CLINICAL STUDY PROTOCOL

ALK8700-A302 / NCT03093324

Study Title:	A Phase 3 Study in Subjects with Relapsing Remitting Multiple Sclerosis to Evaluate the Tolerability of ALKS 8700 and Dimethyl Fumarate
Document Date:	v 2.0 (incorporates Amendment 1.0): 15 Dec 2016 Original Protocol: 08 Feb 2016
Sponsor:	Alkermes, Inc. 852 Winter Street Waltham, MA 02451 USA

CONTACT INFORMATION

Table 1: Study Contact Information

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2. SYNOPSIS

Name of Sponsor/Company: Alkermes, Inc.	
Name of Investigational Product: ALKS 8700	
Name of Active Ingredient: ALKS 8700	
Title of Study: A Phase 3 Study in Subjects with Relapsing Remitting Multiple Sclerosis to Evaluate the Tolerability of ALKS 8700 and Dimethyl Fumarate	
Investigators: This study will be a multicenter study.	
Study Period: Estimated date of first subject's consent: Q1 2017 Estimated date of last subject's last visit: Q4 2018	**Phase of Development:** 3

Objectives:

- Evaluate the utility of two GI symptom scales (IGISIS and GGISIS) and endpoints derived from the scales in assessing GI tolerability in adult subjects with relapsing remitting multiple sclerosis (RRMS) (after administration of ALKS 8700 or DMF in Part A
- Compare the GI tolerability of ALKS 8700 and DMF in adult subjects with RRMS using two GI symptom scales (IGISIS and GGISIS) in Part B with endpoints informed from Part A
- Evaluate the safety and tolerability of ALKS 8700 in adult subjects with RRMS in Parts A and B

Methodology (Part A and Part B): This is a randomized, double-blind, multicenter study in adult subjects with RRMS conducted in two parts (Parts A and B). The study design is an adaptive approach where data from Part A can be used to modify the GI tolerability endpoint(s) in Part B.

Both Parts A and B are identical in study design and include a 5-week, double-blind treatment period with two blinded treatment arms (ALKS 8700 and DMF). Part A is exploratory and Part B is confirmatory. The first 120 eligible subjects will be randomized to one of the two treatment groups in Part A (n=60 per group). Once the randomization for Part A is complete, the next 300 eligible subjects will be randomized into one of the two treatment groups in Part B (n=150 per group). Accordingly, subjects 1-120 will be randomized into Part A and subjects 121-420 will be randomized into Part B. Subjects randomized in Part A will not be eligible to participate in Part B.

Following completion of Part A, the sponsor will conduct a planned, unblinded analysis of the Part A GI tolerability and safety data. Part B will be ongoing during the analysis of the Part A data. Data from Part A can be used to modify the Part B GI tolerability endpoint(s). A pooled analysis of Parts A and B will not be conducted.

All study visits in Parts A and B will be completed on an outpatient basis. The screening period is up to 4 weeks (28 days) including a 1-week lead-in period (prior to randomization) during which subjects will complete two self-administered GI symptom scales daily using e-diaries.

In Part A and Part B, subjects meeting the eligibility criteria will be randomized in a 1:1 ratio to one of two blinded treatment groups as follows:

- Group 1: ALKS 8700 462 mg BID (with 1-week titration)

- Group 2: DMF 240 mg BID (with 1-week titration).

In each part, both ALKS 8700 and DMF will be administered orally BID as blinded study drug; either ALKS 8700 462 mg BID or DMF 240 mg BID with an initial 1-week dose titration period. No dose reductions will be permitted during the study. If a subject does not tolerate the study drug during the initial 1-week dose titration period or after the dose titration period, the subject will be discontinued from the study.

Subjects will be instructed to take study drug with or without food. However subjects will be instructed to avoid taking study drug with a high-fat, high-calorie meal.

The study duration for each part is approximately 11 weeks, which includes up to 4 weeks for screening (including a 1-week lead-in period), a 5-week double-blind treatment period (with 1-week titration), and a 2-week follow-up period (for subjects not continuing into the ALK8700-A301 long-term safety study). During the 5-week treatment period (Visits 3-8), subjects will return to the clinic for weekly scheduled visits for assessments of safety, tolerability, [redacted], and clinical status. Any subject who prematurely discontinues from the study will return to the clinic for an ET visit (Visit 8) and a follow-up visit (Visit 9).

Subjects completing the entire 5 weeks of double-blind treatment in either Part A or Part B of the study will be eligible to enroll in a long-term, open-label safety study (Study ALK8700-A301) and receive ALKS 8700 for up to 96 weeks. Subjects not enrolling in the long-term safety study will return to the clinic 2 weeks following Visit 8 for a follow-up visit (Visit 9).

Number of Subjects Planned (Part A and Part B): Approximately 420 subjects randomized (120 in Part A and 300 in Part B).

Main Criteria for Inclusion (Part A and Part B): Male and female subjects between ages 18 and 65 years (inclusive) with a confirmed diagnosis of RRMS according to the revised McDonald criteria (Polman, Reingold et al. 2011) are eligible for the study. Subjects must be neurologically stable with no evidence of relapse within 30 days prior to randomization. All subjects must agree to use contraception while participating in the study and for 30 days after their last dose of study drug unless surgically sterile or post-menopausal.

Investigational Product, Dosage, Duration and Mode of Administration (Part A and Part B): ALKS 8700 capsules (231 mg) consist of delayed-release (DR) (enteric-coated) minitablets contained within a hydroxypropyl methylcellulose (HPMC) capsule for oral administration.

The doses of ALKS 8700 to be used in this study are 231 mg BID (administered as one 231 mg capsule and one placebo capsule BID for the first week) and 462 mg BID (administered as two 231 mg capsules BID for the next four weeks). Subjects will be instructed to take both capsules simultaneously for both morning and evening doses. Subjects will be instructed to take study drug with or without food. However subjects will be instructed to avoid taking study drug with a high-fat, high-calorie meal.

Reference Therapy, Dosage, Duration and Mode of Administration (Part A and Part B): Commercially available DMF (Tecfidera®; manufactured by Biogen Inc. of Cambridge, MA) will be administered as either one 120 mg capsule or one 240 mg capsule for oral administration. The DMF capsule will be over-encapsulated to create blinded study drug. The placebo matched to the ALKS 8700 and DMF drug product consists of placebo minitablets contained within the same HPMC capsule used for over-encapsulation of DMF drug product for oral administration. Placebo will be used within the treatment period to maintain the blind.

The doses of DMF to be used in this study are 120 mg BID (administered as one 120 mg capsule and one placebo capsule BID for the first week) and 240 mg BID (administered as one 240 mg capsule and one placebo capsule BID for the next four weeks). Subjects will be instructed to take study drug with or without food. Subjects will be instructed to take both capsules simultaneously for both morning and evening doses.

Duration of Study (Part A and Part B): The study duration for each part is approximately 11 weeks, which includes up to 4 weeks for screening, including a 1-week lead-in period (prior to randomization), a 5-week double-blind treatment period (with 1-week titration), and a 2-week follow-up period (for subjects not continuing in the ALK8700-A301 long-term safety study).

Criteria for Evaluation (Part A and Part B):

Endpoints:

Primary Endpoint:

The number of days with any IGISIS individual symptom intensity score ≥3 relative to exposure days in Part B.

Secondary Endpoints:

- AUC for the total IGISIS symptom intensity score relative to exposure days in Part B
- Number of days with a GGISIS symptom intensity score ≥3 relative to exposure days in Part B.

The primary and secondary endpoints may be modified based on data obtained from Part A.

Safety and Tolerability (Part A and Part B): Safety and tolerability will be assessed using the following:

- Individual GI Symptom and Impact Scale (IGISIS)
- Global GI Symptom and Impact Scale (GGISIS)
- Adverse events (AEs)
- Vital signs (temperature, respiratory rate, pulse, systolic and diastolic blood pressure)
- Clinical laboratory parameters (chemistry, hematology, urinalysis including urine albumin, urine beta-2-microglobulin, and urine creatinine)
- Electrocardiogram (ECG) parameters (heart rate, RR, QT, QTcF, QTcB, PR, and QRS intervals)
- Columbia Suicide Severity Rating Scale (C-SSRS).

Exploratory Efficacy (Part A and Part B): [redacted]

Statistical Methods (Part A and Part B):

Sample Size Considerations (Part A and Part B): The sample size calculation is based on the endpoint of the mean number of days with any IGISIS individual symptom intensity score ≥3.

Assuming the mean number of days with any IGISIS individual symptom intensity score ≥3 is 4.5 and 2.5 for the DMF and ALKS 8700 treatment groups, respectively, a sample size of 150 randomized subjects per group (300 subjects in total) in Part B will provide at least 90% power to detect about a 45% reduction in the number of days with any IGISIS individual symptom intensity score ≥3 for the ALKS 8700 treatment group relative to the DMF treatment group, at an alpha level of 0.05 (two-sided) using a negative binomial regression approach. The sample size calculation assumes a standard deviation of 5.5 in the number of days with any IGISIS individual symptom intensity score ≥3 relative to exposure days for the DMF treatment group in Part B.

With the same assumption, 60 randomized subjects per group (120 subjects in total) in Part A will provide at least 80% power to detect about a 45% reduction in the number of days with any IGISIS individual symptom intensity score ≥3 for the ALKS 8700 treatment group relative to the DMF treatment group, at an alpha level of 0.1 (two-sided).

Study Populations (Part A and Part B): The safety population includes all randomized subjects who received at least one dose of study drug (ALKS 8700 or DMF).

The Full Analysis set (FAS) Population includes all subjects who receive at least one dose of study drug and complete at least one post baseline GI tolerability assessment.

[redacted]

Safety Analyses (Part A and Part B): All safety data will be summarized using descriptive statistics for Part A and Part B separately using safety population. The number and percentage of subjects with treatment-emergent adverse events (TEAEs) will be summarized by treatment group and overall by system organ class and by preferred term. Serious Adverse Events (SAEs) and AEs resulting in discontinuation will also be summarized.

The number and percentage of subjects with suicidal ideation or behavior as assessed by C-SSRS will also be summarized by treatment group. Change from baseline in other safety parameters (clinical laboratory parameters, vital signs, and ECG) will be summarized by treatment group and visit.

GI Tolerability Analyses (Part A and Part B): All GI tolerability analyses based on the IGISIS and GGISIS will be summarized using descriptive statistics for Part A and Part B separately using the FAS population. There are no formal statistical comparisons planned for Part A; Part A is exploratory, Part B is confirmatory.

The analyses of the primary endpoint will be carried out using a negative binomial regression with treatment as factor and total intensity score from 5 individual symptoms at baseline as a covariate.

Area under the curve (AUC) for the total IGISIS symptom intensity score relative to days exposed will be analyzed using an analysis of covariance model (ANCOVA) with treatment as a factor and the total intensity score from 5 individual symptoms at baseline as a covariate.

Exploratory Efficacy Analyses (Part A and Part B): [redacted]

[redacted]

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4. LIST OF ABBREVIATIONS

The following abbreviations are used in this study protocol.

Abbreviation or Term	Explanation or Definition
AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
AUC	Area Under the Concentration-Time curve
AUC_{last}	Area under the plasma concentration versus time curve calculated using the trapezoidal method from time zero to the last observed concentration above the lower limit of quantification
BID	Twice Daily
CI	Confidence Interval
C_{max}	Maximum observed concentration
CRO	Contract research organization
CSA	Clinical Study Agreement
C-SSRS	Columbia Suicide Severity Rating Scale
CV%	Percent coefficient of variation
DMF	Dimethyl Fumarate (Tecfidera®)
DMT	Disease-Modifying Therapies
DR	Delayed Release
IEC	Independent Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated glomerular filtration rate
EDSS	Expanded Disability Status Scale
ET	Early Fermination
EQ-5Q-5L	EuroQoL Group health outcome measure
FAS	Full Analysis Set
FS	Functional System
GCP	Good Clinical Practice
GI	Gastrointestinal
GGISIS	Global GI Symptom and Impact Scale

Abbreviation or Term	Explanation or Definition
HIV	Human Immunodeficiency Virus
HPMC	Hydroxypropyl Methylcellulose
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IGISIS	Individual GI Symptom and Impact Scale
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
MMF	Monomethyl Fumarate
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
PK	Pharmacokinetic
PML	Progressive Multifocal Leukoencephalopathy
QTcB	QT interval corrected using Bazett's formula
QTcF	QT interval corrected using Fridericia's formula
RDC-6567	Metabolite of ALKS 8700
RRMS	Relapsing-Remitting Multiple Sclerosis
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
[redacted]	[redacted]
[redacted]	[redacted]
TEAE	Treatment-Emergent Adverse Event
TSH	Thyroid-Stimulating Hormone
ULN	Upper limit of Normal
WHO	World Health Organization

5. INTRODUCTION

5.1. Disease Overview

Multiple sclerosis (MS) is a progressive neurological disease marked by demyelination and axonal destruction that currently affects approximately 2.5 million people worldwide with 5 to 10 new cases per 100,000 people each year (Ropper 2012); (Tremlett, Zhao et al. 2010). Relapsing-remitting MS (RRMS) is the most common form of MS with 80 to 90% of all MS patients initially presenting with an RRMS disease course. Without treatment, patients can experience frequent relapses, a significant decrease in quality of life, and can develop the more severe type, secondary-progressive MS, leading to severe physical disability.

