ADS-AMT-MS303

A MULTICENTER, OPEN-LABEL SAFETY AND EFFICACY STUDY OF ADS-5102 AMANTADINE EXTENDED RELEASE CAPSULES IN PATIENTS WITH MULTIPLE SCLEROSIS AND WALKING IMPAIRMENT

Investigational Product: ADS-5102 (amantadine Extended Release Capsules)

Sponsor:

Adamas Pharmaceuticals, Inc.
1900 Powell Street, Suite 750
Emeryville, California 94608
United States of America

Telephone: +1 (510) 450-3500
Facsimile: +1 (510) 428-0519

Medical Monitor: Robert Elfont, MD

Document Date: 19 April 2018

Version: 1.0

APPROVALS:

Reviewed and Approved by:

20 Apr. 2018

Robert Elfont, MD, PhD
Senior Vice President, Clinical Research
Adamas Pharmaceuticals, Inc.

Date

Lily Llorens, PhD
Statistics
Adamas Pharmaceuticals, Inc.

Date

19 April 2018

Aurora Sosa
Regulatory Affairs
Adamas Pharmaceuticals, Inc.

Date

C. Souza-Prien

19 APR 2018

Cindy Souza-Prien
Clinical Program Manager, Clinical Operations
Adamas Pharmaceuticals, Inc.

Date

APPROVALS:

Reviewed and Approved by:

Robert Elfont, MD, PhD
Senior Vice President, Clinical Research
Adamas Pharmaceuticals, Inc.

Date

Lily Llorens, PhD
Statistics
Adamas Pharmaceuticals, Inc.

19 April 2018
Date

Aurora Sosa
Regulatory Affairs
Adamas Pharmaceuticals, Inc.

Date

Cindy Souza-Prien
Clinical Program Manager, Clinical Operations
Adamas Pharmaceuticals, Inc.

Date

2. SYNOPSIS

<table>
<tr><td colspan="2">Name of Sponsor/Company: Adamas Pharmaceuticals, Inc.</td></tr>
<tr><td colspan="2">Name of Investigational Product: ADS-5102 (Amantadine Extended Release Capsules)</td></tr>
<tr><td colspan="2">Name of Active Ingredient: Amantadine</td></tr>
<tr><td colspan="2">Title of Study: A Multicenter, Open-Label Safety and Efficacy Study of ADS-5102 Amantadine Extended Release Capsules in Patients with Multiple Sclerosis and Walking Impairment
(Protocol ADS-AMT-MS303)</td></tr>
<tr><td colspan="2">Study Centers: Approximately 80 sites</td></tr>
<tr><td>Studied period: Approximately 2 years (from enrollment of first subject to last subject’s last visit)
Estimated Date First Subject Enrolled: July 2018</td><td>Phase of development: 3</td></tr>
<tr><td colspan="2">Objectives:
Primary:
To evaluate the safety and tolerability of ADS-5102 in subjects with multiple sclerosis (MS) and walking impairment.
Secondary:
To characterize the efficacy of ADS-5102 in subjects with MS and walking impairment as measured by the Timed 25-Foot Walk (T25FW, feet/second) at Week 52.
To characterize the efficacy of ADS-5102 in subjects with MS and walking impairment as measured by the Timed Up and Go (TUG) test, the 2-Minute Walk Test (2MWT), and the Multiple Sclerosis Walking Scale-12 (MSWS-12) at Week 52.
To characterize the efficacy of ADS-5102 in subjects with MS and walking impairment as measured by the T25FW, the TUG test, the 2MWT, and the MSWS-12 at Weeks 12 and 24, and across all three time points (Weeks 12, 24 and 52).</td></tr>
<tr><td colspan="2">Study Design:
This is a multicenter, open-label extension (OLE) study of ADS-5102 (amantadine) extended release capsules) in subjects with MS and walking impairment who completed study drug treatment for 16 weeks and completed a Week 16 visit in Study ADS-AMT-MS301.
Eligibility for inclusion in this study will require all subjects to be willing to abstain from prohibited medications.
All enrolled subjects, will receive ADS-5102 at 137 mg for the first week, 205.5 mg for the second week, and 274 mg for the remainder of the 52-week open-label treatment period.
Subjects will return to the clinic for safety and efficacy assessments at Weeks 4, 12, 24, and 52. In addition, a telephone visit for safety assessments will be conducted at Week 2 and Week 38. Subjects who withdraw from the study prior to completion of the Week 52 visit will have an early termination (ET) visit that includes safety and efficacy assessments. Subjects who complete 52 weeks of open-label treatment will have a final visit for post-treatment safety follow-up and efficacy assessment at 54 weeks, 2 weeks after their Week 52 visit. The end of study (EOS) is defined as when a subject completes the safety follow-up or ET visit.</td></tr>
</table>

All study visits and efficacy assessments should be scheduled to occur at approximately the same time of day for each individual subject. Each subject's efficacy assessment should be performed by the same clinical rater, if possible.

Adverse events (AEs) and concomitant medications will be recorded beginning with the first dose of study drug and continuing through the last study visit.

Number of Subjects (Planned): Up to approximately 540 subjects will be enrolled.

Diagnosis and Eligibility Criteria:

Inclusion Criteria:

1. Signed a current IRB-approved informed consent form
2. Successful completion of the following in Study ADS-AMT-MS301:
   - Study drug treatment for 16 weeks
   - A Week 16 Visit
3. Willing to abstain from prohibited medications

Exclusion Criteria:

1. Based on the judgement of the investigator or Medical Monitor, participation in the study would jeopardize the safety of the subject.
2. If female, is pregnant or lactating
3. If a sexually active female, is not surgically sterile or at least 2 years post-menopausal, or does not agree to utilize a highly effective hormonal method of contraception (an IUD, or vasectomized male partner is also acceptable), in combination with a barrier method, from baseline through at least 4 weeks after the completion of study treatment. If a sexually active male, does not agree to utilize condoms from screening through at least 4 weeks after the completion of study treatment.
4. Anticipated treatment with any amantadine formulation other than ADS-5102
5. Planned participation in another interventional clinical trial

Investigational Product, Dosage and Mode of Administration:

ADS-5102 (amantadine) extended release capsules will be administered orally, as 2 capsules once daily at Bedtime.

The dosing regimen is 137 mg/d for 1 week (1 x 137 mg capsule + 1 placebo capsule), followed by 205.5 mg/d (1 x 137 mg capsule + 1 x 68.5 mg capsule) for 1 week, followed by 274 mg/d (2 x 137 mg capsules) for 50 weeks.

Reference Therapy, Dosage and Mode of Administration:

Not applicable

Duration of Treatment: Maximum duration of subject participation is up to approximately 54 weeks and will include a 52-week treatment period (including a 2-week forced up-titration and a 50-week maintenance period) followed by a 2-week post-treatment safety follow-up period.

Criteria for Evaluation:

Efficacy Measures: T25FW (measured in seconds but calculated to feet/second), MSWS-12, TUG (seconds), and 2MWT (meters)

Safety Measures: Adverse events (AEs), safety laboratory tests (hematology, clinical chemistry, and urinalysis), vital signs (blood pressure and pulse rate), Columbia-Suicide Severity Rating Scale (C-SSRS), and Expanded Disability Status Scale (EDSS)

Statistical Methods:

Sample Size Determination

This is an open-label, single-arm safety and efficacy study. Subjects completing Study ADS-AMT-MS301 (up to approximately 540 subjects) will be eligible for enrollment.

Analysis Sets

The safety analysis set will include all subjects who receive at least one dose of study drug in study ADS-AMT-MS303 according to the treatment sequence actually received.

The modified intent-to-treat (MITT) analysis set will include all subjects enrolled in the study who received at least one dose of study drug in study ADS-AMT-MS303 according to the randomized treatment sequence. It is understood that randomization here refers to the randomized assignment in study ADS-AMT-MS301.

The per-protocol (PP) analysis set will include all randomized and dosed subjects who provide Week 52 efficacy data and do not have any major protocol deviations that could confound this assessment.

Efficacy Endpoints

Endpoints will be derived using the Week 0 assessments as the baseline value. These endpoints will consist of the changes from Baseline/Week 0 at Weeks 12, 24, and 52 in the:

- T25FW (ft/sec) and also T25FW (sec)
- TUG (sec)
- 2MWT
- MSWS-12
- The proportion of Novel Responders at each study visit, where a Novel Responder is defined as a subject who has a ≥ 20% increase from Baseline/Week 0 to the study visit in walking speed measured using the T25FW. Subjects who fail to have an increase of at least 20% at the given study visit in the T25FW (ft/sec) (non-responders) or who discontinue the study prior to this visit will be included in the denominators.

Efficacy Analyses

All efficacy analyses will be based on the MITT, as well as the PP analyses set.

Endpoints will be summarized by treatment sequence depending on the treatment received in Study ADS-AMT-MS301:

Sequence No.	Study ADS-AMT-MS301 Treatment	Study ADS-AMT-MS303 Treatment
1	Placebo	274 mg/d ADS-5102
2	137 mg/d ADS-5102	274 mg/d ADS-5102
3	274 mg/d ADS-5102	274 mg/d ADS-5102

Efficacy results will be analyzed by treatment sequences 1, 2, and 3 shown above and also by sequences 2 and 3 combined (ie, treatment sequence 1 versus 2 and 3 combined). Descriptive statistics (ie, mean, standard error, median, minimum/maximum, 95% confidence intervals [CI] for the changes from baseline) for each parameter at each study visit will be generated. Missing data will not be imputed. Graphical depictions of changes over time will be provided.

The proportion of Novel Responders in walking speed for each treatment sequence as well as pooled sequences 2 and 3 will also be characterized. The counts and percentages of Novel Responders, Non-Responders and discontinuations at each study visit will be presented.

For parameters measured on a continuum (eg, MSWS-12, T25FW (ft/sec)), the treatment-sequence time trend will be explored using a Mixed Model Repeated Measures (MMRM) model with the change from baseline as the dependent variable, fixed effects of treatment-sequence, study visit (ie week 12, 24 and 52), treatment-sequence by study visit interaction, baseline value as a covariate and an unstructured variance-covariance matrix for the within-subject residual variability. Appropriate contrasts comparing specific weeks between treatment-sequences will be derived from this model. For the proportion responders, a GEE (generalized estimating equation) model for a binomial variate will be used.

Details of all analyses will be provided in the statistical analysis plan (SAP) for this study.

Safety and Tolerability Analyses

All safety analyses will be based on the Safety analyses set. Adverse events in Study ADS-AMT-MS303 will be recorded starting immediately upon completion of the last study procedure for Study ADS-AMT-MS301 at a Week 16 Visit for that study (which also serves as the first study visit for Study ADS-AMT-MS303). All AEs will be listed by subject and period of onset: pre-dose and treatment-emergent adverse events (TEAEs).

The incidence of TEAEs will be summarized by treatment sequences 1, 2, and 3, and overall for all subjects. Summaries will be presented by system organ class (SOC) and preferred term (PT) within SOC in the safety analysis set, which will include all subjects who received at least one dose of open-label study medication.

Clinical laboratory test parameters will be listed for individual subjects and values outside of the reference ranges will be flagged. The incidence of potentially clinically significant changes in laboratory parameters at each study visit will be tabulated. Vital signs measurements at each timepoint will be listed by subject. The incidence of potentially clinically significant changes at each study visit will be summarized.

Descriptive statistics for the mean and mean changes in the C-SSRS will be generated by study visit. Results will also be graphically depicted.

