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	29 May 2018 / Version 3.0
Replaces Version	28 November 2017 / Version 2.0

[redacted]

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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
CCI [redacted]	
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

CCI	[redacted]
IAP	Integrated analysis plan
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	Intention To Treat
IV	intravenous
IWRS	Interactive Web Response System
LLN	Lower limit of normal
LLOQ	Lower limit of quantification
LTBI	Latent Tuberculosis Infection
MCS	Mental component summary
mITT	Modified ITT
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
NB	Negative binomial
CCI	[redacted]
OLE	Open-label extension
PCS	Physical component summary
CC	[redacted]
CC	[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	CCI [redacted]
FDA covered trial	Yes
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
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.

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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. For subjects who received Tecfidera during the 48-week main study and choose to enter the OLE Period, there will be a minimum 4-week washout period before starting open-label M2951. Following completion or early termination of treatment, 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]

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. Approximately 200 subjects are expected to participate in the OLE.

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

Secondary endpoints:

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

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

Additional secondary endpoints:

To evaluate the efficacy of M2951 compared to placebo:

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

To evaluate efficacy within M2951 dose groups:

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

To evaluate the efficacy and safety of Tecfidera:

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

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

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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. For subjects who choose to enroll in the OLE, M2951 may be administered for up to 160 weeks.

Reference therapy: dose/mode of administration/dosing schedule: Tecfidera (120 or 240 mg hard capsules) will be used as an active control. For the first 7 days, Tecfidera is administered orally at 120 mg twice daily. Following this and for the duration of treatment, Tecfidera is administered orally at 240 mg twice daily orally. Detailed recommendations for the use of this product are described in the summary of product characteristics or prescribing information.

Planned trial and treatment duration per subject: Total duration of subject participation is approximately 156 to 160 weeks for subjects who choose to participate in the optional OLE Period and 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
- Optional 24-month OLE Period (96 weeks)
- 4-week Safety Follow-Up/End of Trial Visit: 28 days (4 weeks).

After completing the 48-week main study, subjects will be offered the opportunity to participate in an optional 96-week OLE Period with M2951.

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 (3) a final analysis, triggered when 100% of subjects enrolled in the OLE complete the OLE or discontinue prematurely from the OLE.

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

Primary Endpoint

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

Other Efficacy Endpoints, Baseline to 24 weeks:

The comparison of a M2951 treatment group to placebo group using ARR at Week 24 will be based on the rate ratio estimated from an NB model for qualified relapse count, with offset equal to the log of years on study, with M2951 dose group or placebo group as a factor, and adjustment for covariates based on randomization strata and 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.

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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	
CCI																								
CCI																								
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, CCI , 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, CCI

a. Informed consent must be obtained at the Screening visit prior to initiating any Screening procedures or collecting any data. An addendum ICF must be obtained following the IDMC recommendation (October 2017).
b. Informed consent for the OLE Period will be obtained at the End of Treatment Visit for all subjects who received Tecfidera during the 48-week main study and who choose to enter the OLE Period.
c. An additional physical examination may be performed at the additional safety visits (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 C CI 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 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.
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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.

Table 2 Schedule of Assessments – Optional OLE Period

Activity/Assessment	OLE Day 1[a]	On Treatment Visits																			Unscheduled Visit	OLE End of Treatment	End of Trial Visit
Visit number (for OLE)	1	1.1	2[a]	2.1	3[a]	3.1	4	4.1, 4.2, 4.4	5	5.2, 5.4	6	6.2, 6.4	7	7.2, 7.4	8	8.2, 8.4	9	9.2, 9.4	10	10.2, 10.4		11	12
Study Week	W0	W2	W4	W 6	W8	W10	W12	W14 W16 W20	W24	W28 W32	W36	W40 W44	W48	W52 W56	W60	W64 W68	W72	W76 W80	W84	W88 W92		W96	W100
Study Day ± Visit Window	1±3	±3	28±7	±3	56±7	±3	84±7	±3	168±7	±3	252±7	±3	336±7	±3	420±7	±3	504±7	±3	588±7	±3		672±7	700 ±7
Obtain ICF[b]	X																						
Physical examination[c]	X						X		X		X		X		X		X		X		X		
Vital signs[d]	X		X		X		X		X		X		X		X		X		X		X	X	X
Neurological examination	X						X		X		X		X		X		X		X		X	X	X
Hematology[d]	X		X		X		X		X		X		X		X		X		X		X	X	X
Clinical chemistry[d]	X		X		X		X		X		X		X		X		X		X		X	X	X
Supplemental Safety Visits including LFTs[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
CCI [redacted]																							
Immuno-globulin levels[d]	X								X				X				X					X	

Activity/Assessment	OLE Day 1[a]	On Treatment Visits																			Unscheduled Visit	OLE End of Treatment	End of Trial Visit
Visit number (for OLE)	1	1.1	2[a]	2.1	3[a]	3.1	4	4.1, 4.2, 4.4	5	5.2, 5.4	6	6.2, 6.4	7	7.2, 7.4	8	8.2, 8.4	9	9.2, 9.4	10	10.2, 10.4		11	12
Study Week	W0	W2	W4	W 6	W8	W10	W12	W14 W16 W20	W24	W28 W32	W36	W40 W44	W48	W52 W56	W60	W64 W68	W72	W76 W80	W84	W88 W92		W96	W100
Study Day ± Visit Window	1±3	±3	28±7	±3	56±7	±3	84±7	±3	168±7	±3	252±7	±3	336±7	±3	420±7	±3	504±7	±3	588±7	±3		672±7	700±7
Urinalysis (microscopy, urine protein/creatinine ratio)[g]	X								X						X						X	X	X
B, CCI [redacted] count[h]	X												X									X	X
Urine pregnancy test (all countries)[i,j]	X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
12-lead ECG	X												X								X	X	
Chest X-ray	X																						
EDSS	X												X								X	X	
Relapse assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MRI scan	X												X									X	
Concomitant medications and procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
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

Activity/Assessment	OLE Day 1[a]	On Treatment Visits																			Unscheduled Visit	OLE End of Treatment	End of Trial Visit
Visit number (for OLE)	1	1.1	2[a]	2.1	3[a]	3.1	4	4.1, 4.2, 4.4	5	5.2, 5.4	6	6.2, 6.4	7	7.2, 7.4	8	8.2, 8.4	9	9.2, 9.4	10	10.2, 10.4		11	12
Study Week	W0	W2	W4	W 6	W8	W10	W12	W14 W16 W20	W24	W28 W32	W36	W40 W44	W48	W52 W56	W60	W64 W68	W72	W76 W80	W84	W88 W92		W96	W100
Study Day ± Visit Window	1±3	±3	28±7	±3	56±7	±3	84±7	±3	168±7	±3	252±7	±3	336±7	±3	420±7	±3	504±7	±3	588±7	±3		672±7	700±7
Dispense IMP[k]	X		X[l]		X[l]		X		X		X		X		X		X		X				
IMP compliance	X		X		X		X		X		X		X		X		X		X			X	
CCI [redacted]																							
HRQo[n]	X												X									X	
C-SSRS (Since Last Visit Scale)	X												X									X	

AE=adverse event, ALT=alanine aminotransferase, AST=aspartate aminotransferase, CCI [redacted], CMV=cytomegalovirus, C-SSRS=Columbia-Suicide Severity Rating Scale, EA=early antigen, EBNA=Epstein-Barr nuclear antigen, ECG=electrocardiogram, eCRF=electronic case report form, EDSS=expanded disability status scale, ESR=erythrocyte sedimentation rate, GGT=γ-glutamyl-transferase, HAV=hepatitis A virus, HBc=hepatitis B core antigen, HEV=hepatitis E virus, CCI [redacted], hsCRP=high sensitivity C-reactive protein, ICF=informed consent form, Ig=immunoglobulin, IMP=investigational medicinal product, INR=international normalized ratio, MRI=magnetic resonance imaging, MS=multiple sclerosis, CCI [redacted], OLE=Open-label Extension, PTT=partial thromboplastin time, SF-36v2=Short Form 36-item Health Status Survey version 2.0, VCA=viral capsid antigen.

