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PHASE OF DEVELOPMENT: 4

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PROTOCOL TITLE: A Multicenter, Double-Blind, Placebo-Controlled Study of Montelukast on Gastrointestinal Tolerability in Patients With Relapsing Forms of Multiple Sclerosis Receiving TECFIDERA® (Dimethyl Fumarate) Delayed-Release Capsules

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Version 3
FINAL

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TABLE OF CONTENTS

1.	SPONSOR INFORMATION	9
2.	LIST OF ABBREVIATIONS AND DEFINITIONS	10
3.	SYNOPSIS	11
4.	STUDY SCHEMATIC AND SCHEDULE OF EVENTS FOR STUDY 109MS414.....	21
4.1.	Study Schematic	21
4.2.	Schedule of Events	22
4.3.	Additional Information	25
4.4.	Gastrointestinal Symptom Rating Scale	25
5.	INTRODUCTION	26
5.1.	Profile of Previous Experience	26
5.1.1.	Nonclinical Experience With Dimethyl Fumarate	26
5.1.2.	Clinical Experience With Dimethyl Fumarate	26
5.2.	Study Rationale.....	28
5.3.	Rationale for Dose and Schedule Selection.....	29
6.	STUDY OBJECTIVES AND ENDPOINTS.....	30
6.1.	Objectives	30
6.1.1.	Primary Objective.....	30
6.1.2.	Secondary Objectives	30
6.1.3.	Exploratory Objective.....	30
6.2.	Endpoints	30
6.2.1.	Primary Endpoint.....	30
6.2.2.	Secondary Endpoints	31
6.2.3.	Exploratory Endpoints	31
7.	STUDY DESIGN	32
7.1.	Study Overview	32
7.2.	Overall Study Duration and Follow-Up	33
7.2.1.	Screening Visit.....	33
7.2.2.	Screening Period.....	33
7.2.3.	Randomization Visit	33
7.2.4.	DMF-GI Monitoring Period	33

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7.2.5.	Treatment	34
7.2.6.	Post-Treatment	34
7.3.	Study Stopping Rules	34
7.4.	End of Study	34
8.	STUDY POPULATION	35
8.1.	Inclusion Criteria	35
8.2.	Exclusion Criteria	35
9.	ENROLLMENT AND RANDOMIZATION PROCEDURES	37
9.1.	Enrollment and Screening	37
9.2.	Randomization of Subjects	37
9.3.	Blinding Procedures	37
10.	TREATMENT OF SUBJECTS	38
10.1.	Study Treatment Schedule and Administration	38
10.1.1.	Dimethyl Fumarate	38
10.1.1.1.	Treatment Precautions	38
10.1.1.2.	Treatment Adherence	38
10.1.2.	Montelukast and Placebo	38
10.1.2.1.	Administration	38
10.1.2.2.	Treatment Precautions	39
10.1.2.3.	Treatment Adherence	39
10.2.	Continuation of Treatment	39
10.3.	Concomitant Therapy and Procedures	39
10.3.1.	Prohibited Concomitant Medications	39
10.3.2.	Symptomatic Therapy to Treat Dimethyl Fumarate-Related Gastrointestinal Events	39
10.4.	Recording Concomitant Medication	40
11.	STUDY TREATMENT MANAGEMENT	41
11.1.	Dimethyl Fumarate	41
11.1.1.	Dimethyl Fumarate Accountability	41
11.2.	Montelukast and Placebo	41
11.2.1.	Montelukast and Placebo Accountability	41

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12.	WITHDRAWAL OF SUBJECTS FROM STUDY TREATMENT AND/OR THE STUDY	42
13.	EFFICACY ASSESSMENTS	43
13.1.	Clinical Efficacy Assessments.....	43
13.2.	Exploratory Assessments.....	43
13.3.	Future Biomarker and Genetic Assessments (Optional)	43
14.	SAFETY ASSESSMENTS	45
14.1.	Clinical Safety Assessments	45
15.	SAFETY DEFINITIONS, MONITORING, AND REPORTING	46
15.1.	Definitions	46
15.1.1.	Adverse Event.....	46
15.1.2.	Serious Adverse Event.....	46
15.2.	Monitoring and Recording Events.....	46
15.2.1.	Adverse Events	46
15.2.2.	Serious Adverse Events	47
15.2.3.	All Events	47
15.2.4.	Immediate Reporting of Serious Adverse Events.....	47
15.2.4.1.	Deaths	48
15.3.	Safety Classifications.....	48
15.3.1.	Relationship of Events to Study Treatment.....	48
15.3.2.	Severity of Events.....	49
15.3.3.	Expectedness of Events	49
15.4.	Prescheduled or Elective Procedures or Routinely Scheduled Treatments	49
15.5.	Procedures for Handling Special Situations	50
15.5.1.	Overdose	50
15.5.2.	Medical Emergency	50
15.5.3.	Contraception Requirements	50
15.5.4.	Pregnancy	50
15.5.5.	Regulatory Reporting.....	51
15.5.6.	Unblinding for Medical Emergencies.....	51
15.6.	Investigator Responsibilities.....	51
15.7.	Biogen Responsibilities	52

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16.	STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE.....	53
16.1.	Description of Objectives and Endpoints	53
16.2.	Description of Endpoints	53
16.3.	Demography and Baseline Disease Characteristics.....	53
16.4.	Efficacy Data	53
16.4.1.	Analysis Population	53
16.4.2.	General Methods of Analysis	53
16.4.3.	Primary Endpoint Analysis.....	53
16.4.4.	Secondary Endpoints Analysis	53
16.4.5.	Exploratory Endpoints Analysis	54
16.5.	Safety Data.....	54
16.5.1.	Analysis Population	54
16.5.2.	Methods of Analysis	54
16.6.	Interim Analyses	54
16.7.	Sample Size Considerations	54
17.	ETHICAL REQUIREMENTS	55
17.1.	Declaration of Helsinki.....	55
17.2.	Institutional Review Board (IRB).....	55
17.3.	Subject Information and Consent	55
17.4.	Subject Data Protection	56
17.5.	Compensation for Injury.....	56
17.6.	Conflict of Interest.....	56
17.7.	Registration of Study and Disclosure of Study Results.....	56
18.	ADMINISTRATIVE PROCEDURES	57
18.1.	Study Site Initiation	57
18.2.	Quality Assurance.....	57
18.3.	Monitoring of the Study.....	57
18.4.	Study Funding.....	57
18.5.	Publications.....	57
19.	FURTHER REQUIREMENTS AND GENERAL INFORMATION	58
19.1.	External Contract Organizations.....	58

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19.1.1.	Contract Research Organization	58
19.1.2.	Interactive Voice/Web Response System	58
19.1.3.	Electronic Data Capture	58
19.1.4.	Central Laboratories for Laboratory Assessments	58
19.1.5.	Home Visiting Company	58
19.2.	Study Committees	58
19.3.	Changes to Final Study Protocol	58
19.4.	IRB Notification of Study Completion or Termination	59
19.5.	Retention of Study Data	59
19.6.	Study Report Signatory	59
20.	REFERENCES	60
21.	SIGNED AGREEMENT OF THE STUDY PROTOCOL	61

LIST OF TABLES

Table 1:	Schedule of Events	22
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LIST OF FIGURES

Figure 1:	Study Design	21
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1. SPONSOR INFORMATION

This study is sponsored by Biogen MA Inc. Refer to the Study Reference Manual that contains all study contacts for complete contact information.

Biogen MA Inc.
250 Binney Street
Cambridge, MA 02142
United States of America

In the event of a medical emergency requiring immediate attention, study site staff will apply appropriate medical intervention, according to current standards of care. The Investigator or staff member should contact the medical emergency contact number listed in the prevailing product label of the product being administered to the subject.

Primary contact for urgent medical issues:

[REDACTED] MD
[REDACTED]
[REDACTED]

Office telephone number: [REDACTED] Mobile telephone number: [REDACTED]

24-hour urgent medical contact:

Contact directly, on the mobile telephone/office telephone listed above, for urgent issues.

The following additional number is also available for urgent contact:

[REDACTED] Medical Emergency Center: [REDACTED] or [REDACTED] (alternative number)

Refer to the Study Reference Manual for further contact information.

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2. LIST OF ABBREVIATIONS AND DEFINITIONS

AE	adverse event
ANCOVA	analysis of covariance
████	████████████████
CNS	central nervous system
CRF	case report form
DMF	dimethyl fumarate
EDC	electronic data capture
EDSS	Expanded Disability Status Scale
eDiary	electronic diary
ET	early termination
GCP	Good Clinical Practice
Gd	gadolinium
GI	gastrointestinal
GSRS	Gastrointestinal Symptom Rating Scale
ICF	informed consent form
ICH	International Conference on Harmonisation
██	████████████████
██	████████████████
ITT	Intent-to-treat
IXRS	Interactive Voice and Web Response System
██	████████████████
MMF	monomethyl fumarate
MRI	magnetic resonance imaging
MS	multiple sclerosis
Nrf2	nuclear factor (erythroid-derived 2)-related factor 2
██	████████████████
PHI	protected health information
RNA	ribonucleic acid
RRMS	relapsing-remitting multiple sclerosis
SAE	serious adverse event
SUSAR	suspected unexpected serious adverse reaction
US	United States
USPI	United States Prescribing Information
Wk	week

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3. SYNOPSIS

This is a brief summary. For details, refer to the body of the protocol.

Protocol Number:	109MS414
Protocol Title:	A Multicenter, Double-Blind, Placebo-Controlled Study of Montelukast on Gastrointestinal Tolerability in Patients With Relapsing Forms of Multiple Sclerosis Receiving TECFIDERA [®] (Dimethyl Fumarate) Delayed-Release Capsules
Version Number:	3
Name of Study Treatment:	TECFIDERA [®] (dimethyl fumarate)
Study Indication:	Relapsing forms of multiple sclerosis (MS)
Phase of Development:	4
Rationale for the Study:	<p>Two large Phase 3 studies (Study 109MS301 [DEFINE] and Study 109MS302 [CONFIRM]) and 1 Phase 2 study (Study C-1900) of dimethyl fumarate (DMF) in patients with relapsing-remitting MS demonstrated substantial benefits over placebo across a range of clinical and radiologic measures of disease activity. While the overall safety profile was favorable in these studies, the incidence of adverse events (AEs) associated with gastrointestinal (GI) tolerability, including diarrhea, nausea, abdominal pain, vomiting, and dyspepsia, was increased in DMF-treated patients compared with those who received placebo.</p> <p>This study will investigate the impact of 10 mg montelukast once daily on GI tolerability in patients with relapsing forms of MS receiving DMF delayed-released capsules in order to potentially increase patient compliance and adherence to treatment and ultimately maximize the therapeutic potential of DMF.</p>
Study Objectives and Endpoints:	<p>Objectives</p> <p>Primary:</p> <p>The primary objective of this study is to evaluate whether montelukast can reduce the severity of GI events, measured by the Gastrointestinal Symptom Rating Scale (GSRS), after</p>

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oral administration of DMF in subjects with relapsing forms of MS.

Secondary:

Secondary objectives in this study population are as follows:

- To evaluate whether montelukast after oral administration of DMF in subjects with relapsing forms of MS:
 - decreases discontinuations due to GI events
 - reduces the number of subjects taking symptomatic therapies for GI events
- To investigate the effect of montelukast on the incidence of flushing events after oral administration of 240 mg DMF in subjects with relapsing forms of MS

Exploratory:

[REDACTED]

Endpoints

Primary:

The primary endpoint of this study is the proportion of subjects with a worsening in the severity of GI AEs, measured by the average change from Day 0 to Day 10 in GSRS score. Day 0 is defined as the GSRS score of the day prior to the first dose of randomized study treatment.

Secondary:

The secondary endpoints of this study are as follows:

- Average change of GI severity scores from Day 0 to Day 10 as measured by total change of GSRS scores from Day 0 over the first 10 days (Day 1 to Day 10) divided by total number of days with GSRS recorded

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- Average change of GI severity scores from Day 0 to Week 10 as measured by total changes of GSRS score from Day 0 over the first 10 weeks (Day 1 to Week 10) divided by total number of days with GSRS recorded
- Time to first worsening of GSRS in GI severity
- Time to recovery to Day 0 GSRS score from the last occurrence of the worst score in GI severity
- Average change of GSRS score from Day 0 score to Weeks 1, 2, 3, 4, 5, 6, and 8
- Average change of GSRS score from Day 0 to 72 hours from the initiation of randomized study treatment
- Proportion of subjects who require GI symptomatic therapy during the study
- Percentage of subjects who discontinue DMF therapy due to GI-related AEs from Day 0 to Week 10
- Proportion of subjects who experience flushing events

Exploratory:

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Study Design:

This multicenter study will evaluate the effect of montelukast on GI tolerability in approximately 118 subjects with relapsing forms of MS treated with DMF. Subjects will enter a 2-week Screening Period and record pertinent information regarding GI-related events to allow characterization (using the GSRS score) of background GI-related events. Subjects will use an electronic diary (eDiary) to record GI events.

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Subjects will be required to be $\geq 75\%$ compliant in the 14 days prior to randomization to remain eligible to participate in the study. Subjects will also use the eDiary to record DMF dosing, randomized study medication dosing, and any symptomatic concomitant medications/procedures. Subsequently, eligible subjects will initiate DMF therapy and record GI-related events in the eDiary for up to 28 days (DMF-GI Monitoring Period). During this period, subjects will take DMF, and GSRS scores will be monitored. Subjects who reach a specific threshold (GSRS score of ≥ 3 in 1 question for 1 day or a GSRS score of ≥ 2 in 1 question for 2 consecutive days) will receive an alert through their eDiary to start taking randomized study treatment the same day, in accordance with the prescribing and labeling information. Subjects who do not meet the threshold by the end of the 28 days will be discontinued from the study. Eligible subjects, who reach the GSRS score threshold and initiate randomized study treatment (montelukast or placebo), will return to the study site at Weeks 0, 2, 4, 8, and at Week 10 for evaluation by study site staff (visits at Weeks 2 and 8 can alternatively be performed remotely by a contracted home health nurse). Weeks 2, 4, and 8 will have a visit window of ± 2 days, and Week 10 will have a visit window of ± 3 days. The Safety Follow-Up Telephone Interview will be conducted 2 weeks (± 5 days) after the Week 10 study visit or date of the Early Termination Visit.

Subjects who withdraw from the study after initiating randomized study treatment will not be replaced.

The dose of DMF used will be as described in the United States Prescribing Information (USPI). Subjects will take DMF for up to 14 weeks and the randomized study treatment (montelukast or placebo), concomitantly, for 8 weeks and record pertinent information regarding GI-related events in an eDiary.