Although MS remains an incurable, chronic disease, recent therapeutic advancements have led to significant improvement in the management of the disease. Disease-modifying therapies (DMTs) are widely used for the treatment of relapsing forms of MS (Multiple Sclerosis Coalition 2015) and have been demonstrated to delay disease progression, prevent disability, and improve quality of life. Of the approved DMTs, Tecfidera® (dimethyl fumarate [DMF] (Biogen 2015) is a first-line oral therapy that has become one of the most commonly prescribed agents for the treatment of relapsing forms of MS due to its robust efficacy and overall favorable safety profile (Dubey, Kieseier et al. 2015).

DMF is a fumaric acid ester salt that undergoes rapid presystemic hydrolysis to its active metabolite, monomethyl fumarate (MMF) (Phillips and Fox 2013) (Werdenberg, Joshi et al. 2003) . While DMF and, by extrapolation, its metabolite, MMF, have demonstrated robust efficacy and a favorable safety profile in Phase 3 pivotal clinical trials (DEFINE and CONFIRM; (Gold, Kappos et al. 2012); (Phillips and Fox 2013), gastrointestinal (GI) adverse events (AEs) were commonly reported and the leading cause of study drug discontinuation due to AEs (Center for Drug Evaluation and Research 2013). The greatest incidence of GI AEs occurred in the first month of treatment (Center for Drug Evaluation and Research 2013);(Phillips, Selmaj et al. 2015). In addition, more than a third of patients experiencing GI symptoms during the first three months of treatment had their DMF dosage interrupted, reduced, or discontinued, which could lead to less than optimal levels of MMF (Phillips, Selmaj et al. 2015).

In addition to the Phase 3 studies, subsequent DMF clinical trials utilizing GI symptom questionnaires (Fox, Vasquez et al. 2014); (O'Gorman, Russell et al. 2015); (Tornatore, Li et al. 2014) as well as "real world" registry studies (Chaves, Ganguly et al. 2015) have reported even higher rates of GI events and discontinuations due to GI events, perhaps reflective of a more accurate and complete picture of patient experience. Clinical data indicate that GI events represent an important issue for patients taking DMF, and there is a need to improve on GI-related tolerability to mitigate related negative consequences, including issues with treatment adherence and discontinuation.

Alkermes is developing ALKS 8700 as an oral treatment for relapsing forms of MS. ALKS 8700 is an amino ethyl ester of MMF that undergoes hydrolysis through esterases to produce MMF. MMF is the active metabolite in the approved drug, Tecfidera® (dimethyl fumarate [DMF]), which is effective in treating relapsing forms of MS. The ALKS 8700 drug product is a twice daily (BID), delayed release (DR) oral dosage form known as ALKS 8700 DR (for convenience,

however, it will be referred to as "ALKS 8700" in this document). Based on nonclinical studies to date, ALKS 8700 is rapidly converted to MMF in vivo, and systemic ALKS 8700 exposure has not been observed. The ALKS 8700 drug product yields MMF exposure comparable to DMF, and is expected to provide efficacy comparable to DMF with potentially improved GI tolerability.

5.2. Clinical Studies

Four Phase 1 studies to evaluate the safety, tolerability, and pharmacokinetics (PK) of ALKS 8700 in healthy adults (Study ALK8700-001, ALK8700-A102, ALK8700-A103, and ALK8700-A104) have been completed. Four Phase 1 studies (ALK8700-A105, ALK8700-A106, ALK8700-A107, and ALK8700-A109) have been clinically completed and the data analyses are ongoing.

The general pharmacokinetic characteristics have been evaluated in the abovementioned completed Phase 1 studies. ALKS 8700 undergoes rapid presystemic hydrolysis to MMF with a dose proportionate increase in MMF exposure over the ALKS 8700 dose range tested (49 to 980 mg; ALK8700-001).

Administration of ALKS 8700 420 mg with a high-fat, high-calorie meal delayed absorption of MMF, resulting in a significant decrease in maximum observed concentration (C_{max}) (44%) and a modest reduction in AUC_{last} (11%) (ALK8700-A102). Minimal accumulation of MMF was observed in plasma following repeated administration of 210 to 630 mg BID for 5 days (ALK8700-A102). In addition, RDC-6567 has been identified as a major human metabolite of ALKS 8700 that is primarily eliminated in urine (ALK8700-A105).

The relative bioavailability of ALKS 8700 462 mg compared with DMF 240 mg was initially evaluated in a fasted condition (ALK8700-A103) as well as in the presence of a high-fat, high-calorie meal (ALK8700-A104). ALKS 8700 462 mg resulted in similar MMF exposure to DMF 240 mg under fasted conditions and met the PK criteria for bioequivalence to DMF based on C_{max} and AUC (ALK8700-A103). ALKS 8700 462 mg resulted is similar MMF exposure to DMF 240 mg with a high-fat, high-calorie meal and met the PK criteria for bioequivalence to DMF for AUC, but C_{max} was 26% lower for ALKS 8700 as compared to DMF (ALK8700-A104).

Given the reduction in C_{max} with a high-fat, high-calorie meal, an additional study was conducted evaluating meal compositions with lower fat and caloric content. In this study (ALK8700-A109), MMF AUC for ALKS 8700, when administered with medium-fat, medium-calorie and low-fat, low-calorie meals, was comparable to DMF under fasted conditions. Administration of ALKS 8700 with medium-fat, medium-calorie and low-fat, low-calorie meals resulted in reductions in C_{max} that were less than that observed for DMF when administered with a high-fat, high-calorie meal (ALK8700-A109).Therefore, when co-administered with medium-fat, medium-calorie and low-fat, low-calorie meals, ALKS 8700 resulted in MMF exposure within the accepted therapeutic exposure range for DMF. Accordingly, ALKS 8700 can be administered with or without food but should be avoided with high-fat, high-calorie meals as described in Section 9.1.

Overall safety analyses from the abovementioned completed Phase 1 clinical studies have demonstrated that ALKS 8700 has been generally well tolerated at all doses tested (49 mg to

980 mg) with no reported serious adverse events (SAEs) and no unanticipated or unforeseen clinical safety issues after single or repeat dosing in healthy subjects. All reported treatment emergent adverse events (TEAEs) have been mild or moderate in severity (predominantly mild), and there have been no relevant differences in tolerability between single and repeat dosing at the same dose levels. The most commonly reported TEAEs have been flushing followed by GI-TEAEs which have both occurred in a dose-dependent manner. GI-TEAEs have been observed with ALKS 8700 at consistently low rates throughout the studies at dose levels comparable (in terms of MMF exposure) to the therapeutic maintenance dose of DMF (240 mg). Results from Phase 1 clinical investigations available to date on the pharmacokinetics, safety, and tolerability of ALKS 8700 are summarized in the Investigator's Brochure.

5.3. Nonclinical Studies

A comprehensive series of nonclinical studies were conducted to support the clinical development of ALKS 8700 and are described in more detail in the ALKS 8700 Investigator's Brochure.

Results from genetic toxicity assays showed that ALKS 8700 was non-mutagenic in bacteria in vitro and was associated with chromosomal aberrations in vitro in human peripheral blood lymphocytes but not in vivo in rats. ALKS 8700 had limited capacity to inhibit hERG (human ether-à-go-go-related gene) potassium channel activity in a human cell line (ie, IC50 >300 µM). Inhibition of hERG current has been associated with increased duration of the cardiac action potential and prolongation of the QT interval.

General toxicology findings were generally similar to those described for DMF and consisted of target organ effects in kidney (tubular degeneration/necrosis with regeneration, tubular hypertrophy, and interstitial fibrosis in rats, mice, and/or monkeys), gastrointestinal tract (mucosal hyperplasia of the nonglandular stomach and duodenum of rats and/or mice), bone (physeal dysplasia of proximal and distal femur and proximal tibia in monkeys), heart (inflammation/necrosis in rats), and testes (minimal degeneration in mice).

ALKS 8700 was evaluated for developmental and reproductive toxicity in rats and rabbits. In fertility studies in male and female rats, no notable fertility or embryonic developmental findings occurred. In embryo-fetal development studies in rats and rabbits, noteworthy findings of fetal vertebral malformations were observed in rabbits but not in rats.

The safety evaluation of ALKS 8700 and its metabolites (ie, MMF, RDC-6567, and RDC-8439) was adequate as systemic exposures of these analytes in nonclinical studies were similar to or exceeded those in humans at the Phase 3 clinical dose of 924 mg/day (462 mg BID) of ALKS 8700. For the major human metabolites MMF and RDC-6567, the exposures associated with adverse findings in nonclinical safety studies are detailed in the ALKS 8700 Investigator's Brochure.

Data generated through additional nonclinical studies will continue to be evaluated as they become available, including any potential influence on the risk-benefit profile of ALKS 8700.

5.4. Dose Selection

The selected dose level of ALKS 8700 (462 mg) is supported by clinical safety, tolerability, and PK data from prior clinical studies (Study ALK8700-001, ALK8700-A102, ALK8700-A103, and ALK8700-A104).

The doses of ALKS 8700 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 a completed single ascending dose study (Study ALK8700-001) and in a completed repeat dose clinical study (Study ALK8700-A102). Safety data from both studies (Study ALK8700-001 and ALK8700-A102) indicate that doses of 210 mg, 420 mg and 630 mg (bracketing the doses to be used in this study), administered either as a single dose or twice daily for five days in healthy subjects were generally well tolerated with no relevant differences in safety or tolerability between single or repeat dosing at each dose level. In addition, from Study ALK8700-A102, it was demonstrated that the incidence of flushing with ALKS 8700 was lower in the fed condition (37.5% of subjects) compared to the fasted condition (50.0% of subjects).

The appropriateness of a maintenance 462 mg dose of ALKS 8700 was confirmed by two relative bioavailability studies (Study ALK8700-A103 and ALK8700-A104) where PK results show that ALKS 8700 462 mg results in comparable MMF exposure to DMF 240 mg under fasted conditions, as well as in the presence of a high-fat, high-calorie meal. MMF exposure following administration of ALKS 8700 provides comparable exposure to DMF in the fasted condition (Study ALK8700-A103) and met the PK criteria for bioequivalence to DMF for AUC and C_{max}. While total systemic exposure to MMF was comparable between ALKS 8700 and DMF in the presence of a high-fat, high-calorie meal, C_{max} was 26% lower (ALK8700-A104). In a subsequent study (ALK8700-A109), it was found that medium-fat, medium-calorie and low-fat, low-calorie meals resulted in reductions in C_{max} that were no greater than that observed with DMF when co-administered with a high-fat, high-calorie meal. Therefore, ALKS 8700 can be taken with or without food. However, subjects will be instructed to avoid taking study drug with a high-fat, high-calorie meal. Administration with food may reduce the incidence of flushing (as observed in Study ALK8700-A102).

The dose levels of DMF in this study (120 mg BID during initial dose titration followed by 240 mg BID as maintenance dose) are consistent with the approved dose administration information in the Tecfidera label (Biogen 2015). Additionally, the Tecfidera label states that Tecfidera can be taken with or without food and that administration with food may reduce the incidence of flushing (Biogen 2015).

5.5. Study Rationale

Completed Phase 1 clinical studies to date with ALKS 8700 in healthy volunteers have indicated low rates of GI AEs with a potentially favorable GI tolerability profile compared to DMF. This Phase 3 study, conducted in two parts (A and B), is designed to further evaluate the GI tolerability of ALKS 8700 in relation to DMF in a patient population with RRMS using two subject-rated GI symptom scales: the Individual GI Symptom and Impact Scale [IGISIS] and the Global GI Symptom and Impact Scale [GGISIS].