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

b. Signed consent will be obtained prior to participation in the optional OLE Period. Subjects entering from M2951 will sign the ICF at OLE Day 1, and subjects entering from Tecfidera will sign at the Week 48 End of Treatment Visit.

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

d. The following will be obtained predose: vital signs (Section 7.4.4.1), hematology and chemistry (Table 7), and total Ig levels (IgM, IgA, IgG) (see Section 7.4.5).

e. Supplementary LFTs include AST, ALT, alkaline phosphatase, GGT, and bilirubin for subjects on M2951.

CCI [redacted]

g. Urine samples for urinalysis will be obtained predose on OLE Day 1 and at Weeks 24, 60, 96/OLE End of Treatment, 4-week Safety Follow-up/End of Trial Visit, and unscheduled visits. If local urinalysis by dipstick is abnormal, urine microscopy should be performed by a central laboratory. If at least 1+ protein is detected, urine protein/creatinine ratio should be determined.

h. Blood samples for B, CCI [redacted] cell numbers and B, CCI [redacted] cell subclasses will be obtained predose on OLE Day 1, Week 48, and Week 96/OLE End of Treatment visits. 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).

i. Urine pregnancy tests will also be performed at home at Week 16, Week 20, Week 28, Week 32, Week 40, Week 44, Week 52, Week 56, Week 64, Week 68, Week 76, Week 80, Week 88, and Week 92 for women of childbearing potential. Subjects will be supplied with at-home test kits.

j. Phone calls: To be done only if urine pregnancy test is completed at home: The Principal Investigator and/or delegated site staff will call subject at Week 16, Week 20, Week 28, Week 32, Week 40, Week 44, Week 52, Week 56, Week 64, Week 68, Week 76, Week 80, Week 88, and Week 92 to confirm completion of home pregnancy testing and discuss results.

k. The IMP will be dispensed on OLE Day 1 and at indicated visits thereafter. All remaining IMP will be collected at the Week 96/OLE End of Treatment Visit.

l. For subjects switching from Tecfidera.

CCI [redacted]

n. HRQoL will be assessed with the SF-36v2 questionnaire at OLE Day 1, Week 48, and Week 96/OLE End of Treatment Visit. At all applicable visits, patient-reported outcome questionnaires (ie, HRQoL) must be performed prior to any other assessments.

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). For the Open-label Extension (OLE) Period, enrollment will continue at the sites used during the Screening and Treatment periods.

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

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

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

The Sponsor will enlist the support of a 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. The OLE Period will allow for assessment of long-term safety and efficacy of M2951.

The findings in Section 3 clearly support the pathogenic contribution of B cells to MS damage. In contrast, a failed clinical trial with another B cell targeting agent, atacicept, supports the notion that certain B cell subtypes may mediate beneficial anti-inflammatory effects (11). Novel non-depleting B cell therapies may deliver a more favorable benefit-risk profile than current B cell-directed therapeutic approaches.

CCI [redacted]

Refer to the Investigator's Brochure for further information about the 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.

CCI [redacted]

CCI [redacted]

[redacted]

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.

CCI [redacted]

- CCI [redacted]

[redacted]

CCI [redacted]

5 Investigational Plan

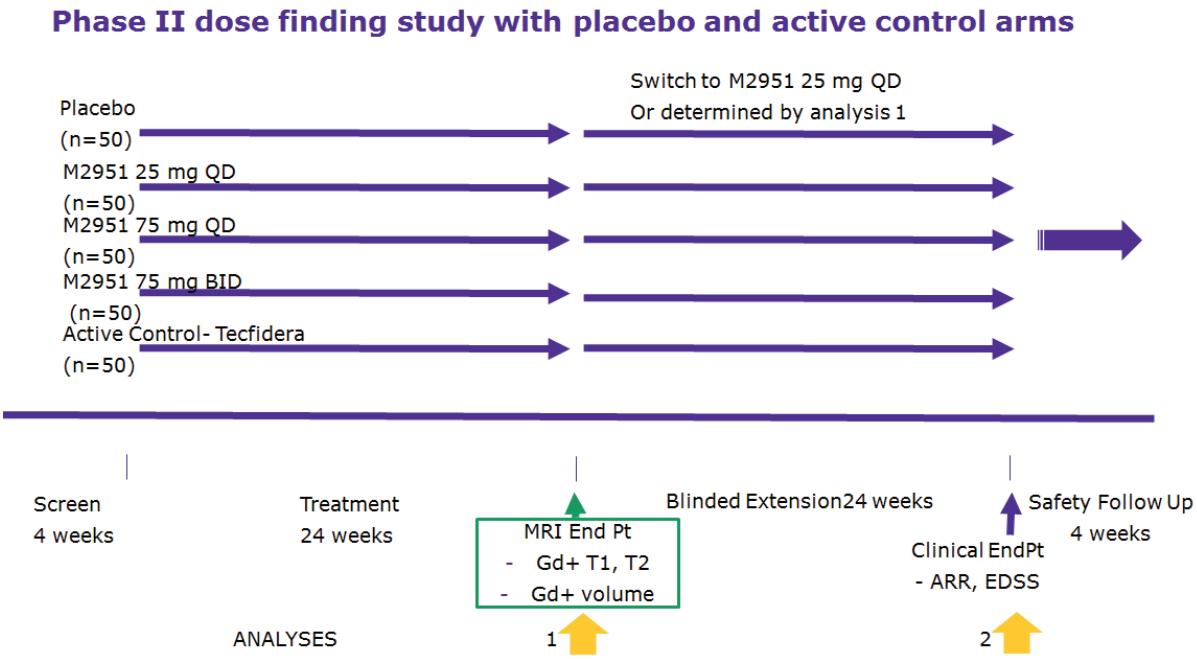
5.1 Overall Trial Design and Plan

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). All subjects who choose to enter the OLE 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 (Figure 2). Subjects transitioning from Tecfidera will complete a washout period of at least 4 weeks prior to initiating M2951 treatment in the OLE Period (see Section 5.5.1 and Figure 3). 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.

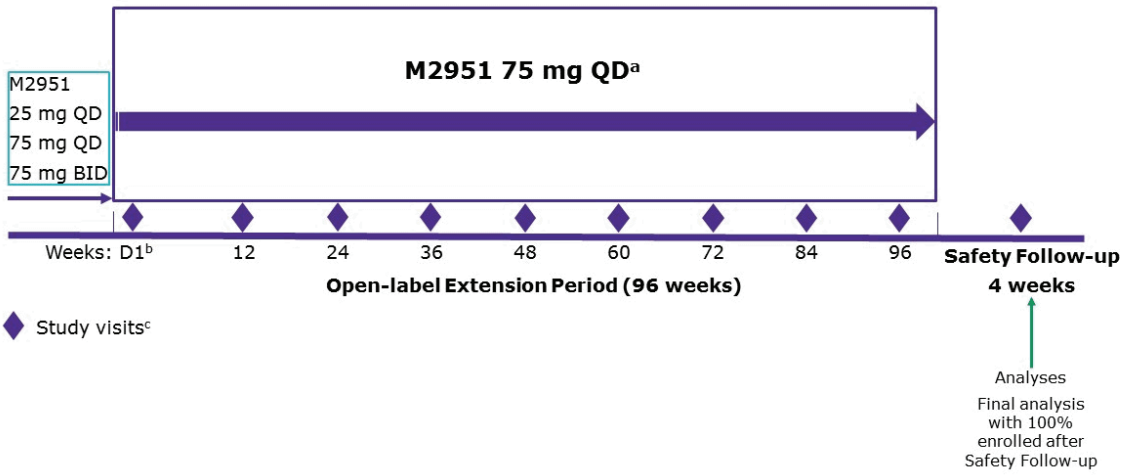
Approximately 50 subjects will be enrolled in each treatment group to obtain 44 evaluable subjects per group (total = approximately 250), assuming a 12% drop-out rate per year, and to compile an adequate safety database. Approximately 200 subjects are expected to be enrolled in the OLE.

