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
NCT number:	NCT05083923
Document Date:	03-May-2024

STATISTICAL ANALYSIS PLAN

Version No.: Final 1.0

Date: 03 MAY 2024

Authors: [redacted]

Study 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

Name of Study Treatment: BIIB098 (also known as ALKS 8700)

Protocol No.: 272MS303

Study Phase: 3

APPROVAL

This document has been reviewed and approved by:		
[redacted]		
SMT Statistician	Signature	Date
[redacted]		
CDT Statistician	Signature	Date
[redacted]		
SMT Medical Director	Signature	Date

VERSION HISTORY

SAP Version	Date	Primary Reasons for Amendment
1.0	03 May 2024	Not applicable

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ALC	absolute lymphocyte count
ALT	alanine aminotransferase
[redacted]	[redacted]
AST	aspartate aminotransferase
BL	baseline
CI	confidence interval
CRF	case report form
C-SSRS	Columbia Suicide Severity Rating Scale
DMF	dimethyl fumarate
DMT	disease-modifying therapy
DRF	diroximel fumarate
ECG	electrocardiogram
[redacted]	[redacted]
ET	early termination
EOT	end of treatment
EOS	end of study
[redacted]	[redacted]
FU	follow-up Visit
[redacted]	[redacted]
GI	gastrointestinal
HES	2-hydroxyethyl succinimide
LLN	lower limit of normal
LM	lymphocyte monitoring
MedDRA	Medical Dictionary for Regulatory Activities
MMF	monomethyl fumarate
[redacted]	[redacted]
MS	multiple sclerosis
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy
RMS	relapsing forms of MS
RNA	ribonucleic acid
RRMS	relapsing-remitting MS
SAE	serious adverse event
SAP	statistical analysis plan
TC	telephone contact
ULN	upper limit of normal

1. Introduction

This Statistical Analysis Plan (SAP) describes the statistical methods that will be used during the analysis and reporting of data collected under Biogen, MA Inc. Protocol 272MS303. This SAP should be read in conjunction with the study protocol and electronic case report form (eCRF). This version of the SAP has been developed using Protocol Amendment 4 dated 23 May 2023 and the eCRF dated 11 August 2023.

2. Study Overview

2.1. Study Objectives and Endpoints

Table 1: 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 1) to Week 24 in clinical laboratory parameters, ECGs, and vital signs • Incidence of C-SSRS events at Baseline (Visit 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 2: 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 1) to Week 48 in clinical laboratory parameters, ECGs, and vital signs • Incidence of C-SSRS events at Baseline (Visit 1) and through Week 48

[redacted]

2.2. 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.

Approximately 50 Japanese participants and 50 Chinese participants are planned to be enrolled.

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.

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.

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 Week 48/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 (see, schedule of assessments in Appendix A).

Intensive blood samples will be collected pre-dose (-30 to 0 minutes pre-dose) and at various timepoints post-dose (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 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 pre-dose (-30 to 0 minutes pre-dose) and 2 to 3 hours post-dose on Day 29 (Visit 3) and Day 57 (Visit 4) for all participants not included in the intensive PK cohort, as well as for those included in both the sparse and intensive PK cohorts if it is determined that intensive PK sampling is not feasible by Day 57. For those participants in the intensive PK cohort in which intensive PK sampling is completed on Day 29 or Day 57, sparse PK sampling will not be required for said days) (see, study design schematic in Appendix B).

2.3. 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.

3. Definitions

3.1. Dates and Points of Reference

- Study Day 1: the date of the first dose of study treatment
- Study relative day:
    - For a date on or after Study Day 1

      Study Day = (Date of Interest) – (Study Day 1) + 1
    - For a date before Study Day 1

      Study Day = (Date of Interest) – (Study Day 1)
- Unless otherwise specified, baseline for assessments is defined as the last non-missing measurement taken on or prior to the first drug administration.
- Unscheduled visit measurements will not be included in the by visit summaries but will be included in the shift tables for safety parameters.
  The determination of baseline values will be based on all measurements from both scheduled and unscheduled visits.
- No visit window analysis will be defined unless otherwise specified. Nominal visits/ time points will be used for all statistical summaries.
- If a participant is terminated early from this study, he/she will be encouraged to complete the ET Visit at the time of study drug discontinuation and the Safety Follow-up Visit. In summary tables and statistical tests, all [redacted] and safety parameters measured at the ET Visit will be re-allocated according to the following rules:
    - If the ET Visit is closer to the previous scheduled visit for a given parameter and there is no measurement at that visit, the ET Visit will be re-allocated to the previous scheduled visit.
    - If the ET Visit is closer to the next scheduled visit for a given parameter and there is no measurement at that visit, the ET Visit will be re-allocated to the next scheduled visit.
    - Otherwise, the ET Visit will remain unassigned to a nominal visit.