The study will utilize an adaptive approach, where data from Part A can be used to modify the GI tolerability endpoint(s) in Part B. (The content of the two GI symptom scales themselves will

not be modified between Part A and Part B.) Accordingly, Part A will serve as an initial exploratory evaluation of the two GI symptom scales (Section 8.3.10.1) and endpoints derived from the scales while Part B will serve as a confirmatory evaluation of the scales and related endpoints as informed from Part A. In addition, this two-part design allows for uninterrupted and sequential enrollment of Part A and Part B under one protocol with associated logistical efficiencies.

Both Parts A and B are identical in study design and include a 5-week, double-blind treatment period with two blinded treatment arms (ALKS 8700 and DMF). Each part, however, will be analyzed separately and will not be pooled.

6. OBJECTIVES

The objectives of this study are to:

- Evaluate the utility of two GI symptom scales (IGISIS and GGISIS) and endpoints derived from the scales in assessing GI tolerability in adult subjects with RRMS after administration of ALKS 8700 or DMF in Part A
- Compare the GI tolerability of ALKS 8700 and DMF in adult subjects with RRMS using two GI symptom scales (IGISIS and GGISIS) in Part B with endpoints informed from Part A
- Evaluate the safety and tolerability of ALKS 8700 in adult subjects with RRMS in Parts A and B

7. SELECTION AND WITHDRAWAL OF SUBJECTS

7.1. Subject Inclusion Criteria

1. Is willing and able to provide informed consent
2. Capable of understanding and complying with the protocol
3. Male and female adults aged 18 to 65 years, inclusive, at screening (Visit 1)
4. Has a confirmed diagnosis of RRMS according to the revised 2010 McDonald criteria (Polman, Reingold et al. 2011)
5. Baseline Expanded Disability Status Scale (EDSS) score of 0.0-6.0 at screening (Visit 1) and randomization (Visit 3)
6. Neurologically stable with no evidence of relapse within 30 days prior to randomization (Visit 3)
7. Agrees to use an acceptable method of contraception for the duration of the study and for 30 days after any study drug administration or is surgically sterile or post-menopausal (see Section 8.4.1)

7.2. Subject Exclusion Criteria

1. Have any finding(s) that in the view of the Investigator or the Medical Monitor would compromise the safety of the subject, affect the subject's ability to adhere to the protocol visit schedule or to fulfill visit requirements, or would make the subject unsuitable for participation in the study (including overall clinical assessment)
2. Diagnosis of primary progressive, secondary progressive, or progressive relapsing MS as defined by Lublin and Reingold (Lublin and Reingold 1996)
3. History of clinically significant cardiovascular, pulmonary, gastrointestinal (including inflammatory bowel disease, peptic ulcer disease and irritable bowel syndrome), dermatologic, psychiatric, neurologic (other than MS), endocrine, renal and/or other major disease that would preclude participation in a clinical trial
4. History of GI surgery (except appendectomy that occurred more than 6 months prior to screening; other prior surgeries may be permitted based on Medical Monitor approval)
5. History of clinically significant recurring or active gastrointestinal symptoms (eg, nausea, diarrhea, dyspepsia, constipation) within 3 months of screening
6. Chronic use (≥7 days) of medical therapy to treat any GI symptoms within 1 month of screening, unless an exception is granted by the Medical Monitor
7. Has a clinically significant medical condition or observed abnormality at screening (eg, clinically significant physical examination finding, vital sign result, ECG result, or laboratory test result)

8. Two or more Individual GI Symptoms and Impact Scale (IGISIS) individual symptom intensity scores ≥3 during the 1-week lead-in evaluation period prior to randomization (Visit 3)
9. Completes <75% of the IGISIS and/or GGISIS ediary entries scheduled to be completed during the lead-in period prior to randomization (Visit 3) unless an exception is granted by the Medical Monitor
10. History of malignancy, unless an exception is granted by the Medical Monitor (eg, subjects with basal cell carcinoma that has been completely excised prior to study entry may remain eligible)
11. History of a myocardial infarction, including a silent myocardial infarction identified on ECG, or unstable angina
12. History of clinically significant drug or alcohol abuse within the past year prior to screening (per Investigator judgment)
13. Positive serology test for hepatitis C antibody, hepatitis B surface antigen (HBsAg), or human immunodeficiency virus (HIV) antibody at screening (Visit 1)
14. Any of the following abnormal blood tests at screening (Visit 1):
    - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥2 times the upper limit of normal (ULN)
    - Thyroid-stimulating hormone (TSH) level higher than the ULN by 10% or more at screening
    - Estimated glomerular filtration rate (eGFR) ≤60 mL/min/1.73m^2 (using the CKD-EPI equation; (Levey, Stevens et al. 2009)
    - Lymphocyte count <0.9 x 10^3/µL
15. Any of the following abnormal urine tests at screening (Visit 1):
    - Beta-2 microglobulin >0.3 µg/mL
    - Albumin to creatinine ratio >200 mg/g
16. Clinically significant history of suicidal ideation or suicidal behavior in the last 12 months as assessed by the Columbia Suicide Severity Rating Scale (C-SSRS) at screening (Visit 1)
17. History of treatment with or has received the following:
    - Fumaderm®, Tecfidera, total lymphoid irradiation, cladribine, T-cell or T-cell receptor vaccination, total body irradiation or total lymphoid irradiation at any time
    - Stem cell transplantation at any time
    - Mitoxantrone or other immunosuppressant agents (eg, cyclosporine, cyclophosphamide, methotrexate, mycophenolate) within 2 years prior to randomization (Visit 3)

- Teriflunomide within 2 years of Visit 2, unless the serum/plasma concentration of teriflunomide is <0.020 mcg/mL (<20 ng/mL) to randomization (Visit 3) (an accelerated elimination procedure for teriflunomide with cholestyramine is permitted during screening)
- Natalizumab within 8 weeks prior to randomization (Visit 3), or any prior use of alemtuzumab
- Fingolimod within 90 days prior to randomization (Visit 3)
- Daclizumab within 6 months prior to Visit 3
- B-cell targeted therapies for the treatment of MS (eg, ocrelizumab, rituximab) within 12 months of screening; greater than 12 months of screening is permissible with evidence that the CD19 cells have returned to within normal range (per local lab reference range)
- 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 24 months will be determined on a case-by-case basis by the Medical Monitor
- Steroids, with the exception of topical or inhaled steroids, or IV immunoglobulin within 30 days prior to randomization (Visit 3)

18. Current or prior participation in a clinical trial within 3 months of screening (Visit 1)
19. Subject is pregnant or breastfeeding or plans to become pregnant or begin breastfeeding at any point during the study and for 30 days after any study drug administration
20. Unwillingness or inability to comply with the requirements of the protocol, including the presence of any condition (physical, mental, or social) that is likely to affect the subject's ability to comply with the protocol.
21. Employed by Alkermes, contract research organization (CRO) or study site (permanent, temporary contract worker, or designee responsible for the conduct of the study) or is immediate family of an Alkermes, CRO, or study site employee. Immediate family is defined as a spouse, parent, sibling or child, whether biological or legally adopted.

7.3. Subject Withdrawal

In each Part, a treatment completer will be a subject who completes the 5-week treatment period. Subjects completing Visit 8 will be categorized as completing the study. A subject may be discontinued from the study at any time if the subject, Investigator, or Sponsor determines that it is not in the best interest of the subject to continue participation. Reasons for discontinuation include:

- Adverse event
- Lack of efficacy
- Lost to follow-up
- Withdrawal by subject

- Protocol deviation (non-compliance with Study Drug or Study Procedures)
- Physician decision
- Pregnancy
- Study terminated by sponsor
- Other

If a subject withdraws from the study for any reason (except for withdrawal of consent), any ongoing AEs will be followed until resolution, until deemed stable by the Investigator, or until the subject is deemed by the Investigator to be lost to follow-up. If, in the opinion of the Investigator, it is necessary to monitor a subject beyond the safety follow-up visit, the follow-up period may be extended as necessary. In such instances, the Sponsor and Investigator will agree to an acceptable follow-up schedule.

In the event that a subject chooses to withdraw from the study, the Investigator should make a reasonable effort to ascertain the reason(s) for withdrawal, while fully respecting the subject's rights. Subjects discontinuing study drug and withdrawing from the study are to be asked to return to the clinic for an Early Termination (ET) visit (Visit 8) and a follow-up visit (Visit 9). The ET visit (Visit 8) should be scheduled as close as possible to the subject's last dose and will mimic the assessments scheduled to be conducted at Visit 8 for subjects who complete the 5-week treatment period (see Table 2). If the subject fails or refuses to return to the study center, an attempt must be made to contact the subject by telephone in order to assess as many safety and efficacy parameters as possible. All data collected over the telephone must be documented and kept in the subject's record.

The Investigator must maintain a record of all subjects who fail to complete the study. The reason for study discontinuation will be documented on the appropriate electronic case report form (eCRF). If a subject is lost to follow-up, a reasonable attempt to contact the subject must be made and documented.

7.4. Replacement of Subjects

Subjects who withdraw after receiving the first dose of study drug in this study will not be replaced.

8. STUDY DESIGN

8.1. Overall Study Design and Plan

This is a randomized, double-blind, multicenter study in adult subjects with RRMS conducted in two parts (Parts A and B). The study design is an adaptive approach where data from Part A can be used to modify the GI tolerability endpoint(s) in Part B.

Both Parts A and B are identical in study design and include a 5-week, double-blind treatment period with two blinded treatment arms (ALKS 8700 and DMF). Part A is exploratory and Part B is confirmatory. The first 120 eligible subjects will be randomized to one of the two treatment groups in Part A (n=60 per group). Once the randomization for Part A is complete, the next 300 eligible subjects will be randomized into one of the two treatment groups in Part B (n=150 per group). Accordingly, subjects 1-120 will be randomized into Part A and subjects 121- 420 will be randomized into Part B. Subjects randomized in Part A will not be eligible to participate in Part B.

Following completion of Part A, the sponsor will conduct a planned, unblinded analysis of the Part A GI tolerability and safety data. Part B will be ongoing during the analysis of the Part A data. Data from Part A can be used to modify the Part B GI tolerability endpoint(s). A pooled analysis of Parts A and B will not be conducted.

All study visits in Parts A and B will be completed on an outpatient basis. The screening period is up to 4 weeks including a 1-week lead-in period (prior to randomization) during which subjects will complete two self-administered GI symptom scales daily using e-diaries.

In Part A and Part B, subjects meeting the eligibility criteria will be randomized in a 1:1 ratio to one of two blinded treatment groups as follows:

- Group 1: ALKS 8700 462 mg BID (with 1-week titration)
- Group 2: DMF 240 mg BID (with 1-week titration)

In each part, both ALKS 8700 and DMF will be administered orally BID as blinded study drug; either ALKS 8700 462 mg BID or DMF 240 mg BID with an initial 1-week dose titration period (Table 4). Subjects will be instructed to take study drug with or without food. However subjects will be instructed to avoid taking study drug with a high-fat, high-calorie meal. Dosing is described in detail in Section 9.1.

No dose reductions will be permitted during the study. If a subject does not tolerate the study drug during the initial 1-week dose titration period or after the dose titration period, the subject will be discontinued from the study.

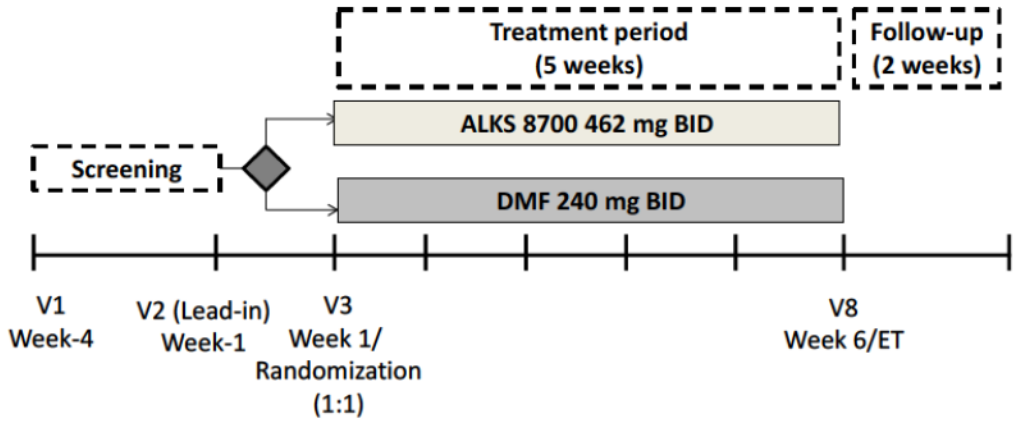
The study duration for each part is approximately 11 weeks, which includes up to 4 weeks for screening (including a 1-week lead-in period), a 5-week double-blind treatment period (with 1-week titration), and a 2-week follow-up period (for subjects not continuing into the ALK8700-A301 long-term safety study). During the 5-week treatment period (Visits 3-8), subjects will return to the clinic for weekly scheduled visits for assessments of safety, tolerability, [redacted], and clinical

status (see Figure 1). Any subject who prematurely discontinues from the study will return to the clinic for an ET visit (Visit 8) and a follow-up visit (Visit 9).