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.

Figure 2 Trial Design – Optional OLE Period (for Subjects Entering from M2951 Treatment Arm)



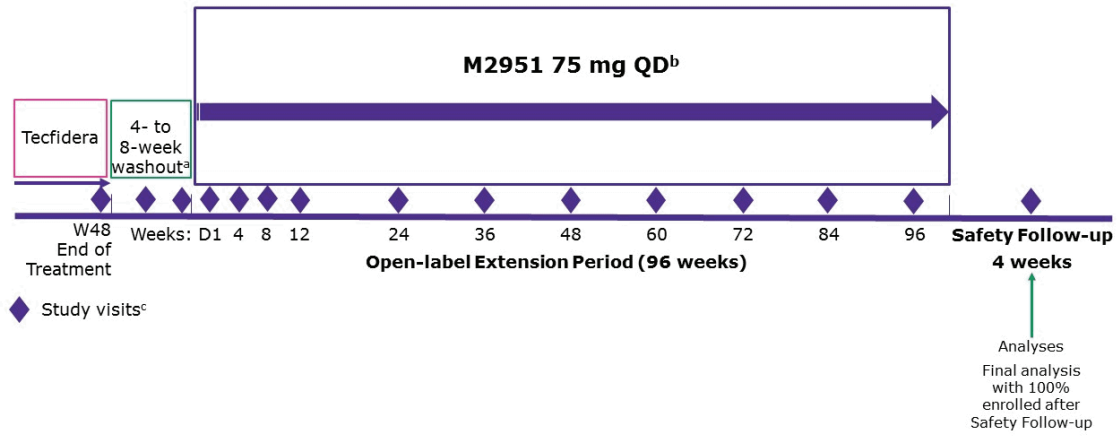
OLE=Open-label Extension; QD=once a day.

a Subjects will receive an initial dose of 75 mg QD and may change to the eventual Phase III dose when decided.

b For subjects entering the Open-label Extension after receiving M2951 during the 48-week main study, the Week 48 visit is considered the Day 1 visit for the Open-label Extension period.

c Denotes efficacy visits only. Safety visits will be conducted every 2 weeks during the first 16 weeks of treatment and then monthly during the Open-label Extension period.

Figure 3 Trial Design – Optional OLE Period (for Subjects Entering from Tecfidera Treatment Arm)



OLE=Open-label Extension.

a Treatment with M2951 will only commence if a subject who received Tecfidera during the 48-week main study has an absolute lymphocyte count ≥ 800/mm3 following 4 weeks of washout. If the subject does not have an absolute lymphocyte count ≥ 800/mm3 following 8 weeks of washout, he or she will be discontinued from the study.

b Subjects will receive an initial dose of 75 mg QD and may change to the eventual Phase III dose when decided.

c Denotes efficacy visits only. Safety visits will be conducted every 2 weeks during the first 16 weeks of treatment and then monthly during the Open-label Extension period.

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. Subjects who choose to enter the OLE Period will receive open-label M2951 for 2 years (96 weeks).

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. All subjects who choose to enter the OLE Period will receive M2951 at a starting dose of 75 mg once daily and may change to the eventual Phase III dose when decided.

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.

CCI [redacted]

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 $< 3500/mm^3$

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

5.4 Criteria for Randomization and Initiation of Trial Treatment

Randomization should occur on Day 1 after all Screening procedures have been completed; 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 Criteria for Entry into OLE Period

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. Only subjects who have completed the 48-week main study are eligible to participate in the OLE Period. Subjects who choose to enter the OLE Period will receive open-label M2951 75 mg once daily or the eventual Phase III dose when decided.

5.5.1 Subjects Entering OLE Period after Receiving Tecfidera

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

Table 4 Washout Period for Subjects on Tecfidera Treatment Arm before Entering OLE Period

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

OLE=Open-label Extension, WO=washout.

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

b. 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 described in Table 1. This End of Trial Visit should be completed within 14 days ± 7 days from the time the decision is reached that the subject is not eligible to enter the OLE Period.

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

d. Treatment with M2951 will only commence if a subject who received Tecfidera during the 48-week main study has an absolute lymphocyte count ≥ 800/mm^3 following 4 weeks of washout. If the subject does not have an absolute lymphocyte count ≥ 800/mm^3 at Tecfidera Washout Visit 2, he or she will be excluded from the OLE Period. At any time during the washout period, the subject may choose to discontinue from the study and begin a different treatment regimen in agreement with the Investigator.

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. Only subjects who have completed the 48-week main study are eligible to participate in the OLE Period. 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.

Subjects who choose to participate in the OLE Period will receive open-label M2951 75 mg once daily or the eventual Phase III dose when decided. Subjects who do not participate in the OLE Period will no longer receive M2951 or Tecfidera.

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. All subjects who choose to enter the OLE Period will receive open-label M2951 75 mg once daily or the eventual Phase III dose.

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.

CCI

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 up to Grade 3, 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.

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. Re-initiate IMP after discussion with Medical Monitor if no further downward trend is observed

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 [redacted] 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. For subjects entering the OLE Period at the End of Treatment visit (Week 48), the data will no longer be blinded.

All breaks of the trial blind must be adequately documented.

6.10 Emergency Unblinding

The trial blind may be broken for an individual only if knowledge of the IMP is essential for clinical management of the 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.

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

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

- Urine testing for β-human chorionic gonadotropin will be conducted at the local laboratories.
- Urine dipstick results will be interpreted locally. Please see Table 1 for information regarding abnormal dipstick results.
- [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 CCI, collection of demographic and other Baseline characteristics (MS history and other medical history, including medication history), review of concomitant medications and procedures, evaluation of AEs, a physical examination, vital signs, a neurological examination, MRI, EDSS. The MRI scan should be acquired before

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

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

7.1.2 Treatment Visits, Including Blinded Treatment Extension Phase

At all trial visits, scheduled assessments will be performed before administration of the trial medication, with the exception of relevant blood draws (eg, CCI and CCI as noted in Table 1). After Day 1, all scheduled visits during the treatment period may take place within ± 3 days of the protocol-specified day. 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
- CCI
- Review of concomitant medications and procedures, evaluation of AEs, disease activity assessment (EDSS), vital signs, and a neurologic exam
- Blood sample collection for Ig levels, B, CCI cell counts; CCI CCI ; 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:

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

- IMP compliance
- 12-lead ECG (Week 24 only)
- Blood sample collection for safety assessments (hematology, chemistry); Ig levels (Week 4, 16, and 24 only); B, CCI cell count and CCI (Week 4 and 24 only); CCI ; 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)
- During the OLE period, safety visits will be conducted every 2 weeks until Week 16, then monthly at Weeks 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, 84, 88 and 92 (see Table 2).

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 CC 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):

- CCI [redacted]
- 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 CCI .
- Urine collection for urinalysis and, if necessary, microscopy and protein:creatinine ratio; urine pregnancy testing (women only).
- MRI assessment.

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

7.1.6 Open-label Extension Period

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

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

Scheduled assessments will be performed according to Table 2 before administration of the IMP. All scheduled visits during the OLE Period may take place within the visit windows specified in Table 2. Subjects who discontinue early must return for the OLE End of Treatment Visit (Visit 11).

7.1.7 Open-label Extension End of Treatment Visit

The OLE End of Treatment Visit (Visit 11) will be performed at Week 96 ± 7 days of early termination of OLE treatment with the IMP. Subjects will undergo assessments as described in Table 2. In case of premature discontinuation, the patient-reported outcomes assessment must be completed at the OLE End of Treatment Visit. Subjects will enter the Safety Follow-up Period after completing the OLE End of Treatment Visit.

