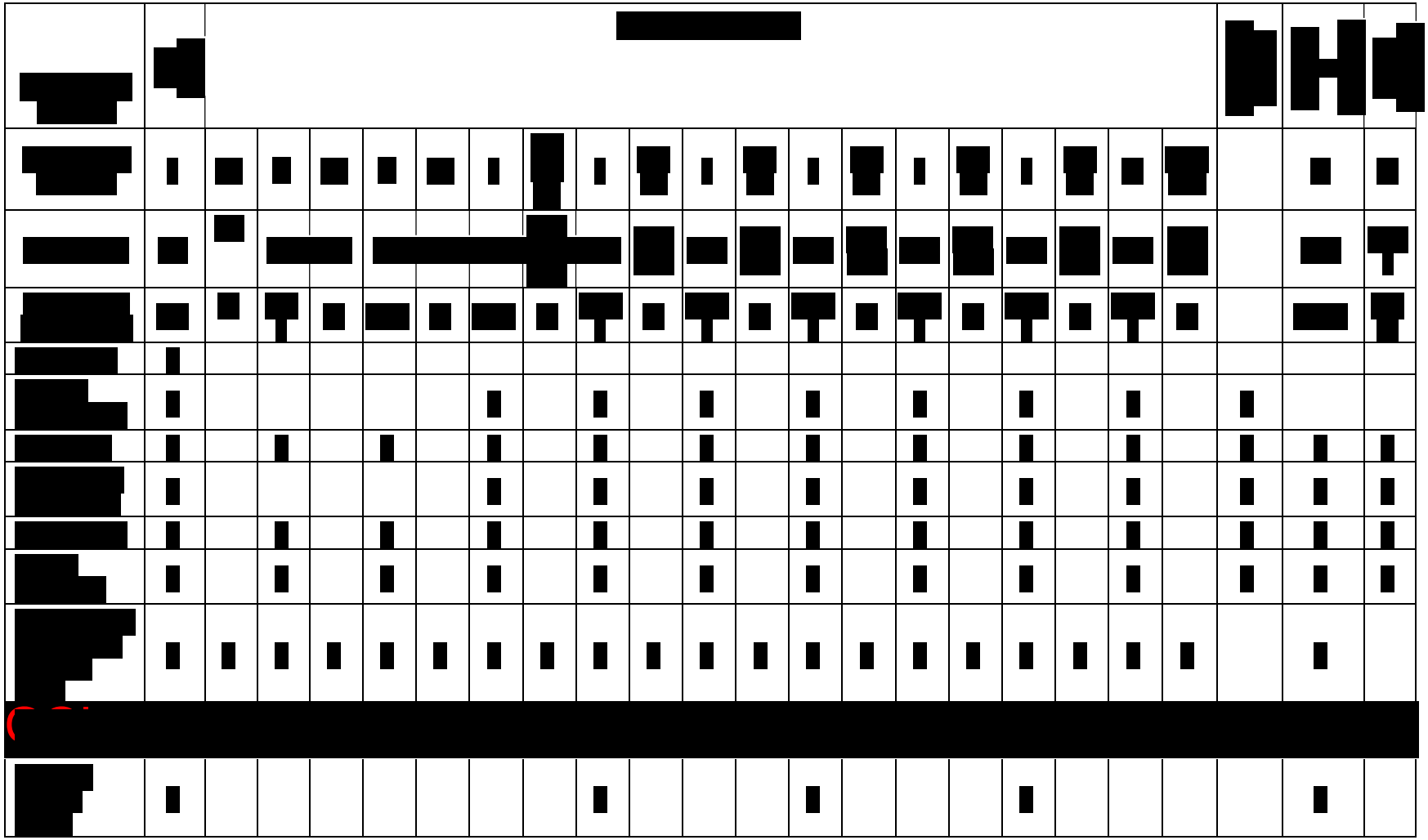
AE=adverse event, CCI , CMV=cytomegalovirus, C-SSRS=Columbia-Suicide Severity Rating Scale, CXR=chest X-ray,ECG=electrocardiogram, eCRF=electronic case report form, EDSS=expanded disability status scale, ESR=erythrocyte sedimentation rate, FSH=follicle-stimulating hormone, HBsAg=hepatitis B surface antigen, HBV=hepatitis B virus, HCV=hepatitis C virus, HIV=human immunodeficiency virus, HRQoL=health-related quality of life, 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 , OLE=Open-label Extension, CCI , PTT=partial thromboplastin time, SF-36v2=Short Form 36-item Health Status Survey version 2.0.

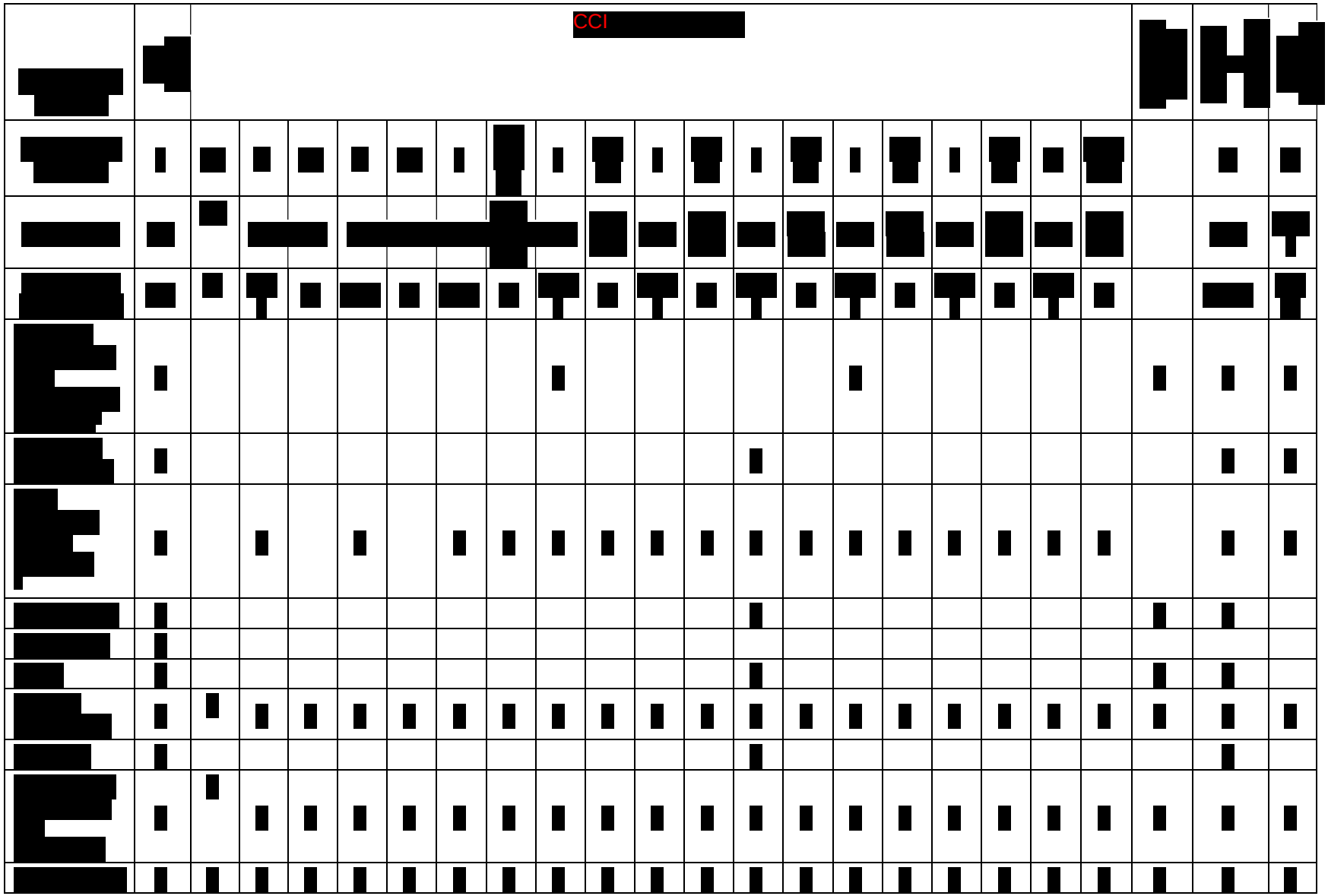
a. Informed consent must be obtained at the Screening visit prior to initiating any Screening procedures or collecting any data. An addendum ICF must be obtained following the IDMC recommendation (October 2017).
b. CCI
c. An additional physical examination may be performed at the additional safety visits (eg, 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; subject eligibility must be reviewed again and confirmed at the site on Day 1 prior to randomization.
g. Blood samples for hematology and chemistry (Table 7) to be obtained at Screening, predose at all Visits when collected except Day 1.
h. For subjects in the placebo/M2951 arms, supplemental LFT monitoring (Table 7) will be conducted, and additional CCI 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 B, CCI cell numbers and B, CCI cell subclasses 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. Subjects will be supplied with at-home test kits. The Principal Investigator and/or delegated site staff will call subject 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. Subjects 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.
q. CCI

CCI [redacted]

w. All subjects 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.

CCI [redacted]

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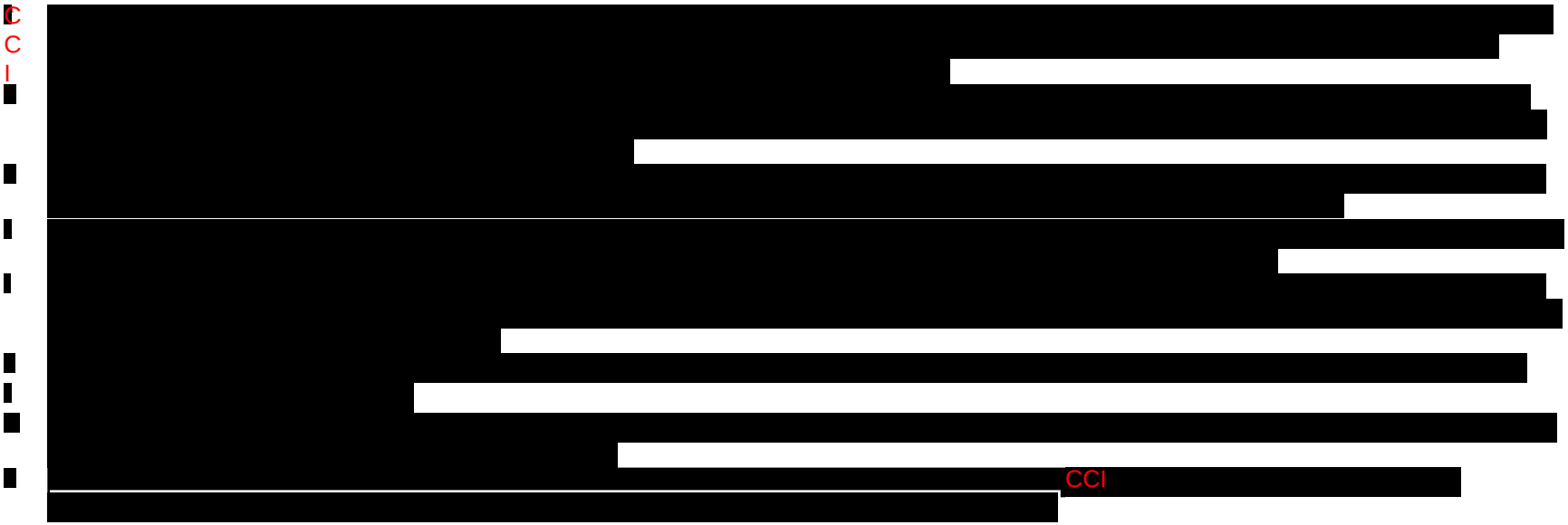
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2 Sponsor, Investigators and Trial Administrative Structure

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 rest of the world (RoW). CCI [redacted].

The Coordinating Investigator, PPD [redacted], 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 contract research organization (CRO), to conduct the clinical part of the trial including trial set-up, operation of an Interactive Web Response System (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 independent data monitoring committee (IDMC) will be responsible for safety monitoring until the last randomized subject 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 Safety Monitoring Committee (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.

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.

Investigational medicinal product (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

Multiple sclerosis (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 relapsing MS (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 disease-modifying drugs (DMDs) with varying levels of efficacy, and distinct safety and tolerability profiles. Most active RMS patients initiate treatment with an interferon-beta or glatiramer acetate (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 (ie, progressive multifocal leukoencephalopathy [PML]) to autoimmunity and cancer. Switching among these DMDs occurs primarily due to perceived lack of efficacy or the occurrence of adverse events (AEs), as well as individual patient preferences.

Despite the recent approvals of newer therapies for the treatment of MS, there remains an unmet need for highly effective and well-tolerated therapies for patients with RMS at all stages of the disease. Early treatment with a highly efficacious, but safe 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 safe 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 Bruton's Tyrosine kinase (BTK) in development for the treatment of autoimmune and inflammatory diseases, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and MS. BTK mediates signaling through the B cell receptor and has been described downstream of several other receptors, including Fc receptor, Toll Like 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 rheumatoid arthritis (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 anti-CD20 therapies in Phase II and Phase III clinical trials in RMS and progressive MS (2-5). Ocrelizumab inhibited the formation of new inflammatory magnetic resonance imaging (MRI) lesions up to 90% (Hauser, 2008) in Phase II RMS trials and high efficacy on MRI (-94%), annualized relapse rate (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 anti-CD20 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 anti-CD20 in B cell antigen presentation, a recent publication of Li et al (7) describes a diminished proinflammatory myeloid cell response in Ocrelizumab-treated MS subjects. M2951 shows inhibition of myeloid cell activation by immune complexes.

Anti-CD20 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, experimental autoimmune encephalomyelitis (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 anti-CD20 therapies, should the need to interrupt or stop therapy arise. This suggests a more favorable benefit to risk profile for M2951 vs. anti-CD20 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 anti-CD20 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. CCI [redacted].

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 non-depleting B cell therapies may deliver a more favorable benefit-risk profile than current B cell-directed therapeutic approaches.

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

3.2 Benefit-Risk

M2951 is being considered for the treatment of autoimmune diseases, including RA and SLE as well as MS. M2951 is the first agent with a mechanism of action that directly targets both B cells and myeloid cells, and it is reasonable to anticipate that M2951 may represent a significant advance in the treatment of MS and other autoimmune diseases.

No identified risks or new potential risks have emerged from clinical studies thus far. In the first in human study EMR200527-001, M2951 was well tolerated at single doses up to 500 mg and at multiple doses up to 200 mg for 14 days. In the completed Phase Ib study in subjects with SLE (Study EMR200527-002) M2951 was well tolerated. There were no SAEs reported during the study and no new safety signals were identified. Evidence of clinical benefit was not expected in this 4-week safety study.

Important potential risks to subjects are based on nonclinical safety data of M2951 and clinical data on adverse drug effects associated with compounds of a similar pharmacological class. They include infection, leukopenia, thrombocytopenia, hemorrhage, gastrointestinal intolerance, renal toxicity, hepatocellular injury, atrial fibrillation, drug-drug interactions, and embryo-fetal toxicity. Asymptomatic elevations in amylase and/or lipase have been observed in completed clinical studies of M2951. The clinical significance and risk status of these observations are being assessed. The Sponsor is also assessing the clinical significance of convulsions observed in dogs at very high levels of exposure. In view of the observation of asymptomatic elevated transaminases in a number of subjects randomized to M2951 or placebo in this 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 continually reviews available safety and tolerability data and is mandated to make immediate decisions regarding the conduct of the trial.

The doses of M2951 (up to 150 mg daily) selected for the proposed trial are within the dose ranges studied in Trial EMR200527-001 in healthy volunteers and represent doses associated with high levels of target occupancy.

Noting the finding of asymptomatic increases in transaminases in subjects in this study, evobrutinib has generally been well tolerated and no new safety signals have been confirmed. No deaths have been reported in clinical trials of evobrutinib as of the release date of this Investigator's Brochure. There is monitoring of liver function tests in ongoing clinical studies and assessment of amylase and lipase following adverse events (AE) of asymptomatic amylase or lipase elevation reported in healthy volunteers and subjects with SLE.

Refer to the current Investigator's Brochure for more detailed results from the completed and ongoing clinical studies.

This clinical trial will be conducted in compliance with the clinical trial protocol, ICH GCP, and any additional applicable regulatory requirements. 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 gadolinium-positive (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.

4.3 Exploratory Objectives

The exploratory objectives are as follows:

[redacted]

- To explore the benefit of M2951 treatment on patient-reported health-related quality of life (HRQoL) versus placebo, and to evaluate the effect of Tecfidera on HRQoL.

[redacted]

5 Investigational Plan

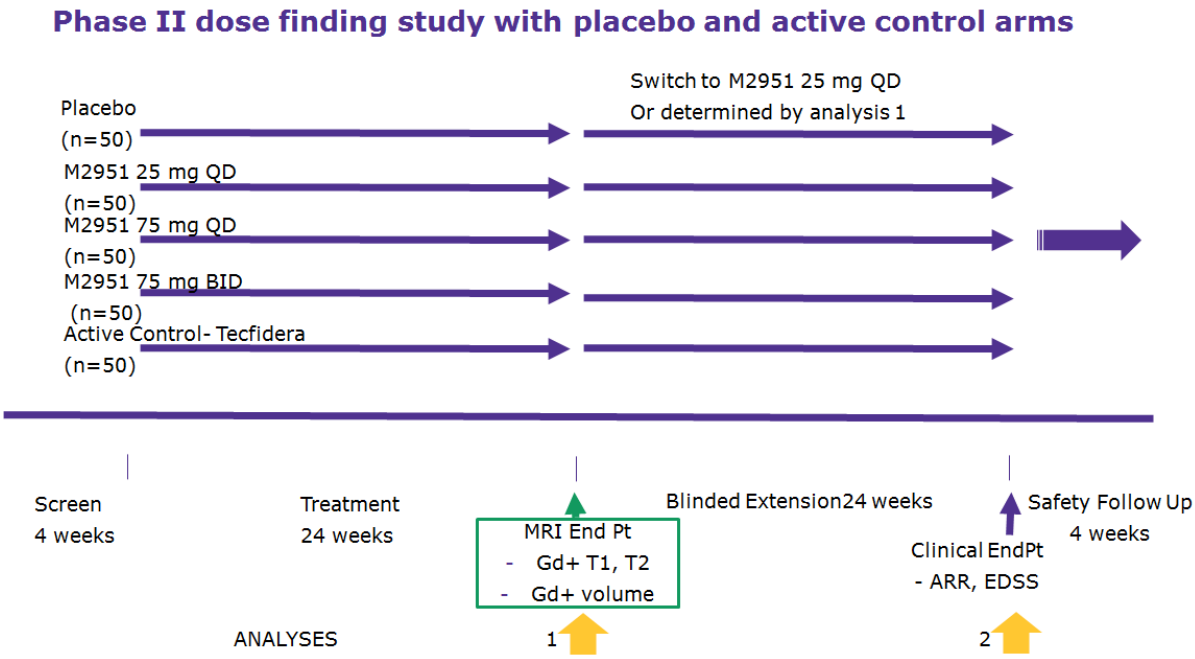
5.1 Overall Trial Design and Plan

This will be a randomized, double-blind, placebo-controlled study in subjects 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 subjects on placebo will be switched to M2951(Figure 1), and (iv) an optional OLE Period. At the end of the 48-week main study, subjects will be in 1 of 4 treatment groups (M2951 25 mg daily, 75 mg once daily, or 75 mg twice daily or Tecfidera). [redacted] ollowing completion or early termination of treatment, subjects will return after 4 weeks for safety evaluation. It is planned that placebo subjects will be switched to the 25 mg M2951 once daily dose after Week 24.

Approximately 50 subjects will be enrolled in each treatment group to obtain 44 evaluable subjects per group (total = approximately 250), assuming a 12% drop-out rate per year, and to compile an adequate safety database. [redacted]

Figure 1 Trial Design – Main Study



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

CCI [redacted]

CCI [redacted]

[redacted]

[redacted]

Detailed schedules of study procedures are provided in Table 1, and Table 2. The Tecfidera washout period is described in Table 4.

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 subjects exposed to placebo (up to 50) and short duration (24 weeks) is acceptable. Furthermore, all placebo subjects 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. CCI [redacted]

5.2.2 Justification for Dose

CCI [redacted]

CCI [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]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[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. 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 Expanded Disability Status Scale (EDSS), qualifying relapse-free status, and patient-reported outcome measures.

The SF-36v2 is one of the most widely used generic patient-reported HRQoL instruments and has been applied in a number of MS studies. The SF-36v2 is an essential part of a number of other more comprehensive MS instruments like the MSQoL-54 or the MSQLI. The SF-36v2 is a multi-purpose, short-form health survey with only 36 questions. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary (13).

5.2.4 Inclusion of Special Populations

Not applicable.

5.3 Selection of Trial Population

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

Subjects 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 subject will receive a new identification number. All other testing is required to be redone at rescreening.

5.3.1 Inclusion Criteria

1. Subjects with a diagnosis of relapsing multiple sclerosis (may include subjects with Secondary PMS [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. Expanded Disability Status Scale 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 follicle-stimulating hormone [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 (subject must be able to understand the informed consent) indicating that the subject 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 (subject reported adequate in absence of written medical record) in subjects with EDSS of 2 or less.
3. Treatment with rituximab, ocrelizumab, mitoxantrone, or lymphocyte-depleting therapies (eg, alemtuzumab, anti-CD4, 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 (eg, natalizumab, fingolimod) within 24 weeks prior to randomization.
5. Use of intravenous (IV) immunoglobulins (Ig), 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 (ie, 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 human immunodeficiency virus (HIV), hepatitis C (HCV) antibody and/or polymerase chain reaction, hepatitis B surface antigen (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 subject:

    - Has a history of or current diagnosis of active tuberculosis (TB)

    or

    - Is currently undergoing treatment for latent TB infection (LTBI)

    or

    - Has an untreated LTBI as determined by documented results within 3 months of the Screening visit of a positive TB skin test with purified protein derivative with induration $\geq$ 5 mm

    or

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

    Subjects 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. Subjects 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 Columbia-Suicide Severity Rating Scale (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. Subjects 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 cytochrome P450 3A (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 electrocardiogram (ECG), or an active infective process or any other clinically significant abnormality on Screening chest X-ray (CXR) taken within 4 weeks of the first dose, per Investigator opinion. If a CXR has been taken within the previous 3 months and results are available and normal, the CXR does not need to be carried out.
33. Estimated glomerular filtration rate (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 (eg, acute renal insufficiency).
34. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), amylase, or lipase > 2× above upper limit of normal (ULN) of laboratory reference range, total bilirubin > 1.5× ULN, any other clinically significant laboratory abnormality.
35. B cell (CD19) count < 50% of the lower limit of normal 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 $< 3500/mm^3$

CCI [redacted]

5.4 Criteria for Randomization and Initiation of Trial Treatment

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

Eligible subjects 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 CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

5.6 Criteria for Subject Withdrawal

Subjects 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 electronic case report form (eCRF) and source documents, and should be followed up by the Investigator.