Subjects completing the entire 5 weeks of double-blind treatment in either Part A or Part B of the study will be eligible to enroll in a long-term, open-label safety study (Study ALK8700-A301) and receive ALKS 8700 for up to 96 weeks. Subjects not enrolling in the long-term safety study will return to the clinic 2 weeks following Visit 8 for a follow-up visit (Visit 9).

A schematic of the study design is provided in Figure 1 below.

Figure 1: Study Design Schematic (Part A and Part B)



*Subjects completing the 5-week treatment period will either continue into the ALK8700-A301 long-term safety study or enter the safety follow-up period and return to Visit 9

8.2. Schedule of Visits and Assessments

The schedule of visits and assessments is shown in Table 2.

For a missed visit, the site should attempt to contact the subject to reschedule.

Premature discontinuation procedures are provided in Section 7.3.

Table 2: Schedule of Assessments (Part A and Part B)

	Screening		5-Week Randomized Treatment[1]						Follow-up
Visit	**1[2]**	**2[3]**	**3**	**4**	**5**	**6**	**7**	**8 (ET)**	**9**
Week	**-4**	**-1 (±2 days)**	**1 (±3 days)**	**2 (±3 days)**	**3 (±3 days)**	**4 (±3 days)**	**5 (±3 days)**	**6 (±3 days)**	**8 (±4 days)**
Informed Consent	X								
Eligibility Criteria Review	X		X[4]						
Demographics	X								
Medical History	X								
Height	X								
Weight	X		X[4]					X	
Physical Exam[5]	X		X[4]					X	X
Concomitant Medication Review	X	X	X	X	X	X	X	X	X
Adverse Event Monitoring	X	X	X	X	X	X	X	X	X
Serology Testing[6]	X								
Pregnancy Test[7]	X		X[4]						
Vital Signs[8]	X		X[4]	X	X	X	X	X	X
Standard 12-Lead ECG[9]	X		X[4]		X			X	X
[redacted]									
Biochemistry, Urinalysis, & Hematology Samples[11]	X		X[4]		X			X	X

Table 2: Schedule of Assessments (Part A and Part B) (Continued)

	Screening		5-Week Randomized Treatment[1]						Follow-up
Visit	**1[2]**	**2[3]**	**3**	**4**	**5**	**6**	**7**	**8 (ET)**	**9**
Week	**-4**	**-1 (±2 days)**	**1 (±3 days)**	**2 (±3 days)**	**3 (±3 days)**	**4 (±3 days)**	**5 (±3 days)**	**6 (±3 days)**	**8 (±4 days)**
Brain MRI	X[12]								
IGISIS		X[13]	X[14]	X[14]	X[14]	X[14]	X[14]	X[14]	
GGISIS		X[13]	X[14]	X[14]	X[14]	X[14]	X[14]	X[14]	
C-SSRS[15]	X		X[4]		X			X	X
[redacted]									
Randomization			X						
Study Drug Dispensation/Accountability			X	X	X	X	X	X	

Abbreviations: C-SSRS=Columbia Suicide Severity Rating Scale; ECG=electrocardiogram; [redacted]; ET=early termination; [redacted]; GI=gastrointestinal; GGISIS=Global GI Symptom and Impact Scale; IGISS=Individual GI Symptom and Impact Scale; MRI=magnetic resonance imaging; [redacted]

[2] To be conducted within 4 weeks (-28 days) of randomization (Visit 3).

[3] To be conducted at the beginning of the 1-week lead-in period (during the 4 week screening period).

[redacted]

A complete physical examination at screening (Visit 1); a brief physical examination at all other scheduled visits.

[6] Serology testing includes hepatitis B surface antigen, hepatitis C antibody, and human immunodeficiency virus antibody.

[7] Serum pregnancy at screening (Visit 1); urine pregnancy at randomization (Visit 3).

[8] Vital sign measurements include temperature, respiratory rate, blood pressure, and heart rate. Vital signs to be collected predose at randomization (Visit 3) and at any time at all other scheduled visits. Blood pressure, respiratory rate, and heart rate will be measured after the subject has been in a seated or supine position for at least 5 minutes.

[9] ECGs to be collected predose at randomization (Visit 3) and at any time at all other scheduled visits. ECGs will be collected after the subject has been in a supine position for at least 5 minutes.

[10] [redacted]

[11] Urinalysis includes urine dipstick, urine microscopy (as applicable), urine beta-2-microglobulin, urine albumin, and urine creatinine.

[12] MRI to be performed at any time between screening (Visit 1) and randomization (Visit 3) provided all other screening criteria have been checked for subject eligibility. MRI must not be performed within 30 days of receiving a course of steroids.

[13] The IGISIS will be completed twice daily (with at least 6 hours in between each completion) and the GGISIS will be completed once daily using e-diaries during the 1-week lead-in period prior to randomization (Visit 3).

[14] The IGISIS will be completed twice daily (should be completed within 9 hours after taking each dose of study drug) and the GGISIS will be completed once daily (each morning prior to taking the morning dose of study drug) using e-diaries during the randomized treatment period (Visit 3 to Visit 8).

[15] Use "Screening" version at screening (Visit 1) and "Since-Last-Visit" version for all subsequent time points.

8.3. Study Procedures Descriptions

Details of the study procedures are described below. The overall schedule of assessments is provided in Table 2.

8.3.1. Informed Consent

The nature of the study and its risks and benefits will be explained to the subject by the Principal Investigator or designated study personnel as outlined in Section 17.3.

Prior to the administration of any study-specific procedures, authorized study personnel will obtain written informed consent from each potential subject.

8.3.2. Confirmation of Willingness to Continue in the Study

[redacted] In addition, the Investigator will discuss the event with the subject, and, if agreed upon to continue participation in the study, the subject will sign an institutional review board (IRB)/independent ethics committee (IEC) approved form confirming willingness to continue.

8.3.3. Eligibility Review

An eligibility review will be conducted by the Investigator at the visits specified in Table 2 using the subject inclusion criteria in Section 7.1 and exclusion criteria in Section 7.2.

[redacted]

8.3.4. Demographics and Medical History

Subject's demographic data and medical history will be reviewed and documented at the time point(s) specified in Table 2.

8.3.5. Concomitant Medication Review

At screening (Visit 1), all subjects will be asked about medications they have taken in the last 30 days. For a potential subject to qualify for the study, those exclusions outlined in Section 7.2 and Section 8.4.2 must be ruled out. At each subsequent study visit, review of concomitant medications taken since the last visit will be repeated for all participating subjects. Concomitant medications to be reviewed at each study visit include prescription and nonprescription medications, vitamins, and supplements.

The Investigator will record the following data on all medications used by the subject: name, dose, regimen, route of administration, start and stop dates, and the indication for use.

8.3.6. Vital Signs

Vital signs (ie, blood pressure, pulse, respiratory rate, and temperature) will be assessed at the time points specified in Table 2. Blood pressure, pulse, and respiratory rate will be measured after the subject has been resting in a seated or supine position for at least 5 minutes. Consistent measures and procedures should be used for all assessments.

As specified in Table 2, on the first day of dosing (at randomization, Visit 3), vital signs are to be measured predose.

8.3.7. Physical Examination

A physical examination will be performed at the time point(s) specified in Table 2. A full physical exam will be conducted at screening (Visit 1) and brief, symptom-directed physical examinations will be conducted at all other time points. During visits where brief, symptom-directed physical examinations are scheduled, if a subject does not report any symptoms, vital signs at minimum will be measured.

8.3.8. Body Height and Weight

Measurement of body height and weight will be performed at the time points specified in Table 2.

8.3.9. 12-Lead Electrocardiogram

A 12-lead electrocardiogram (ECG) will be conducted at the time points specified in Table 2. ECGs will be collected predose on Visit 3 and at any time at all other scheduled visits. All scheduled ECGs must be performed after the subject has rested quietly for at least 5 minutes in a supine position.

ECGs will be conducted using calibrated equipment and assessed by a qualified clinician. ECGs will be evaluated at the sites and by a central reader.

8.3.10. Structured Interviews and Questionnaires

8.3.10.1. GI Symptom Scales

The GI symptom scales (Individual GI Symptom and Impact Scale [IGISIS] and Global GI Symptom and Impact Scale [GGISIS]) will be completed by subjects using e-diaries. Approximately one week prior to randomization (Week -1), eligible subjects will return to the site (Visit 2) to be trained on the completion of the GI symptom scales using e-diaries (see Table 2). Subjects will complete both scales using e-diaries daily for 7 days prior to randomization (Visit 3) to facilitate familiarity with the scales as well as to evaluate for exclusionary GI symptomatology (see Section 7.2, Exclusion Criterion #8).

Following randomization (Visit 3), subjects will complete the IGISIS twice-daily (should be completed within 9 hours after taking each dose of study drug) and the GGISIS once-daily (each morning prior to taking the morning dose of study drug; see Table 2).

8.3.10.1.1. Individual GI Symptom and Impact Scale

The IGISIS is designed to assess the incidence, intensity, onset, duration, and functional impact of 5 individual GI symptoms: nausea, vomiting, upper abdominal pain, lower abdominal pain, and diarrhea. This scale will be subject-completed using e-diaries. These 5 symptoms were included in the IGISIS as they were the most commonly reported GI symptoms in the Tecfidera Phase 3 placebo-controlled trials (Biogen 2015). Subjects will be asked to rate the severity of each individual symptom via an 11-point numeric rating scale ranging from 0 (did not have) to 10 (extreme) (see Appendix A).

Subjects will also be asked to indicate the start and stop times of each GI symptom. Additionally, subjects will be asked to indicate how much each symptom has interfered with their ability to accomplish their regular daily activities using a 5-point Likert scale (not at all, slightly, moderately, quite a bit, extremely).

8.3.10.1.2. Global GI Symptom and Impact Scale

The GGISIS is a global scale to assess the overall intensity, bothersomeness, and functional impact of GI symptoms experienced during the previous 24 hours. This scale will be subject-completed using e-diaries. Subjects will be asked to rate the intensity and bothersomeness of GI symptoms experienced using an 11-point numeric rating scale (see Appendix B). Additionally, subjects will be asked to indicate:

- How much their GI symptoms have interfered with their ability to accomplish their regular daily activities using a 5-point Likert scale (not at all, slightly, moderately, quite a bit, extremely),
- Number of hours of work missed due to GI symptoms,
- Impact of GI symptoms on work productivity using a 5-point Likert scale (not at all, slightly, moderately, quite a bit, extremely).

[redacted]

[redacted]

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

Suicidal ideation and behavior will be assessed using the C-SSRS (Posner, Brown et al. 2011). The "Screening" version of the instrument will be administered to subjects at the screening visit (Visit 1) to assess suicidal ideation and behavior over the 12 months prior to screening. The "Since-Last-Visit" version will be administered to all participating subjects at all other visits according to the schedule in Table 2. The Investigator or designee will be trained and certified to administer the C-SSRS.

8.3.11. Brain Magnetic Resonance Imaging

Brain Magnetic Resonance Imaging (MRI) assessment will be conducted at any time between screening (Visit 1) and randomization (Visit 3) once all other eligibility criteria are met (as shown in Table 2). MRI data will be evaluated locally for safety and evaluated at a central MRI reading facility to record MRI parameters with and without gadolinium.

Additional details regarding MRI procedures will be described in the MRI Protocol.