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. CCI [redacted].

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 (or Week 96 for the OLE Period), all assessments should be completed prior to the administration of study medication.

7.3.1 Brain Magnetic Resonance Imaging Scans

MRI scans will be performed at Screening, at 4-week intervals from Week 12 to 24, and at the End of Treatment Visit at Week 48 (including for subjects receiving Tecfidera who choose to enter the OLE Period). For subjects in the OLE Period, an MRI will also be performed at Day 1 (except for subjects who received Tecfidera during the 48-week parent study and had an MRI at the End of Treatment Visit at Week 48), Week 48, and the OLE End of Treatment Visit at Week 96. 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). For subjects in the OLE Period, MS relapse will be assessed at all visits. A qualifying relapse is defined as new, worsening or recurrent neurological symptoms attributed to MS that last for at least 24 hours without fever or infection, or adverse reaction to prescribed medication, preceded by a stable or improving neurological status of at least 30 days. This relapse must be accompanied by new clinical signs (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 [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 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	• Platelet count • White blood cell count • B, CCI [redacted] cell count[a]	• White blood cell differentials and absolute counts:

	• Mean corpuscular volume • Mean corpuscular hemoglobin • Mean corpuscular hemoglobin concentration • Reticulocyte count	• Immunoglobulin and subclass concentrations[a,b]	○ 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. For subjects in the OLE Period, a 12-lead ECG will also be conducted at OLE Day 1, Week 48, unscheduled visits, and the OLE End of Treatment visit. The 12-lead ECG recordings will be obtained after 10 minutes of rest in a semisupine position.

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

The printout of the ECG is to be signed, dated, and filed in the Investigator's Site File along with a signed and dated copy (if the printouts are not on archive-quality paper).

Posterioanterior CXRs will be performed during Screening according to local standard practice. For subjects in the OLE Period, a CXR will be performed at OLE Day 1. 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). For subjects in the OLE Period, samples will also be collected at OLE Day 1, Week 48, and Week 96/OLE End of Treatment 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 [redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted].

CCI [redacted]

[redacted]

[redacted]

7.6 CCI [redacted]

[redacted]

7.6.1 CCI [redacted]

[redacted]

[redacted]

[redacted]

7.6.2 CCI [redacted]

[redacted]

7.6.3 CCI [redacted]

[redacted]

See Section 7.4.6 for sampling, analysis, and storage information.

7.6.4 CCI [redacted]

[redacted]

7.6.5 Use of Samples for Additional Analysis

CCI [redacted]

CCI [redacted]

7.8 Columbia-Suicide Severity Rating Scale

The C-SSRS will be used for prospective suicidality assessment. The C-SSRS will be a tool used at Screening to identify eligible 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 C-SSRS Since Last Visit Scale will be used in the OLE. The structured interview prompts recollection of suicidal ideation, including the intensity of the ideation, behavior and attempts with actual/potential lethality.

The scale will be administered by the Treating Investigator or a qualified designee. Please note that assessing the risk of suicide is a difficult and complex task when applied to the individual patient. No single clinical scale can replace a thorough medical examination and suicide risk assessment. Ultimately, the determination of the presence of suicidality depends on clinical judgment.

8 Statistics

8.1 Sample Size

A per-group sample size of 44 evaluable 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. Assuming an 80% rate of continuation to OLE, approximately 200 subjects are expected to enter the OLE Period.

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:

- CCI [redacted]

CCI [redacted]

CCI [redacted]

8.3.5 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 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]

[redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

[redacted]

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 non-convergence, 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, CCI , 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 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.

CCI [redacted]

CCI [redacted]

CCI [redacted]

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

CCI [redacted]

CCI [redacted]

Safety data collected during the 100-week OLE Period will be analyzed as described in Section 8.5.4.1.

8.5.4.4 CCI [redacted]

[redacted]

8.5.4.5 CCI [redacted]

[redacted]

CCI [redacted].

8.5.4.6 CCI [redacted]

[redacted]

8.5.4.7 CCI [redacted]

[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 (3) a final analysis, triggered when 100% of subjects enrolled in the OLE complete the OLE, or discontinue prematurely from the OLE. 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.

Final Analysis

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

9 Ethical and Regulatory Aspects

9.1 Responsibilities of the Investigator

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

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

The signed and dated declaration of informed consent will remain at the Investigator's site, and must be safely archived so that the forms can be retrieved at any time for monitoring, auditing, and inspection purposes. A copy of the signed and dated information and ICF should be provided to the 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. After completion of the OLE Period, an additional clinical trial report will be written by the Sponsor in consultation with the Coordinating Investigator following the guidance in ICH Topic E3 within the legally required period for participating countries.

10.6.2 Publication

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

Posting of data on clinicaltrials.gov is planned and will occur 12 months after the last clinic visit of the final trial 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:	CCI [redacted]
EudraCT Number:	2016-001448-21
Clinical Trial Protocol Date / Version:	29 May 2018 / Version 3.0

Protocol Lead responsible for designing the clinical trial:

I approve the design of the clinical trial:

PPD [redacted] _____ PPD [redacted] _____

Signature Date of Signature

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

Signature Page –Coordinating Investigator

Trial Title	A Randomized, Double-Blind, Placebo-Controlled Phase II Study of M2951 with a Parallel, Open-Label, Active Control Group (Tecfidera), in Patients with Relapsing Multiple Sclerosis to Evaluate Efficacy, Safety, Tolerability, Pharmacokinetics, and Biological Activity
IND Number	CCI [redacted]
EudraCT Number	2016-001448-21
Clinical Trial Protocol Date / Version	29 May 2018 / Version 3.0

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 [redacted] PPD [redacted]

Signature Date of Signature

Name, academic degree: PPD [redacted]

Function / Title: PPD [redacted]

Institution: PPD [redacted]

Address: PPD [redacted]

Telephone number: PPD [redacted]

Fax number: PPD [redacted]

E-mail address: PPD [redacted]

Signature Page – Principal Investigator

Trial Title	A Randomized, Double-Blind, Placebo-Controlled Phase II Study of M2951 with a Parallel, Open-Label, Active Control Group (Tecfidera), in Patients with Relapsing Multiple Sclerosis to Evaluate Efficacy, Safety, Tolerability, Pharmacokinetics, and Biological Activity.
IND Number	CCI [redacted]
EudraCT Number	2016-001448-21
Clinical Trial Protocol Date / Version	29 May 2018 / Version 3.0
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 [redacted] cell count	10	5	50
CCI [redacted]			
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], 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.

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 [redacted] CCI			
Total			**382**

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

[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

Table of Amendments

Amendment Number	Substantial (Y/N)	Date	Region or Country	Included in the current document (Y/N)
Amendment 1.0	Y	22 May 2017	Poland	Y
Amendment 2.0	Y	28 Nov 2017	Global	Y
Amendment 3.0	Y	29 May 2018	Global	Y

Amendment # 3

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.

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
- CCI [redacted]
- 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.

Changes to the clinical study protocol text are presented in the table below. Additions and amended text are shown in bold. If the original clinical study protocol text was already bold, changes are shown in bold and underlined. Deletions are marked using strikethrough.

Administrative and Editorial Changes

- Minor edits for clarity and consistency that do not affect the substance of the protocol are not individually listed here.