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

5.6.1 Withdrawal from Trial Therapy

Subjects 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 subject must be withdrawn if any of the following occur:

- Withdrawn from study (see Section 5.6.2)
- Adverse events, if discontinuation of IMP is desired or considered necessary by the Investigator and/or subject
- Use of prohibited medications, as defined in Section 6.4.2. However, any medications that are considered necessary for the subject's well-being may be given at the discretion of the Investigator. Use of a prohibited medication may be cause for a subject 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 subject
- 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 subject 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

Subjects may withdraw from the trial at any time without giving a reason. Withdrawal of consent will be considered withdrawal from the trial. Subjects 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. Subjects 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 subject 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)
- Subject withdrew consent
- Participation in another clinical trial
- Lost to follow-up
- Any events that endanger the safety of the subject.
- Sponsor decision to end clinical trial.

If a subject fails to return for the post-treatment safety visit, all attempts should be made to contact the subject to ensure the reason for not returning is not an AE. Likewise, if a subject wishes to discontinue from the trial (eg, for personal reasons), attempts should be made to establish the true reason is not an AE (bearing in mind the subject 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 subject'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 subject has failed to attend scheduled trial assessments, the Investigator must determine the reasons and the circumstances as completely and accurately as possible.

Subjects who have withdrawn after randomization (eg, due to AEs or lack of efficacy) will not be replaced and will not be eligible to participate in the OLE Period. CCI [redacted] Subjects 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 subjects should be made and documented (2 phone calls and 1 acknowledgement of receipt letter).

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 Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) will be informed about the discontinuation of the trial in accordance with applicable regulations.

5.8 Definition of End of Trial

The end of the trial is defined as the last contact date with the last subject who participates in this trial (last subject's last visit).

A clinical trial protocol may not be considered closed as long as:

- Any subject 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 subject
- 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 subject.

6 Investigational Medicinal Product and Other Drugs Used in the Trial

The term "Investigational Medicinal Product" refers to the investigational drug undergoing study (ie, 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 Good Manufacturing Practice (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 European Union (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

Subjects 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), subjects will self-administer study medication at a schedule similar to the 75 mg M2951 twice daily dosing schedule (ie, 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.

CCI [redacted]

Subjects will self-administer the IMP at a set time each day (every 12 hours ± 2 hours). Subjects 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 [redacted]) are completed.

If a dose is missed, the subject 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 subject 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 subject should refrain from taking their scheduled morning dose and take their dose of IMP when instructed at the visit.

Subjects will be asked to record the date and time of dosing and food intake around dosing in a subject diary.

Subjects 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, subjects will resume the 240 mg twice daily dosing. If the subject is still unable to tolerate the study treatment, the subject must permanently discontinue study treatment as described in Section 6.4.4.2.

6.3 Assignment to Treatment Groups

Eligible subjects 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. CCI

6.4 Concomitant Medications and Therapies

All concomitant medications taken by the subject 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 subject's previous treatment and will therefore not be provided by the Sponsor. Any such medications prescribed or used should be recorded in the eCRF.

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

•Up to 1 g daily of methylprednisolone administered intravenous for up to 5 consecutive days.

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

Subjects 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 subjects' 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 subject from the IMP (see Section 5.6.1).
- Oral or parenteral steroids, except rescue medication to treat a relapse of MS, or adrenocorticotropic hormone.
- Biologic therapies
- Intravenous Ig therapy and/or plasmapheresis
- Treatment with teriflunomide
- Daclizumab
- Live and live-attenuated vaccines
- Changes in dalfampridine dose (subject 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 5 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.
- Any investigational drug or experimental procedure for MS.

Table 5 Examples of Inhibitors or Inducers of CYP3A Enzymes or Substrates with Narrow Therapeutic Range

Inhibitors		
Strong	**Moderate**	**Weak**
Boceprevir, clarithromycin, conivaptan, grapefruit juice,[a] indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, and voriconazole	Amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice,[a] imatinib, and verapamil	Alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, ginkgo, goldenseal, isoniazid, nilotinib, oral contraceptives, ranitidine, ranolazine, tipranavir/ritonavir, and zileuton
Inducers		
Strong	**Moderate**	**Weak**
Avasimibe, carbamazepine, phenytoin, rifampin, and St. John's wort	Bosentan, efavirenz, etravirine, modafinil, and nafcillin	Amprenavir, aprepitant, armodafinil, echinacea, pioglitazone, prednisone, and rufinamide
Substrates With a Narrow Therapeutic Range		
Alfentanil, astemizole,[b] cisapride,[b] cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine[b]		

CYP=cytochrome P450.

[a] The effect of grapefruit juice varies widely among brands and is concentration, dose, and preparation dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation is used (eg, high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation is used (eg, low dose, single strength).

[b] Withdrawn from the USA and certain other markets because of safety reasons.

Note: This is not an exhaustive list. For an updated list, see Tables 5, 6, and 7 in the following link: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm

Note: A strong inhibitor is defined as an inhibitor that increases the area under the plasma concentration time-curve (AUC) of a substrate sensitive for that CYP ≥ 5-fold or decreases clearance by > 80%, and a strong inducer decreases AUC of a substrate by ≥ 80%.

Note: A moderate inhibitor is defined as an inhibitor that increases the AUC of a substrate sensitive for that CYP ≥ 2-fold but < 5-fold or decreases clearance by 50%-80%, and a strong inducer decreases AUC by 50%-80%.

Note: A weak inhibitor is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP < 2-fold or decreases clearance 20%-50%, and a weak inducer decreases AUC by 20%-50%.

Note: CYP substrates with narrow therapeutic range refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns (eg, Torsades de pointes).

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 re-occur (also see Table 6), as relevant, and re-initiation following temporarily withholding of IMP should be discussed with the Medical Monitor:

- For a neutrophil count < 500/mm^3 or platelet count < 25,000/mm^3 (Grade 4) or neutrophil count 500 to 999/mm^3 (Grade 3) with fever 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 decrease to Grade 2, temporarily hold the IMP and recheck the value. Re-initiate the IMP after discussion with the Medical Monitor if no further downward trend is observed.
- For an increase in AST or ALT to > 3× ULN and increase in bilirubin to > 1.5× ULN (Grade 2 or higher), the IMP should be permanently withdrawn. The subject should be followed with additional testing as needed until a return to ULN. Consultations with specialists, such as a hepatologist, can be considered at the discretion of the Investigator and in conjunction with the Medical Monitor.
  - For an increase in AST or ALT to > 5× ULN without bilirubin elevation, the IMP should be permanently withdrawn. The subject should be followed with additional testing as needed until a return to ULN. Consultations with specialists, such as a hepatologist, can be considered at the discretion of the Investigator and in conjunction with the Medical Monitor.
  - For any other increase in AST, ALT, or an increase in bilirubin to Grade 2, temporarily hold the IMP and recheck the value. At which time, the Investigator in conjunction with the Medical Monitor should review the results and if necessary consult with specialists, such as a hepatologist (at the discretion of the Principal Investigator), and then re-initiate the IMP after final discussion with the Sponsor.

A comprehensive hepatic panel is requested for subjects 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:

- INR, PTT, fibrinogen, hsCRP
- Hepatitis serology: anti-HAV IgG, anti-HAV IgM, HBsAg, anti-HBc, anti-HBsAg, anti-HCV, anti-HEV IgG and IgM, anti-VCA IgG and IgM, anti-EA IgG, anti-EBNA IgG, anti-CMV IgG and IgM
- Antinuclear antibody, anti-smooth muscle antibody, antibody to liver-kidney microsomes

- Albumin

- 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 to 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 re-initiate 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× from Baseline, temporarily hold the IMP and recheck the value within 24 hours of receipt. Discontinue the IMP if the value does not decrease, or re-initiate 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 (ie, returns to Grade 2), IMP can be resumed.

Table 6 Guidelines for Withholding or Permanent Withdrawal of IMP

Parameters	Grade 1	Grade 2	Grade 3	Grade 4[b]
Neutrophil count decreased	No change to IMP	No change to IMP	< 1000 – 500/mm^3; < 1.0 – 0.5 × $10e^9$/L[a]	< 500/mm^3; < 0.5 × $10e^9$/L
Platelet count decreased			< 50000 – 25000/mm^3; < 50.0 – 25.0 × $10e^9$/L[a]	< 25000/mm^3; < 25.0 × $10e^9$/L
Neutrophil count with fever			500/mm^3 - 999/mm^3	
Platelet count with bleeding			25000 – 49999/mm^3	
AST or ALT		> 3.0 – 5.0 × ULN[a]	> 5.0 – 20.0 × ULN[b]	> 20.0 × ULN
AST or ALT with bilirubin increased >1.5 × ULN		> 3.0 – 5.0 × ULN[b]	> 5.0 – 20.0 × ULN[b]	> 20.0 × ULN
Bilirubin	> ULN - 1.5 × ULN[a]	> 1.5 – 3.0 × ULN[b]	> 3.0 – 10.0 × ULN[b]	> 20.0 × ULN

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

Permanently withdraw IMP.

a. Temporarily withhold and recheck value. The subject should be followed with additional testing as needed until a return to the ULN. At which time, the Investigator in conjunction with the Medical Monitor should review the results and if necessary consult with specialists, such as a hepatologist (at the discretion of the Principal Investigator), and then re-initiate the IMP after final discussion with the Sponsor.

b. Permanently withdraw IMP.

6.4.4.2 For Tecfidera Only

- For a lymphocyte count < 500/mm^3 for > 24 weeks, Tecfidera should be temporarily withheld and the subject monitored until lymphocyte counts are back to the lower limit of normal (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 subject 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 (eg, 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 Common Terminology Criteria for AEs (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 30°C. 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 subject 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 subject trial numbers.

The Investigator site should maintain records, which adequately document that subjects 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 subject may be redispensed to a different subject.

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 subject(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 and Table 2. All other dosing will be done by the subject or subject's caregiver at home throughout the rest of the trial. Subjects or subject's caregiver will be asked to record the date and time of dosing and food intake around dosing in a subject diary.

Subjects will be instructed to bring all IMP, including the used packaging and all blisters, to each trial visit indicated in Table 1 and Table 2, and to allow for the assessment of compliance with trial treatment. Prior to discharge from each scheduled visit, subjects 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 and Table 2, 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 subjects, 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.

The bioanalytical laboratory(ies) responsible for the analysis of the CCI and CCI samples will be allowed to be partially unblinded during study conduct using masked subject identifiers, to support association of CCI data with M2951 dose and placebo treatment codes for timely decision making, but prevent association of treatment codes with any other clinical data, such as efficacy or safety data.

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 subject 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 subjects, site staff, and the Investigator blinded to M2951 dose group, and with the Assessing Neurologist and central MRI reader blinded to all treatments. CCI

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 subject. 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 subject emergency card provided to each subject (see Section 9.4).

Under certain circumstances, the IDMC or Drug Safety may be required to unblind the treatment assignment for an individual subject following a serious adverse event (SAE) or other serious event; eg, 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 subject 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 Subjects after End of Trial

After a subject has completed the trial or has withdrawn early, the subject is free to access further treatment as deemed appropriate by the Treating Investigator. The Sponsor will not provide any additional care to subjects after they leave the trial because such care should not differ from what is normally expected for subjects 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 subject, the Investigator will obtain written informed consent as described in Section 9.2.

Throughout the trial, subjects will undergo the assessments detailed in Table 1 and Table 2, including collection of patient-reported HRQoL data and blood sampling. Completion of the HRQoL instrument SF-36v2 shall always be done before any other procedure or Investigator interaction of the visit takes place. 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.
- CCI [redacted]
- 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 subject 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 subject's clinical response and laboratory findings. The Treating Investigator will also be responsible for the treatment of relapses and determining if non-MS-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 subject's treatment, laboratory data, adverse event 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 subject's neurological state, where possible. Both the Treating Investigator and the subject 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 non-MS 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 subject'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 subject to participate in the trial. If a subject does not meet eligibility criteria, the subject can be retested and rescreened once at the Investigator's discretion.

If there are no clinically significant findings and the subject meets all protocol-defined inclusion criteria and none of the exclusion, the subject will be considered as eligible to be enrolled in the trial. Subjects 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 subjects who failed Screening: informed consent, demographics, reason for screen failure, AEs from the date of informed consent until the subject 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 SF-36v2 HRQoL questionnaire, 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 (eg, CCI and CCI occupancy 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. Subjects 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
- SF-36v2 HRQoL questionnaire
- 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, B, CCI cell counts; CCI occupancy; and 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:

- SF-36v2 HRQoL questionnaire
- 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); B, CCI cell count and CCI (Week 4 and 24 only); CCI
- 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 subject 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 subjects to self-administer the urine pregnancy test, and will contact the subject 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 main study, for subjects 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)
- CCI

Safety visits will be conducted after obtaining subject'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 patients, these evaluations will start after Visit 4. It is preferable for chemistry monitoring to be performed at the Investigator's site. Patients who are visiting the site will be asked for additional blood samples for CCI evaluation at these visits. An additional physical examination may be performed at the Investigator's discretion based on the subject'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 subject cannot return to the site for the additional blood draws, chemistry monitoring should be done locally; any subjects completing a supplemental safety visit locally will not have CCI samples collected at that visit.

7.1.4 Unscheduled Visit for Neurological Worsening and Relapse Assessment

Subjects 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 subject 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 non-qualifying 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 subject being exposed to gadolinium more than once in a 4-week period, ie, 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 subjects who do not continue in the OLE or subjects who received Tecfidera during the 48-week main study and choose to participate in the OLE):

- SF-36v2 HRQoL questionnaire
- 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; B, CCI cell and subtype count; and CCI .
- Urine collection for urinalysis and, if necessary, microscopy and protein:creatinine ratio; urine pregnancy testing (women only).
- MRI assessment.

CCI [redacted]

CCI [redacted]

[redacted]

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 subjects who do not participate in the OLE Period or 28 days (± 7-day window) after the OLE End of Treatment Visit for subjects who participate in the OLE Period. There will be only one 4-week Safety Follow-up/End of Trial Visit per subject, 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. If a subject 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 subject is not eligible to enter the OLE Period.

See Table 1 and Table 2 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); B, 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 subject, 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 chest X-ray will be assessed. Baseline disease will be assessed by EDSS and MRI. Baseline QoL using the SF-36v2 questionnaire will also be assessed.

7.3 Efficacy Assessments

The following efficacy assessments will be undertaken, as outlined in the Schedule of Assessments (Table 1 and Table 2). During treatment, ie, Day 1 to Week 48 (CCI), 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 subjects receiving Tecfidera who choose to enter the CCI If a subject 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, subjects with acute renal insufficiency (eGFR < 45 mL/min/1.73m^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 non-MS 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 subjects 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 subject being exposed to gadolinium more than once in a 4-week period, ie, 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 subject's level of disability will be assessed using the EDSS as outlined in Table 1 and Table 2.

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 subject 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

Subjects will be assessed for MS relapse at visits as outlined in Table 1and Table 2 beginning at Week 4. Relapse will also be assessed at any Unscheduled Visit for Neurological Worsening and Relapse Assessment (see Section 7.1.4). CCI [redacted] 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 (ie, 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. Subjects 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 non-permitted medication (see Section 5.6.2).

A non-qualifying 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 B, CCI cell counts).

Comprehensive assessment of any apparent toxicity experienced by each subject 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 subject (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 subject or clinical investigation subject 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 (eg, 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 (eg, 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 (eg, 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 subject 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 subject 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 (eg, an overnight stay to facilitate intravenous therapy) are not considered SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (eg, 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 subject will be queried on changes in his or her condition. During the reporting period, any unfavorable changes in the subject's condition will be recorded as AEs, whether reported by the subject 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 subject 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.

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 (eg, medical history, concomitant drugs). Additional documents may be provided by the Investigator, if available (eg, 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 (eg, 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 subjects 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 subjects, 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 Subjects with Adverse Events

Adverse events 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. All SAEs ongoing at the 4-week Safety Follow-up/End of Trial Visit must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the subject 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 (eg, 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 subjects and to pregnancies in female partners of male subjects. 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 subjects 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 subject 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 subject occurring during the course of the trial, the subject must be discontinued from trial medication immediately. The Sponsor/designee must be notified without delay and the subject 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 and Table 2). All samples should be clearly identified. Sample collection, preparation, and handling/shipment procedures are described in the Laboratory Manual.

Table 7 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

Supplementary LFT visits	• Aspartate aminotransferase • Alanine aminotransferase • Alkaline phosphatase • γ-Glutamyl-transferase	• Bilirubin (total)	
Hepatic panel	• International normalized ratio • Partial thromboplastin time • Fibrinogen • hsCRP	• Hepatitis serology: anti-HAV IgG, anti-HAV IgM, HBsAg, anti-HBc, anti-HBsAg, anti-HCV, anti-HEV IgG and IgM, anti-VCA IgG and IgM, anti-EA IgG, anti- EBNA IgG, anti-CMV IgG and IgM	• Antinuclear antibody, anti-smooth muscle antibody, antibody to liver-kidney microsomes • Albumin
Hematology	• Hematocrit • Hemoglobin • Red blood cell count • Mean corpuscular volume • Mean corpuscular hemoglobin • Mean corpuscular hemoglobin concentration • Reticulocyte count	• Platelet count • White blood cell count • B, 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

βhCG=β-human chorionic gonadotropin, CMV=cytomegalovirus, EA=early antigen, EBNA=Epstein-Barr nuclear antigen, eGFR=estimated glomerular filtration rate, ESR=erythrocyte sedimentation rate, FSH=follicle-stimulating hormone, HAV=hepatitis A virus, HBc=hepatitis B core antigen, HBsAg=hepatitis B surface antigen, HBV=hepatitis B virus, HCV=hepatitis C virus, HEV=hepatitis E virus, HIV=human immunodeficiency virus, hsCRP=high sensitivity C-reactive protein, IDMC=independent data monitoring committee, Ig=immunoglobulin, CCI VCA=viral capsid antigen.

a. To be done only when specified in Table 1 and Table 2 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.

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 and Table 2). 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 subject's arm unconstrained by clothing or other material. The blood pressure should be assessed on the same arm for each subject throughout the trial.

7.4.4.2 Physical Examinations

Physical examinations will be assessed at each site as indicated in Table 1 and Table 2. 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. CCI [redacted]. 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).

Posterioanterior CXRs will be performed during Screening according to local standard practice. CCI [redacted] Subjects 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 and Table 2.

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.

7.4.6 B Cell Counts

Blood samples for B cell counts will be obtained predose at Screening, on Day 1, and at Weeks 4, 24, and 48. An additional sample will be collected at the 4-week Safety Follow-up/End of Trial Visit (main and OLE study). CCI [redacted]

The actual date and time of each sample will be recorded. Samples will be analyzed by the central laboratory selected by the Sponsor using an appropriately validated bioanalytical method. Samples will be collected, labeled, processed, stored, and shipped according to the instructions in the Laboratory Manual.

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CCI [redacted]

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CCI [redacted]

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[redacted]

7.6.5 Use of Samples for Additional Analysis

CCI [redacted]

7.7 Health-Related Quality of Life Assessments

7.7.1 Short Form 36-item Health Status Survey

The SF-36v2 is a 36-item questionnaire that measures 8 areas of subject reported health rated from 0 to 100 for a total score ranging from 0 to 800 (21-25). The areas are:

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

The SF-36v2 will be measured in all subjects as indicated in Table 1 and Table 2. Completion of the SF-36v2 shall be done before any other procedure or Investigator interaction takes place.

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 subjects. The C-SSRS will be measured in all subjects as indicated in Table 1 and Table 2. The C-SSRS Screening Scale will be used in the main study and CCI [redacted] 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 subjects 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 negative binomial (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 subjects 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 subjects will enter the main study. CCI [redacted]

The Family-wise Type I error rate (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 subjects 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:

- Annualized relapse rate (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
- 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, 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
- Annualized relapse rate, 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.

8.3.3 Exploratory Endpoints

Exploratory endpoints are as follows:

- [redacted] CCI [redacted]
- Change in HRQoL as measured with SF-36v2 (physical component summary [PCS]/mental component summary [MCS] and sub-domains) over time (area under the curve) in all subjects

- Change in HRQoL as measured with SF-36v2 (PCS/MCS and sub-domains) from Baseline to Week 24 and from Baseline to Week 48 in all subjects
- CCI

CCI

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 subjects who receive at least 1 dose of trial treatment. Subjects 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 subjects randomly allocated to a treatment, based on the intention to treat "as randomized" principle (ie, the planned treatment regimen rather than the actual treatment given in case of any difference).

Modified Intent-To-Treat Analysis Set

The modified ITT (mITT) Analysis Set consists of all subjects who belong to both the ITT and Safety Analysis Sets, and who have at least one baseline and one post-baseline MRI assessment.

Per-Protocol (PP) Analysis Set

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

CCI [redacted]

CCI [redacted]

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 integrated analysis plan (IAP) will be developed.

Continuous variables will be summarized descriptively using the number of observations, mean, standard deviation (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 subjects in the treatment group and analysis set being presented, unless otherwise specified (eg, on some occasions, percentages may be calculated out of the total number of subjects 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% confidence intervals (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 subjects will be included in individual subject 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 Clinical Trial Report (CTR). Additional exploratory analyses will be conducted as deemed appropriate.

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 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 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 negative binomial 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 subject in a given M2951 treatment group, and Y denotes the primary endpoint evaluated for a subject in the placebo group. The FWER, ie, 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 subject-years of observation.

The multiple-comparison procedure for testing the key secondary efficacy endpoints will be provided in the IAP. Other secondary efficacy endpoints will be analyzed for exploratory purposes. 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 pre-baseline 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 subject being qualified relapse-free at Week 24, where subjects 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 pre-baseline 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 an analysis of covariance (ANCOVA) model of 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.

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.

8.5.4 Analysis of Safety and Other Endpoints

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

8.5.4.1 Safety

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

Serious AEs, 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.

Adverse events 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 subjects 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 subject and time point.

8.5.4.2 Patient-reported Health-Related Quality of Life (HRQoL)

Descriptive statistics for each time point and change from baseline will be provided for each health domain score and the physical and mental component summary scores (PCS/MCS) for each assessment time point.

In addition, change in HRQoL for PCS/MCS and sub-domains over time (area under the curve) will be compared between different M2951 treatment arms and placebo.

Further details on psychometric analyses will be presented in the IAP that will be finalized before database lock.

8.5.4.3 CCI [redacted]

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CCI [redacted]

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CCI [redacted]

CCI [redacted]

CCI [redacted]

8.6 Interim and Additional Planned Analyses

There will be 3 analyses: (1) a primary analysis, triggered when 100% of subjects enrolled reach Week 24 of treatment, or prematurely discontinue from treatment; (2) a Week 52 analysis, triggered when 100% of subjects enrolled either reach Week 52 (4-week Safety Follow-up Visit) and complete the study, enroll in the OLE, or prematurely discontinue from study; and (CCI [redacted] No interim analyses are planned.

Primary Analysis

When the last subject 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.

Week 52 Analysis

The Week 52 analysis will occur when the last subject 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.

CCI [redacted]

[redacted].

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 subjects 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 US Food and Drug Administration (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 Sub-investigators 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 Subject Information Sheet and Informed Consent

An unconditional prerequisite for each subject 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 subject by the Investigator or an appropriate designee (if local regulations permit) before informed consent is obtained.