The above re-allocation of the ET Visit will be performed for each [redacted] and safety parameter based on its individual scheduled visits in the protocol.

3.2. Study Treatment

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.

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.

3.3. Study Periods

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

3.4. Key Derived Variables

- Study period in Part 1 is defined as the period from treatment start date to the latest study visit date for Week 24 or the study early termination visit date prior to Week 24 for discontinued subjects from study visit page.
- Study period in Part 2 is defined as the period from treatment start date to last study visit date from end of study page unless otherwise specified. This is a combined study period.
- Treatment period in Part 1 is defined as period from treatment start date to last exposure date on or prior to study scheduled day corresponding to Week 24 from either drug accountability or drug administration page whichever is the latest.
- Treatment period in Part 2 is defined as period from treatment start date to last exposure date from either drug accountability or drug administration page whichever is the latest. This is a combined treatment period.

- Treatment-emergent Adverse Event (TEAE): an adverse event is considered a treatment-emergent if it starts or worsens on or after the date of the first dose of study drug in the study until 1 day after the last dose of treatment.
- Concomitant medications are defined as medications taken during the period between the first dose date and the last dose date of study drug, as well as medications taken prior to the first dose date and which are ongoing on or after the first dose date.
- [redacted]

[redacted]

3.5. 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 post-dose plasma concentration for MMF and HES; this set will be used in the PK analysis with the following subsets of participants:

- with intensive PK Analysis Set
- with sparse PK Analysis Set

4. List of Planned Study Analyses

Statistical analyses will be performed using cleaned electronic clinical report form (eCRF) data collected. This SAP covers all planned analyses of the study.

4.1. Interim Analysis

The interim analysis of the Part 1 data will be performed after all the participants in the Japanese Cohort have completed the first 24-week Treatment Period (i.e., completed the Week 24 visit or discontinued the study before the Week 24 assessment). The analysis will evaluate the primary and secondary endpoints, [redacted] defined by Week 24 for Japan regulatory interaction.

The interim analysis of the combined data (Part 1 and Part 2) may be performed after all the participants in the Japanese Cohort have completed the first 48-week Treatment Period (i.e., completed the Week 48 visit or discontinued the study before the Week 48 assessment). The analysis will evaluate the primary and secondary endpoints, [redacted] defined by Week 48 for Japan regulatory interaction.

Additional interim analysis or post-hoc analysis may be performed to support regulatory interaction.

4.2. Final Analysis

The final analysis will be performed after all the participants in the Japanese and Chinese Cohorts have completed the 48-week Treatment Period along with 2-week Safety Follow-up Period or discontinued the study before the Week 48 assessment). In case, there is at least one participant who enters Lymphocyte Monitoring Period after 2-week Safety Follow-up Period, the final analysis will be performed upon having completed all required assessments for participant in Lymphocyte Monitoring Period. The analysis will evaluate the primary and secondary endpoints, [redacted] defined by End of the Study.

5. Statistical Methods for Planned Analyses

5.1. General Principles

5.1.1. Summary statistics

In general, descriptive summary statistics will be presented by cohort and overall for Part 1 data and combined data (Part 1 and Part 2). Categorical data will be generally summarized with counts and percentages of participants. The denominator used for the percentage calculation will be clearly defined. For all non-PK summaries, continuous variables will be summarized with the following descriptive statistics: n (number of observations), (arithmetic) mean, standard deviation, median, Q1, Q3, minimum and maximum. For PK summaries, variables will be summarized additionally with geometric mean and geometric CV%. Arithmetic CV% may also be provided. Two-sided 95% CIs will be presented for selected PK parameters and [redacted] as appropriate.