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

LIST OF TABLES

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 1: Abbreviations and Specialist Terms

Abbreviation	Explanation
2MWT	2-Minute Walk Test
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CFR	Code of Federal Regulations
CI	Confidence interval
CNS	Central nervous system
CRF	Case report form (paper and/or electronic)
C-SSRS	Columbia-Suicide Severity Rating Scale
EDC	Electronic Data Capture
EDSS	Expanded Disability Status Scale
eGFR	Estimated glomerular filtration rate
EOS	End of study
ER	Extended release
ET	Early termination
GCP	Good Clinical Practice
ICF	Informed consent form
ICH	International Council on Harmonisation
IEC	Independent ethics committee
IR	Immediate release
IRB	Institutional review board
IRT	Interactive response technology
IUD	Intrauterine device
MDRD	Modification of Diet in Renal Disease
MI	Myocardial infarction
MITT	Modified intent-to-treat
MMRM	Mixed Model Repeated Measures

Table 1: Abbreviations and Specialist Terms (Continued)

Abbreviation	Explanation
MS	Multiple sclerosis
MSWS-12	Multiple Sclerosis Walking Scale-12
OLE	Open-label extension
PD	Parkinson's disease
PI	Principal Investigator
REB	Research ethics board
SAE	Serious adverse event
SAP	Statistical analysis plan
STEAE	Serious treatment-emergent adverse event
T25FW	Timed 25-Foot Walk
TEAE	Treatment-emergent adverse event
TIA	Transient ischemic attack
t_{max}	Time to maximum observed concentration
TUG	Timed Up and Go
US	United States
WBC	White blood cell(s); leukocyte(s)

5. INTRODUCTION

This is an open-label extension (OLE) study for subjects who complete 16 weeks of study drug treatment and a Week 16 visit in Study ADS-AMT-MS301, "A 3-Arm, Multicenter, Double-Blind, Placebo-Controlled, Randomized Study to Assess the Efficacy and Safety of ADS-5102 Amantadine Extended Release Capsules in Multiple Sclerosis Patients with Walking Impairment." The primary purpose of this study is to extend the evaluation of the safety and tolerability of ADS-5102, an extended-release (ER) capsule formulation of amantadine administered at 274 mg/d, in subjects with multiple sclerosis (MS) and walking impairment from 12 weeks, as in Study ADS-AMT-MS301, to 52 weeks or 64 weeks (including the duration of ADS-AMT-MS301). Additionally, this study is intended to provide supportive evidence of the efficacy of ADS-5102 as a treatment for walking impairment in MS (by way of treating the former ADS-AMT-MS301 placebo subjects), as well as an assessment of the durability of efficacy up to 64 weeks.

5.1. Walking Impairment in Multiple Sclerosis

Adamas is developing ADS-5102, an extended-release (ER) capsule formulation of amantadine hydrochloride (HCl), as a treatment to improve walking in patients with multiple sclerosis (MS).

MS is a chronic, usually progressive, autoimmune-mediated disorder of the central nervous system (CNS). The prevalence of MS in the United States (US), based on recently reported analyses of healthcare databases, is on the order of 400,000 to 675,000 individuals (Dilokthornsakul et al., 2016; Wallin, 2017). Patients generally become symptomatic early in adulthood and continue to accumulate disability throughout most of their lives. The autoimmune assault in MS can involve any part of the CNS, and by definition, affects multiple regions over time (Schumacher, 1950; Kantarci and Wingerchuk, 2006). This feature of MS makes neurological functions that depend on the integration of multiple CNS systems particularly susceptible to disability. Walking, which depends on the coordinated functioning of multiple CNS motor and sensory systems, is frequently impaired in MS. About 50% of MS patients become dependent on some form of walking aid after 15 years with the disease (Kantarci and Wingerchuk, 2006).

While there are now numerous drugs approved to reduce inflammation, and slow the progression of disability in MS, there are limited options available for the treatment of frequent, and often persistent, neurological deficits, with only one drug, dalfampridine (4-aminopyridine [4-AP]; Ampyra®) currently approved to treat walking impairment. Dalfampridine was approved in 2010 as a treatment to improve walking in patients with MS, as demonstrated by an increase in walking speed. However, this product appears to benefit only a subset of patients, comprising some 30%-60% (Goodman et al., 2009; Goodman et al., 2010; Prugger and Berger, 2013; Ruck et al., 2014 Korsen et al., 2016) of those who try it. Consequently, there remains an unmet medical need for additional therapies to treat impaired mobility in MS patients.

5.2. ADS-5102 for Walking Impairment in Multiple Sclerosis

Amantadine has been reported to possess multiple pharmacological activities. The precise mechanism through which amantadine may exert its beneficial effects in MS has not been completely elucidated, and multiple pharmacological activities may contribute to amantadine's

effects in this indication. Amantadine is known to be a low affinity, uncompetitive inhibitor of the N-methyl-D-aspartate (NMDA) receptor (Kornhuber et al., 1991; Bresink et al., 1995; Parsons et al., 1995, Parsons et al., 1996). Nonclinical studies have demonstrated that amantadine decreases neuronal toxicity associated with excessive glutamate release (Danysz et al., 1997) and improves cognitive function (Wang et al., 2014). Amantadine has been shown to increase the action potential duration in rat atria to a similar degree as dalfampridine (Northover, 1994), which suggested that amantadine may also block potassium channels. Studies conducted by Adamas with amantadine in rat coronal brain slices demonstrated that amantadine blocked neuronal potassium channels over a wide concentration range (10-1000 μM). Blockade of potassium channels is the putative mechanism by which dalfampridine is believed to exert its clinical benefit in MS walking (Ampyra package insert). In addition, amantadine has been shown to modulate cholinergic signaling (Albuquerque, et al., 1978), affect serotonin levels (Wesemann et al., 1979), inhibit microglial activation, and increase the release of glial cell-derived nerve growth factor (Ossola et al., 2011).

Adamas conducted a Phase 2 study of ADS-5102 in MS patients, Study ADS-AMT-MS201, to assess the safety and tolerability of ADS-5102 in patients with MS. Secondary objectives were to assess the potential benefit of ADS-5102 on walking speed, functional mobility, walking distance, fatigue, depression, and cognition of patients with MS. Walking speed was prespecified as the key secondary outcome, and trial participants were screened for the presence of walking impairment on the basis of performing the Timed 25-Foot Walk (T25FW) test in 8 to 45 seconds, inclusive.

This 4-week, placebo-controlled, proof-of-concept study showed a manageable safety and tolerability profile for ADS-5102 in participants with MS. The safety data were similar to the previously published results in Parkinson's disease (PD) (Pahwa et al., 2015; Pahwa et al., 2017). The types of AEs reported were also consistent with the known safety profile of immediate-release amantadine.

A statistically significant effect ($p = < 0.05$) on the percent change in walking speed from baseline was observed, and a greater proportion of ADS-5102-treated participants (8 out of 27 subjects) experienced a $\geq 20\%$ improvement. Trends suggesting benefit, which did not reach statistical significance (p-values < 0.1), were observed for the Timed Up and Go (TUG) test, and less so on the 2-Minute Walk Test (2MWT) (Cohen et al., 2018: see also Investigator's Brochure). Previous studies indicate these tests are less sensitive, requiring longer follow-up and larger sample size to demonstrate benefit (Hobart, 2017). Results on participant-reported walking ability, measured by the MSWS-12 over 4 weeks, did not demonstrate benefit. The short duration of the study may not have provided sufficient time to detect a treatment effect on this patient-reported outcome, as the recall period for the questionnaire is 2 weeks.

The goal of the Phase 3 study, ADS-AMT-MS301, ongoing as of the start of the OLE study, ADS-AMT-MS303, is to confirm the efficacy, safety, and tolerability of ADS-5102 as a treatment to improve walking in patients with MS, as suggested by the results of the Phase 2 study. The goal of Study ADS-AMT-MS303 is to provide additional supportive evidence of the safety and efficacy of ADS-5102 as a treatment to improve walking in patients with MS.

5.3. Product (Formulation) Rationale

The ADS-5102 investigational drug product is a capsule containing ER coated pellets of amantadine HCl. The rationale for a formulation that slows the release of amantadine is based upon the nature and timing of the CNS side effects associated with immediate release (IR) amantadine relative to dosing, as well as observations with other CNS active drugs. Immediate release formulations of amantadine HCl have a short time to maximum observed concentration (t_{max}) of 2-4 hours (Aoki and Sitar, 1988), and the most commonly reported side effects are CNS-related, including dizziness (lightheadedness), agitation, hallucinations, and insomnia, which can occur within a few hours of dosing (Jackson et al., 1967; Hayden et al., 1981). The AEs reported with amantadine therapy in MS (Murray, 1985; Canadian MS Research Group 1987; McEvoy et al., 1987; Rosenberg and Appenzeller, 1988; Chiba et al., 1992; Krupp et al., 1995; Ashtari et al., 2009; Berger, 2011) are overall similar to those observed with amantadine treatment in PD. The increased frequency of AEs at higher doses, in particular CNS events and sleep disturbances, limits the routine use of amantadine IR at doses of 300 mg/day or higher. The pharmacologic rationale for improved tolerability of an ER formulation of amantadine is that the reduction in the rate of rise in plasma concentration may reduce the CNS adverse effects.

Recent preclinical experiments have shown that the rate of rise in amantadine plasma concentrations may contribute to CNS impairment, with a more rapid rise in plasma concentrations resulting in greater CNS impairment. Studies conducted by Adamas have demonstrated that rapid bolus infusion with amantadine resulted in greater CNS impairment, as determined by time balancing on a rotating rod (Rotarod, a validated model of safety pharmacology in rodents), whereas as a slower rate of infusion reaching the same final plasma concentration produced no discernible CNS side-effects. These results are consistent with favorable tolerability profile of ADS-5102 as demonstrated in clinical studies supporting the dyskinesia indication in patients with Parkinson’s disease.

5.4. Dose Selection

At the start of this OLE study (Study ADS-AMT-MS303), two dosages of ADS-5102 will be in testing in Study ADS-AMT-MS301, 137 mg/d and 274 mg/d. The 274 mg dose was selected for Study ADS-AMT-MS301 because it showed a statistically significant effect on walking speed in the Timed 25-Foot Walk (T25FW) test in the Phase 2 study, Study ADS-AMT-MS201. The 137 mg dose was selected to adequately characterize the dose-response curve. It was, and continues to be, anticipated that ADS-5102 will evidence a dose-response curve for its effect on walking impairment in patients with MS, as it did for its effect on dyskinesia in patients with PD (Pahwa et al., 2015), with the 274 mg dose showing greater efficacy than a lower dose. Moreover, it was concluded from the Phase 2 study, Study ADS-AMT-MS201, that the safety and tolerability of the 274 mg dose in subjects with MS was adequate to support continued clinical testing; and it is anticipated that this conclusion will be supported by the results from the Phase 3 study, Study ADS-AMT-MS301. On the basis of these two anticipated results from Study ADS-AMT-MS301, and the supporting evidence underlying them, the 274 mg dose of ADS-5102 has been selected for this OLE study (Study ADS-AMT-MS303) to evaluate the long-term safety and to characterize the efficacy of ADS-5102 in subjects with MS and walking impairment. Should either of the anticipated results from Study ADS-AMT-MS301 not be borne out, the protocol for Study ADS-AMT-MS303 will be amended.

5.5. Dosing Regimen and Justification

ADS-5102 is to be taken once daily at Bedtime. The t_{max} for ADS-5102 is expected to occur at 12 to 14 hours post dose. ADS-5102 is designed to maintain high concentrations throughout most of the waking day, with concentrations decreasing in the evening. This pharmacokinetic profile could enable higher daily doses to be tolerated with a once-nightly ER preparation than are typically reported for dosing with an amantadine IR formulation. The once daily at Bedtime dosing regimen may also provide enhanced convenience and improve compliance.

The 52-week Open-Label Treatment Period includes a 2-step, forced titration phase followed by a maintenance phase of approximately 50 weeks at the 274 mg dose of ADS-5102. The titration phase is intended to promote the tolerability of 274 mg ADS-5102. The titration occurs over approximately the first 2 weeks of the study, with dosing in the first week at 137 mg/d, and in the second week at 205.5 mg/d.

