COVER PAGE

Official Title:	An Open-Label, Single-Arm, Multicenter, Phase 3 Study to Evaluate the Safety and Tolerability, and Pharmacokinetics of Diroximel Fumarate (BIIB098) in Adult Participants From the Asia-Pacific Region With Relapsing Forms of Multiple Sclerosis
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PHASE OF DEVELOPMENT: 3

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1.1. Synopsis

Protocol Title:	An Open-Label, Single-Arm, Multicenter, Phase 3 Study to Evaluate the Safety and Tolerability, and Pharmacokinetics of Diroximel Fumarate (BIIB098) in Adult Participants From the Asia-Pacific Region With Relapsing Forms of Multiple Sclerosis	
Protocol Number:	272MS303	
Version Number:	4	
Name of Study Treatment:	Research Name:	BIIB098 (also known as ALK8700)
	Generic Name:	Diroximel Fumarate (DRF)
	Trade Name:	Vumerity
Study Phase:	3	
Study Indication:	Relapsing Forms of Multiple Sclerosis (RMS)	
Study Rationale:	The main goal of the current study is to assess the safety and tolerability, and PK profile of DRF administered orally in adult East Asian participants with RMS. DRF was developed as a modified-release oral treatment for RMS. In October 2019, DRF under the trade name VUMERITY® was approved by the US FDA for the treatment of adult patients with RMS, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease. In participants with RRMS, DRF demonstrated safety and tolerability, in 2 global Phase 3 studies: Study ALK8700-A301 (EVOLVE-MS-1; currently ongoing) and Study ALK8700-A302 (EVOLVE-MS-2; completed). In both studies, DRF at a dose of 231 mg twice daily for 1 week followed by 462 mg twice daily for 96 weeks (in Study ALK8700-A301) and at a dose of 462 mg twice daily for 4 weeks (in Study ALK8700-A302) had an acceptable safety profile and was well tolerated. Although the complex and multifactorial pathogenesis of MS is considered to be	

	generally similar across Caucasian and Asian populations, there are currently limited safety, tolerability, and efficacy data on DRF in the Asian population, including the East Asian MS populations; therefore, additional data are warranted in this population. This Phase 3 study is designed to collect data in East Asian participants with RMS who are treated with DRF. DRF is an aminoethyl ester of MMF that undergoes rapid hydrolysis through esterases to produce MMF. MMF is also the active metabolite of the approved drug product, DMF. An oral form of DMF under the trade name Tecfidera™ has been approved by the US FDA since 2013 for the treatment of patients with RMS. The 462 mg dose of DRF and the 240 mg dose of DMF administered orally provide bioequivalent exposure of MMF. The safety and efficacy profile of DRF is expected to be similar to that of DMF based on the bioequivalence of MMF. Of note, DMF's efficacy and safety in the East Asian population were explored in a randomized, double-blind, placebo-controlled Phase 3 DMF study (Study 109MS305 [APEX]). The results from Study 109MS305 demonstrated that DMF was well tolerated and showed sustained efficacy at Week 24 (double-blind period) and at Week 48 in East Asian participants with RRMS. These results were comparable to the registration studies conducted for DMF.
Rationale for Dose and Schedule Selection:	The DRF dosage selected for this study (231 mg twice daily for the first 7 days and 462 mg twice daily thereafter) is the approved dose regimen in the US for the treatment of patients with RMS and has been selected as the recommended dose in marketing applications to other health authorities. The doses of DRF to be used for initial dose titration (231 mg) and for treatment maintenance (462 mg) in this study are within the range of doses evaluated in completed Phase 1 studies.

Study Objectives and Endpoints

Part 1

Primary Objective	Primary Endpoint
To determine the safety and tolerability of DRF administered for up to 24 weeks in adult East Asian participants with RMS	• Incidence of AEs and SAEs at Week 24

	• Quantitative and qualitative changes from Baseline Visit (Day 1) to Week 24 in clinical laboratory parameters, ECGs, and vital signs • Incidence of C-SSRS events at Baseline Visit (Day 1) and through Week 24
Secondary Objective To evaluate the PK of DRF metabolites (MMF and HES) following multiple doses of DRF in a subset of adult East Asian participants with RMS	Secondary Endpoints • Plasma concentrations of MMF and HES • Noncompartmental plasma PK parameters of MMF and HES, including the following: – C_{max} – AUC_{last} – T_{max} – $t_{½}$ (MMF only)
Part 2	
Primary Objective To determine the safety and tolerability of DRF administered for up to 48 weeks in adult East Asian participants with RMS	Primary Endpoint • Incidence of AEs and SAEs up to Week 48 • Quantitative and qualitative changes from Baseline Visit (Day 1) to Week 48 in clinical laboratory parameters, ECGs, and vital signs • Incidence of C-SSRS events at Baseline Visit (Day 1) and through Week 48

Exploratory objectives and endpoints are listed in Section 4.

Study Design:	This is a multicenter, open-label, single-arm, Phase 3 study to evaluate the safety and tolerability, and PK of DRF administered orally to East Asian participants with RMS. This study will be conducted in 2 parts: Part 1 is designed to evaluate the PK, safety, and tolerability of DRF administered orally. Part 2 is designed as a 24-week safety extension period for participants from Part 1.
Study Location:	Approximately 45 sites from Japan and China are planned.

Study Population:	This study will be conducted in male and female participants who meet the following criteria:
	
	• aged 18 to 65 years at the time of informed consent
	
	  • For participants in Japan aged < 20 years, written informed consent should be obtained from the participant and their legally acceptable representative.
	
	  • Informed consent from a legally acceptable representative is not mandatory if the participant is classified as an adult based on the latest applicable local laws.
	
	• diagnosed with RMS according to study eligibility criteria
	
	Detailed criteria are described in Section 6.

Number of Planned Participants:	Approximately 50 Japanese participants and 50 Chinese participants are planned to be enrolled. The Sponsor may enroll fewer than 50 participants per cohort based on the observed recruitment rate in these regions.
Treatment Groups:	The study will consist of 2 treatment cohorts as follows: • Cohort 1: approximately 50 Japanese participants with RMS

- Cohort 2: approximately 50 Chinese participants with RMS

Study treatment includes DRF 231 mg administered as 1 capsule twice daily and DRF 462 mg administered as two 231 mg capsules twice daily. Participants will titrate from DRF 231 mg twice daily for the first week on treatment to 462 mg twice daily from Day 8 onwards.

Sample Size Determination:

A sample size of approximately 50 participants per cohort is based on feasibility considerations and is deemed sufficient to characterize the safety and tolerability profile. With this sample size, the probability of observing at least 1 SAE with a background incidence of 4% would be 87% based on data from the 24-week Treatment Period in Study ALK8700-A301 (DRF global Phase 3 study) in RRMS participants who were naïve to DRF treatment. In addition, assuming that the incidence of GI AEs at 24 weeks is 27.5%, as observed in de novo participants recruited in Study ALK8700-A301, the sample size of approximately 50 participants per cohort will provide a 96% probability of observing a point estimate of GI AE incidence rate < 39% in Part 1 of the study (at 24 weeks). A 24-week incidence rate of 39% was observed in East Asian participants who received DMF twice daily in Study 109MS305.

Based on observed MMF PK parameters in healthy volunteers (Study ALK8700-A103), a sample size of 7 participants in the Japanese cohort will provide a reasonable precision of the PK parameters of MMF and HES.

Visit Schedule:

Participants will have up to 15 visits during the study. During Part 1, participants will have up to 8 visits during the Treatment Period (i.e., Baseline Visit [Day 1], Week 2, Week 4, Week 8, Week 12, Week 16, Week 20, and Week 24) and will be contacted via telephone twice.

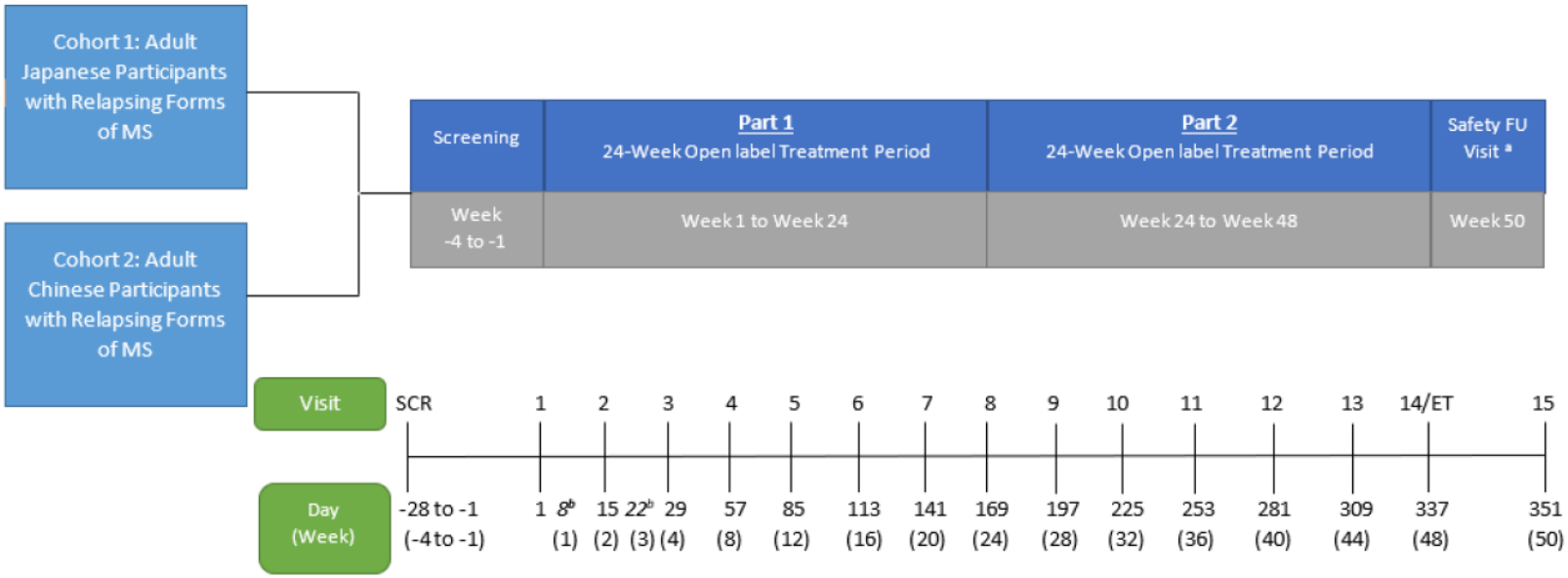
During Part 2, participants will report to the study site every 4 weeks up to Week 48 during the Treatment Period, for a total of up to 7 visits, and will have the Safety Follow-Up Visit 2 weeks later (Week 50) after the end of the Treatment Period.

Study assessments conducted at each visit are listed in the Schedule of Activities (Table 1).

Duration of Study Participation:	Study duration for participants who complete the study will be up to 54 weeks: • 4-week Screening Period • 24-week Treatment Period in Part 1 • 24-week Treatment Period in Part 2 • 2-week Safety Follow-Up Period
Benefit-Risk Analysis:	The potential benefits of participation in this study are expected to outweigh the risks. The safety profile of DRF relies on the well-known safety profile of the reference drug, DMF. The safety of DMF has been established in 2 randomized, placebo-controlled, double-blind, pivotal Phase 3 studies (Study 109MS301 and Study 109MS302) and further established in extensive postmarketing experience. Data from DRF studies have shown comparability to the DMF safety profile, with no new safety issues identified to date.

1.2. Study Design Schematic

Figure 1: Study Design Schematic



Intensive PK Sampling at timepoints[c,d]:
-30 to 0 minutes (pre-dose), and at 0.5, 1, 2, 3, 4, 6, and 8 hours (post-dose) at any timepoint in the period between Week 4 (Day 29, Visit 3 ± 3 days) and Week 24 (Day 169, Visit 8 ± 5 days), both inclusive.
Sparse PK Sampling[d] on Days 29 and 57 at pre-dose and approximately 2 to 3 hours post-dose

BL = baseline; ET = early termination; FU = follow-up; MS = multiple sclerosis; PK = pharmacokinetic; SCR = screening; TC = telephone contact

[a]Lymphocyte monitoring follow-up visits (maximum 3 visits within 6 months) may be required after this visit

[b]Telephone contact at Day 8 (Week 1) and Day 22 (Week 3) for safety and tolerability assessments

[c]Chinese participants will not have intensive PK sampling.

[d]In the event that a participant is enrolled in both the sparse and intensive PK cohorts and intensive PK sampling was completed on Day 29 or Day 57 for a participant, sparse PK sampling will not be required for those days. However, if it is determined that intensive PK is not feasible by Day 57, sparse PK sampling will be completed according to protocol, and intensive PK should be completed at later visits.

1.3. Schedule of Activities

Table 1: Schedule of Activities

		Part 1: 24-Week Open-Label Treatment[1]										Part 2: 24-Week Open-Label Treatment[1]						Safety FU[2]
Visit	**SCR**	**BL 1**	**TC[3]**	**2**	**TC[3]**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14/ ET**	**15**
Day	**-28 to -1**	**1**	**8 (±2)**	**15 (±3)**	**22 (±2)**	**29 (±3)**	**57 (±5)**	**85 (±5)**	**113 (±5)**	**141 (±5)**	**169 (±5)**	**197 (±5)**	**225 (±5)**	**253 (±5)**	**281 (±5)**	**309 (±5)**	**337 (±5)**	**351 (±5)**
Week	**-4 to -1**		**1**	**2**	**3**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**50**
Informed Consent	X																	
Inclusion/ Exclusion Criteria	X	X[4]																
Demographics and Medical History	X																	
Physical Examination[5]	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X																	
Weight	X	X[4]				X	X	X			X		X	X	X		X	X
FSH Test[6]	X																	
Serum Pregnancy Test[7,8]	X																	X
Urine Pregnancy Test[7,9]		X[4]		X		X	X	X	X	X	X	X	X	X	X	X	X	
HIV/Hepatitis Screen	X																	
TSH Test	X																	
Screening for TB (IGRA)	X																	
Biochemistry, Urinalysis, and Hematology[10]	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X
PK Sampling						X[11, 12, 13, 14]	X[11, 12, 13, 14]	X[11, 12, 13, 14]	X[11, 12, 13, 14]	X[11, 12, 13, 14]	X[11, 12, 13, 14]							
Vital Signs[15]	X	X[4]		X		X	X	X	X	X	X	X	X	X	X	X	X	X

		Part 1: 24-Week Open-Label Treatment[1]										Part 2: 24-Week Open-Label Treatment[1]						Safety FU[2]
Visit	**SCR**	**BL 1**	**TC[3]**	**2**	**TC[3]**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14/ ET**	**15**
Day	**-28 to -1**	**1**	**8 (±2)**	**15 (±3)**	**22 (±2)**	**29 (±3)**	**57 (±5)**	**85 (±5)**	**113 (±5)**	**141 (±5)**	**169 (±5)**	**197 (±5)**	**225 (±5)**	**253 (±5)**	**281 (±5)**	**309 (±5)**	**337 (±5)**	**351 (±5)**
Week	**-4 to -1**		**1**	**2**	**3**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**50**
12-Lead ECG	X	X[4]		X			X	X	X		X	X		X	X	X	X	X
[redacted]																		
C-SSRS[19]	X	X[4]		X		X	X	X	X	X	X	X	X	X	X	X	X	X
AE Recording		----------X----------																
SAE Recording	----------X----------																	
Concomitant Therapy and Procedure Recording	----------X----------																	
Study Treatment Dispensation		X		X		X	X	X	X	X	X	X	X	X	X	X		

[1] Unscheduled visits may occur at any time as per protocol requirement.
[2] Any participant who prematurely discontinues study treatment or withdraws from the study will be asked to return to the clinic to complete all study assessments for Visit 14/ET Visit and for the Safety Follow-Up Visit 2 weeks later (Visit 15).
[3] Safety and tolerability assessments (including AEs and concomitant medications) will be conducted by telephone on these days.
[4] To be conducted predose at Visit 1.
[5] Full physical examination at Screening. Brief physical examination, symptom-directed, at all other visits.
[6] To confirm postmenopausal status (in postmenopausal female participants only).
[7] To be performed only in women of childbearing potential; results must be negative to continue participation in study.
[8] Samples for serum pregnancy test are to be analyzed by the central laboratory. Results must be known prior to study treatment distribution.
[9] Samples for urine pregnancy test are to be analyzed by the local laboratory.
[10] Laboratory assessment as per Table 5.
[11] Intensive PK samples will be collected in a subset of PK population (n = 7 Japanese cohort only) at any timepoint in the period between Week 4 (Day 29, Visit 3 ± 3 days) and Week 24 (Day 169, Visit 8 ± 5 days), both inclusive; see the PK sampling timepoints in Table 6.
[12] In both Japanese and Chinese participants, on Days 29 and 57, PK samples will be taken -30 to 0 minutes predose and approximately 2 to 3 hours postdose for those participants whose intensive PK samples are not collected on this day (non-PK population).
[13] No intense PK sampling will be conducted in Chinese MS participants. Chinese MS participants will have sparse PK on Days 29 and 57.

[14]In the event that a participant is enrolled in both the sparse and intensive PK cohorts and intensive PK sampling was completed on Day 29 or Day 57 for a participant, sparse PK sampling will not be required for said days. However, if it is determined that intensive PK is not feasible by Day 57, sparse PK sampling will be completed according to protocol and intensive PK should be completed at later visits.

