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**PROTOCOL NUMBER:** ALK8700-A301/ NCT02634307

**PHASE OF DEVELOPMENT:** 3

**PROTOCOL TITLE:** A Phase 3 Open Label Study to Evaluate the Long-Term Safety and Tolerability of ALKS 8700 in Adults With Relapsing Remitting Multiple Sclerosis

**EUDRA CT NUMBER:** 2015-005160-41

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**FINAL**

# SPONSOR INFORMATION

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For urgent medical issues in which the study Medical Director should be contacted, please refer to the Study Reference Manual's Official Study Contact List for complete contact information.

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

# SPONSOR SIGNATURE PAGE

Protocol ALK8700-A301 was approved by:

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# 1. KEY STUDY ELEMENTS

## 1.1. Synopsis

| | |
|---|---|
| Protocol Title: | A Phase 3 Open Label Study to Evaluate the Long-Term Safety and Tolerability of ALKS 8700 in Adults With Relapsing Remitting Multiple Sclerosis |
| Protocol Number: | ALK8700-A301 |
| Version Number: | 5.0 |
| Name of Study Treatment: | ALKS 8700 (also known as BIIB098 and diroximel fumarate) |
| Study Phase: | 3 |
| Study Indication: | Multiple sclerosis (MS) |
| Study Rationale: | Disease-modifying therapies are widely used for the treatment of relapsing forms of MS and have been demonstrated to delay disease progression, prevent disability, and improve quality of life. The ALKS 8700 drug product is a modified-release oral dosage form that provides a monomethyl fumarate (MMF) exposure profile that may limit gastrointestinal (GI) effects associated with dimethyl fumarate (DMF) treatment while maintaining efficacy comparable to that demonstrated with DMF. Accordingly, ALKS 8700 has the potential to address an unmet medical need for patients with relapsing forms of MS who are unable to tolerate DMF, particularly due to GI effects. |
| Rationale for Dose and Schedule Selection: | Unless otherwise specified all doses referred to are administered twice daily (BID). The selected dose level of ALKS 8700 delayed release (DR; 462 mg) is supported by clinical safety, tolerability, and pharmacokinetic (PK) data from prior clinical studies. 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 and in a completed repeat dose clinical study. Safety data from both studies indicate that doses of 210 mg, 420 mg, and 630 mg (231 mg and 462 mg doses to be used in this study), administered either as a single dose or BID for 5 days in healthy volunteers were generally well tolerated with no relevant differences in safety or tolerability between single or repeat dosing at each dose level. In addition, it was |

demonstrated that the incidence of flushing with ALKS 8700 DR 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 DR was confirmed by 2 relative bioavailability studies in which PK results showed that ALKS 8700 462 mg results is comparable MMF exposure to DMF 240 mg under fasted conditions, as well as in the presence of a high-fat, high-calorie meal.

Study Objectives and Endpoints

| Objective | Endpoint |
|---|---|
| To evaluate the long-term safety and tolerability of ALKS 8700 for up to 96 weeks of treatment in adult subjects with relapsing-remitting multiple sclerosis (RRMS) | Adverse events, vital signs, clinical laboratory parameters, electrocardiogram parameters, and Columbia Suicide Severity Rating Scale. |
| To evaluate treatment effect over time in adult subjects with RRMS treated with ALKS 8700 | Clinical: annualized relapse rate (ARR), proportion of subjects experiencing MS relapse, progression of disability on the Expanded Disability Status Scale (EDSS), timed 25-foot walk test (T25FW), EuroQol Group health outcome measure (5 level; EQ-5D-5L), and 12-item Short Form Health Survey (SF-12).<br>Exploratory: [redacted] |

| | |
|---|---|
| Study Design: | This Phase 3, multicenter, open-label study will evaluate the long-term safety and tolerability of ALKS 8700. |
| Study Location: | Approximately 125 sites in North America and Europe. |
| Study Population: | Subjects will enter into the study in one of two ways, as either De Novo or Rollover Subjects. |

This study will be conducted in De Novo Subjects who meet the following criteria:

- Male and female adults aged 18 to 65 years, inclusive, at Screening
- Has a confirmed diagnosis of RRMS according to the revised 2010 McDonald criteria
- EDSS score of 0.0-6.0 at screening and Visit 2
- Neurologically stable with no evidence of relapse within 30 days prior to Visit 2

This study will be conducted in Rollover Subjects who meet the following criterion:

- Completed the full treatment period of any eligible study of ALKS 8700 within 7 days of Visit 2

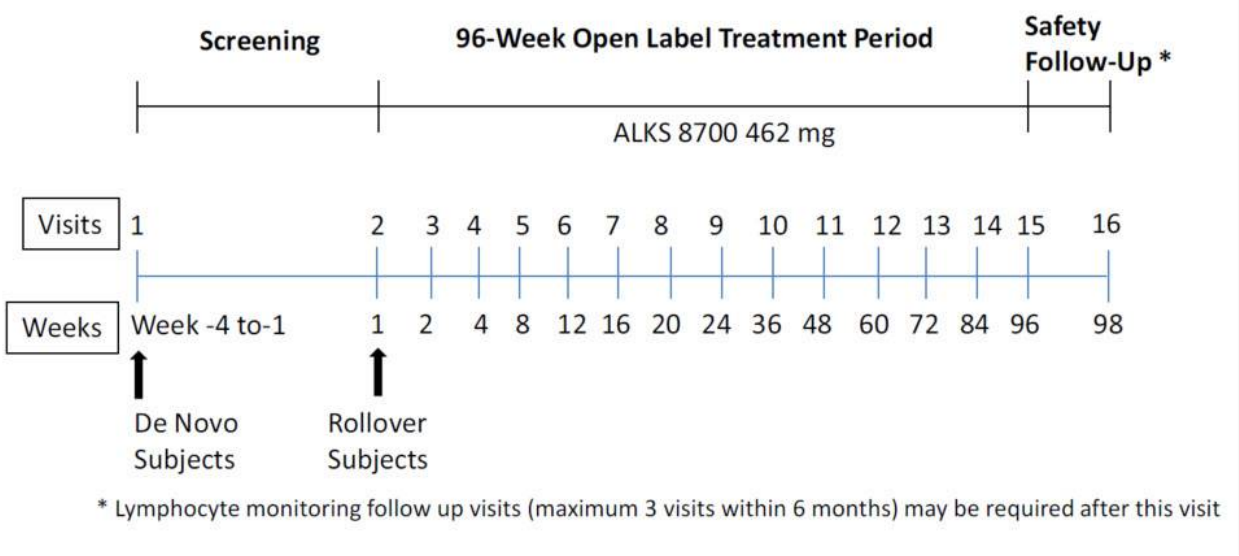
Detailed criteria are described in Section 6.

| | |
|---|---|
| Number of Planned Subjects: | Approximately 1000 subjects will be dosed. |
| Treatment Groups: | Study treatment includes ALKS 8700 231 mg administered as one capsule and ALKS 8700 462 mg administered as two 231 mg capsules.<br><br>This study will enroll both De Novo and Rollover Subjects. Any subject not currently receiving ALKS 8700 or DMF will titrate from ALKS 8700 231 mg BID for the first week on treatment followed by 462 mg BID from Day 8 onwards. For those subjects already receiving ALKS 8700 or DMF, the initial ALKS 8700 dose will be 462 mg BID starting from Day 1.<br><br>Capsules will be administered orally BID. Study staff will administer the first dose of ALKS 8700 at Visit 2 (Day 1). From that point on during the treatment period, the staff will dispense ALKS 8700 for participations' self-administration. Subjects will be instructed to take study treatment with or without food. However, subjects will be instructed to avoid taking study treatment with a high-fat, high-calorie meal. |
| Sample Size Determination: | No formal sample size calculation is performed for this study. A sample size of approximately 1000 subjects will contribute to the |

| | |
|---|---|
| | long-term safety experience of ALKS 8700 in subjects with RRMS, taking into account International Council for Harmonisation guidance on the extent of patient exposures required to assess clinical safety for a new drug. |
| Visit Schedule: | Subjects will have up to 16 visits during the study.<br><br>Study assessments conducted at each visit are listed in the Schedule of Activities (Table 1). |
| Duration of Study Participation: | Study duration for each subject will be approximately 102 weeks:<br><br>• 4-week screening period (De Novo Subjects only)<br>• 96-week treatment period<br>• 2-week follow-up period |
| Benefit-Risk Analysis: | The potential risks related to participation in this study are justified by the anticipated benefit to subjects.<br><br>The modified-release oral dosage form may provide an MMF exposure profile that may limit GI effects associated with DMF treatment while maintaining efficacy. Accordingly, ALKS 8700 has the potential to address an unmet medical need for patients with relapsing forms of MS who are unable to tolerate DMF. |

## 1.2. Study Design Schematic

**Figure 1: Study Design Schematic**




*Dosing is twice daily.
De Novo Subjects and Rollover Subjects defined in Section 5.1.

## 1.3. Schedule of Activities

### Table 1: Schedule of Assessments

| | **Screening** | **96-Week-Open-Label Treatment**[1] | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | 1[2] | 2[3] | TC[4] | 3 | TC[4] | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15/ET | 16 Follow-Up |
| **Day** | -28 to -1 | 1 | 8 (±2) | 15 (±3) | 22 (±2) | 29 (±3) | 57 (±5) | 85 (±5) | 113 (±5) | 141 (±5) | 169 (±5) | 253 (±5) | 337 (±5) | 421 (±5) | 505 (±5) | 589 (±5) | 673 (±5) | 687 (±5) |
| **Week** | -4 to -1 | 1 | | 2 | | 4 | 8 | 12 | 16 | 20 | 24 | 36 | 48 | 60 | 72 | 84 | 96 | 98 |
| Informed consent[5] | X | | | | | | | | | | | | | | | | | |
| Eligibility Criteria Review | X | X[6] | | | | | | | | | | | | | | | | |
| Demographics and Medical History | X | | | | | | | | | | | | | | | | | |
| Physical Examination[7] | X | X[7] | | X | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Height[8] | X | | | | | | | | | | | | | | | | | |
| Weight | X | X[6] | | | | X | X | X | | | X | X | X | X | X | X | X | X |
| Urine Pregnancy Test | X | X[6] | | X | | X | X | X | X | X | X | X | X | X | X | X | | |
| Serology Testing[8] | X | | | | | | | | | | | | | | | | | |

| | **Screening** | **96-Week-Open-Label Treatment**[1] | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | 1[2] | 2[3] | TC[4] | 3 | TC[4] | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15/ET | 16 Follow-Up |
| **Day** | -28 to -1 | 1 | 8 (±2) | 15 (±3) | 22 (±2) | 29 (±3) | 57 (±5) | 85 (±5) | 113 (±5) | 141 (±5) | 169 (±5) | 253 (±5) | 337 (±5) | 421 (±5) | 505 (±5) | 589 (±5) | 673 (±5) | 687 (±5) |
| **Week** | -4 to -1 | 1 | | 2 | | 4 | 8 | 12 | 16 | 20 | 24 | 36 | 48 | 60 | 72 | 84 | 96 | 98 |
| Biochemistry, Urinalysis[9], and Hematology | X | X[6] | | X | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Vital Signs[10] | X | X[6] | | X | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Standard 12-Lead ECG | X | X[6] | | X | | X | X | X | | | X | X | X | | X | | X | X |
| PK sampling[11] | | X[6] | | X | | X | X | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | |
| Timed 25-Foot Walk | X | X[6] | | | | | | X | | | X | X | X | X | X | X | X | |
| EDSS | X | X[6] | | | | | | X | | | X | X | X | X | X | X | X | |
| SF-12 | | X[6] | | | | | | | | | X | | X | | X | | X | |
| EQ-5D-5L | | X[6] | | | | | | | | | X | | X | | X | | X | |
| C-SSRS[15] | X | X[6] | | X | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant Medication Review | X | X | X[4] | X | X[4] | X | X | X | X | X | X | X | X | X | X | X | X | X |
| AE Monitoring | X | X | X[4] | X | X[4] | X | X | X | X | X | X | X | X | X | X | X | X | X |

| | **Screening** | **96-Week-Open-Label Treatment**[1] | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | 1[2] | 2[3] | TC[4] | 3 | TC[4] | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15/ET | 16 Follow-Up |
| **Day** | -28 to -1 | 1 | 8 (±2) | 15 (±3) | 22 (±2) | 29 (±3) | 57 (±5) | 85 (±5) | 113 (±5) | 141 (±5) | 169 (±5) | 253 (±5) | 337 (±5) | 421 (±5) | 505 (±5) | 589 (±5) | 673 (±5) | 687 (±5) |
| **Week** | -4 to -1 | 1 | | 2 | | 4 | 8 | 12 | 16 | 20 | 24 | 36 | 48 | 60 | 72 | 84 | 96 | 98 |
| Study treatment Dispensation | | X | | X | | X | X | X | X | X | X | X | X | X | X | X | | |
| Study treatment Accountability | | | | X | | X | X | X | X | X | X | X | X | X | X | X | X | |
| Emergency Treatment Card[16] | | X | | X | | X | X | X | X | X | X | X | X | X | X | X | X | |

AE = adverse event; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; EDSS = Expanded Disability Status Scale; EQ-5D-5L = EuroQoL Group health outcome measure 5-level version; ET = early termination; [redacted]; PK = pharmacokinetic; SF-12 = 12-item Short Form Health Survey; TC = telephone call.