5.1.2. Adjustment for covariates

In [redacted], the choice of covariate(s) to be included in the model will be guided by prior knowledge of previous studies conducted in east Asian

population, as well as by an interest in expanding basic disease area knowledge. Selected covariates will be clearly presented in the statistical outputs and CSR.

5.1.3. Subgroup Variables

A subgroup analyses may be performed as a post-hoc analysis based on scientific feasibility and interest, as well as regulatory request.

5.1.4. Pooling Data of Study Centers

Data from study centers will be pooled for all analyses.

5.1.5. Handling of Missing Data

The missing data will not be imputed. All analyses will be performed based on the observed data, unless otherwise specified.

5.1.6. Handling of BLQ Values in PK Analysis

The full details for handling of BLQ values and missing concentration during NCA analysis are provided in Pharmacokinetic Analysis Plan (PKAP).
For all descriptive statistics and mean concentration plots, the measurements that are BLQ will be set to zero. The measurements that are BLQ will be set to missing for the semi-log plots. Missing concentrations at any sampling time point will not be imputed and therefore will remain not evaluable for the analysis of concentration data.

5.1.7. Handling Partial dates

Imputation of partial dates will be performed with standard methods based on the following guiding principles:

1. Imputed dates cannot exceed the participant's study end date.
2. Worst case-scenario (WCS) is considered when imputing dates. A participant having a treatment emergent adverse event or on-treatment intervention is considered WCS.
3. Partial dates will be imputed in a manner that maximizes duration of the event or intervention, but not to override guiding principles #1 and #2.

5.1.8. Scope of Data Impacted by Public Health Emergency

Due to the public health emergency (e.g., COVID-19), study data may impact. All efforts should be made to collect data impacted by public health emergency, including treatment and study discontinuation, protocol alternations, AEs, non-drug related therapies, concomitant medications.

5.1.9. Coding Conventions for Events and Medications

All adverse events, medical history and non-drug therapy will be coded with the Medical Dictionary for Regulatory Activities (MedDRA) using the version 26.1 or higher.

Concomitant medications will be coded using the World Health Organization – Drug Dictionary (WHO-DD) based on the version September 2023 or higher.

5.1.10. Analysis Software

Data processing, tabulation of descriptive statistics, parameter estimation, and graphical representations will be performed primarily using SAS (release 9.4 or higher) for Windows. If the use of other software is warranted, the final CSR will detail what software was used and for what purposes.

All non-compartmental analysis (NCA) will be performed using a validated software, Phoenix® WinNonlin® Version 8.3 or higher (Certara, USA).

5.2. Participant Accountability

The number and percentage of participants will be summarized by cohort and overall, for the following categories:

- Participants enrolled
- Screen failure
- [redacted]
- Safety analysis set
- PK analysis set (intensive and sparse)
- Participants completed the 24-week Treatment Period
- Participants discontinued the treatment during the 24-week Treatment Period and reasons for treatment discontinuation
- Participants withdrawn from study during the 24-week Treatment Period and reasons for study withdrawal
- Participants completed Overall Treatment Period based EOT form
- Participants discontinued the overall study treatment and reasons for treatment discontinuation
- Participants completed Overall study based on EOS form
- Participants withdrawn from the overall study and reasons for study withdrawal

Percentages for all categories of participants will be calculated using the number of participants dosed or Safety Analysis Set. Disposition data will also be presented in a listing.

In addition, data listings will be provided for screening, prior subject participation, and screening laboratory assessments.

5.3. Demographics and Baseline Disease Characteristics

Participant demographic data including age, age categories in years (e.g., <=40, >40), gender, race, ethnicity, height, weight, weight categories in kilograms (e.g., <=40, >40), BMI will be summarized descriptive summary statistics by cohort and overall in Safety Analysis Set.

The following baseline disease characteristics will be summarized using descriptive summary statistics by cohort and overall, for Safety Analysis Set: [redacted], time

since MS diagnosis, time since MS onset, number of prior DMTs and [redacted] in previous 12 months.

Medical history will be summarized using system organ class and preferred term by cohort and overall, in the Safety Analysis Set.

Demographics, baseline disease characteristics and medical history data will be presented in listings.