Comparison with Clinical Trial Protocol Version 2.0, 28 November 2017

Change	Section	Page	Previous Wording	New Wording	Rationale
Updated text to clarify the study periods	Synopsis Methodology	13	The study will consist of **4** ~~3~~ 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, ~~and~~ **(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)**. … All subjects who choose to enter the ~~Open-label Extension (~~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.	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). … 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.	For clarity
Removed language on interim analyses	Synopsis Methodology	13	Following completion or early termination of treatment, subjects will return after 4 weeks for safety evaluation. ~~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 the study.~~ It is planned that placebo subjects will be switched to the 25 mg M2951 once daily 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~~.	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.	To remove interim analyses due to fast recruitment of subjects occurring for the primary analysis

Change	Section	Page	Previous Wording	New Wording	Rationale
Included information on a Safety Monitoring Committee (SMC)	Synopsis Methodology	13	An independent data monitoring committee (IDMC) will be responsible for ~~both~~ safety monitoring ~~and futility analyses.~~ **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.**	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.	For clarification on when the IDMC responsibility ends, include transition to an SMC and remove futility analysis
Updated number of subjects	Synopsis Planned number of subjects	13	Approximately 50 subjects will be enrolled in each treatment group, for a total of approximately 250 enrolled subjects. **Approximately 200 subjects are expected to participate in the OLE.**	Approximately 50 subjects will be enrolled in each treatment group, for a total of approximately 250 enrolled subjects. Approximately 200 subjects are expected to participate in the OLE.	For clarification on the number of subjects to be included in the OLE
CCI [redacted]	CCI [redacted]	15	• CCI [redacted]	• CCI [redacted]	For clarification and internal consistency

Change	Section	Page	Previous Wording	New Wording	Rationale
Removed interim analyses	Synopsis Statistical Methods	18	There **will** ~~may~~ be ~~4~~ **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; (2~~**1**) a primary analysis, triggered when 100% of subjects enrolled reach Week 24 of treatment, or prematurely discontinue from treatment; (~~3~~**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 (4**3**) a final analysis, triggered when 100% of subjects enrolled in the OLE complete the OLE, or discontinue prematurely from the OLE. ~~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~~	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 (3) a final analysis, triggered when 100% of subjects enrolled in the OLE complete the OLE, or discontinue prematurely from the OLE.	For clarification and internal consistency

Change	Section	Page	Previous Wording	New Wording	Rationale
Added SMC	2 Sponsor, Investigators and Trial Administrative Structure	30	An independent data monitoring committee (IDMC) will be responsible for ~~both~~ safety monitoring ~~and the futility analysis~~ **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 and Coordinating Investigator. An SMC charter will be provided once the transition from the IDMC has been completed.**	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 and Coordinating Investigator. An SMC charter will be provided once the transition from the IDMC has been completed.	For clarification on when the IDMC responsibility ends, include transition to an SMC and remove futility analysis
Updated dose of M2951	3.2 Benefit-Risk	33	CCI [redacted] … Refer to the current Investigator's Brochure for more detailed results from the completed **and ongoing** clinical studies.	CCI [redacted] … Refer to the current Investigator's Brochure for more detailed results from the completed and ongoing clinical studies.	To correct an error in the previous version of the protocol and add a clarification

Change	Section	Page	Previous Wording	New Wording	Rationale
Clarified the number of study periods, removed interim analysis and update the number of subjects enrolled in the OLE	5.1 Overall Trial Design and Plan	35	The study will consist of **4** ~~3~~ 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, ~~and~~ **(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**. ... Following completion or early termination of treatment, subjects will return after 4 weeks for safety evaluation. ~~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 the study.~~ It is planned that placebo subjects will be switched to the 25 mg **M2951** once daily 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 is the IA trigger date is sufficiently close (ie, 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. **Approximately 200 subjects are expected to be enrolled in the OLE.**	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. **…** 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. 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. Approximately 200 subjects are expected to be enrolled in the OLE.	For clarification and internal consistency based on updates to other sections of the protocol

Change	Section	Page	Previous Wording	New Wording	Rationale
Updated figure title and footnote	5.1 Overall Trial Design and Plan Figure 2 Trial Design – OLE Period (for Subjects Entering from M2951 Treatment Arm), footnote c	37	Figure 2 Trial Design – **Optional** OLE Period (for Subjects Entering from M2951 Treatment Arm) Denotes efficacy visits only. Safety visits will be conducted every 2 weeks **during the first 16 weeks of treatment and then monthly** during the Open-label Extension period.	Figure 2 Trial Design – Optional OLE Period (for Subjects Entering from M2951 Treatment Arm) Denotes efficacy visits only. Safety visits will be conducted every 2 weeks during the first 16 weeks of treatment and then monthly during the Open-label Extension period.	For clarification and internal consistency
Updated figure title and footnote	5.1 Overall Trial Design and Plan Figure 3 Trial Design – OLE Period (for Subjects Entering from Tecfidera Treatment Arm), footnote c	37	Figure 3 Trial Design – **Optional** OLE Period (for Subjects Entering from Tecfidera Treatment Arm) Denotes efficacy visits only. Safety visits will be conducted every 2 weeks **during the first 16 weeks of treatment and then monthly** during the Open-label Extension period.	Figure 3 Trial Design – Optional OLE Period (for Subjects Entering from Tecfidera Treatment Arm) Denotes efficacy visits only. Safety visits will be conducted every 2 weeks during the first 16 weeks of treatment and then monthly during the Open-label Extension period.	For clarification and internal consistency
Removed interim analyses	5.2.1 Scientific Rationale for Trial Design	37	… 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.~~	… Furthermore, all placebo subjects will be switched to M2951 during the blinded treatment extension phase.	For clarification and internal consistency
Removed futility analyses	5.2.2 Justification for Dose	39	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 ~~interim and/or~~ primary analyses.	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.	For clarification and internal consistency
Added text suggested by the Czech Republic Regulatory	5.6.1 Withdrawal from Trial Therapy	46	• 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.**	• 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.	To meet the requirements of the Czech Republic RA
Removed interim analyses	5.7 Premature Termination of the Trial	47	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~~	The Sponsor may discontinue the trial if the trial becomes unjustifiable for medical or ethical reasons, the trial experiences poor enrollment, or	For clarification

Change	Section	Page	Previous Wording	New Wording	Rationale
			~~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.	due to discontinuation of clinical development of an IMP or withdrawal of an IMP or comparator from the market for safety reasons.	and internal consistency
Removed interim analyses	6.2 Dosage and Administration	48	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~~ IA or~~ primary analysis.	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.	For clarification and internal consistency
Included a cross reference and updated the grade level for lab values	6.4.4.1 For M2951 only	52	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 any other increase in AST, ALT **up to Grade 3**, 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.	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 any other increase in AST, ALT up to Grade 3, 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 clarification and internal consistency
Added guidelines for discontinuation of tecfidera	6.4.4.2 For Tecfidera only	54	… • **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.**	… • Discontinue Tecfidera if clinically significant liver injury induced by Tecifidera 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 clarification and internal consistency.
Removed interim analyses	6.9 Blinding	56	… ~~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~~	… The IDMC will also be unblinded to treatment, as described in the IDMC charter. …	For internal consistency.

Change	Section	Page	Previous Wording	New Wording	Rationale
			~~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. … 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.~~	All other staff other than those identified above will remain blinded to the placebo and M2951 treatments.	
Updated that urine pregnancy testing may be performed at the site	7.1.2 Treatment Visits, Including Blinded Treatment Extension Phase	61	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 ~~(Poland only)~~ **or at the site**.	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.	
Added schedules for the supplemental safety visits	7.1.3 2- Week Safety Visit	61	**7.1.3 ~~2- Week Visit~~ 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)** • **During the OLE period, safety visits will be conducted every 2 weeks until Week 16, then monthly at Weeks 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, 84, 88 and 92 (see Table 2)**. **Safety visits will be conducted** after obtaining subject's informed consent. These ~~every 2 week~~ safety evaluations have been implemented by a	**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) • During the OLE period, safety visits will be conducted every 2 weeks until Week 16, then monthly at Weeks 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, 84, 88 and 92 (see Table 2). 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.	To provide additional clarification and guidelines for the supplemental safety visits