[15]Vital sign measurements include temperature, respiratory rate, blood pressure, and pulse rate. Blood pressure, respiratory rate, and pulse rate will be measured after the participant has been in a seated or supine position for at least 5 minutes.

[redacted]

[19]Use the "Baseline Screening" version at Screening; use the "Since Last Visit" version at all other scheduled visits.

Table 2: Additional Follow-Up for Participants with Lymphopenia

Assessments	LM Visits[1]		
	LM Visit 1 (2 months after Safety Follow-Up Visit ± 7 days)	LM Visit 2 (4 months after Safety Follow-Up Visit ± 7 days)	LM Visit 3 (6 months after Safety Follow-Up Visit ± 7 days)
Lymphocyte Count	X	X	X
Concomitant Medication	X	X	X

[1] Participants who complete the study or who terminate the study early and have a last measured lymphocyte count < LLN will return to the clinic for additional LM visits every 2 months starting from Visit 15 (or from the ET visit for participants who terminate the study early) for a period of 6 months (i.e., a maximum of 3 visits), until lymphocyte counts reach normal limits (≥ LLN), or until another DMT is started that may affect lymphocyte counts (in this case, lymphocyte monitoring for that DMT will apply), whichever occurs first. All assessments required for the Safety Follow-Up Visit (Visit 15, Table 1) should be completed for these participants prior to initiation of the LM visits.

2. LIST OF ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
[redacted]	[redacted]
anti-HBc	hepatitis B core antibody
anti-HBs	hepatitis B surface antibody
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{last}	area under the concentration-time curve from time zero to time of last measurable concentration
AUC_{tau}	area under the concentration-time curve within a dosing interval
BL	baseline
CD19	cluster of differentiation 19
CI	confidence interval
CIS	clinically isolated syndrome
CL/F	apparent total body clearance
C_{max}	maximum observed concentration
CRF	case report form
CRO	contract research organization
C-SSRS	Columbia Suicide Severity Rating Scale
CV of AUC	cross validated area under the curve
DHA	Directions for Handling and Administration
DMF	dimethyl fumarate
DMT	disease-modifying therapy
DRF	diroximel fumarate
ECG	electrocardiogram
[redacted]	[redacted]
eGFR	estimated glomerular filtration rate
EQ-5D	EuroQoL-5 Dimensions questionnaire
ET	early termination
EU	European Union
[redacted]	[redacted]
FDA	Food and Drug Administration
FS	functional system
FSH	follicle-stimulating hormone
FU	Follow-Up Visit
GA	glatiramer acetate
GCP	Good Clinical Practice
[redacted]	[redacted]
GGT	gamma-glutamyl transferase

GI	gastrointestinal
HBsAg	hepatitis B surface antigen
HES	2-hydroxyethyl succinimide
HCV	hepatitis C virus
HDPE	high density polyethylene
HIV	human immunodeficiency virus
HPMC	hydroxypropyl methylcellulose
ICF	informed consent form
ICH	International Council for Harmonisation
IFN-α	interferon-alpha
IFN-β	interferon-beta
IGRA	interferon-gamma release assay
IMP	investigational medicinal product
IRT	interactive response technology
IV	intravenous(ly)
IVMP	intravenous methylprednisolone
LDH	lactate dehydrogenase
LLN	lower limit of normal
LM	lymphocyte monitoring
MedDRA	Medical Dictionary for Regulatory Activities
MMF	monomethyl fumarate
[redacted]	[redacted]
MS	multiple sclerosis
PCS	potentially clinically serious
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy
RMS	relapsing forms of MS
RNA	ribonucleic acid
RRMS	relapsing-remitting MS
S1P	sphingosine 1-phosphate
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(ly)
SCR	screening
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	elimination half-life
TB	tuberculosis
TC	telephone contact
T_{lag}	lag time
T_{max}	time to reach C_{max}
TSH	thyroid stimulating hormone
ULN	upper limit of normal
US	United States
V_Z/F	apparent volume of distribution

3. INTRODUCTION

Diroximel fumarate (DRF; BIIB098) was developed as a modified-release oral treatment for RMS. In October 2019, DRF, under the trade name VUMERITY®, was approved by the US FDA for the treatment of adults with RMS, including CIS, relapsing-remitting disease, and active secondary progressive MS. DRF is an aminoethyl ester of MMF that undergoes presystemic hydrolysis through esterases to produce MMF [TECFIDERA® USPI 2022]. MMF is also the active metabolite of the approved drug product DMF, also known as Tecfidera™ [TECFIDERA® USPI 2022].

3.1. Study Rationale

The main goal of the current study is to assess the safety and tolerability, and PK profile of DRF administered orally in adult East Asian participants with RMS.

DRF was developed as a modified-release oral treatment for RMS. In October 2019, DRF under the trade name VUMERITY® was approved by the US FDA for the treatment of adult patients with RMS, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease.

In participants with RRMS, DRF demonstrated safety and tolerability in 2 global Phase 3 studies, Study ALK8700-A301 (EVOLVE-MS-1; currently ongoing) and Study ALK8700-A302 (EVOLVE-MS-2; completed). In both studies, DRF at a dose of 231 mg twice daily for 1 week followed by 462 mg twice daily for 96 weeks (in Study ALK8700-A301) and at a dose of 462 mg twice daily for 4 weeks (in Study ALK8700-A302) had an acceptable safety profile and was well tolerated.

DRF is an aminoethyl ester of MMF that undergoes rapid hydrolysis through esterases to produce MMF. MMF is also the active metabolite of the approved drug product, DMF. An oral form of DMF under the trade name Tecfidera® has been approved by the US FDA since 2013 for the treatment of patients with RMS. The 462 mg dose of DRF and the 240 mg dose of DMF administered orally provide bioequivalent exposure of MMF. The overall safety and efficacy profile of DRF is expected to be similar to that of DMF based on the bioequivalence of MMF. DRF demonstrated clinically significant improved GI tolerability compared with DMF in the 5-week, randomized, Phase 3 Study ALK8700-A302. DRF provides an MMF exposure profile that may limit the GI effects associated with DMF treatment while maintaining efficacy comparable to that demonstrated by DMF. Therefore, DRF has the potential to address an unmet medical need for patients with relapsing forms of MS who are unable to tolerate DMF, particularly due to GI effects.

Of note, DMF's efficacy and safety in the East Asian population were explored in a randomized, double-blind, placebo-controlled Phase 3 DMF study (Study 109MS305 [APEX]). The results from Study 109MS305 demonstrated that DMF was well tolerated and showed sustained efficacy at Week 24 (double-blind period) and at Week 48 in East Asian participants with RRMS. These results were comparable to the registration studies conducted for DMF.

3.1.1. Rationale for Study Population

Although the complex and multifactorial pathogenesis of MS is considered to be generally similar across Caucasian and Asian populations, there are currently limited safety and tolerability, and efficacy data on DRF in the Asian population, including the East Asian MS populations. Therefore, additional data are warranted in this population. This Phase 3 study is designed to collect data in East Asian participants with RMS who are treated with DRF.

3.1.2. Rationale for Dosing Regimen

The DRF dosage selected for this study (231 mg twice daily for the first 7 days and 462 mg twice daily thereafter) is the approved dose regimen in the US for the treatment of patients with RMS and has been selected as the recommended dose in marketing applications to other health authorities. The doses of DRF to be used for initial dose titration (231 mg) and for treatment maintenance (462 mg) in this study are within the range of doses evaluated in completed Phase 1 studies.

As noted above, DRF shares the common active metabolite MMF with DMF. In the Phase 1 study of DRF and DMF in healthy volunteers (ALK8700-A103), at different strengths, DRF (462 mg) and DMF (240 mg) showed bioequivalent exposures of MMF and are therefore expected to have similar efficacy and safety profiles. Results of the DMF PK, safety, and tolerability study in Japanese, Chinese, and Caucasian adult healthy volunteers (Study 109HV108) indicate that the PK behavior of DMF across the 3 ethnic groups is similar and consistent with the observed exposure in mixed-race populations in previous studies with either healthy volunteers or MS patients. These observations further support the implementation of a 462 mg twice daily dosing regimen of DRF in the current study.

3.2. Background

3.2.1. Overview of Multiple Sclerosis

MS is a chronic inflammatory, demyelinating, and neurodegenerative disease of the CNS in which activated immune cells invade the CNS and cause inflammation, demyelination, axonal loss, and gliosis [Popescu 2013a; Popescu 2013b]. MS is the most common disabling neurological disease of young adults [Browne 2014], with first symptoms manifesting in approximately 70% of patients between 20 and 40 years of age [Flachenecker and Stuke 2008; Weinshenker 1989]. The disease is more common in women than men [Harbo 2013], and prevalence generally increases with latitude [Browne 2014]. MS is a major cause of the overall neurological disease burden [Group 2017], with approximately 2.3 million individuals affected worldwide and a median global MS prevalence of 33 per 100,000 [Browne 2014].

Most MS patients present initially with the CIS or relapsing-remitting form of the disease (85%), with relapses and remissions caused by focal demyelinating lesions, or “plaques,” disseminated in time and space in the CNS. About 10% to 15% of MS patients present with an insidious progressive course from onset, termed primary progressive MS [Hurwitz 2009]. Without treatment, RRMS in majority of patients evolves to secondary progressive MS characterized by progressive accrual of disability [Giovannoni 2016]. Physical disability typically manifests

within 15 to 20 years after presentation with MS [Tremlett 2010]. With treatment, the median life span of commercially insured MS patients in the US is approximately 6 years shorter than non-MS individuals from the same population [Kaufman 2014].

3.2.2. Current Therapies for Multiple Sclerosis

The current standard of care in relapsing MS uses 2 general approaches: (1) immunomodulatory drugs aimed at reducing the frequency and severity of relapses as well as the accumulation of physical disability and (2) drugs/interventions that provide symptomatic treatment as needed for depression, bladder dysfunction, mobility impairment, spasticity, and other common comorbidities/sequelae of MS disease. Immunomodulatory drugs currently available for MS vary by country and include interferon-beta products (Avonex®, Rebif®, Betaseron®/Betaferon®/Extavia®, and Plegridy®), GA (Copaxone®), fingolimod (Gilenya®), teriflunomide (Aubagio®), DMF (Tecfidera), natalizumab (Tysabri™), alemtuzumab (Lemtrada®), ocrelizumab (Ocrevus®), ofatumumab (Kesimpta®), mitoxantrone (Novantrone®), cladribine (Mavenclad®), and siponimod (Mayzent®).

3.2.3. Profile of Previous Experience With DRF

The primary evaluation of DRF efficacy is based on a PK bridging approach, which demonstrated comparable MMF PK parameters for DRF and DMF after oral administration of 462 mg and 240 mg, respectively. The PK bridging was established by generating comparative MMF bioavailability PK data for DRF and DMF under a number of dietary conditions in different clinical studies. Conditions were identified that resulted in MMF exposures that fell within the range of exposures generated when DMF was taken with and without food.

The effect of food on MMF PK after administration of DRF is nearly identical to the effect that food has on DMF PK. DRF and DMF produce bioequivalent exposure (AUC) of MMF across all tested dietary conditions, while the MMF C_{max} after DRF administration is within the C_{max} range determined for DMF.

The effect of food on MMF overall exposure (AUC) after DRF administration was similar to that of DMF. The impact of meal type on the MMF C_{max} was related to the fat or caloric content, as reflected by reductions of approximately 12%, 25%, and 44% with low-fat, medium-fat, and high-fat meals, respectively [TECFIDERA® USPI 2022].

In the ongoing open-label Study ALK8700-A301 (N = 1057 participants received study treatment) evaluating the long-term effects of DRF in participants with RRMS, interim results have shown that DRF is generally well tolerated for up to 96 weeks, and no new safety signals have been identified. In a completed Phase 3 study, Study ALK8700-A302 (N = 504 participants received study treatment), which was a randomized, double-blind, controlled study, the GI tolerability of DRF and DMF in participants with RRMS was compared. The results have shown that the duration, incidence, and severity of participant-reported GI symptoms were significantly lower in the group treated with DRF compared with the group treated with DMF.

See the Investigator's Brochure for detailed information on relevant nonclinical and clinical studies.

3.3. Benefit-Risk Assessment

The potential risks related to participation in this study are justified by the anticipated benefit to participants.

Detailed information about the known and expected benefits and risks and reasonably expected AEs of DRF is provided in the Investigator's Brochure and ICF. A high-level summary of those benefits and risks known during study design is provided here.

The safety profile of DRF relies on the well-known safety profile of the reference drug, DMF.

The safety of DMF has been established in 2 randomized, placebo-controlled, double-blind, pivotal Phase 3 studies (Study 109MS301 and Study 109MS302) and further established in extensive postmarketing experience. Flushing and GI events (abdominal pain, nausea, diarrhea, and vomiting) were among the most commonly experienced AEs with DMF in the 2 pivotal Phase 3 studies [Phillips 2017]. Study 109MS305 showed that DMF had an acceptable safety profile in East Asian participants that was consistent with the profile established in the studies with global participants. Important identified risks for DMF and, hence, DRF include decreases in lymphocyte counts and PML. Data from DRF studies have shown comparability to the DMF safety profile, with no new safety issues identified to date.

In Study ALK8700-A302, which was a 5-week prospective, randomized, blinded control study in participants with RRMS that formally explored differences in GI tolerability between DRF (N = 253) and DMF (N = 251), the duration, incidence, and severity of participant-reported GI symptoms were significantly lower across a multitude of endpoints (including the primary endpoint) in the group of participants treated with DRF compared with the group of participants treated with DMF. The incidence of GI AEs in the DRF group was lower compared with the DMF group (34.8% and 49.0%, respectively), and discontinuations during the Treatment Period due to GI events were also notably less in the DRF group compared with the DMF group (0.8% and 4.8%, respectively) [Naismith 2020]. In Study ALK8700-A301 (N = 1057), interim results showed that DRF is generally well tolerated for up to 96 weeks, and no new safety signals have been identified. The incidence of GI AEs in de novo recruited participants at Week 24 was 27.5%. [redacted]

These results from the Phase 3 DRF studies support a favorable safety and efficacy profile in patients with RRMS. It is anticipated that the above favorable results reported in global Phase 3 studies with DRF will also benefit participants who receive DRF treatment in this study.

4. STUDY OBJECTIVES AND ENDPOINTS

Table 3: Part 1 Study Objectives and Endpoints

Primary Objective	**Primary Endpoints**
To determine the safety and tolerability of DRF administered for up to 24 weeks in adult East Asian participants with RMS	• Incidence of AEs and SAEs at Week 24 • Quantitative and qualitative changes from Baseline Visit (Day 1) to Week 24 in clinical laboratory parameters, ECGs, and vital signs • Incidence of C-SSRS events at Baseline Visit (Day 1) and through Week 24
Secondary Objective	**Secondary Endpoints**
To evaluate the PK of DRF metabolites (MMF and HES) following multiple doses of DRF in a subset of adult East Asian participants with RMS	• Plasma concentrations of MMF and HES • Noncompartmental plasma PK parameters of MMF and HES, including the following: – C_{max} – AUC_{last} – T_{max} – $t_{½}$ (MMF only)
[redacted]	

[redacted]

Table 4: Part 2 Study Objective and Endpoints

Primary Objective	Primary Endpoints
To determine the safety and tolerability of DRF administered for up to 48 weeks in adult East Asian participants with RMS	• Incidence of AEs and SAEs up to Week 48 • Quantitative and qualitative changes from Baseline Visit (Day 1) to Week 48 in clinical laboratory parameters, ECGs, and vital signs • Incidence of C-SSRS events at Baseline Visit (Day 1) and through Week 48

[redacted]

5. STUDY DESIGN

5.1. Study Overview

This is a multicenter, open-label, single-arm, Phase 3 study to evaluate the safety and tolerability, and PK of DRF administered orally to East Asian participants with RMS. This study will be conducted in 2 parts:

Part 1 is designed to evaluate the PK, safety, and tolerability of DRF administered orally.

Part 2 is designed as a 24-week safety extension period in participants from Part 1.

Study assessments conducted at each visit are listed in Table 1.

After eligibility for the study has been confirmed during Screening, all eligible, consenting participants will begin open-label treatment at the Baseline Visit (Day 1). Participants will initiate treatment with DRF 231 mg twice daily on Day 1 through Day 7, followed by 462 mg twice daily from Day 8 onwards, with allowable dose reduction for tolerability from Day 8 onwards. Study staff will administer the first dose of DRF at the Baseline Visit (Day 1).

Starting on Day 8 of treatment, dose reduction to DRF 231 mg twice daily is permitted at the Investigator's discretion for participants who are unable to tolerate DRF 462 mg twice daily due to flushing or GI disturbances. Once a participant has stabilized after dose reduction, attempts should again be made to achieve and maintain the target maintenance dose of DRF 462 mg twice daily. If a participant remains unable to tolerate DRF 462 mg twice daily after 1 month on treatment, further dose reduction will not be permitted, and the participant will be discontinued from the study.

Participants will undergo periodic safety assessments that are scheduled every 2 weeks up to Week 4 and then every 4 weeks until the end of the Treatment Period at Week 48 (Visit 14) and will have a Safety Follow-Up Visit 2 weeks later at Week 50 (Visit 15).

Any participant who prematurely discontinues study treatment or withdraws from the study will be asked to return to the clinic to complete all study assessments for Visit 14/ET Visit and for the Safety Follow-Up Visit 2 weeks later (Visit 15).