Unscheduled visit may occur at any time as per protocol requirements.

[2] Only De Novo Subjects will participate in the Screening Visit.

[3] For Rollover Subjects, identical assessments taken at the last treatment visit in the antecedent study do not need to be repeated at Visit 2 in the current study.

[4] Safety and tolerability assessments (including AEs and concomitant medications) will be conducted by telephone on these days.

[5] Eligible, consenting De Novo Subjects will give written consent at screening. Eligible, consenting Rollover Subjects will give written consent prior to participating in any study-specific procedures at Visit 2. Written confirmation of a subject's willingness to continue in the study will be required if one or more of the following occur during the study: MS relapse, disability progression, [redacted]

[6] To be conducted predose at Visit 2.

[7] Full physical examination at screening. Brief physical examination, symptom-directed, at all other visits.

[8] For Rollover Subjects, height will be carried over from information recorded in the antecedent ALKS 8700 study in which they participated.

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

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

[10] Vital signs measurements include temperature, respiratory rate, blood pressure, and heart rate. 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.

[11]PK samples will be collected in a subset of De Novo Subjects at selected sites. Samples will be collected predose, and at 0.5, 1, 2, 3, 4, 6, and 8 hours after the morning dose on Days 1 and 29. Additional PK samples will be collected prior to and approximately 2 to 3 hours following the morning or evening dose on Days 15 and 57. Specifics of the study visits for PK sample collection and PK sampling procedures will be communicated with the sites outside of this protocol.

[redacted]

[15]Use "Screening" version at screening; use "Since Last Visit" version at all other scheduled visits.

[16]At Visit 2, dispense Emergency Treatment Card to De Novo Subjects and confirm possession/redispense if necessary for Rollover Subjects. At all other visits, confirm subject's possession of card and redispense if necessary.

**Table 2: Additional Follow-Up for Subjects With Lymphopenia**

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

LM = lymphocyte monitoring.

[1] Subjects who complete the study or who terminate the study early and have a last measured lymphocyte count < 0.8 x $10^3$/µL will return to the clinic for additional LM visits every 2 months starting from Visit 16 for a period of 6 months (i.e., a maximum of 3 visits) or until lymphocyte counts reach normal limits (≥ 0.91 x $10^3$/µL), whichever occurs first. All assessments required for the Safety Follow-Up Visit (Visit 16, Table 1) should be completed for these subjects prior to initiation of the lymphocyte monitoring visits.

# 2. LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | adverse event |
| ALT | alanine aminotransferase |
| ARR | annualized relapse rate |
| 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 |
| $C_{max}$ | maximum observed concentration |
| CRO | contract research organization |
| CSA | Clinical Study Agreement |
| C-SSRS | Columbia-Suicide Severity Rating Scale |
| DMF | dimethyl fumarate |
| DMT | disease-modifying therapy |
| DR | delayed release |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| eGFR | estimated glomerular filtration rate |
| EDSS | Expanded Disability Status Scale |
| EQ-5D-5L | EuroQol Group health outcome measure (5-level) |
| ET | early termination |
| FAS | full analysis set |
| FS | functional system |
| GCP | Good Clinical Practice |
| GdE | gadolinium-enhancing |
| [redacted] | |
| GI | gastrointestinal |
| GMP | Good Manufacturing Practice |
| HDPE | high density polyethylene |
| hERG | human ether-à-go-go-related gene |
| HIV | human immunodeficiency virus |
| ICF | informed consent form |
| ICH | International Council for Harmonisation |
| IRB | institutional review board |
| IFN | interferon |
| IRT | interactive response technology |
| IV | intravenous |
| LM | lymphocyte monitoring |
| MMF | monomethyl fumarate |
| [redacted] | |

| | |
|---|---|
| MS | multiple sclerosis |
| NEDA | No Evidence of Disease Activity |
| PK | pharmacokinetic(s) |
| PML | progressive multifocal leukoencephalopathy |
| RRMS | relapsing-remitting multiple sclerosis |
| SAE | serious adverse event |
| SF-12 | Short Form-12 Health Survey |
| SF-12v2 | Short Form-12 Health Survey Version 2 |
| T25-FW | Timed 25-Foot Walk |
| TEAE | treatment-emergent adverse event |
| TSH | thyroid-stimulating hormone |
| $T_{max}$ | time to reach $C_{max}$ |
| ULN | upper limit of normal |
| VAS | Visual Analog Scale |

# 3. INTRODUCTION

## 3.1. Study Rationale

### 3.1.1. Rationale for Study Population

The majority of patients with multiple sclerosis (MS) initially have a form known as relapsing-remitting MS (RRMS). Early and effective treatment is necessary to improve quality of life and to reduce the risk of patients developing more progressive forms of the disease leading to severe physical disability.

### 3.1.2. Rationale for Dosing Regimen

The selected dose level of ALKS 8700 DR (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). All doses referred to in this section are twice daily (BID).

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 (231 mg and 462 mg doses to be used in this study), administered either as a single dose or BID for 5 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 DR 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 DR was confirmed by 2 relative bioavailability studies (Study ALK8700-A103 and ALK8700-A104) in which PK results showed that ALKS 8700 462 mg results in comparable monomethyl fumarate (MMF) exposure to dimethyl fumarate (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 area under the concentration-time curve (AUC) and maximum observed concentration ($C_{max}$). 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 treatment with a high-fat, high-calorie meal. Administration with food may reduce the incidence of flushing (as observed in Study ALK8700-A102).

## 3.2. Background

### 3.2.1. Overview of Multiple Sclerosis

MS is a chronic, debilitating disease of the central nervous system that currently affects approximately 2.5 million people worldwide with 5 to 10 new cases per 100,000 people each year [Ropper 2012; Tremlett 2010].

### 3.2.2. Current Therapies for Multiple Sclerosis

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 [Costello 2014] and have been demonstrated to delay disease progression, prevent disability and improve quality of life.

The most commonly used first-line MS therapies are interferons (IFNs) and glatiramer acetate [Waldman 2011]. Relative to placebo, IFNs have been shown to reduce relapse rate by approximately 27% to 36% [Calabresi 2014; Jacobs 1996; PRISMS Study Group 1998; The IFNB Multiple Sclerosis Study Group 1993], and glatiramer acetate by approximately 30% [Johnson 1995]. The IFN beta-1a products have also been shown to delay disability progression [Jacobs 1996; PRISMS Study Group 1998].

Other currently approved therapies for MS include the following:

- Natalizumab: a humanized monoclonal antibody directed against α4 integrins [Polman 2006]
- Fingolimod: a selective oral immunosuppressant that is metabolized to a functional antagonist of sphingosine 1-phosphate receptors on lymphocytes [Kappos 2010]
- Mitoxantrone: a synthetic antineoplastic anthracenedione that intercalates into deoxyribonucleic acid and interferes with ribonucleic acid [Chitnis 2012]
- Teriflunomide: an immunomodulatory drug inhibiting pyrimidine synthesis by blocking dihydroorotate dehydrogenase [O'Connor 2011]
- Alemtuzumab: a humanized monoclonal antibody targeting CD-52 antigen expressed on the surface of most leukocytes [Coles 2012]

### 3.2.3. Profile of Previous Experience With ALKS 8700

#### 3.2.3.1. Clinical Studies

Five Phase I studies to evaluate the safety, tolerability, and pharmacokinetics (PK) of ALKS 8700 in healthy adults (ALK8700-001, ALK8700-A102, ALK8700-A103 and ALK8700-A104, ALK8700-A105) have been completed. Three Phase 1 studies (ALK8700-106, ALK8700-107, and ALK8700-A109) have been clinically completed and the data analyses are ongoing.

The general PK characteristics for ALKS 8700 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 $C_{max}$ (44%) and a modest reduction in 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 ($AUC_{last}$ 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 in 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 7.1.

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-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 gastrointestinal (GI)-related TEAEs which have both occurred in a dose-dependent manner. GI-related 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 PK, safety, and tolerability of ALKS 8700 are summarized in the Investigator's Brochure.

#### 3.2.3.2. 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 human ether-à-go-go-related gene (hERG) potassium channel activity in a human cell line (i.e., concentration resulting in 50% inhibition of response [$IC_{50}$] > 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), GI 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 (i.e., 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.

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

## 3.3. Benefit-Risk Assessment

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

Detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of ALKS 800 is provided in the Investigator's Brochure and informed consent form (ICF). A high-level summary of those benefits and risks known during study design is provided here.

ALKS 8700 is being developed as a modified-release oral treatment for relapsing forms of MS. ALKS 8700 is an aminoethyl ester of MMF that undergoes hydrolysis through esterases to produce MMF. MMF is also the active metabolite of the approved drug product, DMF. An oral form of DMF has been approved by the US Food and Drug Administration since 2013 under the trade name Tecfidera® for the treatment of patients with relapsing forms of MS [Tecfidera® Prescribing Information 2017/SmPC 2017].

In clinical trials, DMF and, by extrapolation, its metabolite, MMF, have demonstrated robust efficacy in modulating the course of disease in patients with RRMS. Compared with placebo, DMF treatment resulted in significant reductions in annualized relapse rate (ARR), disability progression, as well as the number of new gadolinium-enhancing (GdE) lesions and new or enlarging T2 lesions [Fox 2012; Gold 2012; Kappos 2008].

The safety profile of DMF is well understood and GI-related tolerability is a recognized tolerability concern. As noted in the Summary Review of the Drug Approval Package for Tecfidera, in placebo-controlled trials of Tecfidera, 40% of DMF-treated subjects experienced one or more GI AEs. Reviewers described "a panoply of uncomfortable and fairly common GI AEs" that are an "obstacle to tolerability," including nausea, vomiting, diarrhea, and abdominal pain [FDA 2013]. In addition, GI AEs were the leading cause of discontinuations due to AEs [FDA 2013]. The frequency and severity of the GI-related side effects are an important issue for patients taking DMF and is a barrier to treatment adherence and can lead to drug discontinuation which increases risk of relapse [Phillips 2014; Utz 2014]. This underscores the need for an efficacious agent with improved tolerability to optimize patient satisfaction and treatment outcomes [Phillips and Fox 2013].

The ALKS 8700 drug product is a modified-release oral dosage form that provides an MMF exposure profile that may limit GI effects associated with DMF treatment while maintaining efficacy comparable to that demonstrated with DMF. Accordingly, ALKS 8700 has the potential to address an unmet medical need for patients with relapsing forms of MS who are unable to tolerate DMF, particularly due to GI effects.

# 4. STUDY OBJECTIVES AND ENDPOINTS

| Objective | Endpoints |
|---|---|
| To evaluate the long-term safety and tolerability of ALKS 8700 for up to 96 weeks of treatment in adult subjects with RRMS | AEs, vital signs, electrocardiogram (ECG) parameters, Columbia Suicide Severity Rating Scale (C-SSRS), and clinical laboratory parameters |
| To evaluate treatment effect over time in adult subjects with RRMS treated with ALKS 8700 | Clinical: ARR, proportion of subjects experiencing MS relapse, progression of disability on the Expanded Disability Status Scale (EDSS), Timed 25-Foot Walk Test (T25-FW), EuroQol Group health outcome measure (5 level; EQ-5D-5L), and 12-item Short Form Health Survey (SF-12)<br><br>Exploratory: [redacted] |

# 5. STUDY DESIGN

## 5.1. Study Overview

This multicenter, open-label study will evaluate the long-term safety and tolerability of ALKS 8700 up to 96 weeks in approximately 1000 subjects. The target population for this study will be adults, aged 18 to 65 years, diagnosed with RRMS. The study will be conducted at approximately 125 sites in North America and Europe.

See Figure 1 for a schematic of the study design.

## 5.2. Study Duration for Subjects

Subjects will enter into the study in one of two ways:

De Novo Subjects: Those who have not participated in any prior eligible study of ALKS 8700.

Rollover Subjects: Those who have completed the treatment period for any prior eligible study of ALKS 8700.

For De Novo Subjects, the study duration is expected to be up to 102 weeks, which includes up to 4 weeks for screening, a 96-week open-label treatment period, and a 2-week follow-up period.