Information on AEs and serious adverse events (SAEs) will be collected for possible correlation with GI-related events. For the purposes of this study, relapses of MS will not be considered AEs, and data related to relapses will only be captured if they are deemed an SAE or result in a subject's discontinuation. Relapses of MS resulting in hospitalization are considered SAEs but will not be reported as SAEs in the study unless the relapse is complicated by other SAEs or is

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	<p>fatal.</p>
<p>Rationale for Dose and Schedule Selection:</p>	<p>Dimethyl fumarate (DMF) will be taken in accordance with the USPI. The starting dose for DMF is 120 mg twice daily orally. After 7 days, the dose should be increased to the maintenance dose of 240 mg twice daily orally.</p> <p>Montelukast will be taken per product label: one 10-mg tablet once daily in the evening.</p>
<p>Study Location:</p>	<p>United States (US)</p>
<p>Number of Planned Subjects:</p>	<p>It is expected that approximately 295 subjects will be initially randomized to obtain the number of planned dosed subjects.</p> <p>Approximately 118 subjects in total will be dosed with randomized study treatment, with approximately 59 subjects dosed with randomized study treatment per treatment arm.</p> <p>Not all randomized subjects will be eligible to be dosed with randomized study treatment. Randomized subjects will be required to reach a predefined threshold of GI symptom severity before dosing with randomized study treatment will be initiated.</p>
<p>Study Population:</p>	<p>This study will be conducted in subjects with relapsing forms of MS. Detailed criteria are presented in the protocol.</p>
<p>Treatment Groups:</p>	<p>DMF + montelukast or DMF + placebo</p>
<p>Duration of Treatment and Follow-up:</p>	<p>The duration of a subject's participation will be up to 18 weeks, including a 2-week (+14 days) Screening Period, up to 14 weeks of DMF therapy, including 8 weeks of concomitant randomized study treatment, and the Safety Follow-Up Telephone Interview. Subjects who discontinue the study early will complete the same assessments specified for the Week 10 Visit.</p>

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Criteria for Evaluation:

This study is to be conducted in subjects with relapsing forms of MS. To be eligible to participate in this study, candidates must meet the following eligibility criteria at the Screening Visit:

1. Have the ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information in accordance with national and local subject privacy regulations.
2. Age ≥ 18 years at the time of informed consent.
3. Reside in the US and have a confirmed diagnosis of a relapsing form of MS and satisfy the therapeutic indication as described in the local label.
4. Female subjects of childbearing potential who are not surgically sterile must practice effective contraception during their participation in the study and be willing and able to continue contraception for 30 days after they complete or withdraw from the study. All men must practice effective contraception and should not donate sperm, throughout the study and for at least 90 days after their last dose of study treatment.
5. As perceived by the Investigator, have the ability to comply with all requirements of the study protocol and to operate the eDiary required to record GI-related events.

Candidates will be excluded from study entry if any of the following exclusion criteria exist at the Screening Visit or at the timepoint defined in the individual criterion:

1. Inability to comply with the study requirements or, at the discretion of the Investigator, is deemed unsuitable for study participation.
6. Female subjects who are currently pregnant or breastfeeding or who are considering becoming pregnant during the study.
7. History of significant GI disease (e.g., irritable bowel disease, peptic ulcer disease, history of major GI surgery, eosinophilic GI disease, or food allergies).
8. Chronic use (≥ 7 consecutive days) of bismuth

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- subsalicylate, simethicone, calcium carbonate, loperamide, proton-pump inhibitors, or ondansetron within 1 month prior to the Screening Visit. From Screening up to Day 10, use of such therapies is not permitted. From Day 11 (inclusive), subjects are permitted to take these therapies.
9. Use of the following medications: montelukast, immunotherapy, mast cell stabilizers, or parenteral, inhaled, or oral steroids up to 1 month prior to the Screening Visit. Use of these medications is also not permitted for the duration of the study (except for the use of montelukast as per study protocol) and will lead to discontinuation.
 10. Treatment with montelukast is contraindicated for any reason.
 11. Exposure to fumarates in the 3 months prior to the Screening Visit. Exposure is also not permitted for the duration of the Screening Period.
 12. Have 1 or more major comorbidities that, in the opinion of the Investigator, may affect the outcome of the study.
 13. History of malignancy (except for basal cell carcinoma that had been completely excised prior to study entry), severe allergic or anaphylactic reactions or known drug hypersensitivity, abnormal laboratory results indicative of any significant disease, and/or a major disease that would preclude participation in a clinical study.
 14. Prior confirmed diagnosis or medical history of chronic eosinophilia.
 15. Current enrollment in any other interventional clinical studies.
 16. Subjects meeting the inclusion criteria as defined in Section 8.1, and who do not meet any of the exclusion criteria will be eligible to commence with a 2-week (+14 days) Screening Period. At the end of the Screening Period (at the Randomization Visit), GSRS scores and concomitant medication will be evaluated. Subjects who meet the following criterion will be discontinued and counted as screen failures: a GSRS score of ≥ 5 in 1 question for 1 day, a GSRS

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score of ≥ 4 in 1 question for 2 consecutive days, or a GSRS score of ≥ 3 in 1 question for 3 consecutive days.


17. Subjects who did not meet the required eDiary compliance ($\geq 75\%$) in the 14 days prior to randomization.

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Efficacy:

An evaluation of whether montelukast administered with DMF reduces the severity of GI events as measured by GSRS scores will be performed. The use of symptomatic GI therapy will be monitored. The occurrence and frequency of discontinuations from DMF therapy due to GI-related events will be reported. In addition, the occurrence of flushing will be monitored.



Safety:

Safety assessments include observation and evaluation of AEs and SAEs collected throughout the study. Demographics, baseline disease characteristics, vital signs, and clinical laboratory parameters will also be measured.

Statistical Methods:

General Methods of Analysis

In general, continuous variables will be presented with summary statistics (mean, standard deviation, median, and range), and categorical variables will be presented with frequency distributions. All analyses will be conducted using 2-sided tests at the type I error rate (α -level) of 0.05 unless otherwise stated.

Primary Endpoint Analysis

Change from Day 0 to Day 10 in GSRS rating will be computed. The proportion of subjects with worsening, defined as increase in GSRS rating in GI AEs, will be estimated to obtain the rate of worsening in the 2 arms. The difference in the rate of worsening in GI AEs will be analyzed using a chi-square test and the logistic regression model adjusting for covariates and confounding factors.

Secondary Endpoints Analysis

The average change of GI severity score from Day 0 to Week 10 will be analyzed using an analysis of covariance (ANCOVA) model to adjust for covariates and confounding factors such as early drop-outs. Time to first worsening and time to recovery from the last worst GSRS score to Day 0 GSRS score will be analyzed using Kaplan-Meier methods and a Cox proportional hazards model. The average change

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of GSRS score from Day 0 score at various timepoints will be analyzed using an ANCOVA model adjusting for covariates and confounding factors.

The proportion of subjects who require GI symptomatic therapy during the study period will be compared using the chi-square test. The percentage of subjects who discontinue DMF therapy due to GI-related events from the Randomization Visit to Week 10 will be summarized by treatment arm. The proportion of subjects who experience flushing events in each treatment group will also be summarized.

Exploratory Endpoints Analysis

[REDACTED]

Interim Analysis:

No interim analysis will be performed.

Sample Size Determination:

Assuming that 40% of the placebo subjects will be improving (by chance) without any intervention, a total sample size of 118 (dosed with randomized study treatment), 59 per treatment arm (after randomization), would provide approximately 80% power to detect a 30% difference between the treatment arm and placebo arm in proportion of subjects with any improvement in GI severity, as measured by the average change from Day 0 in GSRS score to Day 10, including an early discontinuation of 15%.

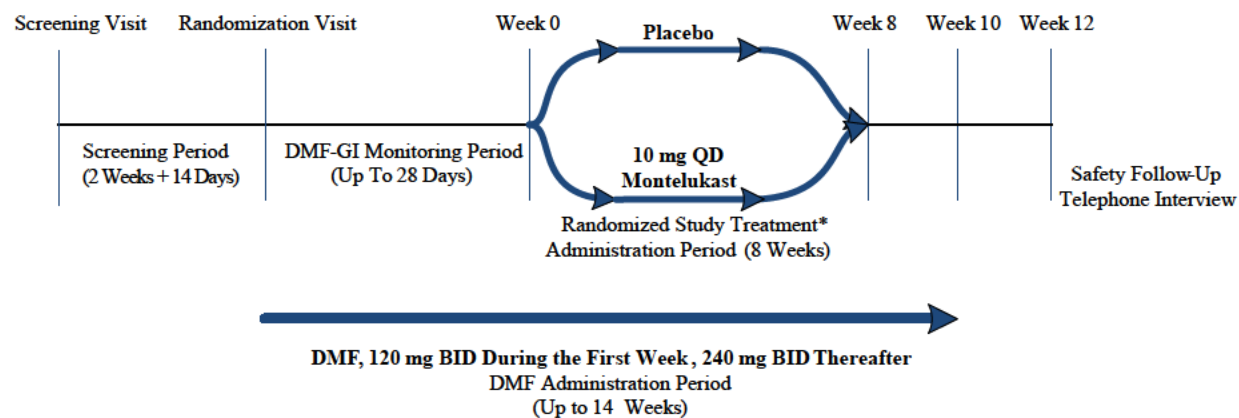
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4. STUDY SCHEMATIC AND SCHEDULE OF EVENTS FOR STUDY 109MS414

4.1. Study Schematic

Figure 1: Study Design



Abbreviations: BID = twice daily; DMF = dimethyl fumarate; GI = gastrointestinal; QD = once daily.

*Use of symptomatic therapies, as specified in Section 10.3.2, is permitted from Day 10 onward.

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4.2. Schedule of Events

Table 1: Schedule of Events

Assessment	Screening Visit ^a	Screening Period (2 Weeks +14 Days)	Randomization Visit ^a (Week -4)	DMF-GI Monitoring Period (up to 28 Days)	Wk 0 ^{a,b}	Wk 2 ^c	Wk 4 ^a	Wk 8 ^c	Wk 10 ^a /ET	Safety Follow-Up ^d (± 5 days)
Clinic Visit	X		X		X	X	X	X	X	
Informed Consent	X									
Eligibility Criteria	X		X ^e							
Demographics	X									
Vital signs ^f	X									
Medical History (incl. MS disease status) ^g	X									
Alcohol Consumption	X									
Tobacco Use	X									
Pregnancy Testing ^h	X		X							
Concomitant Medications/ Procedures	X		X		X	X	X	X	X	X
Blood Biomarkers (optional) ^j			X				X		X	
Dispense eDiary	X									
eDiary Training	X									
eDiary Entries (Daily) ^k										
Return eDiary to Clinical ^l			X ^m	X ^m					X	

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Assessment	Screening Visit ^a	Screening Period (2 Weeks +14 Days)	Randomization Visit ^a (Week -4)	DMF-GI Monitoring Period (up to 28 Days)	Wk 0 ^{a,b}	Wk 2 ^c	Wk 4 ^a	Wk 8 ^c	Wk 10 ^a /ET	Safety Follow-Up ^d (± 5 days)
Dispense DMF With Dosing Instructions			X							
DMF Administration (Daily)			DMF administration will occur every day as per the USPI							
Randomization			X							
Dispense Randomized Study Treatments			X ⁿ							
Randomized Study Treatment Administration (Daily)					Randomized study treatment administration will occur every day as per the prescribing information.					
SAEs	SAE data will be collected from the signing of the informed consent up to the Safety Follow-Up Telephone Interview. MS relapses resulting in hospitalization are considered SAEs but will not be reported as SAEs in the study unless the relapse is complicated by other SAEs or is fatal.									
AEs				AE data will be collected from the first dose of DMF up to the Safety Follow-Up Telephone Interview.						

Note: Weeks 2, 4, and 8 will have a visit window of ±2 days, and Week 10 will have a visit window of ± 3 days.

Abbreviations: AE = adverse event; [REDACTED]; DMF = dimethyl fumarate; DNA = deoxyribonucleic acid; eDiary = electronic diary; EDSS = Expanded Disability Status Scale; ET = early termination; GI = gastrointestinal; GSRS = Gastrointestinal Symptom Rating Scale; [REDACTED]; [REDACTED]; MS = multiple sclerosis; [REDACTED]; RNA = ribonucleic acid; SAE = serious adverse event; USPI = United States Prescribing Information; Wk = week.

^a This visit must be performed in clinic.

^b Subjects will receive an alert through the eDiary if their GSRS scores reach the appropriate threshold. This alert will tell the subject to begin taking the randomized study treatment the same day. At this time, study site should arrange the Week 0 Visit as soon as possible after the first administration of randomized study treatment. Visit dates will be measured from the first administration of randomized study treatment.

^c This visit may be performed remotely if more convenient for the subject; site must telephone the subject to document concomitant medications/procedures and AEs.

^d The safety follow-up will be performed as a telephone interview 2 weeks (±5 days) after the Week 10/ET visit.

^e GI symptom and eDiary compliance assessment.

^f Including height and weight measurements and vital signs (temperature, blood pressure, and sitting blood pressure).

^g Medical history, including MS disease status, will include collection of information on duration of MS, relapse history, EDSS score, and treatment for MS.

^h Dipstick test (only for women of childbearing potential).

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- i [REDACTED]
- j Serum, RNA, and DNA samples will be collected for biomarker analysis and future use analysis in subjects who provide additional consent. A single DNA sample can be taken at any of prespecified timepoints.
- k Subjects will be required to record their daily GI symptoms in the eDiary every day from the Screening Visit up to Week 10.
- l eDiaries will be returned if (1) the subject fails during the Screening Period, (2) the subject does not reach the required GI symptom threshold during the DMF-GI Monitoring Period, or (3) the subject completes or discontinues the study.
- m Subjects who do not reach the GI symptom threshold during the DMF-GI Monitoring Period (a GSRS score of ≥ 5 in 1 question for 1 day, ≥ 4 in 1 question for 2 consecutive days, or ≥ 3 in 1 question for 3 consecutive days) will be discontinued.
- n Subjects are dispensed randomized study treatment at this visit but must not begin taking the medication until alerted about their eDiary.

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4.3. Additional Information

After initial eligibility has been confirmed at the Screening Visit, subjects will enter a 2-week (+14 days) Screening Period. At the end of this period, eligible subjects will return to the clinic for a Randomization Visit. The eligibility criteria will be rechecked, and additionally, the gastrointestinal (GI) symptoms noted in an electronic diary (eDiary) will be assessed. Individuals with Gastrointestinal Symptom Rating Scale (GSRS, Section 4.4) score of ≥ 5 in 1 question for 1 day, a GSRS score of ≥ 4 in 1 question for 2 consecutive days, or a GSRS score of ≥ 3 in 1 question for 3 consecutive days will be discontinued and counted as screen failures. An eDiary compliance check will also be performed. Subjects will be required to be $\geq 75\%$ compliant in the 14 days prior to randomization to remain eligible to participate in the study. Subjects who fulfill the eligibility criteria and meet the GI symptom assessment criteria will be randomized to 1 of 2 treatment arms. At this time, subjects will start commercial dimethyl fumarate (DMF) and will receive (but will not begin taking) their randomized study treatment. Subjects will then enter the DMF-GI Monitoring Period (up to 28 days). During this period, subjects will take DMF and note their daily GI symptoms in the eDiary. If at any time during this period, the GSRS scores noted are ≥ 3 in 1 question for 1 day or ≥ 2 in 1 question for 2 consecutive days, the subject will receive an alert through his/her eDiary to start taking the randomized study treatment the same day. Any subjects who do not reach this threshold during the 28-day period will be discontinued from the study. It will be the decision of the Investigator to continue with DMF therapy after the subject has been withdrawn from the study.

4.4. Gastrointestinal Symptom Rating Scale

The GSRS is a weekly recall scale that has been modified for daily recall in this study.