8.3.12. Laboratory Assessments

8.3.12.1. Hematology, Biochemistry, and Urinalysis

Blood and urine samples for laboratory assessments will be collected at the time points specified in Table 2. Specific hematology, biochemistry, and urinalysis assessments are listed in Table 3. Samples will be collected in accordance with the site's usual procedures and analyzed by a central laboratory.

Table 3: Clinical Laboratory Assessments

Hematology	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	Triglycerides	Protein
	Glucose	Glucose
	TSH[1]	Bilirubin
	Calcium	Nitrite
	Magnesium	Urobilinogen
	Phosphate	Occult blood
	Uric Acid	Microscopic examination of sediment *only if urinalysis dipstick results are abnormal*
	Creatinine	Urine albumin
	Total protein	Urine beta-2-microglobulin
	Blood urea nitrogen (BUN)	Urine creatinine
	Albumin	
	Total bilirubin	
	ALT	
	AST	
	Lactic dehydrogenase (LDH)	
	Alkaline phosphatase (ALK-P)	
	Creatine phosphokinase (CPK)	
	Lipid profile: blood cholesterol, high-density lipoprotein, low-density lipoprotein, and triglycerides	

1 To be assessed at screening (Visit 1) only.

8.3.12.2. Pregnancy Testing

As specified in Table 2, a serum pregnancy test will be performed for all women regardless of child bearing potential at screening (Visit 1); results must be negative for the subject to be eligible for the study. A urine pregnancy test will be performed at randomization (Visit 3, see Table 2). Results must be negative for initial study eligibility and continued participation. A positive pregnancy test result at any time will necessitate the subject's immediate withdrawal from the study. Additional follow-up may be required as detailed in Section 8.4.1.

8.3.12.3. Serology Testing

A blood sample will be obtained for serology panel testing of hepatitis B surface antigen, hepatitis C antibody, and HIV antibody at screening (Visit 1) as specified in Table 2, and must be negative to qualify for study participation.

8.3.13. Randomization

At the time point(s) specified in Table 2, subjects will be randomized at Visit 3 as outlined in Section 9.3.

8.3.14. Drug Dispensation and Reconciliation

Section 9 provides information related to drug dispensing procedures. Study drug will be dispensed/administered at the time point(s) specified in Table 2. The study drug use and storage information will be explained to/reviewed with the subject.

8.3.15. Adverse Event Monitoring

AEs will be monitored continuously from the time a subject signs the informed consent document until the completion of the final study visit (Visit 9, see Table 2). AEs and SAEs are defined in Section 11.1 and 11.2, respectively. Section 11.4 provides guidance on the monitoring and recording requirements for AEs. Section 11.5 provides guidance on the reporting requirements for SAEs.

8.4. Study Requirements and Restrictions

[redacted]

Should progressive multifocal leukoencephalopathy (PML) be suspected by the treating neurologist based on symptoms or signs during the [redacted] visit, study drug will be withheld and an appropriate diagnostic work-up should be performed as soon as possible [redacted]. If PML is excluded based on the diagnostic workup, the subject may resume taking study drug if approved by the Medical Monitor. If the diagnostic work-up exceeds 14 days, the subject will be discontinued from the study. Should a diagnosis of PML be confirmed, the subject will be discontinued from the study and provided with appropriate medical care.

If serious infection occurs, study treatment should be withheld until it has resolved.

Study drug must also be temporarily withheld if any of the following laboratory parameters meet the following threshold limits:

- AST or ALT >3×ULN; confirmed by repeat testing as soon as possible. If the value remains >3×ULN for ≥2 weeks after discontinuation of study treatment, the subject must permanently discontinue study treatment
- Lymphocyte count $<0.5 \times 10^9$/L; confirmed by repeat testing as soon as possible. If the value remains $<0.5 \times 10^9$/L for ≥2 weeks after discontinuation of study treatment, the subject must permanently discontinue study treatment
- Estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2; confirmed by repeat testing as soon as possible. If the eGFR remains <60 mL/min/1.73m^2 for ≥2 weeks after discontinuation of study treatment, the subject must permanently discontinue study treatment
- Urine albumin to urine creatinine ratio >200 mg/g; confirmed by repeat testing as soon as possible. If the urine albumin to urine creatinine ratio remains >200 mg/g for ≥2 weeks after discontinuation of study treatment, the subject must permanently discontinue study treatment

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

8.4.1. Contraception and Pregnancy

All male and female subjects must agree to the use of two methods of contraception for the duration of the study and 30 days after the final dose of study drug. This includes at least one form of highly effective method of contraception and one acceptable method of contraception (and additional restrictions, if required, will be clarified in the locally approved informed consent form [ICF]). Subjects who are abstinent are eligible, provided they agree to the use of two contraceptive methods (at least one being a highly effective method) should they become sexually active.

Highly effective methods may include:

- Oral, intravaginal, or transdermal combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral contraceptives must have been initiated at least 30 days prior to screening)
- Oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation (oral contraceptives must have been initiated at least 30 days prior to screening)
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner (provided that partner is sole sexual partner of subject and partner has received medical assessment of surgical success)
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire study period through at least 30 days after the final dose of study drug)

Acceptable methods may include:

- Double-barrier protection (eg, male condom, female condom, cervical cap or contraceptive sponge with spermicide, or a diaphragm with spermicide)

Subjects who are surgically sterile are exempt from the requirement to use contraception. Women who have undergone a documented complete hysterectomy, bilateral tubal ligation, or bilateral salpingo-oophorectomy at least 6 months prior to screening are considered surgically sterile. Men who have undergone a vasectomy are considered surgically sterile as long as medical confirmation of azoospermia is provided. Women who are postmenopausal are also exempt from the requirement to use contraception. For the purpose of this study, postmenopausal is defined as the permanent cessation of menstruation for at least 12 months prior to screening in women who are 45 years of age or older.

If any female subject becomes or is found to be pregnant while participating in the study, she will be discontinued from study drug immediately. Pregnancies in female subjects and female partners of male subjects should be handled in the same manner. The investigator must fill out a Pregnancy Report Form and submit the information to the sponsor within 24 hours of awareness of the pregnancy, irrespective of whether an adverse event has occurred. The early termination and safety follow-up visits will be scheduled.

The investigator will follow the pregnancy until completion or until pregnancy termination and notify the outcome to the sponsor. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE the investigator should follow the procedure of reporting SAEs (see Section 11.5). Additional follow-up may be required.

8.4.2. Prohibited Medications

Immunomodulatory treatments besides study drug for the treatment of RRMS are prohibited during treatment with study drug unless approved by the medical monitor. [redacted] Prohibited immunomodulatory therapies include, but are not restricted to the following:

- Any alternative drug treatments directed toward the treatment of MS such as chronic immunosuppressant therapy or other immunomodulatory treatments (including, but not limited to: interferon-beta, interferon-alpha, glatiramer acetate, natalizumab, cyclophosphamide, methotrexate, azathioprine, teriflunomide and fingolimod)
  - Of note, the timing of discontinuing interferon-beta, interferon-alpha, or glatiramer acetate prior to initiating treatment with study drug (Visit 3) is at the investigator's discretion
- Total lymphoid irradiation, cladribine, T-cell or T-cell receptor vaccination, any therapeutic monoclonal antibody, mitoxantrone, cyclosporine, intravenous immunoglobulin, plasmapheresis or cytapheresis

Any investigational product, including investigational symptomatic therapies for MS and investigational therapies for non-MS indications, is not permitted.

[redacted]

Symptomatic therapy, such as treatment for spasticity, depression or fatigue is not prohibited but should be optimized as early as possible after screening in an attempt to maintain consistent treatment during the study.

Immunizations using inactivated, killed, or viral particle vaccines (eg, influenza vaccine) are permitted and can be administered according to Investigator judgment. Vaccines using live or attenuated viruses should not be administered unless approved by the Medical Monitor.

Subjects should be instructed not to start taking any new medications, including non-prescribed drugs, unless they have received permission from the Investigator.

See Section 8.3.5 for details regarding the concomitant medication review.

9. TREATMENT OF SUBJECTS

9.1. Study Drug Dose and Administration

Capsules will be administered orally, BID. Study staff will administer the first dose of study drug at Visit 3 (Randomization). From that point on during the treatment period, according to the schedule of visits shown in Table 2, the staff will dispense study drug for subjects' self-administration. Subjects will take two capsules of blinded study drug BID during the 5-week double-blind treatment period as shown in Table 4. Placebo capsules are included in order to keep the number of capsules at each administration consistent between treatment groups to maintain the study blind. Subjects will be instructed to take both capsules simultaneously for both morning and evening doses.

Subjects will be instructed to take study drug with or without food. However, subjects will be instructed to avoid taking study drug with a high-fat, high-calorie meal. Detailed dosing instructions will be provided to the patients by the site personnel.

No dose reductions will be permitted during the study. If a subject does not tolerate the study drug during the initial 1-week dose titration period or after the dose titration period, the subject will be discontinued from the study.

Table 4: Study Drug Dosing Schedule (Part A and Part B)

Blinded Treatment Group	Week 1 (Titration) (Days 1-7; 4 capsules per day)	Weeks 2-5 (Days 8-35, 4 capsules per day)
ALKS 8700 462 mg BID (Total daily dose: 924mg)	Morning: 1 capsule of 231mg, 1 capsule of placebo Evening: 1 capsule of 231mg, 1 capsule of placebo	Morning: 2 capsules of 231mg Evening: 2 capsules of 231mg
DMF 240 mg BID (Total daily dose: 480 mg)	Morning: 1 capsule of 120 mg, 1 capsule of placebo Evening: 1 capsule of 120 mg, 1 capsule of placebo	Morning: 1 capsule of 240 mg, 1 capsule of placebo Evening: 1 capsule of 240 mg, 1 capsule of placebo

9.2. Treatment Adherence

According to the schedule in Table 2, at each specified dispensing visit, subjects will receive a supply of study drug to last until the following visit. Subjects will be instructed to bring any unused study drug and the bottle(s) with them to each subsequent visit. Study drug adherence will be reviewed with subjects at each visit.

9.3. Randomization/Method of Assigning Subjects to Treatment

Separate randomization schedules will be prepared for Part A and for Part B of the study. Once Part A of the study is completed (ie, the last subject has completed the last visit in Part A), the database for Part A will be locked and unblinded, and an analysis of the Part A data will be

conducted. Individual treatment assignments will remain blinded to the sites until completion of Part B.

9.4. Blinding

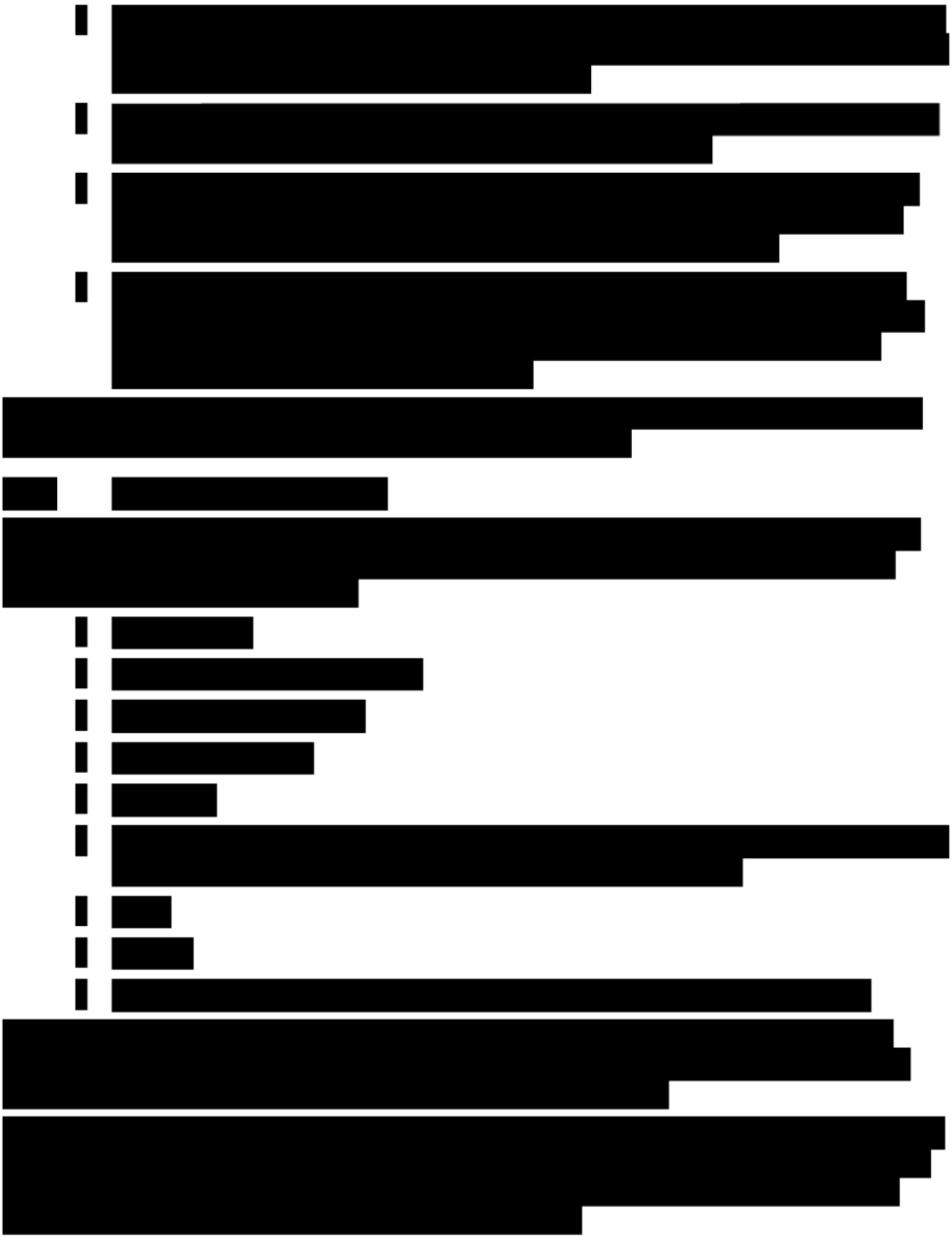
The treatment period will be double-blind. If the Investigator deems it necessary to break the study blind in the interest of a subject's medical safety, he or she must make every effort to contact the Medical Monitor before the blind is broken. If the site is unable to contact the Medical Monitor prior to breaking the blind, the Medical Monitor must be contacted within 24 hours following disclosure of study drug assignment.

