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

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

US IND Number: 125,381

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2. SYNOPSIS

Name of Sponsor/Company: Adamas Pharmaceuticals, Inc.	
Name of Investigational Product: ADS-5102 (Amantadine Extended Release Capsules)	
Name of Active Ingredient: amantadine	
Title of Study: 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 (Protocol ADS-AMT-MS301)	
Study Centers: Approximately 80 sites	
Number of Subjects (Planned): Approximately 570 subjects are to be enrolled in the Single-Blind Placebo Run-In Period to ensure that 540 subjects complete the Single-Blind Placebo Run-In Period and are eligible to be randomized into the Double-Blind Treatment Period.	
Studied period: Approximately 18 months (from randomization of first subject to last subject last visit) **Estimated Date First Subject Enrolled:** March 2018	**Phase of development:** 3

Objectives:

Primary:

- To evaluate the efficacy of 274 mg ADS-5102 in subjects with multiple sclerosis (MS) with walking impairment as measured by the Timed 25-foot Walk (T25FW, feet/second) at Week 16.

Secondary:

Key:

- To evaluate the efficacy of 274 mg ADS-5102 in subjects with MS and walking impairment as measured by the T25FW, Timed Up and Go (TUG) test, and the 2-Minute Walk Test (2MWT) at Week 16.
- To evaluate the efficacy of 137 mg ADS-5102 in subjects with MS and walking impairment as measured by the T25FW, the TUG test, and the 2MWT at Week 16.

Supportive:

- To evaluate the efficacy of 274 mg ADS-5102 and 137 mg ADS-5102 in subjects with MS and walking impairment as measured by the T25FW, the TUG, and the 2MWT across all study visits.
- To evaluate the efficacy of 274 mg ADS-5102 and 137 mg ADS-5102 in subjects with MS and walking impairment as measured by the Multiple Sclerosis Walking Scale-12 (MSWS-12) in subjects treated with 274 mg ADS-5102 and subjects treated with 137 mg ADS-5102.

Safety:

- To evaluate the safety and tolerability of 274 mg and 137 mg of ADS-5102 in subjects with MS and walking impairment.

Study Design:

This is a multicenter, 3-arm, randomized, placebo-controlled, double-blind, parallel-group study of ADS-5102 (amantadine extended release [ER] capsules) in MS patients with walking impairment, incorporating a Single-Blind Placebo Run-In Period prior to randomization, and forced up-titration for the high-dose group.

Eligibility for inclusion in this study will require all subjects to be on a stable medication regimen for at least 30 days prior to screening, and to continue the same dosing regimen for the duration of their study participation. Subjects may not have been treated with dalfampridine within 30 days prior to screening.

Consented subjects who complete the up to 3-week screening period will undergo a 4-week Single-Blind Placebo Run-In Period during which subjects will receive placebo as 2 capsules once daily at bedtime.

Subjects who complete the Single-Blind Placebo Run-In Period and continue to meet study eligibility criteria will be randomized with equal probability to 1 of 3 treatment groups: placebo or ADS-5102 at 137 mg or 274 mg per dose. Study drugs will be administered as 2 capsules once daily at bedtime.

Subjects who are randomized to placebo will receive placebo capsules throughout the 12-week Double-Blind Treatment Period.

Subjects who are randomized to 137 mg of ADS-5102 will receive 137 mg of ADS-5102 throughout the Double-Blind Treatment Period.

Subjects who are randomized to 274 mg of ADS-5102 will receive 137 mg for the first week, 205.5 mg for the second week, and 274 mg for the remainder of the 12-week Double-Blind Treatment Period.

During the Double-Blind Treatment Period, subjects will return to the clinic for safety and efficacy assessments at Weeks 6, 8, 12, and 16. In addition, telephone visits for safety assessments will be conducted at Weeks 5 and 7.

Subjects who complete the study through the Week 16 visit will be eligible to enter an optional open-label extension (OLE) study, protocol ADS-AMT-MS303. Subjects who withdraw from the study prior to completion of the Week 16 visit will have an early termination visit that includes safety follow-up and efficacy assessments. Subjects who complete 12 weeks of double-blind treatment and elect not to participate in the OLE study will have a final post-treatment safety and efficacy assessment 2 weeks after their Week 16 visit. The end of study (EOS) is defined as when a subject completes the Week 16 visit (if electing to enter the OLE study) or the safety follow-up visit (if electing not to enter the OLE study).