Change	Section	Page	Previous Wording	New Wording	Rationale
			letter to Investigators as an urgent safety measure. … Patient compliance to ~~every 2 week~~ **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 ~~2 week~~ **supplemental** safety visit locally will not have C CI samples collected at that visit	… 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 C CI samples collected at that visit.	
Added clarification on the visits that are applicable for subjects who received tecfidera in the main study	7.1.6 Open-label Extension Period	62	The OLE Visits 2 (**Week 4**) and 3 (**Week 8**) are only applicable for subjects who received Tecfidera in the 48-week main study. All subjects participating in the OLE (including subjects who received Tecfidera during the 48-week main study) will complete the ~~2-week~~ **supplemental** safety visits described in Section 7.1.3.	The OLE Visits 2 (Week 4) and 3 (Week 8) are only applicable for subjects who received Tecfidera in the 48-week main study. All subjects participating in the OLE (including subjects who received Tecfidera during the 48-week main study) will complete the supplemental safety visits described in Section 7.1.3.	For clarification and internal consistency
CCI [redacted]					
Clarified C-SSRS assessment timepoints	7.8 Columbia-Suicide Severity Rating Scale	78	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 C-SSRS Since Last Visit will be used in the OLE.**	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 C-SSRS Since Last Visit will be used in the OLE.	For clarification

Change	Section	Page	Previous Wording	New Wording	Rationale
Removed interim analyses	8.1 Sample Size	80	~~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.	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.	For internal consistency
CCI [redacted]	[redacted]	[redacted]	• [redacted]	CCI [redacted]	For clarification and internal consistency

CCI [redacted]

Change	Section	Page	Previous Wording	New Wording	Rationale
CCI [redacted]					
Removed Interim analyses	8.6 Interim and Additional Planned Analyses	88	There ~~may~~ **will** be 4 ~~–~~ **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; (2~~**1**) a primary analysis, triggered when 100% of subjects enrolled reach Week 24 of treatment, or prematurely discontinue from treatment; (~~3~~**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 (4**3**) a final analysis, triggered when 100% of subjects enrolled in the OLE complete the OLE, or discontinue prematurely from the OLE. ~~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.~~ **No interim analyses are planned.** ~~**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 once daily 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.~~	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 (3) a final analysis, triggered when 100% of subjects enrolled in the OLE complete the OLE, or discontinue prematurely from the OLE. No interim analyses are planned.	For clarification and internal consistency

Change	Section	Page	Previous Wording	New Wording	Rationale
			~~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 Week 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 Week 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 IAP, 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) of the effect of treatment on total number of Gd+ T1 lesions at Week 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 the primary efficacy endpoint, will be performed as a supportive analysis~~		

Revised Table 1

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	~~9.3~~	9.4	~~9.5~~		10	11
~~Supplemental Safety visits~~[a]					~~X~~		~~X~~		~~X~~		~~X~~		~~X~~	~~X~~	~~X~~	~~X~~	~~X~~		~~X~~	~~X~~	~~X~~	~~X~~	~~X~~			
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 42~~	W 44	~~W 46~~		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	~~294 ±3~~	308 ±3	~~322 ±3~~		336 ±3	364 ±5
Obtain ICF[ba]	X																								X[eb]	
Inclusion / Exclusion criteria	X	X																								
Medical history /demographics	X																									
MS history	X																									
Physical examination	X				X[dc]	X	X[dc]		X[dc]		X[dc]	X	X[dc]	X[dc]	X[dc]	X[dc]	X[dc]		X[dc]	X[dc]	X[dc]	X[d]	X[dc]	X		
Vital signs[ed]	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[fe]	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	~~9.3~~	9.4	~~9.5~~		10	11
~~Supplemental Safety visits~~[a]					~~X~~		~~X~~		~~X~~		~~X~~		~~X~~	~~X~~	~~X~~	~~X~~	~~X~~		~~X~~	~~X~~	~~X~~	~~X~~	~~X~~			
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 42~~	W 44	~~W 46~~		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	~~294 ±3~~	308 ±3	~~322 ±3~~		336 ±3	364 ±5
Randomization[g] [f]		X																								
Hematology[h] [g]	X		X	X		X		X		X		X						X						X	X	X
Clinical chemistry[h] [g]	X		X	X		X		X		X		X						X						X	X	X
Supplemental **Safety Visits including** LFTs ~~[a]~~ [h]			**X**	**X**	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																									

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	~~9.3~~	9.4	~~9.5~~		10	11
~~Supplemental Safety visits~~[a]					~~X~~		~~X~~		~~X~~		~~X~~		~~X~~	~~X~~	~~X~~	~~X~~	~~X~~		~~X~~	~~X~~	~~X~~	~~X~~	~~X~~			
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 42~~	W 44	~~W 46~~		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	~~294 ±3~~	308 ±3	~~322 ±3~~		336 ±3	364 ±5
~~Urine pregnancy test (all countries except Poland)~~[l]		~~X~~	~~X~~	~~X~~		~~X~~		~~X~~		~~X~~		~~X~~						~~X~~							~~X~~	~~X~~
Urine pregnancy test (**all countries** ~~Poland only~~)[m]		X	X	X		X		X		X		X		X~~m~~		X~~m~~		X		X~~m~~		X~~m~~			X	X
12-lead ECG[en]	X											X												X	X	
Chest X-ray[en]	X																									
EDSS	X	X				X						X						X						X	X	
Relapse assessment			X	X		X		X		X		X						X						X	X	X
MRI scan	X~~po~~					X		X		X		X													X	
Concomitant medications and procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	~~X~~	X	~~X~~	X	X	X
AE evaluation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	~~X~~	X	~~X~~	X	X	X
Dispense IMP~~qp~~		X	X	X		X		X		X		X						X								
IMP Administration		Oral Administration																								
IMP compliance			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	~~9.3~~	9.4	~~9.5~~		10	11
~~Supplemental Safety visits~~[a]					~~X~~		~~X~~		~~X~~		~~X~~		~~X~~	~~X~~	~~X~~	~~X~~	~~X~~		~~X~~	~~X~~	~~X~~	~~X~~	~~X~~			
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 42~~	W 44	~~W 46~~		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	~~294 ±3~~	308 ±3	~~322 ±3~~		336 ±3	364 ±5
CCI																										
CCI																										
C-SSRS **(Screening Scale)**	X																									
CCI																										
ESR, hsCRP, and fibrinogen[xw]																		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, CCI , 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, CCI

a. Informed consent must be obtained at the Screening visit prior to initiating any Screening procedures or collecting any data. An addendum ICF must be obtained following the IDMC recommendation (October 2017).

b. Informed consent for the OLE Period will be obtained at the End of Treatment Visit for all subjects who received Tecfidera during the 48-week main study and who choose to enter the OLE Period.

c. An additional physical examination may be performed at the additional safety visits (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 ~~(see Table 6)~~.

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 6~~ **Table 7**) will be conducted, and additional C CI 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 [redacted] cell numbers and B, CCI [redacted] 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. ~~(All countries except Poland)~~ 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. ~~(Poland only) Serum pregnancy test collected at Screening, and urine tests collected predose at every monthly trial visit. If necessary to confirm postmenopausal status, FSH testing will be done at Screening in postmenopausal women.~~

m. ~~(Poland only)~~ 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.

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[redacted]

[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.