5.6. Rationale for ADS-AMT-MS303 Study Design

This study is designed to further investigate the safety and tolerability profile of ADS-5102 oral capsules administered over a duration of 12 months at a dose of 274 mg once daily at Bedtime for the treatment of walking impairment in subjects with MS. Additionally, this study will characterize the duration of ADS-5102 effect on walking impairment as assessed by the T25FW, the TUG test, the 2MWT, and the Multiple Sclerosis Walking Scale-12 (MSWS-12).

5.7. Population to be Studied

Patients with MS and impaired walking who completed treatment in Study ADS-AMT-MS301 will be enrolled into the study.

6. TRIAL OBJECTIVES AND PURPOSE

6.1. Primary Objective

- To evaluate the safety and tolerability of ADS-5102 in subjects with MS and walking impairment.

6.2. Secondary Objectives

- To characterize the efficacy of ADS-5102 in subjects with MS and walking impairment as measured by the T25FW (feet/second) at Week 52.
- To characterize the efficacy of ADS-5102 in subjects with MS and walking impairment as measured by the Timed Up and Go (TUG) test, the 2 Minute Walk Test (2MWT), and the Multiple Sclerosis Walking Scale-12 (MSWS-12) at Week 52.
- To characterize the efficacy of ADS-5102 in subjects with MS and walking impairment as measured by the T25FW, the TUG test, the 2MWT, and the MSWS-12 at Weeks 12 and 24, and across all three time points (Weeks 12, 24 and 52).

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a multicenter, open-label study of ADS-5102 (amantadine) extended release capsules in subjects with MS and walking impairment who completed study drug treatment for 16 weeks and completed a Week 16 visit in Study ADS-AMT-MS301.

Eligibility for inclusion in this study will require all subjects to be willing to abstain from prohibited medications.

All enrolled subjects will receive ADS-5102 at 137 mg for the first week, 205.5 mg for the second week, and 274 mg for the remainder of the 52-week open-label treatment period.

Subjects will return to the clinic for safety and efficacy assessments at Weeks 4, 12, 24, and 52. In addition, a telephone visit for safety assessments will be conducted at Week 2 and Week 38 Subjects who withdraw from the study prior to completion of the Week 52 visit will have an early termination (ET) visit that includes safety and efficacy assessments. Subjects who complete 52 weeks of open-label treatment will have a final visit for post-treatment safety follow-up and efficacy assessment at 54 weeks, 2 weeks after their Week 52 visit. The end of study (EOS) is defined as when a subject completes the safety follow-up or ET visit.

All study visits and efficacy assessments should be scheduled to occur at approximately the same time of day for each individual subject. Each subject's efficacy assessment should be performed by the same clinical rater, if possible.

Adverse events (AEs) and concomitant medications will be recorded beginning with the first dose of study drug and continuing through the last study visit.

7.2. Number of Subjects

Up to approximately 540 subjects will be eligible for enrollment.

7.3. Treatment Assignment

In this OLE study, all consented subjects will be treated with ADS-5102 at 274 mg/d following a two-week forced titration period.

7.4. Dose Adjustment Criteria

7.4.1. Dose Adjustment for Renal Impairment

Subjects whose estimated glomerular filtration rate (eGFR) falls below 60 mL/min/1.73 m^2, confirmed by repeat testing, should discontinue study drug (see Section 8.5).

7.4.2. Dose Adjustment for Adverse Events

Study drug may only be withheld for the evaluation or treatment of an adverse event (AE). If, in the judgement of the investigator, study drug should be withheld for the evaluation or treatment of an AE, the investigator may have the subject do so for up to 3 consecutive days, and is then to have the subject resume dosing at the same dose level. If, in the judgement of the investigator, study drug needs to be withheld for more than 3 consecutive days, the investigator must contact

one of the study's Medical Monitors to determine whether drug may be withheld for a longer period or the subject should be permanently discontinued from study drug. This procedure applies to the withholding of study drug throughout the study with the exception of the titration phase.

If study drug is withheld for the evaluation or treatment of an AE occurring during the titration phase (ie, Week 0 to Week 2), the investigator may have the subject stop dosing for up to 3 consecutive days, and then have the subject resume dosing at the same dose level. The subject is to finish the remaining capsules in the blister pack, ie, including the 2-dose overage. Provision must be made for the subject to come to the clinic to be resupplied with study drug without missing any additional doses.

After Week 12, down titration from 274 mg to 137 mg due to adverse events may be considered after consultation with the Medical Monitor.

7.5. Criteria for Study Termination

The sponsor reserves the right to discontinue the trial at any time; reasons will be provided if this occurs. The Principal Investigator (PI) reserves the right to discontinue participation in the study for safety or other reasons at any time in collaboration with the sponsor. The investigator should notify the institutional review board (IRB) in writing of the trial's completion or early termination and provide a copy of the notification to the sponsor.

7.6. Duration of Subject Participation

Maximum duration of subject participation is up to approximately 54 weeks and will include a 52-week treatment period (including a 2-week forced up-titration and a 50-week maintenance period), and a 2-week post-treatment safety follow-up period.

7.7. Estimated Study Duration

The estimated study duration is approximately 2 years, from enrollment of the first subject to the last subject's last visit.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Inclusion Criteria

1. Signed a current IRB-approved informed consent form
2. Successful completion of the following in Study ADS-AMT-MS301:
   - Study drug treatment for 16 weeks
   - A Week 16 Visit
3. Willing to abstain from prohibited medications (see Section 9.7)

8.2. Subject Exclusion Criteria

1. Based on the judgement of the investigator or Medical Monitor, participation in the study would jeopardize the safety of the subject.
2. If female, is pregnant or lactating
3. If a sexually active female, is not surgically sterile or at least 2 years post-menopausal, or does not agree to utilize a highly effective hormonal method of contraception (an IUD, or vasectomized male partner is also acceptable), in combination with a barrier method, from baseline through at least 4 weeks after the completion of study treatment. If a sexually active male, does not agree to utilize condoms from screening through at least 4 weeks after the completion of study treatment.
4. Anticipated treatment with any amantadine formulation other than ADS-5102
5. Planned participation in another interventional clinical trial

8.3. Subject Withdrawal Criteria

Subjects will be advised that they are free to withdraw from the study at any time. Reasons that subjects may be withdrawn from the study include the following:

- Subject discontinued study drug (see Section 8.5) and wishes to withdraw
- Subject consent is withdrawn
- Sponsor decision, after discussion with the investigator

If a subject is withdrawn from the study, all efforts will be made to complete the early termination visit that includes efficacy assessments and safety follow-up. In addition, women of childbearing potential will have a post-study pregnancy test performed at the early termination visit.

All information, including the reason for withdrawal, should be reported on the applicable pages of the case report form (CRF).

For subjects who are lost to follow-up, three documented attempts will be made to contact the subject for follow-up information, including reason for discontinuation and follow-up of AEs.

Subjects who withdraw from the study will not be replaced.

8.4. Subject Enrollment

All subjects must sign and date an IRB-approved informed consent form (ICF) before any study procedures, including screening procedures, are performed. Subjects will be considered enrolled into the study after they have signed the ICF and have met all study-mandated inclusion/exclusion criteria.

8.5. Discontinuation of Study Drug

Subjects should discontinue study drug if judged necessary by the investigator or sponsor, and reasons may include any of the following:

- eGFR falls below 60 mL/min/1.73 m^2, confirmed by repeat testing
- Need to take a medication that is excluded or that may interfere with study measurements
  - Subjects requiring MS treatment adjustment due to disease exacerbation or progression should be discussed with one of the Medical Monitors
- Intolerable or unacceptable AEs
- Positive pregnancy test

Subjects who discontinue study drug will be withdrawn from the study, and will have an early termination visit that includes efficacy assessments and safety follow-up (see Section 12.8).

9. STUDY DRUG MATERIALS AND MANAGEMENT

9.1. Study Drug

The clinical supplies will include open-label 137 mg and 68.5 mg ADS-5102 capsules.

Amantadine is designated generically as amantadine hydrochloride and chemically as 1-adamantanamine hydrochloride. All dose quantities however are based on quantity of amantadine, as per FDA requirements regarding drug products containing salt drug substances.

The clinical formulation is shown in the table below.

Table 2: Clinical Formulation for Study ADS-AMT-MS303

Formulation	**ADS-5102 137 mg and 68.5 mg** Extended release coated pellets of amantadine in an oral capsule
Dose Strength	137 mg amantadine per capsule 68.5 mg amantadine per capsule
Description	White to off-white pellets filled in white opaque/white opaque colored hard gelatin capsule, size 0.
Excipients	Microcrystalline cellulose, NF/EP Hypromellose, USP/EP Copovidone, NF/EP Talc, USP/EP Ethyl cellulose, USP/NF/EP Povidone, USP/EP Medium chain triglycerides, USP/EP/NF Magnesium stearate, USP/NF/EP

USP: United States Pharmacopeia; NF: National Formulary; EP: European Pharmacopoeia.

9.2. Study Drug Packaging and Labeling

The study drug will be packaged in child-resistant blister wallets and bottles. Blister wallets will contain 36 capsules to allow for 2 weeks of dosing during the forced titration period (2 capsules per dose, allowing a 2-week supply plus 2 extra doses for each week). Bottles will contain 60 capsules (30-day supply of study drug) of 137 mg ADS-5102. All blister wallets and bottles will be labeled with, at a minimum, the protocol number, route of administration, number of capsules to be administered, lot number, storage conditions, sponsor's name and address, investigator's name, subject number, and applicable investigational drug caution statements.

The study drug will be assigned by an interactive response technology (IRT) system per the assigned dosing schedule and titration scheme at designated study visits. Details of the dispensation schedule will be included in the IRT user manual.

9.3. Study Drug Storage

All study drugs must be stored at 25°C (77°F) with excursions permitted to 15-30°C (59-86°F) in a secured location with access limited to authorized personnel.

An authorized pharmacist or designated staff member will dispense the study drug. The dispensing and administration will be recorded in a drug accountability log.

9.4. Administration

The dosing regimen is as follows:

- 137 mg/d (1 x 137 mg capsule + 1 placebo capsule) for one week, followed by
- 205.5 mg/d (1 x 137 mg capsule + 1 x 68.5 mg capsule) for 1 week, followed by
- 274 mg/d (2 x 137 mg capsules) for 50 weeks.

Each dose will be administered as 2 oral capsules once daily at Bedtime.

Capsules are to be swallowed intact, and can be taken with any nonalcoholic beverage, with or without food.

While taking study drug, **concomitant use with alcohol is not recommended**, as it may increase the potential for CNS effects such as dizziness, confusion, lightheadedness, and orthostatic hypotension and may result in dose-dumping.

Dosing will continue through Week 52.

9.5. Study Drug Accountability

All study drug supplied is for use only in this clinical study and must not be used for any other purpose. The investigator is responsible for the study drug accountability, reconciliation and record maintenance at the investigational site. In accordance with all applicable regulatory requirements, the investigator or designated site staff must maintain study drug accountability records throughout the course of the study. This person will document the amount of study drug received and the amount supplied and/or administered to and returned by subjects, if applicable. Copies of all packing slips for the study drug shipments must be retained.

A Study Drug Accountability Record must be kept current and will contain at a minimum the following information:

- The identification of the subject to whom the drug was dispensed
- The date(s) and quantity of the drug dispensed to the subject
- Any product accidentally or deliberately destroyed
- Current quantity of total study drug supply

Subjects will be instructed to return all used and unused blister cards of study drug for drug accountability purposes. All used and unused blister cards must be saved for reconciliation by the sponsor's study monitor or an assigned designee.

During the study, the study drug and all shipment, accountability and dispensing records must be available for inspection by the study monitor. Drug supply reconciliation is required at the end of the study by the study monitor.