5.4. Protocol Deviations

Participants with major protocol deviations categorized according to Protocol Deviations Management Plan (PDMP) will be summarized by cohort and overall in Safety Analysis Set, using counts and percentage. All protocol deviations will be presented in a data listing.

5.5. Study Treatment Exposure, Compliance and Concomitant Medications

The extent of treatment exposure will be assessed by the duration of treatment exposure, which will be defined as the total number of days a participant is exposed to study drug, regardless of unplanned intermittent discontinuations. The duration of treatment exposure will be calculated as the total number of days from the first dose date (Study Day 1) to the last dose date of Week 24 or Week 48.

The treatment exposure will be summarized by cohort and overall, in Safety Analysis Set, using continuous descriptive summary statistics, and summarized categorically by counts and percentage of participants with appropriate interval categories and cumulatively according to these categories.

Percent Compliance = [(total number of capsules taken) / (total number of capsules participant is expected to take)] *100.
The total number of capsules that the participant is expected to take is defined as the number of days the participant is in the study (until Week 24, or until Week 48) multiplied by 4 (4 capsules is the expected number per day), except for the first week where 2 capsules a day is expected. The percent compliance will be summarized by cohort and overall, in Safety Analysis Set, using continuous descriptive statistics, and summarized categorically by counts and percentage of participants for each of the following interval categories and cumulatively according to these categories (e.g., <70%, >=70%, >=80%, >=90%, >=100%).

Prior disease modifying treatment will be summarized by preferred terms. Concomitant medications will be summarized using preferred terms and non-drug related therapies will be summarized using system organ class and preferred term by cohort and overall in the Safety Analysis Set. Supportive listings will be provided.

[redacted]

[redacted]

5.7. Safety Endpoints

5.7.1. General Considerations

All safety analysis will be carried out using the Safety Analysis Set and will be summarized by each cohort and overall.

5.7.2. Adverse Events

An overview table, including number of participants with any TEAEs, TEAEs by severity, study treatment-related TEAEs, SAEs, study treatment-related SAEs, TEAEs

leading to drug interruption or dose reduction, TEAEs leading to study withdrawal or study treatment discontinuation will be provided by cohort and overall. SAEs leading to death will be summarized in the same table.

The incidence of TEAEs will be summarized for each cohort and overall, as follows:

- TEAEs by system organ class and preferred term (sorted by decreasing frequency and alphabetical order)
- TEAEs by system organ class
- TEAEs by preferred term
- TEAEs experienced by >=5% of participants by preferred term
- TEAEs by 4-week intervals by preferred term
- TEAEs of Special Interest by System Organ Class and Preferred Term
- Severe TEAEs by system organ class and preferred term
- Severe TEAEs by preferred term
- TEAEs by maximum severity by system organ class and preferred term
- TEAEs by maximum severity by preferred term
- Related TEAEs by system organ class and preferred term
- TEAEs that led to discontinuation of study treatment by system organ class and preferred term
- TEAEs that led to withdrawal from study by system organ class and preferred term
- TEAEs that led to drug dose reductions or interruptions by system organ class and preferred term
- TESAEs by system organ class and preferred term
- TESAEs by preferred term
- Related TESAEs by system organ class and preferred term

All AEs will be included in the participant-level listings. Supporting listings of SAEs, AEs leading to study treatment discontinuation, AEs leading to withdrawal from study, and AEs leading to death will be provided.

If more than one event occurred with the same preferred term for the same participant, the participant will be counted only once for that preferred term using the most severe occurrence for the summary table by severity. Similarly, if a participant has the same AE on multiple occasions, the closest relationship to study drug recorded for the event will be presented in the summary table for related events.

5.7.3. Adverse Events of Special Interest

Anaphylaxis and angioedema (serious events), PML (all events), Pancreatitis (all events), Serious and Opportunistic infections (serious events), Infections (serious), Lymphopenia and leucopenia (serious events), Liver injury (serious events and events leading to

treatment discontinuation), Pre-malignant conditions (all events), Malignancies (all events), Renal tubular injury (serious events), GI disorder (serious events or events leading to treatment discontinuation), Flushing and related events (serious events) and Cardiac disorders (all events).