The 7 severities of each of the 15 questions of the GSRS have a number assigned and will be summarized for a GSRS score as follows:

- no discomfort at all = 0
- minor discomfort = 1
- mild discomfort = 2
- moderate discomfort = 3
- moderately severe discomfort = 4
- severe discomfort = 5
- very severe discomfort = 6

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5. INTRODUCTION

5.1. Profile of Previous Experience

5.1.1. Nonclinical Experience With Dimethyl Fumarate

In nonclinical studies, DMF and its primary metabolite, monomethyl fumarate (MMF), were found to promote stabilization, nuclear translocation, and transcriptional activity of nuclear factor (erythroid-derived 2)-related factor 2 (Nrf2) as well as expression of Nrf2 target genes in cultured human cells and in vivo [Linker 2011]. Previous ex vivo and in vivo studies have demonstrated a central role of the Nrf2 pathway in protection of cells and tissues against oxidative, metabolic, and inflammatory stress. Loss of Nrf2 function via genetic silencing has been shown to cause exaggerated inflammatory response and lead to development of systemic autoimmunity and central nervous system (CNS) alterations, including widespread gliosis and white matter lesions. Conversely, pharmacological agents known to activate Nrf2 have been shown in nonclinical studies to exert anti-inflammatory effects, protect neurons from oxidative and excitotoxic stress-induced death, and improve the blood-brain barrier integrity of the CNS. Activation of the Nrf2 pathway by Tecfidera® (DMF) gastro-resistant hard capsules (hereinafter referred to as DMF) in multiple sclerosis (MS) may contribute to inhibition of inflammation and help support CNS integrity by promoting cellular resistance to oxidative stress.

5.1.2. Clinical Experience With Dimethyl Fumarate

Clinical Pharmacokinetic Studies

In single-dose and short-term multiple-dose studies in healthy volunteers and subjects with MS, DMF was rapidly converted to its major metabolite (MMF) upon oral administration. Exposure (maximum plasma concentration and area under the curve) was generally dose proportional across the dose range (120 to 360 mg) and dosing frequencies (twice daily and 3 times daily) studied. No accumulation of exposure was detected with repeated dosing due to rapid elimination of the drug. In these studies, DMF was most frequently associated with flushing; no serious adverse events (SAEs) or deaths in healthy volunteers who received DMF were reported.

Clinical Efficacy and Safety in Multiple Sclerosis

The DMF clinical development program at the time the DMF marketing authorization applications were filed included 6 clinical studies in subjects with MS. In 4 of the studies (Phase 2 and 3 placebo-controlled efficacy and safety studies and their uncontrolled extensions), 2513 subjects with relapsing-remitting multiple sclerosis (RRMS) received DMF and were followed for periods up to 6 years, with an overall exposure of 6133 patient-years. Approximately 1056 subjects received >2 years of treatment with DMF.

Study C-1900 was a Phase 2, randomized, multicenter, placebo-controlled, double-blind, parallel-group, dose-ranging study composed of 2 parts: a 24-week double-blind, placebo-controlled safety and efficacy phase (Part 1) followed by a 24-week dose-blinded, safety extension phase (Part 2). The primary efficacy endpoint was the total number of new gadolinium

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(Gd)-enhancing lesions at Weeks 12, 16, 20, and 24 (calculated as the sum of the 4 magnetic resonance imaging [MRI] scans). A total of 257 subjects were randomly assigned to receive 120 mg DMF once daily, 120 mg DMF 3 times daily, or 240 mg DMF 3 times daily. Subjects treated with 240 mg DMF 3 times daily had a 69% reduction in the mean number of new Gd-enhancing lesions versus placebo as measured on monthly MRI from Weeks 12 to 24 of the study, and a 48% and 53% reduction in new or enlarging T2 hyperintense lesions and new nonenhancing T1 hypointense lesions at Week 24 compared with placebo, respectively.

For both Phase 3 studies, the primary and secondary endpoints assessed the effect of DMF versus placebo on measures of relapse and disability progression, as well as MRI disease activity. Each study was a randomized, double-blind, and placebo-controlled study in which subjects were treated for 2 years.

In Study 109MS301 (DEFINE), 1237 subjects were randomized in a 1:1:1 ratio to receive 240 mg DMF twice daily, 240 mg DMF 3 times daily, or matching placebo. The primary endpoint was the proportion of subjects relapsed at 2 years. Dimethyl fumarate twice daily and 3 times daily reduced the risk of relapse at 2 years by 49% ($p < 0.0001$) and 50% ($p < 0.0001$), respectively. A significant reduction in the risk of 12-week confirmed progression was observed. In this study, the estimated proportion of placebo-treated subjects with 12-week confirmed progression at 2 years was 0.271 compared with 0.164 for twice daily and 0.177 for 3 times daily (38% reduction for twice daily and 34% reduction for 3 times daily relative to placebo; $p = 0.0050$ and $p = 0.0128$, respectively). Dimethyl fumarate twice daily and 3 times daily reduced the number of new or newly enlarging T2 hyperintense lesions that developed over 2 years by 85% and 74%, respectively, compared with placebo ($p < 0.0001$ for both comparisons). Dimethyl fumarate twice daily and 3 times daily reduced the odds of having greater Gd-enhancing lesion activity at 2 years by 90% and 73%, respectively, compared with placebo ($p < 0.0001$ for both comparisons). The most common adverse events ([AEs]; incidence $\geq 5\%$) that occurred at an incidence $\geq 3\%$ higher in the total DMF group than the placebo group included flushing and hot flush, GI-related events (diarrhea, nausea, abdominal pain upper, abdominal pain, and dyspepsia), skin events (pruritus, rash, and erythema), proteinuria, alanine aminotransferase/serum glutamate-pyruvate transaminase increased, and albumin urine present.

In Study 109MS302 (CONFIRM), 1430 subjects were randomized in a 1:1:1:1 ratio to 240 mg DMF twice daily, 240 mg DMF 3 times daily, DMF-matching placebo, or 20 mg glatiramer acetate subcutaneous injection once daily. The primary endpoint was the annualized relapse rate at 2 years. Treatment with DMF 240 mg administered twice daily and 3 times daily reduced the annualized relapse rate at 2 years by 44% and 50.5%, respectively, compared with placebo ($p < 0.0001$ for both comparisons). Compared with placebo, treatment with 240 mg DMF twice daily and 3 times daily significantly reduced the number of new or enlarging T2 hyperintense lesions that developed over 2 years by 71% and 73%, respectively ($p < 0.0001$ for both comparisons). Treatment with DMF twice daily and 3 times daily significantly reduced the number of new T1 hypointense nonenhancing lesions that developed over 2 years by 57% and 65%, respectively, compared with placebo ($p < 0.0001$ for both comparisons). Treatment with DMF twice daily and 3 times daily significantly reduced the proportion of subjects who relapsed at 2 years by 34% ($p = 0.0020$) and 45% ($p < 0.0001$), respectively, compared with placebo. Numerical changes in disability progression favoring DMF were seen: the estimated proportion

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of subjects with 12-week confirmed progression at 2 years was 16.9% for placebo, 12.8% for twice daily, and 13% for 3 times daily (21% reduction for twice daily and 24% reduction for 3 times daily relative to placebo; $p = 0.2536$ and $p = 0.2041$, respectively). The most common AEs (incidence $\geq 5\%$ in the total DMF group) that occurred at an incidence $\geq 3\%$ higher in the total DMF group than in the placebo group included flushing and hot flush, GI-related events (diarrhea, nausea, abdominal pain upper, abdominal pain, and vomiting), upper respiratory tract infections, and skin events (pruritus, rash, and erythema). Additional information on DMF is provided in the Full Prescribing Information.

5.2. Study Rationale

Two large Phase 3 studies and 1 Phase 2 study of DMF in subjects with RRMS demonstrated substantial benefits over placebo across a range of clinical and radiologic measures of disease activity (Phase 3 Study 109MS301 [DEFINE], Phase 3 Study 109MS302 [CONFIRM], and Phase 2 Study C-1900). While the overall safety profile was favorable in these studies, the incidence of AEs associated with GI tolerability, including diarrhea, nausea, abdominal pain, vomiting, and dyspepsia, was increased in DMF-treated subjects compared with those who received placebo. Between 27% and 38% of all DMF-treated subjects in the 3 studies experienced GI events within the first 3 months of treatment, and whereas 11% to 16% of subjects used GI-related symptomatic therapies, it was unclear whether these were taken in response to a GI-related AE that occurred in conjunction with dosing or if the therapy was effective. The incidence of these events was higher during the first month of treatment and decreased in the second and subsequent months of treatment. The majority of subjects reported these AEs to be of mild to moderate severity. Nevertheless, study discontinuations due to GI events were increased in DMF-treated subjects ($\leq 5\%$) compared with placebo-treated subjects ($\leq 2\%$, pooled Phase 2 and Phase 3 subjects). In addition, a recently completed single-arm, open-label, Phase 4 Study (109MS403 [MANAGE]) as well as a placebo-controlled study of Pepto-Bismol[®] (bismuth subsalicylate) on GI tolerability (Study 109HV110 [PREVENT]) showed similar results in terms of time course, severity, and incidence of GI events. Histopathology from biopsies taken from a subset of subjects in PREVENT suggested some evidence of GI mucosal eosinophil infiltration. In an independent, open-label, 30-day study (21 subjects) investigating the effect of montelukast in DMF-related GI symptoms, GI symptoms were significantly attenuated in the majority of subjects; GSRS scores decreased on average by 81% within 72 hours [Tornatore and Amjad 2014]. The effect of montelukast may suggest that the pathogenesis of the GI symptoms with DMF could be due to a local immunomodulatory effect of DMF. Montelukast is an approved product for asthma with a well-established safety profile [[SINGULAIR[®] USPI 2014]]. If a larger randomized, controlled study could demonstrate a benefit on decreasing the known GI tolerability events during initiation of therapy, it would be a clear benefit for subjects choosing DMF to treat MS who experience GI side effects.

This study will investigate the impact of 10 mg montelukast once daily on GI tolerability in patients with relapsing forms of MS receiving DMF delayed-released capsules in order to potentially increase patient compliance and adherence to treatment and ultimately maximize the therapeutic potential of DMF.

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5.3. Rationale for Dose and Schedule Selection

Dimethyl fumarate will be taken in accordance with the United States (US) Prescribing Information (USPI). The starting dose for DMF is 120 mg twice daily orally. After 7 days, the dose should be increased to the maintenance dose of 240 mg twice daily orally. Montelukast will be taken per product label: one 10-mg tablet once daily in the evening.

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6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Objectives

6.1.1. Primary Objective

The primary objective of this study is to evaluate whether montelukast can reduce the severity of GI events, measured by the GSRS, after oral administration of DMF in subjects with relapsing forms of MS.

6.1.2. Secondary Objectives

The secondary objectives of this study in this study population are as follows:

- To evaluate whether montelukast after oral administration of DMF in subjects with relapsing forms of MS:
 - decreases discontinuations due to GI events
 - reduces the number of subjects taking symptomatic therapies for GI events
- To investigate the effect of montelukast on the incidence of flushing events after oral administration of 240 mg DMF in subjects with relapsing forms of MS

6.1.3. Exploratory Objective

[REDACTED]

[REDACTED]

6.2. Endpoints

6.2.1. Primary Endpoint

The primary endpoint of this study is the proportion of subjects with a worsening in the severity of GI AEs, measured by the average change from Day 0 to Day 10 in GSRS score. Day 0 is defined as the GSRS score of the day prior to the first dose of randomized study treatment.

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6.2.2. Secondary Endpoints

The secondary endpoints of this study are as follows:

- Average change of GI severity scores from Day 0 to Day 10 as measured by total change of GSRS scores from Day 0 over the first 10 days (Day 1 to Day 10) divided by total number of days with GSRS recorded
- Average change of GI severity scores from Day 0 to Week 10 as measured by total changes of GSRS score from Day 0 over the first 10 weeks (Day 1 to Week 10) divided by total number of days with GSRS recorded
- Time to first worsening of GSRS in GI severity
- Time to recovery to Day 0 GSRS score from the last occurrence of the worst score in GI severity
- Average change of GSRS score from Day 0 score to Weeks 1, 2, 3, 4, 5, 6, and 8
- Average change of GSRS score from Day 0 to 72 hours from the initiation of randomized study treatment
- Proportion of subjects who require GI symptomatic therapy during the study
- Percentage of subjects who discontinue DMF therapy due to GI-related events from Day 0 to Week 10
- Proportion of subjects who experience flushing events

6.2.3. Exploratory Endpoints

[REDACTED]

■

[REDACTED]

■

[REDACTED]

■

[REDACTED]

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7. STUDY DESIGN

7.1. Study Overview

This multicenter study will evaluate the effect of montelukast on GI tolerability with relapsing forms of MS treated with DMF at approximately 50 study sites in the US. It is expected that approximately 295 subjects will be initially randomized to obtain approximately 118 subjects dosed with randomized study treatment (59 subjects dosed with randomized study treatment per treatment arm). Not all randomized subjects will be eligible to be dosed with randomized study treatment. Randomized subjects will be required to reach a predefined threshold of GI symptom severity before dosing with randomized study treatment will be initiated. Subjects who withdraw from the study after initiating randomized study treatment will not be replaced.

Subjects will enter a 2-week (+14 days) Screening Period and record pertinent information regarding GI-related events to allow characterization of background GI-related events using the eDiary. Subjects will be required to be $\geq 75\%$ compliant in the 14 days prior to randomization to remain eligible to participate in the study. Subsequently, eligible subjects will initially take DMF (120 mg twice daily orally for the first week, 240 mg twice daily orally thereafter) for up to 28 days (DMF-GI Monitoring Period) and record GI-related events in the eDiary. During this period, subjects will take DMF, GSRS scores will be monitored, and subjects who reach a specific threshold will receive an alert through the eDiary to start taking randomized study treatment (10 mg once daily montelukast or placebo) the same day in accordance with the prescribing and labeling information. Subjects who do not meet the threshold or do not demonstrate $\geq 75\%$ compliance with the eDiary in the 14 days prior to randomization will be discontinued. Subjects will also use the eDiary to record DMF dosing, randomized study medication dosing, and any symptomatic concomitant medications/procedures. Eligible subjects will return to the study site at Weeks 0, 2, 4, 8 and at Week 10 for evaluation by study site staff. Weeks 2, 4, and 8 will have a visit window of ± 2 days, and Week 10 will have a visit window of ± 3 days. If more convenient for the subject, visits at Weeks 2, and 8 may be performed remotely by a contracted home health nurse. The Safety Follow-Up Telephone Interview will be conducted 2 weeks (± 5 days) after the Week 10 study visit or date of the Early Termination (ET) Visit.

The dose of DMF used will be as described in the USPI. Subjects will take DMF for up to 14 weeks, including 8 weeks with the concomitant randomized study treatment (montelukast or placebo), and will record pertinent information regarding GI-related events in an eDiary.

Information on AEs and SAEs will be collected for possible correlation with GI-related events. For the purposes of this study, relapses of MS will not be considered AEs, and data related to relapses will be captured only if the event is deemed an SAE (see Section 15.1.2) or results in a subject's discontinuation. Relapses of MS resulting in hospitalization are considered SAEs and will be reported to the FDA. However, they will not be reported as SAEs in the study unless the relapse is complicated by other SAEs or is fatal.

See [Figure 1](#) for a schematic of the study design.

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7.2. Overall Study Duration and Follow-Up

The study period consists of a 2-week (+14 days) Screening Period, up to a total of 14 weeks of DMF therapy (including DMF-GI Monitoring Period and randomized treatment administration period), including 8 weeks of concomitant randomized study treatment (DMF + montelukast or DMF + placebo), and the Safety Follow-Up Telephone Interview. The duration of a subject's participation will be up to 18 weeks. Subjects who discontinue the study early will complete the same assessments specified for the Week 10 Visit. Refer to [Section 1](#) for the timing of assessments to be performed in this study.

7.2.1. Screening Visit

Subject eligibility for the study will be determined at the Screening Visit after receipt of the signed and dated informed consent form (ICF). Eligible subjects will be given an eDiary after training on how to use the device.