Revised Table 2

Table 2 **Schedule of Assessments – Optional OLE Period**

Activity/Assessment	OLE Day 1[a]	On Treatment Visits																			Unscheduled Visit	OLE End of Treatment	End of Trial Visit
Visit number (for OLE)	1	1.1	2[a]	2.1	3[a]	3.1	4	4.1, **4.2, 4.4** ~~to 4.5~~	5	~~5.1 to 5.5~~**5.2, 5.4**	6	~~6.1 to 6.5~~**6.2, 6.4**	7	~~7.1 to 7.5~~**7.2, 7.4**	8	~~8.1 to 8.5~~**8.2, 8.4**	9	~~9.1 to 9.5~~**9.2, 9.4**	10	~~10.1 to 10.5~~**10.2, 10.4**		11	12
~~Supplemental Safety Visits~~		~~X~~		~~X~~		~~X~~		~~X~~		~~X~~		~~X~~		~~X~~		~~X~~		~~X~~		~~X~~			
Study Week	W0	W2	W4	W 6	W8	W10	W12	**W 14, W16, W20,** ~~W22~~	W24	~~W 26 to W34~~ **W28, W32**	W36	~~W38 to W 46~~**W 40, W44**	W48	~~W 50 to W58~~ **W52, W56**	W60	~~W62 to W70~~ **W64, W68**	W72	~~W74 to W82~~ **W76, W80**	W84	~~W86 to W94~~ **W88, W92**		W96	W100
Study Day ± Visit Window	1±3	**±3**	28±7	**±3**	56±7	**±3**	84±7	**±3**	168±7	**±3**	252±7	**±3**	336±7	**±3**	420±7	**±3**	504±7	**±3**	588±7	**±3**		672±7	700±7
Obtain ICF[b]	X																						
Physical examination[c]	X						X		X		X		X		X		X		X		X		
Vital signs[d]	X		X		X		X		X		X		X		X		X		X		X	X	X
Neurological examination	X						X		X		X		X		X		X		X		X	X	X
Hematology[d]	X		X		X		X		X		X		X		X		X		X		X	X	X
Clinical chemistry[d]	X		X		X		X		X		X		X		X		X		X		X	X	X
Supplemental **Safety Visits including** LFTs[e]	**X**	X	**X**	X	**X**	X	**X**	X	**X**	X	**X**	X	**X**	X	**X**	X	**X**	X	**X**	X		**X**	

Activity/Assessment	OLE Day 1[a]	On Treatment Visits																			Unscheduled Visit	OLE End of Treatment	End of Trial Visit
Visit number (for OLE)	1	1.1	2[a]	2.1	3[a]	3.1	4	4.1, **4.2, 4.4** ~~to 4.5~~	5	~~5.1 to 5.5~~**5.2, 5.4**	6	~~6.1 to 6.5~~**6.2, 6.4**	7	~~7.1 to 7.5~~**7.2, 7.4**	8	~~8.1 to 8.5~~**8.2, 8.4**	9	~~9.1 to 9.5~~**9.2, 9.4**	10	~~10.1 to 10.5~~**10.2, 10.4**		11	12
~~Supplemental Safety Visits~~		~~X~~		~~X~~		~~X~~		~~X~~		~~X~~		~~X~~		~~X~~		~~X~~		~~X~~		~~X~~			
Study Week	W0	W2	W4	W 6	W8	W10	W12	**W 14, W16, W20,** ~~W22~~	W24	~~W 26 to W34~~ **W28, W32**	W36	~~W38 to W 46~~**W 40, W44**	W48	~~W 50 to W58~~ **W52, W56**	W60	~~W62 to W70~~ **W64, W68**	W72	~~W74 to W82~~ **W76, W80**	W84	~~W86 to W94~~ **W88, W92**		W96	W100
Study Day ± Visit Window	1±3	**±3**	28±7	**±3**	56±7	**±3**	84±7	**±3**	168±7	**±3**	252±7	**±3**	336±7	**±3**	420±7	**±3**	504±7	**±3**	588±7	**±3**		672±7	700±7
CCI [redacted]																							
Immunoglobulin levels[d]	X								X				X				X					X	
Urinalysis (microscopy, urine protein/creatinine ratio)[fg]	X								X						X						X	X	X
B, CCI [redacted] cell count[tgh]	X												X									X	X
~~Urine pregnancy test (all countries except Poland)~~	~~X~~		~~X~~		~~X~~		~~X~~		~~X~~		~~X~~		~~X~~		~~X~~		~~X~~		~~X~~			~~X~~	~~X~~

Activity/Assessment	OLE Day 1[a]	On Treatment Visits																			Unscheduled Visit	OLE End of Treatment	End of Trial Visit
Visit number (for OLE)	1	1.1	2[a]	2.1	3[a]	3.1	4	4.1, **4.2, 4.4** ~~to 4.5~~	5	~~5.1 to 5.5~~**5.2, 5.4**	6	~~6.1 to 6.5~~**6.2, 6.4**	7	~~7.1 to 7.5~~**7.2, 7.4**	8	~~8.1 to 8.5~~**8.2, 8.4**	9	~~9.1 to 9.5~~**9.2, 9.4**	10	~~10.1 to 10.5~~**10.2, 10.4**		11	12
~~Supplemental Safety Visits~~		~~X~~		~~X~~		~~X~~		~~X~~		~~X~~		~~X~~		~~X~~		~~X~~		~~X~~		~~X~~			
Study Week	W0	W2	W4	W 6	W8	W10	W12	**W 14, W16, W20,** ~~W22~~	W24	~~W 26 to W34~~ **W28, W32**	W36	~~W38 to W 46~~**W 40, W44**	W48	~~W 50 to W58~~ **W52, W56**	W60	~~W62 to W70~~ **W64, W68**	W72	~~W74 to W82~~ **W76, W80**	W84	~~W86 to W94~~ **W88, W92**		W96	W100
Study Day ± Visit Window	1±3	**±3**	28±7	**±3**	56±7	**±3**	84±7	**±3**	168±7	**±3**	252±7	**±3**	336±7	**±3**	420±7	**±3**	504±7	**±3**	588±7	**±3**		672±7	700±7
Urine pregnancy test ~~(Poland only)~~[h,ii,j]	X		X	~~X~~	X		X	**X**	X	X	X	X	X	X	X	X	X	X	X	X		X	X
12-lead ECG	X												X								X	X	
Chest X-ray	X																						
EDSS	X												X								X	X	
Relapse assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MRI scan	X												X									X	
Concomitant medications and procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
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
Dispense IMP[jk]	X		X[kl]		X[kl]		X		X		X		X		X		X		X				

Activity/Assessment	OLE Day 1[a]	On Treatment Visits																			Unscheduled Visit	OLE End of Treatment	End of Trial Visit
Visit number (for OLE)	1	1.1	2[a]	2.1	3[a]	3.1	4	4.1, **4.2, 4.4** ~~to 4.5~~	5	~~5.1 to 5.5~~**5.2, 5.4**	6	~~6.1 to 6.5~~**6.2, 6.4**	7	~~7.1 to 7.5~~**7.2, 7.4**	8	~~8.1 to 8.5~~**8.2, 8.4**	9	~~9.1 to 9.5~~**9.2, 9.4**	10	~~10.1 to 10.5~~**10.2, 10.4**		11	12
~~Supplemental Safety Visits~~		~~X~~		~~X~~		~~X~~		~~X~~		~~X~~		~~X~~		~~X~~		~~X~~		~~X~~		~~X~~			
Study Week	W0	W2	W4	W 6	W8	W10	W12	**W 14, W16, W20,** ~~W22~~	W24	~~W 26 to W34~~ **W28, W32**	W36	~~W38 to W 46~~**W 40, W44**	W48	~~W 50 to W58~~ **W52, W56**	W60	~~W62 to W70~~ **W64, W68**	W72	~~W74 to W82~~ **W76, W80**	W84	~~W86 to W94~~ **W88, W92**		W96	W100
Study Day ± Visit Window	1±3	**±3**	28±7	**±3**	56±7	**±3**	84±7	**±3**	168±7	**±3**	252±7	**±3**	336±7	**±3**	420±7	**±3**	504±7	**±3**	588±7	**±3**		672±7	700±7
IMP compliance	X		X		X		X		X		X		X		X		X		X			X	
CCI [redacted]																							
HRQoL[mm]	X												X									X	
C-SSRS **(Since Last Visit Scale)**	X												X									X	