5.7.4. Clinical Laboratory Parameters

Laboratory assessments include hematology, blood chemistry, and urinalysis with specified parameters in Appendix C.
Descriptive summary statistics for actual values, change from baseline and percent change from baseline will be provided for all quantitative laboratory parameters and presented by cohort and overall.

Mean plots with the corresponding standard error (SE) for selected hematology and chemistry laboratory parameters will be presented for each cohort overlaid on the same plot.

Hematology, blood chemistry, and urinalysis data will be summarized using shift tables. Hematology, chemistry, and continuous/numerical urinalysis laboratory values will be flagged as 'low,' 'normal,' or 'high' relative to the parameter's normal range. Non-numerical urinalysis laboratory values will be flagged as 'normal' (e.g., if result is 'negative' or 'none seen') or else as abnormal. The number and percentage of participants with shifts from baseline to high or, low, or abnormal status will be presented by cohort. Shift to low includes results from normal to low, high to low, and unknown to low. Shift to high includes results from normal to high, low to high, and unknown to high. Shift to abnormal includes normal to abnormal and unknown to abnormal. For tests with a lower normal range of 0, shift to low is not applicable and will not be displayed.

In each summary, the denominator for the percentage is the number of participants at risk for the shift. The number at risk for the shift to low is the number of participants whose baseline value is not low and who have at least one post-baseline value (based on scheduled and unscheduled visits). The number at risk for the shift to high is the number of participants whose baseline value is not high and who have at least one post-baseline value. The number at risk for the shift to abnormal is the number of participants whose baseline value is not abnormal and who have at least one post-baseline value. A participant will be counted only once for each parameter and each type of shift if there is more than one occurrence for that parameter and that type of shift among post-dose assessments.
In addition, the number and percentage of subjects with values considered potentially clinically significant (PCS) occurring at any post-baseline visit for selected parameters will be summarized using the criteria listed in Table 3.

Table 3: Criteria for Potentially Clinically Significant Laboratory Parameters

Laboratory Parameters	Criteria
Hematology	
White blood cells	≤2.8 x 10^9/L
Lymphocytes	<0.91 x 10^9/L <0.8 x 10^9/L <0.5 x 10^9/L
Neutrophils	<1.5 x 10^9/L <=1 x 10^9/L
Eosinophils	>1 x 10^9/L
Hemoglobin	≤95g/L (female) ≤115g/L (male)
Platelet count	≤75 x 10^9/L ≥700 x 10^9/L
Blood Chemistry	
Alanine aminotransferase (ALT)	≥3 x ULN >5 x ULN >10 x ULN
Aspartate aminotransferase (AST)	≥3 x ULN >5 x ULN >10 x ULN
ALP	>3 x ULN >5 x ULN >10 x ULN
GGT	>=3x ULN
Total bilirubin	>1.5 x ULN >2 x ULN
Blood urea nitrogen (BUN)	>10.71 mmol/L
Creatinine	≥176.8 umol/L
Bicarbonate	<15 mmol/L >31 mmol/L
Urinalysis	
Ketones	≥ ++++

Protein	≥ ++

For evaluation of potential serious hepatoxicity, the graphical display of x-y plot of maximum Total bilirubin will be plotted over maximum ALT (alanine aminotransferase) or AST (aspartate aminotransferase), as multiples of ULN in log scale.

Liver function data for participants with potential serious hepatoxicity that is Total bilirubin >2xULN and ALT/AST ≥ 3xULN will be provided in the listings.

For each participant with potential serious hepatoxicity, liver function data will be plotted over time as multiples of ULN in log scale.

All abnormal laboratory data will be included in the participant-level listings. A supporting listing for participants who require additional lymphocyte count monitoring visits, as per the protocol, will also be provided.

5.7.5. Vital Signs and Physical Examination

The selected vital signs parameters, performed at scheduled or unscheduled visits, will be analyzed to determine the incidence of abnormalities using the criteria listed in Table 4. The percentages will be calculated relative to the number of participants with at least 1 post-baseline value for the specific vital sign (except Weight for which it would be participants with both baseline and post-baseline assessments). The numerator is the total number of participants with at least 1 post-baseline abnormal value.