De Novo Subjects will be initially evaluated for eligibility at screening (Visit 1) that may last up to 28 days (4 weeks) prior to Visit 2. For Rollover Subjects, Visit 2 will be the first visit of the study and there will not be a separate screening visit. For these subjects, Visit 2 of this study will occur at the time of or within 7 days of the subject's end of treatment visit in the antecedent study. Completed assessments taken at the end of treatment visit of the antecedent study will be carried forward and do not need to be repeated at Visit 2 of this study unless otherwise specified in the schedule of assessments. At Visit 2, all eligible, consenting subjects will begin open-label treatment. Any subject not currently receiving ALKS 8700 or DMF will initiate treatment with ALKS 8700 231 mg BID on Day 1 through Day 7 followed by 462 mg BID from Day 8 onwards. For those subjects already receiving ALKS 8700 or DMF prior to Day 1, the initial ALKS 8700 dose will be 462 mg BID starting from Day 1.

Dosing is described in detail in Section 7.1. From Day 8 onwards, all participating subjects will take ALKS 8700 462 mg BID, with allowable dose reduction for tolerability as described in Section 7.2.

Study staff will administer the first dose of ALKS 8700 at Visit 2 (Day 1). From that point on during the treatment period, according to the schedule of assessments as shown in Table 1, the staff will dispense ALKS 8700 for subjects' self-administration. Subjects will be instructed to take study treatment with or without food. However, subjects will be instructed to avoid taking study treatment with a high-fat, high-calorie meal.

During the 96-week treatment period (Visits 2-15), subjects will return to the clinic for periodic scheduled visits for the assessment of safety, tolerability, PK (in a subset of de novo subjects in selected sites), and clinical status. Two safety and tolerability assessments by phone will be scheduled (one between Visits 2 and 3 and one between Visits 3 and 4). See Figure 1 for a study schematic.

Subjects will return to the clinic for a safety follow-up visit (Visit 16) 2 weeks after the end of treatment visit (Visit 15). Any subject who prematurely discontinues from either study treatment or the study will be asked to return to the clinic for an early termination (ET) visit (Visit 15) as well as a safety follow-up visit 2 weeks later (Visit 16).

Subjects who complete the study or who terminate the study early and have a last measured lymphocyte count $< 0.8 \times 10^3/\mu L$ will return to the clinic for additional lymphocyte count monitoring visits every 2 months starting from Visit 16 for a period of 6 months (i.e., a maximum of 3 visits) or until lymphocyte counts reach normal limits ($\geq 0.91 \times 10^3/\mu L$), whichever occurs first.

A treatment completer will be a subject who completes the 96-week treatment period (i.e., through Visit 15). Subjects completing the follow-up visit will be categorized as completing the study.

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

## 5.3. Study treatment Dose Adjustment and Stopping Rules

Starting on Day 8 of treatment, dose reduction to ALKS 8700 231 mg BID is permitted at the Investigator's discretion for subjects who are unable to tolerate ALKS 8700 462 mg BID. Once a subject has stabilized after dose reduction, attempts should again be made to achieve and maintain the target maintenance dose of ALKS 8700 462 mg BID. If a subject remains unable to tolerate ALKS 8700 462 mg BID after 1 month on treatment (i.e., by Visit 4), further dose reduction will not be permitted, and the subject will be discontinued from the study.

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

## 5.4. Unscheduled Visits

Data collected during unscheduled visits should be recorded in electronic case report forms (eCRFs) only if the data support protocol objectives and/or are required for safety monitoring.

An Unscheduled Relapse Visit will be conducted in the event of a suspected relapse (Section 7.2.2). This visit should occur as early as possible but within 7 days of the onset of the potential relapse. The following assessments will be made:

- Physical examination
- Concomitant medication review
- AE monitoring
- Urine pregnancy test
- Vital signs
- Safety laboratory assessments
- Relapse assessment
- EDSS

## 5.5. Follow-up

Subjects will return to the clinic for a safety follow-up visit (Visit 16) 2 weeks after the end of treatment visit (Visit 15) for the required assessments (Table 1). Any subject who prematurely discontinues from the study will be asked to return to the clinic for an ET visit (Visit 15) as well as a safety follow-up visit 2 weeks later (Visit 16) for the required assessments (Table 1).

Subjects who complete the study or who terminate the study early and have a last measured lymphocyte count $< 0.8 \times 10^3/\mu L$ at the last study visit (Visit 16) will be required to return to the clinic for additional lymphocyte count monitoring visits every 2 months (± 7 days) starting from the last study visit for a period of 6 months (i.e., a maximum of 3 visits) or until lymphocyte counts reach normal limits ($\geq 0.91 \times 10^3/\mu L$), whichever occurs first (Table 2).

During the lymphocyte count monitoring visits, blood samples will be collected to measure lymphocyte count and any concomitant medications the subjects are taking will be recorded (Section 7.7).

## 5.6. End of Study

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

# 6. STUDY POPULATION

## 6.1. Inclusion Criteria

To be eligible to participate in this study, candidates must meet the following eligibility criteria as listed in Table 1 or at the timepoint specified in the individual eligibility criterion listed.

### 6.1.1. Rollover Subjects

In order to qualify for participation in this study, Rollover Subjects must meet all of the following criteria:

1. Is willing and able to provide informed consent.
2. Capable of understanding and complying with the protocol.
3. Agrees to use an acceptable method of contraception for the duration of the study and for 30 days after any study treatment administration or is surgically sterile or postmenopausal (see Section 11.5).
4. Completed the full treatment period of any eligible study of ALKS 8700 within 7 days of Visit 2.

### 6.1.2. De Novo Subjects

In order to qualify for participation in this study, De Novo Subjects must meet all of the following criteria:

1. Is willing and able to provide informed consent.
2. Capable of understanding and complying with the protocol.
3. Agrees to use an acceptable method of contraception for the duration of the study and for 30 days after any study treatment administration or is surgically sterile or postmenopausal (see Section 11.5).
4. Male and female adults aged 18 to 65 years, inclusive, at screening.
5. Has a confirmed diagnosis of RRMS according to the revised 2010 McDonald criteria [Polman 2011].
6. EDSS score of 0.0-6.0 at screening and Visit 2.
7. Neurologically stable with no evidence of relapse within 30 days prior to Visit 2.

## 6.2. Exclusion Criteria

### 6.2.1. Rollover Subjects

Rollover Subjects will be excluded from participation in this trial if they meet any of the following criteria:

1. Have any finding(s) that in the view of the Investigator or Medical Monitor would compromise the safety of the subject, affect their ability to adhere to the protocol visit schedule, or to fulfill visit requirements or make the subject unsuitable for participation in the study (including overall clinical assessment).

2. 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 treatment administration.

3. Is employed by Biogen, 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 a Biogen, CRO, or study site employee. Immediate family is defined as a spouse, parent, sibling, or child, whether biological or legally adopted.

### 6.2.2. De Novo Subjects

De Novo Subjects will be excluded from participation in this trial if they meet any of the following criteria:

1. Have any finding that in the view of the Investigator or the Medical Monitor would compromise the safety of the subject or affect their ability to adhere to the protocol visit schedule or fulfill visit requirements or 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, GI (e.g., inflammatory bowel disease, peptic ulcer disease), dermatologic, psychiatric, neurologic (other than MS), endocrine, renal and/or other major disease that would preclude participation in a clinical trial.

4. History of clinically significant recurring or active GI symptoms (e.g., nausea, diarrhea, dyspepsia, constipation) within 3 months of screening, including symptoms that require the initiation of symptomatic medical treatment (e.g., initiation of a medication to treat gastroesophageal reflux disease) or a change in symptomatic medical treatment (e.g., an increase in dose) within 3 months of screening.

5. History of malignancy, unless an exception is granted by the Medical Monitor (e.g., subjects with basal cell carcinoma that has been completely excised prior to study entry remain eligible).

6. Has a clinically significant medical condition or observed abnormality at screening (e.g., clinically significant physical examination finding, vital sign result, ECG result, or laboratory test result).

7. History of a myocardial infarction, including a silent myocardial infarction identified on ECG, or unstable angina.

8. History of clinically significant drug or alcohol abuse within the past year (per Investigator judgment).

9. Has a positive serology test for hepatitis B surface antigen, hepatitis C antibody, or human immunodeficiency virus (HIV) antibody at screening.

10. Has any of the following abnormal blood tests at screening:

    - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 2 times the upper limit of normal (ULN)

    - Thyroid-stimulating hormone (TSH) level >10% of the ULN at screening

    - Estimated glomerular filtration rate (eGFR) ≤ 60 mL/min/1.73 $m^2$ (using the Chronic Kidney Disease Epidemiology Collaboration equation) [Levey 2009]

    - Lymphocyte count < $0.9 \times 10^3/\mu L$

11. Has any of the following abnormal urine tests at screening:

    - Beta-2 microglobulin > 0.3 µg/mL

    - Albumin to creatinine ratio > 200 mg/g

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

13. Has previously discontinued treatment with Tecfidera due to tolerability issues and/or lack of efficacy.

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

    - 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 (e.g., cyclosporine, cyclophosphamide, methotrexate, mycophenolate) within 2 years prior to Visit 2

- Teriflunomide within 2 years of Visit 2, unless the serum/plasma concentration of teriflunomide is < 0.020 µg/mL (< 20 ng/mL) prior to Visit 2 (an accelerated elimination procedure for teriflunomide with cholestyramine is permitted during screening)

- Natalizumab within 2 months prior to Visit 2 or any prior use of alemtuzumab

- Fingolimod within 90 days prior to Visit 2

- Daclizumab within 6 months prior to Visit 2

- B-cell targeted therapies for the treatment of MS (e.g., 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 laboratory 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 intravenous (IV) immunoglobulin within 30 days prior to Visit 2

15. Current or prior participation in a clinical trial within 3 months of screening.

16. 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 treatment administration.

17. Is employed by Biogen, CRO, or study site (permanent, temporary contract worker, or designee responsible for the conduct of the study) or is immediate family of a Biogen, CRO, or study site employee. Immediate family is defined as a spouse, parent, sibling, or child, whether biological or legally adopted.

## 6.3. Screening, Retesting, and Screen Failures

### 6.3.1. Screening

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

### 6.3.2. Retesting

Not applicable.

### 6.3.3. Screen Failures

Not applicable.

# 7. STUDY TREATMENT

## 7.1. Regimen

Study treatment includes ALKS 8700 231 mg administered as one capsule and ALKS 8700 462 mg administered as two 231 mg capsules.

This study will enroll both De Novo and Rollover Subjects. Any subject not currently receiving ALKS 8700 or DMF will titrate from ALKS 8700 231 mg BID for the first week on treatment followed by 462 mg BID from Day 8 onwards. For those subjects already receiving ALKS 8700 or DMF, the initial ALKS 8700 dose will be 462 mg BID starting from Day 1.

Capsules will be administered orally BID. Study staff will administer the first dose of ALKS 8700 at Visit 2 (Day 1). From that point on during the treatment period, the staff will dispense ALKS 8700 for subjects' self-administration. Subjects will be instructed to take study treatment with or without food. However, subjects will be instructed to avoid taking study treatment with a high-fat, high-calorie meal. Detailed dosing instructions will be provided to the patients by the site personnel.

## 7.2. Modification of Dose and/or Treatment Schedule

Starting on Day 8 of treatment, dose reduction to ALKS 8700 231 mg BID is permitted at the Investigator's discretion for subjects who are unable to tolerate ALKS 8700 462 mg BID. Once a subject has stabilized after dose reduction, attempts should again be made to achieve and maintain the target maintenance dose of ALKS 8700 462 mg BID. If a subject remains unable to tolerate ALKS 8700 462 mg BID after 1 month on treatment (i.e., by Visit 4), further dose reduction will not be permitted, and the subject will be discontinued from the study.

In the event of a suspected relapse (new symptoms or worsening symptoms), subjects will be asked to call the treating neurologist within 48 to 72 hours of the onset of the symptoms to determine the necessity of an Unscheduled Relapse Visit. An Unscheduled Relapse Visit will be conducted as described in Section 5.4. Further instruction is also provided in Section 7.2.2.

Should progressive multifocal leukoencephalopathy (PML) be suspected by the treating neurologist based on symptoms or signs during the relapse visit, study treatment will be withheld and an appropriate diagnostic work-up should be performed as soon as possible (within 14 days of the relapse visit). If PML is excluded based on the diagnostic work-up, the subject may resume taking study treatment 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 treatment 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 ≥ 4 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 ≥ 4 weeks after discontinuation of study treatment, the subject must permanently discontinue study treatment. (Subjects who permanently discontinue the study with a last measured lymphocyte count < $0.8 \times 10^3$/µL will require additional follow-up to monitor their lymphocyte counts.)

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

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

The study may be stopped at any time or study sites may be closed at the Sponsor's discretion.

### 7.2.1. Rescue

Subjects will be eligible to remain on assigned study treatment for 96 weeks, even if they experience a relapse (see Section 7.2.2). In the event of a confirmed acute event (relapse), the treating neurologist may opt to prescribe 1000 mg of oral or IV methylprednisolone treatment (administered once daily or in divided doses) for 3-5 days with no taper. Treatment with oral or IV methylprednisolone will not affect the subject's eligibility to continue in the study. The subject will continue on study treatment while being treated with methylprednisolone. Subjects may also refuse relapse treatment. Any deviations from this recommended treatment must first be discussed with the Medical Monitor.