7.2.2. Screening Period

During this 2-week (+14 days) period, subjects will record pertinent information regarding GI-related events every day in the eDiary. Individuals with a GSRS score of ≥ 5 in 1 question for 1 day, a GSRS score of ≥ 4 in 1 question for 2 consecutive days, or a GSRS score of ≥ 3 in 1 question for 3 consecutive days during the Screening Period will be discontinued and counted as screen failures.

7.2.3. Randomization Visit

Subjects will return to the study site for a recheck of eligibility criteria (only GSRS scores and concomitant medications/procedures will be checked). Individuals with GSRS score of ≥ 5 in 1 question for 1 day, a GSRS score of ≥ 4 in 1 question for 2 consecutive days, or a GSRS score of ≥ 3 in 1 question for 3 consecutive days during the Screening Period will be discontinued and counted as screen failures. Subjects will be required to be $\geq 75\%$ compliant in the 14 days prior to randomization to remain eligible to participate in the study, and sites should continue to monitor eDiary compliance throughout the study. Concomitant medications/procedures will be checked to ensure compliance with study restrictions. Once eligibility has been rechecked and it is confirmed that a subject is eligible to continue on the study, blood samples will be collected for the assessment of clinical laboratory parameters and serum biomarkers (optional). Eligible subjects will be randomized and provided with blinded randomized study treatment (montelukast or placebo) at this time.

Eligible subjects will receive commercial DMF through their specialty pharmacy or, in the case of insufficient insurance coverage, through the Biogen Patient Services Free Drug Program, for up to 14 weeks. The Investigator will submit the DMF prescription to Patient Services during the Screening Visit, and DMF will be shipped directly to subjects.

7.2.4. DMF-GI Monitoring Period

The duration of the DMF-GI Monitoring Period will be up to 28 days. On the first full day after the Randomization Visit, subjects will start taking DMF per the prescribing instruction. Subjects

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will make daily entries in the eDiary, recording pertinent information regarding GI-related events to allow the characterization of events that occur while taking DMF. During this period, if a subject meets the threshold of a GSRS score of ≥ 3 in 1 question for 1 day or a GSRS score of ≥ 2 in 1 question for 2 consecutive days, the subject will receive an alert through his/her eDiary to begin taking the randomized study treatment the same day. Any subject who does not reach the GSRS threshold during the DMF-GI Monitoring Period will be discontinued.

7.2.5. Treatment

Eligible subjects will take DMF for up to 14 weeks (from the start of the DMF-GI Monitoring Period to Week 10) and blinded randomized study treatment (either montelukast or placebo) for 8 weeks (from Weeks 0 to 8).

Subjects will be asked to return to the study site at Weeks 0, 2, 4, 8, and 10/ET for blood sampling for assessment of clinical laboratory parameters and AEs (optional serum biomarker samples will be drawn at Weeks 4 or 10/ET). Visits at Weeks 0, 4, and 10/ET must be performed at the study site. If more convenient for the subject, visits at Weeks 2 and 8 may be performed remotely by a contracted home health nurse; in this situation, an appropriately qualified person from the study site must call the subject on each occasion to document any concomitant medication/procedures and AEs. Study windows are ± 2 days for the Weeks 2, 4, and 8 Visits and ± 3 days for the Week 10/ET Visit. Study site should arrange the Week 0 Visit as soon as possible after the first administration of randomized study treatment.

7.2.6. Post-Treatment

Two weeks (± 5 days) after the Week 10 Visit or date of the ET Visit, subjects will be interviewed by telephone as a safety follow-up (collection of information on any AEs, SAEs, or changes in concomitant medications/procedures).

7.3. Study Stopping Rules

Biogen may terminate this study at any time, after informing Investigators, institutional review boards (IRBs), and regulatory authorities when applicable. Investigators will be notified by Biogen or designee if the study is placed on hold, completed, or closed.

7.4. End of Study

The end of study is the last subject, last assessment collection for final collection of data for the primary outcome.

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8. STUDY POPULATION

8.1. Inclusion Criteria

To be eligible to participate in this study, candidates must meet the following eligibility criteria at the Screening Visit:

1. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (PHI) in accordance with national and local subject privacy regulations.
2. Age ≥ 18 years at the time of informed consent.
3. Reside in the US and have a confirmed diagnosis of a relapsing form of MS and satisfy the therapeutic indication as described in the local label.
4. Female subjects of childbearing potential who are not surgically sterile must practice effective contraception during their participation in the study and be willing and able to continue contraception for 30 days after they complete or withdraw from the study. All men must practice effective contraception and should not donate sperm, throughout the study and for at least 90 days after their last dose of study treatment.
5. As perceived by the Investigator, have the ability to comply with all requirements of the study protocol and to operate the eDiary required to record GI-related events.

8.2. Exclusion Criteria

Candidates will be excluded from study entry if any of the following exclusion criteria exist at the Screening Visit or at the timepoint defined in the individual criterion listed:

1. Inability to comply with the study requirements or, at the discretion of the Investigator, is deemed unsuitable for study participation.
2. Female subjects who are currently pregnant or breastfeeding or who are considering becoming pregnant during the study.
3. History of significant GI disease (e.g., irritable bowel disease, peptic ulcer disease, history of major GI surgery, eosinophilic GI disease, or food allergies).
4. Chronic use (≥ 7 consecutive days) of bismuth subsalicylate, simethicone, calcium carbonate, loperamide, proton-pump inhibitors, or ondansetron within 1 month prior to the Screening Visit. From Screening up to Day 10, use of such therapies is not permitted. From Day 11 (inclusive), subjects are permitted to take these therapies.
5. Use of the following medications: montelukast, immunotherapy, mast cell stabilizers, or parenteral, inhaled, or oral steroids up to 1 month prior to the Screening Visit. Use of these medications is also not permitted for the duration of the study (except for the use of montelukast as per study protocol) and will lead to discontinuation.
6. Treatment with montelukast is contraindicated for any reason.

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7. Exposure to fumarates in the 3 months prior to the Screening Visit. Exposure is also not permitted for the duration of the Screening Period.
8. Have 1 or more major comorbidities that, in the opinion of the Investigator, may affect the outcome of the study.
9. History of malignancy (except for basal cell carcinoma that had been completely excised prior to study entry), severe allergic or anaphylactic reactions or known drug hypersensitivity, abnormal laboratory results indicative of any significant disease, and/or a major disease that would preclude participation in a clinical study.
10. Prior confirmed diagnosis or medical history of chronic eosinophilia.
11. Current enrollment in any other interventional clinical studies.
12. Subjects meeting the inclusion criteria as defined in Section 8.1, and who do not meet any of the exclusion criteria will be eligible to commence with a 2-week Screening Period. At the end of the Screening Period (at the Randomization Visit), GSRS scores and concomitant medication will be evaluated. Subjects who meet the following criterion will be excluded from further study participation: a GSRS score of ≥ 5 in 1 question for 1 day, a GSRS score of ≥ 4 in 1 question for 2 consecutive days, or a GSRS score of ≥ 3 in 1 question for 3 consecutive days.
13. Subjects who did not meet the required eDiary compliance ($\geq 75\%$) in the 14 days prior to randomization.

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9. ENROLLMENT AND RANDOMIZATION PROCEDURES

Once the investigational site has been activated for study participation, subjects may be enrolled if they have met the inclusion criteria in Section 8.1 and have not been excluded based on the exclusion criteria in Section 1.

9.1. Enrollment and Screening

Subjects must be consented before any screening tests or assessments are performed. At the time of consent, the subject will be considered enrolled into the study. Participating study sites are required to document all screened candidates initially considered for inclusion in this study. If a subject is excluded from the study, the reasons for exclusion will be documented in the subject's source documents and on the screening log. Subjects will be screened and eligibility will be confirmed after all screening assessments (Screening Visit and 2-week [+14 days] Screening Period) have been completed and after the Investigator has verified that they are eligible per the criteria in Sections 8.1 and 1.

9.2. Randomization of Subjects

Subjects must be consented before any screening baseline tests or assessments are performed. At the time of consent, the subject will be registered into the study. Participating study sites are required to document all registered candidates initially considered for randomization in the study. If the subject is not randomized in the study, the reasons will be documented in the subject's source documents and on the registration log.

Subjects will be randomized at the Randomization Visit. At this visit, eligible subjects will be randomized to 1 of 2 treatment arms (DMF + montelukast or DMF + placebo) in a 1:1 ratio. Subjects will be instructed not to take the blinded randomized study treatment until they receive an alert through their eDiary. This alert will appear if a subject meets the criteria of GSRS score of ≥ 3 in 1 question for 1 day or a GSRS score of ≥ 2 in 1 question for 2 consecutive days.

No subjects may begin treatment prior to randomization and assignment of a unique subject identification number. Any subject identification numbers that are assigned will not be reused, even if the subject does not receive treatment. Subject identification numbers will be assigned by the Interactive Voice and Web Response System (IXRS).

Refer to the Study Reference Manual for details on registration.

As confirmation, Biogen will provide the Investigator with verification of the subject's registration.

9.3. Blinding Procedures

All study staff will be blinded to the subject treatment assignments. To maintain the study blind, it is imperative that subject treatment assignments are not shared with the subjects, their families, or any member of the study team, either at the study site or at Biogen, except the unblinded Pharmacist (or designee) and the unblinded Pharmacy Monitor.

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10. TREATMENT OF SUBJECTS

Refer to Section 11 (Study Treatment Management) for specifics on the preparation, storage, handling, disposal, and accountability of study treatment.

10.1. Study Treatment Schedule and Administration

Refer to Section 4.1 for a schematic on the study design.

10.1.1. Dimethyl Fumarate

Subjects will receive a supply of commercial DMF through their specialty pharmacy or, in the case of insufficient insurance coverage, through the Biogen Patient Services Free Drug Program.

Dimethyl fumarate should be administered according to the prevailing product label (i.e., USPI). Dimethyl fumarate will be administered orally as 120 mg twice daily during the first 7 days and as 240 mg twice daily thereafter.

Subjects should swallow each DMF capsule whole. The capsule and its contents are not to be crushed, divided, dissolved, sucked, or chewed.

Subjects are to contact the Investigator immediately if more than the prescribed dose is taken.

If a dose is missed, the missed dose can be taken if there is at least 4 hours between the morning and evening doses. Otherwise, treatment should be continued with the next dose as planned.

After Day 10, dose modifications are at the discretion of the Investigator. The prevailing product label (i.e., USPI) should be used as a guideline. Dose modifications should be captured in the case report form (CRF).

10.1.1.1. Treatment Precautions

Refer to the Package Insert for the treatment precautions.

10.1.1.2. Treatment Adherence

Compliance with dosing will be monitored and recorded by study site staff. Subjects are to return all unused DMF and used and unused packaging at each visit. Study site staff will be responsible for recording study treatment accountability and treatment compliance information based on the unused study treatment returned by the subject at each visit.

10.1.2. Montelukast and Placebo

10.1.2.1. Administration

Montelukast (10 mg once daily in the evening) should be administered according to the prevailing product label (Singulair®). Randomized treatments (montelukast or placebo) will be administered only until Week 8 of the study.

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If a subject does not remember to take a dose within 8 hours of the scheduled time (i.e., at least 4 hours before the next scheduled dose), the dose should be skipped, and the next dose should be taken as scheduled. Doses should not be doubled-up, or a missed dose taken the next day, to make up for missed doses.

10.1.2.2. Treatment Precautions

Refer to the Package Insert for treatment precautions [[SINGULAIR® USPI 2014](#)].

10.1.2.3. Treatment Adherence

Compliance with dosing will be monitored and recorded by study site staff. Subjects are to return all unused study treatment and used and unused packaging at each visit. Study site staff will be responsible for recording study treatment accountability and treatment compliance information based on the unused study treatment returned by the subject at each visit.

10.2. Continuation of Treatment

Dimethyl fumarate and montelukast are approved treatments in the US, and continuing treatment following completion of the study requirements will be left to the discretion of the subject and Investigator.

10.3. Concomitant Therapy and Procedures

A concomitant therapy is any drug or substance administered between the time the subject is enrolled in the study and the Safety Follow-Up Telephone Interview/ET Visit.

Apart from the treatments listed below and those listed in the exclusion criteria (see Section 1), the use of concomitant medications is left to the discretion of the Investigator. The prevailing product label should be used as a guideline.

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy and physical therapy) or diagnostic assessment (e.g., blood gas measurement and bacterial cultures) performed between the time the subject is enrolled in the study and the Safety Follow-Up Telephone Interview/ET Visit.

10.3.1. Prohibited Concomitant Medications

Use of symptomatic treatments to treat GI symptoms is prohibited, with the exception of therapies described below.

10.3.2. Symptomatic Therapy to Treat Dimethyl Fumarate-Related Gastrointestinal Events

From Day 10 onward, but not before, subjects may use the following medications: bismuth subsalicylate, simethicone, calcium carbonate, loperamide, proton-pump inhibitors, and ondansetron.

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10.4. Recording Concomitant Medication

All concomitant therapies or procedures must be recorded on the subject's CRF according to instructions for CRF completion. The reason for initiation of such therapies or procedures must also be recorded on the CRF.

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11. STUDY TREATMENT MANAGEMENT

Study site staff should review procedures for the handling and administration of DMF, montelukast, and placebo with subjects at the Randomization Visit, in addition to referring subjects to the relevant USPI for specific instructions on the handling, administration, storage, and preparation of study treatments.

11.1. Dimethyl Fumarate

Dimethyl fumarate will be obtained via commercial methods and should be handled, administered, stored, and disposed of according to the prevailing Package Insert. For further details on the DMF drug product, refer to the local USPI for more information.

11.1.1. Dimethyl Fumarate Accountability

Subjects are to be instructed to bring all unused DMF to the study site. The site will perform and document accountability based on the DMF that the subject presents at the study visits.

11.2. Montelukast and Placebo

Montelukast and placebo must be stored in a secure location. Accountability for this is the responsibility of the Investigator or qualified site staff. More details concerning this responsibility are included in Section [11.2.1](#).

Montelukast and placebo must only be dispensed by a Pharmacist or appropriately trained staff and only to subjects participating in this study. Once montelukast or placebo is dispensed to a subject, it can only be taken by that subject.

Additionally, Investigators should manage the treatment of subjects in compliance with the prevailing product label for montelukast treatment and ensure that subjects are fully informed about the potential risks and benefits of their treatments.

11.2.1. Montelukast and Placebo Accountability

The study site must maintain accurate records demonstrating dates and amounts of montelukast and placebo treatment received, to whom dispensed (subject-by-subject accounting), amount returned by subject, and accounts of any montelukast or placebo accidentally or deliberately destroyed. Subjects are to be instructed to return all montelukast and placebo kits, both used and unused, to the site. Unless otherwise notified, all montelukast and placebo kits, both used and unused, must be saved for study treatment accountability. At the end of the study, reconciliation must be made between the amount of montelukast and placebo supplied and dispensed; after reconciliation, montelukast and placebo will be destroyed at the study site or returned to Biogen. A written explanation must be provided for any discrepancies.

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12. WITHDRAWAL OF SUBJECTS FROM STUDY TREATMENT AND/OR THE STUDY

A subject *must* permanently discontinue study treatment and be withdrawn from the study for any of the following reasons:

- Failure to meet the required eDiary compliance criteria ($\geq 75\%$) in the 14 days prior to randomization.
- Failure to meet the GSRS score criteria during the DMF-GI Monitoring Period.
- The subject experiences a medical emergency that necessitates permanent discontinuation of study treatment.
- The subject uses prohibited concomitant medications (as outlined in Sections 1 and 10.3.1).
- The subject withdraws consent.
- At the discretion of the Investigator for medical reasons or for noncompliance.
- The subject has a concurrent illness or injury, or abuses alcohol or drugs to the extent that, in the judgment of the Investigator and/or Sponsor, it would affect assessments of clinical status to a significant degree.