Table 4: Criteria for Potentially Clinically Significant Vital Signs

Vital Sign Parameters	Criteria
Temperature	<36 degrees C >38 degrees C
Pulse	<60 bpm >100 bpm
Systolic blood pressure	<90 mmHg >140 mmHg >160 mmHg
Diastolic blood pressure	<50 mmHg >90 mmHg >100 mmHg
Weight	7% or more increase from baseline 7% or more decrease from baseline
Respiratory Rate	<12 breaths/min >20 breaths/min

In addition, summary statistics for actual values and change from baseline will also be presented for all quantitative vital sign parameters. These tables will be presented for each cohort and overall. Participants with abnormal vital signs data will be included in the listings.

Abnormal new or worsening findings that occurred during or after administration of study treatment and are deemed by the Investigator as clinically significant will be reported as AEs and included in AE analysis, findings that occurred prior to administration of study treatment should be reported under medical history and included in the medical history analysis.

5.7.6. ECG

The number and percentage of participants with shifts to categorical values of ECG interpretation (e.g. abnormal) will be presented by each cohort and overall. The numerator in these calculations will be the number of participants with a shift. Shift to 'abnormal includes normal or unknown to 'abnormal'. The denominator in these calculations will be the number at risk. The number at risk is the number of dosed participants whose baseline ECG was normal or unknown and who had at least one post-baseline ECG result (based on scheduled and unscheduled visits).

The incidence of abnormalities for QTcF absolute values and increases from baseline will also be provided as the number and percentage of participants with any baseline and/or post-baseline QTcF values according to criteria listed in Table 5.

Table 5: Criteria for Potentially Clinically Significant QTcF

ECG Parameters	Criteria
QTcF	> 450 msec > 480 msec > 500 msec
	Change from baseline > 30 msec Change from baseline > 60 msec

In addition, summary statistics for actual values and change from baseline will also be presented for all quantitative ECG parameters. These table will be presented for each cohort and overall. Participants with abnormal ECG values and abnormal ECG interpretations will be included in the listings.

5.7.7. Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a questionnaire used to measure the presence and intensity of suicidal ideation and behavior. Suicidal behavior, suicidal ideation and non-suicidal self-injurious behavior will be summarized by each cohort and overall. The number and percentages of participants meeting one of the criteria at any post-baseline visit will be summarized for each of the categories as described in Table 6. The percentages will be calculated relative to the number of participants in safety analysis set who does not experience respective criteria at baseline.

Table 6: C-SSRS Categories for Analysis

Category	C-SSRS Item response is "YES"
Suicidal behavior	Preparatory acts or behavior Interrupted attempt Aborted attempt Suicidal behavior Complete Suicide
Suicidal ideation	Wish to be dead Non-specific active suicidal thoughts Active suicidal ideation with any methods (not plan) without intent to act Active suicidal ideation with some intent to act, without specific plan Active suicidal ideation with specific plan and intent
Non-suicidal self-injurious behavior	Present

Participants meeting one of the C-SSRS criteria at post-baseline will be included in the listings.

5.7.8. Analysis of Data impacted by Public Health Emergency

If there are enough participants, the descriptive summary statistics will be provided by cohort and overall in Safety Analysis Set for the following - Reason for treatment and study discontinuation, overview table with TEAEs, TEAEs by SOC and PT, concomitant medications by PT and non-drug related therapies by SOC and PT,. Otherwise, all data impacted by public health emergency will be provided in the corresponding listings.

5.8. Pharmacokinetic Endpoints

5.8.1. Pharmacokinetic Concentrations

The PK Analysis Set with intensive blood sample collection will consist of a subset of 7 participants in Japanese cohort.

The PK Analysis Set with sparse blood sample collection will consist of approximately 43 Japanese participants (total participants in the Japanese cohort except for the subset of participants enrolled in the intensive PK sample in which sparse PK samples are not being collected) and approximately 50 Chinese participants (total participants in the Chinese cohort).