9.6. Study Drug Handling and Disposal

After reconciliation, all unused drug supplies will be disposed of according to instructions provided by the sponsor. Records shall be maintained by the investigator of any such disposition of the study drug, which must show the identification and quantity of each unit returned.

9.7. Prohibited Medications and Restrictions

The following medications are prohibited during study participation:

- Amantadine, other than provided study drug
- Live attenuated influenza vaccine

Medications that may affect urinary pH, including, but not limited to, carbonic anhydrase inhibitors, sodium bicarbonate, urinary acidification agents, quinine, quinidine, triamterene, or trimethoprim, can affect the elimination of ADS-5102. The excretion rate of amantadine increases rapidly when the urine is acidic, hence, the administration of urine acidifying drugs may increase the elimination of the drug from the body. Alterations of urine pH towards the alkaline condition may lead to an accumulation of the drug, with a possible increase in adverse reactions. Consequently, subjects should be monitored for changes in efficacy or adverse reactions under conditions that alter the urine pH to more acidic or alkaline, respectively.

Products with anticholinergic properties may potentiate the anticholinergic-like side effects of amantadine. Subjects should be monitored for anticholinergic effects. The investigator should consider reducing the dose of anticholinergic drugs, if atropine-like effects appear when these drugs are used concurrently.

While taking study drug, **concomitant use with alcohol is not recommended**, as it may increase the potential for CNS effects such as dizziness, confusion, lightheadedness, and orthostatic hypotension and may result in dose-dumping.

9.8. Concomitant Medications

Information regarding medications taken by the subject throughout the study will be collected and recorded on the Prior/Concomitant Medications CRF. This information will include the name of the medication, dosage information (including frequency and route of administration), dates taken, reason for use, and stop date, if available.

As a general rule, any new medication initiated during the course of the study should be to treat an AE. Hence, the start date of a new concomitant medication should always coincide with a date of an AE, including an MS exacerbation or worsening of MS. Changes to existing, or initiation of new, MS medications (including disease modifying and symptomatic) should only be made after Week 12. If new MS medications are initiated during study participation, please inform the Medical Monitor in a timely manner.

9.9. Treatment Compliance

Subjects will be instructed to return all used/unused blister cards or bottles at the next study visit, when the designated study site staff will review the number of returned capsules to assess subject compliance.

9.10. Randomization and Blinding

This is an open-label study, during which all subjects will receive ADS-5102 titrated to a dose of 274 mg/d.

10. ASSESSMENT OF EFFICACY

Evaluations relating to efficacy to be performed during the study are described in the following table, and should be performed in the order shown: MSWS-12, T25FW, TUG, and the 2MWT. Full details on how efficacy assessments are to be performed will be provided in the study manual.

Table 3: Efficacy Assessments

Assessment	Study Visit	Description
Timed 25-Foot Walk (T25FW)	Baseline/Week 0 Week 12 Week 24 Week 52 (or ET) Safety Follow-Up	The T25FW is a measure of lower extremity function. The subject is directed to a clearly marked 25-foot course and is instructed to walk 25 feet as quickly as possible, but safely. The task is immediately administered again by having the subject walk back the same distance. The result is reported as time to complete (seconds) or speed (feet per second). Improvement is indicated by a decrease in time or an increase in speed.
Timed Up and Go (TUG)	Baseline/Week 0 Week 12 Week 24 Week 52 (or ET) Safety Follow-Up	The TUG is a measure of lower extremity strength, balance, and coordination. The subject stands up from a chair, walks 3 meters then turns around and walks back to the chair to sit down. The result is reported in seconds. Improvement is indicated by negative change scores.
2-Minute Walk Test (2MWT)	Baseline/Week 0 Week 12 Week 24 Week 52 (or ET) Safety Follow-Up	The 2MWT is a measure of lower extremity function. The subject is instructed to walk as far as possible in 2 minutes, and the distance is measured in meters. Improvement is indicated by positive change scores.
Multiple Sclerosis Walking Scale-12 (MSWS-12)	Baseline/Week 0 Week 12 Week 24 Week 52 (or ET) Safety Follow-Up	The MSWS-12 is a 12-item walking scale that is a measure of patient-reported walking ability during the past 2 weeks. Each item is scored on a 1 to 5 scale. A total score can be generated and transformed to a 0 to 100 scale. Improvement is indicated by negative change scores.

11. ASSESSMENT OF SAFETY

11.1. Physical Assessments Relating to Safety

Procedures that are shared between Week 16 of Study ADS-AMT-MS301 and the Baseline visit of the present study do not need to be repeated and the data will be captured in both studies.

11.1.1. Scheduled Physical Assessments Relating to Safety

Physical examinations relating to safety to be performed during the study are described in the following table.

Table 4: Physical Examination Assessments Relating to Safety

Assessment	Study Visit	Description
Complete physical examination	Baseline/Week 0 Week 52 (or ET)	Physical examination including: skin, head-neck, eyes-ears-nose-throat, lungs-chest, heart, abdomen, extremities.
Symptom-directed physical examination, as needed	Weeks 4, 12, 24, and Safety Follow-Up	Physical examination adequate to evaluate fully the diagnosis and severity of an AE or AEs having occurred up to the date of the visit.
Weight	Baseline/Week 0 Week 52 (or ET)	Weight will be recorded in kilograms. Subjects may be weighed in their undergarments or in light clothing (no jackets or shoes). Measuring weight must be done consistently, using the same set of weighing scales when possible.
Vital signs	Baseline/Week 0 Week 4 Week 12 Week 24 Week 52 (or ET) Safety Follow-Up	Systolic and diastolic blood pressures, heart rate, and body temperature should be recorded after the subject has been seated quietly for at least 5 minutes. Blood pressure, respiratory rate, heart rate, and temperature will be measured once each day assessed.

Table 4: Physical Examination Assessments Relating to Safety (Continued)

Assessment	Study Visit	Description
Expanded Disability Status Scale (EDSS)	Week 52	The Expanded Disability Status Scale (EDSS) is an ordinal scale, 0 to 10, based on a comprehensive neurological examination, used to quantify disability in multiple sclerosis. The EDSS utilizes scoring in 8 functional systems (visual, brainstem, pyramidal, cerebellar, sensory, bowel and bladder, cerebral, and other) and ambulation. A score of 0 indicates a normal neurological exam and a score of 10 is death. EDSS steps 1 to 4.5 are defined by functional system scoring in patients who are fully ambulatory. EDSS steps 5.0 to 9.5 are defined by the extent of walking impairment.

11.1.2. Unscheduled Physical Assessments Relating to Safety

If, at a scheduled or unscheduled study visit, a subject reports experiencing, or having experienced, an AE, or is observed to be having an AE, the investigator should perform those examinations necessary to evaluate fully the diagnosis and severity of the AE.

If the AE is one of dizziness, lightheadedness, pre-syncope, syncope, or a related event, the examination must include, at a minimum, testing for orthostatic hypotension. After the seated blood pressure has been obtained, the measurement will be repeated within 3 minutes of the subject standing up. This procedure may be repeated, if appropriate, following hydration. If repeated, a total of two additional pairs of blood pressure assessments (sitting/standing) should be obtained, and the results of the last attempt should be reported.

11.2. Clinical Laboratory Tests

The clinical laboratory and other tests relating to safety to be performed during the study are described in the following table. The estimated total blood volume collected throughout the study (for clinical laboratory tests) is expected to be approximately 30 mL for safety serum chemistry and hematology laboratory evaluations.

Table 5: Clinical Laboratory and Other Assessments

Assessment	Study Visit	Description
Hematology	Baseline/Week 0 Week 52 (or ET)	Blood samples (5 mL) will be collected. Hematology parameters include: hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), red blood cell (RBC) count, white blood cell (WBC) count, WBC differential count, and platelet count.
Serum Chemistry	Baseline/Week 0 Week 52 (or ET)	Blood samples (10 mL) will be collected (fasting is not required). Routine serum chemistry parameters include alkaline phosphatase, albumin, blood urea nitrogen, calcium, carbon dioxide, chloride, creatinine, γ-glutamyl transferase, glucose, inorganic phosphorus, potassium, alanine aminotransferase (ALT), lactate dehydrogenase, aspartate aminotransferase (AST), sodium, total bilirubin, and total protein.
Urinalysis	Baseline/Week 0 Week 52 (or ET)	Urinalysis will be performed using sponsor-supplied dipsticks, including leukocytes, specific gravity, pH, protein, ketones, glucose, nitrite, blood, urobilinogen, and bilirubin. If nitrite, blood, or protein tests are positive, a microscopic examination will be performed.
Serum pregnancy test (if applicable)	Baseline/Week 0 Week 52 (or ET) Safety Follow-Up	Serum pregnancy test will be performed for all female subjects of childbearing potential.
Urine pregnancy test (if applicable)	Week 4 Week 12 Week 24	Urine pregnancy test will be performed for all female subjects of childbearing potential.

Estimated glomerular filtration rate (eGFR) will be calculated by the central laboratory using Modification of Diet in Renal Disease (MDRD).

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

The C-SSRS will be performed at every visit. Full details on how this assessment is to be performed will be provided in the study manual.

While the C-SSRS can provide valuable information as to the presence and intensity of suicidal ideation, determining the need for, and appropriate level of, therapeutic intervention depends on clinical judgment. The Joint Commission has published guidelines for treating suicidal ideation, "Sentinel Event Alert 56: Detecting and treating suicide ideation in all settings," along with other resources that may prove useful to the investigator, available at: https://www.jointcommission.org/sea_issue_56/.

Subjects should also be monitored for depression, depressed mood, confusional state, and/or apathy, as well as suicidal ideation or behavior. New or worsening depression should be captured as an adverse event and treated appropriately per the Investigator's obligation and judgement.

12. EVALUATIONS BY VISIT

A schedule of study evaluations is provided in Appendix A.

All study visits should occur on the day scheduled ± 2 days.

12.1. Baseline/Week 0

Potential subjects for the study will be fully informed about the nature of the study and possible AEs. Subjects who wish to participate in the study must read and understand the consent form and sign the document after the investigator has answered all questions to the candidate's satisfaction. Further procedures can begin only after the consent form has been signed.

The Week 16 Visit of Study ADS-AMT-MS301 will serve as the Baseline/Week 0 study visit of Study ADS-AMT-MS303 for those subjects who consent to participate. Per the Schedule of Events in Appendix A, procedures that are shared between Study ADS-AMT-MS301 (Week 16 Visit) and the Baseline/Week 0 visit of the present study do not need to be repeated and the data will be captured in both studies.