The reason for discontinuation of study treatment and withdrawal from the study must be recorded in the subject's CRF.

Subjects who discontinue study treatment will be withdrawn from the study. Whenever possible, subjects who prematurely discontinue study treatment should complete an ET Visit (undergoing the same assessments as the Week 10 Visit).

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13. EFFICACY ASSESSMENTS

13.1. Clinical Efficacy Assessments

The following efficacy assessments will be performed at multiple timepoints between the Randomization Visit and Week 10/ET Visit:

- GSRS scores
- Use of symptomatic GI therapy
- Occurrence and frequency of discontinuations from DMF therapy due to GI-related events
- Occurrence and frequency of flushing events

A numerical scale from 0 to 6 will be used for the GSRS scores as follows:

- No discomfort at all = 0
- Minor discomfort = 1
- Mild discomfort = 2
- Moderate discomfort = 3
- Moderately severe discomfort = 4
- Severe discomfort = 5
- Very severe discomfort = 6

Refer to Section 4.2 for the timing of assessments.

13.2. Exploratory Assessments



13.3. Future Biomarker and Genetic Assessments (Optional)

In subjects who provide additional consent, serum, RNA, and DNA samples may be collected for future biomarker/genetic analysis. Subjects will sign a separate, written ICF if they opt for their sample to be collected and used in this way.

The samples collected from the substudy may be utilized to identify or verify putative prognostic and predictive markers associated with disease and markers of therapeutic response to DMF

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treatment. Background and dynamic (on-study) clinical disease characteristics and associated biomarker data will be utilized to predict subsequent disease worsening (severity), identify high-risk patient subgroups, and identify predictors of response to DMF treatment.

Refer to Section [4.2](#) for the timing of assessments.

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14. SAFETY ASSESSMENTS

14.1. Clinical Safety Assessments

The following clinical assessments will be performed at multiple timepoints between the Screening Visit and Week 12/ET Visit:

- AEs
- SAEs

Refer to Section [4.2](#) for the timing of assessments.

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15. SAFETY DEFINITIONS, MONITORING, AND REPORTING

Throughout the course of the study, every effort must be made to remain alert to possible AEs. If an AE occurs, the first concern should be for the safety of the subject. If necessary, appropriate medical intervention should be provided.

At the signing of the ICF, each subject must be given the names and telephone numbers of study site staff for reporting AEs and medical emergencies.

15.1. Definitions

15.1.1. Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a 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 related to the medicinal product.

15.1.2. Serious Adverse Event

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

- results in death
- in the view of the Investigator, places the subject at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity, or
- results in a congenital anomaly/birth defect.

An SAE may also be any other medically important event that, in the opinion of the Investigator, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization.)

15.2. Monitoring and Recording Events

15.2.1. Adverse Events

Any non-SAE (including flushing) experienced by the subject between the time of first dose of study treatment and the Safety Follow-up Telephone Interview is to be recorded on the CRF, regardless of the severity of the event or its relationship to study treatment.

There are 2 exceptions to this:

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- Any GI-related AE experienced by the subject between the time of the first dose of DMF and study completion is to be recorded by the subject in his/her eDiary. Any GI AEs that lead to permanent study discontinuation or withdrawal or are serious must be recorded.
- Non-SAEs of MS relapse will not be collected unless leading to permanent treatment discontinuation or study withdrawal.

Nonserious GI AEs should be recorded in the eDiary and not in the eCRF.

For subjects who permanently discontinue DMF during the study, AEs should be recorded through the Safety Follow-Up Telephone Interview conducted 2 weeks (± 5 days) after the subjects' Final Clinic Visit.

15.2.2. Serious Adverse Events

Any SAE experienced by the subject between the time of signing informed consent and the Safety Follow-Up Interview is to be recorded on an SAE Form, regardless of the severity of the event or its relationship to study treatment. For subjects who permanently discontinue DMF during the study, SAEs should be reported through the Safety Follow-Up Telephone Interview after the subjects' Final Clinic Visit. All SAEs must be reported to [REDACTED].

Any SAE ongoing when the subject completes the study or withdraws from the study will be followed by the Investigator until the event has resolved, stabilized, or returned to baseline status.

15.2.3. All Events

All events must be assessed to determine the following:

- If the event meets the criteria for an SAE as defined in Section 15.1.2.
- The relationship of the event to study treatment as defined in Section 15.3.1.
- The severity of the event as defined in Section 15.3.2.

15.2.4. Immediate Reporting of Serious Adverse Events

In order to adhere to all applicable laws and regulations for reporting an SAE, the study site must formally notify [REDACTED] within 24 hours of the study site staff becoming aware of the SAE. It is the Investigator's responsibility to ensure that the SAE reporting information and procedures are used and followed appropriately.

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Reporting Information for SAEs

Any Serious Adverse Event that occurs between the time that the subject has signed informed consent and Safety Follow-Up Telephone Interview must be reported to [REDACTED] within 24 hours of the study site staff becoming aware of the event.

A report *must be submitted* to [REDACTED] regardless of the following:

- whether or not the subject has undergone study-related procedures
- whether or not subject has received study treatment
- the severity of the event
- the relationship of the event to study treatment

To report initial or follow-up information on a Serious Event, fax or email a completed SAE Form to the following:

Fax: [REDACTED]

Email: [REDACTED]

15.2.4.1. Deaths

Death is an outcome of an event. The event that resulted in death should be recorded and reported on the appropriate CRF. All causes of death must be reported as SAEs. The Investigator should make every effort to obtain and send death certificates and autopsy reports to [REDACTED].

15.3. Safety Classifications

15.3.1. Relationship of Events to Study Treatment

The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study treatment:

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Relationship of Event to Commercial Drug	
Not related	An AE will be considered “not related” to the use of the drug if there is not a possibility that the event has been caused by the product. Factors pointing toward this assessment include, but are not limited to: the lack of reasonable temporal relationship between administration of the drug and the event, the presence of a biologically implausible relationship between the product and the adverse event (e.g., the event occurred before administration of drug), or the presence of a more likely alternative explanation for the AE.
Related	An AE will be considered “related” to the use of the drug if there is a possibility that the event may have been caused by the product. Factors that point toward this assessment include, but are not limited to: a positive rechallenge, a reasonable temporal sequence between administration of the drug and the event, a known response pattern of the suspected drug, improvement following discontinuation or dose reduction, a biologically plausible relationship between the drug and the adverse event, or a lack of an alternative explanation for the AE.

15.3.2. Severity of Events

The following definitions should be considered when evaluating the severity of AEs and SAEs:

Severity of Event	
Mild	Symptom(s) barely noticeable to subject or does not make subject uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptom(s) but may be given because of personality of subject.
Moderate	Symptom(s) of a sufficient severity to make subject uncomfortable; performance of daily activity is influenced; subject is able to continue in study; treatment for symptom(s) may be needed.
Severe	Symptom(s) cause severe discomfort; symptoms cause incapacitation or significant impact on subject’s daily life; severity may cause cessation of treatment with study treatment; treatment for symptom(s) may be given and/or subject hospitalized.

15.3.3. Expectedness of Events

Expectedness of all AEs and SAEs will be determined according to the prevailing product label.

15.4. Prescheduled or Elective Procedures or Routinely Scheduled Treatments

A prescheduled or elective procedure or a routinely scheduled treatment will not be considered an SAE, even if the subject is hospitalized; the study site must document all of the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the subject’s consent to participate in the study.
- The condition requiring the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the

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Investigator between the subject's consent to participate in the study and the time of the procedure or treatment.

- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission.

15.5. Procedures for Handling Special Situations

15.5.1. Overdose

An overdose is any dose of study treatment given to a subject or taken by a subject that exceeds the dose described in the protocol. Overdoses are not considered AEs; however, all overdoses should be recorded on an Overdose Form and faxed to [REDACTED] within 24 hours. An overdose should be reported even if it does not result in an AE. Overdoses do not need to be recorded in the CRF; dosing information is recorded on a CRF.

15.5.2. Medical Emergency

In a medical emergency requiring immediate attention, study site staff will apply appropriate medical intervention, according to current standards of care. The Investigator or designee should contact the [REDACTED] Medical Advisor listed in the current Contact List (found in the Study Reference Manual) or the [REDACTED] 24-Hour Urgent Medical Contact Center at [REDACTED] or [REDACTED] (alternative number).

15.5.3. Contraception Requirements

All women of childbearing potential must practice effective contraception throughout the study and for 30 days after they complete or withdraw from the study. All men must practice effective contraception and should not donate sperm, throughout the study and for at least 90 days after their last dose of study treatment.

The Investigator must discuss contraceptive measures with the subject in relation to protocol requirements when initially determining suitability and desire to prescribe.

15.5.4. Pregnancy

The Investigator should refer to the approved local label for guidance if female subjects become pregnant during the study.

At the Screening Visit and the Randomization Visit, female subjects of childbearing potential should be asked about their pregnancy status and possible pregnancies/spontaneous abortions since the last visit or contact. Spontaneous abortions are considered to be SAEs and must be reported as such. The Investigator should report the pregnancy to [REDACTED] (using the Pregnancy Form provided) within 24 hours of the site becoming aware of the pregnancy. The Investigator should follow the outcome of the pregnancy and provide the outcome to [REDACTED] using the appropriate Pregnancy Form.

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If the partner of a male subject receiving DMF becomes pregnant at any time during the study, the Investigator should follow the pregnancy outcome and report any congenital anomaly or birth defect as an SAE to [REDACTED].

15.5.5. Regulatory Reporting

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are unexpected and judged by the Investigator or the Sponsor to be related to the study treatment administered.

Appropriate personnel in Biogen Safety and Benefit-Risk Management (or designee) will unblind SUSARs for the purpose of regulatory reporting. Biogen will submit SUSARs (in blinded or unblinded fashion) to Regulatory Agencies according to local law. Biogen will submit SUSARs to Investigators in a blinded fashion.

15.5.6. Unblinding for Medical Emergencies

In this study, emergency decoding will be made available to the Investigator and designated personnel at Biogen and the contract research organization through an IXRS.

In a medical emergency when knowledge of the subject's treatment assignment may possibly influence the subject's clinical care, the Investigator may access the subject's treatment assignment by IXRS. However, prior to unblinding, the Investigator should attempt to contact the [REDACTED] Medical Advisor listed in the current Contact List (found in the Study Reference Manual) to discuss the emergency. It is of note that the [REDACTED] Medical Advisor cannot provide approval for unblinding.

The Investigator must document the reasons for unblinding in the subject's source documents. The Investigator is strongly advised not to divulge the subject's treatment assignment to any individual not directly involved in managing the medical emergency, nor to personnel involved with the analysis and conduct of the study.

15.6. Investigator Responsibilities

The Investigator's responsibilities include the following:

- Monitor and record all AEs, including SAEs, regardless of the severity or relationship to study treatment.
- Determine the seriousness, relationship, and severity of each event.
- Determine the onset and resolution dates of each event.
- Monitor and record all pregnancies and follow-up on the outcome of the pregnancy.
- Complete an SAE Form for each serious event and fax it to [REDACTED] within 24 hours of the study site staff becoming aware of the event.
- Pursue SAE follow-up information actively and persistently. Follow-up information must be reported to [REDACTED] within 24 hours of the study site staff becoming aware of new information.

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- Ensure all AE and SAE reports are supported by documentation in the subjects' medical records.
- Report SAEs to local IRBs, as required by local law.

15.7. Biogen Responsibilities

Biogen's responsibilities include the following:

- Before study site activation and subject enrollment, the Clinical Monitor or designee is responsible for reviewing with study site staff the definitions of AE and SAE, as well as the instructions for monitoring, recording, and reporting AEs and SAEs.
- Biogen is to notify all appropriate regulatory authorities, central IRBs, and Investigators of SAEs, as required by local law, within required time frames.

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16. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

16.1. Description of Objectives and Endpoints

The objectives for this study are presented in Section 6.1.

16.2. Description of Endpoints

The endpoints for this study are presented in Section 6.2.

16.3. Demography and Baseline Disease Characteristics

Demographics and background disease data will be summarized by presenting frequency distributions or summary statistics.

16.4. Efficacy Data

16.4.1. Analysis Population

The intent-to-treat (ITT) population defined below will be used for the efficacy analysis.

The ITT population is defined as all randomized subjects who receive at least 1 dose of randomized study treatment (montelukast or placebo).

16.4.2. General Methods of Analysis

In general, continuous variables will be presented with summary statistics (mean, standard deviation, median, and range), and categorical variables will be presented with frequency distributions. All analyses will be conducted using 2-sided tests at the type I error rate (α -level) of 0.05 unless otherwise stated. All efficacy analyses will be conducted using the efficacy population.

16.4.3. Primary Endpoint Analysis

Change from Day 0 to Day 10 in GSRS rating will be computed. The proportion of subjects with worsening in GI AEs, defined as increases in GSRS ratings, will be estimated to obtain the rate of worsening in the 2 arms. The difference in the rate of worsening in GI AEs will be analyzed using a chi-square test and the logistic regression model, adjusting for covariates and confounding factors.

16.4.4. Secondary Endpoints Analysis

The average change of GI severity score from Day 0 to Week 10 will be analyzed using an analysis of covariance (ANCOVA) model to adjust for covariates and confounding factors such as early drop-outs. Time to first worsening and time to recovery from the last worst GSRS score to Day 0 GSRS score will be analyzed using Kaplan-Meier methods and a Cox proportional

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hazards model. The average change of GSRS score from Day 0 score at various timepoints will be analyzed using an ANCOVA model adjusting for covariates and confounding factors.

The proportion of subjects who require GI symptomatic therapy during the study period will be compared using the chi-square test. The percentage of subjects who discontinue DMF therapy due to GI-related events from the Randomization Visit to Week 10 will be summarized by treatment arm. The proportion of subjects who experience flushing events in each treatment group will also be summarized.

16.4.5. Exploratory Endpoints Analysis

[REDACTED]

16.5. Safety Data

16.5.1. Analysis Population

The safety population will be defined as all subjects who received at least 1 dose of DMF.

16.5.2. Methods of Analysis

All safety data will be coded using the Medical Dictionary for Regulatory Activities and evaluated based on treatment emergence. The incidence of all AEs and SAEs will be presented by system organ class and preferred term. The incidence of all AEs will be summarized by severity and by relationship to study treatment. Adverse events leading to withdrawal from the study will also be summarized. Percentage of subjects who experienced flushing will be summarized.

16.6. Interim Analyses

Not applicable.

16.7. Sample Size Considerations

Assuming that 40% of the placebo subjects will be improving (by chance) without any intervention, a total sample size of 118, 59 per treatment arm (dosed with randomized study treatment), would provide approximately 80% power to detect a 30% difference between the treatment arm and placebo arm in proportion of subjects with any improvement in GI severity, as measured by the average change from Day 0 in GSRS score to Day 10, including an early discontinuation of 15%.

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17. ETHICAL REQUIREMENTS

Biogen and the Investigator must comply with all instructions, regulations, and agreements in this protocol and applicable International Conference on Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines and conduct the study according to local regulations.

17.1. Declaration of Helsinki

This study will be performed in alignment with the ethical principles outlined in the Declaration of Helsinki.

17.2. Institutional Review Board (IRB)

The Investigator must obtain IRB approval of the protocol, ICF, and other required study documents prior to starting the study.

If the Investigator makes any changes to the ICF, Biogen must approve the changes before the ICF is submitted to the IRB. A copy of the approved ICF must be provided to Biogen. After approval, the ICF must not be altered without the agreement of the relevant IRB and Biogen.