Blood samples for PK analysis of metabolites MMF and HES will be collected at the following timepoints on any day [from Day 29 to Day 169] for intensive blood samples and on [Day 29 and Day 57] for sparse blood samples:

- Intensive blood sample collection on any day [from Day 29 to Day 169]: pre-dose (within 30 minutes), 0.5±5min, 1±5min, 2±15min, 3±15min, 4±15min, 6±15min, 8±15min hours post-dose

- Sparse blood sample collection on [Day 29 and Day 57]: pre-dose, 2 – 3 hours post-dose

MMF and HES plasma concentrations will be analyzed using the PK Analysis Set. The plasma concentrations will be presented separately for intensive and sparse subsets of data. The Plasma concentrations for sparse subsets of data will be presented by cohort. Additionally, the descriptive summary statistics and box plots will be constructed to descriptively compare MMF (post-dose) and HES (pre-dose and post dose) plasma concentrations between Japanese and Chinese participants of this study and all participants with sparse PK concentrations from ALK8700-A301.
The descriptive summary statistics will be provided by nominal sampling times of PK Study Day. Plots of individual concentrations over actual sampling time and mean concentrations (with SD/SE as error bars) over nominal sampling time will be presented both on a linear and semi-logarithmic scale for intensive subset of participants only. In addition, geometric mean concentrations (with 95% CI as error bars) over nominal sampling time will be presented both on a linear and semi-logarithmic scale for intensive subset of participants only.
LLOQ for plasma concentration of MMF and HES is 25 ng/mL and 50 ng/mL respectively.
PK parameters and/or timepoints with PK concentrations excluded from the PK analysis and summary statistics will be flagged and presented in listings.
MMF and HES plasma concentrations for all study participants will be listed.

5.8.2. Pharmacokinetic Parameters

The MMF and HES concentrations collected based on intensive blood samples will also be used to calculate the following PK parameters:

Pharmacokinetic Parameter	Definition
C_{max}	Maximum observed concentration
T_{max}	Time to reach maximum observed concentration
AUC_{last}	Area under the concentration-time curve from time zero to time of the last quantifiable concentration
AUC_{tau}	Area under the concentration-time curve over the 12-hour dosing interval
$T_{1/2}$ (MMF only)	Terminal half-life
CL/F	Apparent total body clearance at steady-state, calculated as Dose / AUCtau, assuming a systemic availability (F) of 1 for both metabolites
V_z/F	Apparent volume of distribution based on the terminal phase at steady-state (MMF only), calculated as Dose / (λ_z*AUC_{tau}), assuming F of 1 for the MMF metabolite
T_{lag}	Lag time
C_{12hr}	Imputed concentration at 12-hour postdose

The full details for derivation of PK parameters, handling of BLQ values and missing

concentration during NCA analysis are provided in the Pharmacokinetic Analysis Plan (PKAP).

All PK parameters will be summarized using descriptive statistics for intensive subset of data. For selected PK parameters, the descriptive summary statistics and box plots will be constructed to descriptively compare MMF and HES PK parameters between Japanese participants of this study and all participants with PK parameters from ALK8700-A301.

Additional PK parameters may be summarized if appropriate.

The records excluded from summary statistics will be flagged and presented in the listings. MMF and HES PK parameters for all participants will be listed.
The diagnostic statistics for PK parameters from regression analysis which are outlined in the PKAP will be provided in the listings.

The geometric mean, geometric CV%, 95% CI will be calculated assuming data follows lognormal distribution. Parameter estimates calculated from natural log transformed data will be exponentiated to obtain estimates on the original lognormal data.

6. Changes from Protocol-Specified Analyses

Not Applicable

7. Summary of Changes from the Previous Version of the SAP

Not Applicable

8. References

Not Applicable

APPENDICES

Appendix A: 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

		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**
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
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 of the protocol.
[11] Intensive PK samples will be collected in a subset of PK population (n = 7 Japan 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 of the protocol.
[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]