### 7.2.2. Relapse

Efficacy analyses related to MS relapse include only events of protocol-defined relapse. Protocol-defined relapse consists of the following:

- New or recurrent neurologic symptoms, not associated with fever or infection, lasting for at least 24 hours, accompanied by one or more of the following:

- New objective neurological findings upon examination by the treating neurologist that are functionally consistent with findings on the EDSS (performed within 7 days of onset of symptoms) with an increase over the prior visit of ≥ 0.5 for the total score,

- An increase of ≥ 2 in 1 functional system (FS), except bladder/cognitive changes, and/or,

- An increase of ≥ 1 in 2 FS, except bladder/cognitive changes.

New or recurrent neurologic symptoms that evolve gradually over months should be considered disability progression, not an acute relapse, and should not be treated with corticosteroids. New or recurrent neurologic symptoms that occur less than 30 days following the onset of a protocol defined relapse should be considered part of the same relapse and would not be treated with oral or IV methylprednisolone within the protocol.

- Subjects who experience new neurologic symptoms must contact the treating nurse or neurologist within 48-72 hours of the onset of symptoms to determine the necessity of an Unscheduled Relapse Visit (see Section 5.4).

- If required, the subject will then be evaluated in person by the neurologist *as early as possible* but within 7 days of the onset of the potential relapse.

- The neurologist is to perform a relapse assessment and obtain an EDSS score. New objective findings on neurological examination performed by the neurologist in conjunction with the EDSS changes described above will confirm whether the suspected protocol-defined relapse has occurred.

- Treatment of the acute event may then proceed at the discretion of the neurologist (according to the methylprednisolone regimen described in Section 7.2.1) only after the neurologist has completed his/her examination. Treatment of an acute event of relapse with oral or IV methylprednisolone will not affect the subject's eligibility to continue in the study.

- Subjects must provide written confirmation of their willingness to continue participation in the study upon any determined event of MS relapse as described in Section 13.5.

## 7.3. Study Treatment Management

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

Study treatment must be dispensed only by a pharmacist or appropriately qualified staff. Study treatment is to be dispensed only to subjects enrolled in this study. Once study treatment is

prepared for a subject, it can be administered only to that subject. Study treatment is for one-time use only; do not use any study treatment remaining in the vial for another subject.

### 7.3.1. ALKS 8700

ALKS 8700 DR capsules consist of enteric-coated, pH sensitive, DR minitablets contained within a hydroxypropyl methylcellulose capsule for oral administration.

The doses of ALKS 8700 DR to be used in this study are 231 mg (administered as one capsule) and 462 mg (administered as two 231 mg capsules). Capsules will be administered orally, BID.

#### 7.3.1.1. Packaging and Labeling

ALKS 8700 DR capsules are supplied in both 20-count, 100 cc, induction sealed, high density polyethylene (HDPE) bottle and 64 count, 150 cc, induction sealed, HDPE bottle configuration.

Labeling will meet all applicable local and regulatory requirements.

#### 7.3.1.2. Storage

All study materials are to be stored at room temperature not to exceed 25°C in a secure location.

#### 7.3.1.3. Handling and Disposal

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 GMP, as applicable.

#### 7.3.1.4. Accountability

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

Unless otherwise notified, all packaging both used and unused, must be saved for study treatment accountability. By the end of the study, reconciliation must be made between the amount of ALKS 8700 supplied, dispensed, and subsequently destroyed, lost, or returned to the Sponsor. A written explanation must be provided for any discrepancies.

## 7.4. Blinding Procedures

Not applicable. The study is open-label.

## 7.5. Precautions

In the event of a confirmed acute event (relapse), the treating neurologist may opt to prescribe 1000 mg of oral or IV methylprednisolone treatment (administered once daily or in divided doses) for 3 to 5 days with no taper. Treatment with oral or IV methylprednisolone will not affect the subject's eligibility to continue in the study. The subject will continue on study treatment while being treated with methylprednisolone. Subjects may also refuse relapse treatment. Any deviations from this recommended treatment must first be discussed with the Medical Monitor.

## 7.6. Compliance

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

According to the schedule in Table 1, at each specified dispensing visit, subjects will receive a supply of ALKS 8700 to last until the following visit. Subjects will be instructed to bring any unused drug and the bottle(s) with them to each subsequent visit. Drug adherence will be reviewed with subjects at each visit.

## 7.7. Concomitant Therapy and Procedures

### 7.7.1. Concomitant Therapy

A concomitant therapy is any drug or substance administered between the time the subject is enrolled in the study and until the completion of the safety follow-up visit (Visit 16).

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

#### 7.7.1.1. Allowed Concomitant Therapy

At screening all De Novo Subjects will be asked about the medications they have taken in the last 30 days. For a potential subject to qualify for the study, those exclusions outlined in Section 7.7.1.2 must be ruled out. At each subsequent study visit, review of concomitant medications will be repeated for all 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 subjects: name, dose, regimen, route of administration, start and stop dates, and the indication for use.

#### 7.7.1.2. Disallowed Concomitant Therapy

Immunomodulatory treatments for RRMS (besides study treatment) are prohibited during treatment with study treatment unless approved by the Medical Monitor. 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: IFN-beta, IFN-alpha, glatiramer acetate, DMF, natalizumab, cyclophosphamide, methotrexate, azathioprine, teriflunomide, and fingolimod)

  - Of note, the timing of discontinuing IFN-beta, IFN-alpha, glatiramer acetate, or DMF prior to initiating treatment with study treatment (Visit 2) is at the Investigator's discretion

  - The initiation of a DMT for the treatment of RRMS is permitted if initiated after the last dose of study treatment (it is also preferable that it be initiated at least 1 day after Visit 15 and not on Visit 15)

- Any investigational product, including investigational symptomatic therapies for MS and investigational therapies for non-MS indications

- Total lymphoid irradiation, cladribine, T-cell or T-cell receptor vaccination, any therapeutic monoclonal antibody, mitoxantrone, cyclosporine, IV immunoglobulin, plasmapheresis, or cytapheresis

The use of corticosteroids for the treatment of clinical relapses and steroids that are administered by nonsystemic routes (e.g., inhaled or topical) are permitted.

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.

Immunization using inactivated, killed, or viral particle vaccines (e.g., influenza vaccine) is 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 nonprescribed drugs, unless they have received permission from the Investigator.

See Section 7.7.1.1 for details regarding the concomitant medication review.

### 7.7.2. Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed between the time the subject is enrolled in the study and until the completion of the safety follow-up visit (Visit 16).

## 7.8. Continuation of Treatment

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

# 8. DISCONTINUATION OF STUDY TREATMENT AND WITHDRAWAL OF SUBJECTS FROM THE STUDY

## 8.1. Discontinuation of Study Treatment

A subject *must* permanently discontinue ALKS 8700 for any of the following reasons:

- The subject becomes pregnant. Study treatment must be discontinued immediately. Report the pregnancy according to the instructions in Section 11.4.1.
- The subject withdraws consent to continue study treatment.
- The subject experiences an AE that necessitates permanent discontinuation of study treatment.
- At the discretion of the Investigator for medical reasons.

The primary reason for discontinuation of study treatment must be recorded in the subject's eCRF.

Any subject who prematurely discontinues from either study treatment or the study will be asked to return to the clinic for an ET visit (Visit 15) as well as a safety follow-up visit 2 weeks later (Visit 16) for the required assessments. Please see Section 5.5 for the follow-up of subjects with lymphopenia.

## 8.2. Lost to Follow-Up

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

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

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether the subject wishes to and/or should continue in the study.
- In cases in which the subject is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the subject. These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, that subject will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

## 8.3. Withdrawal of Subjects From the Study

A treatment completer will be a subject who completes the 96-week treatment period (i.e., through Visit 15). Subjects completing the follow-up visit will be categorized as completing the study.

A subject may be withdrawn 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:

- AE
- Lack of efficacy
- Lost to follow-up
- Withdrawal by subject
- Protocol deviation (noncompliance with study treatment or study procedures)
- Physician decision
- Pregnancy
- Study terminated by Sponsor
- Other

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. 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 the Investigator will agree to an acceptable follow-up schedule. If a subject withdraws from the study and has a last lymphocyte count which is $< 0.8 \times 10^3/\mu L$, the subject will return to the clinic for additional lymphocyte count monitoring visits every 2 months starting from the safety follow-up for up to 6 months (i.e., a maximum of 3 visits) or until the lymphocyte count reaches normal limits ($\geq 0.91 \times 10^3/\mu L$), whichever occurs first.

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 treatment and withdrawing from the study are to be asked to return to the clinic for an ET visit. The ET visit should be scheduled as close as possible to the subject's last dose and will mimic the assessments scheduled to be conducted at Visit 15. Following the ET visit, subjects will be asked to participate in the safety follow-up period. If the subject fails or refuses to return to the study site, 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 and made on the appropriate eCRF. If a subject is lost to follow-up, a reasonable attempt to contact the subjects must be made and documented.

Subjects who withdraw from the study after receiving the first dose of study treatment may not be replaced.

# 9. EFFICACY AND PHARMACOKINETIC ASSESSMENTS

See Section 1.3 for the timing of all assessments.

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

## 9.1. Clinical Efficacy Assessments

ALKS 8700 treatment effect over time will be assessed in an exploratory manner based on the following:

[redacted]

- Clinical assessments
  - MS relapse
  - T25-FW
  - Progression of disability as assessed by EDSS
- Other assessments
  - EQ-5D-5L
  - SF-12

[redacted]

[redacted]

### 9.1.2. Structured Interviews and Questionnaires

#### 9.1.2.1. Expanded Disability Status Scale

The EDSS [Kurtzke 1983] is used to measure and evaluate MS patients' level of functioning. The EDSS provides a total score on a scale that ranges from 0 to 10. The first levels 1.0 to 4.5 refer to people with a high degree of ambulatory ability and the subsequent levels 5.0 to 9.5 refer to the loss of ambulatory ability. The range of main categories include (0) = *normal neurologic examination*; to (5) = *ambulatory without aid or rest for 200 meters; disability severe enough to impair full daily activities*; to (10) = *death due to MS*. In addition, it also provides 8 subscale measurements called FS scores: pyramidal (motor function); cerebellar; brainstem, sensory; bowel and bladder; visual, cerebral or mental; and other. FS are scored on a scale of 0 (low level of problems) to 5 (high level of problems) to best reflect the level of disability observed clinically. The total EDSS score is determined by 2 factors: gait and FS scores. Expanded disability status scale scores below 4.0 are determined by the FS scores alone. Expanded disability status scale scores between 4.0 and 9.5 are determined by both gait abilities and FS scores. For this study, the fatigue score should be recorded but not included in the calculation of the cerebral FS score.

The Investigator or designee will complete the EDSS according to the schedule in Table 1. A sample of the EDSS will be provided to the study sites outside of this protocol.

Progression of disability that is sustained for 12 weeks is defined by one of the following: an EDSS increase of at least 1.5 points from baseline EDSS = 0, an EDSS increase of at least a 1.0 point from baseline EDSS between 1.0 and 5.5 (inclusive), or an EDSS increase of at least 0.5 points from baseline EDSS = 6.0.

If a subject experiences progression of disability as defined above, the subject must be informed of this progression. If the Investigator determines the subject may continue participation and the subject is willing, subjects will also be required to provide written confirmation of their willingness to continue participation in the study as described in Section 13.5. Subjects who prematurely discontinues either the study or study treatment will complete an ET visit and all safety follow-up assessments as described in Section 8.

#### 9.1.2.2. EuroQol Group Health Outcome Measure (5 level; EQ-5D-5L)

The EQ-5D-5L™ is a trademark of the EuroQol Group© and is an instrument designed to assess decrements in health. The EQ-5D-5L includes a Visual Analog Scale (VAS) and a descriptive system that defines health in terms of 5 dimensions: Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression. Each dimension has 5 response categories corresponding to the level of severity (i.e., no problems, slight problems, moderate problems, severe problems, and unable to/extreme problems). Subjects will complete the questionnaire according to the schedule in Table 1. A sample of the EQ-5D-5L will be provided to study sites outside of this protocol.

### 9.1.3. Timed 25-Foot Walk

The T25-FW [Kaufman 2000] is a reliable quantitative mobility and leg function performance test based on a timed 25-foot walk. The subject is directed to one end of a clearly marked 25-foot course and is instructed to walk 25 feet as quickly as possible, but safely. Subjects are allowed to use assistive devices (canes, crutches, walkers) as needed. The time is calculated from when the lead foot crosses the start point to when the subject has reached the 25-foot mark. The task is immediately administered again by having the subject walk back the same distance. The score for the T25-FW is the average of the 2 completed trials.