It is the responsibility of the Principal Investigators to ensure that all aspects of institutional review are conducted in accordance with current governmental regulations.

Biogen must receive a letter documenting IRB approval, which specifically identifies the protocol, protocol number, and ICF, prior to the initiation of the study. Protocol amendments will be subject to the same requirements as the original protocol.

A progress report must be submitted to the IRB at required intervals and not less than annually.

At the completion or termination of the study, the investigational site must submit a close-out letter to the IRB and Biogen.

17.3. Subject Information and Consent

Prior to performing any study-related activities under this protocol, including screening tests and assessments, written informed consent with the approved ICF must be obtained from the subject or subject's legally authorized representative, as applicable, in accordance with local practice and regulations. Written informed consent must be obtained from all subjects participating in a clinical study conducted by Biogen.

The background of the proposed study, the procedures, the benefits and risks of the study, and that study participation is voluntary for the subject must be explained to the subject. The subject must be given sufficient time to consider whether to participate in the study.

A copy of the ICF, signed and dated by the subject, must be given to the subject. Confirmation of a subject's informed consent must also be documented in the subject's medical record prior to any testing under this protocol, including screening tests and assessments.

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Each consent form should contain an authorization allowing the Principal Investigator(s) and Biogen to use and disclose PHI (i.e., subject-identifiable health information) in compliance with local law.

The signed consent form will be retained with the study records.

17.4. Subject Data Protection

Prior to any testing under this protocol, including screening tests and assessments, candidates must also provide all authorizations required by local law (e.g., PHI authorization in North America).

The subject will not be identified by name in the CRF or in any study reports, and these reports will be used for research purposes only. Biogen, its partner(s) and designee(s), IRBs, and various government health agencies may inspect the records of this study. Every effort will be made to keep the subject's personal medical data confidential.

17.5. Compensation for Injury

Biogen maintains appropriate insurance coverage for clinical studies and will follow applicable local compensation laws.

17.6. Conflict of Interest

The Investigators should address any potential conflicts of interest (e.g., financial interest in the Sponsor) with the subject before the subject makes a decision to participate in the study.

17.7. Registration of Study and Disclosure of Study Results

Biogen will register the study and post study results regardless of outcome on a publicly accessible website in accordance with the applicable laws and regulations.

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18. ADMINISTRATIVE PROCEDURES

18.1. Study Site Initiation

The Investigator must not screen any subjects prior to completion of a study initiation visit, conducted by Biogen or designee. This initiation visit will include a detailed review of the protocol and study procedures.

18.2. Quality Assurance

During and/or after completion of the study, quality assurance officers named by Biogen or the regulatory authorities may wish to perform on-site audits. The Investigator will be expected to cooperate with any audit and to provide assistance and documentation (including source data) as requested.

18.3. Monitoring of the Study

The Principal Investigator(s) must permit study-related monitoring by providing direct access to source data and to the subjects' medical histories.

The Clinical Monitor(s) will visit the Investigator(s) at regular intervals during the course of the study and after the study has completed, as appropriate.

During these visits, CRFs and supporting documentation related to the study will be reviewed and any discrepancies or omissions will be resolved.

The monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, study treatment accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

18.4. Study Funding

Biogen is the Sponsor of the study and is funding the study. All financial details are provided in the separate contract(s) between the institution, Investigator, and Biogen.

18.5. Publications

Details are included in the clinical trial agreement for this study.

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19. FURTHER REQUIREMENTS AND GENERAL INFORMATION

Biogen will be responsible for all administrative aspects of this study including, but not limited to, study initiation, monitoring, management of AEs, and data management.

19.1. External Contract Organizations

19.1.1. Contract Research Organization

██████████ will be responsible for administrative aspects of the study including, but not limited to, study initiation, monitoring, management of SAE reports, and data management. Before subjects are screened at each study site, ██████████ will review study responsibilities with the Investigators and other study site staff, as appropriate.

19.1.2. Interactive Voice/Web Response System

An IXRS will be used in this study. Before subjects are screened or enrolled, the IXRS vendor will provide each study site with appropriate training and a user manual.

19.1.3. Electronic Data Capture

Subject information will be captured and managed by study sites on electronic CRFs. Electronic data will be captured and managed using an electronic data capture (EDC) system supported and configured by the EDC vendor. ██████████ will provide oversight to the EDC.

19.1.4. Central Laboratories for Laboratory Assessments

A central laboratory has been selected by Biogen to analyze all samples collected for this study.

19.1.5. Home Visiting Company

A home visiting company has been selected by Biogen to perform home visits, where permitted, if appropriate.

19.2. Study Committees

Not applicable.

19.3. Changes to Final Study Protocol

All protocol amendments must be submitted to the IRBs and Regulatory Authorities if required by local law. Protocol modifications that affect subject safety, the scope of the investigation, or the scientific quality of the study must be approved by the IRBs before implementation of such modifications to the conduct of the study. If required by local law, such modifications must also be approved by the appropriate regulatory agency prior to implementation.

However, Biogen may, at any time, amend this protocol to eliminate an apparent immediate hazard to a subject. In this case, the appropriate regulatory authorities will be notified subsequent to the modification.

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In the event of a protocol modification, the subject consent form may require similar modifications (see Sections **Error! Reference source not found.** and [17.3](#)).

19.4. IRB Notification of Study Completion or Termination

Where required, the Health Authorities and IRBs must be notified of completion or termination of this study, and sent a copy of the study synopsis in accordance with necessary timelines.

19.5. Retention of Study Data

The minimum retention time for study records will meet the strictest standard applicable to that site, as dictated by any institutional requirements or local laws or regulations. Prior to proceeding with destruction of records, the Investigator must notify Biogen in writing and receive written authorization from Biogen to destroy study records. In addition, the Investigator must notify Biogen of any changes in the archival arrangements including, but not limited to, archival at an off-site facility or transfer of ownership if the Investigator leaves the site.

19.6. Study Report Signatory

Biogen will designate one of the participating Study Investigators as a signatory for the study report. This determination will be made by several factors, including, but not limited to, the Investigator's experience and reputation in the studied indication, the Investigator's contribution to the study in terms of design, management, and/or subject enrollment, or by other factors determined to be relevant by Biogen.

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21. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, “A Multicenter, Double-Blind, Placebo-Controlled Study of Montelukast on Gastrointestinal Tolerability in Patients With Relapsing Forms of Multiple Sclerosis Receiving TECFIDERA[®] (Dimethyl Fumarate) Delayed-Release Capsules,” and agree to conduct the study according to the protocol and the applicable ICH guidelines and GCP regulations, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

Investigator’s Signature

Date

Investigator’s Name (Print)

Study Site (Print)



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Signature Page

Document Name: 109MS414 Protocol V3 Final 01-Feb-2016

Document Title: A Multicenter, Double-Blind, Placebo-Controlled Study of Montelukast on Gastrointestinal Tolerability in Patients With Relapsing Forms of Multiple Sclerosis Receiving TECFIDERA® (Dimethyl Fumarate) Delayed Release Capsules

Signed by	Role	Date / Time (UTC)
	Signing as Approver	02/05/2016 21:21:11
	Signing as Reviewer	02/05/2016 17:15:11

109MS414 / NCT02410278

Biogen - BG00012 in MS
Statistical Analysis Plan



BIOGEN

STATISTICAL ANALYSIS PLAN

A Multicenter, Double-Blind, Placebo-Controlled Study of Montelukast on
Gastrointestinal Tolerability in Patients With Relapsing Forms of Multiple Sclerosis
Receiving TECFIDERA[®] (Dimethyl Fumarate) Delayed-Release Capsules

Protocol 109MS414 Statistical Analysis Plan

Study Phase: 4

Date of Protocol: 01 February 2016 Version 3 Final

Date of Statistical Analysis Plan of Version 2.0: 8 March 2017

Author:

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13 Mar 2017
Date

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Biogen Inc.

Approved by:

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3/12/2017
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TABLE OF CONTENTS

Table of Contents

1	INTRODUCTION	6
2	STUDY OBJECTIVES AND ENDPOINTS.....	6
2.1	Primary Objective and Endpoint.....	6
2.2	Secondary Objectives and Endpoints.....	6
2.3	Exploratory Objectives and Endpoints	7
3	STUDY DESIGN.....	7
3.1	Study Overview	7
3.1	Definition of the GSRS threshold.....	9
3.2	Overall Study Duration and Follow-Up.....	9
4	SCHEDULE OF EVENTS	10
5	INTERIM ANALYSIS	13
6	SAMPLE SIZE JUSTIFICATION	13
7	STATISTICAL ANALYSIS METHODS	13
7.1	Analysis population	13
7.1.1	Modified ITT population	13
7.1.2	Safety population	13
7.1	Analysis of baseline data	14
7.2	Study subjects	14
7.2.1	Analysis population	14
7.2.2	Accounting of Subjects.....	15
7.2.3	Protocol Deviations.....	15
7.2.4	Demographic and Baseline Characteristics.....	15
7.2.5	MS Treatment History	15
7.2.6	Medical History.....	16
7.2.7	Extent of Exposure and eDiary Compliance	16
7.2.8	Concomitant Medications	17
7.3	Efficacy Analysis.....	17
7.3.1	Analysis Population	17
7.3.2	GSRS score.....	17
7.3.3	Analysis Methods-Primary endpoints.....	18
7.3.4	Analysis Methods-Secondary endpoints	18
7.3.5	Analysis methods-Exploratory endpoints.....	21

7.4	Safety Data.....	22
	7.4.1 Safety analysis Population	22
	7.4.2 Analysis Methods.....	22
8	LIST OF TABLES	23
9	LIST OF LISTINGS.....	26
10	LIST OF FIGURES	26

LIST OF ABBREVIATIONS

AE	adverse event
ANCOVA	analysis of covariance
BMI	body mass index
████	████████████████
CI	confidence interval
CRF	case report form
DMF	dimethyl fumarate
eDiary	electronic diary
ET	early termination
GI	gastrointestinal
GSRS	Gastrointestinal Symptom Rating Scale
██	██████████████
██	██████████
ITT	intent-to-treat
██	████████████
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effects model for repeated measures
MS	multiple sclerosis
OR	odds ratio
████	████████████
PT	preferred term
Q1	25 th percentile
Q3	75 th percentile
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	System Organ Class
WHO	World Health Organization

1 INTRODUCTION

This statistical analysis plan (SAP) reflects detailed statistical methods to be used for studying Montelukast on Gastrointestinal Tolerability in patients with Relapsing Forms of Multiple Sclerosis receiving Tecfidera® (Dimethyl Fumarate) Delayed-Release Capsules. The SAP is based on the final version of protocol 109MS414 (Version 3) dated 01 February 2016.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary Objective and Endpoint

The primary objective of this study is to evaluate whether Montelukast can reduce the severity of gastrointestinal (GI) events, measured by the Gastrointestinal Symptom Rating Scale (GSRS), after oral administration of Dimethyl Fumarate (DMF) in subjects with relapsing forms of multiple sclerosis (MS).

The primary endpoint of this study is the proportion of subjects with a worsening in the severity of GI adverse events (AEs), measured by the average change from Day 0 to Day 10 in GSRS score. If a patient takes the randomized study treatment one day after his or her GSRS score reaches the GI threshold, Day 0 is defined as the day prior to the first dose of randomized study treatment. If a patient takes the randomized study treatment on the same day when the GSRS score reaches the GI threshold, Day 0 is defined as the day with the first dose of randomized study treatment. If a patient missed the randomized study treatment for a few days after the GSRS score reached the GI threshold, Day 0 is the day immediately prior to the first dose when the GI threshold was reached. Day 10 is defined as 10 days after Day 0.

2.2 Secondary Objectives and Endpoints

The secondary objectives in this study population are:

- To evaluate whether Montelukast after oral administration of DMF in subjects with relapsing forms of MS:
 - decreases discontinuations due to GI events
 - reduces the number of subjects taking symptomatic therapies for GI events
- To investigate the effect of Montelukast on the incidence of flushing events after oral administration of 240 mg DMF in subjects with relapsing forms of MS

The secondary endpoints are:

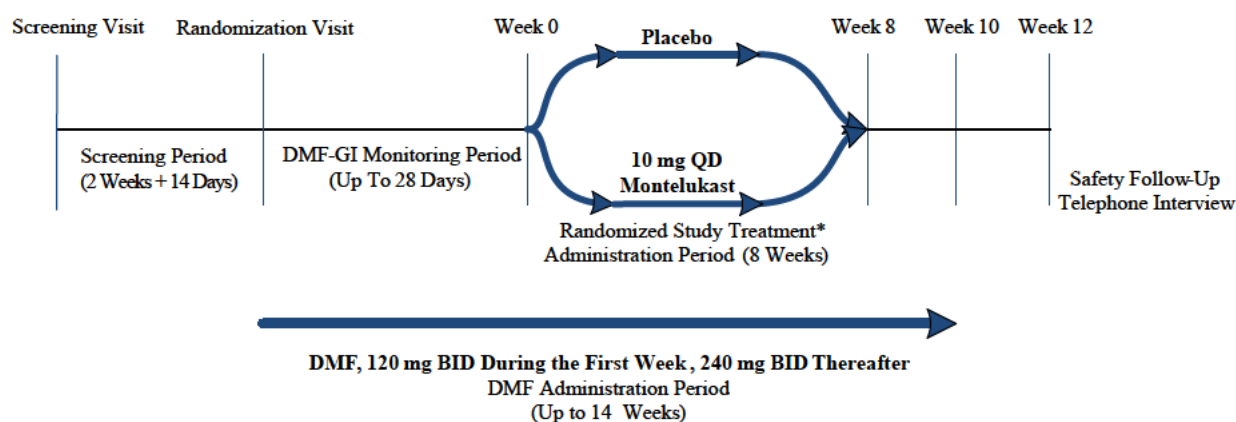
- Average change of GI severity scores from Day 0 to Day 10, as measured by the total change of GSRS scores from Day 0 over the first 10 days (Day 1 to Day 10), divided by the total number of days with GSRS recorded
- Average change of GI severity scores from Day 0 to Week 10, as measured by the total change of GSRS score from Day 0 over the first 10 weeks (Day 1 to Week 10), divided by the total number of days with GSRS recorded

Subjects will enter a 2-week (+14 days) Screening Period and record pertinent information regarding GI-related events to allow characterization of background GI-related events using the electronic diary (eDiary). Subjects will be required to be $\geq 75\%$ compliant in the 14 days prior to randomization to remain eligible to participate in the study. Subsequently, eligible subjects will initially take DMF (120 mg twice daily orally for the first week, 240 mg twice daily orally thereafter) for up to 28 days (DMF-GI Monitoring Period) and record GI-related events in the eDiary. During this period, subjects will take DMF, GSRS scores will be monitored, and subjects who reach a specific threshold will receive an alert through the eDiary to start taking randomized study treatment (10 mg once daily Montelukast or placebo) the same day in accordance with the prescribing and labeling information. Subjects who do not meet the threshold or do not demonstrate $\geq 75\%$ compliance with the eDiary in the 14 days prior to randomization will be discontinued. Subjects will also use the eDiary to record DMF dosing, randomized study medication dosing, and any symptomatic concomitant medications/procedures. Eligible subjects will return to the study site at Weeks 0, 2, 4, 8 (± 2 days) and Week 10 (± 3 days) for evaluation by study site staff. If more convenient for the subject, visits at Weeks 2 and 8 may be performed remotely by a contracted home health nurse. The Safety Follow-Up Telephone Interview will be conducted 2 weeks (± 5 days) after the Week 10 study visit or date of the Early Termination (ET) Visit.