Participants who complete the study or who terminate the study early and have a last measured lymphocyte count < LLN will return to the clinic for additional LM visits every 2 months starting from Visit 15 (or from the ET visit for participants who terminate the study early) for a period of 6 months (i.e., a maximum of 3 visits), until lymphocyte counts reach normal limits (≥ LLN), or the participant commences therapy with another DMT, whichever occurs first (Table 2).

At every visit (excluding Visits 14 and 15), the study staff will dispense DRF for participants' self-administration. Participants will be instructed to take study treatment with or without food.

Intensive blood samples will be collected predose (-30 to 0 minutes predose) and at various timepoints postdose (0.5, 1, 2, 3, 4, 6, and 8 hours postdose) at any timepoint in the period between Week 4 (Day 29, Visit 3 ± 3 days) and Week 24 (Day 169, Visit 8 ± 5 days), both inclusive, for 7 Japanese participants who will take DRF after 10 hours of fasting, and no food will be allowed for at least 4 hours after the dose of DRF. Participants will be allowed water ad libitum, except for 1 hour before and 2 hours after administration of the dose of DRF. Sparse blood samples will be collected for all remaining participants (as well as for those participants who are enrolled both in the intensive PK and the sparse PK cohorts) predose (-30 to 0 minutes predose) and 2 to 3 hours postdose on Day 29 (Visit 3) and Day 57 (Visit 4).

Participation in the sparse PK cohort does not preclude enrollment in the intensive PK cohort as well. In the event that a participant is enrolled in both the sparse and intensive PK cohorts and intensive PK sampling was completed on Day 29 or Day 57 for a participant, sparse PK sampling will not be required for those days. However, if it is determined that intensive PK is not feasible by Day 57, sparse PK sampling will be completed according to protocol and intensive PK should be completed at later visits.

See Figure 1 for a schematic of the study design.

5.2. Study Duration for Participants

Study duration for participants who complete the study will be up to 54 weeks:

- 4-week Screening Period
- 24-week Treatment Period in Part 1
- 24-week Treatment Period in Part 2
- 2-week Safety Follow-Up Period

During Part 1, participants will have up to 8 visits during the Treatment Period (i.e., Baseline Visit [Day 1], Week 2, Week 4, Week 8, Week 12, Week 16, Week 20, and Week 24) and will be contacted via telephone twice.

During Part 2, participants will report to the study site every 4 weeks up to Week 48 during the Treatment Period, for a total of 7 visits, and will have the Safety Follow-Up Visit 2 weeks later (Week 50) after the end of the Treatment Period.

All visits should be performed within the time frame from the nominal visit day, as shown in Table 1. Visit days are calculated with respect to Day 1 (the date of first dose).

The end of study date for a participant may be the last study visit, last follow-up telephone conversation, or last protocol-specified assessment; if the participant has ongoing AEs that are being followed, the date may be the date of AE resolution.

5.3. Study Stopping Rules

The Sponsor may terminate this study at any time, after informing Investigators. The Sponsor will notify Investigators when the study is to be placed on hold, completed, or terminated.

5.4. Unscheduled Visits

Data collected during unscheduled visits should be recorded on CRFs only if the data support protocol objectives and/or are required for safety monitoring.

[redacted]

5.5. End of Study

The end of study is last participant, last visit for final collection of data.

6. STUDY POPULATION

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

6.1. Inclusion Criteria

1. Ability of the participant to understand the purpose and risks of the study, to provide informed consent, and to authorize the use of confidential health information in accordance with national and local privacy regulations.

2. Male and female participants aged 18 to 65 years old, inclusive, at the time of informed consent.

   - For participants in Japan aged < 20 years, written informed consent should be obtained from the participant and their legally acceptable representative.

   - Informed consent from a legally acceptable representative is not mandatory if the participant is classified as an adult based on the latest applicable local laws.

3. All women of childbearing potential and all men must practice contraception during the study and for at least 30 days after their last dose of study treatment (see Section 11.5). In addition, participants should not donate sperm or eggs during the study and for at least 30 days after their last dose of study treatment.

4. Must have a diagnosis of RMS, as defined by revised 2017 McDonald's criteria [Lublin 2014; Thompson 2018].

5. EDSS score between 0.0 and 5.0, inclusive, at Screening and Baseline Visit (Day 1).

6. Neurologically stable with no evidence of relapse within 30 days prior to Baseline Visit (Day 1).

7. For Japanese participants:

   a. Was born in Japan and biological parents and grandparents were of Japanese origin. If previously lived outside of Japan for more than 5 years, must not have had a significantly modified diet since leaving Japan.

8. For Chinese participants:

   a. Was born in China, and biological parents and grandparents were of Chinese origin. If previously lived outside of China for more than 5 years, must not have had a significantly modified diet since leaving China.

6.2. Exclusion Criteria

Medical History and Current Health Status

1. Has an MS relapse that has occurred within the 30 days prior to randomization and/or the participant has not stabilized from a previous relapse prior to randomization.

2. History of any clinically significant cardiac, endocrinologic, hematologic, hepatic, immunologic, infectious, metabolic, urologic, pulmonary, neurologic, dermatologic, psychiatric, and renal or other major disease that would preclude participation in a clinical trial, as determined by the Investigator.

3. History of severe allergic or anaphylactic reactions or of any allergic reactions that, in the opinion of the Investigator, are likely to be exacerbated by any component of the study treatment.

4. History of, or ongoing, malignant disease, including solid tumors and hematologic malignancies (with the exception of basal cell carcinomas and squamous cell carcinomas of the skin that have been completely excised and considered cured at least 1 year prior to Day -1). Participants with cancers in remission for greater than 5 years prior to Baseline Visit (Day 1) may be included after discussion with/approval by the Sponsor.

5. Has a history of GI surgery (except appendectomy or cholecystectomy that occurred more than 6 months prior to Screening), irritable bowel syndrome, inflammatory bowel disease (Crohn's disease, ulcerative colitis), or other clinically significant and active GI condition per the Investigator's discretion.

6. History of clinically significant recurring or active GI symptoms (e.g., nausea, diarrhea, dyspepsia, constipation) within 90 days of Screening, including symptoms that require the initiation of symptomatic medical treatment (e.g., initiation of a medication to treat gastroesophageal reflux disease) or a change in symptomatic medical treatment (e.g., an increase in dose) within 90 days prior to Screening.

7. Participant has a mental or physical condition that would preclude performing [redacted] and safety assessments.

8. Systolic blood pressure > 150 mmHg or < 90 mmHg after sitting for 5 minutes at Screening or prior to dosing. If out of range, testing may be repeated once at Screening and once prior to dosing. Participants must not be dosed if the repeated value is still out of range.

9. Participant has second- or third-degree atrio-ventricular block or sick sinus syndrome, uncontrolled atrial fibrillation, severe or unstable angina, congestive heart failure, myocardial infarction within 3 months of the Screening visit, or significant ECG abnormality, including QTc > 450 msec (males) or 470 msec (females), where QTc is based on Fridericia's correction method.

10. Plans to undergo elective procedures or surgeries at any time after signing the ICF through the Follow-Up Visit.

11. Any condition affecting study treatment absorption (e.g., gastrectomy).

12. History of sensitivity to heparin or heparin-induced thrombocytopenia.

13. History of systemic hypersensitivity reaction to DRF, DMF, MMF or other fumaric esters, the excipients contained in the formulation, and if appropriate, any diagnostic agents to be administered during the study.

14. Participant has an abnormality that the investigator deems to be clinically significant on medical history, physical examination, ECG, or a diagnostic laboratory test that may confound study results or pose risk to the subject through participation in the study, in the opinion of the Investigator.

Infection Risk

15. Evidence of current SARS-CoV-2 infection within 14 days prior to Screening, between Screening and Baseline Visit (Day 1), or at Baseline Visit (Day 1), including but not limited to a fever (temperature > 37.5°C), new and persistent cough, breathlessness, or loss of taste and/or smell.

Note: If a SARS-CoV-2 test (PCR or other regulatory approved method) is performed per the discretion of the Investigator in accordance with local site practice, the test result must be negative in order for the participant to be enrolled in the trial.

Participants with evidence of current SARS-CoV-2 infection within 14 days prior to Screening or during Screening, will be eligible for rescreening, provided that the participant is asymptomatic for 14 days prior to rescreening.

16. Have close contact within 14 days prior to Day 1 with individual(s) with suspected SARS-CoV-2 infection. Close contact is defined as:
    a. face-to-face contact with a probable or confirmed case within 1 meter and for at least 15 minutes;
    b. direct physical contact with a probable or confirmed case;
    c. direct care for a patient with probable or confirmed COVID-19 disease without the use of recommended PPE; or
    d. other situations as indicated by local risk assessments.

Participants who had close contact with individual(s) with suspected SARS-CoV-2 infection within 14 days prior to Day 1, as determined by the Investigator, will be eligible for rescreening, provided that the participant is asymptomatic for 14 days after the contact.

17. History or positive test result at Screening for HIV.

18. Current hepatitis C infection (defined as positive HCV antibody and detectable HCV RNA). Participants with positive HCV antibody and undetectable HCV RNA are eligible to participate in the study (United States Centers for Disease Control and Prevention).

19. Current hepatitis B infection (defined as positive for HBsAg and/or total anti-HBc). Participants with immunity to hepatitis B from previous natural infection (defined as

negative HBsAg, positive anti-HBc, and positive anti-HBs) or vaccination (defined as negative HBsAg, negative anti-HBc, and positive anti-HBs) are eligible to participate in the study.

20. Chronic, recurrent, or serious infection (e.g., pneumonia, septicemia) within the 90 days prior to Baseline Visit (Day 1).

21. Participants with any of the following TB-related criteria:
    a. Active TB infection.
    b. History of active TB infection involving any organ system or findings in other organ systems consistent with TB, unless adequately treated according to WHO/CDC therapeutic guidance and proven to be fully recovered upon consult with a TB specialist.
    c. Latent TB infection (defined as a confirmed positive IGRA result or 2 successive indeterminate IGRA results) unless appropriate prophylaxis is initiated at least 4 weeks prior to study medication dosing on Baseline Visit (Day 1) and will be continued to completion of prophylaxis.
22. Symptoms of bacterial, fungal, or viral infection(s) (including upper respiratory tract infection) within 28 days prior to Baseline Visit (Day 1), unless the participants recovered completely prior to Baseline Visit (Day 1) and the infections were considered mild per Investigator's judgment. Participants who have not recovered prior to Baseline Visit (Day 1), as judged by the Investigator, will be eligible for rescreening.

Medications

23. Previous participation in this study or previous studies with DRF, DMF, or MMF.

24. Use of any traditional and/or unlicensed medicines and/or therapies and/or herbal preparations, which are known or considered by the treating neurologist to affect MS and endpoints that are being considered in the study, including safety, PK, and [redacted].

25. Participant received treatment with opioids within 28 days prior to the screening visit.

26. Any live or attenuated immunization or vaccination given within 28 days prior to Baseline Visit (Day 1) or planned to be given during the study period.

27. Has a history of treatment with or has received the following:
    a. Total lymphoid irradiation, cladribine, T-cell or T-cell receptor vaccination, or total body irradiation at any time
    b. Stem cell transplantation at any time
    c. Mitoxantrone or other immunosuppressant agents (e.g., cyclosporine, cyclophosphamide, methotrexate, mycophenolate) within 12 months prior to Baseline Visit (Day 1); azathioprine within 6 months prior to Baseline Visit (Day 1).
    d. Treatment with any of the following medications or procedures within 6 months prior to Baseline Visit (Day 1): plasmapheresis, IV immunoglobulin, or cytapheresis

e. Teriflunomide within 12 months of Baseline Visit (Day 1), unless the serum/plasma concentration of teriflunomide is < 0.020 µg/mL (< 20 ng/mL) prior to Baseline Visit (Day 1) or an accelerated elimination procedure for teriflunomide with cholestyramine is successfully completed during screening.
f. Natalizumab within 60 days prior to Baseline Visit (Day 1)
g. Any prior use of alemtuzumab
h. S1P receptor modulators (fingolimod, siponimod or ozanimod) within 90 days prior to Baseline Visit (Day 1)
i. B-cell targeted therapies for the treatment of MS (e.g., ocrelizumab, rituximab) within 12 months prior to Baseline Visit (Day 1). Participants who have received B-cell targeted therapies more than 12 months prior to Baseline Visit (Day 1) will require CD19 testing to confirm that CD19 cells have returned to within normal range. Participants who have received B-cell targeted therapies less than 12 months prior to Baseline Visit (Day 1) will be excluded from the study.
j. Has previously discontinued treatment with Tecfidera due to tolerability issues and/or lack of efficacy
k. Eligibility related to prior treatment with an investigational drug and/or a commercially available drug for the treatment of MS not listed above within the past 2 years will be determined on a case-by-case basis by the Medical Monitor
l. Steroids, with the exception of topical or inhaled steroids within 30 days prior to Baseline Visit (Day 1)

Laboratory Values

28. Clinically significant abnormal laboratory test values (those that may confound study results or pose risk to the subject through participation in the study), as determined by the Investigator, at Screening or Baseline Visit (Day 1).

29. Has any of the following abnormal blood tests at Screening:

    a. ALT, AST, or GGT ≥ 3 × ULN or bilirubin > 2 × ULN.
    b. TSH level > 10% of the ULN
    c. eGFR ≤ 60 mL/min/1.73 m^2 (using the Chronic Kidney Disease Epidemiology Collaboration equation) [Levey 2009]
    d. Lymphocyte count < LLN

30. Has any of the following abnormal urine tests at Screening:

    a. Beta-2 microglobulin > 0.3 µg/mL
    b. Albumin to creatinine ratio > 22.6 mg/mmol

For the parameters listed in Exclusion Criteria 29d and 30, out-of-range values that are clinically not significant, as determined by the Investigator, may be repeated once, and the participant may be enrolled only if the repeated value is within the normal range.

Other

31. Blood donation (1 unit or more) within 90 days prior to Screening, plasma donation within 1 week prior to Screening, and platelet donation within 6 weeks prior to Screening.

32. History of alcohol or substance abuse within the past year (as determined by the Investigator).

33. Participants who are pregnant or currently breastfeeding and those intending to become pregnant or begin breastfeeding at any point during the study and for 30 days after completing study treatment.

34. Current or prior participation in a clinical trial within 90 days of Screening. Participants who have previously participated in a clinical trial but have not received any IMP treatment within 90 days of Screening will be eligible if the Investigator confirms that the participant meets all other Inclusion and Exclusion criteria and there are no other safety concerns.

35. Has a clinically significant history of suicidal ideation or suicidal behavior occurring in the past 12 months as assessed by the C-SSRS at Screening.

36. Unwillingness or inability to comply with study requirements.

37. Other unspecified reasons that, in the opinion of the Investigator or Sponsor, make the participant unsuitable for enrollment.

6.3. Screening, Retesting, and Screen Failures

6.3.1. Screening

Once informed consent is obtained, screening assessments can occur. At this time, a unique identification number is assigned that will be used on study-related documents pertaining to the participant. Any identification numbers that are assigned will not be reused, even if the participant does not receive treatment or continue in the study. Study sites are required to document all screened participants initially considered for inclusion in the study.

The screening period can be extended up to a maximum of 42 days (i.e., an additional 2 weeks) with prior approval of the medical monitor if the testing of teriflunomide levels or confirmation of accelerated elimination (per exclusion criterion 27e; Section 6.2) or minimum of 4 weeks' TB prophylaxis (per exclusion criterion 21c; Section 6.2) cannot be completed within the 28-day screening period.

6.3.2. Retesting

For the parameters listed in exclusion criteria 29d and 30, out-of-range values that are not clinically significant, as determined by the Investigator, may be repeated once, and the participant may be enrolled only if the repeated value is within the normal range.

Participants who have abnormal laboratory test values as described in exclusion criteria 29a, 29b, and 29c should not be retested.

6.3.3. Screen Failures

Screen failures are defined as participants who sign the ICF but are not subsequently dosed. If a participant is considered a screen failure, the reasons for exclusion must be documented in the participant's source documents and on the screening log. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

All participants with incomplete enrollment due to a public health emergency (e.g., travel restrictions, participants who recovered after getting infected) will be eligible for rescreening provided that the participants met all eligibility criteria during the initial screening period, and that the reason for rescreening is incomplete enrollment due to a public health emergency. These participants will be reported as screen failed and then rescreened. Participants may have been provided with a unique identification number during Screening. The previously issued unique identification number will no longer be used, and a separate unique identification number will be provided during rescreening.