A Subject 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 subject, the Investigator or a designate will inform the subject verbally of all pertinent aspects of the trial, using language chosen so that the information can be fully and readily understood by laypersons. The subject 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 subject 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 subject and the Investigator. CCI [redacted]

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

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

CCI [redacted]

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 subject prior to participation.

Whenever important new information becomes available that may be relevant to informed consent, the Investigator will revise the Subject Information Sheet and any other written information to be provided to the subjects and submit them to the IRB for review and opinion. Using the approved revised Subject Information Sheet and other written information, the Investigator will explain the changes to the previous version to each trial subject and obtain new written consent for continued participation in the trial. The subject 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 Subject Identification and Privacy

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

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing subject data. Subjects 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 Subject Card

Subjects will be provided with Emergency Medical Support cards supplied by the Sponsor for use during trial participation in order to provide clinical trial subjects 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 subject. 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 subject. 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 (eg, 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 subject concerned.

9.5 Clinical Trial Insurance and Compensation to Subjects

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 Subject 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 (eg, IMP Dossier, Subject 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 subject 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 Subject Files

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

- Subject'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, ie, the Sponsor trial number for this clinical trial, and subject 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 subject 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 subject 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 subject 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 subject data in the eCRF to be considered source data.

Electronic subject 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 Subject Identification List and the signed subject ICFs. If archiving of the Investigator Site File is no longer possible at the site, the Investigator must notify the Sponsor/designee.

All original subject 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 subject.

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 subject'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. CCI [redacted]

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 subject or another appropriate date to meet applicable requirements.

11 References Cited in the Text

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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:	129428
EudraCT Number:	2016-001448-21
Clinical Trial Protocol Date / Version:	08 August 2018 / Version 4.0

Protocol Lead responsible for designing the clinical trial:

I approve the design of the clinical trial:

_____ _____

Signature Date of Signature

Name, academic degree:	PPD
Function / Title:	PPD
Institution:	EMD Serono Research & Development Institute, Inc.
Address:	PPD
Telephone number:	PPD
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	129428
EudraCT Number	2016-001448-21
Clinical Trial Protocol Date / Version	08 August 2018 / Version 4.0

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.

_____ _____

Signature Date of Signature

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

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	129428
EudraCT Number	2016-001448-21
Clinical Trial Protocol Date / Version	08 August 2018 / Version 4.0
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:

Sponsor Responsible Persons not Named on the Cover Page

Name, academic degree:	PPD
Function / Title:	Clinical Trial Leader
Institution:	Merck KGaA
Address:	PPD
Telephone number:	PPD
Fax number:	PPD
E-mail address:	PPD

Name, academic degree:	PPD
Function / Title:	Biostatistician
Institution:	EMD Serono Research & Development Institute, Inc.
Address:	PPD
Telephone number:	PPD
Fax number:	PPD
E-mail address:	PPD

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. CCI [redacted] 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 subjects participating in the optional Open-label Long Term Extension Period, an additional 382 mL of blood (approximately) will be collected over the 100 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, Anti-HCV, 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
B, CCI cell count	10	5	50
CCI [redacted]			
Total			**604**

ALP=alkaline phosphatase, ALT=Alanine aminotransferase, AST=Aspartate aminotransferase, CCI [redacted], 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 [redacted] 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 7.

[c] Supplemental LFTs are included in this row as shown in Table 7.

[redacted] CCI [redacted]

Total Blood Volume during Open-label Extension Period

Assay	Approximate Sample Volume(mL)	Number of Samples	Approximate Subtotal Volume (mL)
Hematology, chemistry[a,b]	5	48	240
Immunoglobulins	5	4	20
B, CCI cell count	6	4	24
CCI			
Total			**382**

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 CO2, blood urea nitrogen, glucose, sodium, potassium, chloride, calcium, magnesium, phosphate as shown in Table 7.

[b] Supplemental LFTs are included in this row as shown in Table 7.

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 and a revised global amended protocol (Version 2.0) was issued on 28 November 2017. The revised global amended protocol (Version 3.0) was issued on 29 May 2018.

Amendment # 2

Rationale

The protocol was revised to include the recommendations from the Czech Republic Regulatory Authority (RA) 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 RA, 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:

- Update exploratory endpoints
- 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
- Clarify the schedule of collection of additional PK samples
- 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 subject randomized to the M2951/placebo arm
- Addition of a comprehensive hepatic panel for subjects 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 subjects 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 pharmacokinetic endpoints and statistical analyses
- Clarification of pharmacodynamics endpoints
- Clarification that separate informed consent will be collected for the MRI dummy run
- Clarification that soluble factors may be measured from pharmacokinetic blood samples if there is sufficient volume

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

Integrated Analysis Plan

Clinical Trial Protocol Identification No.	MS200527-0086
Title:	A Randomized, Double-Blind, Placebo-Controlled Phase II Study of Evobrutinib with a Parallel, Open-Label, Active Control Group (Tecfidera), in Patients with Relapsing Multiple Sclerosis to Evaluate Efficacy, Safety, Tolerability, Pharmacokinetics, and Biological Activity.
Trial Phase	II
Investigational Medicinal Product(s)	Evobrutinib
Clinical Trial Protocol Version	05 July 2016 / Version 1.0

Integrated Analysis Plan Authors

Coordinating Author	
Biostatistics, Merck	
Function	**Author(s) / Data Analyst(s)**
Biostatistician, PPD	PPD
Pharmacokineticist, PPD	PPD
Clinical Pharmacokineticist, Merck	PPD

Integrated Analysis Plan Date and Version	14 February 2018 / Version 1.0

Integrated Analysis Plan Reviewers

Merck/EMD-Serono Reviewers:

Function	Name
Lead Program Statistician	PPD
PPD	PPD
Lead Statistical Programmer	PPD
Global Patient Safety Product Lead	PPD
PPD	PPD
Medical Writing Lead	PPD
PPD	PPD
Principal Clinical Data Sciences Lead	PPD
Trial Data Manager	PPD
Clinical Biomarkers and Companion Diagnostics Lead	PPD
Clinical Pharmacology Consultant	PPD
PPD	PPD
PPD	PPD
Clinical Trial Lead	PPD

PPD Reviewers:

Function	Name
Statistical Scientist	PPD
Medical Responsible	PPD
Lead Medical Writer	PPD
Lead Statistical Programmer	PPD
Pharmacokineticist	PPD
Pharmacokineticist	PPD
Statistical Scientist	PPD

Signature Page

Statistical Analysis Plan: MS200527-0086
A Randomized, Double-Blind, Placebo-Controlled Phase II Study of Evobrutinib with a Parallel, Open-Label, Active Control Group (Tecfidera), in Patients with Relapsing Multiple Sclerosis to Evaluate Efficacy, Safety, Tolerability, Pharmacokinetics, and Biological Activity.

Approval of the IAP by all Merck Data Analysis Responsible is documented within ELDORADO.

Wet ink signature to be provided by PPD responsible for PPD use only.

Merck responsible	**Date**	**Signature**
PPD, Lead Program Statistician		
PPD **responsible**		
PPD, Biostatistician		

1 Table of Contents

2 List of Abbreviations and Definition of Terms

ADaM	Analysis Data Model
AE	Adverse Event
AIC	Akaike Information Criterion
ALT	Alanine Amino-Transferase
ARR	Annualized Relapse Ratio
AST	Aspartate Amino-Transferase
ATC	Anatomical Therapeutic Class
BE	Blinded Extension
BEA	Blinded Extension Analysis
BID	Twice daily
BOA	Biostatistics Outputs Assembly
BTK	Bruton's tyrosine kinase
CFB	Change From Baseline
CI	Confidence Interval
CDF	Cumulative distribution function
CS	Clinically Significant
CSR	Clinical Study Report
C-SSRS	Columbia- Suicide Severity Rating Scale
CXR	Chest X-Ray
EAIR	Exposure Adjusted Incidence Rate
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
EEA	European Economic Area
ETA	Inter-individual random error estimate
FOCE(I)	First order conditional estimation (with interaction)
FSFD	First subject first dose
FWER	Family-wise Type I error rate
Gd+	Gladolinium-positive
GI	Gastrointestinal

GLMM	Generalized Linear Mixed Model
HRQoL	Health-related quality of life
IA	Interim Analysis
IAP	Integrated Analysis Plan
IDMC	Independent Data Monitoring Committee
Ig	Immunoglobulin
IMP	Investigational Medical Product
IOV	Interoccasion variability
IV	Intravenous
IWRS	Interactive Web Response System
LOCF	Last Observation Carried Forward
MAR	Missing At Random
MCAR	Missing Completely At Random
MCS	Mental component summary
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intention to Treat
MMRM	Mixed-effect Model for Repeated Measures
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
M&S	Modeling and simulation
NB	Negative binomial
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NONMEM	Non-linear mixed effects modeling software
(Δ)OFV	(Difference in) Objective function value
PCS	Physical component summary
PD	Pharmacodynamics
PiC	Powder in capsule
PK	Pharmacokinetics
PsN	Perl-speaks-NONMEM
PT	Preferred Term

QD	Once daily
Q1	25th Percentile
Q3	75th Percentile
RoW	Rest of the World
RRMS	Relapsing-Remitting Multiple Sclerosis
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SCR	Screening Analysis Set
SDTM	Study Data Tabulation Model
SD	Standard Deviation
SE	Standard Error
SF-36v2	Short Form 36-item Health Status Survey version 2.0
SLDR	Subject Level Data Review
SOC	System Organ Class
SPMS	Secondary progressive multiple sclerosis
TEAE	Treatment Emergent Adverse Event
TLF	Table /Listing/Figure
ULN	Upper Limit of Normal
VPC	Visual predictive check
VS	Vital Signs
WHO-DD	World Health Organization Drug Dictionary

3 Modification History

Unique Identifier for SAP Version	Date of SAP Version	Author	Changes from the Previous Version
1.0	14 Feb 2018	PPD	NA – first version

4 Purpose of the Integrated Analysis Plan

The purpose of this Integrated Analysis Plan (IAP) is to document technical and detailed specifications for analyses of data collected for protocol MS200527-0086 dated 05 July 2016 (version 1.0). The IAP is based upon Section 8 (Statistics) of the trial protocol and is prepared in compliance with International Conference on Harmonization E9.

The first version (version 1.0) of the IAP includes details for the primary and blinded extension statistical analyses.

Results of the analyses described in this IAP will be included in the Clinical Study Report (CSR). Additionally, the planned analyses identified in this IAP will be included in regulatory submissions or future manuscripts. Any post-hoc, or unplanned analyses performed to provide results for inclusion in the CSR but not identified in this prospective IAP will be clearly identified in the CSR.

The final clinical database cannot be locked until the final IAP has been approved and signed.

Another SAP document (MS200527-0086_IDMC_SAP_v1.0) detailed specifications for the Independent Data Monitoring Committee (IDMC) analyses.

5 Objectives and Endpoints

	Objective	Endpoint	IAP section
Primary Objective	The primary objective is to evaluate the efficacy and dose-response of Evobrutinib on the number of gadolinium-positive (Gd+) T1 magnetic resonance imaging (MRI) lesions versus placebo after 24 weeks of treatment.	Primary Endpoint: • Total number of gadolinium-enhancing T1 lesions at Weeks 12, 16, 20, and 24	14.1
Key Secondary Objectives	To evaluate the efficacy and dose-response of Evobrutinib on clinical endpoints over 24 weeks versus placebo	Secondary Endpoints: • 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	14.2.1
	To evaluate the safety of Evobrutinib	Secondary Endpoint: • Safety as assessed by the nature, severity, and incidence 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).	15
Other Secondary Objectives	To evaluate the efficacy of Evobrutinib on additional MRI parameters over 24 weeks versus placebo	Secondary Endpoints: • Total number of new Gd+ T1 lesions at Weeks 12, 16, 20, and 24 • Mean per-scan number of Gd+ T1 lesions at Weeks 12, 16, 20, and 24 • Total number of new or enlarging T2 lesions at Weeks 12, 16, 20, and 24	14.2.2

		• 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 the efficacy of Evobrutinib on clinical and MRI endpoints from Weeks 24 to 48	Secondary Endpoints: • 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	14.2.2
	To evaluate the efficacy of Tecfidera on clinical and MRI endpoints over 24 weeks	Secondary Endpoints: • Total number of gadolinium-enhancing T1 lesions at Weeks 12, 16, 20, and 24 • Mean per-scan number of Gd+ T1 lesions at Weeks 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 EDSS at Week 24 • Total number of new Gd+ T1 lesions at Weeks 12, 16, 20, 24 • Total number of new or enlarging T2 lesions at Weeks 12, 16, 20, 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	14.2.2
	To evaluate the efficacy of Tecfidera on clinical and MRI endpoints from Weeks 24 to 48	Secondary Endpoints: • 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	14.2.2

	To evaluate the safety of Tecfidera	Secondary Endpoint: • Safety as assessed by the nature, severity, and incidence 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	15
Exploratory Objective	CCI [redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	14.2.9
	To explore the benefit of Evobrutinib treatment on patient-reported health related quality of life (HRQoL) versus placebo, and to evaluate the effect of Tecfidera on HRQoL	Exploratory Endpoints: • Change in HRQoL as measured with SF-36v2 (physical component summary [PCS]/mental component summary [MCS] and sub-domains) over time (area under the curve) in all subjects • Change in HRQoL as measured with SF-36v2 (PCS/MCS and sub-domains) from Baseline to Week 24 and from Baseline to Week 48 in all subjects	14.2.3

6 Overview of Planned Analyses

This IAP (Version 1.0) covers the analyses for futility, efficacy, CCI [redacted], and safety based on the data cut-offs for the primary and blinded extension analyses. Section 9 describes how data collected after the cut-off date will be handled.

6.1 Independent Monitoring Committee review

An IDMC will be set up to continually review available safety and tolerability data and will be mandated to make immediate decisions regarding the conduct of the trial; no additional risk minimization measures are proposed. IDMC meetings will take place every 4 months or as requested by the IDMC members. Details of the statistical analyses of the IDMC are provided in the IDMC SAP v1.0 and the IDMC charter v1.0.

6.2 Interim Analysis

If performed, the aim of the Interim Analysis (IA) was to evaluate overall futility based on the highest dose of Evobrutinib to determine whether or not to continue the study. The IA was to be triggered when the first 50% of subjects enrolled out of the planned enrollment reach Week 24 of treatment. It was planned that placebo subjects would continue at the 25 mg QD dose after Week 24, with consideration given to changing this dose based on data from the IA. CCI [redacted] analyses were not to be included in the IA.

When the last subject was enrolled in the study in July 2017, it was determined that only approximately 14 weeks would elapse between the first 50% of enrolled subjects reaching Week 24 (IA trigger point) and 100% of enrolled subjects reaching Week 24 (primary analysis trigger point). It was decided that the IA would not be conducted, as it would occur too late to support early decision-making, and IA conduct would interfere with preparations for the primary analysis. Thus this IAP does not provide specifications for the analysis of IA endpoints.

6.3 Primary Analysis

When the last subject 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 (including CCI [redacted]).

6.4 Blinded Extension Analysis

The blinded extension analysis will occur only when the last subject completes the Week 52 safety follow-up or discontinues early, the protocol violations are determined, and the database is locked for the blinded extension analysis. All endpoints based on Baseline to Week 52 data will be evaluated (except for CCI [redacted] endpoints collected to Week 24 which will have been fully evaluated at the Primary Analysis).

7 Changes to the Planned Analyses in the Clinical Trial Protocol

CTCAE Grades for Relevant Laboratory Parameters

The Grade 1 definitions for the laboratory parameters AST, ALT, bilirubin, amylase, and lipase in Table 4 in the protocol Version 1.0 were cited incorrectly. All laboratory abnormalities will be graded as specified in CTCAE (2), version 4.03. This table is also now removed from protocol version 2.0.

CCI [redacted]

[redacted]

Region Randomization Stratum

Due to extreme imbalance in enrollment between Eastern Europe and Western Europe, region will not be used for adjustment or stratification in the different analyses.

Secondary Endpoints wording

In the description of lesion endpoints in this protocol, the word "total" refers to summing over assessments at weeks 12, 16, 20, 24. So "total" does not apply to the lesion count observed at a single timepoint, such as week 48. To avoid confusion, wording of MRI secondary endpoints at Week 48 was changed by removing the word "total".

Wording of "Proportion of subjects who remain qualified relapse-free at Week 24" endpoint was changed to "Qualified relapse-free status at Week 24". The same correction was applied to this endpoint at Week 48. This update is also performed in protocol version 2.0.

Per-Protocol (PP) Analysis Set definition

The protocol defined the PP analysis set as all subjects who belong to the mITT Analysis Set, complete 24 weeks of treatment, and do not have any important protocol deviations. The definition has been clarified to specify "do not have any clinically important protocol deviations. "Clinically important" protocol deviations comprise the subset of important protocol deviations that lead to exclusion of a subject from an analysis set.

Pharmacodynamic (PD) Analysis Set definition

The protocol defined the PD analysis set as all subjects who receive at least 1 dose of Evobrutinib or placebo and have at least 1 measured PD endpoint, not including CCI [redacted], at a scheduled PD time point postdose without deviations or important events affecting PD, and who provide evaluable PD data.
Postdose is to be understood as post-baseline which can be confusing given the fact PD parameters are evaluated predose. Therefore, to avoid confusion, postdose was replaced with post-baseline.

Analysis of Secondary Endpoints

In the analysis of the key secondary endpoint, change from baseline (CFB) in EDSS at Week 24, the rank ANCOVA analysis decribed in Section 8.5.3 of the protocol will be replaced with Hodges-Lehmann estimation of the shift in distribution location, and a stratified Wilcoxon rank-sum test [Healy *et al* 2011], one test for each Evobrutinib versus placebo comparison, where the stratification will at a minimum adjust for categorical baseline EDSS. Categories such as ≤ 3.0 versus > 3.0, corresponding to a clinically meaningful threshold close to the median baseline (BL) value, will be considered. Descriptive statistics for Week 24 EDSS CFB values treated as continuous variables (i.e., mean, median, and range) will be reported. Per EMA Guideline on Clinical Investigation of Medicinal Products for the Treatment of Multiple Sclerosis (2015), mean EDSS CFB is not considered an appropriate efficacy parameter. Therefore, descriptive statistics for categorical Week 24 EDSS CFB, i.e., number and proportion improving, stable, or worsening, will also be reported. Here improvement is defined as a decrease of 1.0 point or more, stable condition as a change of no more than half a point in either direction, and worsening as an increase of 1.0 point or more.

In the analysis of the secondary endpoint CFB in T2 lesion volume at Week 24, the ANCOVA model of the appropriately transformed variable, described in Section 8.5.3 of the protocol, will be replaced with a Mixed-effect Model for Repeated Measures (MMRM) approach for the appropriately transformed variable. This approach will better exploit the data available at earlier timepoints (i.e., weeks 12, 16, 20) for subjects missing the Week 24 assessment, assuming data are missing at random (MAR). At a minimum, the model will adjust for baseline T2 lesion volume.

In the analysis of the secondary endpoint CFB in Gd+ T1 lesion volume at Week 24, the ANCOVA model of the appropriately transformed variable, described in Section 8.5.3 of the protocol, will be replaced with Hodges-Lehmann estimation of the shift in distribution location, and a stratified Wilcoxon rank-sum test, one test for each Evobrutinib versus placebo comparison, where the stratification will adjust for categorical baseline disease activity. Categories such as presence versus absence of Gd+ T1 lesion at baseline will be considered. The distribution of enhancing lesion volume has considerable probability mass at zero [van den Elskamp *et al* 2011], so Gd+ T1 lesion volume CFB is not amenable to transformation to an approximately normal random variable.

SF-36 Exploratory Analysis

In the analysis of SF-36 endpoints, the analysis of area under the curve (AUC), i.e, curve of SF-36 CFB versus time through Week 24, or through Week 48, will be omitted. The analysis of SF-36 score CFB at Week 24, or SF-36 score CFB at Week 48, will be retained and will be based on MMRM. Each model will include treatment, week of visit, and treatment-by-week interaction as fixed effects, random effect for subject and baseline adjustment for the corresponding SF-36 endpoint.

For each SF-36 endpoint, a figure will be added describing the distribution of % CFB at Week 24, with one curve for each treatment group (Evobrutinib or placebo). The estimated cumulative distribution function (CDF) curve for % CFB at Week 24 will display proportion of subjects having a value for % CFB at Week 24 ≤ x, where the range of x depends on the data. Based on blinded baseline data, the minimum baseline value of each SF-36 endpoint is strictly positive, so the % CFB values are well defined for each of the SF-36 endpoints.

Protocol Version 1.0 references to the Final Analysis

An open label extension has been added to the study in version 2.0 of the protocol. Assuming that there will be an analysis at the end of the open label extension period, the analysis planned for the end of the blinded extension period, identified as "final" in version 1.0 of the protocol, will not be the final analysis of the study. Therefore, the analysis planned for the end of the blinded extension period has been renamed as the blinded extension analysis (BEA) in this IAP.

8 Protocol Deviations and Analysis Sets

8.1 Definition of Protocol Deviations and Analysis Sets

Important protocol deviations are protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being.

The following important deviations will be identified and confirmed prior to or at the Data Review Meeting at the latest.

- Subjects who are dosed on the study despite not satisfying the inclusion criteria
- Subjects who develop withdrawal criteria whilst on the study but are not withdrawn
- Subjects who receive the wrong treatment or an incorrect dose
- Subjects who receive an excluded concomitant medication
- Deviation from Good Clinical Practice
- Inclusion and exclusion criteria violations
- Concomitant medication violations

- Other violations/events that may have a relevant influence on the CCI [redacted] (e.g., adverse events (AEs), vomiting, sample processing errors, inaccurate dosing, etc.)

Any important protocol deviations that lead to the exclusion of a subject from an analysis set will be considered clinically important (see Section 10.2).

In addition to protocol deviations that lead to exclusion of a subject from an analysis set, this study will allow for protocol deviations that lead to exclusion of a specific assessment on a subject from an analysis, but not all assessments for that subject. For example, if a subject uses high dose corticosteroids in the 3 weeks prior to a scheduled MRI scan, lesion data from that scan will be excluded from certain analyses and treated as missing.

All important protocol deviations should be documented in Clinical Data Interchange Standards Consortium Study Data Tabulation Model (SDTM) whether identified through sites monitoring, medical review and/or programming based on the inclusion/exclusion criteria presented in the protocol. Important protocol deviations are listed and described in MS200527-0086_List_of_deviations_v1.0.

8.2 Definition of Analysis Sets and Subgroups

Screening Analysis Set (SCR)
The SCR Analysis Set includes all subjects who signed the informed consent.

Safety Analysis Set (SAF)
The SAF consists of all subjects who receive at least one dose of trial treatment. Subjects will be analyzed according to the actual treatment they receive.

For safety analyses based only on the second 24-week treatment period, safety analysis set will be restricted to subjects having entered this period. This restriction will be identified as SAF-BE (Blinded Extension).