The Investigator is responsible for all trial-related medical decisions. When the Investigator deems it necessary, emergency unblinding may be done without contacting a Medical Monitor. Any premature unblinding should be promptly documented and explained to the Medical Monitor. Breaking the blind for a single subject will not affect the blind for the remaining subjects.

9.5. Rescue

Subjects will be encouraged to remain on assigned blinded study treatment for 5 weeks following randomization, [redacted] In the event of a confirmed acute event [redacted], the treating neurologist may opt to prescribe 1000 mg of oral or intravenous [redacted] treatment for 3to 5 days with no taper. Treatment with oral or intravenous [redacted] will not affect the subject's eligibility to continue in the study. The subject will continue on their assigned study treatment while being treated with [redacted]. Any deviations from this recommended treatment must first be discussed with the Medical Monitor.

[redacted]



10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

10.1.1. ALKS 8700

Investigational product for this study is ALKS 8700, provided as capsules for oral administration. ALKS 8700 investigational product consists of delayed-release (DR) (enteric–coated) minitablets contained within a hydroxypropyl methylcellulose (HPMC) capsule. The doses of ALKS 8700 to be used in this study are 231 mg (administered as one capsule during Week 1 [dose titration]) and 462 mg (administered as two 231 mg capsules during Weeks 2-5). Capsules will be administered orally, twice per day.

10.1.2. Dimethyl Fumarate

Reference therapy for this study is commercially available DMF (Tecfidera; manufactured by Biogen Inc. of Cambridge, MA) capsules for oral administration. The DMF capsules will be over-encapsulated in the same HPMC capsule used for the ALKS 8700 drug product to create blinded study drug. The doses of DMF to be used in this study are 120 mg (administered as one capsule during Week 1 [dose titration]) and 240 mg (administered as one capsule during Weeks 2-5). Capsules will be administered orally, twice per day.

10.1.3. Placebo

Placebo capsules are included in this study in order to keep the number of capsules at each oral administration consistent between treatment groups to maintain the study blind. The placebo matched to the ALKS 8700 and DMF drug products will consist of placebo minitablets contained within the same HPMC capsule used for the ALKS 8700 drug product and used to over-encapsulate the DMF drug product. Placebo capsules will be administered orally, twice per day.

10.2. Packaging and Labeling

ALKS 8700 (231 mg) and Placebo capsules are supplied in both 20 count, 100 cc, induction sealed HDPE bottles and 64 count, 150 cc, induction sealed, HDPE bottle configuration.

Labeling will meet all applicable local and regulatory requirements. Alkermes will package and distribute ALKS 8700, DMF, and matching placebo capsules to the clinical site.

10.3. Storage

All study materials are to be stored at room temperature not to exceed 25° Celsius in a secure location. DMF will be stored in accordance with the manufacturer's specifications.

10.4. Accountability

The clinical site is required to maintain current drug dispensation and accountability logs throughout the study. All unused supplies will be checked against the drug movement records during the study and/or at the end of the study.

Refer to Section 9 for additional study drug reconciliation procedures.

10.5. Handling and Disposal

The clinical site is required to maintain current drug dispensation and accountability logs throughout the study. Following completion and verification of accountability logs, all unused and used packages must be destroyed. Packages may be destroyed on site according to Good Clinical Practice (GCP) and site practice. Alternatively, the sponsor may arrange for destruction with a third party vendor operating in accordance with GCP and/or Good Manufacturing Practice (GMP), as applicable.

11. ASSESSMENT OF SAFETY AND TOLERABILITY

Safety and tolerability throughout the study will be assessed using the following:

- IGISIS
- GGISIS
- AEs
- Vital signs (oral temperature, respiratory rate, heart rate, and blood pressure)
- Clinical laboratory parameters (blood biochemistry, hematology, urinalysis [including urine albumin, urine beta-2-microglobulin, and urine creatinine])
- ECG parameters (uncorrected QT, QTcF, QTcB, PR, RR, and QRS intervals)
- C-SSRS

11.1. Definition of Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product. The occurrence, which may or may not have a causal relationship with the investigational treatment, may include any clinical or laboratory change that does not commonly occur in that subject and is considered clinically significant.

Illnesses present prior to the subject signing the ICF are considered to be preexisting conditions and are documented on the medical history eCRF. Pre-existing conditions that worsen during the study are entered on the AE eCRF.

All out-of-range laboratory values will be deemed as clinically significant or not clinically significant by the Investigator. Clinically significant values will be considered AEs and recorded as such on the eCRFs.

Pregnancy is not considered an AE, although a subject will be withdrawn from the study if a pregnancy occurs. As described in Section 8.4.1, the pregnancy must be reported to Alkermes and additional follow-up may be required.

11.2. Definition of Serious Adverse Event

An SAE is any AE, occurring at any dose and regardless of causality that results in one or more of the following:

- Results in death
- Is life-threatening. The subject is at immediate risk of death from the reaction as it occurs. This does not include reaction that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of existing hospitalization. Hospital admission for elective surgery scheduled prior to study entry is not considered an SAE

- Results in disability/incapacity (eg, a substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect

Important medical events that may not result in death, be immediately life threatening, or require hospitalization may be considered to be SAEs when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require intervention to prevent one of the other outcomes listed above.

11.3. Relationship to Study Drug

The assessment of study drug relationship to each AE will be reported on the appropriate source document (and SAE form, in the event of an SAE) by the Investigator (or designated Sub-Investigator) according to his/her best clinical judgment. The criteria listed in Table 5 should be used to guide this assessment. Please note that not all criteria must be present to be indicative of a particular drug relationship. All study drugs are considered "test drugs" for the purposes of the definitions listed in the table.

Table 5: Adverse Event Causality Guidelines

Relationship	Criteria for assessment
Definitely related	There is evidence of exposure to the test drug. AND The temporal sequence of the AE onset relative to administration of the test drug is reasonable. The AE is more likely explained by the test drug than by another cause. Dechallenge (if performed) is positive. Rechallenge (if feasible) is positive. The AE shows a pattern consistent with previous knowledge of the test drug or test drug class.
Probably related	There is evidence of exposure to the test drug. AND The temporal sequence of the AE onset relative to administration of the test drug is reasonable. The AE is more likely explained by the test drug than by another cause. Dechallenge (if performed) is positive.
Possibly related	There is evidence of exposure to the test drug. AND The temporal sequence of the AE onset relative to administration of the test drug is reasonable. The AE could have been due to another equally likely cause. Dechallenge (if performed) is positive.
Probably not related	There is evidence of exposure to the test drug. AND There is another more likely cause of the AE. Dechallenge (if performed) is negative or ambiguous. Rechallenge (if performed) is negative or ambiguous.
Definitely not related	The subject did not receive the test drug. OR Temporal sequence of the AE onset relative to administration of the test drug is not reasonable. OR There is another obvious cause of the AE.

11.4. Monitoring and Recording of Adverse Events

AE data collection will begin after a subject signs the ICF and will continue until completion of the safety follow-up visit (Visit 9). Any AE or SAE having an onset after the safety follow-up visit will not be collected or reported unless the investigator feels that the event may be related to the study drug.

Subjects will be instructed by the Investigator or designee to report the occurrence of any AE. All volunteered, elicited, and observed AEs are to be recorded on the AE eCRFs.

The Investigator will assess all AEs regarding any causal relationship to the study drug (see Section 11.3), the intensity (severity) of the event, action taken, and subject outcome.

The following criteria should be used to guide the assessment of intensity (severity):

- **Mild:** Causes awareness of sign or symptom, but is easily tolerated; does not interfere with usual activities
- **Moderate:** Causes discomfort enough to interfere with usual activities
- **Severe:** Is incapacitating; results in inability to work or perform usual activities

All AEs will be followed until resolution, until deemed stable by the Investigator, or until the subject is deemed by the Investigator to be lost to follow-up.

For clinical study safety reporting purposes, the most recent version of the Investigator's Brochure will be used as the reference document to designate event expectedness.

Withdrawal from the study as a result of an AE and any therapeutic measures that are taken shall be at the discretion of the Investigator. If a subject withdraws from the study for any reason, any ongoing AEs will be followed until resolution, until deemed stable by the investigator, or until the subject is deemed by the Investigator to be lost to follow-up.

11.5. Reporting of Serious Adverse Events

All SAEs must be reported to Alkermes Drug Safety via [redacted] within 1 business day of discovery, by faxing the report to the following:

Attention: [redacted]
Email: [redacted]
Phone Number: [redacted]
FAX Number.: [redacted]

The written report should be submitted on the SAE form provided for this purpose. The report must include the investigator's opinion as to whether the event is study drug-related. If this relationship is determined to be possibly, probably, or definitely related to study drug, evidence to support this assessment must also be provided.

12. ASSESSMENT OF EFFICACY

[redacted]

14. STATISTICS

14.1. Sample Size Considerations

The sample size calculation is based on the endpoint of the mean number of days with any IGISIS individual symptom intensity score ≥3.

Assuming the mean number of days with any IGISIS individual symptom intensity score ≥3 is 4.5 and 2.5 for the DMF and ALKS 8700 treatment groups, respectively, a sample size of 150 randomized subjects per group (300 subjects in total) in Part B will provide at least 90% power to detect about a 45% reduction in the number of days with any IGISIS individual symptoms intensity score ≥3 for the ALKS 8700 treatment group relative to the DMF treatment group, at an alpha level of 0.05 (two-sided) using a negative binomial regression approach. The sample size calculation assumes a standard deviation of 5.5 in the number of days with any IGISIS individual symptom intensity score ≥3 relative to exposure days for the DMF treatment group in Part B.

With the same assumption, 60 randomized subjects per group (120 subjects in total) in Part A will provide at least 80% power to detect about a 45% reduction in the number of days with any IGISIS individual symptom intensity score ≥3 for the ALKS 8700 treatment group relative to the DMF treatment group, at an alpha level of 0.1 (two-sided).

14.2. General Statistical Methodology

In general, summary statistics (n, mean, standard deviation, median, minimum and maximum values for continuous variables, and number and percentage of subjects in each category for categorical variables) will be provided for evaluated variables by treatment group. All individual subject level data will be presented as data listings.

14.2.1. Study Population(s)

The safety population includes all randomized subjects who received at least one dose of study drug (ALKS 8700 or DMF).

The full analysis set (FAS) population includes all subjects who received at least one dose of study drug and complete at least one post baseline GI tolerability assessment.