The following procedures will be performed to establish each subject's qualifications for enrollment into the study:

- The subject is fully informed about the study and gives written informed consent to participate in the study
- Review inclusion/exclusion criteria and evaluate initial subject eligibility
- Record demographic information
- Medical history with an emphasis on the subject's MS and walking impairment, and past treatments for these conditions; alcohol and drug use, other neurological diseases, psychiatric disorders including Major Depressive Disorder or symptom (eg, hallucinations, agitation, paranoia, suicidal ideation), history of seizures, stroke or transient ischemic attack (TIA); history of myocardial infarction (MI) or congestive heart failure (CHF); and history of cancer
- Record all medications currently taken
- Assess and record AEs
- Complete physical examination
- Obtain subject weight in kilograms
- Vital signs (blood pressure, respiratory rate, heart rate, and temperature)
- Blood sample for central laboratory analysis including hematology, serum chemistry, and eGFR
- Urinalysis

- Blood sample for serum pregnancy test in female subjects of childbearing potential
- MSWS-12, T25FW, TUG, and 2MWT assessments (Full details on how individual efficacy assessments are to be performed will be provided in the study manual. These assessments are to be done in this order.)
- Administer the C-SSRS (administration instructions and forms will be provided in the study manual)
- Dispense study drug (1 wallet and 1 bottle)

12.2. Telephone Visit at Week 2

- Assess and record any changes in concomitant medications
- Assess and record AEs
- Remind subject to start taking capsules from the bottles
- If necessary, schedule an unscheduled visit

12.3. Visit at Week 4

- Assess and record concomitant medications
- Assess and record AEs
- Vital signs (blood pressure, respiratory rate, heart rate, and temperature)
- Urine sample for urine pregnancy test in females of childbearing potential
- C-SSRS
- Collect used/unused blister wallet and bottle and evaluate compliance
- Dispense study drug (2 bottles)

12.4. Visit at Week 12

- Assess and record concomitant medications
- Assess and record AEs
- Symptom-directed physical examination, as needed
- Vital signs (blood pressure, respiratory rate, heart rate, and temperature)
- Urine sample for urine pregnancy test in females of childbearing potential
- MSWS-12, T25FW, TUG, and 2MWT assessments (Full details on how individual efficacy assessments are to be performed will be provided in the study manual. These assessments are to be done in this order.)
- C-SSRS
- Collect used/unused bottles and evaluate compliance
- Dispense study drug (3 bottles)

12.5. Visit at Week 24

- Assess and record concomitant medications
- Assess and record AEs
- Symptom-directed physical examination, as needed
- Vital signs (blood pressure, respiratory rate, heart rate, and temperature)
- Urine sample for urine pregnancy test in females of childbearing potential
- MSWS-12, T25FW, TUG, and 2MWT assessments (Full details on how individual efficacy assessments are to be performed will be provided in the study manual. These assessments are to be done in this order.)
- C-SSRS
- Collect used/unused bottles and evaluate compliance
- Dispense study drug (7 bottles)

12.6. Telephone Visit at Week 38

- Assess and record any changes in concomitant medications
- Assess and record AEs

12.7. Visit at Week 52

- Assess and record concomitant medications
- Assess and record AEs
- Complete physical examination
- Obtain subject weight in kilograms
- Vital signs (blood pressure, respiratory rate, heart rate, and temperature)
- Blood sample for central laboratory analysis including hematology, serum chemistry, and eGFR
- Urinalysis
- Blood sample for serum pregnancy test in female subjects of childbearing potential
- Administer the EDSS (administration instructions and forms will be provided separately)
- MSWS-12, T25FW, TUG, and 2MWT assessments (Full details on how individual efficacy assessments are to be performed will be provided in the study manual. These assessments are to be done in this order.)
- C-SSRS
- Collect bottles and evaluate compliance

12.8. Early Termination Visit

- Assess and record concomitant medications
- Assess and record AEs
- Complete physical examination
- Obtain subject weight in kilograms
- Vital signs (blood pressure, respiratory rate, heart rate, and temperature)
- Blood sample for central laboratory analysis including hematology, serum chemistry, and eGFR
- Urinalysis
- Blood sample for serum pregnancy test in female subjects of childbearing potential
- MSWS-12, T25FW, TUG, and 2MWT assessments (Full details on how individual efficacy assessments are to be performed will be provided in the study manual. These assessments are to be done in this order.)
- C-SSRS
- Collect bottles and evaluate compliance
- Completion of Early Termination Visit CRF, including reason for early discontinuation. (If early termination is due to AE, then a brief narrative of the AE will be recorded in the allocated section of the Early Termination Visit CRF)

12.9. Safety Follow-Up/End of Study Visit

Subjects will return to the clinic 2 weeks after their Week 52 visit (Week 54), ie, after being off treatment for approximately 2 weeks and the following will be performed:

- Assess and record concomitant medications
- Assess and record AEs
- Symptom-directed physical examination, as needed
- Vital signs (blood pressure, respiratory rate, heart rate, and temperature)
- A blood sample for a serum pregnancy test will be collected for females of childbearing potential
- MSWS-12, T25FW, TUG, and 2MWT assessments (Full details on how individual efficacy assessments are to be performed will be provided in the study manual. These assessments are to be done in this order.)
- C-SSRS

12.10. Unscheduled Study Visit

- Assess and record concomitant medications
- Assess and record AEs
- Symptom-directed physical examination, as needed
- Vital signs (blood pressure, respiratory rate, heart rate, and temperature)

13. ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, AND ADVERSE EVENTS OF SPECIAL INTEREST

During the study, the investigator or study site personnel will be responsible for querying and recording adverse events (AEs) and serious adverse events (SAEs), as detailed in this section of the protocol. In this study AEs and SAEs will be reported from the time of study drug administration until the last study visit or death, or whichever occurs first.

13.1. Definition of Adverse Events

An adverse event (AE) is any untoward medical occurrence, including the deterioration of a pre-existing medical condition, that occurs in conjunction with the use of a medicinal product in humans, whether or not considered to have a causal relationship to the medicinal product. An AE can, therefore, be any unfavorable or unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

In clinical studies, the temporal association of an AE with the use of a medicinal product, study drug, may be difficult to ascertain; an AE can include an untoward medical occurrence happening at any time, including baseline or washout periods, even if no study treatment has been administered.

13.1.1. Adverse Event (AE) Definition

Any medical condition or clinically significant laboratory abnormality with an onset date before the first date of study drug administration is usually considered to be pre-existing, and should not be documented in the CRF as an AE.

An AE **does** include:

- an exacerbation of a pre-existing illness;
- an increase in frequency or intensity of a pre-existing episodic event or condition;
- a condition detected or diagnosed after study drug administration even though it may have been present prior to the start of the study;
- persistent disease or symptoms present at baseline which worsen following the start of the study.

An AE **does not** include:

- medical or surgical procedures (eg, surgery, endoscopy, tooth extraction, transfusion) Note: in this case, the condition that led to the procedure is an AE;
- pre-existing diseases or conditions present or detected prior to start of study drug administration, which do not worsen;
- the disease or disorder being studied or a sign or symptom associated with that disease (ie, signs or symptoms associated with lack of efficacy will generally be considered to reflect underlying disease, rather than AEs, and are considered anticipated);
  - In this study, walking ability is an efficacy parameter and changes in this measure (both positive and negative) will be reported as efficacy outcomes. Worsening of other MS-associated parameters should be reported as AEs
- situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, elective abortion, social, and/or convenience admissions);
- overdose of either study drug or concomitant medication without any signs or symptoms. (Dosing details will be recorded on the appropriate eCRF(s)).
- pregnancy - Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication (see Section 13.3.3).

All AEs must be fully and completely documented on the AE page of the CRF and in the subject's medical notes. The following attributes must be assigned: description of AE, dates and times of onset and resolution (or whether ongoing), severity (Section 13.1.6), relationship to study drug (Section 13.1.7), whether an SAE or not (Section 13.1.2, and action taken (ie, no action taken; study drug interrupted; study drug discontinued; other).

In the event that a subject is withdrawn from the study because of an AE, it must be recorded on the CRF. The subject should be followed and treated by the investigator until the AE has resolved or a new chronic baseline has been established.

The investigator must report all directly observed AEs and all spontaneously reported AEs. At each visit the investigator will ask the subject a nonspecific question (eg, "Have you noticed anything different since your last visit?") to assess whether any AEs have occurred since the last report or visit. AEs will be identified and documented on the AE page of the CRF in appropriate medical terminology.

13.1.2. Serious Adverse Event (SAE) Definition

A **serious adverse event** (SAE) is any AE occurring during any study phase (ie, baseline, treatment, washout, or follow-up), and at any dose of the investigational product, or placebo, that fulfils one or more of the following:

- results in death;
- is life-threatening (subject is at immediate risk of death at the time of the event);

- requires inpatient hospitalization or results in prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect in the offspring of a subject who received study drug;
- is a significant or important medical event, ie, an event that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the above-mentioned criteria (examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse).

When a causality assessment is provided for an SAE, it is important to include a rationale for the assessment so that a better understanding of the reported event can be compiled. The rationale should be accompanied by all available supporting evidence, including relevant laboratory tests, histopathology evaluations, and the results of other diagnostic procedures. The investigator's rationale with supporting evidence is valuable when the sponsor performs a cumulative analysis of similar events.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs.

13.1.2.1. Clarification of SAE Definition

"Occurring at any dose" does not imply that the subject is receiving study drug at the time of the event. Dosing may have been interrupted temporarily prior to the onset of the SAE, but may have contributed to the event.

"Life-threatening" means that the subject was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death, had it occurred with greater severity.

Complications that occur during hospitalizations are AEs. If a complication prolongs hospitalization, it is an SAE.

"Inpatient hospitalization" does not imply that the subject must have had an overnight stay in the hospital. If the subject was admitted to the hospital for less than a day for the purpose of treatment or observation, the definition of "inpatient hospitalization" is met. Brief treatment in an outpatient clinic or Emergency department does not constitute "inpatient hospitalization."

The term "severe" is often used to describe the intensity (severity) of a specific event (see Section 13.1.6); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

An SAE is considered "unexpected" if it is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed. It is the responsibility of the sponsor to make this determination.

13.1.2.2. Clarification of Subject Deaths

All subject deaths (regardless of relationship to study drug) should be reported within 24 hours for subjects while on study protocol up to and including the safety follow-up visit. This should be recorded on the subject CRF and the SAE form.

Death is an outcome of an AE and not an AE in itself. All reports of subject death should include an AE term for the cause of the death unless the protocol provides other specific instructions (eg, mortality related to underlying disease is an efficacy endpoint). For all reports in which an AE term is not provided (other than "Death"), follow-up for the cause of death will be required. Only in the rare occurrence that no verbatim description of an AE can be obtained from the investigative site, then "Death – Unknown Cause" will be used as the event term.

13.1.3. Adverse Event of Special Interest (AESI)

There are two AEs of special interest (AESIs) in this study:

- Hallucinations (including visual, auditory, or other sensory modality)
- Suicidality (including suicidal ideation and attempted suicide)

For either AESI, a specific AESI CRF page will be filled out at the time the investigator becomes aware of the event, including a brief narrative summary of the event.

Additional AESIs may also be identified by the Medical Monitor. Significant AEs of particular clinical importance, other than SAEs, AESIs pre-specified above, and those AEs leading to discontinuation of a subject from the study, may also be classified at or by study's end as AESIs. For each such AESI, additional information may be requested from the investigator so that a brief narrative of the event may be written and included in the Clinical Study Report.

13.1.4. Assessment of Adverse Events

The investigator should attempt to establish a diagnosis of the event based on the signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the AE (and SAE if serious) and not the individual signs/symptoms.

13.1.5. Type of Adverse Events (AE, SAE, or AESI)

An investigator must make the determination as to whether an AE qualifies as an SAE or an AESI.

13.1.6. Severity of Adverse Events

The severity of each AE/SAE should be classified into one of three defined categories as follows:

- **Mild:** there is awareness of a sign or symptom, but the AE is easily tolerated by the subject, causes minimal discomfort, and does not interfere in a significant manner with the subject's normal functioning level or activities;
- **Moderate:** the AE is sufficiently uncomfortable to interfere with normal everyday activities, but is not hazardous to health;

- **Severe:** the AE produces significant impairment of functioning or incapacitation, with inability to perform normal activities, and is a definite hazard to the subject's health.

These three categories are based on the investigator's clinical judgment, which in turn depends on consideration of various factors such as the subject's reports, the physician's observations, and the physician's prior experience. The severity of the AE should be recorded in the appropriate section on the AE page of the CRF.

The evaluation of severity must be distinguished from the evaluation of "seriousness"; severity is a measure of intensity whereas seriousness is defined by the criteria under Section 13.1.6. A severe event might not meet the criteria for seriousness and a serious event might be evaluated as mild or moderate. For example, a subject might have a **severe** headache that does not require hospitalization and is consequently **not serious**; or a subject might have a **mild** myocardial infarction that requires hospitalization and is therefore **serious**. It is important to distinguish between serious and severe AEs.

13.1.7. Relationship to Study Drug

An investigator must make the determination of relationship to the investigational product for each AE. The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the AE should be classified as "not related." If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related."