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

Modified Intent-To-Treat Analysis Set (mITT)
The mITT Analysis Set consists of all subjects who belong to both the ITT and Safety Analysis Sets, and who have at least one baseline and one post-baseline MRI assessment. Subjects will be analyzed according to the treatment they were randomized to.

For efficacy analyses based only on the second 24-week treatment period, mITT will be restricted to subjects having an MRI assessment in this period. This restriction will be identified as mITT-BE.

Per-Protocol (PP) Analysis Set

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

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CCI [redacted]

The use of the analysis sets in the different analyses is summarized in the following table:

Table 1: Analysis sets

Analyses	SCR Analysis Set	ITT Analysis Set	SAF Analysis Set	SAF-BE Analysis Set	PP Analysis Set	mITT Analysis Set	mITT-BE Analysis Set	C CI [redacted]	[redacted]	CCI [redacted]
Subject Disposition status	✓									
Analysis sets	✓									
Important Protocol Deviations		✓								
Demographic and Baseline Assessments						✓				
Prior Medications			✓							
Concomitant Medications			✓	✓						
Concurrent procedures			✓	✓						
Compliance and Exposure			✓	✓						

Analyses	SCR Analysis Set	ITT Analysis Set	SAF Analysis Set	SAF-BE Analysis Set	PP Analysis Set	mITT Analysis Set	mITT-BE Analysis Set	C CI		CCI
Safety Analysis			✓	✓						
Primary Efficacy Analysis		✓			✓	✓				
Secondary Efficacy Analysis and exploratory HRQoL Analysis						✓	✓			
CCI CCI										
Randomization listing		✓								

Descriptive statistics for number of Gd+ T1 lesions over time until Week 24 will be presented for the following subgroups:

- ≤ 1 versus ≥ 2 relapses in last 2 yrs (i.e., approximately low versus high disease activity)
- EDSS ≤ 3.0 vs EDSS ≥ 3.5 (i.e., approximately lower versus higher risk of transitioning from RRMS to SPMS with relapses).

9 General Specifications for Statistical Analyses

All statistical analyses will be performed by PPD.

Treatment groups and Investigational Medical Product (IMP)

Treatment groups are defined as placebo, Evobrutinib 25 mg QD, Evobrutinib 75 mg QD, Evobrutinib 75 mg BID, and Tecfidera. Unless otherwise indicated, all analyses will be presented separately for the five treatment groups. The IMPs are placebo, Evobrutinib, and Tecfidera.

Actual Treatment Assignment

For the first 24-week treatment period, a subject who received 2 different types of kits over the course of treatment, should be tabulated according to the kit received most frequently. If there is a "tie", the highest dose will be chosen.

For the second 24-week treatment period, the same rule as for the first 24-week treatment period will be applied, with a distinction between subjects taking Placebo in the first period and Evobrutinib 25 mg in the second period.

If by mistake, a subject taking placebo in the first period was to take Evobrutinib 75 mg QD in the second period, this subject would be analyzed in "Evobrutinib 75 mg QD" treatment group.

For overall tables that do not present within-group analyses, only subjects assigned to Evobrutinib or Tecfidera in the first period will be analyzed. Each subject will be tabulated according to the type of kit he/she received most frequently overall.

Presentation of Tables/Figures/Listings

For all analyses, Tables and Figures will be produced using true treatment groups. When data from only the first 24 weeks are reported, the following labels will be used: 'Placebo', 'Evobrutinib 25 mg QD', 'Evobrutinib 75 mg QD', 'Evobrutinib 75 mg BID', 'Tecfidera'. When data from week 24-48 or week 0-48 are reported, the Placebo label will be changed to 'Placebo + Evobrutinib 25 mg QD'.

Tables and figures will be sorted by treatment group (in the order stated above) and chronological scheduled time point (where applicable).

All data recorded during the trial will be presented in individual data listings, performed on the Safety Analysis Set (SAF), unless otherwise specified. All listings will be sorted by treatment group, subject, and scheduled time point (where applicable), if not otherwise stated. Further details are provided in the appropriate section for the analysis of the specific parameter.

Listings presented on the actual treatment, will consider the overall treatment assigned for subjects taking either Evobrutinib or Tecfidera in the first period. For subjects taking placebo in the first treatment period, treatment label will be either "Placebo" or "Placebo + Evobrutinib 25 mg QD" depending on whether they have entered the second period or not.

Presentation by Time Period

The time period corresponding to the first 24 weeks of treatment is of special interest, as the primary endpoint of the study is at Week 24, and subjects randomized to placebo will be switched to Evobrutinib at Week 24. Therefore, tabular summaries may include data from the period up through Week 24, from the period after Week 24, and from the overall study period. Listings will always present all available data in the database transfer.

For previous/concomitant medications, exposure duration, cumulative dose, compliance and safety (AEs, Labs, ECGs, vital signs, Ig levels, total B cell number), tables will be presented as follows:

For the primary analysis

When applicable, three sets of tables will be made based on data overall, data through Week 24 (first 24-week treatment period, including data from Safety Follow-up where appropriate), and data after Week 24 through Week 48 (second 24-week treatment period, including data from Week 52 Safety Follow-up visit where appropriate).

For the blinded extension analysis

When applicable, two sets of tables will be made. One set considering data overall and another one only considering data from after Week 24 through Week 48 (second 24-week treatment period, including data from Week 52 Safety Follow-up visit where appropriate).

Overall tables that do not present within-group analyses will be restricted to subjects receiving either Evobrutinib or Tecfidera in the first period. Overall tables that present within-group analyses will include all treatment groups, including subjects who receive placebo in the first period, and switch to Evobrutinib in the second.

For safety analyses not including biochemistry parameters or adverse events, any assessment performed until 30 minutes after drug intake on Week 24 will considered in the first 24-week treatment period.

Data handling after cut-off date for a planned analysis

A cut-off date will be applied at the SDTM level: for the primary analysis (resp. blinded extension analysis), all data posterior to the last dose of the last patient during the first (resp. second) 24-week treatment period will be removed from the database. Details on the implementation of this cut-off date are available in the document named *SDTM Cut-off date implementation rules_BTKi(M2951)-Compound_v2.0.docx*

Subjects discontinuing treatment early will have their data from the Safety Follow-up visit included in the primary analysis (resp. blinded extension analysis) if the Safety Follow-up visit occurs prior to the planned cut-off date. If there are subjects discontinuing treatment early whose Safety Follow-up visit occurred after the planned cut-off date, the exclusion of their Safety Follow-up data due to data cut-off will be mentioned in a footnote, where appropriate.

Data other than the date of death obtained after the cut-off will not be displayed in any listings or used for summary statistics.

Presentation of continuous and qualitative variables

Continuous variables including CC but not CC will be summarized using the following descriptive statistics:

- number of subjects (N)
- number and percentage of non-missing values
- number and percentage of missing values.
- mean, standard deviation (SD)
- median, 25th Percentile - 75th Percentile (Q1-Q3)
- minimum, and maximum

The number of digits for non-derived and derived data, presented in outputs or available in ADaM (Analysis Data Model) datasets, is specified in the Biostatistics Outputs Assembly (BOA) document.

For both continuous and qualitative variables, percentages such as 0% or 100% should be reported with the same format used for the column, together with the count of observations. For example, if the count of observations is zero, then display ‘0 (0.0)’; if the count of observations is 100% then display ‘xx (100.0)’.

Qualitative variables will be summarized by counts and percentages. The “Missing” category should always be displayed at baseline – even when there are no missing data at baseline. At timepoints other than baseline, the “Missing” category should only be displayed when there are missing data.

Unless otherwise stated, the calculation of proportions will be based on the number of subjects in the analysis set of interest. Therefore counts of missing observations will be included in the denominator and presented as a separate category.

The total of missing and non-missing observations at each timepoint will reflect the population still in the trial at that time. For example, if a subject is still in the trial at the timepoint but with missing data, that subject should be counted in the number of missing observations.

CCI [redacted]

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[redacted]

Definition of baseline

For the purpose of statistical analysis, baseline is defined as the last non-missing measurement (including those collected at an Unscheduled visit) prior to the first dose of study drug, as described in the following table. If baseline cannot be defined, then the baseline value will be treated as missing.

Table 2: Definition of baseline.

Randomized	Time Period	Baseline
Placebo	Initial 24-week treatment period	Last non-missing measurement prior to the first dose of study drug in the initial 24-week treatment period
	Blinded Extension (second 24-week treatment period)	Last non-missing measurement prior to the first dose of study drug in the Blinded Extension.
	Overall treatment period	Baseline definition will depend on whether the assessment being compared to baseline is from the initial 24-week treatment period or the Blinded Extension.
Evobrutinib/Tecfidera	All treatment periods	Last non-missing measurement prior to the first dose of study drug in the initial 24-week treatment period

Definition of change from baseline (CFB)

CFB and percent CFB at a given post-baseline visit will be computed as follows:

- CFB = visit value – baseline value
- Percent CFB = 100 * (visit value – baseline value) / baseline value

At the baseline visit, the CFB will be equal to zero and the percent CFB will be missing. For a given post-baseline visit, when the baseline value and the absolute value are both equal to zero, then the CFB and the percent CFB will be equal to zero as well.

Definition of duration

Duration will be calculated as the difference between start and stop dates plus 1 (eg, AE duration (days) = AE end date - AE start date + 1). Durations will be calculated only when both dates are available (imputed dates cannot be used for the duration computation) unless otherwise specified.

The time since an event will be calculated as:

- reference date minus date of event +1 (eg, days in study at onset of AE = AE start date - date of randomization + 1) if date of event is equal or greater than reference date
- reference date minus date of event (eg, days in study at onset of AE = AE start date - date of randomization) otherwise.

Conversion factors

The following conversion factors will be used to convert days into months or years: 1 month = 30.4375 days, 1 year = 365.25 days. For time windows calculation, 1 month is expressed as 30 days.

Presentation of missing data

In all subject data listings, partial dates, which are not to be imputed according to this IAP, will be presented using the format "_____YYYY".
When presented, imputed dates will be flagged (ie, D for day, M for month).

Missing statistics, eg, when they cannot be calculated, should be presented as 'nd', with 'nd' standing for 'not done'. For example, if n = 1, the measure of variability (SD) cannot be computed and should be presented as 'nd'.

In case of zero records available for presentation in a given TLF, an empty output with 0 occurrence or a sentence stating that there are no data will be provided. For tables of Adverse Events and Deaths (outputs required for EudraCT and/or clinicaltrial.gov), if there is no

observation, the output must contain the first line 'Subject with…' or 'Subject who died' displayed with 0 occurrence.

If a System Organ Class (SOC) or Anatomical Therapeutic Class (ATC) term is missing/not coded yet, then 'Uncoded SOC' (or 'Uncoded ATC') will be indicated at the ADaM level. When a Preferred Term (PT) is missing, it will be set to 'Uncoded PT:' TEAE verbatim text.

Handling of missing efficacy and HRQoL data

Total number of lesions at Weeks 12, 16, 20, 24

The imputation approach for the total number of lesions endpoint depends on whether the analysis is model-based or nonparametric.

When analyzing the total number of lesions endpoint using a NB model, no imputation is needed for subjects missing 1-3 of the 4 planned scans, as the offset parameter adjusts for the number of available scans. If a subject lacks any post-baseline evaluable MRI assessment, then scan count and lesion count are imputed using median values for scan count and lesions per-scan among subjects with available post-baseline scans, who are in the same treatment group, and who have the same value for the categorical baseline covariate. For example, a subject's imputed lesion count would be the product of the median number of scans (i.e., 4) and median lesions per-scan (i.e., 0.2), where the median values are based on subjects in the same treatment group, with the same value for the categorical baseline covariate. The imputed count (i.e., 0.8) will be rounded to an integer value (i.e., 1) as the NB model requires that the response variable be integer-valued.

In the longitudinal Poisson analysis of number of lesions at a single scan, which makes use of assessments at Weeks 12, 16, 20, and 24, no imputation is needed for subjects having at least one post-baseline score assessment prior to Week 24. If a subject lacks any post-baseline evaluable MRI assessment, then lesion count will be imputed for only the first post-baseline timepoint used in the GLMM analysis (i.e., Week 12), using the median lesion count at that timepoint among subjects with a scan at that timepoint, who are in the same treatment group, and who have the same value for the categorical baseline covariate.

When analyzing the total number of lesions endpoint using a nonparametric method (H-L estimate, Wilcoxon rank-sum test, Jonckheere test), the method assumes that the response variable arises from the same observation effort for each subject, so missing data must be imputed. If a subject is missing 1-3 of the 4 planned scans, missing scan values will be imputed with the average of available scan values. For example, if a subject has a lesion count of 3 from the week 12 scan, 1 from the week 16 scan, 1 from the week 20 scan, and missing value for the week 24 scan, a count of 1.67 will be imputed for week 24, leading to a total count of 6.67 for weeks 12-24. If a subject lacks any post-baseline evaluable MRI assessment, lesion count is imputed as the product of "4" and the median lesions per-scan, where the median is among subjects with available post-baseline scans, who are in the same treatment group, and who have the same value for the categorical baseline covariate. The imputed count will not be rounded to an integer value as the nonparametric analysis does not require that the response variable be integer-valued.

Mean lesions per-scan at Weeks 12, 16, 20, 24

No imputation is needed for subjects missing 1-3 of the 4 planned scans, as the variable amount of scans experienced by a subject is accounted for in the mean lesions per-scan response variable. If a subject lacks any post-baseline scan, then the endpoint is imputed using the median value for mean lesions per-scan, where the median is among subjects with available post-baseline scans, who are in the same treatment group, and who have the same value for the categorical baseline covariate.

Number of lesions at Week 48

In the analysis of lesion count at Week 48, a missing assessment at Week 48 will be imputed by the median Week 48 value among subjects having a Week 48 scan, who are in the same treatment group, and who have the same value for the categorical baseline covariate.

CFB in volume of T2 lesions at Week 24

In the MMRM analysis of the Week 24 CFB in volume of T2 lesions, appropriately transformed, which makes use of assessments at Weeks 12, 16, 20, and 24, no imputation is needed for subjects having at least one post-baseline volume assessment prior to Week 24. If a subject lacks any post-baseline evaluable MRI assessment, then Week 24 CFB in transformed T2 lesion volume will be imputed for only the first post-baseline timepoint used in the MMRM analysis (i.e., Week 12), using the mean CFB in transformed T2 lesion volume at that timepoint among subjects with an assessment at that timepoint, who are in the same treatment group, and who have a baseline covariate in the same quartile.

CFB in volume of T2 lesions at Week 48

In the nonparametric analysis of CFB in T2 lesion volume at Week 48, a missing scan value at Week 48 will be imputed by the median Week 48 CFB value among subjects having a Week 48 scan, who are in the same treatment group, and who have the same value for the categorical baseline covariate.

CFB in volume of Gd+ T1 lesions at Week 24 or Week 48

In the nonparametric analysis of CFB in T1 Gd+ lesion volume at Week 24, a missing scan value at Week 24 will be imputed by the median Week 24 CFB value among subjects having a Week 24 scan, who are in the same treatment group, and who have the same value for the categorical baseline covariate. The same approach will be used for CFB in T1 Gd+ lesion volume at Week 48.

ARR at Week 24 or Week 48

Subjects discontinuing treatment before Week 24 or Week 48 will be followed for relapse through Safety Follow-up visit.

When analyzing the ARR endpoint using a NB model, no imputation is needed, as the offset parameter specifies the time under observation, which adjusts for subjects who discontinue treatment before Week 24 or Week 48.

When analyzing the ARR endpoint using the Jonckheere test applied to subject-specific ARR (i.e., number of relapses experienced by the subject divided by follow-up experienced by the subject), there is again no need for imputation, as the variable amount of follow-up experienced by a subject is accounted for in the subject-specific ARR response variable.

Qualified relapse-free status at Week 24 or Week 48

In the analysis of proportion qualified relapse-free at Week 24, subjects who discontinue study prior to Week 24, without having a qualified relapse are counted as not being qualified relapse-free at Week 24. This imputation approach will be used for both the logistic model analysis and the Cochran-Armitage test. The same approach used for qualified relapse-free status Week 0-24 will be used for qualified relapse-free status Week 25-48.

Sensitivity analyses of this endpoint will apply other methods of imputation, as described in Section 14.2.1.

CFB in EDSS at Week 24 or Week 48

In the analysis of change from baseline (CFB) in EDSS at Week 24 using nonparametric analyses (H-L estimate, Wilcoxon rank-sum test, Jonckheere test), a missing assessment at Week 24 will be imputed by the median Week 24 CFB value among subjects who have a Week 24 assessment, who are in the same treatment group, and who have the same value for the categorical baseline covariate. The same approach will be used for CFB in EDSS at Week 48. A sensitivity analysis of this endpoint will apply another method of imputation, as described in Section 14.2.1.

CFB in HRQoL SF-36 score at Week 24 or Week 48

In the MMRM analysis of CFB in HRQoL (SF-36v2) score at Week 24, which makes use of assessments at Weeks 4, 8, 12, 16, 20, and 24, no imputation is needed for subjects having at least one post-baseline score assessment prior to Week 24. If a subject lacks any post-baseline score assessment, then Week 24 CFB in score will be imputed for only the first post-baseline timepoint used in the MMRM analysis (i.e., Week 4), using the mean CFB in score at that timepoint among subjects with an assessment at that timepoint, who are in the same treatment group, and who have a baseline covariate in the same quartile.

The same approach will be used for the MMRM analysis of CFB in HRQoL score at Week 48, which makes use of assessments at Weeks 12, 24, 36, and 48.

CDF for % CFB at Week 24

In the estimation of the CDF curve for % CFB at Week 24 (for each SF-36 endpoint and treatment group), a subject missing an assessment at Week 24 will have the assessment imputed via the last-observation-carried-forward (LOCF) value.

Descriptive Statistics

Missing data will not be imputed for descriptive statistics.

Handling of missing or partial adverse events dates

For defining the TEAE flag, missing or partial adverse event dates will be imputed as follows:

- In case the onset date is missing completely or missing partially but the onset month and year, or the onset year are equal to the start of IMP, then the onset date will be replaced by the minimum of start of IMP and AE resolution date.
- In all other cases the missing onset day or missing onset month will be replaced by 1.
- Incomplete stop dates will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of subject's death. In the latter case the date of death will be used to impute the incomplete stop date.
- Further information collected after the cut-off for an analysis (such as a fatal outcome) may be extracted from the Safety data base and presented separately in the CSR.

Imputed dates will be used for defining the TEAE flag only.

Handling of partially missing MS onset or diagnosis date

For time since MS onset or MS diagnosis, a missing onset day/month will be replaced by 1 for the duration derivation.

Trial day / Treatment day

Trial day is defined relative to the date of randomization. Treatment day is defined relative to the date of start of treatment.

In the case of subjects initially randomized to placebo, there will be a second start of treatment on the day of first administration of Evobrutinib in the second 24-week treatment period.

The day before the start date of treatment is defined as treatment day -1, i.e., there is no treatment day zero.

Repeated and unscheduled measurements

An assessment (safety or efficacy) at an unscheduled time point is linked to the previous scheduled visit in the SDTM dataset. Per schedule of assessments, EDSS and relapse data are collected at an unscheduled visit for neurological worsening and relapse assessment. Per the

eCRF package for the study, EDSS, relapse, and HRQoL data may be collected at any unscheduled visit.

Any relapse assessment for a subject at an unscheduled visit will contribute to the ARR estimate for that subject's treatment group, for the period including that timepoint.

EDSS and SF-36 assessments at unscheduled visits will contribute to by-visit summaries and inferential analyses (i.e., analysis of Week 24 CFB in EDSS, analysis of lesions summed over visits at Weeks 12-24, analysis of Week 24 CFB in SF-36 score via MMRM with visit as a covariate) based on analysis visit windowing, as defined in Tables 3-5.

For safety shift tables, assessments associated with unscheduled time points will be used in the definition of the worst assessment during the study.

Unique to this study, additional biochemistry assessments were associated with Unscheduled visits, necessitating the definition of windows for by-visit tabulations. Apart from biochemistry parameters, for by-visit tabulations, in case of multiple assessments (including unscheduled) linked to the same visit, the first available assessment (in chronological order) will be included in the summary of a visit.

Repeated and unscheduled measurements will be reported in the listings.

Early treatment and early trial termination assessments

EDSS, relapse, MRI, and HRQoL data are collected at the early treatment termination visit. In addition, relapse is assessed at the early trial termination visit.

By-visit summary statistics should be programmed such that the summary for the Early Treatment Termination visit is distinct from the summary for the Week 48 visit, and the summary for the Early Trial Termination visit is distinct from the summary for the Week 52 visit. This will support convenient comparison between treatment completers (at week 48) and discontinuers, and trial completers (at week 52) and discontinuers.

Any relapse assessment at an early treatment termination or early trial termination visit will contribute to the ARR estimate for the period including that timepoint.

EDSS, MRI, and SF-36 assessments at early treatment termination visits will contribute to inferential analyses (i.e., analysis of Week 24 CFB in EDSS, analysis of lesions summed over visits at Weeks 12-24, analysis of Week 24 CFB in SF-36 score via MMRM with visit as a covariate) based on analysis visit windowing, as defined in Tables 3-5.

For analyses by time period, data from safety follow-up will be included in the period in which the subject has discontinued.

Analysis visit windows

Assessments may be made at times other than the nominal times of planned visits, due to patient scheduling issues, unscheduled visits for neurological worsening or relapse assessment, or early treatment termination visits.

Explicit analysis visit windows for efficacy and HRQoL assessments, defined below, will be used to incorporate unscheduled assessments in by-visit summaries of EDSS, MRI endpoints, and SF-36v2, or inferential analyses that depend on assessments at specific visits. (Relapse will be summarized by time period, not by visit, so analysis visit windows are not needed.)

In by-visit summaries, assessments collected at early treatment termination visits will be summarized separately (i.e., visit windowing will not be applied), to support convenient comparison between treatment completers and discontinuers. However, in inferential analyses, analysis visit windows will be used to incorporate assessments collected at early treatment termination visits.

Table 3: Analysis visit windows for EDSS through Week 48

Analysis visit	Nominal analysis visit day	Analysis visit window (days)
		All treatment groups
Day 1	1	[1, 1]
Week 12	84	[2, 126)
Week 24	168	[126, 189)
Week 36	252	[189, 294)
Week 48	336	[294, 339)

Table 4: Analysis visit windows for MRI through Week 48

Analysis visit	Nominal analysis visit day	Analysis visit window (days)
		All treatment groups
Week 12	84	[2, 98)
Week 16	112	[98, 126)
Week 20	140	[126, 154)
Week 24	168	[154, 189)
Week 48	336	[189, 339)

Table 5: Analysis visit windows for HRQoL through Week 48

Analysis visit	Nominal analysis visit day	Analysis visit window (days)
		All treatment groups
Day 1	1	[1, 1]
Week 4	28	[2, 42)
Week 8	56	[42, 70)
Week 12	84	[70, 96)
Week 16	112	[96, 126)
Week 20	140	[126, 154)
Week 24	168	[154, 189)
Week 36	252	[189, 294)

Week 48	336	[294, 339)

After the first IDMC meeting, additional biochemistry assessments were added to the Schedule of Assessments. Sites were instructed to record these additional assessments as Unscheduled visits. Analysis visit windows, defined below, will be used to incorporate unscheduled assessments in by-visit summaries of the biochemistry parameters. By-visit summaries will summarize assessments collected at early treatment termination visits separately (i.e, visit windowing will not be applied to assessments collected at the early treatment termination visit), to support convenient comparison between treatment completers (at week 48) and discontinuers.