#### 9.1.3.1. Short Form 12 Health Survey

Quality of life will be assessed using the 12-item Short-Form health survey Version 2 (SF-12v2) [Maruish 2012]. Subjects will complete the questionnaire according to the schedule in Table 1. A sample of the SF-12 will be provided to the study sites outside of this protocol.

#### 9.1.3.2. Columbia-Suicide Severity Rating Scale

The C-SSRS is a clinician-administered instrument that assesses suicidal ideation and behavior [Posner 2011]. The “Screening” version of the instrument will be administered to De Novo Subjects at the screening visit. The “Since Last Visit” version will be administered to all participating subjects at all other visits specified in Table 1. A sample of the C-SSRS will be provided to the study sites outside of this protocol.

## 9.2. Pharmacokinetic Assessments

PK samples will be collected from a subset of de novo subjects (approximately 50) enrolled at selected sites.

The following parameters, but are not limited to, will be calculated to assess the PK of ALKS 8700:

- Maximum observed concentration ($C_{max}$)
- Time to reach $C_{max}$ ($T_{max}$)
- $AUC_{last}$

Concentrations of analytes considered appropriate for further evaluation (e.g., MMF, RDC-6567, and RDC-8439) will be quantified in plasma samples collected for PK evaluation. See Section 12.5 for further details.

# 10. SAFETY ASSESSMENTS

See Section 1.3 for the timing of all safety assessments.

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

## 10.1. Clinical Safety Assessments

The following clinical assessments will be performed to evaluate the safety profile of ALK 8700:

- AEs and SAEs will be monitored continuously from the time a subject signs the ICF until the completion of the final study visit (Table 1) and additional follow-up, if required.
- Medical history.
- Physical examinations: A full physical examination and measurement of body height and weight will be performed at screening. For Rollover Subjects, height will be carried over from information recorded in the antecedent study in which they participated. All subjects will have brief, symptom-directed physical examinations and will be weighed at timepoints specified in Table 1.
- Vital sign measurements (temperature, heart rate, systolic and diastolic blood pressure, and respiratory rate): Blood pressure, heart rate, and respiratory rate will be measured after the subject has been resting in a seated or supine position for at least 5 minutes. Consistent measurements and procedures should be used for all assessments (Table 1).
- 12-Lead ECGs will be performed after the subject has rested quietly for at least 5 minutes in the supine position. ECGs will be conducted using calibrated equipment and assessed by a qualified clinician (Table 1).
- C-SSRS administered by the clinician: The “Screening” version of the instrument will be administered to De Novo subjects at the Screening Visit. The “Since Last Visit” version will be administered to all subjects at all other visits specified in Table 1.
- Concomitant therapy and procedure recording.

## 10.2. Laboratory Safety Assessments

Blood and urine samples for laboratory assessments will be collected at the timepoints specified in Table 1. Specific hematology, biochemistry, and urinalysis assessments to evaluate the safety

profile of ALKS 8700 are listed in Table 3. Samples will be collected in accordance with the site's usual procedures and analyzed by a central laboratory.

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

**Table 3: Clinical Laboratory Assessments**

| **Hematology**[1] | **Biochemistry** | **Urinalysis** |
|---|---|---|
| Hematocrit | Sodium | Color |
| Hemoglobin | Potassium | pH |
| Red blood cell count | Chloride | Specific gravity |
| Total and differential (absolute) white blood cell count | Bicarbonate | Ketones |
| Platelets | Glucose | Protein |
| | Thyroid-stimulating hormone (TSH)[2] | Glucose |
| | Calcium | Bilirubin |
| | Uric Acid | Nitrite |
| | Creatinine | Urobilinogen |
| | Total protein | Occult blood |
| | Blood urea nitrogen | Microscopic examination of sediment *only if urinalysis dipstick results are abnormal* |
| | Albumin | Urine albumin |
| | Total bilirubin | Urine beta-2-microglobulin |
| | Alanine aminotransferase (ALT) | Urine creatinine |
| | Aspartate aminotransferase (AST) | |
| | Lactic dehydrogenase (LDH) | |
| | Alkaline phosphatase | |
| | Creatine phosphokinase | |
| | Lipid profile: blood cholesterol, high-density lipoprotein, low density lipoprotein, and triglycerides | |

[1] Additional hematology assessments will be collected for subjects requiring follow-up for lymphopenia at the time of study completion or early termination.
[2] To be assessed at screening only.

### 10.2.1. Pregnancy Testing

A urine pregnancy test will be administered to all women regardless of childbearing potential at the timepoints specified in Table 1. Results must be negative for initial study eligibility and continued participation.

### 10.2.2. Serology Testing

A blood sample for a serology panel testing for hepatitis B surface antigen, hepatitis C antibody, and HIV antibody will be performed at screening only (Table 1).

# 11. SAFETY DEFINITIONS, RECORDING, REPORTING, AND RESPONSIBILITIES

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

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

## 11.1. Definitions

### 11.1.1. Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject (subject) administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal assessment such as an abnormal laboratory value), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

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

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

### 11.1.2. Serious Adverse Event

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

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

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

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

### 11.1.3. Prescheduled or Elective Procedures or Routinely Scheduled Treatments

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

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the subject's consent to be in the study.
- The condition requiring the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the Investigator between the subject's consent to be in the study and the time of the procedure or treatment.
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission.
    - If a subject is hospitalized due to local requirements for administration of the study treatment, the hospitalization should not be considered an SAE unless one of the requirements in Section 11.1.2 is met.

## 11.2. Safety Classifications

### 11.2.1. Investigator Assessment of Events

All events must be assessed to determine the following:

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

### 11.2.2. Relationship of Events to Study Treatment

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

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

### 11.2.3. Severity of Events

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

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

### 11.2.4. Expectedness of Events

Expectedness of all SAEs will be determined by the Sponsor according to the ALKS8700 Investigator's Brochure.

## 11.3. Monitoring and Recording Events

### 11.3.1. Adverse Events

Any AE experienced by the subject between the time of first dose of study treatment and until the completion of the safety follow-up visit (Visit 16) is to be recorded on the eCRF, regardless of the severity of the event or its relationship to study treatment. At each study visit, the Investigator will assess the subject for AEs and will record any new AEs or updates to previously reported AEs on the eCRF. 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 treatment.

The following events will not be collected as AEs:

- Disability progression based on the EDSS is captured in the MS efficacy assessments and is not to be recorded as an AE unless the event meets the definition of an SAE (see Section 11.1.2). Events of MS relapse, whether protocol-defined or not, are to be recorded as AEs (or as SAEs [see Section 11.1.2]).

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

- Pregnancy is not considered an AE, although a subject will be withdrawn from the study if a pregnancy occurs. As described in Section 11.4.1, the pregnancy must be reported to Biogen and additional follow-up may be required.

The Investigator will assess all AEs regarding any causal relationship to the study treatment (see Section 11.2.2), the severity of the event, action taken, and subject outcome.

The criteria set out in Section 11.2.3 should be used to guide the assessment of severity.

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 version of the Investigator's Brochure at the time of the event occurrence 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.

### 11.3.2. Serious Adverse Events

Any SAE experienced by the subject between the time of the signing of the ICF and until the completion of the safety follow-up visit (Visit 16) is to be recorded on an SAE form, regardless of the severity of the event or its relationship to study treatment. SAEs must be reported to the Sponsor within 24 hours as described in Section 11.3.3. Follow-up information regarding an SAE also must be reported within 24 hours.

Subjects will be followed for all SAEs until the completion of the safety follow-up visit (Visit 16). Thereafter, the event should be reported to the Sponsor only if the Investigator considers the SAE to be related to study treatment.

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

### 11.3.3. Immediate Reporting of Serious Adverse Events

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

**Reporting Information for SAEs**

A report ***must be submitted*** to the Sponsor regardless of the following:

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

To report initial or follow-up information on an SAE, fax or email a completed SAE form; refer to the Study Reference Manual's Official Study Contact List for complete contact information.

#### 11.3.3.1. Deaths

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

### 11.3.4. Suspected Unexpected Serious Adverse Reactions

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

## 11.4. Procedures for Handling Special Situations

### 11.4.1. Pregnancy

Subjects should not become pregnant or impregnate their partners during the study and for 90 days after their last dose of study treatment. If a female subject becomes pregnant, study treatment must be discontinued *immediately*.

The Investigator must report a pregnancy from first dose of study treatment to 90 days after that last dose of study treatment by faxing or emailing the appropriate form to the Sponsor within 24 hours of the site staff becoming aware of the pregnancy. Refer to the Study Reference Manual's Official Study Contact List for complete contact information. The Investigator or site staff must report the outcome of the pregnancy to the Sponsor. A pregnancy is not considered an AE and should not be recorded on the AE eCRF.

Congenital abnormalities and birth defects in the offspring of male or female subjects should be reported as an SAE if conception occurred during the study treatment period or within 90 days from their last dose of study treatment.

### 11.4.2. Overdose

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

### 11.4.3. Medical Emergency

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

## 11.5. Contraception Requirements

All male and female subjects must agree to the use of 2 methods of contraception for the duration of the study and 30 days after the final dose of study treatment. This includes at least 1 form of highly effective method of contraception and 1 acceptable method of contraception (and additional restrictions, if required, will be clarified in the locally approved ICF). Subjects who are abstinent are eligible, provided they agree to the use of 2 contraceptive methods (at least 1 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 treatment)

**Acceptable methods may include:**

- Double-barrier protection (e.g., 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 subjects become or is found to be pregnant while participating in the study, she will be discontinued from study treatment 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 AE has occurred. The ET 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 11.3.3). Additional follow-up may be required.

Pregnancy reporting is described in Section 11.4.1.

## 11.6. Safety Responsibilities

### 11.6.1. The Investigator

The Investigator's responsibilities include the following:

- Monitor and record all AEs, including SAEs, on the eCRF regardless of the severity or relationship to study treatment.
- Determine the seriousness, relationship, and severity of each event.
- Determine the onset and resolution dates of each event.
- Monitor and record all pregnancies and follow up on the outcome of all pregnancies.

- Complete an SAE form for each SAE and fax or email it to the Sponsor within 24 hours of the site staff becoming aware of the event.

- Pursue SAE follow-up information actively and persistently. Follow-up information must be reported to the Sponsor within 24 hours of the site staff becoming aware of new information.

- Ensure all AE and SAE reports are supported by documentation in the subjects' medical records.

- Pursue AE follow-up information, if possible, until the event has resolved or become stable. Record AE follow-up information, including resolution, on the eCRF, as applicable.

- Report SAEs to local ethics committees, as required by local law.

### 11.6.2. The Sponsor

The Sponsor's responsibilities include the following:

- Before a site can enroll any subjects, the Clinical Monitor (or designee) is responsible for reviewing with site staff the definitions of AE and SAE, as well as the instructions for monitoring, recording, and reporting AEs and SAEs.

- The Sponsor is to notify all appropriate regulatory authorities, central ethics committees, and Investigators of SAEs, as required by local law, within required time frames.

# 12. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

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

## 12.1. General Considerations

The statistical analysis methods are described below. Additional details will be provided in the Statistical Analysis Plan.

In general, summary statistics (number of subjects, 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 all parameters. All statistical results will be presented based on observed values. All individual subject level data will be presented as data listings.

## 12.2. Analysis Sets

### 12.2.1. Safety Population

The safety population, defined as all enrolled subjects who receive at least 1 dose of ALKS 8700, will be used in the safety analyses.

### 12.2.2. Efficacy Population

The exploratory efficacy endpoints to assess treatment effect over time will be analyzed using data from the full analysis set (FAS), defined as all subjects who receive at least 1 dose of ALKS 8700 and receive 1 postbaseline efficacy assessment.

## 12.3. Demographics and Baseline Characteristics

For De Novo Subjects, baseline is defined as Visit 2. For Rollover Subjects, baseline is defined as the baseline visit in the antecedent study.

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

## 12.4. Methods of Analysis for Efficacy Endpoints

Efficacy analyses of treatment effect over time will be based on data from the FAS population.

All endpoints listed below will be summarized by study timepoint and by change from baseline using descriptive statistics as appropriate.

[redacted]

Clinical endpoints

- ARR
- Proportion of subjects experiencing a relapse
- EDSS score
- T25-FW score
- Proportion of subjects with No Evidence of Disease Activity (NEDA) at Week 96

Other endpoints

- SF-12 (domain score)
- EQ-5D-5L VAS scores

The ARR will be summarized as number of relapses per subject per year, in which subject study duration is calculated as the time from first dose to last dose of study medication +1. NEDA will indicate an absence of select clinical (MS relapse and disease progression) [redacted] outcomes.

## 12.5. Methods of Analysis for Pharmacokinetic Endpoints

PK analyses will be performed using the PK population. Individual plasma concentrations will be listed by actual sampling times and summarized by nominal sampling times using descriptive statistics. Plots of individual and mean concentrations over time will also be generated. PK parameters will be calculated using noncompartmental analysis. Parameters will be estimated using actual elapsed time from dosing and summarized using descriptive statistics. A subject listing of individual PK parameters will be provided.