The dose of DMF used will be as described in the USPI. Subjects will take DMF for up to 14 weeks, including 8 weeks with the concomitant randomized study treatment (Montelukast or placebo), and will record pertinent information regarding GI-related events in an eDiary.

Information on AEs and SAEs will be collected for possible correlation with GI-related events. For the purposes of this study, relapses of MS will not be considered AEs, and data related to relapses will be captured only if the event is deemed an SAE or results in a subject's discontinuation. Relapses of MS resulting in hospitalization are considered SAEs and will be reported to the FDA. However, they will not be reported as SAEs in the study unless the relapse is complicated by other SAEs or is fatal.

Figure 1: Study Design



Abbreviations: BID = twice daily; DMF = dimethyl fumarate; GI = gastrointestinal; QD = once daily.

*Use of symptomatic therapies, as specified in Protocol Section 10.3.2, is permitted from Day 10 onward.

3.1 Definition of the GSRS threshold

Two definitions of the GSRS threshold were used in this study.

Definition in the version 1 of the protocol: GSRS score of ≥ 5 in one question for 1 day or a GSRS score of ≥ 4 in one question for 2 consecutive days or GSRS score of ≥ 3 in one question for 3 consecutive days.

Definition in the 2nd and higher Protocol versions: GSRS score of ≥ 3 in one question for 1 day or a GSRS score of ≥ 2 in one question for 2 consecutive days.

3.2 Overall Study Duration and Follow-Up

The study period consists of a 2-week (+14 days) Screening Period, up to a total of 14 weeks of DMF therapy (including DMF-GI Monitoring Period and randomized treatment administration period), including 8 weeks of concomitant randomized study treatment (DMF + Montelukast or DMF + placebo), and the Safety Follow-Up Telephone Interview. The duration of a subject's participation will be up to 18 weeks. Subjects who discontinue the study early will complete the same assessments specified for the Week 10 Visit.

4 SCHEDULE OF EVENTS

Table 1 includes details on the schedule of activities in Study 109MS414.

Table 1: Schedule of Activities

Assessment	Screening Visit ^a	Screening Period (2 weeks +14 days)	Randomization Visit ^a (Week -4)	DMF-GI Monitoring Period (up to 28 days)	Wk 0 ^{a,b}	Wk 2 ^c	Wk 4 ^a	Wk 8 ^c	Wk 10 ^a /ET	Safety Follow-Up ^d (± 5 days)
Clinic Visit	X		X		X	X	X	X	X	
Informed Consent	X									
Eligibility Criteria	X		X ^e							
Demographics	X									
Vital signs ^f	X									
Medical History (incl. MS disease status) ^g	X									
Alcohol Consumption	X									
Tobacco Use	X									
Pregnancy Testing ^h	X		X							
Concomitant Medications/ Procedures	X		X		X	X	X	X	X	X
Blood Biomarkers (optional) ^j			X				X		X	

Assessment	Screening Visit ^a	Screening Period (2 weeks +14 days)	Randomization Visit ^a (Week -4)	DMF-GI Monitoring Period (up to 28 days)	Wk 0 ^{a,b}	Wk 2 ^c	Wk 4 ^a	Wk 8 ^c	Wk 10 ^a /ET	Safety Follow-Up ^d (± 5 days)
Dispense eDiary	X									
eDiary Training	X									
eDiary Entries (Daily) ^k										
Return eDiary to Clinical ^l			X ^m	X ^m					X	
Dispense DMF With Dosing Instructions			X							
DMF Administration (Daily)			DMF administration will occur every day as per the USPI							
Randomization			X							
Dispense Randomized Study Treatments			X ⁿ							
Randomized Study Treatment Administration (Daily)					Randomized study treatment administration will occur every day as per the prescribing information.					
SAEs	SAE data will be collected from the signing of the informed consent up to the Safety Follow-Up Telephone Interview. MS relapses resulting in hospitalization are considered SAEs but will not be reported as SAEs in the study unless the relapse is complicated by other SAEs or is fatal.									
AEs				AE data will be collected from the first dose of DMF up to the Safety Follow-Up Telephone Interview.						

Note: Weeks 2, 4, and 8 will have a visit window of ±2 days, and Week 10 will have a visit window of ± 3 days.

Abbreviations: AE = adverse event; [REDACTED] DMF = dimethyl fumarate; DNA = deoxyribonucleic acid; eDiary = electronic diary; EDSS = Expanded Disability Status Scale; ET = early termination; GI = gastrointestinal; GRS = Gastrointestinal Symptom Rating Scale; [REDACTED]; MS = multiple sclerosis; [REDACTED]; RNA = ribonucleic acid; SAE = serious adverse event; USPI = United States Prescribing Information; Wk = week.

^a This visit must be performed in clinic.

^b Subjects will receive an alert through the eDiary if their GRS scores reach the appropriate threshold. This alert will tell the subject to begin taking the randomized study treatment the same day. At this time, study site should arrange the Week 0 Visit as soon as possible after the first administration of randomized study treatment. Visit dates will be measured from the first administration of randomized study treatment.

^c This visit may be performed remotely if more convenient for the subject; site must telephone the subject to document concomitant medications/procedures and AEs.

^d The safety follow-up will be performed as a telephone interview.

^e GI symptom and eDiary compliance assessment.

^f Including height and weight measurements and vital signs (temperature, blood pressure, and sitting blood pressure).

^g Medical history, including MS disease status, will include collection of information on duration of MS, relapse history, EDSS score, and treatment for MS.

^h Dipstick test (only for women of childbearing potential).

ⁱ [REDACTED]

^j Serum, RNA, and DNA samples will be collected for biomarker analysis and future use analysis in subjects who provide additional consent. A single DNA sample can be taken at any of prespecified timepoints.

^k Subjects will be required to record their daily GI symptoms in the eDiary every day from the Screening Visit up to Week 10.

^l eDiaries will be returned if (1) the subject fails during the Screening Period, (2) the subject does not reach the required GI symptom threshold during the DMF-GI Monitoring Period, or (3) the subject completes or discontinues the study.

^m Subjects who do not reach the GI symptom threshold during the DMF-GI Monitoring Period (a GSRS score of ≥ 5 in 1 question for 1 day, ≥ 4 in 1 question for 2 consecutive days, or ≥ 3 in 1 question for 3 consecutive days) will be discontinued.

ⁿ Subjects are dispensed randomized study treatment at this visit but must not begin taking the medication until alerted about their eDiary.

5 INTERIM ANALYSIS

No interim analysis will be performed. The study will be stopped for administrative reasons. Enrollment will be closed when approximately 60 patients are randomized and dosed up to Day 10. Enrolled patients will be followed until they complete the safety follow up visit. Results will be reviewed at the group level when these patients complete the study up to Day 10, and at the subject level when these patients complete the whole study.

6 SAMPLE SIZE JUSTIFICATION

Assuming that 40% of the placebo subjects will be improving (by chance) without any intervention, a total sample size of 118 (dosed with randomized study treatment), 59 per treatment arm (after randomization), would provide approximately 80% power to detect a 30% difference between the treatment arm and placebo arm in proportion of subjects with any improvement in GI severity, as measured by the average change from Day 0 in GSRS score to Day 10. Power was estimated assuming a 15% early discontinuation rate.

7 STATISTICAL ANALYSIS METHODS

The statistical software, SAS[®], will be used for all summaries and statistical analyses.

Summary statistics will be used throughout. For continuous endpoints, the summary statistics will generally include: the number of subjects with data, mean, standard deviation (SD), median, 25th and 75th percentile (Q1, Q3), minimum and maximum. For categorical endpoints, the summary statistics will generally include: number of patients randomized and dosed, the number of patients with data, and the number and percent of subjects with data in each category.

All statistical tests will be 2-sided with a type I error rate of 5%, unless otherwise specified.

7.1 Analysis population

7.1.1 Modified ITT population

The modified intent-to-treat (modified ITT) population consists of all patients who were randomized, received at least one dose of DMF treatment, received at least one dose of study treatment (Montelukast or placebo) on/after the first DMF dose date, and had at least one GSRS score measurement during the Day 1 – Day 10 period.

7.1.2 Safety population

Montelukast/placebo safety analysis population

The primary safety analysis population consists of all patients who received at least 1 dose of randomization study treatment (Montelukast or placebo).

DMF safety analysis population

The DMF safety analysis population will consist of all patients who received at least 1 dose of DMF. Selected analyses will be presented in the DMF safety analysis population.

7.1 Analysis of baseline data

Baseline GSRS score is defined as the score collected at Day 0.

Baseline data of demographics and disease characteristics are defined as data collected at the Screening visit. If there is more than one value on or before the screening visit, the Baseline value will be selected from all measurements collected before or on the date of the screening visit; the value closest to the date of screening visit will be used as the Baseline value.

Definition of baseline value for clinical laboratory data

Tecfidera baseline value

The Tecfidera baseline value is defined as the measurement collected before or on the date of the Randomization visit. If there is more than one value on or before the Randomization visit date, then the Tecfidera baseline value will be selected from all measurements collected before or on the date of the Randomization visit; the value closest to the date of Randomization visit will be used as the Tecfidera baseline value.

Montelukast baseline value

The Montelukast baseline value is defined as the measurement collected before or on the date of first dose of Montelukast /placebo. If there is more than one value on or before the first dose date of Montelukast /placebo, then the Montelukast baseline value will be selected from all measurements collected prior to or on the date of the first dose of Montelukast/placebo; the value closest to the date of the first dose date will be used as the Montelukast baseline value.

7.2 Study subjects

7.2.1 Analysis population

Unless otherwise stated, the analysis population for the efficacy analyses will be the modified ITT population. Safety analyses will be summarized in the Montelukast/placebo safety analysis population, while selected outputs will be performed in the DMF safety analysis population.

7.2.2 Accounting of Subjects

The following subject categories will be summarized for this study using numbers and percentages based on all patients enrolled in the study:

- Number of subjects randomized
- Number of subjects who were dosed with DMF (DMF safety analysis population)
- Number of subjects dosed with study treatment (modified ITT population, Montelukast/placebo safety analysis population)
- Number of subjects completed study treatment
- Number of subjects discontinued study treatment
 - Reason for study treatment discontinuation
- Number of subjects continuing DMF at the Week 10 visit
- Number of subjects discontinued DMF by Week 10 or at Week 10
 - Reason for DMF treatment discontinuation
- Number of subjects completed the study
- Number of subjects withdraw from the study
 - Reason for study withdrawal

Subjects who discontinued treatment or withdrew from the study and the reasons for discontinuation or withdrawal will be listed. In certain cases, case report form (CRF) text detailing the reasons for discontinuation may suggest additional clarification of the reason provided on the CRF. Therefore, additional information for subject accounting may be presented, utilizing reasons for discontinuing treatment from the study reclassified based on the detailed CRF text.

7.2.3 Protocol Deviations

Protocol deviations identified in the study will be listed.

7.2.4 Demographic and Baseline Characteristics

Demographic data, including age (years), age category (≤ 40 , > 40) and gender will be summarized. In addition, baseline height, weight, body mass index (BMI), systolic blood pressure, diastolic blood pressure and temperature will also be summarized.

Baseline disease characteristics will also be summarized using descriptive statistics. These include years since disease (MS) onset, years since diagnosis, days from the most recent pre-study relapse, total number of relapses in the past 12 months, 2 years and 3 years and Baseline EDSS score.

7.2.5 MS Treatment History

MS treatment prior to the study will be summarized by the type of approved therapy. Number and percentage of patients with a particular approved therapy will be presented.

7.2.6 Medical History

Medical history and MS disease history will be summarized as the number and percentage of patients with history of a medical condition in each body system.

7.2.7 Extent of Exposure and eDiary Compliance

Montelukast/placebo treatment exposure and compliance

The total number of days on study treatment (Montelukast or placebo) will be summarized for the modified ITT population. The number of days on study treatment is calculated as the number of days from the date of the first dose of the study treatment (Montelukast or Placebo) to the date of the last dose of study treatment, plus 1.

In addition, the number of doses of study treatment taken between Day 0 and Day 10 will be summarized for the modified ITT population.

Study treatment compliance rate will also be summarized in the modified ITT population. Study treatment compliance rate will be defined as the total number of study treatment doses taken divided by the total number of study treatment doses expected to be taken. Study treatment compliance will be summarized in each of the following periods:

- From Day 0 to Day 10
- From Day 0 to Week 8

DMF treatment exposure and compliance

In the DMF safety analysis population, the total number of days on DMF will be summarized. The number of days on DMF is calculated as the number of days from the date of the first dose of DMF after randomization to the date of the last dose of DMF, plus 1.

In addition, the number of doses of DMF taken between Day 0 and Day 10 will be summarized for the modified ITT population.

The DMF compliance rate will also be summarized. The DMF compliance rate will be defined as the total number of DMF doses taken divided by the total DMF doses expected to be taken during the period. DMF compliance will be summarized in the modified ITT population in each of the following periods:

- From the randomization visit to Week 10
- From the randomization visit to Day 0
- From Day 0 to Day 10
- From Day 0 to Week 10

Time on study

Time on study, based on the number of days from the date of the first dose of DMF to the last date on study plus 1, will also be summarized, for the Montelukast/placebo safety analysis population. The last known date on the study will be taken as the last visit/evaluation date from all relevant data for a subject.

GSRS compliance

GSRS score compliance rate will be summarized in the modified ITT population. GSRS score compliance rate will be defined as the total number of days when the GSRS score is recorded divided by the total number of days when the GSRS score is expected to be recorded. GSRS score compliance will be summarized in each of the following periods:

- From Day 0 to Day 10
- From Day 0 to Week 10

7.2.8 Concomitant Medications

Concomitant medications, any drug or substance administered on or after the day of the first dose of DMF will be summarized. Concomitant medications will be coded using the World Health Organization (WHO) drug dictionary.

Data on concomitant medications treating for GI symptoms are collected in the eDairy. Data on concomitant medications treating for non-GI symptoms are collected in the CRF. Number and percentage of patients taking concomitant medication will be summarized.

7.3 Efficacy Analysis

7.3.1 Analysis Population

The primary analysis population will be the modified intent-to-treat (modified ITT) population defined in 7.1.1.

7.3.2 GSRS score

GSRS is an interview-based rating scale consisting of 15 items for assessment of GI symptoms. Items are scored for intensity on a 7-grade Likert scale, defined by descriptive anchors such that 0 = none, 1 = minor, 2 = mild, 3 = moderate, 4 = moderately severe, 5 = severe, and 6 = very severe discomfort. The overall GSRS score is the mean of these 15 items, varying from 0 to 6; a score of 0 indicates that no symptoms are present, and a score of 6 indicates the worst possible degree of all symptoms. In addition, these 15 items can be grouped into 5 dimensions: abdominal pain syndrome (3 items, abdominal pain, hunger pain and nausea), reflux syndrome (2 items, heartburn and acid regurgitation), indigestion syndrome (4 items, abdominal distension, increased flatulence, borborygmus and eructation), diarrhea syndrome (3 items, loose stools, diarrhea and urgency of defecation) and constipation syndrome (3 items, constipation, hard stools and

feeling of incomplete evacuation). A dimension score is calculated as the mean of the items belonging to the specific syndrome. The primary analysis will be based on the overall GSRS score and sensitivity analysis will be based on the 5 dimension score as appropriate.