Table 6: Analysis visit windows for biochemistry parameters through Week 48

Analysis visit	Nominal analysis visit day	Analysis visit window (days)
		All treatment groups
Day 1	1	[1, 1]
Week 4	28	[2, 42)
Week 8	56	[42, 63)
Week 10	70	[63, 77)
Week 12	84	[77, 91)
Week 14	98	[91, 105)
Week 16	112	[105, 119)
Week 18	126	[119, 133)
Week 20	140	[133, 147)
Week 22	154	[147, 161)
Week 24	168	[161, $X^{[1]}$]
Week 26	182	($X^{[1]}$, $X^{[1]}$ + 21)
Week 28	196	[$X^{[1]}$ + 21, $X^{[1]}$ + 35)
Week 30	210	[$X^{[1]}$ + 35, $X^{[1]}$ + 49)
Week 32	224	[$X^{[1]}$ + 49, $X^{[1]}$ + 63)
Week 34	238	[$X^{[1]}$ + 63, $X^{[1]}$ + 77)
Week 36	252	[$X^{[1]}$ + 77, $X^{[1]}$ + 91)
Week 38	266	[$X^{[1]}$ + 91, $X^{[1]}$ + 105)
Week 40	280	[$X^{[1]}$ + 105, $X^{[1]}$ + 119)
Week 42	294	[$X^{[1]}$ + 119, $X^{[1]}$ + 133)
Week 44	308	[$X^{[1]}$ + 133, $X^{[1]}$ + 147)
Week 46	322	[$X^{[1]}$ + 147, $X^{[1]}$ + 161)
Week 48	336	[$X^{[1]}$ + 161, $X^{[1]}$ + 171)
$X^{[1]}$ corresponds to the time + 30 minutes where subjects are exposed for the first time to Evobrutinib in the second 24-week treatment period.		

Control of multiplicity

The truncated Hochberg test and a multistage testing algorithm (Dmitrienko *et al* 2011) will be used to control the family-wise error rate (FWER) due to multiple comparisons associated with evaluating 3 dose groups based on one primary endpoint and 3 key secondary efficacy endpoints.

The 3 hypotheses associated with the primary endpoint will be considered family F_1.

Consider the ordered p-values that arise from comparing the 3 Evobrutinib treatment groups to placebo on the basis of the primary endpoint: $p_{(1)} \leq p_{(2)} \leq p_{(3)}$. The truncated Hochberg test is a step-up test based on the following critical values:

$$a_i = \left[\frac{\gamma}{4-i} + \frac{1-\gamma}{3}\right]\alpha, i = 1, \ldots, 3$$

where $0 \leq \gamma < 1$ is the truncation fraction ($\gamma = 1$ implies the regular Hochberg test, while $\gamma = 0$ implies Bonferroni). Starting with F_1, the family of 3 hypotheses associated with the primary endpoint, the truncated Hochberg's step-up method proceeds as follows:

- Step 1. If $p_{(3)} < a_3$, reject $H_{(1)}$, $H_{(2)}$, and $H_{(3)}$ (i.e., conclude all 3 dose groups are more efficacious than placebo on the basis of the primary endpoint) and then stop; otherwise go to Step 2.
- Step 2. If $p_{(2)} < a_2$, reject $H_{(1)}$ and $H_{(2)}$, and then stop; otherwise go to Step 3.
- Step 3. If $p_{(1)} < a_1$, reject $H_{(1)}$ (i.e., conclude that only the dose group associated with the smallest p-value is more efficacious than placebo on the basis of the primary endpoint) and stop.

Given 2-sided $\alpha = 0.05$ for family F_1, the critical values (a_1, a_2, a_3) equal (0.0167, 0.0242, 0.0467) and (0.0167, 0.025, 0.05) for $\gamma = 0.9$ (truncated Hochberg) and $\gamma = 1.0$ (regular Hochberg), respectively.

The error rate function e(I) of the truncated Hochberg test, where I is the index set {1, …, |I|}, and |I| is the size of the index set, is given by:

$e(\{1\}) = 1\text{-}P(a_1) = a_1$

$e(\{1, 2\}) = 1\text{-}P(a_1, a_2) = 1 - (1-a_2)(1-2a_1+a_2)$

$e(\{1, 2, 3\}) = 1\text{-}P(a_1, a_2, a_3) = 1\text{-} (1-a_3)(1-3a_1+a_3\text{-}3(a_2)^2 + 6a_1a_2 \text{-}3\ a_1a_3 + (a_3)^2)$

Using the critical values calculated for family F_1, the error values (e({1}), e({1, 2}), e({1, 2, 3})) are equal to approximately (0.0167, 0.0332, 0.0495) for both $\gamma = 0.9$ (truncated Hochberg) and $\gamma = 1.0$ (regular Hochberg), respectively.

Let F_2 be the family of hypotheses associated with the key secondary endpoint ARR at Week 24, F_3 be the family of hypotheses associated with the key secondary endpoint qualified relapse-free status at Week 24, and F_4 be the family of hypotheses associated with the key secondary endpoint EDSS CFB at Week 24. Let A_i denote the index set corresponding to the retained hypotheses in F_i and $e_i(I)$ denote the error rate used in F_i, i=1, .., 3. The multistage testing algorithm for testing primary and key secondary endpoints in this study is as follows:

- Family F_1: The 3 hypotheses (concerning the primary endpoint) are tested at an α_1 level using the truncated Hochberg test ($\gamma < 1$) described above, with $\alpha_1 = \alpha = 0.05$.
- Family F_2: The 3 hypotheses (concerning the key secondary endpoint ARR at 24 weeks) are tested at an α_2 level using the truncated Hochberg test ($\gamma < 1$) described above, with $\alpha_2 = \alpha_1 - e_1(A_1)$.

- Family F_3: The 3 hypotheses (concerning the key secondary endpoint qualified relapse-free status at Week 24) are tested at an α_3 level using the truncated Hochberg test ($\gamma < 1$) described above, with $\alpha_3 = \alpha_2 - e_2(A_2)$.
- Family F_4: The 3 hypotheses (concerning the key secondary endpoint EDSS CFB at Week 24) are tested at an α_4 level using the regular Hochberg test ($\gamma = 1$) described above, with $\alpha_4 = \alpha_3 - e_3(A_3)$.

With this algorithm, the type 1 error rate is controlled over the multiple families of hypotheses due to the primary and key secondary endpoints at the 0.05 2-sided level. Other endpoints specified in the protocol will be assessed at a nominal significance level of 0.05, 2-sided, but the results will be viewed as exploratory.

Note that the portion of α to be carried from F_1 to F_2 depends on the set of primary null hypotheses retained by the 2-stage gatekeeping procedure, and is quantified via the error rate function of the first component of the 2-stage procedure. For this portion to be positive when at least one primary null hypothesis is rejected, it is required that the procedure be separable, i.e., $e_1(I_1|\alpha) < \alpha$ for all proper subsets I_1 of N_1, where N_1 is the index set of hypotheses included in family F_1. The Bonferronni procedure is separable, but the regular Hochberg procedure ($\gamma = 1$) is not. The truncated Hochberg procedure is separable and allows the multistage testing algorithm to be able to carry positive α from F_1 to F_2, from F_2 to F_3, and from F_3 to F_4. For the F_4 family, the regular Hochberg procedure (γ=1) may be used.

It is prespecified that $\gamma = 0.9$ will be used in the multistage testing algorithm whenever the truncated Hochberg test is used, although γ could be any value ≥ 0 and < 1, and could differ from family to family.

The penalty paid for performing multiple inferences in the families corresponding to the key secondary endpoints, F_i, i=2, 3, 4, depends on the number of hypotheses rejected at earlier stages. The sequence α_1, α_2, α_3, α_4 is non-increasing, so a hypothesis tested later in the sequence faces a higher hurdle unless all hypotheses are rejected in previously examined families.

A table summarizing the results of the multi-stage testing procedure will be provided that includes the p-values for each comparison of Evobrutinib treatment group to placebo treatment group, for the hypothesis family corresponding to the primary endpoint, and for the hypothesis families corresponding to each of the 3 key secondary endpoints. The critical value used to assess each p-value for significance will be reported next to the p-value, with an annotation indicating significance, illustrating the point in the procedure at which hypothesis testing halted. This summary table will be in addition to tables that summarize the analysis of a given endpoint.

Software

All statistical analyses will be performed using SAS® (Statistical Analysis System, SAS-Institute, Cary, North Carolina Windows Version 9.4 or higher). Graphics may be prepared with SAS Version 9.4, or higher; or Sigmaplot® 12.5, or higher (Systat Software, Inc., San Jose, California).

10 Trial Subjects

The subsections in this section include specifications for reporting subject disposition and treatment/trial discontinuations. Additionally procedures for reporting protocol deviations are provided.

10.1 Disposition of Subjects and Discontinuations

A table on screened subjects describing the number and percent of subjects in each of following disposition categories will be produced by treatment group:

- Total number of screened subjects, ie, subjects that gave informed consent (overall summary only);
- Number of subjects who discontinued prior to randomization and reason (overall summary only)
- Number of randomized subjects
- Number of randomized subjects who did not start treatment
- Number of randomized subjects who started treatment
- Number of randomized subjects with on-going treatment prior to Week 24 (applicable for dry run of the primary analysis)
- Number of randomized subjects who completed the first 24 weeks of treatment
- Number of randomized subjects who permanently discontinued treatment prior to Week 24 and reason
- Number of randomized subjects who were treated after Week 24
- Number of randomized subjects with on-going treatment after Week 24
- Number of randomized subjects who completed 48 weeks of treatment
- Number of randomized subjects who permanently discontinued treatment after Week 24 and prior to Week 48 and reason
- Number of randomized subjects in the follow-up phase who have not completed the trial (ie, treatment completed or discontinued and lack Safety Follow-up/End of Trial Visit)
- Number of randomized subjects who completed the trial
- Number of randomized subjects who discontinued from trial after randomization and reason

A table of randomized subjects not treated as randomized in the first (resp. second) double blind treatment period, including reason for not being treated as randomized will be produced by randomized treatment group for the primary (resp. blinded extension) analysis.

A table based on screened subjects describing the number and percent of subjects in each analysis set by treatment groups, will be produced:

- Number of screened subjects
- Number of subjects included in the ITT
- Number of subjects included in the SAF
- Number of subjects included in the SAF-BE
- Number of subjects included in the mITT
- Number of subjects in the mITT-BE
- Number of subjects included in the PP
- Number of subjects included in the CCI [redacted]
- Number of subjects included in the CCI [redacted]
- Number of subjects included in the CCI [redacted]

A table based on screened subjects describing the number of subjects by region, country within region and site will be produced by analysis set.

For the primary analysis, a listing of randomized subjects with subject number, randomization date, and randomized treatment group, ordered by randomization number within randomization stratum, will be produced for the purpose of assessing whether randomization was conducted as planned.

Subjects' information on informed consent, screening and randomization will be listed.

Subjects who discontinued/completed treatment or study will be listed with their reason for discontinuation (if applicable).

The list of re-screened subjects and corresponding subject identifiers will be provided. Only the second subject identifier will be used in statistical descriptions and analyses. The first identifier will not be considered in the disposition counts.

10.2 Protocol Deviations

10.2.1 Important Protocol Deviations

For the primary analysis and the blinded extension analysis, the following summary tables and listings of important protocol deviations will be provided (separately for pre-/post inclusion deviations):

- Table providing frequency for each type of important protocol deviation
- Listing of important protocol deviations

10.2.2 Reasons Leading to the Exclusion from an Analysis Set

For the primary and blinded extension analyses, for subjects excluded from the mITT or PP analysis sets, the reasons for exclusion will be summarized, and the subjects excluded will be listed:

- By-reason table of number of subjects excluded from the mITT or PP analysis set, where a subject is counted for every reason that excludes that subject from the respective analysis set.
- By-subject listing of all reasons that excluded the subject from the mITT or PP analysis set

High dose corticosteroid use

If a subject uses high dose corticosteroids in the 3 weeks prior to a scheduled MRI scan, lesion data from that scan will be excluded from the primary analysis based on the mITT analysis set and treated as missing. A by-subject listing will be provided of all subjects who have at least one scan excluded from the primary analysis on the basis of high dose corticosteroid use. The listing will indicate the date of use, identity of the corticosteroid used, and dose and frequency of use.

Corticosteroid use is considered "high dose" when the cumulative dose in prednisone equivalent over the 21 days preceding the MRI assessment is ≥ 210 mg.

The worst case scenario will be applied in case missing or partial corticosteroid use dates are not definitively outside the 3 weeks windows preceding the MRI scan.

In such a situation, missing or partial start dates will be treated as follows:

- Same month as MRI scan and day missing, then corticosteroid use day start will be imputed to 01.
- Same year as MRI scan and month missing, then corticosteroid day/month start will be imputed to 01.
- Date completely missing, then corticosteroid start date is considered 3 weeks before the MRI scan.

Missing end dates will be imputed to the day of the MRI scan.

If the dose of the corticosteroid is missing then a dose of 10 will be considered. In case unit is missing then mg will be used. When frequency is missing QD will be considered.

A concomitant medication will be defined as a corticosteroid if the ATC code begins with "H02A"

The tables below will be used to define the cumulative dose:

Table 7: Conversion factors in prednisone equivalent

WHO-drug Term	Conversion factor in prednisone equivalent
METHYLPREDNISOLONE	1,25
METHYLPREDNISOLONE SODIUM SUCCINATE	1,25
METHYLPREDNISOLONE ACETATE	1,25
HYDROCORTISONE	0,25
BETAMETHASONE	6,667
BETAMETHASONE DIPROPIONATE	6,667
BETAMETHASONE VALERATE	6,667
DEXAMETHASONE	6,667
TRIAMCINOLONE	1,25
CORTISONE	0,2
PREDNISOLONE	1
PREDNISONE	1
DEFLAZACORT	0,83333
MEPREDNISONE	1,25
PARAMETHASONE	2,5
CRONOLEVEL	8,333
BETROSPAM	8,333

Table 8: Frequency conversions for corticosteroids

Frequency	Conversion factor	Numerical Conversion factor
OAM	1/30	0,0333
QOD	1/2	0,5000
QW	1/7	0,1429
QWK	1/7	0,1429
BID	2	2,0000
TID	3	3,0000
QD	1	1,0000
ONCE	1	1,0000
QAM	1	1,0000
Q2H	12	12,0000
Q3H	8	8,0000
Q4H	6	6,0000
Q6H	4	4,0000
Q8H	3	3,0000
QHS	1	1,0000
QID	4	4,0000
QPM	1	1,0000
QH	24	24,0000
Q3W	1/21	0,0476
TIW	3/7	0,4286
Q4W	1/28	0,0357
BIW or Twice a week	2/7	0,2857
EVERY 3 HOURS	8	8,0000
X1	1	1,0000
EVERY OTHER DAY	1/2	0,5000
EVERY OTHER DAY ALTERNTATLY WITH30 MG Q0D	1/2	0,5000
EVERY OTHER DAY ALTERNTATLY	1/2	0,5000

Frequency	Conversion factor	Numerical Conversion factor
WITH 20 MG QOD		
ONCE A WEEK	1/7	0,1429
QD(EVERY MORNING)	1	1,0000
SINGLE DOSES	1	1,0000
ALTERNATE DAYS	1/2	0,5000

11 Demographics and Other Baseline Characteristics

For the primary analysis, demographics, baseline disease characteristics, and other baseline characteristics will be summarized based on the mITT analysis set, presented by treatment group and overall.

Supportive listings will be based on the ITT analysis set, with subjects flagged according to membership in the mITT and SAF analysis sets.

11.1 Demographics

- Demographic characteristics
  - Sex: male, female
  - Race: White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other
  - Ethnicity: Hispanic or Latino, Not Hispanic or Latino
  - Age (years) at informed consent: summary statistics
- Pooled Region (US or Western Europe, Eastern Europe, Rest of the World)
- Geographic/Capability Region (US, Western Europe, Eastern Europe and BTKO capable, Eastern Europe and not BTKO capable, Rest of the World)
- European Economic Area (EEA)

Specifications for computation:

- Age (years):
  1. (date of given informed consent - date of birth + 1) / 365.25
  2. In case of missing day for at least one date, but month and year available for both dates, the day of informed consent and the day of birth will be set to 1 and the formula above will be used.
  3. In case of missing month for at least one date, but year available for both dates, the month of informed consent and the day and month of birth will be set to 1 and the formula above will be used.
- Site codes will be used for the determination of the subject's geographic region.

11.2 Medical History

For the primary analysis, the medical history will be summarized using Medical Dictionary for Regulatory Activities (MedDRA), current version, PT as event category and MedDRA SOC body term as Body System category. The MedDRA version used will be indicated in footnote. Medical history will be tabulated by SOC and PT. SOC and PT will be alphabetically sorted. Medical history will be also listed.

11.3 Other Baseline Characteristics

11.3.1 Disease history

For the primary analysis, information on MS baseline disease characteristics based on data on Day 1 predose and during screening will be summarized in total and listed. Descriptive statistics will be presented for:

- Type of MS, either relapsing-remitting MS (RRMS) or secondary progressive MS (SPMS)
- Time (years) since MS onset (first symptom)
- Time (years) since MS diagnosis
- Major systems affected
- Number of relapses in the year prior to randomization
- Number of relapses in the last 2 years
- EDSS score
- Scores for each of the 7 Functional Systems (Visual, Brainstem, Pyramidal, Cerebellar, Sensory, Bowel/Bladder, Cerebral) and score for Ambulation used to derive EDSS score.
- Presence of at least 1 Gadolinium-positive (Gd+) T1 lesion within 6 months prior to randomization
- Number of Gd+ T1 lesions
- Volume of Gd+ T1 lesions
- Volume of T2 lesions
- Short Form 36-item Health Status Survey Version 2.0 (SF-36v2) normalized score for each of the 8 health domain scales
- SF-36v2 Physical Component Summary score (PCS) and Mental Component Summary score (MCS)

For SF-36v2 score derivation, refer to Appendix 2.

11.3.2 Other

For the primary analysis, descriptive statistics and listings will be presented for:

- Physical examination as continuous variables: Height (cm), Weight (kg) and BMI (kg/m²)

- CXR interpretation category (Normal, Abnormal Not Clinically Significant, Abnormal Clinically Significant, and Abnormal Overall).

Other screening baseline characteristics like viral serology, β-human chorionic gonadotropin, follicle stimulating hormone, quantiferon TB test, hepatitis B surface antigen and prior surgeries will be listed only.

Baseline characteristics such as ECG, vital signs and laboratory values will be presented in the safety summary tables by visit.

11.3.3 Columbia- Suicide Severity Rating Scale (C-SSRS)

The Columbia-Suicide Severity Rating Scale (C-SSRS) is a numerical score derived from 10 categories. The C-SSRS assesses the suicidal behavior and suicidal ideation in subjects.

Occurrence of suicidal behavior is defined as having answered "yes" to a least 1 of the 4 suicidal behavior subcategories (actual attempt, interrupted attempt, aborted attempt, and preparatory acts or behavior).

Occurrence of suicidal ideation is defined as having answered "yes" to at least one of the suicidal ideation sub-categories (wish to be dead, non-specific active suicidal thoughts, active suicidal ideation with any methods [not plan] without intent to act, active suicidal ideation with some intent to act [without specific plan], and active suicidal ideation with specific plan and intent).

Occurrence of suicidality is defined as having at least one occurrence of suicidal ideation or at least one occurrence of suicidal behavior.

For the primary analysis, the number and percentage of subjects with occurrence of suicidal behavior, occurrence of suicidal ideation and occurrence of suicidality at screening will be summarized.

12 Previous or Concomitant Medications/Procedures

Medications/procedures will be presented according to table 9.

Table 9: Data handling for medications/procedures

Analysis	Period covered	Data summarized	Treatment groups	Analysis sets
Primary analysis	Initial 24-week treatment period + safety follow-up	Previous medications + concomitant medications + concomitant procedures	ALL	SAF
Blinded Extension analysis	Second 24-week treatment period + safety follow-up	Concomitant medications + concomitant procedures	ALL	SAF-BE
Blinded Extension analysis	Overall	Concomitant medications + concomitant procedures	Evobrutinib 25 mg QD Evobrutinib 75 mg QD Evobrutinib 75 mg BID Tecfidera	SAF

Concomitant medications are medications, other than IMPs, which are taken by subjects any time on-trial (on or after the first day of IMP treatment for each subject). Concomitant medications include those started prior to and continued during administration of IMP, as well as those that were started after first administration of IMP. If the date values do not allow a medication to be classified as a non-concomitant medication, the medication will be considered as a concomitant medication.

Previous medications are medications, other than trial medications, which started before first administration of IMP. Previous medications include those that were continued during administration of IMP, as well as those discontinued prior to first administration of IMP. If the date values do not allow a medication to be classified as a non-previous medication, the medication will be considered as a previous medication.

The ATC-second level and preferred term will be tabulated as given from the World Health Organization Drug Dictionary (WHO-DD) current version. In case multiple ATCs are assigned to a drug, all ATC-2nd level terms will be used for reporting.

Tables will be presented by descending frequency of ATC 2nd level term and then by descending frequency of PT in total column. If multiple ATCs/PTs have the same frequency, they will be sorted alphabetically. The WHO-DD version used will be indicated in footnote.

Concomitant procedures are procedures which were undertaken any time on trial.

The number and proportion of subjects with previous medications or concomitant medications will be separately summarized by treatment group and listed.

Concomitant procedures will be classified by medical review. Number of subjects with concomitant procedures (prior, on or after the first day of IMP) and by type of procedure (as classified by medical review) will be summarized by treatment group and listed.

13 Treatment Compliance and Exposure

Exposure will be presented according to table 10.

Table 10: Data handling for exposure

Analysis	Period covered	Data summarized	Treatment groups	Analysis set
Primary analysis	Initial 24-week treatment period	Exposure time + Cumulative dose + Compliance	ALL	SAF
	Second 24-week treatment period	Exposure time	ALL	SAF-BE
	Overall	Exposure time	Evobrutinib 25 mg QD Evobrutinib 75 mg QD Evobrutinib 75 mg BID Tecfidera	SAF
Blinded Extension Analysis	Second 24-week treatment period	Exposure time + Cumulative dose + Compliance	ALL	SAF-BE
	Overall	Exposure time + Cumulative dose + Compliance	Evobrutinib 25 mg QD Evobrutinib 75 mg QD Evobrutinib 75 mg BID Tecfidera	SAF

Planned administration of Placebo and Evobrutinib

Each treatment kit contains 17 wallets of 12 tablets which is enough medication for the administration of 6 tablets per day for 4 weeks and 6 days (ie, 204 tablets). From Day 1 until Week 20, subjects will receive one treatment kit per planned visit. At the Week 24 and Week 36 visits, subjects will receive 3 treatment kits at each visit. At each trial visit, subjects will be given treatment kits containing the number of tablets needed up to the next planned trial visit. Subjects will self-administer IMP in a blinded manner at a set time each day (every 12 hours ± 2 hours) as three matching tablets BID for 48 weeks. Subjects 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.