7. STUDY TREATMENT

7.1. Regimen

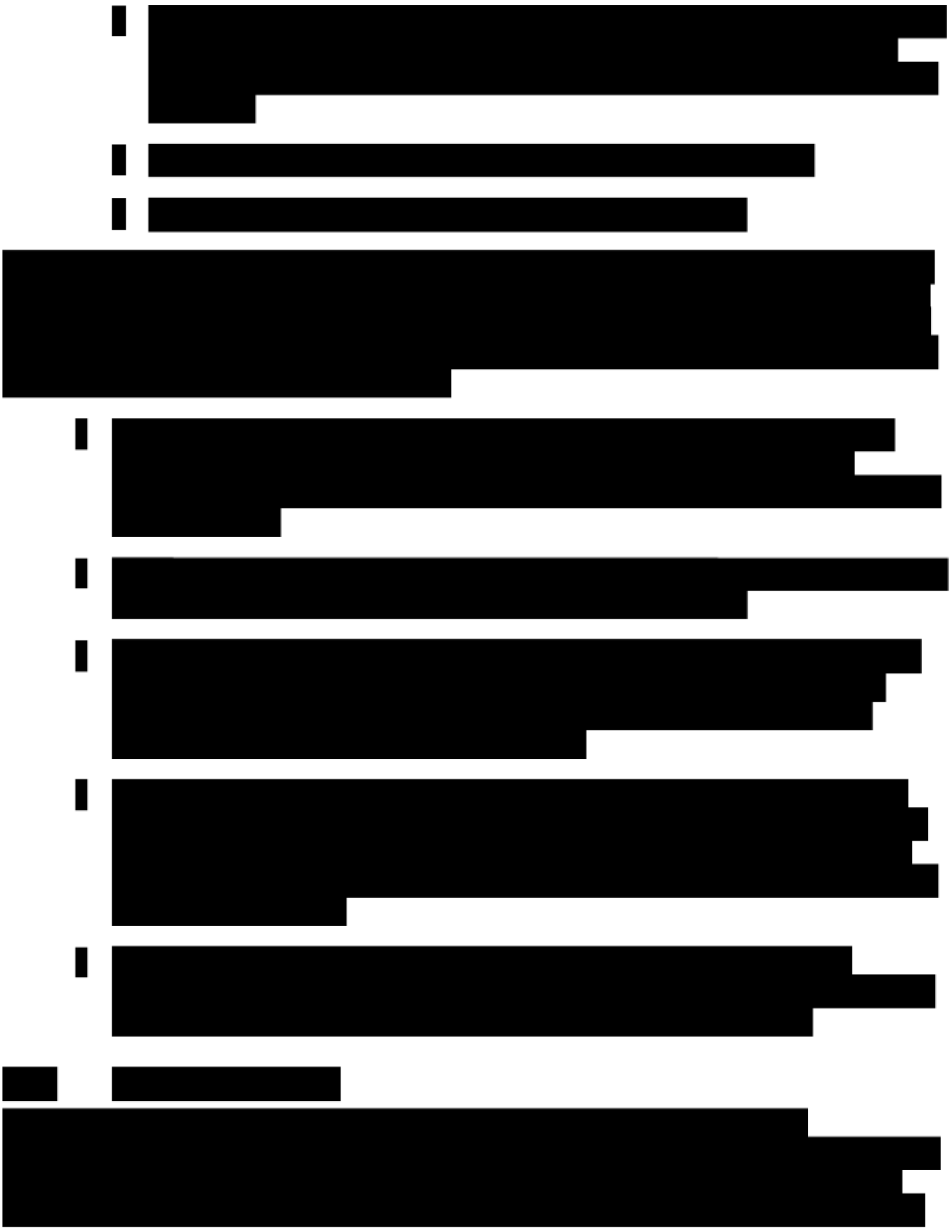
Refer to and follow the DHA.

Participants will initiate treatment with DRF 231 mg twice daily on Day 1 through Day 7, followed by 462 mg twice daily from Day 8 onwards, with allowable dose reduction for tolerability from Day 8 onwards. Study staff will administer the first dose of DRF at the Baseline Visit (Day 1).

If a participant misses a dose, doses should not be doubled up to make up for the missed dose. The participant may take the missed dose only if they leave 6 hours between doses. If the participant does not remember to take the dose within 6 hours, this dose should be skipped, and the next dose should be taken as scheduled.

7.2. Modification of Dose and/or Treatment Schedule

Starting on Day 8 of treatment, dose reduction to DRF 231 mg twice daily is permitted at the Investigator's discretion for participants who are unable to tolerate DRF 462 mg twice daily due to flushing or GI disturbances. Once a participant has stabilized after dose reduction, attempts should again be made to achieve and maintain the target maintenance dose of DRF 462 mg twice daily. If a participant remains unable to tolerate DRF 462 mg twice daily after 1 month on treatment, further dose reduction will not be permitted, and the participant will be discontinued from the study.



[redacted]

7.3. Study Treatment Management

Study treatment will be manufactured, handled, and stored in accordance with applicable Good Manufacturing Practice.

Site staff should follow the DHA for specific instructions on the handling, preparation, administration, and disposal of the study treatment. The DHA aligns with all other references, including the protocol.

Study treatment must be dispensed only by a pharmacist or appropriately qualified staff. Study treatment is to be dispensed only to participants enrolled in this study. Once study treatment is prepared for a participant, it can be administered only to that participant.

7.3.1. DRF

DRF is formulated as enteric-coated minitablets in HPMC capsules for oral administration. Each capsule consists of [redacted] minitablets and contains 231 mg DRF. DRF is a white to off-white powder.

DRF delayed-release capsules are supplied in 120-count, 200 cc HDPE bottle configuration.

The contents of the DRF label will be in accordance with all applicable regulatory requirements. At a minimum, the label will include a study reference code, study treatment identifier, quantity of dosage units, lot number, and other pertinent information in accordance with local law. The expiry or use-by date is stored in the IRT system, and printable assignment reports are available to site staff. Study treatment should not be used after the expiry or use-by date.

7.3.1.1. Preparation

The individual preparing DRF should carefully review the instructions provided in the DHA.

If the packaging is damaged, or if there is anything unusual about the appearance or attributes of the bottles or the capsules, do not use the capsules. The bottle in question should be saved at the study site and the problem immediately reported to the Sponsor.

Contact information for reporting a problem is provided in the Study Reference Guide.

7.3.1.2. Storage

DRF is to be stored at room temperature (not to exceed 25°C) in a monitored and locked cabinet, with limited access. For the most up-to-date storage requirements, follow the instructions provided in the DHA.

7.3.1.3. Handling and Disposal

The Investigator must return all used and unused bottles of DRF as instructed by the Sponsor unless approved for onsite destruction.

If any DRF supplies are to be destroyed at the study site, the institution or appropriate site staff must obtain prior approval from the Sponsor, by providing, in writing, the destruction policy or details of the method of destruction. After such destruction, the Sponsor must be notified, in writing, of the details of the study treatment destroyed (e.g., lot or kit numbers, quantities), the date of destruction, and proof of destruction.

7.3.1.4. Accountability

Accountability for study treatment is the responsibility of the Investigator. The study site must maintain accurate records demonstrating dates and amount of study treatment received, to whom dispensed, amount returned by the participant, and accounts of any study treatment accidentally or deliberately destroyed or lost.

Unless otherwise notified, all bottles both used and unused, must be saved for study treatment accountability. By the end of the study, reconciliation must be made among the amount of DRF supplied, dispensed, and subsequently destroyed, lost, or returned to the Sponsor. A written explanation must be provided for any discrepancies.

7.4. Blinding Procedures

This is an open-label study.

7.5. Precautions

Medications for the treatment of severe hypersensitivity reactions (e.g., epinephrine for SC injections, diphenhydramine for injection) must be available for immediate use.

See the DHA for detailed instructions.

7.6. Compliance

Compliance with treatment dosing is to be monitored and recorded by site staff.

7.7. Concomitant Therapy and Procedures

7.7.1. Concomitant Therapy

A concomitant therapy is any drug or substance administered between the participant's Baseline Visit (Day 1) and last study visit.

7.7.1.1. Allowed Concomitant Therapy

Participants should be instructed to contact their Investigators before taking any new medications, including nonprescription drugs and herbal preparations.

Symptomatic therapy such as treatment for spasticity, depression, or fatigue is not restricted but should be optimized as early as possible during screening to maintain consistent treatment for the duration of the study.

7.7.1.2. Disallowed Concomitant Therapy

Concomitant treatment with any of the following is not allowed while receiving study treatment, unless approved by the Medical Monitor:

- Any opioids.
- Any alternative drug treatments directed toward the treatment of MS such as long-term immunosuppressant therapy or other immunomodulatory treatments (including but not limited to IFN-β, IFN-α, GA, natalizumab, alemtuzumab, B-cell depleting agents, cyclophosphamide, methotrexate, azathioprine, mycophenolate mofetil, DMF, teriflunomide, 4-aminopyridine, S1P receptor modulators such as fingolimod, or related products).
- Any investigational product, including investigational symptomatic therapies for MS and investigational therapies for non-MS indications.
- Any systemic steroid therapy including, but not limited to, oral corticosteroids (e.g., prednisone) or periodic (e.g., monthly) treatment with IVMP. Systemic steroid therapy is permissible for the treatment of [redacted] as per local regulations and/or prescribing practice, for up to 5 days maximum duration. Refer to Section 7.2.2 for allowed use of treatments for [redacted]. Steroids that are administered by nonsystemic routes (e.g., topical, inhaled) are allowed.
- Any live or attenuated immunization or vaccination.
- Total lymphoid radiation, cladribine, T-cell or T-cell receptor vaccination, any therapeutic monoclonal antibody, mitoxantrone, cyclosporine, IV immunoglobulin, plasmapheresis, or cytapheresis.

If another MS treatment is initiated (or if DRF is restarted) before the lymphocyte count returns to LLN during the protocol-required ALC follow-up monitoring period, the participant must be discontinued from the study.

Participants who receive any of these restricted medications without approval from the Medical Monitor will be required to permanently discontinue study treatment and will be withdrawn from the study as described in Section 8.3. Participants who initiate a protocol-defined disallowed concomitant therapy must complete an ET Visit and withdraw from the study.

7.7.2. Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed between the time of the participant's Baseline Visit and last study visit.

7.8. Continuation of Treatment

No further provisions are made for access to the study treatment.

8. DISCONTINUATION OF STUDY TREATMENT AND WITHDRAWAL OF PARTICIPANTS FROM THE STUDY

8.1. Discontinuation of Study Treatment

A participant must permanently discontinue study treatment for any of the following reasons:

- The participant becomes pregnant. Study treatment must be discontinued immediately (Note: Instructions for reporting the pregnancy are provided in Section 11.4.1).
- The participant withdraws consent to continue study treatment.
- The participant experiences an AE that requires permanent discontinuation of study treatment.
- The participant is unwilling or unable to comply with the protocol.
- At the discretion of the Investigator for medical reasons.
- At the discretion of the Sponsor or upon request of a regulatory authority.
- Lymphocyte count $< 0.5 \times 10^3/\mu L$ persisting for > 6 months. An initial lymphocyte count $< 0.5 \times 10^3/\mu L$ should be confirmed by repeat testing. If the value remains $< 0.5 \times 10^3/\mu L$ for > 6 months, the participant must permanently discontinue study treatment. Participants who permanently discontinue the study with a last measured lymphocyte count < LLN will require additional follow-up to monitor their lymphocyte counts; see Table 2.

The reason for discontinuation of study treatment must be recorded in the CRF.

In addition to the reasons provided above for permanent discontinuation of study treatment, study treatment must be temporarily withheld if any of the following laboratory parameters meet the following threshold limits:

- AST or ALT > 3 × ULN; confirmed by repeat testing. If the value remains > 3 × ULN for ≥ 4 weeks after interruption of study treatment, the participant must permanently discontinue study treatment.
- eGFR < 60 mL/min/1.73 m^2; confirmed by repeat testing as soon as possible. If the eGFR remains < 60 mL/min/1.73 m^2 for ≥ 4 weeks after interruption of study treatment, the participant must permanently discontinue study treatment.
- Urine albumin to urine creatinine ratio > 22.6 mg/mmol; confirmed by repeat testing as soon as possible. If the urine albumin to urine creatinine ratio remains > 22.6 mg/mmol for ≥ 4 weeks after interruption of study treatment, the participant must permanently discontinue study treatment.

Resuming study treatment after it has been temporarily withheld is to be considered on a case-by-case basis and must be discussed with the Medical Monitor.

8.2. Lost to Follow-Up

Participants will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and are unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the study.

- In cases in which the participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant. These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, that participant will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8.3. Withdrawal of Participants from the Study

Participants must be withdrawn from the study for any one of the following reasons:

- The participant withdraws consent for participation in the study.

- The participant enrolls into another interventional clinical study in which an investigational treatment or approved therapy for investigational use is administered.

- The participant is unwilling or unable to comply with the protocol.

The primary reason for the participant's withdrawal from the study must be recorded in the participant's CRF. Any participant who prematurely discontinues study treatment or withdraws from the study will be asked to return to the clinic to complete all study assessments for Visit 14/ET Visit as well as the Safety Follow-Up Visit 2 weeks later (Visit 15).

Participants should undergo an ET visit unless withdrawal is due to death or withdrawal of consent. Participants who withdraw from the study for reasons other than safety may be replaced at the discretion of the Sponsor.

Participants with intense PK sampling who withdraw early or require dose reduction or samples not collected per protocol or laboratory manual, may be replaced at the discretion of the Sponsor.

9. [redacted], PHARMACOKINETIC, AND PHARMACODYNAMIC ASSESSMENTS

See Section 1.3 for the timing of all assessments.

Tests and evaluations affecting primary endpoints and/or analyses may need to be repeated if the original results are lost or damaged. In these cases, participants will be asked to return to the study site to have the evaluations repeated.

[redacted]

9.3. Pharmacokinetic Assessments

The subset of 7 Japanese participants must be in the overnight fasted state (10 hours) prior to administration of the dose of DRF on study Day 29, and no food will be allowed for at least 4 hours after the dose of DRF. Participants will be allowed water ad libitum, except for 1 hour before and 2 hours after administration of the dose of DRF.

For the subset of 7 Japanese participants with intensive blood sample collection for PK analysis of metabolites MMF and HES, samples will be obtained at the following:

- -30 to 0 minutes (predose) and at 0.5, 1, 2, 3, 4, 6, and 8 hours (postdose)
- For intensive PK sampling for MMF and HES, noncompartmental plasma PK parameters (AUC_{last}, C_{max}, t_{max}, and $t_{½}$ [MMF only]) will be calculated. The PK parameters (AUC_{last}, C_{max}, t_{max}) for MMF and HES in Study 272MS303 will be compared with those in Study ALK8700-A301.

In addition, sparse blood samples will be collected for PK analysis of the metabolites MMF and HES as follows:

- On Day 29, blood samples will be collected -30 to 0 minutes (predose) and 2 to 3 hours (postdose) for participants with sparse blood sample collection (approximately 43 per Japanese cohort and 50 per Chinese cohort).
- On Day 57, blood samples will be collected -30 to 0 minutes (predose) and 2 to 3 hours (postdose) for all participants with sparse blood sample collection (approximately 50 per cohort).
- Participation in the sparse PK cohort does not preclude enrollment in the intensive PK cohort as well. In the event that a participant is enrolled in both the sparse and intensive PK cohorts and intensive PK sampling was completed on Day 29 or Day 57 for a participant, sparse PK sampling will not be required for said days. However, if it is determined that intensive PK is not feasible by Day 57, sparse PK sampling will be completed according to protocol and intensive PK should be completed at later visits.

The PK sample volume will be approximately 6 mL for each individual sample. For the intensive PK sampling group, there are a maximum of 10 PK sample collection timepoints planned (8 timepoints on Day 29 for the intensive PK sampling and 2 timepoints on Day 57 for the sparse PK sampling). In the advent that intensive PK sampling is not feasible by Day 57, there are a maximum of 12 PK sample collection timepoints planned (2 timepoints on Day 29 and on Day 57 for the sparse PK sampling, respectively and 8 timepoints for the intensive PK sampling at a later visit). Therefore, the maximum PK sample volume for a given participant in the intensive PK sampling group will be approximately 72 mL. This volume will be lower for patients participating only in the sparse PK sample collection and will be approximately 24 mL (2 samples on Day 29 and 2 samples on Day 57).

10. SAFETY ASSESSMENTS

See Section 1.3 for the timing of all safety assessments.

Tests and evaluations affecting primary endpoints and/or analyses may need to be repeated if the original results are lost or damaged. In these cases, participants will be asked to return to the study site to have the evaluations repeated.

10.1. Clinical Safety Assessments

The following clinical assessments will be performed to evaluate the safety profile of DRF:

- AE and SAE recording
- Medical history
- Physical examinations: Full physical examinations will be performed at Screening. An abbreviated physical examination (i.e., examination of general appearance and the following body systems: lymph nodes, thorax and lungs, cardiovascular system, abdomen, and skin) will be performed at other timepoints.
- Vital sign measurements: temperature, pulse rate, systolic and diastolic blood pressure, and respiratory rate
- Weight and height measurements
- 12-lead ECGs
- C-SSRS
- Concomitant therapy and procedure recording

10.2. Laboratory Safety Assessments

Samples will be analyzed using Good Laboratory Practice-validated assays.

The following laboratory assessments will be performed to evaluate the safety profile of DRF:

Table 5: Clinical Laboratory Assessments

Hematology[1]	Biochemistry	Urinalysis
Hematocrit	Sodium	Color
Hemoglobin	Potassium	pH
Red blood cell count	Chloride	Specific gravity
Total and differential (absolute) white blood cell count	Bicarbonate	Ketones
Platelets	Glucose	Protein
	Calcium	Glucose
	Uric acid	Bilirubin
	Creatinine[2]	Nitrite
	Total protein	Urobilinogen
	Blood urea nitrogen	Occult blood
	Albumin	Microscopic examination of sediment *only if urinalysis dipstick results are abnormal*
	Total bilirubin	Urine albumin
	ALT	Urine beta-2-microglobulin
	AST	Urine creatinine
	LDH	
	Alkaline phosphatase	
	GGT	
	Creatine phosphokinase	
	Lipid profile: blood cholesterol, high-density lipoprotein, low-density lipoprotein, and triglycerides	
	Serum FSH (to confirm postmenopausal status)[3]	
	Vitamin D (1,25-(OH)$_2$)	
	TSH[3]	
	Serum pregnancy[4]	
	HIV/Hepatitis screen[3]	
	TB test[3]	

[1] Additional hematology assessments will be collected for participants requiring follow-up for lymphopenia at the time of study completion or ET.
[2] Serum creatinine will be used to calculate eGFR at each timepoint that a creatinine result is generated. Participant's latest weight assessment will be used to calculate eGFR.
[3] Only at Screening.
[4] Only at Screening and Safety Follow-Up (Visit 15).