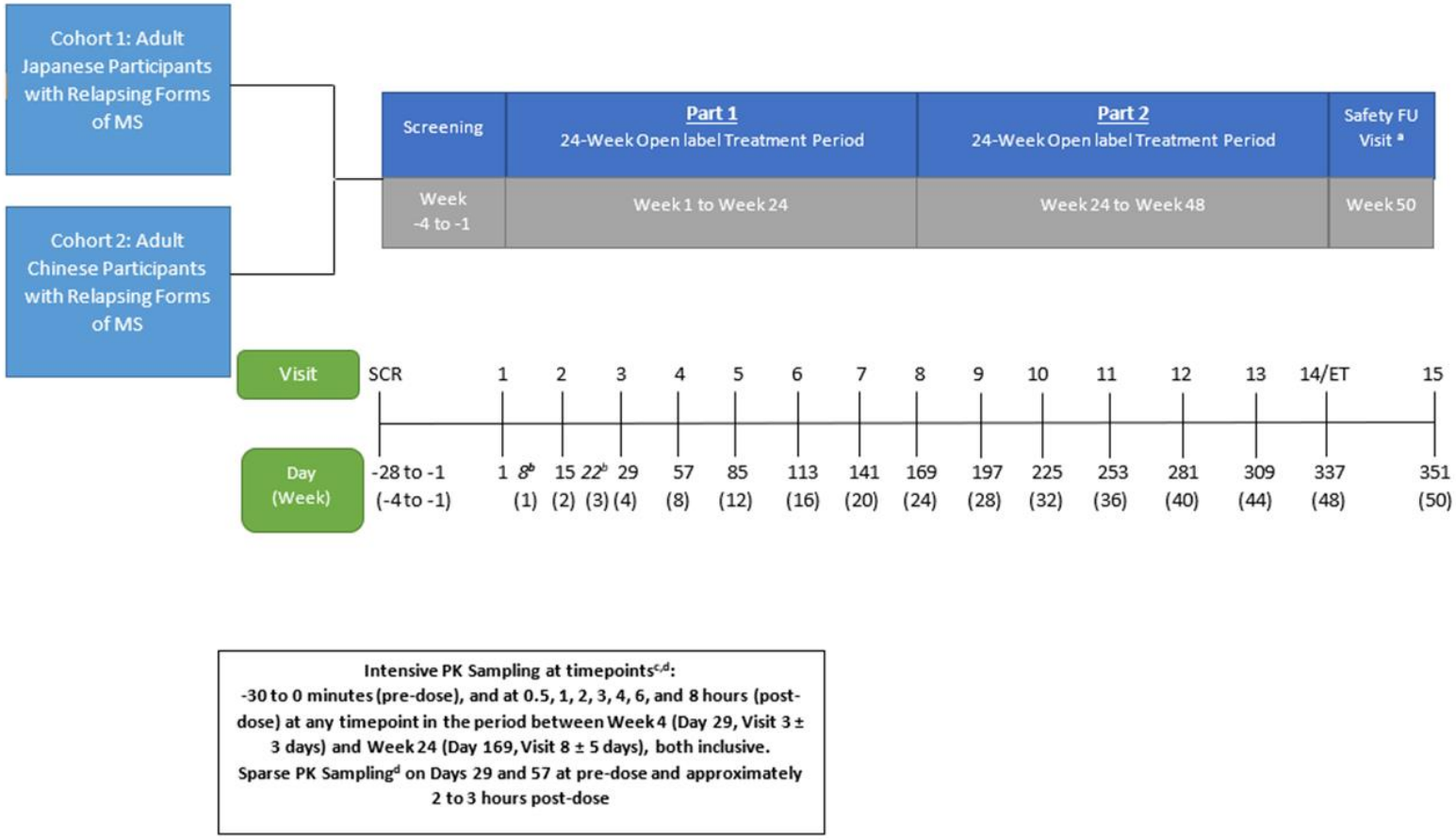
[19] Use the "Baseline Screening" version at Screening; use the "Since Last Visit" version at all other scheduled visits.

Additional Follow-Up for Participants with Lymphopenia

	LM Visits[1]		
Assessments	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) should be completed for these participants prior to initiation of the LM visits.

Appendix B: Study Design Schematics



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 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 visit.

Appendix C: Laboratory Parameters

Hematology[1]	**Biochemistry**	**Urinalysis**
Hematocrit Hemoglobin Red blood cell count Total and differential (absolute) white blood cell count Platelets	Sodium Potassium Chloride Bicarbonate Glucose Calcium Uric acid Creatinine[2] Total protein Blood urea nitrogen Albumin Total bilirubin ALT AST 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]	Color pH Specific gravity Ketones Protein Glucose Bilirubin Nitrite Urobilinogen Occult blood Microscopic examination of sediment *only if urinalysis dipstick results are abnormal* Urine albumin Urine beta-2-microglobulin Urine creatinine

[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.
[3] Only at Screening.
[4] Only at Screening and Safety Follow-Up (Visit 15).