- Subjects randomized to placebo arm will take 6 placebo tablets filled with mannitol for the first 24 weeks. For the 24 weeks following, it is planned that these subjects will be switched to 5 placebo tablets and one tablet filled with 25 mg of Evobrutinib.

- Subjects randomized to Evobrutinib 25 mg QD arm will take 5 tablets filled with mannitol and one tablet filled with 25 mg of Evobrutinib.

- Subjects randomized to Evobrutinib 75 mg QD arm will take 3 tablets filled with mannitol and 3 tablets filled with 25 mg of Evobrutinib.

- Subjects randomized to Evobrutinib 75 mg BID arm will take 3 tablets BID filled with 25 mg of Evobrutinib.

Planned administration of Tecfidera

At the Day 1 visit, the treatment kit contains 14 capsules of 120 mg and 112 capsules of 240 mg which is enough medication for administration for 9 weeks. For the subsequent trial visits, subjects randomized to Tecfidera arm will be given treatment kits wherein the quantity of capsules will not be fixed due to the possibility of down titration in case of adverse event. Subjects randomized to Tecfidera arm will be given 120 mg of Tecfidera BID orally for the first 7 days. Following this, and for the duration of treatment, Tecfidera is given 240 mg BID orally.

On trial visit days, IMP will be administered during the trial visit after the scheduled trial visit procedures (other than post treatment CCI sampling) are completed.

Exposure

Exposure time in weeks will be calculated according to the following formula:

$$\text{exposure (weeks)} = (\text{date of last dose} - \text{date of first dose of the corresponding period} + 1)/7$$

If the end date of the last dose is missing or after the cut-off date then the date of last dose will be replaced by the cut-off date.
If a subject is lost to follow up and hasn't performed end of treatment (EOT) visit, then end of study date will be considered as the end of treatment date.

Exposure time will be presented by summary statistics and according to the following categories

- ≤ 1 week
- > 1 to 8 weeks
- > 8 to 16 weeks
- > 16 to 24 weeks
- > 24 to 36 weeks
- > 36 to 48 weeks

For subjects randomized to placebo, and switched to Evobrutinib after Week 24, any exposure time after Week 24 represents exposure to Evobrutinib.

Cumulative actual dose (mg) per subject will be summarized by treatment groups.

- For Evobrutinib treatment groups, the cumulative actual dose is the number of tablets taken during that period, multiplied by the fraction of tablets that contain Evobrutinib 25 mg according to the actual treatment group, multiplied by 25 mg (dosage of one tablet). The number of tablets ingested will be deduced from the BATCH1 electronic case report form (eCRF).
- For the Tecfidera treatment group, the cumulative actual dose is the number of capsules ingested during that period multiplied by the appropriate dosage of one capsule (either 120 mg or 240 mg). The number of capsules ingested will be deduced from start date, end date, and dose, as recorded on the EXPOSUREDT2 eCRF.
- For subjects randomized to placebo, and switched to Evobrutinib after Week 24, the Evobrutinib cumulative actual dose will be calculated in the same manner as for the Evobrutinib treatment groups, using data from the BATCH1 eCRF, starting with Week 24.
- Study drug administrations will also be listed by treatment group, and subject, with start/end dates of administration and reason for dose change (if applicable).

Compliance

<u>For Evobrutinib or Placebo groups</u>

Compliance with treatment is defined as the number of tablets taken during a period divided by the number of tablets that should have been taken during that period, multiplied by 100 to yield a percentage, ie:

Compliance with treatment $= 100*(\frac{(N_1)}{6 * N_2})$

where N_1 = number of tablets given minus number of tablets returned over N_2 days, deduced from the BATCH1 eCRF,

and N_2 = number of days between treatment start and treatment termination visit (or last visit before cut-off if treatment is ongoing).

For Tecfidera dose group

Compliance with treatment is defined as the actual cumulative dose divided by the planned cumulative dose, multiplied by 100 to yield a percentage, ie:

Compliance with treatment $= 100*(\frac{N_3}{N_4})$

where N_3 = actual cumulative dose for the given time period,

and N_4 = planned cumulative dose for the given time period.

Compliance with treatment and number of ingested tablets/capsules will be tabulated.

The following listings will be provided:

- listing of Evobrutinib/placebo kit numbers with date of dispense, and number of tablets returned (from BATCH1), and Tecfidera kit numbers with date of dispense, and number of capsules returned (from BATCH2) limited to Week 24 for the primary analysis and Week 48 for the blinded extension analysis.
- listing of Evobrutinib/placebo start/end dates with number ingested tablets (from EXPOSUREDT1), and Tecfidera start/end dates with dose (120 or 240 mg) (from EXPOSUREDT2) limited to Week 24 for the primary analysis and Week 48 for the blinded extension analysis.
- listing with exposure time, cumulative dose, and compliance by time period limited to Week 24 for the primary analysis and Week 48 for the blinded extension analysis.

14 Efficacy Analyses

Efficacy endpoints will be included in listings for the primary analysis and the blinded extension analysis.

14.1 Primary Endpoint Analyses

The primary endpoint, total number of Gd+ T1 lesions at Weeks 12, 16, 20, and 24, will be analyzed at the time of the primary analysis. The primary analysis will be based on the mITT analysis set. This analysis will be repeated for the ITT and PP analysis sets only if the respective analysis set differs from the mITT analysis set by > 4 subjects.

The primary analysis of total number of Gd+ T1 lesions, at Weeks 12, 16, 20, and 24, will be an estimate of lesion rate ratio, comparing each Evobrutinib dose group to placebo, together with associated 95% confidence interval (CI) and p-value, based on a negative binomial (NB) model, with offset equal to the log of number of scans. In general, missing scan assessments will be handled via the offset in the NB model, as the offset reflects the number of scans available for a

given subject. Details on missing data handling for subjects lacking any post-baseline scan assessments are provided in Section 9.

In this model, Evobrutinib dose group or placebo group will be a factor and there will be adjustment for baseline disease activity (i.e., presence/absence of Gd+ T1 lesions at baseline). The placebo treatment group and the lower category of baseline disease activity, will be used as references in the model. The p-value reported for each Evobrutinib treatment group tests the null hypothesis that adjusted lesion rate ratio, comparing Evobrutinib treatment to placebo, is equal to 1.

In the primary analysis, if a subject uses high dose corticosteroids in the 3 weeks prior to a scheduled MRI scan, lesion data from that scan will be excluded from the analysis and treated as missing.

The NB regression will be computed with the SAS® GENMOD procedure, using the DIST=NEGBIN option. In addition to the estimates of lesion rate ratio due to treatment and baseline disease activity, the estimates of the intercept and dispersion parameters will be reported.

Sensitivity Analyses

The first sensitivity analysis will analyse the Gd+ T1 lesion count at a single scan using a longitudinal Poisson approach (generalized linear mixed model) via PROC GLIMMIX (i.e., MODEL statement with DIST=POISSON) , based on the mITT analysis set. The model for the lesion rate corresponding to a single scan will include treatment (Evobrutinib dose group or placebo group) and visit (weeks 12, 16, 20, 24) as fixed effects, and a covariate for presence/absence of Gd+ T1 lesions at baseline. No offset parameter is needed as the lesion count data used to fit the model correspond to a single scan. A treatment-by-visit interaction will not be included (i.e., treatment effect assumed constant over time). As in the primary analysis, if a subject uses high dose corticosteroids in the 3 weeks prior to a scheduled MRI scan, lesion data from that scan will be excluded from the analysis and treated as missing. In general, missing scan assessments will be handled via the MAR assumption of the GLMM model. Details on missing data handling for subjects lacking any post-baseline scan assessments are provided in Section 9.

It is planned that both AR(1) correlation between repeated measures (i.e., RANDOM visit / SUBJECT=subjid TYPE=AR(1) RESIDUAL) and a random effect for subject (i.e., RANDOM subjid) will be modeled, yielding estimated lesion rate ratios that have a subject-specific, not population-average, interpretation. However, if there are convergence issues with this approach, the random effect for subject will be omitted, and the correlation between repeated measures will be modeled using a compound symmetric (i.e., RANDOM visit / SUBJECT=subjid TYPE=CS RESIDUAL) or variance components structure.

For each Evobrutinib dose group, the estimated lesion rate ratio relative to placebo will be reported, with 95% CI, and p-value. Assuming a random effect for subject is retained in the model, the p-value reported for each Evobrutinib treatment group tests the null hypothesis that adjusted lesion rate ratio, comparing Evobrutinib treatment to placebo, conditional on random effects, is equal to 1. Other statistics to be reported include the estimated lesion rate (adjusted for

visit and baseline), with 95% CI, for each dose group (Evobrutinib or placebo), estimated lesion rate ratio due to baseline disease activity, intercept, and covariance structure parameters.

The second sensitivity analysis will be based on the same NB model as in the primary analysis, applied to the mITT analysis set, but where all scans will be included in this analysis, regardless of subject use of high dose corticosteroids.

Supplemental Analyses

As a supplemental nonparametric analysis, the stratified Hodges-Lehman estimate of the shift in location of the lesion count distribution, comparing each Evobrutinib dose group to placebo, will be reported, together with associated 95% CI and p-value, based on a stratified Wilcoxon rank-sum test. Strata will be defined according to categorical baseline disease activity, following the approach to covariate adjustment in the NB model. In general, missing scan values for a subject will be imputed with the average of available scan values for that subject. Details on missing data handling for subjects lacking any post-baseline scan assessments are provided in Section 9.

An unstratified version of this nonparametric analysis will be reported as a sensitivity analysis. The second sensitivity analysis will be a stratified analysis that will include all scans, regardless of subject use of high dose corticosteroids.

The p-value reported for each Evobrutinib treatment group tests the null hypothesis that $P(X < Y) + 0.5*P(X = Y) = 0.5$, where X denotes the Gd+ T1 lesion count for a subject in a given Evobrutinib treatment group, Y denotes the Gd+ T1 lesion count for subjects in the placebo group, and P denotes probability.

If the NB model fails to converge, the results of the supplemental nonparametric analysis will be considered as the primary analysis. The supplemental analysis will be repeated for the ITT and PP analysis sets only if the respective analysis set differs from the mITT analysis set by > 4 subjects.

Multiplicity

The truncated Hochberg procedure will be used to adjust for multiplicity in testing the primary endpoint for the 3 Evobrutinib dose groups, to preserve alpha for testing key secondary endpoints (see Section 9). Both raw and multiplicity-adjusted p-values will be reported.

Dose-Response

A monotonic dose-response relationship, between ordered dose groups (placebo, Evobrutinib 25mg QD, Evobrutinib 75mg QD, and Evobrutinib 75mg BID) and ordered categories of Gd+ T1 lesion count for wks 12, 16, 20, 24, will be assessed via the Jonckheere-Terpstra trend test, both without and with stratification by BL factors (i.e., presence/absence of Gd+ T1 lesions at baseline). Prior to defining suitable categories for Gd+ T1 lesion count for wks 12, 16, 20, 14, missing scan data for a subject will be imputed using the same approach as used in the supplemental nonparametric analysis of this endpoint.

After imputation, the categories of Gd+ T1 lesion count (summed over wks 12, 16, 20, 24) will be defined by the quartiles of the distribution as observed when all subjects from the 4 treatment groups are combined. Thus, the unstratified table will be 4x4, and the stratified table will be 4x4x2, assuming a binary stratum covariate. The p-value reported tests the null hypothesis that the lesion count distribution is the same across dose groups, against the alternative that the location of the lesion count distribution is ordered (from largest value to smallest) according to increasing dose group.

In addition to the nonparametric test of monotonic dose-response, a test of linear trend in log lesion rate with increasing dose, adjusted for baseline, will be based on an appropriate contrast from the NB model (i.e., (3, 1, -1, -3)). The p-value reported tests the null hypothesis that the log lesion rate is the same across dose groups, against the alternative that the log lesion rate decreases linearly with increasing dose group order.

Descriptive Analyses

Descriptive statistics for the total number of Gd+ T1 lesions by timepoint through Week 24 will be provided by treatment group (including Tecfidera), based on the mITT analysis set. This analysis will be repeated for the ITT and PP analysis sets only if the respective analysis set differs from the mITT analysis set by > 4 subjects.

Mean number of Gd+ T1 lesions will be presented as a by-visit line plot for each treatment group, with a vertical line segment at each visit representing ± SE (jittered if needed for legibility), and with all treatment groups included in a single figure. Proportion of subjects who are Gd+ T1 lesion-free will be presented as a by-visit line plot for each treatment group (vertical line segment at each visit representing 95% CI may be omitted for legibility), and with all treatment groups included in a single figure. Mean total number of Gd+ T1 lesions from Weeks 12, 16, 20, and 24, will be presented as a by-treatment group bar chart, with a vertical line segment for each bar representing 95% CI, and with the p-value for the comparison with placebo (based on NB model) displayed above each evobrutinib dose group bar.

14.2 Secondary Endpoint Analyses

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

14.2.1 Key secondary endpoint analyses

The key secondary endpoints will be analyzed at the time of the primary analysis. The key secondary efficacy endpoints are:

1. Annualized relapse rate (ARR), based on protocol-defined qualified relapses, at Week 24. The unadjusted ARR is defined as the total number of qualified relapses divided by the number of subject-years of observation on treatment.

2. Qualified relapse-free status at Week 24

3. Change from baseline in EDSS score at Week 24

Collectively, safety endpoints are also considered to be a key secondary endpoint, but are not part of multiplicity adjustment required to control overall type I error rate at the two-sided α=0.05 level. Analyses of safety endpoints are described in Section 15. The multi-stage testing procedure for controlling family-wise error rate (FWER) across the 4 hypothesis families defined by the primary endpoint and the 3 key secondary efficacy endpoints, is described in Section 9.

Inferential analyses of key secondary endpoints will not include the Tecfidera arm. In modeling, the placebo group will be the reference treatment group. If an appropriate categorical BL MRI/relapse/EDSS assessment is adjusted for in the analysis of a key secondary endpoint, the lower disease-activity category will be the reference. For each of the key secondary endpoints, a test for a monotonic dose-response relationship and descriptive statistics will be provided. If the key secondary endpoint is analyzed via a parametric model, then a test of linear trend will also be reported.

ARR at Week 24

The comparison of a Evobrutinib treatment group to the placebo group using ARR at Week 24 will be based on a NB model for qualified relapse count, with offset equal to the log of years on study, with Evobrutinib dose group or placebo group as a factor and adjustment for categorical number of relapses in the last 2 years before randomization ($\leq$ 1 relapse, > 1 relapse). Subjects discontinuing early are analyzed according to number of years of follow-up on treatment and number of qualified relapses observed at the time of discontinuation, including data (both follow-up time and relapse events) from the 4-week Safety Follow-up period. The NB regression will be computed with the SAS® GENMOD procedure, using the dist=NB option in the MODEL statement.

Two sensitivity analyses will be reported, based on early discontinuers, as described below:

- In the first sensitivity analysis, a subject discontinuing early without any qualified relapse in the 30 days prior to discontinuation will be counted as having a relapse on day of discontinuation.
- In the second sensitivity analysis, a subject discontinuing early without any qualified relapse in the 30 days prior to discontinuation will be counted as having a relapse on day of discontinuation if and only if the subject belongs to an Evobrutinib treatment group.

In the table summarizing inferential results (Evobrutinib dose group versus placebo group), the following will be reported for each group: number of qualified relapses, number of total relapses, follow-up on treatment (in subject-years), unadjusted ARR (number of qualified relapses divided by follow-up on treatment), and point estimate of adjusted ARR with 95% CI. For each treatment comparison (Evobrutinib group versus placebo group), the following will be reported: adjusted qualified relapse rate ratio with 95% CI, and p-value for the test that the qualified relapse rate ratio, adjusted for categorical BL relapse activity, is equal to 1.

A monotonic dose-response relationship, between ordered dose groups and ordered categories of ARR estimated on a subject level (i.e., number of qualified relapses experienced by a subject divided by the subject's follow-up), will be assessed via the

Jonckheere-Terpstra trend test, both without and with stratification by categorical BL relapse count (i.e., ≤ 1 relapse, > 1 relapse in the last 2 years before randomization). The categories of subject-level ARR will be defined by the quartiles of the distribution as observed when all subjects from the 4 treatment groups are combined. Thus, the unstratified table will be 4x4, and the stratified table will be 4x4x2, assuming a binary stratum covariate. The p-value reported tests the null hypothesis that the relapse count distribution is the same across dose groups, against the alternative that the location of the relapse count distribution is ordered (from largest value to smallest) according to increasing dose group.

In addition to the nonparametric test of monotonic dose-response, a test of linear trend in log relapse rate with increasing dose, adjusted for baseline, will be based on an appropriate contrast from the NB model (i.e., (3, 1, -1, -3)). The p-value reported tests the null hypothesis that the log relapse rate is the same across dose groups, against the alternative that the log relapse rate decreases linearly with increasing dose group order.

Descriptive statistics for the ARR at Week 24 will be provided by treatment group (including Tecfidera). In particular, at the treatment-group-level, number of qualified relapses, number of total relapses, follow-up on treatment (in subject-years), and unadjusted ARR (number of qualified relapses divided by follow-up on treatment) will be reported. In addition, descriptive statistics of subject-level ARR (number of qualified relapses experienced by a subject by week 24, divided by the follow-up experienced by a subject by week 24) will be summarized for each treatment group, in terms of mean, SD, median, Q1, Q3, min, and max.

ARR at Week 24 will be presented as a by-treatment group bar chart, with a vertical line segment for each bar representing 95% CI, and with the p-value for the comparison between Evobrutinib dose group and placebo (based on NB model) displayed above each Evobrutinib dose group bar.

Qualified relapse-free status at Week 24

The comparison of a Evobrutinib treatment group to the placebo group using proportion qualified relapse-free at Week 24, will be based on a logistic model for the odds of qualified relapse-free status at Week 24, with Evobrutinib dose group or placebo group as a factor and adjustment for categorical number of relapses in the last 2 years before randomization (≤ 1 relapse, > 1 relapse). Subjects who discontinue treatment prior to Week 24 without having a qualified relapse will be counted as not being qualified relapse-free at Week 24.

Two sensitivity analyses will be reported , based on early discontinuers, as described below:

- In the first sensitivity analysis, a subject who discontinues treatment prior to Week 24 without having a qualified relapse is considered as qualified relapse-free at Week 24.
- In the second sensitivity analysis, a subject who discontinues treatment prior to Week 24 without having a qualified relapse is considered as not qualified relapse-free if member of Evobrutinib group, and qualified relapse-free if member of placebo group.

In the table summarizing inferential results (Evobrutinib dose group versus placebo group), the following will be reported for each group: number (proportion) of subjects with ≥ 1

relapse through Week 24 (either treatment discontinuer or completer of 24 weeks of treatment), number (proportion) of subjects with 0 relapses through Week 24, number (proportion) of subjects discontinuing treatment prior to Week 24 among subjects with 0 relapses in that period., and number (proportion) of subjects who are relapse-free at Week 24, using imputation for treatment discontinuers, with 95% CI. For each treatment comparison (Evobrutinib group versus placebo group), the following will be reported: adjusted odds ratio (OR) with 95% CI, and p-value for the test that the OR, adjusted for categorical BL relapse count, is equal to 1.

A monotonic dose-response relationship, between ordered dose groups and proportion qualified relapse-free at Week 24, will be assessed via the Cochran-Armitage trend test, both without and with stratification by BL factor (i.e., ≤ 1 relapse, > 1 relapse in the last 2 years before randomization). The p-value reported tests the null hypothesis that the proportion qualified relapse-free is the same across dose groups, against the alternative that the proportion is ordered (from smallest value to largest) according to increasing dose group. In the Cochran-Armitage test, missing data are handled the same as in the main logistic modeling analysis.

In addition to the nonparametric test of monotonic dose-response, a test of linear trend in log odds of qualified relapse-free status with increasing dose, adjusted for baseline, will be based on an appropriate contrast from the logistic model (i.e., (3, 1, -1, -3)). The p-value reported tests the null hypothesis that the log odds of being qualified relapse-free is the same across dose groups, against the alternative that the log odds increases linearly with increasing dose group order.

Descriptive statistics for qualified relapse-free status up to Week 24 will be provided by treatment group (including Tecfidera), with and without stratification by BL factor (i.e., ≤ 1 relapse, > 1 relapse in the last 2 years before randomization). In particular, number (proportion) of subjects with ≥ 1 relapse, number (proportion) of subjects with 0 relapses, number (proportion) of subjects discontinuing treatment prior to Week 24 among subjects with 0 relapses will be reported.

For each treatment group, the Kaplan-Meier estimate of proportion surviving qualified relapse-free as a function of time (i.e., proportion qualified relapse-free between Week 0 and Week 24) will be presented, with all KM curves in a single figure. A subject discontinuing study prior to Week 24 without relapse will have his/her time to first relapse right-censored at the time of study discontinuation (i.e., the last time at which he/she is at risk of relapse on study). A subject completing 24 weeks of treatment without relapse will have his/her time to first relapse right-censored at 24 weeks. Below the horizontal axis, number of events and number of subjects at risk for the event will be depicted at each event time. The vertical axis may be restricted to 0.50 – 1.0, if none of the curves reach 50%. This KM estimate may be biased if the reason for study discontinuation is informative for relapse.

Change from baseline in EDSS score at Week 24

The comparison of a Evobrutinib treatment group to placebo group using CFB in EDSS at Week 24 will be based on a stratified Wilcoxon rank-sum test, with stratum defined by

categorical BL EDSS score (≤ 3.0 and > 3.0). A subject's missing value for EDSS CFB at Week 24 will be imputed by the median value among subjects having a Week 24 assessment, who are in the same treatment group, and who have the same value for the categorical baseline covariate.

Two sensitivity analyses will be reported as described below:

- Same analysis without any adjustment for strata.
- Same analysis using last observation carried forward (LOCF) post baseline to impute a missing value at Week 24. (Note that the only scheduled assessment of EDSS between baseline and Week 24 is at Week 12.)

In the table summarizing inferential results (Evobrutinib dose group versus placebo group), the following will be reported for each group: mean, median, and range of raw EDSS and EDSS CFB at Week 24. For each treatment comparison (Evobrutinib group versus placebo group), the following will be reported: p-value for the test that the shift in location of the distribution of the Week 24 EDSS CFB value, adjusted for categorical BL EDSS, is zero.

A monotonic dose-response relationship, between ordered dose groups (placebo, Evobrutinib 25mg QD, Evobrutinib 75mg QD, and Evobrutinib 75mg BID) and ordered categories of Week 24 EDSS CFB, will be assessed via the Jonckheere-Terpstra trend test, both without and with stratification by categorical BL EDSS. Prior to defining suitable categories for Week 24 EDSS CFB, missing values will be imputed as described in the main analysis for this endpoint. The categories of EDSS CFB will be defined by the quartiles of the distribution as observed when all subjects from the 4 treatment groups are combined. Thus, the unstratified table will be 4x4, and the stratified table will be 4x4x2, assuming a binary stratum covariate. The p-value reported tests the null hypothesis that the Week 24 EDSS CFB distribution is the same across dose groups, against the alternative that the location of the Week 24 EDSS CFB distribution is ordered (from largest signed CFB value to smallest signed CFB value) according to increasing dose group.