The relationship or association of the AE/SAE to study drug will be characterized as "**related**" or "**not related**". An AE/SAE will be considered to be **not related** to the use of the study drug if any of the following criteria are met:

- An unreasonable temporal relationship between administration of the product and the onset on the AE (eg, the event occurred either before, or too long after administration of the product for it to be considered product-related);
- A causal relationship between the product and the AE is biologically implausible (eg, death as a passenger in an automobile accident);
- A clearly more likely alternative explanation for the AE is present (eg, typical adverse reaction to a concomitant drug).

Adverse events will be considered "**related**" to the use of the study drug if none of the "**not related**" criteria are met.

The investigator will use clinical judgment to determine the relationship of the AE/SAE to study drug. An AE/SAE may be related to the study drug, other concomitant medications, intercurrent illness, a procedure performed in the course of the study, or another reason. Among the potential etiologies, the investigator should make a determination based on the most likely causal relationship. Alternative causes, such as the natural history of any underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study

drug should be considered. The investigator will also take into account the Investigator's Brochure (or Prescribing Information, if applicable) in the causality assessment.

There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always makes an assessment of causality prior to transmission of the SAE report to the sponsor, as the causality assessment is one of the criteria used when determining regulatory reporting requirements. The investigator may change the causality assessment in light of follow-up information, by amending the SAE report accordingly.

13.1.8. Follow-up of Adverse Events and Serious Adverse Events

All AEs and SAEs must be followed until resolution (or return to baseline status), or until the condition stabilizes or is otherwise explained, or until the subject dies or is lost to follow-up. The investigator is responsible for ensuring that follow-up includes any supplemental investigations as may be indicated to elucidate as completely as practical the nature and/or causality of the AE/SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

The sponsor may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations. If a subject dies during participation in the study or during a recognized follow-up period, the investigator should provide the sponsor with a copy of any post-mortem findings, including histopathology.

13.2. Recording Adverse Events

13.2.1. Adverse Event Recording

Adverse events spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site. Any AE (ie, a new event or an exacerbation of a pre-existing condition) with an onset date after start of study drug administration up to and including the designated follow-up safety visit should be recorded as an AE on the CRF.

Information about all AEs, including SAEs, that occur after a subject has been enrolled and completed Study ADS-AMT-MS301, whether before treatment, during treatment, or within 14 days following the cessation of treatment must be recorded. AEs occurring after a subject has begun study drug (ADS-5102) in Study ADS-AMT-MS303 are designated as treatment-emergent adverse events (TEAEs) to distinguish these from AEs occurring after enrollment and completion of Study ADS-AMT-MS301 but before treatment in Study ADS-AMT-MS303.

All AEs must be recorded on the AE CRF regardless of the severity or relationship to study drug. It is important that investigators also report all AEs that result in permanent discontinuation of the study drug being studied, whether serious or non-serious.

Out of range clinical laboratory findings (eg, clinical chemistry, hematology) or findings on other assessments (eg, electrocardiogram, X-rays, vital signs) per se are not reported as AEs. However, if the out of range finding is deemed clinically significant or is associated with signs and/or symptoms, the finding must be recorded as an AE (and additionally as an SAE if it meets the criteria of being serious; see Section 13.1.2), as described above.

The investigator should exercise medical and scientific judgment in deciding whether an out of range clinical laboratory finding or finding on other assessment is clinically significant. Usually, the abnormality should be associated with a clinically evident sign or symptom, or be likely to result in an evident sign or symptom in the near term, in order to be considered clinically significant. A clinically significant laboratory abnormality in the absence of clinical symptoms may jeopardize the subject and may require intervention to prevent immediate consequences. For example, a markedly low serum glucose concentration may not be accompanied by coma or convulsions, yet be of a magnitude to require glucose administration to prevent such sequelae.

For each AE, the investigator will evaluate and report the onset (date and time), resolution (date and time), intensity, causality, action taken, serious outcome (if applicable), and whether or not it caused the subject to discontinue the study.

Pregnancy is not an AE; should a pregnancy occur, it must be recorded on a separate pregnancy form and reported as detailed below (see Section 13.3.3).

13.2.2. Serious Adverse Event Recording

If an AE is determined to be an SAE, in addition to recording the appropriate information on the AE CRF page, the information will also be recorded on an SAE CRF page. Additionally, the basis for determining an AE to be an SAE will be recorded on the SAE CRF. A brief narrative of the SAE must be provided in the allocated section of the SAE CRF page. Follow-up information regarding the SAE, as it becomes available, will also be recorded on the SAE CRF page(s).

13.2.3. Adverse Event of Special Interest Recording

If an AE is determined to be an AESI, in addition to recording the appropriate information on the AE CRF page, the information will also be recorded on the appropriate AESI CRF page. Specific questions pertaining to the AESI will be answered on the AESI CRF page. A brief narrative of the AESI must be provided in the allocated section of the AESI CRF page. Follow-up information regarding the AESI, as it becomes available, will also be recorded on the AESI CRF page(s).

13.3. Reporting Adverse Events

The sponsor has requirements for reporting SAEs to both the local regulatory authority and other regulatory agencies regarding the safety of a drug under clinical investigation. The sponsor or designee must be notified within 24 hours once the investigator determines that an AE meets the protocol definition of an SAE. The procedures for reporting serious adverse events are as follows:

- Complete the “Serious Adverse Event Report”;
- Contact the pharmacovigilance staff member identified on the SAE Report Form and report the Serious Adverse Event within 24 hours of the investigator’s knowledge of the event;
- For fatal or life-threatening events, also fax copies of hospital case reports, autopsy reports, and other documents when requested and applicable.

The investigator must verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and complete, sign and date the SAE pages.

The sponsor or designee may request additional information from the investigator to ensure the timely completion of accurate safety reports.

Any fatal or life-threatening events should also be reported immediately by telephone to the sponsor's designee.

The investigator, or responsible person according to local requirements, must comply with the applicable local regulatory requirements concerning the reporting of SAEs to all applicable regulatory authorities and IRBs. Investigators will also be notified of all unexpected, serious, drug-related events (7/15 Day Safety Reports) that occur during the clinical trial. Each site is responsible for notifying its IRB or IEC of these additional SAEs.

13.3.1. Investigator Reporting Requirements

When an investigative site receives an initial or follow-up notification of an SAE or other safety information (eg, revised Investigator's Brochure) from the sponsor, the responsible person, according to local requirements, must submit this information to the local IRB and keep a copy in their files.

13.3.2. Post-Study Reporting Responsibility

All SAEs, regardless of cause or relationship, which occur from the time of study drug administration up to and including the safety follow-up visit, must be reported to the sponsor or designee. If the investigator learns at any time after a subject has been discharged from the study of an untoward medical occurrence that would have qualified as an SAE during the study, and such event is reasonably related to previous study drug exposure, the investigator should promptly notify the sponsor or designee.

13.3.3. Pregnancy

A pregnancy is not an AE. If a subject becomes pregnant while enrolled in the study following administration of study drug, the sponsor or designee must be notified within 24 hours of the investigator learning of the pregnancy. Administration of study drug will be discontinued immediately and the subject will be followed through the outcome of the pregnancy. The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study. If pregnancy occurs in a female partner of a male subject, they will be asked to be consented to obtain additional information regarding the pregnancy. The investigator will be required to complete a Pregnancy Information Form and fax the information to the sponsor or designee.

14. STATISTICS

14.1. Sample Size Determination

This is an open-label, single-arm safety and efficacy study. Subjects completing Study ADS-AMT-MS301 (up to approximately 540 subjects) will be eligible for enrollment.

14.2. Analysis Sets

The safety analysis set will include all subjects who receive at least one dose of study drug in study ADS-AMT-MS303 according to the treatment sequence (see Section 14.5) actually received.

The modified intent-to-treat (MITT) analysis set will include all subjects enrolled in the study who received at least one dose of study drug in study ADS-AMT-MS303 according to the randomized treatment sequence. It is understood that randomization here refers to the randomized assignment in study ADS-AMT-MS301.

The per-protocol (PP) analysis set will include all randomized and dosed subjects who provide Week 52 efficacy data and do not have any major protocol deviations that could confound this assessment.

14.3. Handling of Missing Data

This will be described in the statistical analysis plan.

14.4. Efficacy Endpoints

Endpoints will be derived using the Week 0 assessments as the baseline value. These endpoints will consist of the changes from Baseline/Week 0 at Weeks 12, 24, and 52 in the:

- T25FW (ft/sec) and also T25FW (sec)
- TUG (sec)
- 2MWT
- MSWS-12
- The proportion of Novel Responders at each study visit, where a Novel Responder is defined as a subject who has a ≥ 20% increase from Baseline/Week 0 to the study visit in walking speed measured using the T25FW. Subjects who fail to have an increase of at least 20% at the given study visit in the T25FW (ft/sec) (non-responders) or who discontinue the study prior to this visit will be included in the denominators.

14.5. Efficacy Analyses

All efficacy analyses will be based on the MITT, as well as the PP analyses set.

Endpoints will be summarized by treatment sequence depending on the treatment received in Study ADS-AMT-MS301:

Sequence No.	Study ADS-AMT-MS301 Treatment	Study ADS-AMT-MS303 Treatment
1	Placebo	274 mg/d ADS-5102
2	137 mg/d ADS-5102	274 mg/d ADS-5102
3	274 mg/d ADS-5102	274 mg/d ADS-5102

Efficacy results will be analyzed by treatment sequences 1, 2, and 3 shown above and also by sequences 2 and 3 combined (ie, treatment sequence 1 versus 2 and 3 combined). Descriptive statistics (ie, mean, standard error, median, minimum/maximum, 95% confidence intervals [CI] for the changes from baseline) for each parameter at each study visit will be generated. Missing data will not be imputed. Graphical depictions of changes over time will be provided.

The proportion of Novel Responders in walking speed for each treatment sequence as well as pooled sequences 2 and 3 will also be characterized. The counts and percentages of Novel Responders, Non-Responders, and discontinuations at each study visit will be presented.

For parameters measured on a continuum (eg, MSWS-12, T25FW (ft/sec)), the treatment-sequence time trend will be explored using an MMRM model with the change from baseline as the dependent variable, fixed effects of treatment-sequence, study visit (ie week 12, 24 and 52), treatment-sequence by study visit interaction, baseline value as a covariate and an unstructured variance-covariance matrix for the within-subject residual variability. Appropriate contrasts comparing time trends between treatment-sequences will be derived from this model. For the proportion responders, a GEE (generalized estimating equation) model for a binomial variate will be used.

Details of all analyses will be provided in the statistical analysis plan (SAP) for this study.

14.6. Safety and Tolerability Analyses

All safety analyses will be based on the Safety analysis set. Adverse events in Study ADS-AMT-MS303 will be recorded starting immediately following completion of the last study procedure for Study ADS-AMT-MS301 at a Week 16 Visit for that study (which also the serves as the first visit for Study ADS-AMT-MS303). All AEs will be listed by subject and period of onset: pre-dose and TEAEs.

The incidence of TEAEs will be summarized by treatment sequences 1, 2, and 3, and overall for all subjects. The incidence of the following will be presented by system organ class (SOC) and preferred term (PT) within SOC in the safety analysis set.

- TEAEs
- Investigator-determined treatment-related TEAEs
- TEAEs leading to drug discontinuation
- TEAEs by severity

- Serious TEAEs (STEAEs)
- Investigator-determined treatment-related STEAEs
- Discontinuation due to STEAEs

Clinical laboratory test parameters will be listed for individual subjects and values outside of the reference ranges will be flagged. The incidence of potentially clinically significant changes in laboratory parameters at each study visit will be tabulated. Vital signs measurements at each timepoint will be listed by subject. The incidence of potentially clinically significant changes at each study visit will be summarized.

Descriptive statistics for the mean and mean changes in the C-SSRS will be generated by study visit. Results will also be graphically depicted.