11. SAFETY DEFINITIONS, RECORDING, REPORTING, AND RESPONSIBILITIES

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

At the signing of the ICF, each participant and/or his/her legally authorized representative and/or main caregiver must be given the names and telephone numbers of site staff for reporting SAEs, pregnancies, overdoses, and medical emergencies. Throughout the protocol, the Sponsor is named, but reporting may be done through a CRO.

11.1. Definitions

11.1.1. Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation participant (participant) 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 assessment such as an abnormal laboratory value), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Determination of whether an abnormal assessment (e.g., laboratory value, vital sign, and ECG) result meets the definition of an AE will be made by the Investigator. Abnormal results are not considered AEs unless one or more of the following criteria are met:

- The result meets the criteria for an SAE.
- The result requires the participant to receive specific corrective therapy.
- The result is considered by the Investigator to be clinically significant.

11.1.2. 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 participant 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.

- Results in a congenital anomaly/birth defect.
- Is a medically important event.

A medically important event is an AE that, in the opinion of the Investigator, may jeopardize the participant 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.)

11.1.3. 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 participant is hospitalized. The study site must document all 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 participant's consent to be 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 Investigator between the participant's consent to be 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.
    - If a participant is hospitalized due to local requirements for administration of the study treatment, the hospitalization should not be considered an SAE unless one of the requirements in Section 11.1.2 is met.

11.2. Safety Classifications

11.2.1. Investigator Assessment of Events

All events must be assessed to determine the following:

- If the event meets the criteria for an SAE as defined in Section 11.1.2
- The relationship of the event to study treatment as defined in Section 11.2.2
- The severity of the event as defined in Section 11.2.3

11.2.2. Relationship of Events to Study Treatment

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

Relationship of Event to Study Treatment	
Not related	An AE will be considered "not related" to the use of the investigational product if there is not a reasonable possibility that the event has been caused by the product under investigation. Factors pointing toward this assessment include but are not limited to the lack of reasonable temporal relationship between administration of the investigational product and the AE, the presence of a biologically implausible relationship between the product and the AE, or the presence of a more likely alternative explanation for the AE.
Related	An AE will be considered "related" to the use of the investigational product if there is a reasonable possibility that the event may have been caused by the product under investigation. Factors that point toward this assessment include but are not limited to a positive rechallenge, a reasonable temporal sequence between administration of the investigational product and the AE, a known response pattern of the suspected product, improvement following discontinuation or dose reduction, a biologically plausible relationship between the product and the AE, or a lack of an alternative explanation for the AE.

11.2.3. Severity of Events

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

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

11.2.4. Expectedness of Events

Expectedness of all SAEs will be determined by the Sponsor according to the DRF IB.

11.3. Monitoring and Recording Events

11.3.1. Adverse Events

Any AE experienced by the participant between the time of first dose of study treatment and until the completion of the safety follow-up visit is to be recorded on the CRF, regardless of the severity of the event or its relationship to study treatment. At each study visit, the Investigator will assess the participant for AEs and will record any new AEs or updates to previously reported AEs on the CRF.

AEs that are ongoing when the participant completes or discontinues the study will be followed by the Investigator until the event has resolved, stabilized, or returned to baseline status. AE outcome will be recorded on the CRF, as applicable.

The following events will not be collected as AEs:

- [redacted] (see Section 11.1.2). [redacted] [see Section 11.1.2]).
- Illnesses present prior to the participant signing the ICF are considered to be pre-existing conditions and are documented on the medical history CRF. Pre-existing conditions that worsen during the study are entered on the AE CRF.
- Pregnancy is not considered an AE, although a participant will be withdrawn from the study if a pregnancy occurs. As described in Section 11.4.1, the pregnancy must be reported to the Sponsor, and additional follow-up may be required.

11.3.2. Adverse Events of Special Interest

An AESI is an AE of scientific and medical concern specific to this study, for which ongoing monitoring is required and rapid communication by the Investigator to the Sponsor may be appropriate.

PML and pancreatitis will be considered AESIs. The study site must formally notify the Sponsor within 24 hours of the site staff becoming aware of the AESI.

11.3.3. Serious Adverse Events

Any SAE experienced by the participant between the time of the signing of the ICF and the participant's final clinic visit (including the Follow-Up Safety Visit) is to be recorded on an SAE form, regardless of the severity of the event or its relationship to study treatment. Thereafter, the event should be reported to the Sponsor only if the Investigator considers the SAE to be related to study treatment.

SAEs must be reported to the Sponsor within 24 hours as described in Section 11.3.4. Follow-up information regarding an SAE also must be reported within 24 hours.

Any SAE that is ongoing when the participant completes or discontinues the study will be followed by the Investigator until the event has resolved, stabilized, or returned to baseline status.

11.3.4. 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 the Sponsor within 24 hours of the 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.

Reporting Information for SAEs
A report ***must be submitted*** to the Sponsor regardless of the following: • Whether or not the participant has undergone study-related procedures • Whether or not the participant 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 an SAE, fax or email a completed SAE form to the Sponsor; refer to the Study Reference Guide's Official Study Contact List for complete contact information.

11.3.4.1. Deaths

Death is an outcome of an event. The event that resulted in death should be recorded on the appropriate CRF. All causes of death must be reported as SAEs within 24 hours of the site becoming aware of the event. The Investigator should make every effort to obtain and send death certificates and autopsy reports to the Sponsor. The term death should be reported as an SAE only if the cause of death is not known and cannot be determined.

11.3.5. 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.

The Sponsor will report SUSARs to the appropriate regulatory authorities and Investigators as required, according to local law.

11.4. Procedures for Handling Special Situations

11.4.1. Pregnancy

Participants should not become pregnant or impregnate their partners during the study and for 30 days after their last dose of study treatment. If a female participant becomes pregnant, study treatment must be discontinued *immediately*.

The Investigator must report a pregnancy occurring in a female participant and female partner of a male participant from first dose of study drug to 30 days after their last dose of study treatment by faxing the appropriate form to the Sponsor within 24 hours of the site staff becoming aware of the pregnancy. Refer to the Study Reference Guide's Official Study Contact List for complete

contact information. The Investigator or site staff must report the outcome of the pregnancy to the Sponsor. A pregnancy is not considered an AE and should not be recorded on the AE CRF.

Congenital abnormalities and birth defects in the offspring of male or female participants should be reported as an SAE if conception occurred during the study treatment period or within 30 days from their last dose of study treatment.

11.4.2. Overdose

An overdose is any dose of study treatment administered to a participant or taken by a participant that exceeds the dose assigned to the participant according to the protocol. Overdoses are not considered AEs and should not be recorded as an AE on the CRF; however, all overdoses must be recorded on an Overdose form and faxed or emailed to the Sponsor within 24 hours of the site becoming aware of the overdose. An overdose must be reported to the Sponsor even if the overdose does not result in an AE. If an overdose results in an AE, the AE must be recorded. If an overdose results in an SAE, both the SAE and Overdose forms must be completed and faxed or emailed to the Sponsor. All study treatment-related dosing information must be recorded on the dosing CRF.

11.4.3. Medical Emergency

In a medical emergency requiring immediate attention, site staff will apply appropriate medical intervention, according to current standards of care. The Investigator (or designee) should contact the study's Medical Monitor. Refer to the Study Reference Guide's Official Study Contact List for complete contact information.

11.5. Contraception Requirements

All women of childbearing potential must ensure that highly effective contraception is used during the study and for 30 days after their last dose of study treatment. All men must ensure that effective contraception is used during the study and for 30 days after their last dose of study treatment. In addition, participants should not donate sperm or eggs for the duration of the study and for at least 30 days after their last dose of study treatment.

For the purposes of this study, women of childbearing potential are defined as all women physiologically capable of becoming pregnant, UNLESS they meet one of the following conditions:

- Postmenopausal
  - 52 continuous weeks of natural (spontaneous) amenorrhea without an alternative medical cause and a serum FSH level > 40 mIU/mL
  - 6 weeks after surgical bilateral oophorectomy with or without hysterectomy
- Posthysterectomy

- Female surgical sterilization (e.g., bilateral tubal ligation) where applicable according to local guidelines

For the purposes of the study, highly effective contraception for females is defined as use of at least 1 of the following:

For females:

- Established use of oral, intravaginal[1], or transdermal[1] combined (estrogen and progestogen containing) hormonal methods of contraception associated with the inhibition of ovulation.

- Established use of oral, injected[1], or implanted[1] progestogen-only hormonal methods of contraception associated with the inhibition of ovulation.

- Placement of an intrauterine device or intrauterine hormone-releasing system.

- Bilateral tubal occlusion.

- Sex with a male who has undergone surgical sterilization (with the appropriate postvasectomy documentation of the absence of sperm in the ejaculate).

For the purposes of the study, effective contraception for males is defined as:

- Vasectomy with negative semen analysis at follow-up. If documentation is not available, the participant must use contraception.

- Condoms with or without spermicide.

True abstinence, when this is consistent with the preferred and usual lifestyle of the participant, can be considered an acceptable method of contraception based on the evaluation of the Investigator who should also take into consideration the duration of the clinical study. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not considered acceptable methods of contraception.

Pregnancy reporting is described in Section 11.4.1.

[1] Intravaginal and transdermal combined hormonal methods of contraception and injected and implanted hormonal methods of contraception are not approved for use in Japan.

11.6. Safety Responsibilities

11.6.1. The Investigator

The Investigator's responsibilities include the following:

- Monitor and record all AEs, including SAEs, on the CRF 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 in female participants and female partners of male participants and follow up on the outcome of all pregnancies.
- Complete an SAE form for each SAE and fax or email it to the Sponsor within 24 hours of the site staff becoming aware of the event.
- Pursue SAE follow-up information actively and persistently. Follow-up information must be reported to the Sponsor within 24 hours of the site staff becoming aware of new information.
- Ensure all AE and SAE reports are supported by documentation in the participants' medical records.
- Pursue AE follow-up information, if possible, until the event has resolved or become stable. Record AE follow-up information, including resolution, on the CRF, as applicable.
- Report SAEs to local ethics committees, as required by local law.

11.6.2. The Sponsor

The Sponsor's responsibilities include the following:

- Before a site can enroll any participants, the Clinical Monitor is responsible for reviewing with site staff the definitions of AE and SAE, as well as the instructions for monitoring, recording, and reporting AEs and SAEs.
- The Sponsor is to notify all appropriate regulatory authorities, central ethics committees, and Investigators of SAEs, as required by local law, within required time frames.

12. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The objectives of the study and the endpoints to be analyzed are listed in Section 4.

12.1. General Considerations

The statistical analysis methods are described below. Additional details will be provided in the SAP.

In general, summary statistics (number of participants, mean, standard deviation, median, minimum and maximum values for continuous variables, and number and percentage of participants in each category for categorical variables) will be provided for all parameters. All statistical results will be presented based on observed values. All individual participant level data will be presented as data listings.

12.2. Analysis Sets

[redacted]

Safety analysis set: defined as all participants who receive at least 1 dose of study treatment; this set will be used in the safety analyses.

PK analysis set: defined as all participants who receive at least 1 dose of study treatment and have had at least 1 postdose plasma concentration for MMF and HES; this set will be used in the PK analysis.

12.3. Methods of Analysis

Summary statistics will be provided for all demographic variables and baseline characteristics. Medical history will be summarized for the safety population using the number of observations and percentage of participants reporting each category.

[redacted]

12.4. Methods of Analysis for Pharmacokinetic Endpoints for Part 1 (only)

The PK population with intensive blood sample collection will consist of a subset of 7 participants in Japanese cohort (7 of the 50 participants).

If a participant in the PK subset with intensive blood sample collection (7 of the 50 participants) discontinues the study before completing the 8-hour PK sampling period or requires dose reduction or samples not collected per protocol or laboratory manual, the participant may be replaced with one of the other enrolled participants. If this is not feasible, additional participants above the anticipated sample size of 50 may be enrolled to ensure adequate number of participants are available for intensive PK sampling.

The PK population with sparse blood sample collection will consist of 43 participants (43 of the approximately 50 participants in the Japanese cohort) and 50 participants (50 of the approximately 50 participants in the Chinese cohort).

MMF and HES plasma concentrations will be summarized using descriptive statistics (mean, standard deviation, median, minimum, and maximum), and the mean values with standard errors will be plotted over time both on a linear and a logarithmic scale (where applicable). The MMF and HES concentrations obtained through intensive blood sample collection will also be used to calculate the following PK parameters using noncompartmental methods.

The following PK parameters will be calculated:

- C_{max}
- AUC_{last}
- T_{max}
- $t_{½}$ (MMF only)
- Other PK parameters can be calculated if feasible (CL/F, Vz/F, T_{lag}).

Each of these PK parameters will be summarized using descriptive statistics (mean, standard deviation, geometric mean, 95% CI, coefficient of variation, median, minimum and maximum for AUC_{last}, C_{max}, $t_{½}$, CL/F, Vz/F; median, minimum, and maximum for T_{max} and T_{lag}).

These PK parameters will also be descriptively compared to PK parameters from non-Japanese participants in Study ALK8700-A301 with respect to ethnic sensitivity and results will be discussed in the Part 1 and 2 study reports.

MMF and HES plasma concentrations predose and at 2 to 3 hours postdose on Day 29 and Day 57 will be summarized using descriptive statistics (mean, standard deviation, geometric mean, 95% CI, coefficient of variation, median, minimum and maximum).

The plasma concentrations in 43 Japanese participants will be compared with those in Study ALK8700-A301 using tabular data and graphics. These results will be discussed in study reports for Parts 1 and 2.

Population PK analysis will be performed by using integrated plasma concentration data, including all plasma concentration data from Study 272MS303, to assess ethnic sensitivity in terms of HES PK. Detailed population PK analysis will be described in a separate report.

Table 6: Pharmacokinetic Analysis Timepoints

	Intensive PK Timepoints[1]							
	Predose	**0.5 h**	**1 h**	**2 h**	**3 h**	**4 h**	**6 h**	**8 h postdose**
Time Window	-30 to 0 min	±5 min	±5 min	±15 min	±15 min	±15 min	±15 min	±15 min

[1] PK analysis will be performed in a subset of 7 participants in the Japanese cohort at any timepoint in the period between Week 4 (Day 29, Visit 3 ± 3 days) and Week 24 (Day 169, Visit 8 ± 5 days), both inclusive. If a participant from the PK subset population discontinues the study during the specimen sampling period, then the participant may be replaced with one of the enrolled participants.

12.5. Methods of Analysis for Safety Endpoints

The safety analysis will be performed using the safety analysis set (Section 12.2). AEs and SAEs will be coded using the MedDRA.

Safety assessments will be summarized using descriptive statistics along with supportive listings.

Listings will be provided for all safety endpoints.

The selected safety data may also be descriptively compared to the similar data from Study ALK8700-A301 and Study 109MS305. The point estimates with associated CIs for selected safety data from the aforementioned studies will be referenced in the study reports whenever possible.

Further details will be provided in the SAP.

12.5.1. Adverse Events

The number and percentage of TEAEs and SAEs will be summarized by system organ class and preferred terms within each system organ class. SAEs and AEs resulting in treatment discontinuation will be summarized.

The incidence rates of TEAEs and SAEs will be summarized by system organ class and preferred terms within each system organ class and presented as number of AEs per participant per year.

Further details will be provided in the SAP.

12.5.2. Clinical Laboratory Results

Number and percentage of participants with values considered PCS occurring at any postbaseline visit for selected parameters will be summarized.

In addition, shifts from baseline to any postbaseline visits during treatment period will be provided for selected chemistry, hematology, and urinalysis parameters.

12.5.3. Vital Signs

Vital sign results (baseline and change from baseline) for each parameter and visit during the entire study will be summarized.

The number and percentage of participants with values considered PCS occurring at any postbaseline visit for selected parameters will be summarized.

12.5.4. ECG

ECG results (baseline and change from baseline) for each parameter and visit during the entire study will be summarized.

The number and percentage of participants with values considered PCS occurring at any postbaseline visit for selected parameters will be summarized.

12.5.5. C-SSRS

The number and percentage of participants meeting one of the criteria occurring at baseline and any postbaseline visit for selected parameters will be summarized.

12.6. Interim Analyses

Interim analyses may be conducted for Part 1, for Part 2, and/or for Part 1 and Part 2 combined, as necessary.

12.7. Sample Size Considerations

A sample size of approximately 50 participants per cohort is based on feasibility considerations and is deemed sufficient to characterize the safety and tolerability profile. With this sample size, the probability of observing at least 1 SAE with a background incidence of 4% would be 87% based on data from the 24-week Treatment Period in Study ALK8700-A301 (a DRF global Phase 3 study) in RRMS participants who were naïve to DRF treatment.