Descriptive statistics for the EDSS score at Week 24 will be provided by treatment group (including Tecfidera). In particular, mean, median, and range of raw EDSS and EDSS CFB at Week 24 will be reported. Mean CFB in EDSS will be presented as a by-visit line plot (BL, Week 12, Week 24) for each treatment group, with a vertical line segment at each visit representing ± SE (jittered if needed for legibility), and with all treatment groups included in a single figure.

14.2.2 Additional secondary endpoint analyses

Secondary efficacy endpoints : baseline to 24 weeks

The following additional secondary endpoints will be evaluated at the time of the primary analysis. Reported p-values will be considered nominal, as these endpoints are not included in the multiple testing strategy. There will be no sensitivity analyses, nor test for trend, as was the case for the primary and key secondary analyses.

Inferential analyses will not include Tecfidera arm, and placebo will be used as a reference for parameter estimates.

Descriptive statistics will be provided for these endpoints along with inferential results, as described below. Another table will describe these endpoints by treatment group (including Tecfidera), without imputed data.

Total number of new Gd+ T1 lesions at Weeks 12, 16, 20, 24

This endpoint will be analyzed similarly to the primary endpoint, using an NB model adjusted for baseline MRI value, with the offset based on the number of scans. Here the baseline MRI value will be presence/absence of Gd+ T1 lesions at baseline, as it is not possible to define "new" Gd+ T1 lesions at baseline. The same strategy as that used for the primary endpoint will be used.

Descriptive statistics for new Gd+ T1 lesions at Weeks 12, 16, 20, 24, similar to those for the primary endpoint, will be provided by treatment group (including Tecfidera). Mean number of new Gd+ T1 lesions will be presented as a by-visit line plot for each treatment group, with a vertical line segment at each visit representing the ±SE, and with all treatment groups included in a single figure.

Total number of new or enlarging T2 lesions at Weeks 12, 16, 20, 24

This endpoint will be analyzed similarly to the primary endpoint, using an NB model adjusted for baseline MRI value, with the offset based on the number of scans. Here the baseline MRI value will be categorical BL T2 lesion volume (≤ 13 cc, > 13cc), as it is not possible to define "new or enlarging" T2 lesions at baseline. In the present study, median T2 volume at baseline was 12.6 cc among the combined Evobrutinib/placebo group.

Descriptive statistics for new and newly enlarging T2 lesions at Weeks 12, 16, 20, 24, similar to those for the primary endpoint, will be provided by treatment group (including Tecfidera). Mean number of new or newly enlarging T2 lesions will be presented as a by-visit line plot for each treatment group, with a vertical line segment at each visit representing ±SE, and with all treatment groups included in a single figure.

Mean per-scan number of Gd+ T1 lesions at Weeks 12, 16, 20, 24

This endpoint will be analyzed similarly to the key secondary endpoint EDSS score CFB at Week 24, using a nonparametric approach. With this endpoint, no imputation is required if a subject is missing 1-3 post-baseline scans, as the endpoint is based on available scans. Details on missing data handling for subjects lacking any post-baseline scan assessments are provided in Section 9. The mean per-scan value (based on scans available from Weeks 12, 16, 20, 24) will be analyzed via Hodges-Lehmann estimation of the shift in distribution location due to Evobrutinib treatment group versus placebo. Each Evobrutinib dose group will be compared to placebo via a stratified Wilcoxon rank-sum test, where the stratification will adjust for categorical baseline disease activity, defined as presence/absence of Gd+ T1 lesions at baseline.

Descriptive statistics for the mean per-scan number of Gd+ T1 lesions, with mean value for each subject based on available scans for that subject at Weeks 12, 16, 20, 24, will be provided by treatment group (including Tecfidera), overall and by baseline disease activity subgroup.

Change from baseline in volume of Gd+ T1 lesions at Week 24

This endpoint will be analyzed similarly to the key secondary endpoint EDSS score CFB at Week 24, using a nonparametric approach, as neither endpoint is expected to be able to be transformed to follow a standard parametric distribution. The distribution of enhanced lesion volume is expected to have substantial probability mass at zero (van den Elskamp *et al* 2011). In the present study, median Gd+ T1 lesion volume at baseline was zero among the combined Evobrutinib/placebo group. The CFB in Gd+ T1 lesion volume at Week 24 will be analyzed via Hodges-Lehmann estimation of the shift in distribution location due to Evobrutinib treatment group versus placebo. Each Evobrutinib dose group will be compared to placebo via a stratified Wilcoxon rank-sum test, where the stratification will adjust for categorical baseline disease activity. A categorical covariate such as zero versus nonzero Gd+ T1 lesion volume at baseline will be considered. A missing value for CFB in Gd+ T1 lesion volume at Week 24 will be imputed using the median value among subjects having an assessment at Week 24, who are in the same treatment group and stratum.

Descriptive statistics for Gd+ T1 lesion volume CFB at Week 24 treated as a continuous variable (i.e., mean, median, and range), and as a categorical variable (i.e., number and proportion with decreasing, constant, or increasing volume), will be provided by treatment group (including Tecfidera). Mean CFB in volume of Gd+ T1 lesions will be presented as a by-visit line plot for each treatment group, with a vertical line segment at each visit representing ±SE, and with all treatment groups included in a single figure.

Change from baseline in volume of T2 lesions at Week 24

The Change from Baseline (CFB) in cube root transformed T2 lesion volume (van den Elskamp et al 2011), will be analyzed using MMRM via PROC MIXED. The model for mean CFB in the cube root of T2 lesion volume will include treatment (Evobrutinib dose group or placebo group), visit (weeks 12, 16, 20, 24), and treatment-by-visit interaction as fixed effects, a covariate for the baseline value of the cube root of T2 lesion volume, and account for correlation between repeated measures (i.e., residual random effects). The AR(1) covariance structure will be considered initially for the equally spaced repeated measures, but other structures (i.e., CS, VC) will be considered if there are convergence issues. For each Evobrutinib dose group, the LSMeans estimate of an appropriate contrast expressing the effect of Evobrutinib on mean cube root of T2 lesion volume CFB at week 24, relative to placebo, will be reported, with 95% CI, and p-value. In addition, the LSMeans estimate of the cube root of T2 lesion volume CFB at week 24 (adjusted for baseline), with 95% CI, will be reported for each dose group (Evobrutinib or placebo). In general, missing scan

assessments will be handled via the MAR assumption of the MMRM model. Details on missing data handling for subjects lacking any post-baseline scan assessments are provided in Section 9.

Descriptive statistics for T2 lesion volume at Week 24, similar to those for Gd+ T1 lesion volume at Week 24, will be provided by treatment group (including Tecfidera). Mean CFB in volume of T2 lesions will be presented as a by-visit line plot for each treatment group, with a vertical line segment at each visit representing ±SE, and with all treatment groups included in a single figure.

Secondary efficacy endpoints: baseline to 48 weeks

The following additional secondary endpoints will be evaluated at the time of the blinded extension analysis. When all subjects will have reached Week 48 or discontinued treatment prematurely, inferential analyses involving Week 48 endpoints will be performed. Reported p-values will be considered nominal, as type-1 error was not controlled for comparisons involving these endpoints.

For each of these endpoints, descriptive statistics at Week 48, similar to those provided at Week 24, will be provided for each treatment group, including Tecfidera, based on the mITT and the mITT-BE analysis sets.

Number of Gd+ T1 lesions at Week 48

The within-group comparison of number of Gd+ T1 lesions at Week 24 and Week 48 will be based on a stratified Wilcoxon signed-rank test, with stratum defined by presence/absence of Gd+ T1 lesions at baseline. A missing value for Gd+ T1 lesion count at Week 24 or Week 48 will be imputed using the median value among subjects having an assessment at that timepoint, who are in the same treatment group and stratum.

For each treatment group, the following will be reported: mean, median, and range of the Gd+ T1 lesion count at weeks 24 and 48, and a p-value for the test that the shift in location of the distribution of Gd+ T1 lesion count between Weeks 24 and 48, adjusted for baseline, is zero. For each dose group, the number of subjects with imputed Week 24 value, and number of subjects with imputed Week 48 value, will be reported.

The by-visit line plots for mean number of Gd+ T1 lesions, and proportion of subjects who are Gd+ T1 lesion-free, for weeks 0-24, provided at the time of the primary analysis, will be extended to include Week 48 at the time of the blinded extension analysis.

Mean total number of Gd+ T1 lesions at Week 24 and Mean total number of Gd+ T1 lesions at Week 48 will be presented as a by-treatment group bar chart, two bars for each treatment group displayed adjacently in a "cluster" (i.e., Week 24, Week 48), with a vertical line segment representing 95% CI extending from each bar, and with the p-value for the Wilcoxon signed-rank test displayed above each dose group "cluster" of 2 bars.

Number of new Gd+ T1 lesions at Week 48, Number of new and enlarging T2 lesions at Week 48, Change from baseline in Gd+ T1 lesion volume at Week 48, Change from baseline in T2 lesion volume at Week 48, Change from baseline in EDSS score at Week 48

These endpoints will be used to compare Week 48 with Week 24 using the same nonparametric approach as with "Number of Gd+ T1 lesions at Week 48." For "Number of new Gd+ T1 lesions at Week 48", the strata will be defined by presence/absence of Gd+ T1 lesions at baseline. For "Number of new and enlarging T2 lesions at Week 48", the strata will be defined by categorical BL T2 lesion volume (≤ 13 cc, > 13cc). For "Change from baseline in Gd+ T1 lesion volume at Week 48", the covariate zero/nonzero Gd+ T1 lesion volume at baseline will be considered for strata definition. For "Change from baseline in T2 lesion volume at Week 48", the strata will be defined by categorical BL T2 lesion volume (≤ 13 cc, > 13cc). For "Change from baseline in EDSS score at Week 48", the strata will be defined by categorical BL EDSS score (≤ 3.0, > 3.0).

A missing value at Week 24 or Week 48 will be imputed using the median value among subjects having an assessment at that timepoint, who are in the same treatment group and stratum.

The descriptive statistics, relevant by-visit lineplots, and barchart figure provided for the "Number of Gd+ T1 lesions at Week 48" endpoint will also be provided for these endpoints.

Qualified relapse-free analysis status at Week 48

The within-group comparison of qualified relapse-free status for Week 0-24 and Week 25-48 will be based on a stratified McNemar (SMN) test, with strata defined by categorical number of relapses in the last 2 years before randomization (≤ 1 relapse, > 1 relapse). Subjects who discontinue treatment between Week 24 and Week 48 without having a qualified relapse will be counted as not being qualified relapse-free for the period Week 25-48.

For each treatment group, the following statistics will be reported describing the period Week 25-48: number (proportion) of subjects with ≥ 1 relapse between Week 24 and Week 48 (either discontinuer or completer of 48 weeks of treatment), number (proportion) of subjects with 0 relapses between Week 24 and Week 48, number (proportion) of subjects discontinuing treatment between Week 24 and Week 48, among subjects with 0 relapses in that period, and number (proportion) of subjects who are relapse-free during Week 25 - 48, using imputation for treatment discontinuers, with 95% CI.

For each treatment group, the following statistics will be reported comparing the period Week 0-24 with the period Week 25-48:

- number (proportion) of subjects whose relapse-free status improves from the period Week 0-24 to the period Week 25-48 (using imputation for treatment discontinuers during Week 25-48), by stratum

- number (proportion) of subjects whose relapse-free status worsens from the period Week 0-24 to the period Week 25-48 (using imputation for treatment discontinuers during Week 25-48), by stratum
- p-value for the test that the proportion of subjects whose relapse-free status improves equals the proportion of subjects whose relapse-free status worsens (using imputation for treatment discontinuers during Week 25-48) adjusted for baseline.

For treatment groups that received a consistent regimen for the entire 48 weeks, the following will be reported:

- proportion relapse-free during Week 0-48, with 95% CI, without and with imputation for treatment discontinuers.
- Kaplan-Meier estimate of proportion surviving qualified relapse-free as a function of time (i.e., proportion qualified relapse-free between Week 0 and Week 48) for each treatment group, with all KM curves in a single figure. A subject discontinuing study prior to Week 48 without relapse will have his/her time to first relapse right-censored at the time of study discontinuation (i.e., the last time at which he/she is at risk of relapse on study). A subject completing 48 weeks of treatment without relapse will have his/her time to first relapse right-censored at 48 weeks. Below the horizontal axis, number of events and number of subjects at risk for the event will be depicted at each event time. The vertical axis may be restricted to 0.50 – 1.0, if none of the curves reach 50%. This KM estimate may be biased if the reason for study discontinuation is informative for relapse.

Annualized relapse rate at Week 48

For each treatment group, the following will be reported: number of qualified relapses during Week 25-48, number of total relapses during Week 25-48, follow-up (in subject-years) during Week 25-48, and unadjusted ARR during Week 25-48 (number of qualified relapses divided by follow-up), with 95% CI.

For treatment groups that receive a consistent regimen for the entire 48 weeks, the following will be reported: number of qualified relapses during Wk 0-48, number of total relapses during Week 0-48, follow-up (in subject-years) during Wk 0-48, and unadjusted ARR at Week 48 (number of qualified relapses divided by follow-up), with 95% CI.

The estimates of ARR at Week 24 and ARR during Week 25-48 will be presented as a by-treatment group bar chart, two bars for each treatment group displayed adjacently in a "cluster" (i.e., 0-24 week, 25-48 week), with a vertical line segment representing 95% CI extending from each bar. The number of subjects contributing to the ARR estimate will be displayed below each bar.

No within-group analysis related to the endpoint ARR at Week 48 is planned.

15 Safety Evaluation

The subsections in this section include specifications for summarizing safety endpoints that are common across clinical trials such as adverse events, laboratory tests and vital signs.

15.1 Adverse Events

Pre-treatment adverse events are defined as those AEs with an onset date on or after the date of informed consent and prior to the date of first dose of IMP.

Treatment-emergent adverse events (TEAEs) are defined as those AEs with an onset date on or after the date of first IMP administration.
The initial 24-week treatment period will include the following TEAEs:

- TEAEs with an onset date on or after first IMP administration and strictly before the first administration in the second 24-week period.
- All TEAEs for subjects discontinuing during the initial 24-week treatment period.

The second 24-week treatment period will include all TEAEs with an onset date on or after the first administration in the second period.

IMP related Adverse Events are those AEs with relationship to study treatment reported by the investigator as related or those of unknown relationship.

Serious Adverse Events are those events reported on the AE eCRF form with the serious field ticked "Yes" or with unknown seriousness.

Adverse Events leading to withdrawal of IMP are those AEs with action taken regarding study treatment as "Drug withdrawn" (as recorded on the AEs eCRF page).

Adverse Events leading to study termination are those AEs with other action taken as "Led to study termination" (as recorded on the AEs eCRF page).

Adverse events will be coded according to the latest MedDRA version available at the time of analysis. The severity of AEs will be graded using National Cancer Institute - Common Terminology Criteria for AEs (NCI-CTCAE version 4.03) toxicity grades.

All Adverse Events recorded during the course of the trial (ie, assessed from signature of informed consent until the end of the Follow-up/End of Trial visit) will be coded according to the MedDRA and assigned to a SOC and PT.

Group/SOC terms will be sorted alphabetically. Preferred terms within each group/SOC will be sorted by the highest active dose of Evobrutinib descending frequency, and alphabetically if multiple preferred terms have the same frequency.

If a subject experiences more than one occurrence of the same TEAE during the trial, the subject will only be counted once for that treatment (the worst severity and the worst relationship to trial treatment will be tabulated).

In case a subject had events with missing and non-missing grades, the maximum of the non-missing grades will be displayed.

All analyses described in Section 15.1 will be based on Treatment Emergent Adverse Events (TEAEs) if not otherwise specified.

15.1.1 All Adverse Events

A TEAE summary table will include a row for the overall frequency of TEAEs of the following types:

- any TEAE
- IMP-related TEAE
- serious TEAE
- IMP-related serious TEAE
- TEAE by intensity (NCI-CTCAE grade 1 to 4)
- IMP-related TEAE by intensity (NCI-CTCAE grade 1 to 4)
- TEAE leading to death
- IMP-related TEAE leading to death

Exposure adjusted incidence rates (EAIR) are calculated as the number of subjects with TEAE divided by the sum of the individual times of all subjects in the safety population from start of treatment to first onset of TEAE in the corresponding time period. The incidence rate multiplied with 1000 would give the number of AEs expected in 1000 subjects within 1 time unit (year). EAIR of TEAEs will be presented by SOC and PT. If a subject has multiple events, the exposure period of the first event will be used. For a subject with no event, the exposure period will be censored at the last follow-up time within the AE summarization period.

The TEAE tables to be prepared are listed below:

	Table design					
	Overall frequency	By primary SOC and PT	By SOC only	By PT only	By HLGT only	By HLT only
TEAE Overview Summary	X	*NA*	*NA*			
TEAE by SOC and PT	X	X				
TEAE by SOC	X		X			
TEAE by PT	X			X		
TEAE by HLGT	X				X	
TEAE by HLT	X					X
IMP-related TEAE by SOC and PT	X	X				

Non-Serious TEAE by SOC and PT*	X	X				
TEAE by worst grade, SOC and PT		X				
IMP-related TEAE by worst grade, SOC and PT		X				
EAIR of TEAEs	X	X				

*A table with all TEAEs will be first provided and then only TEAEs exceeding a frequency of 5% in at least one of the treatment groups (>5%), by SOC and PT will be provided.

Pretreatment and TEAEs will be listed separately by treatment group and subject.

Three-tier Approach to Summarizing and Analysing AEs

The 3-tier approach is a systematic way to summarize and analyze adverse events (AEs) in clinical trials (Crowe 2009). AEs in different tiers are analyzed using different levels of statistical analyses.

This study will not include Tier 1 analyses, as no Tier 1 AEs were identified prior to the bulk of the data being collected. Tier 3 analyses will not be provided, due to the relatively small sample size per treatment group. Only Tier 2 AEs will be defined and the respective analyses provided.

AEs will be classified into Tier 2 based on the Rule-of-3. If there are 3 or more patients with the reported term in any treatment group, that term will be included in Tier 2.

For Tier 2 AEs, the difference in crude rates (between Evobrutinib dose group and placebo group), and the CI for the difference, will be reported. The CI will be based on the unconditional MN method (Miettinen 1985, G.F. Liu 2006). No multiplicity adjustment will be applied for Tier 2 AEs.

EAIR of TEAEs will be presented for Tier 2 AEs, by SOC and PT. The difference in EAIR between Evobrutinib dose group and placebo group will be summarized.

15.1.2 Adverse Events Leading to Treatment Discontinuation

A TEAE summary table will include a row for the overall frequency of TEAEs of the following types:

- TEAE leading to interruption of IMP
- IMP-related TEAE leading to interruption of IMP
- TEAE leading to withdrawal of IMP
- IMP-related TEAE leading to withdrawal of IMP
- TEAE leading to dose reduction of Tecfidera
- IMP-related TEAE leading to dose reduction of Tecfidera
- TEAE leading to concomitant medication
- IMP-related TEAE leading to concomitant medication

- TEAE leading to concomitant procedure
- IMP-related TEAE leading to concomitant procedure
- TEAE leading to study termination
- IMP-related TEAE leading to study termination

The TEAE tables to be prepared are listed below:

	Table design		
	Overall frequency	By primary SOC and PT	By PT only
TEAE leading to discontinuation of IMP/study Overview Summary	X	*NA*	*NA*
TEAE leading to IMP withdrawal by SOC and PT	X	X	
IMP-related TEAE leading to IMP withdrawal by SOC and PT	X	X	
TEAE leading to study termination	X	X	
IMP-related TEAE leading to study termination	X	X	

A listing of TEAEs leading to withdrawal of IMP, and a listing of TEAEs leading to study termination, will be provided.

15.2 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

15.2.1 Deaths

A summary of deaths will be provided including (clinicaltrials.gov requirement):

- Number and percentage of (all) deaths
- Number and percentage of the primary cause of death (categories: disease progression, adverse event, unknown, other)

TEAEs leading to death and IMP-related TEAEs leading to death will be tabulated by SOC and PT along with overall frequency. A listing of deaths, if any, will be provided.

In case there is no death in the trial, only the summary of death required by clinicaltrials.gov will be performed, neither tabulation of TEAE leading to death will be edited, nor the listing of death.

15.2.2 Serious Adverse Events

Serious TEAEs and IMP-related serious TEAEs will be tabulated by SOC and PT along with overall frequency.

A subject listing of serious TEAEs will be provided.

15.3 Clinical Laboratory Evaluation

The clinical laboratory safety parameters measured in this trial , and reported as part of the safety evaluation of hematology, biochemistry, and urinalysis, are specified in the protocol (Table 5 of the Clinical Trial Protocol, Section 7.4.3). Ig levels, B, CCI [redacted] cell count are not considered in this section.

Summaries of Clinical Laboratory Data

Laboratory results will be classified according to the grades defined in NCI-CTCAE Version 4.03 as provided by the central laboratory. If a laboratory parameter has bi-directional toxicities (eg, Potassium), both directions will be presented for the given parameter (ie, Potassium Low and Potassium High). On-treatment values are defined as results of assessments made after the first IMP administration on Day 1. Laboratory results containing a modifier such as "<" or ">=" will be handled case by case for summary statistics and will be reported as collected in the database in subject data listings.

All parameters will also be presented according to the categories based on normal ranges: below normal limits (Low), within normal limits (Normal) and above normal limits (High).

Protocol-specified clinical laboratory parameters (hematology, biochemistry, urinalysis) will be summarized using descriptive statistics appropriate to continuous-valued random variables (see Section 9) by time point and by treatment group. At each time point, both observed value and CFB value will be summarized.

Shift tables of baseline value (low, normal, high) versus worst on-treatment value, presented by treatment group, will be provided for hematology, biochemistry, and urinalysis parameters.

Shift tables of baseline grade versus worst post-baseline grade, presented by treatment group, will be provided for hematology and biochemistry parameters.

Directional laboratory tests (hematology, biochemistry) (Appendix 1) will be summarized by worst on-treatment value and by treatment group.

Graphical Display of Clinical Laboratory Data

Boxplots of laboratory values by treatment arm and timepoint will be provided for the following hematology and biochemistry parameters:

- hemoglobin
- white blood cell count
- absolute neutrophil count
- absolute lymphocyte count
- platelet count
- Alanine Amino-Transferase (ALT)

- Aspartate Amino-Transferase (AST)
- Alkaline Phosphatase (ALP)
- total bilirubin
- Gamma-Glutamyl Transferase (GGT)
- glucose
- creatinine
- sodium
- potassium
- calcium
- lipase
- amylase

Boxplots for the laboratory parameters listed above will be displayed using the unit of measurement. If consistent with BOA standards, the ULN and LLN will be added to the lab parameter boxplot, for any lab parameter where the normal range is the same for all subjects in the analysis set.