Descriptive statistics for the mean and mean change from ADS-AMT-MS301 Screening value in the EDSS will be generated.

14.7. Demographics and Baseline Characteristics

Demographic and baseline characteristics (age at Week 0, gender, weight, height, BMI, race, ethnicity, medical history, physical examination) will be listed for individual subjects and will be summarized. Demographic data and key baseline characteristics will be summarized for the MITT and safety populations.

14.8. Prior and Concomitant Medications

All prior and concomitant medications will be assigned a generic name and a drug class based on the World Health Organization (WHO) Dictionary. Prior and concomitant medications will be listed and summarized.

14.9. Completion of the Study and Withdrawals

Withdrawals and the reason for withdrawal will be tabulated. The number and percentage of subjects who complete the study will be summarized. The number and percentage of subjects who withdraw from the study will be tabulated by treatment sequence. Study drug discontinuations will be summarized in a similar fashion.

14.10. Protocol Deviations

Significant protocol deviations will be listed and categorized (for example, deviations related to entry criteria, dosing, prohibited concomitant medications, other).

15. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

15.1. Study Monitoring

Sponsor representatives and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the study (eg, CRFs and other pertinent data), provided that subject confidentiality is respected.

The study monitor is responsible for inspecting the CRFs at regular intervals throughout the study to verify the following: adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The monitor should have access to subject medical records and other study-related records needed to verify the entries on the CRFs. The investigator must agree to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

15.2. Audits and Inspections

Authorized representatives of the sponsor, a regulatory authority, an Independent Ethics Committee, or an Institutional Review Board may visit the site to perform audits or inspections, including source data verification. The purpose of the sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP) guidelines of the International Council on Harmonization (ICH), and any applicable regulatory requirements.

In accordance with ICH GCP and the sponsor audit plans, this study may be selected for an audit. Inspection of all site facilities (eg, pharmacy, drug storage areas, laboratories) and study-related records contained within these facilities are subject to inspection during an audit.

The investigator should contact the sponsor immediately if contacted by a regulatory agency about an inspection.

15.3. Subject Confidentiality

The investigator must ensure that each subject's anonymity is maintained. Subjects will be identified by a unique Subject Identification Number. Study related documents should be kept in strict confidence by the investigator in compliance with applicable regulations and ICH GCP Guidelines. The investigator and Institution must permit authorized representatives of regulatory agencies, and the IRB/research ethics board (REB)/independent ethics committee (IEC) direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are needed for the evaluation of the study. The investigator is obligated to inform the subject in the ICF that the above-named representatives may review study-related records from subjects.

15.4. Case Report Forms

Electronic CRFs will be completed for each enrolled subject. The participants of the study will not be identified by name on any study documents to be collected by the sponsor or designee.

The PI is required to review and sign-off on all eCRFs. The sign-off is done by an electronic signature within the electronic data capture system (EDC). Also, a CD of all site specific subject data (including PI approval, audit history, and discrepancies) will be sent to each site that has subject data in the system for archival purposes.

16. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, the sponsor may conduct a quality assurance audit. Please see Section 15.2 for more details regarding the audit process.

17. ETHICS

17.1. Ethics Review

The PI must obtain IRB/REB/IEC approval for the investigation. Initial IRB/REB/IEC approval, and all materials approved by the IRB/REB/IEC for this study including the ICF and recruitment materials must be maintained by the investigator and made available for inspection.

This study will be conducted in accordance with the US Code of Federal Regulations (CFR) governing the protection of human subjects (21 CFR 50), IRB/REB/IEC (21 CFR 56), the obligations of clinical investigators (21 CFR 312), and ICH GCP guidelines.

The sponsor expects the PI to comply with local IRB/REB/IEC requirements. The investigator will also comply with current standards of GCP, particularly in reference to the safety and rights of the subjects. Investigators are encouraged to discuss any ethical issues that arise prior to or during the conduct of the study with the sponsor.

The PI at the site is responsible for obtaining IRB/REB/IEC approval for the final protocol, sponsor-approved ICF, and any advertisements to recruit subjects. Written approval of these documents must be obtained from the IRB/REB/IEC before any subject is enrolled at a site.

The PI is also responsible for the following interactions with the IRB/REB/IEC:

- Obtaining IRB approval for any protocol amendments and ICF revisions before implementing the changes;
- Providing the IRB/REB/IEC with any required information before or during the study;
- Submitting progress reports to the IRB/REB/IEC, as required, during the conduct of the study; requesting re-review and approval of the study, as needed; providing copies of all IRB/REB/IEC re-approvals and relevant communication to the sponsor;
- Notifying the IRB/REB/IEC of all serious and unexpected adverse events related to the study drug reported by the sponsor, as required.

17.2. Ethical Conduct of the Study

This study will be conducted in compliance with GCP according to the ICH guidelines (Topic E6: Guideline for Good Clinical Practice), US Code of Federal Regulations (21 CFR), and local ethical and legal requirements that are consistent with the most current version of the Declaration of Helsinki.

17.3. Written Informed Consent

The sponsor must review the draft ICF prior to submission to the IRB/REB/IEC for approval. An IRB/REB/IEC -approved copy of the ICF will be forwarded to the sponsor or designee.

Written informed consent will be obtained from all study subjects prior to any tests or evaluations. The contents and process of obtaining informed consent will be in accordance with all applicable regulatory requirements.

The ICF documents the study-specific information the investigator provides to the subject and the subject's agreement to participate. Among other things, the investigator or designee will fully explain in layman's terms the nature of the study, along with the aims, methods, potential risks, and any discomfort that participation may entail, as well as insurance and other procedures for compensation in case of injury. It will be explained that the study is for research purposes only and may not provide any therapeutic benefit to the individual. The investigator must also explain to the volunteers that they are completely free to refuse to enter the study or to withdraw from it at any time without prejudice. Each subject will acknowledge receipt of this information by giving written informed consent for participation in the study.

Each subject must sign and date the ICF before any study-related procedures are performed. When a protocol amendment (see Section 17.4) substantially alters the study design or the potential risks or burden to subjects, the ICF will be amended and approved by the IRB/REB/IEC, and all active subjects will again provide informed consent. The original and any amended signed and dated ICF(s) must be retained in the subject's file at the study site and a copy must be given to the subject.

The ICF must comply with all applicable US Code of Federal Regulations (21 CFR 50), and ICH Good Clinical Practice guidelines. It should also include any additional information required by local laws relating to institutional review. A statement that subject medical records must be available for investigations into SAEs must be included in the ICF. It should also include any additional information required by local laws relating to institutional review.

17.4. Changes in the Conduct of the Study or Planned Analyses

Only the sponsor may modify the protocol. Any change in study conduct considered necessary by the investigator will be made only after consultation with the sponsor, who will then issue a formal protocol amendment to implement the change. The only exception is when the investigator considers that a subject's safety is compromised without immediate action. The investigator should inform the sponsor and the IRB/REB/IEC within one working day after the emergency occurred. With the exception of minor administrative or typographical changes, all amendments must be reviewed and approved by the IRB/REB/IEC in accordance with IRB/REB/IEC requirements. Amendments that have an impact on subject risk or the study objectives, or require revision of the ICF, must receive approval from the IRB/REB/IEC prior to their implementation. The investigator must send a copy of the approval letter for protocol amendments and changes to the ICF from the IRB/REB/IEC to the sponsor.

17.5. Emergency Contact with Investigator

Suitable arrangements will be made for subjects to make contact with the PI or a medically qualified sub-investigator in the event of an emergency during the study.

18. DATA HANDLING AND RECORDKEEPING

The investigator must make study data accessible to the monitor, other authorized representatives of the sponsor, and Regulatory Agency inspectors upon request. A file for each subject must be maintained that includes the signed ICF and the investigator's copies of all source documentation related to that subject. The investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived.

Investigators are required to maintain all study documentation, including copies of CRFs, ICFs, and adequate records for the receipt and disposition of all study drugs, for a period of 2 years following the FDA or other regulatory approval date of the drug, or until 2 years after the drug investigational program is discontinued, unless a longer period is required by applicable law or regulation. The investigator must not discard any records unless given authorization by the sponsor.

Subject identity information will be maintained for 15 years unless applicable law or regulation requires a longer period.

18.1. Inspection of Records

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

18.2. Retention of Records

The PI must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval (or for the duration specified by the IRB/REB/IEC or local Regulatory Authority, whichever is longer), or if not approved 2 years following the discontinuance of the test article for investigation (or for the duration specified by the IRB/REB/IEC or local Regulatory Authority, whichever is longer). If it becomes necessary for Adamas or the Regulatory Authority to review any documentation relating to the study, the investigator must permit access to such records. In the event that an investigator becomes unable to comply with the storage/maintenance of documentation, he/she must notify the Sponsor immediately, so that arrangements to store the records appropriately elsewhere can be made.

19. INFORMATION DISCLOSURE AND INVENTIONS

19.1. Ownership

All information provided by Adamas Pharmaceuticals, Inc. and all data and information generated by the site as part of the study (other than a subject's medical records) are the sole property of Adamas Pharmaceuticals, Inc.

All rights, title and interests in any inventions, know-how or other intellectual or industrial property rights that are conceived or reduced to practice by site staff during the course of or as a result of the study are the sole property of Adamas Pharmaceuticals, Inc. and are hereby assigned to Adamas Pharmaceuticals, Inc.

If a written contract for the conduct of the study is executed between Adamas Pharmaceuticals, Inc. and a study site and includes ownership provisions that are inconsistent with this section of the protocol that contract's ownership provisions shall apply rather than this statement.

19.2. Confidentiality

All information provided by Adamas Pharmaceuticals, Inc. and all data and information generated by the site as part of the study, other than a subject's medical records, will be kept confidential by the investigator and other site staff. The investigator or other site personnel will not use this information and data for any purpose other than conducting the study. These restrictions do not apply to:

- Information that becomes publicly available through no fault of the investigator or site staff
- Information that it is necessary to disclose in confidence to an IRB solely for the evaluation of the study
- Information that it is necessary to disclose to provide appropriate medical care to a study subject
- Study results that may be published as described in Section 20.

If a written contract for the conduct of the study that includes confidentiality provisions inconsistent with this statement is executed, that contract's confidentiality provisions shall apply rather than this statement.

20. PUBLICATION POLICY

Adamas intends to work with its investigators to rapidly publish the results of this study. No publication of the results shall take place without Adamas Pharmaceuticals, Inc.'s express consent. Prior to submitting for any publication, presentation, use for instructional purposes, or otherwise disclosing the study results generated by the site (collectively, a "Publication"), the investigator shall provide Adamas Pharmaceuticals, Inc. with a copy of the proposed Publication and allow Adamas Pharmaceuticals, Inc. a period of at least thirty (30) days (or for abstracts, at least five [5] working days) to review the proposed Publication. Proposed publications shall not include Adamas Pharmaceuticals, Inc.'s confidential information.

At Adamas Pharmaceuticals, Inc.'s request, the submission or other disclosure of a proposed Publication will be delayed a sufficient time to allow Adamas Pharmaceuticals, Inc. to seek patent or similar protection of any inventions, know how, or other intellectual or industrial property rights disclosed in the proposed Publication.

21. LIST OF REFERENCES

Albuquerque E, Eldefrawi A, Eldefrawi M, Mansour N, Cheng-Ming T. Amantadine: neuromuscular blockade by suppression of ionic conductance of the acetylcholine receptor. *Science.* 1978; 199(4330): 788-790.

Ampyra [package insert]. Ardsley, NY: Acorda Therapeutics, Inc.; 2017.

Aoki F, Sitar D. Clinical pharmacokinetics of amantadine hydrochloride. *ClinPharmacokinet.* 1988; 14(1): 35-51.

Ashtari F, Fatehi F, Shaygannejad V, Chitsaz A. Does amantadine have favourable effects on fatigue in Persian patients suffering from multiple sclerosis? *Neurol Neurochir Pol*. 2009; 43(5): 428-432.