[redacted]

14.3. Endpoints

14.3.1. Primary Endpoint

The number of days with any IGISIS individual symptom intensity score ≥3 relative to exposure days in Part B.

14.3.2. Secondary Endpoints

- AUC for the total IGISIS symptom intensity score relative to exposure days in Part B
- Number of days with a GGISIS symptom intensity score ≥3 relative to exposure days in Part B.

The primary and secondary endpoints may be modified based on data obtained from Part A.

14.4. Demographics and Baseline Characteristics

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

14.5. Safety Analyses (Part A and Part B)

All analyses will be carried out using the respective safety populations for Part A and Part B separately. For each safety parameter, baseline is defined as the last non-missing assessment prior to the first dose of study drug.

Safety will be evaluated based on the occurrence of AEs, vital signs, results of clinical laboratory tests, and ECG findings. Reported AE terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 17).

Treatment-emergent adverse events (TEAEs) are defined as AEs that occur or worsen after the first dose of study drug.

Safety assessments will be summarized using descriptive statistics along with supportive listings based on observed values. Listings will be provided for all safety parameters. The number and percentage of TEAEs will be summarized by treatment group and overall by system organ class, and preferred terms within each system organ class. SAEs and TEAEs resulting in treatment discontinuation will also be summarized.

Observed values and change from baseline in clinical laboratory parameters, vital signs, ECG parameters, and scores on the C-SSRS will be summarized by treatment group and visit for each part of the study. The number and percentage of subjects with suicidal ideation or behavior as assessed by the C-SSRS will also be summarized by treatment group. The number and percentage of subjects with potentially clinically significant (PCS) values at any post-baseline visit will be summarized by treatment group. Listings will be provided for all safety endpoints.

Prior and concomitant medication use will be coded using the World Health Organization (WHO) drug Anatomical Therapeutic Chemical (ATC) classification system. Listings will be provided for all prior and concomitant medications.

Additional details on the safety analysis will be provided in the Statistical Analysis Plan (SAP) for Part A and Part B.

14.6. GI Tolerability Analyses (Part A and Part B)

All GI tolerability analyses based on the IGISIS and GGISIS will be summarized using descriptive statistics for Part A and Part B separately using FAS population. There are no formal statistical comparisons planned for Part A; Part A is exploratory, and Part B is confirmatory.

The number of days with any IGISIS individual symptom intensity score ≥3 relative to days exposed will be analyzed using a negative binomial regression with total intensity score from 5 individual symptoms at baseline as a covariate and treatment as a factor. Treatment difference along with the 95% Confidence Interval (95% CI) will be reported.

AUC for the total IGISIS symptom intensity score relative to days exposed will be analyzed using an ANCOVA with the total intensity score from 5 individual symptoms at baseline as a covariate and treatment as a factor. Treatment difference along with the 95% CI will be reported.

Percentage of subjects with any IGISIS symptom intensity score ≥3 will be analyzed using a logistic regression model with the total intensity score from 5 individual symptoms at baseline as a covariate and treatment as a factor. The odds ratio along with the 95% CI will be reported.

Additional details on the tolerability analysis will be provided in the SAP for Part A and Part B.

14.7. Exploratory Efficacy Analyses (Part A and Part B)

[redacted]

15. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

15.1. Study Monitoring

Monitoring of the study sites (including, but not limited to, reviewing eCRFs for accuracy and completeness) will be performed by an Alkermes monitor or designee.

15.2. Audits and Inspections

By signing the protocol, the Investigator agrees that, within local regulatory restrictions and institutional and ethical considerations, authorized representatives of Alkermes, a regulatory authority, and/or an IRB/ EC may visit the site to perform audits or inspections, including the drug storage area, study drug stocks, drug accountability records, subject charts and source documents, and other records relative to study conduct. The purpose of an Alkermes audit or inspection is to systematically and independently examine all study-related activities and documents (eg, laboratory reports, x-rays, workbooks, subjects' medical records) to determine whether these activities were conducted, and data recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements.

The Investigator should contact Alkermes immediately if contacted by a regulatory agency regarding an inspection.

15.3. Institutional Review Board/Independent Ethics Committee

The Investigator must obtain IRB/IEC approval for the investigation. Initial IRB/IEC approval as well as all materials approved by the IRB/IEC for this study, including the subject consent form and recruitment materials, must be maintained by the Investigator and made available for inspection.

16. QUALITY CONTROL AND QUALITY ASSURANCE

This study will be conducted under GCP and all applicable regulatory requirements. To ensure data accuracy, completeness and compliance, the study site should have processes in place for data review and quality control. Alkermes may also conduct a quality assurance audit. Please see Section 15.2 for details regarding the audit process.

16.1. Case Report Forms

This study will use eCRFs. All eCRF data must be based on source documents or approved to be the original data (ie, data directly reported on the eCRF). All eCRFs will be completed by the clinic staff prior to review by the Alkermes monitor or designated representative.

The Alkermes monitor or designated representative will review all source records on-site and compare them to the data collected on the eCRF.

16.2. Confidentiality of Data

By signing this protocol, the investigator affirms to Alkermes that he or she will maintain in confidence information furnished to him or her by Alkermes and will divulge such information to his or her respective IRB or IEC under an appropriate understanding of confidentiality with such board. All data will be considered the sole property of Alkermes. Please refer to the Clinical Study Agreement (CSA) for details.

17. ETHICAL CONSIDERATIONS

17.1. Ethics Review

The clinical site's IRB/IEC must meet all relevant regulatory requirements. The study protocol and ICF will be reviewed by the IRB/IEC prior to enrolling subjects into the study; written approval from the committee must be received by Alkermes before drug will be released to the Investigator. The protocol must be re-approved by the IRB/IEC upon receipt of amendments and annually, as local regulatory requirements require.

The Investigator is responsible for submitting all protocol changes and SAE reports to the IRB/IEC according to local procedures. At a minimum, all SAEs requiring an investigational new drug safety report must be immediately reported.

All relevant correspondence from the IRB/EC will be forwarded by the respective study site to the sponsor in a timely fashion.

17.2. Ethical Conduct of the Study

This study will be conducted in accordance with the protocol, the ICH Guideline E6, and all applicable local regulatory requirements. GCP is an international ethical and scientific quality standard used for designing, conducting, recording, and reporting studies involving the participation of human subjects. Alkermes is committed to complying with this standard to provide assurance that the rights, safety, and well-being of study subjects will be protected, consistent with the principles having their origin in the Declaration of Helsinki.

17.3. Written Informed Consent

The Investigator (or authorized designee) at each center will ensure that the subject is given full and adequate oral and written information about the nature, purpose, potential and possible risks and benefits of the study. Each prospective subject will receive an IRB/IEC-approved informed consent form (ICF) that summarizes the pertinent study information and will be given ample time to read the form and ask questions about the study. All information is to be provided in a language understandable to the subject and must not include any language that waives the subject's legal rights. Prospective subjects must also be informed of their right to withdraw consent without prejudice at any time during the study. If the subject chooses to participate, he/she must sign the ICF before any study-specific procedures are conducted.

All subjects will be informed of their rights to privacy and will be made aware that the study data will be submitted to Alkermes, the IRB/IEC, the CRO if applicable, and to regulatory authorities for review and evaluation for the duration of the study and until the project has been approved for marketing, or is withdrawn from investigation. They will also be informed that the study monitor may inspect their medical records to verify the accuracy and completeness of the study records and results.

Significant changes to the protocol or product safety information may require a revision of the ICF, which must be reviewed and approved by the IRB/IEC, and then signed by all applicable study participants.

The time that informed consent is obtained must be documented. The Investigator must maintain the original, signed ICF in the subject's source documents. A copy of the signed ICF must be given to the subject.

17.4. Confirmation of Willingness to Continue in the Study

[redacted] In addition, the Investigator will discuss the event(s) with the subject and ensure that the subject is given full information regarding the potential and possible risks and benefits of continuing participation in the study. Each subject will receive an IRB/IEC-approved form that summarizes the pertinent information and will be given ample time to read the form and ask questions.

All information is to be provided in a language understandable to the subject and must not include any language that waives the subject's legal rights. Subjects must also be informed of their right to refuse continued participation in the study without prejudice at any time during the study. If the subject chooses to continue participation in the study, he/she must sign the form indicating his/her willingness to continue before any further study-specific procedures are conducted.

The time of written confirmation of willingness to continue in the study must be documented. The Investigator must maintain the original signed form in the subject's source documents. A copy of the signed form must be given to the subject.

18. DATA HANDLING AND RECORDKEEPING

An overview of study data handling and recordkeeping procedures and restrictions is provided in the subsequent sections; please refer to the CSA for further details.

18.1. Data Capture

As stated in Section 16.1, this study will use eCRFs for capturing data. All entries, corrections, and alterations will be made by the Investigator or other authorized study personnel. All data entries will be verified for accuracy and correctness by independent monitors. The electronic data capture system maintains a full audit trail.

All electronic source data collected outside of the eCRF such as e-diaries, central laboratory, central ECG, or central MRI data will be transferred directly to Alkermes for incorporation into the final datasets. A paper copy of all laboratory reports will remain with the source documents at the study site. All out of range laboratory values will be deemed as clinically significant or not clinically significant by the Investigator. Clinically significant values will be considered AEs and recorded as such on the eCRFs.

AEs will be coded using MedDRA. Concomitant medications will be categorized using the WHO-ATC classification system.

18.2. Inspection of Records

Alkermes or its representative will be allowed to conduct site visits to the investigational facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and source documents, and other records relative to study conduct.

18.3. Retention of Records

Retention and storage of all essential clinical study documents shall be governed by the terms and conditions of the site's CSA and in accordance with ICH guidelines/local regulatory requirements as follows:

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by the terms of the CSA. It is the responsibility of the sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

Subjects' medical files should be retained in accordance with the applicable legislation and in accordance with the maximum period of time permitted by the hospital, institution, or private practice, whichever is longer.

18.4. Use of Information and Publication Policy

Data generated in this study are proprietary information that is the sole property of Alkermes. Results of the study are to be held in confidence by both the Investigators and the sponsor.

Please refer to the CSA for details on the procedures for publishing and presenting data.

19. REFERENCES

Biogen (2015). Prescribing Information: Tecfidera, 2015-04. Cambridge, MA.

Center for Drug Evaluation and Research. (2013, 2/11/2013). "Summary Review: Tecfidera (Dimethyl Fumarate) NDA 204063." from http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204063Orig1s000SumR.pdf.

Chaves, C., R. Ganguly, C. Dionne and A. Camac (2015). Safety and Efficacy of Dimethyl Fumarate in Patients with Multiple Sclerosis- Real World Experience - Abstract. American Academy of Neurology, Washington, DC.

Dubey, D., B. C. Kieseier, H. P. Hartung, B. Hemmer, C. Warnke, T. Menge, W. A. Miller-Little and O. Stuve (2015). "Dimethyl fumarate in relapsing-remitting multiple sclerosis: rationale, mechanisms of action, pharmacokinetics, efficacy and safety." Expert. Rev. Neurother **15**(4): 339-346.

Fox, E. J., A. Vasquez, W. Grainger, T. Ma, C. von Hehn, J. Walsh, J. Li and J. Zambrano (2014). Gastrointestinal Tolerability of Delayed-Release Dimethyl Fumarate in a Multicenter, Open-Label Study of Patients with Relapsing Multiple Sclerosis. 2014 Joint Americas Committee for Treatment and Research in Multiple Sclerosis and European Committee for Treatment and Research in Multiple Sclerosis Meeting, Boston, MA.

Gold, R., L. Kappos, D. L. Arnold, A. Bar-Or, G. Giovannoni, K. Selmaj, C. Tornatore, M. T. Sweetser, M. Yang, S. I. Sheikh and K. T. Dawson (2012). "Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis." N. Engl. J Med **367**(12): 1098-1107.

Kaufman, M., D. Moyer and J. Norton (2000). "The significant change for the Timed 25-foot Walk in the multiple sclerosis functional composite." Mult. Scler **6**(4): 286-290.

[redacted]

Levey, A. S., L. A. Stevens, C. H. Schmid, Y. L. Zhang, A. F. Castro, III, H. I. Feldman, J. W. Kusek, P. Eggers, L. F. Van, T. Greene and J. Coresh (2009). "A new equation to estimate glomerular filtration rate." Ann. Intern. Med **150**(9): 604-612.

Lublin, F. D. and S. C. Reingold (1996). "Defining the clinical course of multiple sclerosis: results of an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis." Neurology **46**(4): 907-911.