For the primary analysis, a by-subject line plot of log ALT by time point (through Week 24), one curve per subject, (i.e., "spaghetti" plot) will be provided. One panel will include subjects from the Evobrutinib treatment groups, displayed so that curves from subjects in the same group have the same color or line type. A second panel will include subjects from the Tecfidera and placebo groups, displayed in a similar manner.

Kaplan-Meier estimates of proportion surviving event-free as a function of time will be presented for the following 3 types of events based on the ALT parameter:

- Time from first dose to first assessment of ≥ Grade 2 ALT (days)
- Time from first dose to first increase in ALT ≥ 1 grade above BL grade (days)
- Time from first dose to first increase in ALT ≥ 2 grade above BL grade (days)

For the primary analysis, the 3 time-to-event figures will be based on data from weeks 0-24; a subject reaching week 24 without experiencing the event will have his/her event time right-censored at the time of the last ALT assessment. A separate KM curve will be estimated for each group: Evobrutinib (any dose), placebo, tecfidera.

For the blinded extension analysis, the 3 time-to-event figures will be based on data from weeks 0-48; a subject reaching week 48 without experiencing the event will have his/her event time right-censored at the time of the last ALT assessment. A separate KM curve will be estimated for each group: Evobrutinib (any dose), tecfidera (i.e., no curve for the group of subjects who switch from placebo to Evobrutinib at week 24).

To be included in a time-to-event figure, a group must have at least one event. Below the horizontal axis of the time-to-event figure, # of events and # of subjects at risk will be displayed at each event time. The vertical axis may be restricted to 0.50 – 1.0, if none of the curves reach 50%.

eDISH (Evaluation of Drug-Induced Serious Hepatotoxicity) figures, as described in Merz *et al* (2014), will be presented for both the primary analysis (limited to data from weeks 0-24) and the blinded extension analysis (all data from weeks 0-48). The figure produced for the primary analysis will include 6 panels: one for each Evobrutinib dose group, one for all dose groups combined, one for placebo, and one for tecfidera. The figure produced for the blinded extension analysis will include only 5 panels, as there will not be a panel for the subjects who switch from placebo to Evobrutinib at week 24.

Listings of Clinical Laboratory Data

By-subject listings of all individual hematology, biochemistry, urinalysis and coagulation values present in the database will be provided.

Laboratory values that are outside the normal range will be flagged in the data listings, along with corresponding normal ranges.

In this study, clinically significant lab abnormalities were recorded as adverse events. In lieu of a listing of clinically significant lab abnormalities for each domain, the following by-subject lab value listings will be provided:

- Listing of Grade ≥ 3 hematology values
- Listing of Grade ≥ 3 biochemistry values
- Listing of urinalysis values with Grade ≥ 3, value ≥ 2 times ULN (not to include values for Specific Gravity or pH parameters), or an increase of "++" for non gradable parameters when applicable.

15.4 Vital Signs

Vital signs (body temperature (°C), SBP (mmHg), DBP (mmHg), respiratory rate (breaths/min) and pulse rate (beats/min)) will be summarized by treatment group using descriptive statistics (see Section 9) for baseline, each applicable time point and CFB to each time point.

Body temperature, SBP, DBP, respiratory rate and pulse rate will be analyzed with shift tables of maximum CFB using the categories defined below:

Table 21: Vital sign categories

Parameter	Unit	Shift	Baseline categories	Post-baseline categories (absolute change)
Temperature	°C	Increase	<37 / ≥37 - <38 / ≥38 - <39 /≥39 - <40 / ≥ 40	≤0* / >0 - <1 / ≥1 - <2 /≥2 - <3 / ≥3
Pulse rate	bpm	Increase and decrease	<100 / ≥100	≤0* / >0 - ≤20 / >20 - ≤40 / >40
SBP	mmHg	Increase and decrease	<140 / ≥140	≤0* / >0 - ≤20 / >20 - ≤40 / >40
DBP	mmHg	Increase and decrease	<90 / ≥90	≤0* / >0 - ≤ 20 / >20 - ≤40 / >40
Respiratory rate	breaths/min	Increase and decrease	<20 / ≥20	≤0* / >0 - ≤5 / >5 - ≤10 / >10

* This category will include the subjects with no changes or decrease/increase in the increase/decrease part of the table respectively.

A listing of maximum CFB and a listing of all vital signs data will be provided.

15.5 12-Lead Electrocardiogram (ECG)

For the 12-lead ECG parameters listed below, observed values and CFB values will be summarized by treatment group using descriptive statistics for continuous random variables:

- Ventricular rate (beats/min)
- Pulse rate interval (msec)
- QRS (msec)
- QT (msec)
- Fridericia corrected QT (QTcF) (msec).

The QTcF parameter will be categorized by observed value into the categories

- ≤ 430 msec,
- > 430 – 450 msec,
- > 450 – 480 msec,
- > 480 – 500 msec,
- > 500 msec

and by CFB value into the categories

- ≤ 30 msec,
- > 30 – 60 msec,
- > 60 msec.

Number and percentage of subjects within each category listed above, based on their post-baseline QTcF data, will be presented by treatment group.

A shift table of rhythm results (Sinus rhythm, Atrial fibrillation, Other, Missing) from baseline to last on treatment category, presented by treatment group, will be provided.

A shift table of morphological assessments (Normal, Abnormal, Missing) from baseline to maximum on treatment category, presented by treatment group, will be provided.

A listing of ECG quantitative values, morphological and rhythm results will be produced.

15.6 Chest X-ray Evaluations

Investigator reported abnormalities in chest x-ray will be listed, refer to Section 11.3.2.

15.7 Physical Examination

No summary table will be provided since physical examination findings during screening will be recorded as medical history events and findings during the trial as AEs.

15.8 Safety/Pharmacodynamic Endpoints: CCI and Immunoglobulin levels

Safety/pharmacodynamic endpoints include CCI and immunoglobulin (Ig) levels. CCI Immunoglobulin (IgM, IgA, and IgG and subclass) levels will be assessed prior to the morning dose on Day 1, Day 28, Day 112, Day 168, and Day 336 (End of Treatment).

For each Safety/PD endpoint, observed value, change from baseline, will be summarized. Descriptive statistics for these variables will be presented as described in Section 9.

15.9 Pregnancy test

Results of pregnancy test (serum and urine beta human chorionic gonadotropin for women only) will be listed for the primary analysis and blinded extension analysis.

16 Analyses of Other Endpoints

16.1 CCI [redacted]

16.2 CCI [redacted]

16.2.1 CCI [redacted]

CCI [redacted]

16.2.3 CCI [redacted]

[redacted]

[redacted]

16.2.3.1 [redacted]

[redacted]

16.2.3.2 [redacted]

[redacted]

CCI

[redacted]

[redacted]

16.2.3.3 CCI [redacted]

[redacted]

16.2.3.4 CCI [redacted]

[redacted]

16.2.3.5 CCI [redacted]

[redacted]

16.2.3.6 CCI [redacted]

[redacted]

16.2.4 CCI [redacted]

[redacted]

16.2.5 CCI [redacted]

[redacted]

16.3 Quality of Life: 36-item Short Form Health Survey (SF-36)

The Medical Outcomes Study SF-36 form asks subjects to reply to questions (items) according to how they have felt over a specifically defined period of time. Items yield scale scores for each of 8 health domains, and 2 summary measures of health: the PCS and the MCS. For more information on the scoring see Appendix 2.

Baseline to 24 weeks

For the primary analysis, data will be available for SF-36 assessments through Week 24. For each treatment group, descriptive statistics appropriate for a continuous random variable will be presented for absolute (raw) value and CFB value for SF-36 endpoints at the following time points: BL, W4, W8, W12, W16, W20, W24, and premature EOT (assuming premature EOT was prior to W24). In addition, for each SF-36 endpoint, the number (proportion) of subjects not worsening, and number (proportion) of subjects worsening, between baseline and Week 24 will be summarized by treatment group.

SF-36 score CFB at Week 24 will be analyzed using MMRM via PROC MIXED. The model for mean SF-36 score CFB will include treatment (Evobrutinib dose group or placebo group), visit (weeks 4, 8, 12, 16, 20, 24), and treatment-by-visit interaction as fixed effects, a covariate for the baseline value of the SF-36 score, and account for correlation between repeated measures (i.e.,

residual random effects). The AR(1) covariance structure will be considered initially for the equally spaced repeated measures, but other structures (i.e., CS, VC) will be considered if there are convergence issues. For each Evobrutinib dose group, the LSMeans estimate of an appropriate contrast expressing the effect of Evobrutinib on mean SF-36 score CFB at week 24, relative to placebo, will be reported, with 95% CI, and p-value. In addition, the LSMeans estimate of the SF-36 score CFB at week 24 (adjusted for baseline), with 95% CI, will be reported for each dose group (Evobrutinib or placebo). In general, missing assessments will be handled via the MAR assumption of the MMRM model. Details on missing data handling for subjects lacking any post-baseline assessments are provided in Section 9.

A figure depicting line plots of Mean CFB at Week 24 for SF-36 sub-domain score versus sub-domain score type (PF, RP, BP, GH, VT, SF, RE, MH), one curve per treatment group, displayed together, will be provided. Mean PCS CFB will be presented as a by-visit line plot for each treatment group, with all treatment groups included in a single figure, and horizontal axis extending to Week 24. A similar by-visit figure will be provided for mean MCS CFB.

For each SF-36 endpoint, a figure will be provided describing the distribution of % CFB at Week 24, one curve per treatment group (Evobrutinib dose group or placebo group). The estimated CDF curve for % CFB at Week 24 will display proportion of subjects having a value for % CFB at Week 24 $\leq$ x, where the range of x depends on the data. For the purpose of estimating the CDF, a subject missing an assessment at Week 24 will have the assessment imputed via the last-observation-carried-forward (LOCF) value.

Baseline to 48 weeks

For the blinded extension analysis, additional data will be available for assessments at Weeks 36 and 48. For each treatment group, descriptive statistics appropriate for a continuous random variable will be presented for absolute (raw) value and CFB value for SF-36 endpoints at the following time points: W36, W48, and premature EOT (assuming premature EOT was prior to W48). In addition, for each SF-36 endpoint, the number (proportion) of subjects not worsening, and number (proportion) of subjects worsening, between baseline and Week 48 will be summarized by treatment group.

SF-36 score CFB at Week 48 will be analyzed using MMRM via PROC MIXED. The model for mean SF-36 score CFB will include treatment (Evobrutinib dose groups only), visit (weeks 12, 24, 36, 48), and treatment-by-visit interaction as fixed effects, a covariate for the baseline value of the SF-36 score, and account for correlation between repeated measures. The AR(1) covariance structure will be considered initially for the equally spaced repeated measures, but other structures (i.e., CS, VC) will be considered if there are convergence issues. For each Evobrutinib dose group, the LSMeans estimate of the SF-36 score CFB at week 48 (adjusted for baseline), will be reported, with 95% CI. Missing data are handled as in the Baseline to 24 weeks analysis.

A figure depicting line plots of Mean CFB at Week 48 for SF-36 sub-domain score versus sub-domain score type, one curve per Evobrutinib dose group, displayed together in a single figure, will be provided. The by-visit figures of mean PCS CFB and mean MCS CFB covering the first

24 weeks provided at the primary analysis, will be extended through 48 weeks for the blinded extension analysis.

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18 Appendices

18.1 Appendix 1: Worst on treatment value based on normal range of laboratory evaluations

Names of Clinical Safety Laboratory Evaluations in Protocol version 1.0, 05 July 2016	**If gradable parameter, corresponding evaluation names in NCI-CTCAE 4.03**	**Worst on treatment value based on normal range**
Albumin	Hypoalbuminemia	LOW
Aspartate aminotransferase	Aspartate aminotransferase increased	HIGH
Alanine aminotransferase	Alanine aminotransferase increased	HIGH
Alkaline phosphatase	Alkaline phosphatase increased	HIGH
γ-Glutamyl-transferase	GGT increased	HIGH
Lactate dehydrogenase		HIGH
Bilirubin (total)	Blood bilirubin increased	HIGH
Protein (total)		LOW
Creatinine	Creatinine increased	HIGH
Estimated Glomerular Filtration Rate		LOW
Amylase	Serum amylase increased	HIGH
Lipase	Lipase increased	HIGH
Total carbon dioxide		LOW
Blood urea nitrogen		HIGH
Glucose	Hyperglycemia	HIGH
Glucose	Hypoglycemia	LOW
Sodium	Hypernatremia	HIGH
Sodium	Hyponatremia	LOW
Potassium	Hyperkalemia	HIGH
Potassium	Hypokalemia	LOW
Chloride		NA
Calcium	Hypercalcemia	HIGH
Calcium	Hypocalcemia	LOW
Magnesium	Hypermagnesemia	HIGH
Magnesium	Hypomagnesemia	LOW
Phosphate	Hypophosphatemia	LOW

Names of Clinical Safety Laboratory Evaluations in Protocol version 1.0, 05 July 2016	**If gradable parameter, corresponding evaluation names in NCI-CTCAE 4.03**	**Worst on treatment value based on normal range**
Hematocrit		LOW/HIGH
Hemoglobin	Hemoglobin increased	HIGH
Hemoglobin	Anemia	LOW
Red blood cell count		NA
Mean corpuscular volume		NA
Mean corpuscular hemoglobin		NA
Mean corpuscular hemoglobin concentration		NA
Reticulocyte count		NA
Platelet count	Platelet count decreased	LOW
White blood cell count	Leukocytosis	HIGH
White blood cell count	White blood cell decreased	LOW
B, CCI cell count		LOW
Immunoglobulin and subclass concentrations		LOW
Total IgG		LOW
Total IgA		LOW
Total IgM		LOW
White blood cell differentials and absolute counts: Basophils		NA
White blood cell differentials and absolute counts: Eosinophils		NA
White blood cell differentials and absolute counts: Lymphocytes	Lymphocyte count increased	HIGH
White blood cell differentials and absolute counts: Lymphocytes	Lymphocyte count decreased	LOW
White blood cell differentials and absolute counts: Monocytes		NA
White blood cell differentials and absolute counts: Neutrophils	Neutrophil count decreased	LOW
pH		NA
Nitrite		NA
Urobilinogen		NA
Bilirubin (urinalysis)		NA
Glucose (urinalysis)		NA
Ketones bodies		NA
Protein (urinalysis)		NA
Microscopy: white blood cells		HIGH
Microscopy: red blood cells		HIGH
Microscopy: casts		NA

Names of Clinical Safety Laboratory Evaluations in Protocol version 1.0, 05 July 2016	If gradable parameter, corresponding evaluation names in NCI-CTCAE 4.03	Worst on treatment value based on normal range
Protein/creatinine ratio		HIGH

18.2 Appendix 2: SF-36 VERSION 2 (1998 US POPULATION)

The SF-36v2 (3) is a multi-purpose questionnaire that measures general health status. It is a self-administered generic measure of health-related quality of life comprised of 36 items illustrating 8 health concepts (see Table A2.1): physical function (PF), bodily pain (BP), general mental health (MH), vitality (VT) (energy and fatigue), social function (SF), physical role (RP) (role limitations due to physical health), emotional role (RE) (role limitations due to personal or emotional problems), general health perceptions (GH). The recall period is 4 weeks. SF-36 also includes a Reported Health Transition (HT) single-item, evaluating the change in health status during the past year, which is not part of any of the above subscales. This item is to be analysed as a categorical variable. Scores for the 8 dimensions/subscales are standardised in order to range from 0 to 100, with higher scores representing better QoL. It is to be noted that 5 of the 8 scales (PF, RP, BP, SF, and RE) define health status as the absence of limitations or disability. This condition is sufficient to reach a high score. For the other three scales (GH, VT, and MH), a high score is reached when the subjects report positive states and evaluate their health favourably.

The SF-36v2 multi-item scales yield a health profile (8 scores) or can be aggregated into two summary scores, the Physical Component Summary score (PCS) and Mental Component Summary score (MCS) obtained through a linear combination of weighted transformed scores from the 8 subscales. PCS and MCS are standardised, with an average of 50 and a standard deviation of 10 in the general American population. PCS and MCS are computed only if all of the 8 scale scores are available.

Table A2.1: Abbreviated Item Content for the SF-36v2 Health Domain Scales

Scale	Original item#	Item# in RMS study	Abbreviated Item Content
Physical Functioning (PF)	3a	3	Vigorous activities, such as running, lifting heavy objects, or participating in strenuous sports
	3b	4	Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf
	3c	5	Lifting or carrying groceries
	3d	6	Climbing several flights of stairs
	3e	7	Climbing one flight of stairs
	3f	8	Bending, kneeling, or stooping
	3g	9	Walking more than a mile

Scale	Original item#	Item# in RMS study	Abbreviated Item Content
	3h	10	Walking several hundred yards
	3i	11	Walking one hundred yards
	3j	12	Bathing or dressing oneself
Role-Physical (RP)	4a	13	Cut down the amount of time spent on work or other activities
	4b	14	Accomplished less than you would like
	4c	15	Limited in kind of work or other activities
	4d	16	Had difficulty performing work or other activities (eg, it took extra effort)
Bodily Pain (BP)	7	21	Intensity of bodily pain
	8	22	Extent pain interfered with normal work
General Health (GH)	1	1	Is your health: excellent, very good, good, fair, poor
	11a	33	Seem to get sick a little easier than other people
	11b	34	As healthy as anybody I know
	11c	35	Expect my health to get worse
	11d	36	Health is excellent
Vitality (VT)	9a	23	Feel full of life
	9e	27	Have a lot of energy
	9g	29	Feel worn out
	9i	31	Feel tired
Social Functioning (SF)	6	20	Extent health problems interfered with normal social activities
	10	32	Frequency health problems interfered with social activities
Role-Emotional (RE)	5a	17	Cut down the amount of time spent on work or other activities
	5b	18	Accomplished less than you would like
	5c	19	Did work or other activities less carefully than usual
Mental Health (MH)	9b	24	Been very nervous
	9c	25	Felt so down in the dumps that nothing could cheer you up
	9d	26	Felt calm and peaceful
	9f	28	Felt downhearted and depressed
	9h	30	Been happy
Self-Evaluated Transition (SET)	2	2	How health is now compared to 1 year ago

Step 1: Recoding Item Response Values

Some of the SF-36v2 items will be re-coded so that across all questions, a higher score will indicate a better health state. Questions 2, 3a-3j, 4a-4d, 5a-5c, 9b, 9c, 9f, 9g, 9i, 10, 11a, 11c will be scored as recorded; the other questions will have the scores transformed as shown in Table A2.2. If multiple answers are given to the same item, then the item score will be left as missing.

Table A2.2: SF-36 Re-Coding

Question	Original code and re-code response					
Question number: 1						
Original response	1	2	3	4	5	
Re-coded response	5	4.4	3.4	2	1	
Questions numbers: 6, 11b, 11d						
Original response	1	2	3	4	5	
Re-coded response	5	4	3	2	1	
Question number: 7						
Original response	1	2	3	4	5	6
Re-coded response	6	5.4	4.2	3.1	2.2	1
Question number: 8 (if question number 7 is answered)						
Original response to #8	1	1	2	3	4	5
Original response to #7	1	2-6	1-6	1-6	1-6	1-6
Re-coded response	6	5	4	3	2	1
Question number: 8 (if question number 7 is NOT answered)						
Original response	1	2	3	4	5	
Re-coded response	6	4.75	3.5	2.25	1	
Questions number: 9a, 9d, 9e, 9h						
Original response	1	2	3	4	5	
Re-coded response	5	4	3	2	1	

Step 2: Determining Health Domain Scale Scores (0-100 Scores)

After item recoding, a total raw score is computed for each health domain scale. The total raw score is the simple algebraic sum of the final response values for all items in a given scale, as shown in Table A2.3. The total raw score for each scale is transformed to a 0-100 scale score using the following formula:

(Raw score – Lowest possible raw score) / Possible raw score range × 100

Table A2.3: Values used in transforming SF-36v2 Health Survey Health Domain Scale Total Raw Scores on the 0-100 Scale

Scale	Sum of Final Response Values	Lowest and highest possible total raw scores	Possible total raw score range
PF	3a+3b+3c+3d+3e+3f+3g+3h+3i+3j	10, 30	20
RP	4a+4b+4c+4d	4, 20	16
BP	7+8	2, 12	10
GH	1+11a+11b+11c+11d	5, 25	20
VT	9a+9e+9g+9i	4, 20	16
SF	6+10	2, 10	8
RE	5a+5b+5c	3, 15	12
MH	9b+9c+9d+9f+9h	5, 25	20

Raw and transformed scale scores are not calculated for the Reported Health Transition (HT) item.

As recommended by the developers of the questionnaire, missing item responses will be treated using the "Half-scale rule", which states that a score can be calculated if the respondent answers at least 50% of the items in a multi-item scale. In such cases, the missing item data will be replaced by the mean of the answered items of its scale. If more than 50% of the items are missing within a scale, the scale score will be missing.

Step 3: Calculating Normalized Health Domain Scores

The normalized scale scores will then be calculated using the following formulas:

1/ Health Domain Z-score = (Health Domain 0-100 score – a) / b

2/ Normalized Health Domain score = 50 + (Health Domain Z-score × 10)

where a and b are the Mean and Standard Deviation of the Health Domain scale in the 1998 U.S. general population as shown in Table A2.4.

Table A2.4: 1998 General US Population Means and Standard Deviations used to Calculate Normalized Health Domain Scores

Health Domain Scales	Mean	Standard Deviation
PF	83.29094	23.75883

RP	82.50964	25.52028
BP	71.32527	23.66224
GH	70.84570	20.97821
VT	58.31411	20.01923
SF	84.30250	22.91921
RE	87.39733	21.43778
MH	74.98685	17.75604

The advantages of the normalization of the eight health domain scales are that results for one health domain scale can be meaningfully compared with those from the other scales and that domain scores have a direct interpretation in relation to the distribution of scores in the 1998 U.S. general population.

Step 4: Scoring the Physical and Mental Component Summary Measures

The Physical Component Summary (PCS) and Mental Component Summary (MCS) measures are scored using a three-step procedure. First, the 8 health domain scale scores are standardized using means and standards deviations from the 1998 U.S. general population (see Table A2.4). Second, these Z-scores are aggregated using weights (factor score coefficient) from the 1990 U.S general population. Third, aggregate PCS and MCS scores are standardized by multiplying the standardized scale by 10 and adding 50.

U.S. general population statistics used in the standardization and in the aggregation of SF-36v2 Health Survey health domain scale scores are presented in Table A2.5.

Table A2.5: Factor Score Coefficients used to Calculate PCS and MCS Scores for the SF-36v2

	Summary component measure factor score coefficients	
Scales	**PCS**	**MCS**
PF	0.42402	-0.22999
RP	0.35119	-0.12329
BP	0.31754	-0.09731
GH	0.24954	-0.01571
VT	0.028877	0.23534
SF	-0.00753	0.26876
RE	-0.19206	0.43407

18.3 Appendix 3: Details on Pharmacometry Evaluation

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MS200527-0086 Integrated Analysis Plan v1

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Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)
PPD	Technical Approval	14-Feb-2018 21:16 GMT+01