Berger JR. Functional improvement and symptom management in multiple sclerosis: clinical efficacy of current therapies. *Am J Manag Care*. 2011;17 Suppl 5 Improving: S146-S153.

Bresink I, Danysz W, Parsons CG, Mutschler E. Different binding affinities of NMDA receptor channel blockers in various brain regions-indication of NMDA receptor heterogeneity. *Neuropharmacology*. 1995; 34(5): 533-540.

Canadian MS Research Group. A randomized controlled trial of amantadine in fatigue associated with Multiple Sclerosis. *Can J Neurol Sci*. 1987;14(3): 273-278.

Chiba S, Ito M, Matsumoto H. Amantadine treatment for refractory pain and fatigue in patients with multiple sclerosis. *Can J Neurol Sci*. 1992; 19(2): 309.

Cohen JA et al, Safety and Efficacy of ADS-5102 (amantadine) extended release capsules to improve walking in multiple sclerosis: A randomized phase 2 trial. *Multiple Sclerosis Journal*, 2018.

Danysz W, Parsons C, Kornhuber J, Schmidt W, Quack G. Aminoadamantanes as NMDA receptor antagonists and antiparkinsonian agents- preclinical studies. *Neurosci Biobehav Rev.* 1997; 21(4): 455-468.

Dilokthornsakul P, Valuck RJ, Nair KV, Corboy JR, Allen RR, Campbell JD. Multiple sclerosis prevalence in the United States commercially insured population. *Neurology*. 2016; 86(11): 1014-21.

Goodman AD, Brown TR, Edwards KR, Krupp LB, Schapiro RT, Cohen R, Marinucci LN, Blight AR; MSF204 Investigators. A phase 3 trial of extended release oral dalfampridine in multiple sclerosis. *Ann Neurol*. 2010; 68(4): 494-502.

Goodman AD, Brown TR, Krupp LB, Schapiro RT, Schwid SR, Cohen R, Marinucci LN, Blight AR, Fampridine MS-F203 Investigators. Sustained-release oral fampridine in multiple sclerosis: a randomised, double-blind, controlled trial. *Lancet*. 2009; 373: 732-738.

Hayden F, Gwaltney J, Van De Castle R, Adams K, Giordani B. Comparative toxicity of amantadine hydrochloride and rimantadine hydrochloride in healthy adults. *Antimicrob Agents Chemother.* 1981; 19(2): 226-233.

Hobart J, Ziemssen T, Feys P, et al. Prolonged-release fampridine induces sustained clinically meaningful improvements in walking ability in people with multiple sclerosis: results from the ENHANCE trial (P6.364). *Neurology*. 2017; 88.

Jackson G, Stanley E, Lee Muldoon R. Chemoprophylaxis of viral respiratory diseases. *Bulletin Pan Am Health Org*. 1967; 147: 595-603.

Kantarci O, Wingerchuk D. Epidemiology and natural history of multiple sclerosis: new insights. *Curr Opin Neurol*. 2006; 19(3): 248-254.

Kornhuber J, Bormann J, Hubers M, Rusche K, Riederer P. Effects of the 1-amino-adamantanes at the MK-801-binding site of the NMDA-receptor-gated ion channel: a human postmortem brain study. *Eur J Pharmacol*. 1991; 206: 297-300.

Korsen M, Kunz R, Schminke U, Runge U, Kohlmann T, Dressel A. Dalfampridine effects on cognition, fatigue, and dexterity. *Brain Behav*. 2016; 7(1): e00559.

Krupp LB, Coyle PK, Doscher C, Miller A, Cross AH, Jandorf L, Halper J, Johnson B, Morgante L, Grimson R. Fatigue therapy in multiple sclerosis: results of a double-blind, randomized, parallel trial of amantadine, pemoline, and placebo. *Neurology*. 1995; 45(11): 1956-1961.

McEvoy JP, McCue M, Spring B, Mohs RC, Lavori PW, Farr RM. Effects of amantadine and trihexyphenidyl on memory in elderly normal volunteers. Am J Psychiatry. 1987 May;144(5):573-7.

Murray TJ. Amantadine therapy for fatigue in multiple sclerosis. Can J Neurol Sci. 1985 Aug;12(3):251-4. PubMed PMID: 3902184.

Northover BJ. Effect of pre-treating rat atria with potassium channel blocking drugs on the electrical and mechanical responses to phenylephrine. *Biochem Pharmacol*. 1994; 47(12): 2163-2169.

Ossola B, Schendzielorz N, Chen S, Bird G, Ruominen R, Mannisto P, Hong J. Amantadine protects dopanine neurons by a dual action: reducing activation of microglia and inducing expression of GNDF in astroglia. *Neurology.* 2011; 61: 574-582.

Pahwa R, Tanner CM, Hauser RA, Isaacson SH, Nausieda PA, Truong DD, Agarwal P, Hull KL, Lyons KE, Johnson R, Stempien MJ. ADS-5102 (amantadine) extended-release capsules for levodopa-induced dyskinesia in Parkinson disease (EASE LID Study): a randomized clinical trial. *JAMA Neurol*. 2017; 74(8): 941-949.

Pahwa R, Tanner CT, Hauser RA, Sethi K, Isaacson S, Truong D, Struck L, Ruby AE, McClure NL, Went GT, Stempien MJ. Amantadine extended release for levodopa-induced dyskinesia in Parkinson's disease (EASED Study). *Mov Disord*. 2015; 30: 788-795.

Parsons CG, Panchenko VA, Pinchenko VO, Tsyndrenko AY, Krishtal OA. Comparative patch-clamp studies with freshly dissociated rat hippocampal and striatal neurons on the NMDA receptor antagonistic effects of amantadine and memantine. *Eur J Neurosci*. 1995; 8: 446-454.

Parsons CG, Quack G, Bresink I, Baran L, Przegalinski E, Kostowski W, Krzascik P, Hartmann S, Danysz W. Comparison of the potency, kinetics and voltage-dependency of a series of uncompetitive NMDA receptor antagonists in vitro with anticonvulsive and motor impairment activity in vivo. *Neuropharmacology*. 1996; 34(10): 1239-1258.

Prugger M, Berger T. Assessing the long-term clinical benefit of prolonged-release fampridine tablets in a real-world setting: a review of 67 cases. *Patient Relat Outcome Meas*. 2013; 4: 75-85.

Rosenberg GA, Appenzeller O. Amantadine, fatigue, and multiple sclerosis. Arch Neurol. 1988 Oct;45(10):1104-6.

Ruck T, Bittner S, Simon OJ, Göbel K, Wiendl H, Schilling M, Meuth SG. Long-term effects of dalfampridine in patients with multiple sclerosis. *J Neurol Sci*. 2014; 337(1-2): 18-24.

Schumacher GA. Multiple sclerosis. *J Am Med Assoc*. 1950; 143(12): 1059-1065.

Wallin MT. The prevalence of multiple sclerosis in the United States: a population-based healthcare database approach. 2017 ECTRIMS Abstract P344.

Wang T, Huang X, Van K, Went T, Nguyen J, Lieth B. Amantadine improved cognitive outcome and increases neuronal survival after fluid percussion traumatic brain injury in rats. *J Neurotrauma.* 2014; 31(4): 370-377.

Wesemann W, Dette-Wildenhahn G, Fellehner G. In vitro studies on the possible effects of 1-aminoadamantanes on the serotonergic system in M. Parkinson. *J Neural Transm.* 1979; 44: 263-285.

22. APPENDICES

APPENDIX A. SCHEDULE OF EVENTS

	Open-Label Treatment Period[a] (±2 day)					Safety Follow-Up (±2 day)	Early Termination
	Baseline						
Visit	**1**	**2**	**3**	**4**	**5**	**6**	
Week	**0**	**4**	**12**	**24**	**52**	**54**	
Informed consent	✓						
Eligibility criteria	✓						
Demographics	✓[b]						
Medical history	✓[b]						
Medication history	✓[b]						
Concomitant medications	✓[b]	✓	✓	✓	✓	✓	✓
Adverse events	✓[b]	✓	✓	✓	✓	✓	✓
Complete physical exam	✓[b]				✓		✓
Symptom-directed physical exam, as needed		✓	✓	✓		✓	
Weight	✓[b]				✓		✓
Vital signs	✓[b]	✓	✓	✓	✓	✓	✓
Hematology	✓[b]				✓		✓
Serum chemistry	✓[b]				✓		✓
Urinalysis	✓[b]				✓		✓
Serum pregnancy test (if applicable)	✓[b]				✓	✓	✓
Urine pregnancy test (if applicable)		✓	✓	✓			
Expanded Disability Status Scale (EDSS)					✓		
Multiple Sclerosis Walking Scale-12 (MSWS-12)[c]	✓[b]		✓	✓	✓	✓	✓
Timed 25-Foot Walk (T25FW)[c]	✓[b]		✓	✓	✓	✓	✓
Timed Up and Go (TUG)[c]	✓[b]		✓	✓	✓	✓	✓
2-Minute Walk Test (2MWT)[c]	✓[b]		✓	✓	✓	✓	✓
Columbia-Suicide Severity Rating Scale (C-SSRS)	✓[b]	✓	✓	✓	✓	✓	✓
Collect returned study drug & assess compliance		✓	✓	✓	✓		✓
Dispense study drug[d]	✓	✓	✓	✓			
Study drug dosing, once daily at Bedtime	✓	✓	✓	✓	✓		

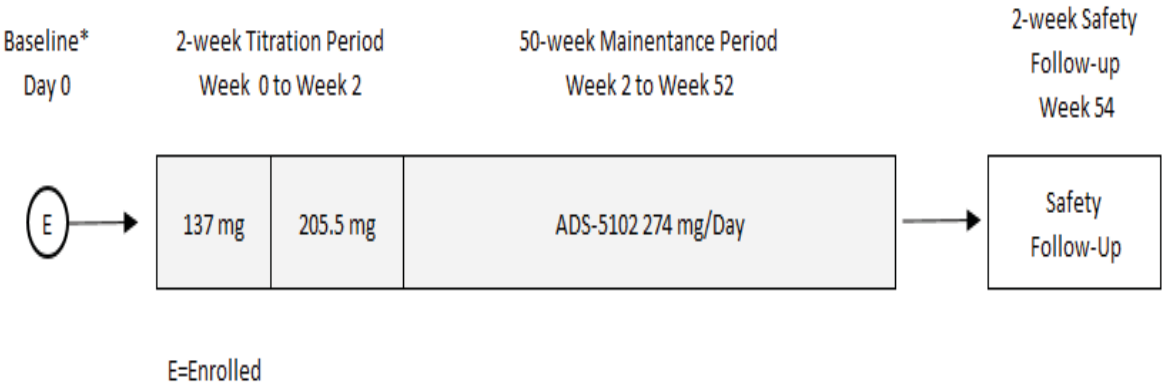
a In addition, a telephone visit will be conducted at Week 2 and Week 38 to assess and record AEs and any changes in concomitant medications and to remind subjects to begin taking capsules from dispensed bottles (only at Week 2).

b Procedures that are shared between Study ADS-AMT-MS301 (Week 16 Visit) and the Baseline/Week 0 visit for ADS-AMT-MS303 do not need to be repeated and the data will be captured in both clinical databases.

c At visits where efficacy measurements are assessed, the order of administration should be as follows: MSWS-12, T25FW, TUG, and 2MWT.

d Study drug will be dispensed as 1 wallet and 1 bottle at the Visit 1 (Baseline/Week 0), 2 bottles at Visit 2 (Week 4), 3 bottles at Visit 3 (Week 12), and 7 bottles at Visit 4 (Week 24).

APPENDIX B. STUDY DESIGN SCHEMATIC



*ADS-AMT-MS301 Week 16/ADS-AMT-MS303 Baseline Visit occur at the same time