In addition, assuming the incidence of GI AEs at 24 weeks of 27.5% as observed in participants naïve to DRF treatment recruited in Study ALK8700-A301, the sample size of approximately 50 participants per cohort will provide a 96% probability of observing a point estimate of GI AE

incidence rate < 39% in Part 1 of the study (at 24 weeks). The 24-week incidence rate of 39% was observed in East Asian participants who received DMF twice daily in Study 109MS305.

Based on the observed DRF PK parameters in fasted participants from ALK8700-A103 study, CV of AUC (last) was estimated to be 30.9; therefore, a sample size of 7 Japanese participants would be needed to evaluate the MMF PK parameters with sufficient precision, which is defined as an evaluation of the PK parameters of MMF with at least 80% power to achieve a 95% CI within 60% to 140% of the geometric mean. Since the variability of HES parameters is significantly lower, the data from 7 participants will also provide a robust assessment of AUC_{last} and C_{max} of HES in Japanese MS participants.

The Sponsor may enroll fewer than 50 participants per cohort based on the observed recruitment rate in these regions.

13. ETHICAL AND REGULATORY REQUIREMENTS

The Sponsor, any contracted third party, and the Investigator must comply with all instructions, regulations, and agreements in this protocol and applicable ICH and GCP guidelines and conduct the study according to local regulations.

The Investigators are responsible for demonstrating timely oversight of all clinical trial data from their site, including data external to the electronic data capture system, such as laboratory, [redacted] and electronic clinical outcomes assessment data. Investigators must approve all their data on completed CRFs by signing electronically, at the participant, visit, or casebook level, at any time prior to an interim lock or database lock, as well as before any subsequent re-lock. The electronic data capture system does not prohibit Investigator approval or signing in any way.

The Investigator may delegate responsibilities for study-related tasks where appropriate to individuals sufficiently qualified by education, training, and experience, in accordance with applicable ICH and GCP guidelines. The Investigator should maintain a list of the appropriately qualified persons to whom significant study-related duties have been delegated. The Investigator is responsible for supervising those individuals and for implementing procedures to ensure the integrity of the tasks performed and any data generated.

13.1. Declaration of Helsinki

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

13.2. Ethics Committee

The Investigator must obtain ethics committee approval of the protocol, ICF, and other required study documents prior to starting the study. The Sponsor will submit documents on behalf of the study sites in countries other than the US.

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

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

The Sponsor must receive a letter documenting ethics committee 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 ethics committee at required intervals and not less than annually.

At the completion or termination of the study, where required, the study site must submit a close-out letter to the ethics committee and the Sponsor.

13.3. Changes to Final Protocol

All protocol amendments must be submitted to the ethics committee and regulatory authorities if required by local law. Protocol modifications that affect participant safety, the scope of the investigation, or the scientific quality of the study must be approved by the ethics committee 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, the Sponsor may, at any time, amend this protocol to eliminate an apparent immediate hazard to a participant. In this case, the appropriate regulatory authorities will be notified subsequent to the modification.

In the event of a protocol modification, the ICF may require similar modifications (see Section 13.4).

13.4. Informed Consent

Prior to performing any study-related activities under this protocol, including screening tests and assessments, informed consent with the approved ICF must be obtained.

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

In addition, participants who have the capacity should provide their assent to participate in the study. The level of information provided to participants should match their level of understanding as determined by the Investigator and in accordance with applicable regulations and guidelines.

A copy of the signed and dated ICF must be given to the participant. The original signed and dated ICF will be retained with the study records. Local regulations must be complied with in respect to the final disposition of the original and copies of the signed and dated ICFs.

Confirmation of informed consent must also be documented in the participant's medical record.

When additional information that may affect participants' willingness to continue in the study becomes available, the Investigators will be notified in a timely manner, according to all local and applicable law. An updated ICF may be required.

[redacted] All signed consent forms will be retained with the participant's study records.

13.5. Participant Data Protection

Prior to any testing under this protocol, including screening tests and assessments, candidates must also provide all authorizations required by applicable national and local privacy regulations (e.g., Protected Health Information authorization in North America).

During the study, participants' race and ethnicity will be collected (unless the collection is not permitted by applicable law or not approved by the governing ethics committee). These data will be used in the analysis of the safety and/or PK profile of the study treatment. Since it is not always known whether the effects of the study treatment are influenced by race or ethnicity, this information will be of value in the analysis of safety.

Study reports will be used for research purposes only. The participant will not be identified by name in CRFs, study-related forms, study reports, or any related publications. The Sponsor, its partners and designees, ethics committees, and various government health agencies may inspect the records of this study. Every effort will be made to keep the participant's personal medical data confidential.

13.6. Compensation for Injury

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

13.7. Conflict of Interest

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

13.8. Study Report Signatory

The Sponsor will designate one of the participating 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 participant enrollment; or by other factors determined to be relevant by the Sponsor.

The Sponsor will follow all applicable local regulations pertaining to study report signatories.

13.9. Registration of Study and Disclosure of Study Results

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

The Sponsor also will notify, when required, the regulatory authorities and ethics committees about the completion or termination of this study and send a copy of the study synopsis in accordance with necessary timelines.

13.10. 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, national, or regional laws or regulations. Prior to proceeding with destruction of records, the Investigator must notify the Sponsor in writing and receive written authorization from the Sponsor to destroy study records. In addition, the Investigator must notify the Sponsor of any changes in the archival arrangements including but not limited to archival at an offsite facility or transfer of ownership if the Investigator leaves the site.

14. KEY ROLES AND STUDY GOVERNANCE COMMITTEES

14.1. Site Staff

The Investigator of the site will designate the appropriate site personnel and their role in the study. See the Study Reference Guide for details.

14.2. Vendors

The Sponsor will ensure oversight of any study-related duties and functions carried out on its behalf and will specify in writing all duties and functions that are transferred.

14.2.1. Contract Research Organization

At least 2 CROs have been selected by the Sponsor to be responsible for administrative aspects of the study including but not limited to study initiation, management of SAE reports, monitoring, and data management.

14.2.2. Interactive Response Technology

IRT will be used in this study. Before participants are screened or enrolled, the IRT vendor will provide each study site with the necessary training, a user manual, and access rights to the system.

14.2.3. Electronic or Remote Data Capture

Participant information will be captured and managed by study sites on electronic CRFs by a Web-based electronic data capture tool configured by the Sponsor or the CRO and hosted by the electronic/remote data capture vendor.

14.2.4. Central Laboratories for Laboratory Assessments

Central laboratories have been selected by the Sponsor to analyze the hematology, blood chemistry, and urine samples collected for this study. PK samples will be analyzed at a laboratory selected by the Sponsor.

14.2.5. Central Facility for Other Assessments

Central facilities have been selected by the Sponsor to read and interpret [redacted] and ECG readings for this study.

14.2.6. Central Review of Raters

The Sponsor has selected a rater management group to establish rater qualifications, provide study-specific training about the rater process, and provide oversight. As part of the oversight process, the rater management group will incorporate a central review of the raters to ensure that data are consistently rated across sites.

14.3. Study Committees

Not applicable.

15. ADMINISTRATIVE PROCEDURES

15.1. Study Site Initiation

The Investigator must not screen any participants prior to the Sponsor completing a study initiation visit. This initiation visit with the Investigator and other site staff, as appropriate, will include a detailed review of the protocol, study procedures, and study responsibilities.

15.2. Quality Control and Quality Assurance

Quality control procedures will be implemented at each stage of data handling to ensure that all data are reliable and have been processed correctly. Data anomalies will be communicated to the sites for clarification and resolution, as appropriate. The Investigator is responsible for endorsing all CRF data prior to any interim or final database lock.

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

15.3. Monitoring of the Study

The Investigator must permit study-related monitoring by providing direct access to source data and to the participants' medical histories. Source data must be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data must be traceable, not obscure the original entry, and be explained if necessary (e.g., with an audit trail). The Investigator should maintain a record of the location(s) of essential documents.

The Clinical Monitor will visit the study site at regular intervals during the study and after the study has completed, as appropriate. A clinical site monitoring plan will detail who performs the monitoring, how often, and the extent of review. It also will provide the monitoring strategy, with emphasis on participant safety, data integrity, and critical data and processes.

During these visits, CRFs, supporting documentation, and essential documentation related to the study will be reviewed and any discrepancies or omissions will be resolved. Documentation of results will be provided to the Sponsor in a timely fashion to allow follow-up and verification of compliance with the monitoring plan. Remote evaluation of data (centralized monitoring) may also be conducted and reported as defined in the monitoring plan.

Monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure the protection of participant rights and well-being, protocol adherence, quality of data (accurate, complete, and verifiable), study treatment accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

15.3.1. Public Health Emergencies

In the event of a public health emergency that results in site closure, travel restrictions, and/or the study being deprioritized at the site such that clinic visit(s) cannot occur, a protocol deviation would be incurred for any deviation from the protocol-specified visits and assessments, with additional notation that this protocol deviation is due to the public health emergency. If a protocol-specified clinical visit cannot occur due to a public health emergency, one or more of the following mitigating options should be pursued in consultation with the medical monitor: 1) transfer to another active study site that is open, 2) telemedicine visit (e.g., by telephone or web conference), and 3) local laboratory visit. These mitigating options only apply in the setting of a public health emergency in which a protocol-specified clinic visit cannot occur and should not be pursued solely due to participant's preference. If the participant does not participate in one or more of these options, a safety telephone call must be conducted within 14 days of the last dosing visit.

If the participant is unable to pick up study treatment during the 48-week Treatment Period because of a public health emergency, arrangements may be made to ship study treatment directly to the participant, where allowed per country or local regulations.

15.4. Study Funding

The Sponsor is responsible for setting up the funding of the study. All financial details are provided in the separate contracts between the institution, Investigator, and the Sponsor organization.

15.5. Publications

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

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17. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "An Open-Label, Single-Arm, Multicenter, Phase 3 Study to Evaluate the Safety and Tolerability, and Pharmacokinetics of Diroximel Fumarate (BIIB098) in Adult Participants From the Asia-Pacific Region With Relapsing Forms of Multiple Sclerosis," 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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AMENDMENT SUMMARY

Biogen Protocol 272MS303

An Open-Label, Single-Arm, Multicenter, Phase 3 Study to Evaluate the Safety and Tolerability, and Pharmacokinetics of Diroximel Fumarate (BIIB098) in Adult Participants From the Asia-Pacific Region With Relapsing Forms of Multiple Sclerosis

Version 4

Date: 23 May 2023

Version 4 of the protocol has been prepared for this amendment, which supersedes Version 3.

PRIMARY REASON FOR AMENDMENT

The primary reason for this amendment to Protocol 272MS303 is to include alternative timepoints for intensive PK sampling for newly enrolled participants and for participants already enrolled in the sparse PK cohort who have not yet reached Week 24.

New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Section 5.1, Study Overview

Now reads:

Intensive blood samples will be collected predose (-30 to 0 minutes predose) and at various timepoints postdose (0.5, 1, 2, 3, 4, 6, and 8 hours postdose) ~~on~~ **at any timepoint in the period between Week 4 (**Day 29, Visit 3 ± 3 days) **and Week 24 (Day 169, Visit 8 ± 5 days), both inclusive,** for 7 Japanese participants who will take DRF after 10 hours of fasting, and no food will be allowed for at least 4 hours after the dose of DRF. Participants will be allowed water ad libitum, except for 1 hour before and 2 hours after administration of the dose of DRF. Sparse blood samples will be collected for all remaining participants (~~excluding~~ **as well as for** those ~~whose samples~~ **participants who** are ~~collected for~~ **enrolled both in the** intensive PK ~~sampling~~ **and the sparse PK cohorts**) predose (-30 to 0 minutes predose) and 2 to 3 hours postdose on Day 29 (Visit 3) and Day 57 (Visit 4).

Rationale: Alternative timepoints for intensive PK sampling when steady state is guaranteed were added to introduce flexibility in PK timepoints, thereby reducing restrictions that may affect participant recruitment. Language was revised to clarify eligibility for enrollment in intensive PK cohort. Guidance for participants who may be enrolled in both the sparse and intensive PK cohorts was included to provide clarity for the conduct of study procedures.

This change also affects the following sections: Section 1.2, Study Design Schematic; Section 1.3, Schedule of Activities; Section 9.3, PK Assessments; Section 12.4, Methods of Analysis of Analysis for PK Endpoints for Part 1 (only).

SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

The following major changes were made to the protocol.

Changes to the protocol are presented chronologically. New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Section 1.1, Synopsis

The synopsis was revised to reflect changes made throughout the protocol.

Section 6.1, Inclusion Criteria

Change: Added text to state that informed consent from a legally acceptable representative is mandatory for participants in Japan, if the participant is aged < 20 years.

Now reads:

2. Male and female participants aged 18 to 65 years old, inclusive, at the time of informed consent.

- **For participants in Japan aged < 20 years, written informed consent should be obtained from the participant and their legally acceptable representative.**
- **Informed consent from a legally acceptable representative is not mandatory if the participant is classified as an adult based on the latest applicable local laws**.

Rationale: This inclusion criterion was updated to clarify that, as of now for participants in Japan, informed consent from a legally acceptable representative is mandatory if the participant is aged < 20 years. This criterion is subject to change per the latest applicable local laws.

Section 6.2, Exclusion Criteria

Change: Language was revised in exclusion criterion 15 regarding rescreening eligibility of participants with evidence of current SARS-CoV-2 infection.**Now reads:**

15. Evidence of current SARS-CoV-2 infection within 14 days prior to Screening, between Screening and Baseline Visit **(Day 1)**, or at Baseline Visit **(Day 1)**, including but not limited to a fever (temperature > 37.5°C), new and persistent cough, breathlessness, or loss of taste and/or smell.

Note: If a SARS-CoV-2 test (PCR or other regulatory approved method) is performed per the discretion of the Investigator in accordance with local site practice, the test result must be negative in order for the participant to be enrolled in the trial.

Participants with evidence of current SARS-CoV-2 infection within 14 days prior to Screening or during Screening, will be eligible for rescreening, provided that the participant is asymptomatic for 14 days prior to rescreening.

Rationale: Language in exclusion criterion 15 was revised to allow rescreening of participants with evidence of current SARS-CoV-2 infection after recovery from symptoms.

Change: Language was revised in exclusion criterion 16 regarding rescreening eligibility of participants who had close contact with individual(s) with suspected SARS-CoV-2 infection within 14 days prior to Day 1.

Now reads:

16. Have close contact within 14 days prior to Day 1 with individual(s) with a ~~SARS-CoV-2 positive individual~~ **suspected SARS-CoV-2 infection**. Close contact is defined as:

a. face-to-face contact with a probable or confirmed case within 1 meter and for at least 15 minutes;
b. direct physical contact with a probable or confirmed case;
c. direct care for a patient with probable or confirmed COVID-19 disease without the use of recommended PPE; or
d. other situations as indicated by local risk assessments.

Participants who had close contact with individual(s) with suspected SARS-CoV-2 infection within 14 days prior to Day 1, as determined by the Investigator, will be eligible for rescreening, provided that the participant is asymptomatic for 14 days after the contact.

Rationale: Language in exclusion criterion 16 was revised to allow rescreening of participants who had close contact with individual(s) with suspected SARS-CoV-2 infection within 14 days prior to Day 1**.**

Change: Language was revised in exclusion criterion 21 regarding history of or ongoing tuberculosis infection.

Now reads:

21. ~~A history of diagnosis of TB or a positive latent TB test result, defined as a positive IGRA result or 2 successive indeterminate IGRA results~~.

Participants with any of the following TB-related criteria:

a. **Active TB infection.**
b. **History of active TB infection involving any organ system or findings in other organ systems consistent with TB, unless adequately treated according to WHO/CDC therapeutic guidance and proven to be fully recovered upon consult with a TB specialist.**
c. **Latent TB infection (**defined as a **confirmed** positive IGRA result or 2 successive indeterminate IGRA results**) unless appropriate prophylaxis is initiated at least 4**

weeks prior to study medication dosing on Baseline Visit (Day 1) and will be continued to completion of prophylaxis.

Rationale: Language in exclusion criterion 21 was revised to provide additional details on the eligibility criteria for participants with TB infection.

Change: Language in exclusion criterion 22 regarding bacterial, fungal, or viral infection was revised.

Now reads:

22. Symptoms of bacterial, fungal, or viral infection (including upper respiratory tract infection) within 28 days prior to Baseline (~~Visit 1~~) **(Day 1)**~~. Participants with local fungal infection (e.g., candidiasis, tinea) are eligible to be rescreened after successful treatment of the infection~~**, unless the participants recovered completely prior to Baseline Visit (Day 1) and the infections were considered mild per Investigator's judgment. Participants who have not recovered prior to Baseline Visit (Day 1), as judged by the Investigator, will be eligible for rescreening.**

Rationale: Language in exclusion criterion 22 was revised to allow enrollment or rescreening of participants with mild bacterial and viral infections.

Change: Exclusion criterion 27c regarding participants who may have received mitoxantrone or other immunosuppressant agents was revised.

Now reads:

27. Has a history of treatment with or has received the following:

> c. Mitoxantrone or other immunosuppressant agents (e.g., cyclosporine, cyclophosphamide, methotrexate, mycophenolate) within ~~2 years~~ **12 months** prior to Baseline (Visit **(Day** 1); **azathioprine within 6 months prior to** Baseline (Visit **(Day** 1)**.**

Rationale: The washout periods for participants who may have received treatment with mitoxantrone, other immunosuppressant agents, and azathioprine were revised while still ensuring that effects of treatment do not interfere with the safety profile of DRF and to avoid unnecessary risks associated with MS therapy use.