Additionally, PK concentration data obtained from this study will may be combined with data from other studies to develop a population PK model, which will be reported separately.

## 12.6. Methods of Analysis for Safety Endpoints

The safety analysis will be carried out using the safety population. Reported AE terms will be coded using the Medical Dictionary for Regulatory Activities.

Safety assessments will be summarized using descriptive statistics along with supportive listings. The number and percentage of TEAEs will be summarized by system organ class, and preferred terms within each system organ class. SAEs and AEs resulting in treatment discontinuation will be summarized.

Observed values and change from baseline in laboratory parameters, vital signs, ECG parameters, and scores on the C-SSRS will be summarized by study visit. The number and percentage of subjects who have met potentially clinically significant criteria at any postbaseline visit will be summarized.

Listings will be provided for all safety endpoints.

## 12.7. Interim Analyses

Not applicable.

## 12.8. Sample Size Considerations

No formal sample size calculation is performed for this study. A sample size of approximately 1000 subjects will contribute to the long-term safety experience of ALKS 8700 in subjects with RRMS, taking into account International Council for Harmonisation (ICH) guidance on the extent of patient exposures required to assess clinical safety for a new drug.

# 13. ETHICAL AND REGULATORY REQUIREMENTS

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

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

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

## 13.1. Declaration of Helsinki

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

## 13.2. Ethics Committee

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

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

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

Initial ethics committee approval as well as all materials approved by the ethics committee for this study, including the subject consent form and recruitment materials, must be maintained by the Investigator and made available for inspection.

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

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

## 13.3. Changes to Final Protocol

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

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

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

## 13.4. Informed Consent

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

A copy of the signed and dated ICF and assent must be given to the subject and/or the subject's legally authorized representative. The original signed and dated ICF will be retained with the study records. Local regulations must be complied with in respect to the final disposition of the original and copies of the signed and dated ICFs.

Confirmation of informed consent and assent must also be documented in the subject's medical record.

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

## 13.5. Confirmation of Willingness to Continue in the Study

Written documentation of a subject's willingness to continue participation in the study will be required if one or more of the following occurs during the study:

- MS relapse
- Disability progression (based on EDSS)

[redacted]

If any of the above events occur, the Investigator will use clinical judgment as to whether or not the subject should continue participation in the study. 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 institutional review board (IRB)/ ethics committee-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.

## 13.6. Subject Data Protection

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

During the study, subjects' race and ethnicity will be collected (unless the collection is not permitted by applicable law or not approved by the governing ethics committee). These data will be used in the analysis of the safety and/or PK profile of the study treatment.

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

## 13.7. Compensation for Injury

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

## 13.8. Conflict of Interest

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

## 13.9. Study Report Signatory

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

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

## 13.10. Registration of Study and Disclosure of Study Results

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

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

## 13.11. Retention of Study Data

Retention and storage of all essential clinical study documents shall be governed by the terms and conditions of the site's Clinical Study Agreement (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. Prior to proceeding with destruction of records, the Investigator must notify the Sponsor in writing and receive written authorization from the Sponsor to destroy study records. In addition, the Investigator must notify the Sponsor of any changes in the archival arrangements including but not limited to archival at an offsite facility or transfer of ownership if the Investigator leaves the site.

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.

# 14. KEY ROLES AND STUDY GOVERNANCE COMMITTEES

## 14.1. Vendors

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

### 14.1.1. Contract Research Organization

A CRO will be responsible for administrative aspects of the study including but not limited to study initiation, management of SAE reports, monitoring, and data management.

Before subjects are screened at each study site, the CRO will review study responsibilities with the Investigators and other study site staff, as appropriate.

### 14.1.2. Interactive Response Technology

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

### 14.1.3. Electronic Data Capture

Subject information will be captured and managed by study sites on eCRFs by a web-based electronic data capture tool configured by [redacted] and hosted by [redacted].

### 14.1.4. Central Laboratories for Laboratory Assessments

A central laboratory has been selected by the Sponsor to analyze all samples listed in Table 3 collected for this study. PK samples will be analyzed at a laboratory selected by the Sponsor.

## 14.2. Study Committees

Not applicable.

# 15. ADMINISTRATIVE PROCEDURES

## 15.1. Study Site Initiation

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

## 15.2. Quality Control and Quality Assurance

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.

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

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

## 15.3. Case Report Forms

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

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

## 15.4. Confidentiality of Data

By signing this protocol, the Investigator affirms to Biogen that he or she will maintain in confidence information furnished to him or her by Biogen and will divulge such information to his or her respective IRB or ethics committee under an appropriate understanding of confidentiality with such board. All data will be considered the sole property of Biogen. Please refer to the CSA for details.

## 15.5. Monitoring of the Study

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

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

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

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

## 15.6. Audits and Inspections

By signing the protocol, the Investigator agrees that, within local regulatory restrictions and institutional and ethical considerations, authorized representatives of Biogen, a regulatory authority, and/or an IRB/ethics committee may visit the site to perform audits or inspections, including the drug storage area, study treatment stocks, drug accountability records, subject charts and source documents, and other records relative to study conduct. The purpose of a Biogen audit or inspection is to systematically and independently examine all study-related activities and documents (e.g., 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 ICH, and any applicable regulatory requirements.

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

## 15.7. Study Funding

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

## 15.8. Publications

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

# 16. REFERENCES

Calabresi PA, Kieseier BC, Arnold DL, et al. Pegylated interferon beta-1a for relapsing-remitting multiple sclerosis (ADVANCE): a randomised, phase 3, double-blind study. Lancet Neurol. 2014;13(7):657-65. Epub 2014 Apr 30.

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# 17. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "A Phase 3 Open Label Study to Evaluate the Long-Term Safety and Tolerability of ALKS 8700 in Adults With Relapsing Remitting Multiple Sclerosis" and agree to conduct the study according to the protocol and the applicable ICH guidelines and GCP regulations, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____

Investigator's Signature Date

_____

Investigator's Name (Print)

_____

Study Site (Print)

# SUMMARY OF CHANGES

**Protocol Amendment 3.0**

Study number: ALKS 8700 A301

Study title: A Phase 3 Open Label Study to Evaluate the Long-term Safety and Tolerability of ALKS 8700 in Adults with Relapsing Remitting Multiple Sclerosis

Amendment date: 26 Jun 2019

Sponsor: Alkermes, Inc.
852 Winter Street
Waltham, MA 02451
Telephone: +1 (781) 609-6000

**CONFIDENTIAL**

# 1. SUMMARY AND RATIONALE OF AMENDMENT

Language in the protocol is being updated to reflect what is being practiced in the conduct of the study, namely that all events of multiple sclerosis (MS) relapse are being recorded as adverse events (AEs). In addition, sample size numbers were made more flexible, sections were revised to allow better clarity of procedures, and last subject last visit date was revised to allow for additional rollover subjects from Study A302. The major changes are listed below:

- Clarify language around MS relapse collection as an adverse event
- Update sample size to approximately 1000
- Clarify timing of disease-modifying therapy (DMT) allowance
- Clarification to the lymphocyte monitoring section
- Clarification of serious adverse event reporting
- Update to Schedule of Assessments table [redacted]
- Update de novo pharmacokinetic (PK) sample size
- Update estimated last subject last visit (LSLV)
- Administrative changes to contact information, and clarifying language was also provided.

Additional changes such as updates to the title page, the Table of Contents, List of Abbreviations, and headers/footers (to reflect the new document version and date) have been made. Corrections for grammatical and other minor consistency errors have also been made throughout the protocol. These changes are not described here.

# 2. OVERVIEW OF CHANGES

| Content Changes |
|---|
| **1. Change: Clarify language around MS relapse collection as an adverse event**<br>**Description of Change:**<br>In Section 8.2.2, bullet 1 was clarified to indicate that **any** MS relapse **as determined by the investigator** required written documentation of a subject's willingness to continue in the study.<br>In Section 8.2.12, language was added to clarify that **efficacy analyses related to MS relapse include only events of protocol-defined relapse.** In addition, language was added to clarify the bulleted list of neurological symptoms.<br>In Section 11.1, the following language was added to clarify the collection of AEs and SAEs for disability progression based on the EDSS and MS relapse: Disability progression based on the EDSS **is captured in the MS efficacy assessments and is not to be recorded as an AE unless the event meets the definition of an SAE (see Section 11.2) Events of MS relapse, whether protocol-defined or not, are to be recorded as AEs (or as SAEs [see Section 11.2]).** ~~and/or relapse of MS will be captured in the MS efficacy assessments, and not recorded as an AE, unless they meet the definition for an SAE see Section 11.2.~~<br>**Rationale for Change:** Language in the protocol is being updated to reflect what is being practiced in the conduct of the study, namely that all events of MS relapse are being recorded as AEs.<br>**Sections Impacted:** Section 8.2.2 (Bullet 1); Section 8.2.12 (first sentence and last 3 bullets); Section 11.1 |
| **2. Change: Update sample size to approximately 1000**<br>**Description of Change:** Expected sample size for the study was increased from 800 to approximately 1000.<br>**Rationale for Change:** With increased sample size and enrollment for the ALK8700-A302 study, more subjects have consequently rolled over to the ALK8700-A301 study. Accordingly, the estimated sample size for the ALK8700-A301 study is being updated. In addition, the rollover rate from study A302 was higher than expected (90%) which increased the sample size for A301.<br>**Sections Impacted:** Section 2: Synopsis (Number of Subjects Planned, Sample Size Considerations); Section 14.1 |

| **Content Changes** |
|---|
| **3. Change: Clarify timing of DMT allowance**<br><br>**Description of Change:** Addition of the following bullet under the bullet regarding any alternate drug treatments for MS: **The initiation of a disease-modifying therapy for the treatment of RRMS is permitted if initiated after the last dose of study drug (it is also preferable that it be initiated at least one day after Visit 15 and not on Visit 15)**<br><br>**Rationale for Change:** The language was revised to avoid any confusion regarding the timing of the last dose of study drug and DMT initiation.<br><br>**Sections Impacted:** Section 8.3.3 |
| **4. Change: Clarification to the lymphocyte monitoring section**<br><br>**Description of Change:** Clarified the study visit used for the last measured lymphocyte count, and, corresponding, the starting date for the beginning of the lymphocyte count monitoring period, is the last study visit (Visit 16).<br><br>**Rationale for Change:** Revised the language to avoid any confusion regarding the timing of additional post-treatment lymphocyte count monitoring.<br><br>**Sections Impacted:** Section 8.2.16.1 |
| **5. Change: Clarification of serious adverse event reporting**<br><br>**Description of Change:** Language was updated to reflect that all SAEs must be reported to Alkermes Drug Safety **immediately, within 24 hours of discovery**, rather than within 1 business day of discovery.<br><br>**Rationale for Change:** Language was changed to reduce delay of reporting that may occur if an event occurs over a weekend. During review of the A302 protocol, the German CA requested a change from 1 business day to 24 hours. An administrative change memo was created to document this change until a protocol amendment was created.<br><br>**Sections Impacted:** Section 11.5 |
| [redacted] |

| **Content Changes** |
|---|
| **7. Change: Update de novo PK sample size**<br>**Description of Change:** The subset of de novo subjects that will contribute to the plasma samples for concentrations of ALKS 8700 analytes (eg, MMF, RDC-6567, and RDC-8439) considered appropriate for further evaluation was updated from ~~n=50~~ to **approximately 50**.<br>**Rationale for Change:** The language was updated to provide appropriate flexibility for the sample number.<br>**Sections Impacted:** Section 2: Synopsis (Pharmacokinetics) and Section 13. |
| **8. Change: Update estimated LSLV**<br>**Description of Change:** The estimated date of last subject's last visit was updated from Q4 2019 to Q3 2021.<br>**Rationale for Change:** A302 German subjects will be rolled over into A301 (2 year) study which will push back the A301 LPLV in Q4 2020 or somewhere in 2021. Q3 2021 was agreed by team.<br>**Sections Impacted**: Section 2: Synopsis (Study Period) |

| **Administrative/Editorial Changes** ***(Deleted text is indicated as ~~strikethrough~~ and new text as bold face)*** |
|---|
| 1. Update [redacted] medical director<br>[redacted] was updated to [redacted]**, MD, FAASM.** Address and phone numbers were also updated. |
| 2. Addition of Alkermes Global Safety Officer<br>[redacted] was added to Table 1 Study Contact Information as the **Alkermes Global Safety Officer** |
| 3. Update [redacted] to [redacted]<br>All instances of [redacted] in the protocol were updated to [redacted]. This included Section 8.2.3.1, Table 1 Study Contact Information, Section 11.5. |
| 4. Updated language for version of IB to be used as reference for "expectedness" of AE.<br>In Section 11.4, the following sentence was updated: For clinical safety reporting purposes, the ~~most recent~~ version of the Investigator's Brochure **at the time of the event occurrence** will be used as the reference document to designate event expectedness. |

# SUMMARY OF CHANGES

## Protocol Amendment 2.0

| | |
|---|---|
| Study Number: | ALK8700-A301 |
| Study Title: | A Phase 3 Open Label Study to Evaluate the Long-term Safety and Tolerability of ALKS 8700 in Adults with Relapsing Remitting Multiple Sclerosis |
| Amendment Date: | 14 Dec 2016 |
| Sponsor: | Alkermes, Inc.<br>852 Winter Street<br>Waltham, MA 02451<br>Telephone: (781) 609-6000 |

# 1. SUMMARY AND RATIONALE OF AMENDMENT

The Sponsor is amending the protocol to provide supplementary instructions on intake of study drug. Preliminary pharmacokinetics (PK) data from a clinically completed Phase 1 relative bioavailability study (Study ALK8700-A109) showed that monomethyl fumarate (MMF) exposure was within the acceptable therapeutic exposure range when ALKS 8700 was taken with either a medium-fat/medium-calorie or low-fat/low-calorie meal. Based on these findings, ALKS 8700 may be taken with or without food and if taken with food, a high-fat, high-calorie meal should be avoided.