Maruish, M. E. E. (2012). User's manual for the SF-12v2 Health Survey, (3rd ed.). M. E. Maruish. Lincoln, RI.

Multiple Sclerosis Coalition (2015). The use of disease modifying therapies in multiple sclerosis- Principles and current evidence: 1-38.

O'Gorman, J., H. K. Russell, J. Li, G. Phillips, N. C. Kurukulasuriya and V. Viglietta (2015). "Effect of Aspirin Pretreatment or Slow Dose Titration on Flushing and Gastrointestinal Events in Healthy Volunteers Receiving Delayed-release Dimethyl Fumarate." Clin. Ther **37**(7): 1402-1419.

Phillips, J. T. and R. J. Fox (2013). "BG-12 in multiple sclerosis." Semin Neurol **33**(1): 56-65.

Phillips, J. T., K. Selmaj, R. Gold, R. J. Fox, E. Havrdova, G. Giovannoni, H. Abourjaily, A. Pace, M. Novas, C. Hotermans, V. Viglietta and L. Meltzer (2015). "Clinical Significance of Gastrointestinal and Flushing Events in Patients with Multiple Sclerosis Treated with Delayed-Release Dimethyl Fumarate." Int J MS Care **17**(5): 236-243.

Polman, C. H., S. C. Reingold, B. Banwell, M. Clanet, J. A. Cohen, M. Filippi, K. Fujihara, E. Havrdova, M. Hutchinson, L. Kappos, F. D. Lublin, X. Montalban, P. O'Connor, M. Sandberg-Wollheim, A. J. Thompson, E. Waubant, B. Weinshenker and J. S. Wolinsky (2011). "Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria." Ann. Neurol **69**(2): 292-302.

Posner, K., G. K. Brown, B. Stanley, D. A. Brent, K. V. Yershova, M. A. Oquendo, G. W. Currier, G. A. Melvin, L. Greenhill, S. Shen and J. J. Mann (2011). "The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults." Am J Psychiatry **168**(12): 1266-1277.

Ropper, A. H. (2012). "The "poison chair" treatment for multiple sclerosis." N Engl J Med **367**(12): 1149-1150.

Tornatore, C., J. Li, T. Ma, C. von Hehn, J. Walsh and J. Zambrano (2014). Effect of Bismuth Subsalicylate on Gastrointestinal Events Associated with Delayed-Release Dimethyl Fumarate: A Double-Blind, Placebo-Controlled Study. 2014 Joint ACTRIMS-EXTRIMS Meeting, Boston, MA.

Tremlett, H., Y. Zhao, P. Rieckmann and M. Hutchinson (2010). "New perspectives in the natural history of multiple sclerosis." Neurology **74**(24): 2004-2015.

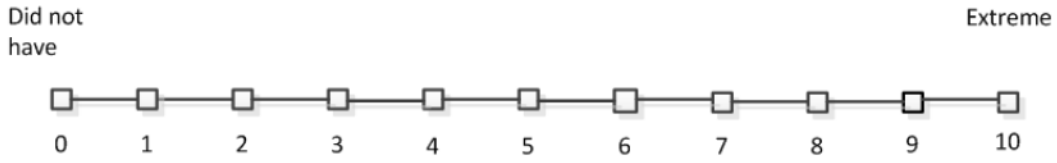
Werdenberg, D., R. Joshi, S. Wolffram, H. P. Merkle and P. Langguth (2003). "Presystemic metabolism and intestinal absorption of antipsoriatic fumaric acid esters." Biopharm. Drug Dispos **24**(6): 259-273.

APPENDIX A. INDIVIDUAL GASTROINTESTINAL SYMPTOM AND IMPACT SCALE (IGISIS)

This questionnaire asks you about potential gastrointestinal symptoms you might feel after taking your study drug. For each of these symptoms, you will indicate whether or not you experienced the symptom and if you did, how intense the symptom was, how long after taking your study drug that it started, how long it lasted, and how much it affected your daily life. The gastrointestinal symptoms you will be asked about in this questionnaire include nausea, vomiting, abdominal pain (both upper and lower in location), and diarrhea. You may experience one or more of these symptoms or none at all.

You should complete this questionnaire within 9 hours after taking your study drug. As you will be taking your study drug twice a day, you will be completing this questionnaire **twice** a day as well. All questions in this questionnaire refer to the period of time **since you last completed this questionnaire** with the exception of when you complete this questionnaire for the first time. When you first complete this questionnaire, the period of time is **since your first dose**.

1. How intense has your **NAUSEA** been on a scale (shown below) from 0 (did not have) to 10 (extreme)?

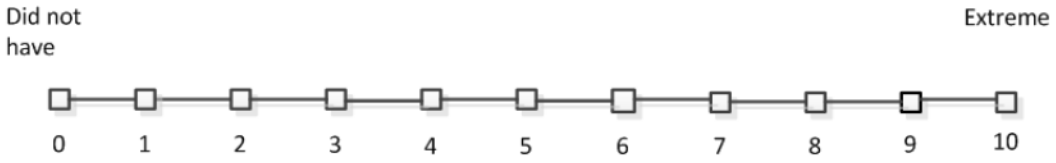


   a. When did your nausea start? _____
   b. When did your nausea stop?_____
   c. How much has your nausea INTERFERED with your ability to accomplish your regular daily activities? (choose one):

      Regular daily activities refer to the things you usually do, such as shopping, household work, taking care of a child or family member, exercising, etc.

      i. Not at all
      ii. Slightly
      iii. Moderately
      iv. Quite a bit
      v. Extremely

2. How intense has your **VOMITING** been on a scale (shown below) from 0 (did not have) to 10 (extreme)?

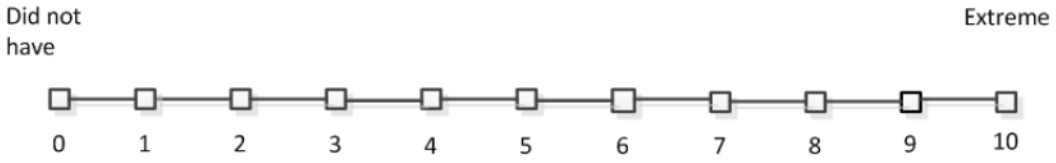


   a. When did your vomiting start? _____
   b. When did your vomiting stop? _____
   c. How much has your vomiting INTERFERED with your ability to accomplish your regular daily activities? (choose one):

   Regular daily activities refer to the things you usually do, such as shopping, household work, taking care of a child or family member, exercising, etc.

      i. Not at all
      ii. Slightly
      iii. Moderately
      iv. Quite a bit
      v. Extremely

3. How intense has your **UPPER ABDOMINAL PAIN** been on a scale (shown below) from 0 (did not have) to 10 (extreme)?

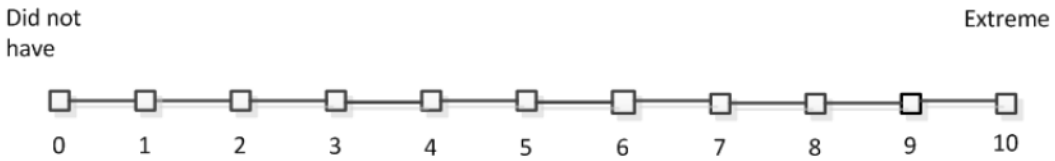


   a. When did your upper abdominal pain start? _____
   b. When did your upper abdominal pain stop? _____
   c. How much has your upper abdominal pain INTERFERED with your ability to accomplish your regular daily activities? (choose one):

Regular daily activities refer to the things you usually do, such as shopping, household work, taking care of a child or family member, exercising, etc.

i. Not at all
ii. Slightly
iii. Moderately
iv. Quite a bit
v. Extremely

4. How intense has your **LOWER ABDOMINAL PAIN** been on a scale (shown below) from 0 (did not have) to 10 (extreme)?

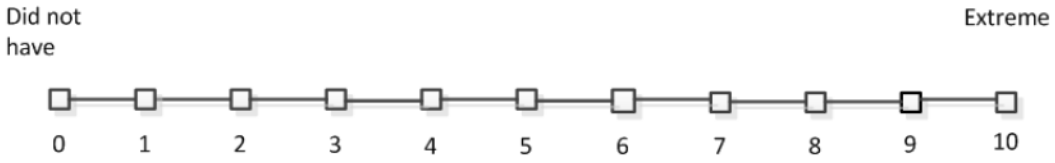


a. When did your lower abdominal pain start? _____
b. When did your lower abdominal pain stop? _____
c. How much has your lower abdominal pain INTERFERED with your ability to accomplish your regular daily activities? (choose one):

Regular daily activities refer to the things you usually do, such as shopping, household work, taking care of a child or family member, exercising, etc.

i. Not at all
ii. Slightly
iii. Moderately
iv. Quite a bit
v. Extremely

5. How intense has your **DIARRHEA** been on a scale (shown below) from 0 (did not have) to 10 (extreme)?



a. When did your diarrhea start? _____
b. When did your diarrhea stop? _____
c. How much has your diarrhea INTERFERED with your ability to accomplish your regular daily activities? (choose one):

Regular daily activities refer to the things you usually do, such as shopping, household work, taking care of a child or family member, exercising, etc.

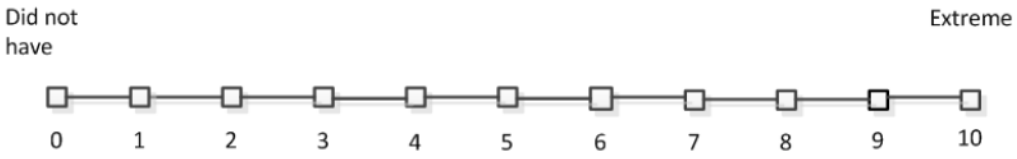
i. Not at all
ii. Slightly
iii. Moderately
iv. Quite a bit
v. Extremely

APPENDIX B. GLOBAL GASTROINTESTINAL SYMPTOM AND IMPACT SCALE (GGISIS)

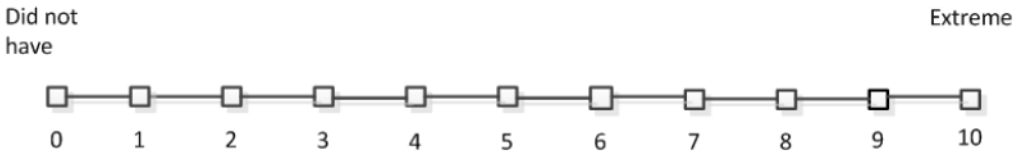
This questionnaire asks you about the overall experience of gastrointestinal symptoms you might feel after taking your study drug. The gastrointestinal symptoms to think about are nausea, vomiting, abdominal pain (both upper and lower in location), and diarrhea. You may experience one or more of these symptoms or none at all.

You should complete this questionnaire in the morning before you take your study medication. You will only complete this questionnaire **once** per day. All questions in this questionnaire refer to your experience **over the past 24 hours**.

1. Rate the **intensity** of your GI symptoms in general over the past 24 hours on a scale from 0 (did not have) to 10 (extreme) as shown below.



2. Rate how **bothersome** your GI symptoms have been in general over the past 24 hours on a scale from 0 (did not have) to 10 (extreme) as shown below.



3. How much have your GI symptoms **interfered** with your ability to accomplish your regular daily activities over the past 24 hours? (choose one):

Regular daily activities refer to the things you usually do, such as shopping, household work, taking care of a child or family member, exercising, etc.

a. Not at all
b. Slightly
c. Moderately
d. Quite a bit
e. Extremely

4. Are you currently employed (working for pay)?

If NO, check "NO" below and you have completed this questionnaire.
If YES, check "YES" below and please answer questions 5 and 6.

___NO
___YES

5. During the past 24 hours, how many hours of work did you miss because of your GI symptoms?

How many hours that you were supposed to work or were scheduled to work did you miss because of your GI symptoms? If you didn't miss any work, indicate "0" hours below. Do not include time you missed to participate in this study.
If you weren't scheduled to work during the past 24 hours, check "Not applicable" below.

___HOURS
___Not applicable

6. How much have your GI symptoms affected your productivity while you were working over the past 24 hours? (choose one)

Was there time during the past 24 hours when you were limited in the amount or kind of work you could do or you accomplished less than you usually do because of your GI symptoms?

a. Not at all
b. Slightly
c. Moderately
d. Quite a bit
e. Extremely