Change: Exclusion criterion 27d regarding participants who may have received plasmapheresis, IV immunoglobulin, or cytapheresis treatment was added.

Now reads:

27. Has a history of treatment with or has received the following:

> d. **Treatment with any of the following medications or procedures within 6 months prior to Baseline Visit (Day 1): plasmapheresis, IV immunoglobulin, or cytapheresis**.

Rationale: The washout periods for participants who may have received treatment with plasmapheresis, IV immunoglobulin, or cytapheresis treatment were included to ensure that effects of treatment with plasmapheresis, IV immunoglobulin, or cytapheresis do not interfere with the safety profile of DRF and to avoid unnecessary risks associated with MS therapy use.

Change: Exclusion criterion 27e regarding participants who may have teriflunomide treatment was revised.

Now reads:

27. Has a history of treatment with or has received the following:

> e. Teriflunomide within ~~2 years~~ **12 months** of Baseline (Visit **(Day** 1), unless the serum/plasma concentration of teriflunomide is < 0.020 µg/mL (< 20 ng/mL) prior to Baseline (Visit **(Day** 1) or an accelerated elimination procedure for teriflunomide with cholestyramine is successfully completed during screening.

Rationale: The washout period for individuals who may have received teriflunomide treatment was revised while still ensuring that effects of treatment do not interfere with the safety profile of DRF and to avoid unnecessary risks associated with MS therapy use

Change: Language in exclusion criterion 27i regarding the washout period for participants who may have received B-cell targeted therapies was revised.

Now reads:

27. Has a history of treatment with or has received the following:

    i. B-cell targeted therapies for the treatment of MS (e.g., ocrelizumab, rituximab) within 12 months ~~of~~ **prior to** Baseline ~~(~~Visit **(Day** 1~~); within).~~ **Participants who have received B-cell targeted therapies** more than 12 months ~~of Screening is permissible with evidence~~ **prior to Baseline Visit (Day 1) will require CD19 testing to confirm** that ~~the~~ CD19 cells have returned to within normal range ~~(per local laboratory reference range)~~. **Participants who have received B-cell targeted therapies less than 12 months prior to Baseline Visit (Day 1) will be excluded from the study.**

Rationale: Language in exclusion criterion 27i was revised due to the discrepancy between 12 months to Baseline or to Screening.

Change: Exclusion criterion 27l regarding participants who may have received treatment with steroids was revised.

Now reads:

27. Has a history of treatment with or has received the following:

    l. Steroids, with the exception of topical or inhaled steroids, ~~or IV immunoglobulin~~ within 30 days prior to Baseline ~~(Visit 1)~~ **(Day 1).**

Rationale: This exclusion criterion was revised because guidance for participants who may have received treatment with IV immunoglobin is discussed in exclusion criterion 27d.

Change: Language in exclusion criteria 29d and 30 regarding retesting of participants who may have out-of-range laboratory results was added.

Now reads:

29. Has any of the following abnormal blood tests at Screening:

    a. ALT, AST, or GGT $\geq 3 \times$ ULN or bilirubin $> 2 \times$ ULN.
    b. TSH level > 10% of the ULN
    c. eGFR $\leq$ 60 mL/min/1.73 m^2 (using the Chronic Kidney Disease Epidemiology Collaboration equation) [Levey 2009]
    d. Lymphocyte count < LLN

30. Has any of the following abnormal urine tests at Screening:

    a. Beta-2 microglobulin > 0.3 µg/mL
    b. Albumin to creatinine ratio > 22.6 mg/mmol

For the parameters listed in exclusion criteria 29d and 30, out-of-range values that are clinically not significant, as determined by the Investigator, may be repeated once, and the participant may be enrolled only if the repeated value is within the normal range.

Rationale: Language was included to clarify the parameters for retesting of participants with out-of-range laboratory results parameters listed in exclusion criteria 29d and 30.

Change: Language was included in exclusion criterion 34 regarding the enrollment of participants who may have prior or current participation in a clinical trial within 90 days of Screening.

Now reads:

34. Current or prior participation in a clinical trial within 90 days of Screening. **Participants who have previously participated in a clinical trial but have not received any IMP treatment within 90 days of Screening will be eligible if the Investigator confirms that the participant meets all other inclusion and exclusion criteria and there are other safety concerns.**

Rationale: Language was included in exclusion criterion 34 to allow enrollment of participants who may have participated in a clinical trial but have not received any IMP treatment within 90 days of Screening, as enrollment of such participant will not compromise Study 272MS303 results.

Section 6.3.1, Screening

Change: Language for rescreening criteria was updated following revision to exclusion criteria 21c regarding extension of screening window in the event that a participant requires 4 weeks' TB prophylaxis.

Now reads:

The screening period can be extended up to a maximum of 42 days (i.e., an additional 2 weeks) with prior approval of the medical monitor if the testing of teriflunomide levels or confirmation of accelerated elimination (**per exclusion criterion ~~27d~~27e; Section 6.2) or minimum of 4 weeks' TB prophylaxis (per exclusion criterion 21c**; Section 6.2) cannot be completed within the 28-day screening period.

Rationale: Wording was updated to align with the revision made to exclusion criteria 21c to provide guidance regarding participants with a latent TB infection.

Section 6.3.2, Retesting

Change: Language for retesting criteria was updated following revision to exclusion criteria 29d and 30 regarding participants with out-of-range laboratory results.

Now reads:

~~Participants who have an out-of-range laboratory result that is not clinically significant can be retested once, as per exclusion criteria, at the discretion of the Investigator.~~

For the parameters listed in exclusion criteria 29d and 30, out-of-range values that are clinically nonsignificant, as determined by the Investigator, may be repeated once, and the participant may be enrolled only if the repeated value is within the normal range.

Participants who have ~~clinically significant~~ abnormal laboratory test values **as described in exclusion criteria 29a, 29b, and 29c** should not be retested.

Rationale: Wording was updated to align with the clarification made for exclusion criteria 29d and 30 to provide guidance regarding out-of-range laboratory test results.

Section 6.3.3, Screen Failures

Change: Language was revised to include participants who may have been considered screen failures due to incomplete enrollment in the event of a public health emergency.

Now reads:

Screen failures are defined as participants who sign the ICF but are not subsequently dosed. If a participant is considered a screen failure, the reasons for exclusion must be documented in the participant's source documents and on the screening log. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

All participants with incomplete enrollment due to a public health emergency (e.g., travel restrictions, participants who recovered after getting infected) will be eligible for rescreening provided that the participants met all eligibility criteria during the initial screening period, and that the reason for rescreening is incomplete enrollment due to a public health emergency. These participants will be reported as screen failed and then rescreened. Participants may have been provided with a unique identification number during Screening. The previously issued unique identification number will no longer be used, and a separate unique identification number will be provided during rescreening.

Rationale: Language was added to specify the requirements for rescreening of participants with incomplete enrollment due to a public health emergency.

Section 9.3, Pharmacokinetic Assessments

Change: Language regarding the PK sample volume for each individual sample was added.

Now reads:The PK sample volume will be approximately 6 mL for each individual sample. For the intensive PK sampling group, there are a maximum of 10 PK sample collection timepoints planned (8 timepoints on Day 29 for the intensive PK sampling and 2 timepoints on Day 57 for the sparse PK sampling). In the advent that intensive PK sampling is not feasible by Day 57, there are a maximum of 12 PK sample collection timepoints planned (2

timepoints on Day 29 and on Day 57 for the sparse PK sampling, respectively and 8 timepoints for the intensive PK sampling at a later visit). Therefore, the maximum PK sample volume for a given participant in the intensive PK sampling group will be approximately 72 mL. This volume will be lower for patients participating only in the sparse PK sample collection and will be approximately 24 mL (2 samples on Day 29 and 2 samples on Day 57).

Rationale: This language was added to provide guidance regarding PK sample volume for the 2 sampling groups.

Section 10.2, Laboratory Safety Assessments

Change: Footnote 2 in Table 5, outlining guidance to calculate the eGFR rate, was revised.

Now reads:

[2] Serum creatinine will be used to calculate eGFR at each timepoint that a creatinine result is generated. **Participant's latest weight assessment will be used to calculate eGFR.**

Rationale: This change was made to clarify that the participant's most recent weight assessment is to be used to calculate eGFR.

Section 11.3.2, Adverse Events of Special Interest

Change: Language was added to include pancreatitis as an AESI.

Now reads:

PML **and pancreatitis** will be considered **AESIs**. The study site must formally notify the Sponsor within 24 hours of the site staff becoming aware of the AESI.

Rationale: Pancreatitis was added as an AESI to better evaluate the safety profile of DRF.

SUMMARY OF MINOR CHANGES TO THE PROTOCOL

The following minor changes were made to the protocol, as appropriate:

- The version number and date were updated throughout the protocol.
- On the Sponsor Signature Page, the Biogen signatory's title was updated.
- Reference to the TECFIDERA® (dimethyl fumarate) Package Insert was updated to the latest available reference (2022).
- In Section 1.1, Synopsis, corrections were made to formatting.
- The term "Baseline (Visit 1)", "Baseline Visit" and "Baseline Visit (Day 1)" had been used interchangeably in the document. These were revised to "Baseline Visit (Day 1)" for consistency, where applicable.
- In Section 6.2, Exclusion criteria, under criterion 27a, which discusses history of treatment, treatment with total lymphoid irradiation was repeated. This repetition was removed.

LIST OF ABBREVIATIONS

ALT	alanine aminotransferase
[redacted]	[redacted]
CD19	cluster of differentiation 19
CDC	Centers for Disease Control and Prevention
COVID-19	coronavirus disease 2019
DRF	diroximel fumarate
eGFR	estimated glomerular filtration rate
GGT	gamma-glutamyl transferase
HES	2-hydroxyethyl succinimide
ICF	informed consent form
ICH	International Council for Harmonisation
IGRA	interferon-gamma release assay
IMP	investigational medicinal product
LLN	lower limit of normal
MS	multiple sclerosis
PCR	polymerase chain reaction
PK	pharmacokinetic(s)
PPE	personal protective equipment
SAE	serious adverse event
TB	tuberculosis
TSH	thyroid stimulating hormone
ULN	upper limit of normal
WHO	World Health Organization

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AMENDMENT SUMMARY

Biogen Protocol 272MS303

An Open-Label, Single-Arm, Multicenter, Phase 3 Study to Evaluate the Safety and Tolerability, and Pharmacokinetics of Diroximel Fumarate (BIIB098) in Adult Participants From the Asia-Pacific Region With Relapsing Forms of Multiple Sclerosis

Version 3

Date: 24 February 2022

Version 3 of the protocol has been prepared for this amendment, which supersedes Version 2.

PRIMARY REASON FOR AMENDMENT

The primary reason for this amendment to Protocol 272MS303 is to provide guidance in case of a public health emergency that results in study site closure, travel restrictions, and/or the study being deprioritized at the study site. As a result, a new section (Section 15.3.1) was added.

New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Section 15.3.1, Public Health Emergency

Now reads:

In the event of a public health emergency that results in site closure, travel restrictions, and/or the study being deprioritized at the site such that clinic visit(s) cannot occur, a protocol deviation would be incurred for any deviation from the protocol-specified visits and assessments, with additional notation that this protocol deviation is due to the public health emergency. If a protocol-specified clinical visit cannot occur due to a public health emergency, one or more of the following mitigating options should be pursued in consultation with the medical monitor: 1) transfer to another active study site that is open, 2) telemedicine visit (e.g., by telephone or web conference), and 3) local laboratory visit. These mitigating options only apply in the setting of a public health emergency in which a protocol-specified clinic visit cannot occur and should not be pursued solely due to participant's preference. If the participant does not participate in one or more of these options, a safety telephone call must be conducted within 14 days of the last dosing visit.

If the participant is unable to pick up study treatment during the 48-week Treatment Period because of a public health emergency, arrangements may be made to ship study treatment directly to the participant, where allowed per country or local regulations.

Rationale: Instructional language was added to provide guidance as to how study disruptions should be handled due to the ongoing public health emergency and in the event of a future public health emergency.

SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

Changes to the protocol are presented chronologically. New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Sponsor Information

Change: Changes were made to the Sponsor information to include Biogen Idec Research Limited and remove Biogen MA Inc.

Now reads:

~~Biogen is responsible for initiating and managing the study.~~

China	**Japan**
~~Biogen MA Inc.~~	Biogen Japan Ltd.
~~225 Binney Street~~	Nihonbashi 1-chome Mitsui
~~Cambridge, MA 02142~~	Building 14F
~~United States~~	4-1 Nihonbashi 1-chome
Biogen Idec Research Limited	Chuo-ku, Tokyo
Innovation House	103-0027 Japan
70 Norden Road	
Maidenhead, Berkshire	
SL6 4AY	
United Kingdom	

For urgent medical issues in which the study Medical Monitor should be contacted, please refer to the Study Contact List.

~~Biogen~~ **The Sponsor** may transfer any or all of its study-related responsibilities to a contract research organization and other third parties; however, ~~Biogen~~ **the Sponsor** retains overall accountability for these activities.

Rationale: Biogen Idec Research Limited is the Sponsor of the clinical trial in China.

This change also affects Section 11.2.4, Expectedness of Events; Section 11.3.1, Adverse Events; Section 11.3.5, Suspected Unexpected Serious Adverse Reactions; Section 14.2, Vendors; Section 14.2.3, Electronic or Remote Data Capture; and Section 15.4, Study Funding.

Section 1.1, Synopsis

The synopsis was revised to reflect changes made throughout the protocol.

Section 6.2, Exclusion Criteria

Change: Exclusion criteria 14, 27d, and 28 were updated.

Now reads:

…

14. Participant has an abnormality that the investigator deems to be clinically ~~relevant~~ **significant** on medical history, physical examination, ECG, or a diagnostic laboratory test **that may confound study results or pose risk to the subject through participation in the study, in the opinion of the Investigator.**

…

27. Has a history of treatment with or has received the following:
    a. Total lymphoid irradiation, cladribine, T-cell or T-cell receptor vaccination, total body irradiation, or total lymphoid irradiation at any time
    b. Stem cell transplantation at any time
    c. Mitoxantrone or other immunosuppressant agents (e.g., cyclosporine, cyclophosphamide, methotrexate, mycophenolate) within 2 years prior to Baseline (Visit 1)
    d. Teriflunomide within 2 years of Baseline (Visit 1), unless the serum/plasma concentration of teriflunomide is < 0.020 µg/mL (< 20 ng/mL) prior to Baseline (Visit 1) **or** ~~[~~an accelerated elimination procedure for teriflunomide with cholestyramine is ~~permitted~~ **successfully completed** during screening~~]~~

…

28. Clinically significant abnormal laboratory test values **that may confound study results or pose risk to the subject through participation in the study**, as determined by the Investigator, at Screening or Baseline (Visit 1).

Rationale: Editorial changes were made, and additional language was added to exclusion criteria 14 and 28 to provide clarification of the term "clinically significant" while leaving the determination to the Investigator's clinical judgement.

Minor edits were made to exclusion criterion 27d to ensure clarity regarding the need to measure the serum/plasma teriflunomide concentration or complete the accelerated elimination procedure for participants who wish to participate in the study but have taken teriflunomide within 2 years of the study Baseline Visit.

Section 6.3.1, Screening

Change: Change was made to allow the screening period to be extended if the testing of teriflunomide levels or confirmation of accelerated elimination was not completed within the 28-day screening period

Now reads:

Once informed consent is obtained, screening assessments can occur. At this time, a unique identification number is assigned that will be used on study-related documents pertaining to the participant. Any identification numbers that are assigned will not be reused, even if the participant does not receive treatment or continue in the study. Study sites are required to document all screened participants initially considered for inclusion in the study.

The screening period can be extended up to a maximum of 42 days (i.e., an additional 2 weeks) with prior approval of the medical monitor if the testing of teriflunomide levels or confirmation of accelerated elimination (per exclusion criterion 27d; Section 6.2) cannot be completed within the 28-day screening period.

Rationale: This change was made to allow additional time and flexibility for sites to receive teriflunomide concentration results needed for exclusion criterion 27d, due to the length of time required for testing.

[redacted]

Change: [redacted]

Now reads:

[redacted]

Rationale: [redacted]

[redacted]

Section 8.1, Discontinuation of Study Treatment

Changes: Editorial changes were made.

Now reads:

A participant must permanently discontinue study treatment for any of the following reasons:

- The participant becomes pregnant. Study treatment must be discontinued immediately (Note: Instructions for reporting the pregnancy are provided in Section 11.4.1).
- The participant withdraws consent to continue study treatment.
- The participant experiences an AE that requires permanent discontinuation of study treatment.
- The participant is unwilling or unable to comply with the protocol.
- At the discretion of the Investigator for medical reasons.
- At the discretion of the Sponsor or upon request of a regulatory authority.
- **Lymphocyte count < 0.5 × 10^3 /µL persisting for > 6 months. An initial lymphocyte count < 0.5 × 10^3/µL should be~~,~~ confirmed by repeat testing ~~as soon as possible~~. If the value remains < 0.5 × 10^3 /µL for > 6 months ~~after treatment interruption~~, the participant must permanently discontinue study treatment. Participants who permanently discontinue the study with a last measured lymphocyte count < LLN will require additional follow-up to monitor their lymphocyte counts; see Table 2.**

The reason for discontinuation of study treatment must be recorded in the CRF.