In addition, the following major changes have been made to the protocol:

- Increase in estimated sample size from 600 to 800 subjects
- Addition of up to 6-month lymphocyte count follow up requirement for subjects completing the study or discontinuing the study early with a last lymphocyte count $\leq 0.8 \times 10^3/\mu L$
- Exclusion of subjects with a history of clinically significant recurring or active gastrointestinal symptoms (eg, nausea, diarrhea, dyspepsia, constipation) within 3 months of screening, including symptoms that require the initiation of symptomatic medical treatment (eg, initiation of a medication to treat gastroesophageal reflux disease) or a change in symptomatic medical treatment (eg, an increase in dose) within 3 months of screening (Exclusion Criterion 7)
- Modification to exclusion criteria: 1, 4, 6, and 17
- The prohibited medications section has been updated to specify therapies which are not allowed during treatment and immunizations which are allowed and not allowed during treatment.
- Screening period has been extended from 3 weeks to 4 weeks.
- The pregnancy testing requirements and pregnancy language have been revised to meet requirements across multiple countries.

Other changes are described within this document. Changes such as updates to the title page, the Table of Contents, List of Abbreviations, and headers/footers (to reflect the new document version and date) have been made. Corrections for grammatical and other minor consistency errors have also been made throughout the protocol. These changes are not described here.

# 2. OVERVIEW OF CHANGES

| Content Changes |
|---|
| **1. New instruction for study drug administration**<br>**Description of Change:** Subjects will be instructed to take study drug with or without food but to avoid taking study drug with a high-fat, high-calorie meal.<br>**Rationale for Change:** The modification of instructions for study drug administration is based on results from previous Phase 1 studies (Studies ALK8700-A103 and ALK8700-A104) and the preliminary results of a recently completed study (Study ALK8700-A109). Monomethyl fumarate exposure following administration of ALKS 8700 provides comparable exposure to dimethyl fumarate (DMF) in the fasted condition (Study ALK8700-A103) and met the PK criteria for bioequivalence to DMF for area under the plasma concentration time curve (AUC) and maximum plasma concentration ($C_{max}$). 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 (Study ALK8700-A104). In the recently completed study (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.<br>**Sections Impacted:**<br>Section 2: Synopsis<br>Section 5.3: Dose Selection<br>Section 8.1: Overall Study Design and Plan<br>Section 9.1: Study Drug Dose and Administration |
| **2. Sample size has been increased and the statistical analysis language has been modified**<br>**Description of Change:** The estimated sample size has been increased from 600 to 800 subjects in this study.<br>Text regarding sample size has been modified to state that no formal sample size calculation was performed for this study. In addition, language has been added to clarify that a sample size of 800 subjects will contribute to the long-term safety experience of ALKS 8700 in subjects with relapsing remitting multiple sclerosis (RRMS), taking into account International council on Harmonisation (ICH) guidance on the extent of patient exposures required to assess clinical safety for a new drug.<br>**Rationale for Change:** These modifications were made to reflect the increased sample size expected from De Novo and Rollover subject enrollment.<br>**Sections Impacted:**<br>Section 2: Synopsis<br>Section 14.1: Sample Size Considerations |
| **3. Follow-up requirement for subjects completing or discontinuing early from the study and experiencing lymphopenia (lymphocyte count <0.8 × $10^3$/µL)**<br>**Description of Change:** Additional follow-up has been added to the protocol for subjects who have lymphocyte counts <0.8 × $10^3$/µL at the completion of the study or upon early termination of the study. This additional follow-up consists of lymphocyte count monitoring visits every two months starting at the time the safety follow-up visit (Visit 16) is completed and extends for a period of up to 6 months or until lymphocyte counts reach normal range, whichever occurs first. |

**Content Changes**

**Rationale for Change:** These additional follow-up visits are being added to monitor lymphocyte counts in subjects with lymphopenia in order to evaluate changes in lymphocyte counts over an extended period of time when patients are not receiving the study drug.

**Sections Impacted:**

Section 2: Synopsis

Section 7.3: Subject Withdrawal

Section 8.1: Overall Study Design and Plan

Section 8.2: Schedule of Visits and Assessments

Section 8.2.13.1: Hematology, Biochemistry, and Urinalysis

Section 8.2.15: Adverse Event Monitoring

Section 8.2.16: Follow-up (*New section*)

Section 8.2.16.1: Monitoring Subjects with Lymphopenia at the Time of Study Completion or Early Termination (*New section*)

Section 8.3: Study Requirements and Restrictions

Table 3 has been added to show the required assessments during lymphocyte monitoring visits.

**4. Changes to the exclusion criteria:**

**Description of Change:**

**Exclusion criterion 7 has been added.**

Exclusion criterion 7 has been added to exclude subjects with a history of clinically significant recurring or active gastrointestinal symptoms within 3 months of screening or a change in symptomatic medical treatment within 3 months of screening.

**Exclusion criteria 1, 4, 6, and 17 have been modified.**

**Exclusion criterion 1** (Rollover subjects) and **Exclusion criterion 4** (De Novo subjects) have been modified to ensure that overall clinical assessment will be considered to determine whether the subject is suitable to participate in the study, along with subject ability to adhere to the protocol visit schedule or fulfill visit requirements and that no screening findings would compromise the subject's safe participation in the study.

**Exclusion criterion 6** has been updated to remove Crohn's disease, ulcerative colitis (already captured under "inflammatory bowel disease"), and to include peptic ulcer disease as examples of gastrointestinal (GI) diseases that would preclude participation and to exclude a history of clinically significant endocrine and renal diseases.

**Exclusion criterion 17** has been modified to exclude subjects with a history of treatment with stem cell transplantation, daclizumab within 6 months prior to Visit 2, B-cell targeted therapies for the treatment on multiple sclerosis (MS) within 12 months of screening or prior treatment with in investigational drug and/or commercially available drug for the treatment of MS within the past 24 months (as determined by the Medical Monitor). In addition, it was added that an accelerated elimination procedure for teriflunomide with cholestyramine is permitted during screening.

**Rationale for Change:** The Sponsor wanted to clarify certain exclusion criteria as well as add certain exclusion criteria for subject safety.

**Sections Impacted:**

Section 7.2 (Section 7.2.1 and Section 7.2.2): Subject Exclusion Criteria

| Content Changes |
|---|
| **5. Update to the prohibited medications**<br>**Description of Change:** The prohibited medications have been updated to specify that use of teriflunomide and fingolimod are prohibited during this study.<br>Additional guidelines related to permitted and prohibited vaccination during the study period has been added as: immunization using inactivated, killed, or viral particle vaccines (eg, influenza vaccine) is 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.<br>**Rationale for Change:** These modifications were made to provide more precise guidelines around MS-related treatments that are prohibited for this study as well as information regarding immunizations.<br>**Sections Impacted:**<br>Section 7.2: Subject Exclusion Criteria<br>Section 8.3.3: Prohibited Medications |
| **6. Modification of the Expanded Disability Status Scale (EDSS) scoring procedure**<br>**Description of Change:** The EDSS scoring procedure has been modified to clarify that the fatigue scores should be recorded but not included in the calculation of the cerebral functional system score.<br>**Rationale for Change:** These modifications were made to clarify the EDSS scoring procedure.<br>**Section Impacted:**<br>Section 8.2.9.1: Expanded Disability Status Scale (EDSS) |
| **7. Extension of screening period**<br>**Description of Change:** The screening period has been extended from 3 to 4 weeks (De Novo).<br>**Rationale for Change:** This change was made per study site feedback to allow longer period for screening.<br>**Sections Impacted:**<br>Section 2: Synopsis<br>Section 8.1: Overall Study Design and Plan<br>Figure 1: Study Design Schematic<br>Section 8.2: Schedule of Visits and Assessments<br>Table 2: Schedule of Assessments |
| **8. Modification to the pregnancy testing and contraceptive requirements**<br>**Description of Change:** Language was added to ensure that a serum pregnancy test at screening will be performed for all women "regardless of child bearing potential".<br>The contraception section (Section 8.3.2) of Amendment 1, v 2.0 has been updated to specify that 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.<br>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.<br>**Rationale for Change:** These modifications were made to clarify the pregnancy testing requirement and to meet contraceptive requirements across multiple countries. |

| **Content Changes** |
|---|
| **Sections Impacted**:<br>Section 8.2.13.2: Pregnancy Testing<br>Section 8.3.2: Contraception and Pregnancy |
| [redacted] |
| **10. Update to the relapse assessment criteria and unscheduled relapse visit**<br>**Description of Change:** Text regarding the assessments to be performed when MS relapse is suspected during a scheduled study visit has been added.<br>**Rationale for Change:** These modifications were made to specify what will be considered as "relapse" and that in such instances, all unscheduled relapse visit assessments as well as all assessments for the scheduled study visit not included in the unscheduled relapse visit are to be performed.<br>**Sections Impacted**:<br>Section 8.2.12: Relapse<br>Section 8.3.1: Unscheduled Relapse Visit |
| **11. Modification of the study drug storage conditions**<br>**Description of Change:** Protocol amendment 1 stated that all study materials are to be stored at: "controlled room temperature in a secure location". This wording has been modified in the amended protocol to: "room temperature not to exceed 25° C in a secure location".<br>**Rationale for Change:** This modification was made to update required study drug storage conditions.<br>**Section Impacted:**<br>Section 10.3: Storage |
| **12. Modification to the Study Requirements and Restrictions**<br>**Description of Change:** Language was added to mention that repeat testing for any laboratory parameters meeting threshold limits should be performed "as soon as possible."<br>**Rationale for Change:** These modifications were made to clarify when repeat testing for any laboratory parameters meeting threshold limits should be performed in this study.<br>**Section Impacted:**<br>Section 8.3: Study Requirements and Restrictions |

| **Content Changes** |
|---|
| **13. Update to the summaries of ALKS 8700 clinical and nonclinical studies**<br>**Description of Change:** The protocol has been updated to mention the total number of completed Phase 1 studies and clinically completed Phase 1 studies with data analyses ongoing. In addition, a concise summary of relevant PK findings was added. Additional data from nonclinical studies have also been added and the overall section was revised to be more concise.<br>**Rationale for Change:** These updates were made as new clinical information is available from the results of recently completed Phase 1 studies.<br>**Sections Impacted:**<br>Section 5.1: Clinical Studies<br>Section 5.2: Nonclinical Studies |

| **Administrative/ Editorial Changes** ***(Deleted text is indicated as ~~strikethrough~~ and new text as bold face)*** |
|---|
| Administrative corrections have been made to reflect that the name of the Sponsor drug safety representative is no longer part of the contact information on the protocol.<br>Administrative correction has been made to clarify the following:<br>[redacted] is the Clinical Research Organization (CRO) Medical Monitor and 24-hour Emergency contact for **North America**.<br>[redacted] **MD, MSc has been added as the CRO Medical Monitor and 24-hour Emergency contact for Europe.** |
| **Footnote 15 has been added to the Schedule of Visits and Assessments table**<br>**Description of Change:**<br>**Safety and tolerability assessments (including adverse events and concomitant medications) will be conducted by telephone on these days.**<br>**Rationale for Change:** This footnote was added to clarify that safety and tolerability assessments (including adverse events and concomitant medications) will be conducted by telephone on these days.<br>**Section Impacted:**<br>Section 8.2 (Table 2): Schedule of Visits and Assessments |
| **Modification to physical examination procedure**<br>**Description of Change:** For De Novo Subjects, a full physical examination and measurement of body height, and weight will be performed at screening. For Rollover Subjects, height will be carried over from information recorded in the antecedent ALKS 8700 study in which they participated. All participating subjects will have brief, symptom-directed physical examinations and will be weighed at timepoints specified in Table 2. Updated language is as follows: **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.** |
| **Rationale for Change:** These modifications were made to clarify language around study-specific procedures.<br>**Section Impacted:**<br>Section 8.2.7: Physical Examination, Body Height, Weight |

| **Administrative/ Editorial Changes** ***(Deleted text is indicated as ~~strikethrough~~ and new text as bold face)*** |
|---|
| New Section 8.2.16 has been created for study Follow-up for better organization of the document. |
| Administrative correction has been made to update the name of the drug manufacturing facility as below:<br>Alkermes **Pharma Ireland, Ltd.**<br>Monksland, Athlone<br>Co Westmeath, Ireland<br>**Section Impacted:**<br>Section 10.2: Packaging and Labeling |

SUMMARY OF CHANGES

Protocol Amendment #1

| | |
|---|---|
| Study Number: | ALK8700-A301 |
| Study Title: | A Phase 3 Open Label Study to Evaluate the Long-term Safety and Tolerability of ALKS 8700 in Adults with Relapsing Remitting Multiple Sclerosis |
| Document Status: | Final |
| Amendment Date: | 29 Jan 2016 |
| Sponsor: | Alkermes, Inc.<br>852 Winter Street<br>Waltham, MA 02451<br>Telephone: (781) 609-6000 |

# 1. SUMMARY AND RATIONALE OF AMENDMENT

The protocol is being amended by the sponsor to include new clinical information available from two Phase 1 relative bioavailability studies (Study ALK8700-A103 and ALK8700-A104) that impact the administration of the study drug (ALKS 8700 DR) in the current study (Study ALK8700-A301). Preliminary pharmacokinetic (PK) results from study ALK8700-A103 and ALK8700-A104 confirmed the comparative bioavailability of monomethyl fumarate (MMF) following a single dose of ALKS 8700 DR to dimethyl fumarate (DMF) in healthy adults in fasted and fed conditions. Based on these findings, the drug administration for ALKS 8700 DR in the current study (Study ALK8700-A301) has been modified to indicate that the study drug can be taken with or without food.