AE=adverse event, ALT=alanine aminotransferase, AST=aspartate aminotransferase, CCI [redacted], CMV=cytomegalovirus, C-SSRS=Columbia-Suicide Severity Rating Scale, EA=early antigen, EBNA=Epstein-Barr nuclear antigen, ECG=electrocardiogram, eCRF=electronic case report form, EDSS=expanded disability status scale, ESR=erythrocyte sedimentation rate, GGT=γ-glutamyl-transferase, HAV=hepatitis A virus, HBc=hepatitis B core antigen, HEV=hepatitis E virus, HRQoL=health-related quality of life, hsCRP=high sensitivity C-reactive protein, ICF=informed consent form, Ig=immunoglobulin, IMP=investigational medicinal product, INR=international normalized ratio, MRI=magnetic resonance imaging, MS=multiple sclerosis, CCI [redacted], OLE=Open-label Extension, PTT=partial thromboplastin time, SF-36v2=Short Form 36-item Health Status Survey version 2.0, VCA=viral capsid antigen.

a. ~~For subjects entering the OLE Period after receiving M2951 during the 48-week main study, OLE Day 1 will occur at Week 48 of main study treatment. Subjects entering the OLE Period after receiving Tecfidera during the 48-week main study must undergo a minimum 4-week washout period before they complete the OLE Day 1 visit (see Table 4 and Section 5.5.1).~~ **Visits 2 (Week 4) and 3 (Week 8) are applicable only for subjects who received Tecfidera, and for subjects who received M2951/placebo these visits are only for LFTs (Section 7.1.6).**

b. Signed consent will be obtained prior to participation in the optional OLE Period. Subjects entering from M2951 will sign the ICF at OLE Day 1, and subjects entering from Tecfidera will sign at the Week 48 End of Treatment Visit.

c. ~~For subjects who received Tecfidera during the 48-week main study, a~~**A**~~n additional~~ physical examination may be performed at ~~the~~ additional chemistry visits at the Investigator's discretion ~~based on the subject's history at the time of the visit~~.

d. The following will be obtained predose: vital signs (Section 7.4.4.1), hematology and chemistry (~~Table 6~~ **Table 7**), and total Ig levels (IgM, IgA, IgG) (see Section 7.4.5).

e. Supplementary LFTs include AST, ALT, alkaline phosphatase, GGT, and bilirubin for subjects on M2951 ~~(not for while subjects are on Tecfidera or in washout)~~.

CCI [redacted]

g. Urine samples for urinalysis will be obtained predose on OLE Day 1 and at Weeks 24, 60, 96/OLE End of Treatment, 4-week Safety Follow-up/End of Trial Visit, and unscheduled visits. If local urinalysis by dipstick is abnormal, urine microscopy should be performed by a central laboratory. If at least 1+ protein is detected, urine protein/creatinine ratio should be determined.

h. Blood samples for B, CCI [redacted] cell numbers and B, CCI [redacted] cell subclasses will be obtained predose on OLE Day 1, Week 48, and Week 96/OLE End of Treatment visits. 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).

i. ~~(Poland only):~~ Urine pregnancy tests will also be performed at home at Week 16, Week 20, Week 28, Week 32, Week 40, Week 44, Week 52, Week 56, Week 64, Week 68, Week 76, Week 80, Week 88, and Week 92 for women of childbearing potential. Subjects will be supplied with at-home test kits.

j. ~~(Poland only)~~ Phone calls: **To be done only if urine pregnancy test is completed at home:** The Principal Investigator and/or delegated site staff will call subject at Week 16, Week 20, Week 28, Week 32, Week 40, Week 44, Week 52, Week 56, Week 64, Week 68, Week 76, Week 80, Week 88, and Week 92 to confirm completion of home pregnancy testing and discuss results.

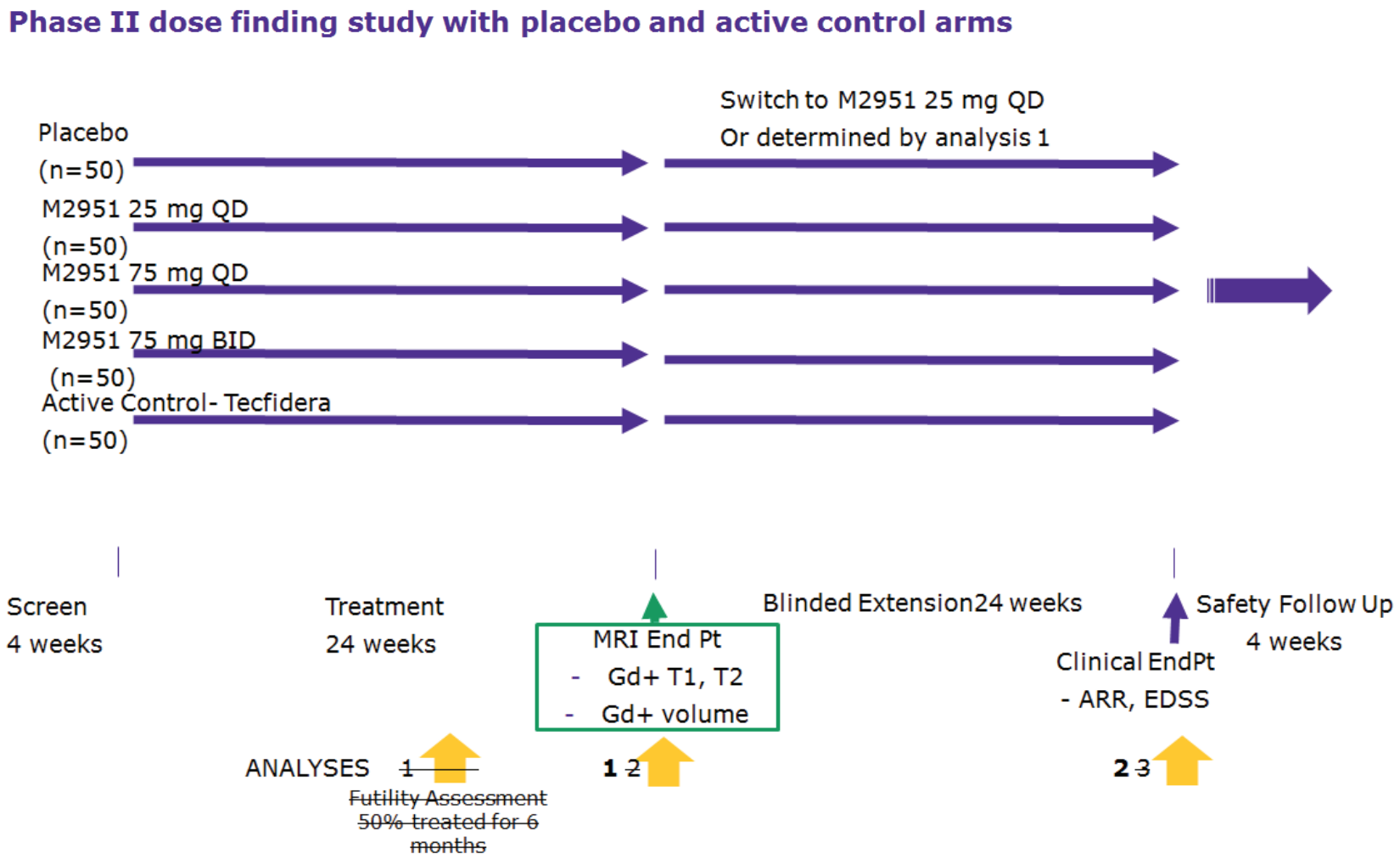
k. The IMP will be dispensed on OLE Day 1 and at indicated visits thereafter. All remaining IMP will be collected at the Week 96/OLE End of Treatment Visit.

l. For subjects switching from Tecfidera.

CCI [redacted]

Revised Figure 1

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.

New Table 6

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. Re-initiate IMP after discussion with Medical Monitor if no further downward trend is observed.

b. Permanently withdraw IMP.

Revised Table 7 (previously Table 6)

Table ~~6~~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[c]/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]	• 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, IgM=immunoglobulin M, CCI , VCA=viral capsid antigen.

a. CCI .

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.