In addition to the reasons provided above for permanent discontinuation of study treatment, study treatment must be temporarily withheld if any of the following laboratory parameters meet the following threshold limits:

- AST or ALT > 3 × ULN; confirmed by repeat testing. If the value remains > 3 × ULN for ≥ 4 weeks after ~~discontinuation~~ **interruption** of study treatment, the participant must permanently discontinue study treatment.

- ~~Lymphocyte count < 0.5 × 10^3/µL, confirmed by repeat testing as soon as possible. If the value remains < 0.5 × 10^3/µL for > 6 months after treatment interruption, the participant must permanently discontinue study treatment. Participants who permanently discontinue the study with a last measured lymphocyte count < LLN will require additional follow-up to monitor their lymphocyte counts; see Table 2.~~

- eGFR < 60 mL/min/1.73 m^2; confirmed by repeat testing as soon as possible. If the eGFR remains < 60 mL/min/1.73 m^2 for ≥ 4 weeks after ~~discontinuation~~ **interruption** of study treatment, the participant must permanently discontinue study treatment.

- Urine albumin to urine creatinine ratio > 22.6 mg/mmol; confirmed by repeat testing as soon as possible. If the urine albumin to urine creatinine ratio remains > 22.6 mg/mmol for ≥ 4 weeks after ~~discontinuation~~ **interruption** of study treatment, the participant must permanently discontinue study treatment

Rationale: Edits were made for clarification. For example, the term "discontinuation" was replaced with "interruption" as appropriate to help avoid confusion between temporary interruption and permanent treatment discontinuation. The second bullet (i.e., prolonged lymphopenia) was revised to align the protocol language more closely to the guidance provided in the diroximel fumarate core data sheet. As a result of this change, the second bullet was moved to the treatment discontinuation section immediately above to align with the revised guidance.

Section 11.5, Contraception Requirements

Changes: Change was made to allow condom use without spermicide as an effective contraception for males.

Now reads:

For the purposes of the study, effective contraception for males is defined as:

- Vasectomy with negative semen analysis at follow-up. If documentation is not available, the participant must use contraception.

- Condoms with **or without** spermicide.

Rationale: Condoms with spermicide may not be available in all countries. Importantly, the protocol requires effective contraception for male participants and highly effective contraception for female participants. Condoms with or without spermicide would be considered an acceptable method of contraception for male participants in this study. The rationale is based on the guidelines provided in the Clinical Trials Facilitation and Coordination Group of the European Heads of Medicines Agencies, Section 4.2.

SUMMARY OF MINOR CHANGES TO THE PROTOCOL

The following minor changes were made to the protocol, as appropriate:

- The version number and date were updated throughout the protocol.
- Minor editorial updates were made throughout the document.
- [redacted]
- In Section 6.2, Exclusion Criteria, formatting changes were made for clarity.
- [redacted]
- Section 10.2, Laboratory Safety Assessments, Table 5, Clinical Laboratory Assessments, was updated to add serum pregnancy testing at Screening and Safety Follow-up (Visit 15) as well as HIV/hepatis and TB testing at Screening. These changes were made to align with Section 1.3, Schedule of Activities, Table 1, Schedule of Activities.
- Section 14.2.1, Clinical Research Organization, was updated to reflect that more than 1 clinical research organization is utilized in the study.
- Section 14.2.4, Central Laboratories for Laboratory Assessments, was updated to reflect that more than 1 central laboratory is utilized in the study.
- Section 14.2.5, Central Facility for Other Assessments, was updated to reflect that more than 1 central facility is utilized in the study.

LIST OF ABBREVIATIONS

Abbreviation	Definition
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
IV	intravenous injection
LLN	lower limits of normal
TB	tuberculosis
ULN	upper limits of normal

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AMENDMENT SUMMARY

Biogen Protocol 272MS303

An Open-Label, Single-Arm, Multicenter, Phase 3 Study to Evaluate the Safety and Tolerability, and Pharmacokinetics of Diroximel Fumarate (BIIB098) in Adult Participants From the Asia-Pacific Region With Relapsing Forms of Multiple Sclerosis

Version 2

Date: 14 June 2021

Version 2 of the protocol has been prepared for this amendment, which supersedes Version 1.

PRIMARY REASON FOR AMENDMENT

The primary reason for this amendment to Protocol 272MS303 is to update the contraception requirements.

New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Section 11.5, Contraception Requirements

Now reads:

All women of childbearing potential ~~and all men~~ must ensure that highly effective contraception is used during the study and for 30 days after their last dose of study treatment. **All men must ensure that effective contraception is used during the study and for 30 days after their last dose of study treatment.** In addition, participants should not donate sperm or eggs for the duration of the study and for at least 30 days after their last dose of study treatment.

[…]

For the purposes of the study, highly effective contraception **for females** is defined as use of **at least** 1 ~~(or 2)~~ of the following:

For females:

- Established use of oral, intravaginal[1], or transdermal[1] combined (estrogen and progestogen containing) hormonal methods of contraception associated with the inhibition of ovulation.
- Established use of oral, injected[1], or implanted[1] **progestogen-only** hormonal methods of contraception associated with the inhibition of ovulation.
- Placement of an intrauterine device or intrauterine hormone-releasing system.
- ~~Barrier methods of contraception where applicable according to local guidelines.~~
- Bilateral tubal occlusion.
- Sex with a male who has undergone surgical sterilization (with the appropriate postvasectomy documentation of the absence of sperm in the ejaculate).

~~For males:~~

For the purposes of the study, effective contraception for males is defined as:

- Vasectomy with negative semen analysis at follow up. If documentation is not available, the participant must use contraception.

- Condoms with spermicide ~~where applicable according to local guidelines~~.
- ~~Sex with a woman who uses the methods described for females if she is of childbearing potential.~~

---

[1] Intravaginal and transdermal combined hormonal methods of contraception and injected and implanted hormonal methods of contraception are not approved for use in Japan.

Rationale: Text in the second bullet was revised to differentiate between the combined hormonal methods mentioned in the first bullet and progestogen-only hormonal methods. Other changes were made to align with the recommendations from the Clinical Trials Facilitation and Coordination Group and to indicate which contraception methods are not approved for use in Japan.

SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

Changes to the protocol are presented chronologically. New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Section 1.1, Synopsis

The synopsis was revised to reflect changes made throughout the protocol.

Section 1.3, Schedule of Activities

Change: The table footnote was revised to align with information provided in Section 5.1, Study Overview.

Table 1: Additional Follow-Up for Participants with Lymphopenia

Assessments	LM Visits[1]		
	LM Visit 1 (2 months after Safety Follow-Up Visit ± 7 days)	LM Visit 2 (4 months after Safety Follow-Up Visit ± 7 days)	LM Visit 3 (6 months after Safety Follow-Up Visit ± 7 days)
Lymphocyte Count	X	X	X
Concomitant Medication	X	X	X

[1] Participants who complete the study or who terminate the study early and have a last measured lymphocyte count < LLN will return to the clinic for additional LM visits every 2 months starting from Visit 15 (or from the ET visit for participants who terminate the study early) for a period of 6 months (i.e., a maximum of 3 visits), until lymphocyte counts reach normal limits (≥ LLN), **or until another DMT is started that may affect lymphocyte counts (in this case, lymphocyte monitoring for that DMT will apply),** whichever occurs first. All assessments required for the Safety Follow-Up Visit (Visit 15, Table 1) should be completed for these participants prior to initiation of the LM visits.

Rationale: The footnote was updated to ensure consistent instructions throughout the protocol regarding follow-up for participants who develop lymphopenia and switch to a different treatment option.

Section 5.1, Study Overview

Change: Dose reduction was clarified to only be allowed due to flushing or GI disturbances, the Day 29 visit window was corrected to ± 3 days, and the fasting requirements for PK blood sample collection were clarified.

Now reads:

[…]

Starting on Day 8 of treatment, dose reduction to DRF 231 mg twice daily is permitted at the Investigator's discretion for participants who are unable to tolerate DRF 462 mg twice daily **due to flushing or GI disturbances**. Once a participant has stabilized after dose reduction, attempts should again be made to achieve and maintain the target maintenance dose of DRF 462 mg twice daily. If a participant remains unable to tolerate DRF 462 mg twice daily after 1 month on treatment, further dose reduction will not be permitted, and the participant will be discontinued from the study.

[…]

Intensive blood samples will be collected predose (-30 to 0 minutes predose) and at various timepoints postdose (0.5, 1, 2, 3, 4, 6, and 8 hours postdose) on Day 29 (Visit 3 ± ~~2 weeks~~**3 days**) for 7 Japanese participants who will take DRF after 10 hours of fasting**, and no food will be allowed for at least 4 hours after the dose of DRF. Participants will be allowed water ad libitum, except for 1 hour before and 2 hours after administration of the dose of DRF**. Sparse blood samples will be collected for all remaining participants (excluding those whose samples are collected for intensive PK sampling) predose (-30 to 0 minutes predose) and 2 to 3 hours postdose on Day 29 (Visit ~~4~~ **3**) and Day 57 (Visit ~~5~~ **4**).

Rationale: The text was updated to align with prior Tecfidera™ studies, which provided precise terminology for the types of events expected that could lead to dose reduction, and with the Vumerity® CDS and USPI. [redacted]. Finally, the visit window for Visit 3 on Day 29 was corrected from ± 2 weeks to ± 3 days, and the designations of the Day 29 and Day 57 visits were corrected to Visit 3 and Visit 4, respectively.

This change also affects Section 7.2, Modification of Dose and/or Treatment Schedule and Section 9.3, Pharmacokinetic Assessments.

[redacted]

Change: [redacted]

Now reads:

[redacted]

[redacted]

Rationale: [redacted]

Section 6.2, Exclusion Criteria

Change: The exclusion criteria were updated to remove those criteria that do not apply to the patient population enrolled, the treatment being studied, or the regions in which the study is being conducted; and to remove redundant criteria.

Now reads:

[…]

2. History of any clinically significant cardiac, endocrinologic, hematologic, hepatic, immunologic, infectious, metabolic, urologic, pulmonary, neurologic, dermatologic, psychiatric, and renal or other major disease that ~~is not well controlled and~~**would preclude participation in a clinical trial,** as determined by the Investigator.

[…]

~~11. Female participants with history of recent menopausal hot flashes, including hot flashes controlled by treatment (e.g., hormone-replacement therapy), per the Investigator's discretion.~~

[…]

~~16. History of any clinically significant cardiac, endocrinologic, hematologic, hepatic, immunologic, metabolic, urologic, pulmonary, neurologic, dermatologic, psychiatric, and renal, or other major disease, as determined by the Investigator.~~

[…]

~~25. Current enrollment or a plan to enroll in any interventional clinical study in which an investigational treatment or approved therapy for investigational use is administered within 30 days prior to Baseline (Visit 1) or 5 half-lives, whichever is longer.~~

[…]

~~27. Use of agents known to significantly inhibit or induce drug-metabolizing enzymes (e.g., barbiturates, phenothiazines), within 28 days prior to the Screening Visit.~~

Rationale: Exclusion criterion 2 was revised to clarify that the listed conditions are exclusionary based on Investigator discretion, not simply due to lack of control. Exclusion criterion 16 was deleted because it was a duplicate of exclusion criterion 2. Exclusion criterion 11 was deleted to clarify that menopausal hot flashes are not exclusionary and not a contraindication in the core data sheet and the USPI. The protocol allows temporary dose reduction to reduce occurrence of flushing. Exclusion criterion 25 was deleted because it was redundant with exclusion criterion 30 j and contradictory to exclusion criterion 38. Exclusion criterion 27 was deleted because DRF is metabolized by esterases and is not induced or inhibited by major drug metabolizing enzymes (e.g., CYP enzymes).

This change also affects Section 7.7.1.2, Disallowed Concomitant Therapy.

Section 6.3.2, Retesting

Change: Information on blood pressure, extending the screening period, and text related to concomitant medication criteria were removed.

Now reads: Participants who have an out-of-range laboratory result ~~or blood pressure result~~ that is not clinically significant can be retested once, as per exclusion criteria, at the discretion of the Investigator. ~~The screening period may be extended for eligible individuals who cannot complete the Day 1 Visit within 28 days of signing the ICF. Individuals who signed the ICF and subsequently do not meet concomitant medication criteria can have their Screening period extended to ensure the requirements for concomitant medication stabilization have been met.~~

Participants who have clinically significant abnormal laboratory test values should not be retested.

Rationale: The relevant information for blood pressure is provided in exclusion criterion 8. The Screening Period extension was removed to avoid confusion and potential deviations and to maintain consistency across participants. The information on concomitant medication stabilization was removed to align with Section 7, Concomitant Therapy and Procedures.

[redacted]

Change: [redacted]

Now reads: [redacted]

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

Rationale: [redacted]

[redacted]

[redacted]

Change: [redacted]

Now reads: [redacted]

[redacted]

Rationale: [redacted]

Section 8.1, Discontinuation of Study Treatment

Change: The follow-up period for participants with low lymphocyte count was revised.

Now reads:

[…]

In addition to the reasons provided above for permanent discontinuation of study treatment, study treatment must be temporarily withheld if any of the following laboratory parameters meet the following threshold limits:

[…]

- Lymphocyte count < $0.5 \times 10^3/\mu L$, confirmed by repeat testing as soon as possible. If the value remains < $0.5 \times 10^3/\mu L$ for ~~≥ 4 weeks~~**> 6 months** after treatment interruption, the participant must permanently discontinue study treatment. Participants who permanently discontinue the study with a last measured lymphocyte count < LLN will require additional follow-up to monitor their lymphocyte counts; see Table 2.

[…]

Rationale: This period was amended to align with the Vumerity CDS and the USPI.

Section 11.3.2, Adverse Events of Special Interest

Change: Progressive multifocal leukoencephalopathy was added as an AESI.

Now reads: An ~~AE of special interest~~ **AESI** is an AE of scientific and medical concern specific to this study, for which ongoing monitoring ~~and reporting are~~ **is** required **and rapid communication by the Investigator to the Sponsor may be appropriate**.

~~Events in this category for DRF will include but not limited to GI tolerability, liver, serious/opportunistic infections, lymphopenia, and cardiac AEs. Further information will be included in the SAP.~~

PML will be considered as an AESI. The Study site must formally notify the Sponsor within 24 hours of the site staff becoming aware of the AESI.

Rationale: The text was updated to align with the DRF Signal Detection Plan.

Section 12.4, Methods of Analysis for Pharmacokinetic Endpoints for Part 1 (only)

Change: The reasons for replacing a PK subset participant were clarified.

Now reads: If a participant in the PK subset with intensive blood sample collection (7 of the 50 participants) discontinues the study on Day 29 before completing the 8-hour PK sampling period **or require dose reduction or samples not collected per protocol or laboratory manual,** the participant may be replaced with one of the other enrolled participants. If this is not feasible, additional participants above the anticipated sample size of 50 may be enrolled to ensure adequate number of participants are available for intensive PK sampling.

Rationale: Text was added to clarify that participants in the PK subset can be replaced under specific circumstances to ensure that enough data are collected to determine the PK of DRF in the studied participant population.

This change also affects Section 8.3, Withdrawal of Participants From the Study.

SUMMARY OF MINOR CHANGES TO THE PROTOCOL

The following minor changes were made to the protocol, as appropriate:

- The version number and date were updated throughout the protocol.
- "Medical Director" was revised to "Medical Monitor" throughout the protocol to conform with Sponsor terminology.
- Section 2, List of Abbreviations was updated.
- Typographical and editorial errors and formatting were corrected.
- The Tecfidera and Vumerity USPI versions were updated from 2020 to 2021.
- In Table 1, Schedule of Activities, the urine pregnancy test was removed on Day 50 because the serum pregnancy test provides a more accurate result for this parameter.
- The footnotes in Table 1, Schedule of Activities, were updated to align with the corresponding descriptions of the assessments in the text of the protocol and to clarify assessment results that must be known before study treatment dosing.
- The units used throughout the protocol were revised to SI units to ensure consistency across study sites.
- Heart rate was revised to pulse rate for consistency of terminology across study sites in different regions.
- In Table 5, Clinical Laboratory Assessments, footnotes were added for clarity.
- The name of the CRO was removed from the protocol.
- In Section 11.3.3, Serious Adverse Events, duplicate text was deleted and the follow-up for SAEs that occur after the Follow-Up Safety Visit was clarified.
- Section 11.4.1, Pregnancy and Section 11.6.1, The Investigator's Safety Responsibilities were updated to clarify that the Investigator must report a pregnancy occurring in a female participant as well as in a female partner of a male participant.
- Section 12.2, Analysis Sets, the Safety analysis definition was updated from “all enrolled participants” to “all participants”.
- In Section 12.5.1, Adverse Events, TEAEs was revised to AEs for consistency in terminology with the SAP.

- In Table 6, Pharmacokinetic Analysis Timepoints, the Predose row header was amended, and the sampling window was added in the Time Window row for consistency and clarity. This change also affects Figure 1, Study Design Schematic.

LIST OF ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
CDS	core data sheet
CRF	case report form
CRO	contract research organization
CYP	cytochrome P450
DRF	diroximel fumarate
[redacted]	[redacted]
GI	gastrointestinal
MS	multiple sclerosis
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy
SAP	statistical analysis plan
TEAE	treatment emergent adverse event
USPI	United States Prescribing Information