In addition, the following changes have been made to the protocol:

- The summary of clinical studies has been modified to include the results from the two completed Phase 1 studies (Study ALK8700-001 and ALK8700-A102), and the preliminary results from two recently completed Phase 1 studies (Study ALK8700-A103 and ALK8700-A104)
- The contact information for the CRO's Medical Monitor has been updated
- The specification that an exception to exclusion criteria #7 can be granted by the sponsor Medical monitor has been modified
- The reference range for the albumin to creatinine ratio in exclusion criteria #13 has been corrected
- The requirement for serum/plasma concentration of Teriflunomide following washout in exclusion criteria #16 has been clarified
- The requirement for oral body temperature collection has been revised
- Detail on the Clinical Surveillance Team (CST) review process has been added
- The description of the Kurtzke Expanded Disability Status Scale (EDSS) has been modified
- The description of the administration procedure for the Timed 25-Foot Walk (T25-FW) has been modified
- Study requirements and restrictions have been added for suspected progressive multifocal leukoencephalopathy (PML)
- The requirements and timing for discontinuing specific prohibited immunomodulatory treatments have been modified
- The description of study drug packaging has been modified
- The description of study drug storage conditions has been modified
- The contact information for reporting of Serious Adverse Events (SAE) has been updated

Additional changes such as updates to the title page, the Table of Contents, List of Abbreviations, and headers/footers (to reflect the new document version and date) have been made. Corrections for grammatical and other minor consistency errors have also been made throughout the protocol. These changes are not described here.

## 2. OVERVIEW OF CHANGES

| Content Changes |
|---|
| **1. Modification of study drug administration**<br>**Rationale for Change:** New clinical information is available from the preliminary results of two recently completed Phase 1 studies (Study ALK8700-A103 and ALK8700-A104). The modification of study drug (ALKS 8700 DR) administration was based on the preliminary PK results of study ALK8700-A103 and ALK8700-A104, which confirmed the comparative bioavailability of monomethyl fumarate (MMF) following a single dose of ALKS 8700 DR to dimethyl fumarate (DMF) in healthy adults in fasted and fed conditions.<br>**Description of Change:** The protocol has been updated to include the preliminary results from study ALK8700-A103 and ALK8700-A104 to provide justification for the modification to study drug administration. The original protocol stated: "Subjects will be instructed to take study drug on an empty stomach, at least one hour before or 2 hours after eating or drinking anything but water". This wording has been modified to: "Subjects will be instructed to take study drug with or without food".<br>**Sections Impacted:**<br>Section 2: Synopsis, Investigational Product, Dosage, Duration and Mode of Administration<br>Section 5.3: Dose Selection<br>Section 8.1: Overall Study Design and Plan<br>Section 9.1: Study Drug Dose and Administration |
| **2. Modification of summary of ALKS 8700 clinical studies**<br>**Rationale for Change:** New clinical information is available from the results of two completed Phase 1 studies (Study ALK8700-001 and ALK8700-A102), and the preliminary results of two recently completed Phase 1 studies (Study ALK8700-A103 and ALK8700-A104).<br>**Description of Change:** The protocol has been updated to include the results of two completed Phase 1 studies (Study ALK8700-001 and ALK8700-A102), and the preliminary results of two recently completed Phase 1 studies (Study ALK8700-A103 and ALK8700-A104).<br>**Sections Impacted:**<br>Section 5.1: Clinical Studies |

**Administrative/Editorial Changes**

**1. Update of Contact Information**

**Rationale for Change:** The update to the contact information for the Clinical Research Organization (CRO) Medical Monitor was based on personnel changes and location changes within the CRO after the protocol was approved and published.

**Description of Change:** The CRO ( ) Medical Monitor was changed from [redacted] MD to [redacted] MD, and the CRO address and telephone numbers were changed.

**Sections Impacted:**

Contact Information

**2. Modification of the specification that an exception to exclusion criteria #7 can be granted by the sponsor Medical Monitor**

**Rationale for Change:** The modification of the specification that an exception to exclusion #7 (for a history of malignancy) can be granted by the sponsor Medical Monitor was based on sponsor feedback after the protocol was approved and published.

**Description of Change:** The specification that an exception to exclusion #7 (for a history of malignancy) can be granted from the sponsor Medical Monitor has been modified to allow either CRO or sponsor Medical monitor to grant this exception.

**Sections Impacted:**

Section 7.2.2: Subject Exclusion Criteria, De Novo Subjects

**3. Correction of the reference range for the albumin to creatinine ratio in exclusion criteria #13**

**Rationale for Change:** The correction of the reference range for the albumin to creatinine ratio in exclusion criteria #13 was based on CRO feedback to correct an inconsistency as compared to the Covance Laboratory Reports.

**Description of Change:** The exclusion criteria #13 in the original protocol stated the albumin to creatinine ratio reference range as: "> 0.2 mg/mg". This reference range has been corrected to: ">200 mg/g".

**Sections Impacted:**

Section 7.2.2: Subject Exclusion Criteria, De Novo Subjects

Section 8.4: Study Requirements and Restrictions

**Administrative/Editorial Changes (contd.)**

**4. Clarification of the requirement for serum/plasma concentration of Teriflunomide following washout in exclusion criteria #16.**

**Rationale for Change:** The clarification of the requirement for serum/plasma concentration of Teriflunomide following washout in exclusion criteria #16 was based on sponsor feedback after the protocol was approved and published.

**Description of Change:** The exclusion criteria #16 in the original protocol stated that a history of Teriflunomide was exclusionary, unless discontinued and subjects agrees to subsequent cholestyramine washout and exhibits "no active agent in serum levels". This has been clarified to: "a serum/plasma concentration of teriflunomide <0.020 mcg/mL (<20 ng/mL) prior to Visit 2".

**Sections Impacted:**

Section 7.2.2: Subject Exclusion Criteria, De Novo Subjects

**5. Revision of the requirement for oral body temperature collection**

**Rationale for Change:** The revision of the requirement for oral body temperature collection was based on CRO feedback after the protocol was approved and published.

**Description of Change:** The requirement for "oral body temperature" was revised to "temperature" to allow either oral or body temperature collection during vital sign assessment.

**Sections Impacted:**

Section 2: Synopsis, Criteria for Evaluation

Section 8.2: Schedule of Visits and Assessments, Table 1, footnotes

Section 8.3.6: Vital Signs

Section 11: Assessment of Safety

**6. Addition of detail on the Clinical Surveillance Team (CST) eligibility review process**

**Rationale for Change:** The addition of detail on the CST eligibility review process was based on CRO feedback after the protocol was approved and published.

**Description of Change:** The original protocol did not include detail on the CST eligibility review process. Detail on the CST eligibility review process has been added to the eligibility review section of the protocol.

**Sections Impacted:**

Section 8.3.3.1: Clinical Surveillance Team Eligibility Review

**Administrative/Editorial Changes (contd.)**

**7. Modification of the description of the Kurtzke Expanded Disability Status Scale (EDSS)**

**Rationale for Change:** The modification of the description of the EDSS was based on sponsor feedback during the development of a new study protocol for this program. Detail on the subscale and total scale scoring for the EDSS was not included in the original protocol.

**Description of Change:** The original protocol did not include detail on the eight subscale scores in the EDSS and the scoring procedures for these subscales. The description of the EDSS has been modified to include additional detail on these subscales and the scoring procedures. The description has also been modified to provide clarification that fatigue should not be included in the calculation of the total EDSS score.

**Sections Impacted:**

Section 8.3.9.1: EDSS

**8. Modification of the description of the administration procedure for the Timed 25-Foot Walk (T25-FW)**

**Rationale for Change:** The modification of the description of the administration procedure for the T25-FW was based on CRO feedback to correct an inconsistency as compared to the Administration and Scoring Manual for the T25-FW regarding when timing of walk should begin.

**Description of Change:** The original protocol stated that: "The time is calculated from the initiation of the instruction to start and ends when the subject has reached the 25-foot mark". This wording has been modified to: "The time is calculated from when the lead foot crosses the start point to when the subject has reached the 25-foot mark".

**Sections Impacted:**

Section 8.3.9.3: Timed 25-Foot Walk (T25-FW)

**9. Addition of study requirements and restrictions for suspected progressive multifocal leukoencephalopathy (PML)**

**Rationale for Change:** The addition of study requirements and restrictions for suspected PML was based on sponsor feedback during the development of a new study protocol for this program. Detail on study restrictions for suspected PML was not included in the original protocol.

**Description of Change:** The original protocol did not include any study requirements and restrictions for suspected PML. This language has been added to the study requirements and restrictions section of the protocol.

**Sections Impacted:**

Section 8.4: Study Requirements and Restrictions

**Administrative/Editorial Changes (contd.)**

**10. Modification of the requirements and timing for discontinuing specific prohibited immunomodulatory treatments**

**Rationale for Change:** The modification of the requirements and timing for discontinuing specific prohibited immunomodulatory treatments was based on CRO feedback after the protocol was approved and published.

**Description of Change:** The original protocol stated that immunomodulatory treatments besides study drug for the treatment of RRMS are prohibited: "from screening through the final follow-up visit". This wording has been modified to: "during treatment with study drug unless approved by the medical monitor". A qualification regarding the timing for discontinuation of specific prohibited immunomodulatory treatments has also been added: "Of note, the timing of discontinuing interferon-beta, interferon-alpha, glatiramer acetate or DMF prior to initiating treatment with study drug (Visit 2) is at the investigator's discretion".

**Sections Impacted:**

Section 8.4.3: Prohibited Medications

**11. Modification of the description of study drug packaging**

**Rationale for Change:** The modification of the description of study drug packaging was based on CRO feedback after the protocol was approved and published.

**Description of Change:** The original protocol did not provide detail of the number of capsules and size of the bottles of study drug to be supplied to the clinical sites. The description of study drug packaging has been modified to include detail on the number of capsules and size of bottles supplied to the clinical sites.

**Sections Impacted:**

Section 10.2: Packaging and Labeling

**12. Modification of the description of study drug storage conditions**

**Rationale for Change:** The modification of the description of study drug storage conditions was based on CRO feedback after the protocol was approved and published.

**Description of Change:** The original protocol stated that all study materials are to be stored at: "room temperature in a secure location". This wording has been modified to: "controlled room temperature in a secure location".

**Sections Impacted:**

Section 10.3: Storage

**Administrative/Editorial Changes (contd.)**

**13. Update of Contact Information for reporting of Serious Adverse Events (SAE)**

**Rationale for Change:** The update to the contact information for reporting of SAEs was based on sponsor feedback after the protocol was approved and published.

**Description of Change:** The procedure for reporting of SAEs was changed from reporting to Alkermes drug safety to reporting to Alkermes drug safety via [redacted] (the CRO). The contact information including the email, phone number, and fax number was changed in the protocol from: "Attention: Drug Safety, Fax Number: [redacted] Email: [redacted]" to: "Attention [redacted] Drug Safety, Email: [redacted] Phone Number: [redacted] FAX Number: [redacted]".

**Sections Impacted:**

Section 11.5: Reporting of Serious Adverse Events