7.3.3 Analysis Methods-Primary endpoints

Proportion of subjects with a worsening in the severity of GI AEs, measured by the average change from Day 0 to Day 10 in GSRS score

The average change of the GSRS score from Day 0 (baseline) to Day 10 will be calculated as the sum of changes from baseline in GSRS score over the first 10 days divided by the total number of days with GSRS recorded. A positive average change of GSRS score from Day 0 to Day 10 means a patient has an overall worsened GI severity. A negative average change of GSRS score from Day 0 to Day 10 means an overall improved GI severity.

The proportion of subjects with worsening will be summarized by treatment and will be estimated from a weighted logistic regression model adjusted for age, weight and baseline GSRS score as continuous variables. Each patient included in this model will be assigned a weight defined as the proportion of days with GSRS score recorded. The weight is used to account for the missing data when patients do not report the GSRS score. The odds ratio (OR) for the Montelukast treatment group compared to placebo will be reported. The corresponding P-value from the likelihood ratio test of the null hypothesis that the $OR = 1$ will be given. Profile likelihood 95% profile likelihood confidence interval (CIs) will be given for the odds ratio.

SAS procedure “genmod” or SAS procedure “logistic” will be used to perform the primary analysis. Below is the example of SAS procedure genmod:

```
proc genmod data=ds1 descending;*assuming ds1 is the name of the data
set
  class trtpn;
  model worsec = trtpn weight age gsrsb/dist=bin link=logit lrci;
  weight pdays;
  lsmeans trtpn / pdiff cl;
  contrast "difference between treatments" trtpn -1 1;
run;
```

Depending on the GSRS, study treatment and/or the DMF compliance, sensitivity analysis may be performed among patients with a compliance rate from Day 0 to Day 10 above a certain threshold. A chi-squared test for the difference in the rate of worsening between the two treatment groups may also be performed.

7.3.4 Analysis Methods-Secondary endpoints

Average change of GI severity scores from Day 0 to Day 10, as measured by the total change of GSRS scores from Day 0 over the first 10 days (Day 1 to Day 10), divided by total number of days with GSRS recorded

Average change of GI severity scores from Day 0 (baseline) to Day 10 will be calculated as the sum of changes from baseline in GSRS score over the first 10 days divided by the total number of days with GSRS recorded. The average change will be summarized by treatment and analyzed using an analysis of covariance (ANCOVA) model adjusted for age, weight and baseline GSRS score. To adjust for missing data, a weight defined as the proportion of days with GSRS score recorded will be assigned to each subject. The difference of the average GSRS score between the two treatment arms will be tested.

Normality assumption of the ANCOVA will be tested. If violated, a rank based ANCOVA will be used.

A sensitivity analysis using a mixed-effects model for repeated measures (MMRM) for the change of the GSRS score from baseline will be conducted. The model will be adjusted for age, weight and baseline GSRS score as continuous variables, and will have unstructured variance-covariance structure. The primary test based on the model will be the test of the null hypothesis of no difference between the two treatment groups in the average change from Day 0 (baseline) between Day 1 and Day 10. Trajectory plot of the change in GSRS score with 95% CIs, by time and by treatment group, estimated from the model, will be presented. Trajectory plot of the mean change in GSRS score by day will be presented as well.

Depending on the GSRS, study treatment and/or DMF compliance, sensitivity analysis may be performed using MMRM in patients with a compliance rate from Day 0 to Day 10 above a certain threshold.

Average change of GI severity scores from Day 0 to Week 10 as measured by total change of GSRS scores from Day 0 over the first 10 weeks (Day 1 to Week 10) divided by total number of days with GSRS recorded

Average change of GI severity scores from Day 0 (baseline) to Week 10 will be calculated as the sum of changes from baseline in GSRS score over the first 10 weeks divided by the total number of days with GSRS recorded. This endpoint will be analyzed by the MMRM as in the analysis of the above endpoint. Sensitivity analyses using ANCOVA model for the average change may be performed. Trajectory plots of mean change and the model based estimated mean change from baseline in GSRS score (with 95% CIs), by time and by treatment group, will be presented.

Time to first worsening of GSRS in GI severity

The GI severity is worsened if the GSRS score increases from baseline (Day 0). Time to first worsening of GSRS in GI severity is defined as the number of days from Day 0 to the first date with a worsened GSRS score. If a patient does not experience any worsening from Day 0 to Day 10, his/her time to first worsening will be censored at Day 10 or the day of study treatment (Montelukast/PBO) discontinuation, whichever comes first.

Time to the first worsening of GSRS by treatment arm will be analyzed using the Kaplan-Meier method and the Cox's proportional hazards model adjusted for age, weight and

baseline GSRS score. If the proportionality assumption does not hold, a log-rank test will be used.

Time to recovery to Day 0 GSRS score from the last occurrence of the worst score in GI severity

The GI severity is recovered to Day 0 GSRS score if the GSRS score is smaller than or equal to the Day 0 score. Time to recovery to Day 0 score from the last occurrence of the worst score is defined as the date of recovery minus the date of the last occurrence of the worst score. If a patient does not experience a worsening in GSRS score, the last occurrence of the worst score is Day 0 and time to recovery is 1. If a patient experiences a worsening of GSRS score but does not experience a recovery before Week 8, his/her time to recovery will be censored at Week 8 or the day of study treatment (Montelukast/PBO) discontinuation or the day of switching to other GI medications listed in I/E criterion 8, whichever comes first.

Time to recovery to Day 0 GSRS score from the last occurrence of the worst score will be analyzed using the Kaplan-Meier method and the Cox's proportional hazards model.

Average change of GSRS score from Day 0 to Week 1, 2, 3, 4, 5, 6 and 8

Average change of GSRS score from baseline (Day 0) to Week 1, 2, 3, 4, 5, 6 and 8 will be summarized; a repeated measures model for the change of the GSRS score from baseline, adjusted for age, weight and baseline GSRS score, will be used to estimate effect at each time point. Sensitivity analyses using ANCOVA model for the average change may be performed.

Average change of GSRS score from Day 0 to 72 hours from the initiation of randomized study treatment

Average change of GSRS score from baseline (Day 0) to 72 hours (Day 3) from the initiation of randomized study treatment will be summarized and analyzed by the repeated measures method. No sensitivity analysis will be performed.

Proportion of subjects who take GI symptomatic therapy during the study

From Day 10 onward, subjects are allowed to use symptomatic therapy to treat DMF-related GI events. The proportion of subjects who take GI symptomatic therapy from Day 10 to Week 10 will be summarized by treatment and analyzed using the Chi-squared test.

Percentage of subjects who discontinue DMF therapy due to the GI-related adverse events from Day 0 to Week 10

The proportion of subjects who discontinue DMF due to the GI-related adverse events from Day 0 to Week 10 will be summarized by treatment and analyzed using the Chi-squared test.

Proportion of subjects who experience flushing events

The proportion of subjects who experience flushing events from Day 0 to Week 10 will be summarized for the modified ITT population by treatment group and analyzed using the Chi-squared test. Flushing event as defined as an event coded to any of the following preferred terms: Flushing, Hot flush (under SOC of Vascular disorders), Erythema, Generalized erythema, Skin burning sensation (under SOC of Skin and subcutaneous tissue disorders), Burning sensation (under SOC of Nervous system disorders), Feeling hot (under SOC of General disorders and Administration site conditions), Hyperaemia (under SOC of Vascular disorders).

7.3.5 Analysis methods-Exploratory endpoints

[REDACTED]

[REDACTED]

- [REDACTED]

- [REDACTED]

[REDACTED]


[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]



7.4 Safety Data

7.4.1 Safety analysis Population

The primary safety analysis population is the Montelukast/placebo safety analysis population. Selected analyses will also be summarized in the DMF safety analysis population.

7.4.2 Analysis Methods

Safety analyses will summarize all adverse events (AEs). In general, SAE and AEs will be analyzed based on incidence, defined as the proportion of subjects who had at least one occurrence of an event out of the number of subjects in the safety population.

7.4.2.1 Clinical Adverse Events

All summary analyses of AEs and SAEs will be based on the principle of treatment emergence assuming this information is available. For the Montelukast /placebo safety analysis population, an event is considered to be treatment emergent if the onset is after the start of the Montelukast /placebo treatment or the event was present before and subsequently worsened after the Montelukast /placebo start date. For the DMF safety analysis population, an event is considered to be treatment emergent if the onset is on or after the first DMF dose date or the event was present before and subsequently worsened on or after the first DMF dose date.

The Medical Dictionary for Regulatory Activities (MedDRA) version 19.1 will be utilized to code and group AEs by System Organ Class (SOC) and Preferred Term (PT). Incidence of AEs and SAEs will be summarized and presented by SOC and PT. Summary analysis of adverse events will be provided. The summaries will include the following numbers and percentages of subjects: in the safety analysis population; with a serious adverse event (SAE); with an AE leading to discontinuation of treatment; and with an AE leading to withdrawal from the study.

The incidence of AEs by relationship to DMF or Montelukast will be summarized by SOC and PT. For a given SOC or PT, a subject with multiple AEs with the different relatedness will be counted once in the most related category.

The incidence of AEs leading to study treatment discontinuation and study withdrawal by severity will be summarized by SOC and PT using severity categories (mild, moderate, and severe). For a given SOC or PT, subjects with multiple AEs with the different severity will be counted once in the category of worst severity.

Deaths that occur will be described in detail in patient narratives. A listing of deaths will also be provided. While the number of deaths is expected to be small, tabulation will be performed if appropriate.

[illegible]

The following list of tables includes main tables for the analyses described in the SAP. Other tables may be added.

Table 2: Summary of demography

Table 3: Summary of alcohol consumption and tobacco use

Table 4: Summary of medical history

Table 5: Summary of MS disease history

Table 6: Summary of prior disease-modifying MS treatment history

Table 7: Summary of time on study treatment

Table 8: Summary of time on DMF treatment

Table 9: Summary of time on study

Table 10.1: Number of doses of study treatment taken between Day 0 and Day 10

Table 10.2: Number of doses of DMF treatment taken between Day 0 and Day 10

Table 11.1: Summary of GSRS compliance rate

Table 11.2: Summary of study treatment compliance rate

Table 11.3: Summary of DMF compliance rate from randomization visit to Week 10

Table 11.4: Summary of DMF compliance rate from Day 0 to Day 10 and to Week 10

Table 11.5: Summary of DMF compliance rate from randomization visit to Day 0

Table 12: Summary of concomitant medications

Table 13: Summary of primary endpoint

Table 14: Summary of primary endpoint among patients with GSRS e-Diary compliance rate $\geq 80\%$, at least 5 doses of study medication, and at least 10 doses of DMF in the Day 0 – Day 10 period

Table 15.1: Summary of average change of GI severity score from baseline (Day 0) by ANCOVA, Day 1 to Day 10: overall and by dimension

Table 15.2: Summary of average change of GI severity score from baseline (Day 0) by ANCOVA with additional covariates, Day 1 to Day 10: overall and by dimension

Table 16: Summary of average change of GI severity score from baseline (Day 0) by repeated measures analysis, Day 1 to Day 10: overall and by dimension

Table 17: Summary of average change of GI severity score from baseline (Day 0) by ANCOVA, Day 1 to Day 10, among patients with GSRS e-Diary compliance rate $\geq 80\%$, at least 5 doses of study medication, and at least 10 doses of DMF in the Day 0 – Day 10 period

Table 18: Summary of average change of GI severity score from baseline (Day 0) by repeated measures analysis, Day 1 to Week 10: overall and by dimension

Table 19: Summary of time to first worsening in GSRS score

Table 20: Summary of time to recovery to Day 0 GSRS score from the last occurrence of worst post-baseline GSRS score

Table 21: Summary of average change of GSRS score from baseline (Day 0) by repeated measures analysis, Day 1 to Weeks 1-8

Table 22: Summary of average change of GSRS score from baseline (Day 0) by repeated measures analysis, at 72 hours from the initiation of randomized study treatment (Day 1 – Day 3)

Table 23: Summary of primary endpoint by baseline demographic and disease characteristics

Table 24: Summary of average change of GI severity score from baseline (Day 0), repeated measures analysis, Day 1 to Day 10, by baseline demographic and disease characteristics

Table 25: Summary of average change of GI severity score from baseline (Day 0), repeated measures analysis, Day 1 to Week 10, by baseline demographic and disease characteristics

Table 26: Summary of proportion of subjects who take GI symptomatic therapy during the study

Table 27: Summary of proportion of subjects who discontinue DMF therapy due to GI-related adverse events from Day 0 to Week 10

Table 28: Summary of proportion of subjects who experience flushing events

Table 29: Summary of biomarker scores, changes and percent changes from Tecfidera baseline, by treatment group and visit, DMF safety analysis population

Table 30: Summary of biomarker scores, changes and percent changes from Montelukast baseline, by treatment group and visit, Montelukast/placebo safety analysis population

Table 31.1: Summary of selected hematology parameters, change and percent change from Montelukast baseline, by treatment group and visit, Montelukast/placebo safety analysis population

Table 31.2: Summary of selected hematology parameters, change and percent change from Tecfidera baseline, by treatment group and visit, DMF safety analysis population

Table 32.1: Summary of hematology abnormalities by CTC grades, by treatment group and visit, DMF safety analysis population

Table 32.2: Summary of hematology abnormalities by CTC grades, by treatment group and visit, Montelukast /placebo safety analysis population

Table 33.1: Incidence of adverse events by system organ class and preferred term, Montelukast/placebo safety analysis population

Table 33.2: Incidence of adverse events by system organ class and preferred term, DMF safety analysis population

Table 34.1: Incidence of serious adverse events by system organ class and preferred term, Montelukast/placebo safety analysis population

Table 34.2: Incidence of serious adverse events by system organ class and preferred term, DMF safety analysis population

Table 35.1: Incidence of adverse events leading to the study treatment discontinuation by system organ class and preferred term, Montelukast/placebo safety analysis population

Table 35.2: Incidence of adverse events leading to DMF discontinuation by system organ class and preferred term, DMF safety analysis population

Table 36.1: Incidence of adverse events leading to study withdrawal by system organ class and preferred term, Montelukast/placebo safety analysis population

Table 36.2: Incidence of adverse events leading to study withdrawal by system organ class and preferred term, DMF safety analysis population

Table 37: Incidence of adverse events by system organ class, preferred term and severity, DMF safety analysis population

Table 38: Incidence of adverse events by system organ class, preferred term and by relationship to the study treatment or DMF, DMF safety population

Supporting tables for Figures 1, 2, 5 and 6:

Table P1: Summary of change in GSRS score from baseline (Day 0) by repeated measures analysis, Day 1 to Day 10

Table P2: Summary of change in GSRS score from baseline (Day 0) by repeated measures analysis, Week 1 to Week 10

9 LIST OF LISTINGS

Listing 1: Listing of subjects who discontinued treatment and/or withdrew from study

Listing 2: Listing of serious adverse events

Listing 3: Listing of adverse events led to study withdrawal

Listing 4: Listing of death

Listing 5: Listing of out of normal range laboratory results

10 LIST OF FIGURES

Figure 1: Mean (SE) change in GSRS score from baseline (Day 0), by time and treatment group, Day 1 to Day 10

Figure 2: Model-based estimated mean change in GSRS score from baseline (Day 0), with 95% CI, by time and treatment group, Day 1 to Day 10

Figure 3: Kaplan-Meier plot for time to the first worsening of GSRS score from Day 0 GSRS score, by treatment group

Figure 4: Kaplan-Meier plot for time to recovery to Day 0 score from the last occurrence of worst GSRS score, by treatment group

Figure 5: Mean (SE) change in GSRS score from baseline (Day 0), by time and treatment group, Day 1 to Week 10

Figure 6: Model-based estimated mean change in GSRS score from Day 0, by time and treatment group, Day 1 to Week 10