All study visits and efficacy assessments should be scheduled to occur at approximately the same time of day for each individual subject. To the extent practicable, study visits and efficacy assessments should be scheduled to occur when a subject is not likely to be experiencing acute side effects from a concomitant medication (e.g., flu-like side effects following interferon-beta injection). Efficacy assessments should be conducted in following sequence: MSWS-12; T25FW; TUG; 2MWT. Subjects using an assistive device during the walking assessments at Screening should use the same assistive device for all subsequent walking tests. 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 during the Single-Blind Placebo Run-In Period and continuing through the last study visit.

Diagnosis and Eligibility Criteria:

Inclusion Criteria:

1. Signed a current IRB-approved informed consent form
2. Male or female subjects between 18 and 70 years of age, inclusive, at the time of Screening
3. Confirmed diagnosis of MS according to the 2017 McDonald criteria (Thompson et al., 2017)
4. Current medication regimen must be stable for at least 30 days prior to screening, and subject must be willing to continue the same dosing regimen for the duration of study participation
5. Maximum Expanded Disability Status Scale (EDSS) score during screening of 6.5
6. Sufficient ambulatory ability (ambulatory aids acceptable if used consistently) to complete two trials of the Timed 25-Foot Walk (T25FW) at the screening visit, with the two trials completed within 5 minutes of each other in accordance with the specific instructions provided by the National MS Society Functional Composite Manual
7. Stable physical activity level (inclusive of prescribed physical therapy) for at least 30 days prior to screening and willing to continue without change for the duration of study participation
8. A score on each of two completed screening T25FW tests between 8 and 45 seconds, inclusive

Exclusion Criteria:

1. Documented inability to tolerate amantadine
2. History of hypersensitivity or allergic reaction to amantadine, rimantadine, or memantine, or to any of the excipients used in the study drug capsules (refer to Table 2)
3. Clinically significant MS relapse with onset less than 30 days prior to screening
4. Presence of neurologic dysfunction or medical condition, the severity of which, in the judgement of the investigator, would preclude the ability to perform walking tests safely
5. Receipt of systemic corticosteroids (intravenous [IV] or oral) or ACTHAR gel within 30 days prior to screening
6. Receipt of dalfampridine (or any 4-aminopyridine or 2,4-diaminopyridine preparation) or amantadine within 30 days prior to screening
7. History of other neurological or medical condition that, in the opinion of the investigator, would affect study outcome assessments
8. History of seizures within 3 years prior to screening
9. History of hallucinations (visual, auditory, or any other type) within 3 years prior to screening
10. History of bipolar disorder, schizophrenia, or psychosis, regardless of treatment
11. For subjects with a history of major depressive disorder, the presence of active depressive symptoms that, in the opinion of the investigator, would affect the subject's ability to complete study assessments, or which would not be in the subject's best interest to participate in the study
12. History of suicide attempt
13. History of suicidal ideation within 3 years of screening, or presence of suicidal ideation at screening, as detected by the Columbia Suicidality Scale (C-SSRS)
14. History of cognitive impairment sufficient, in the clinical judgement of the investigator, to affect the subject's ability to consent or complete study assessments, or to render it not in the subject's best interest to participate in the study
15. History of alcohol or substance dependence or abuse within 2 years prior to screening
16. History of stroke, transient ischemic attack (TIA), or myocardial infarction (MI) within 2 years prior to screening

17. History of cancer within 5 years prior to screening, with the following exceptions: adequately treated non-melanomatous skin cancers, localized bladder cancer, non-metastatic prostate cancer, in situ cervical cancer, or other definitively treated cancer that is considered cured
18. Presence of orthostatic hypotension at screening: a decrease in systolic blood pressure (at least 20 mm Hg) or diastolic blood pressure (at least 10 mm Hg) within 3 minutes of the subject standing up, compared to pressures obtained while sitting
19. Any laboratory test results outside of the central laboratory's normal range at screening that are assessed by the investigator to be clinically significant. Documentation by the investigator of clinical significance or insignificance must accompany out of range laboratory test results at screening
20. Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) screening laboratory results > 2 times the upper limit of normal
21. Estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 (per Modification of Diet in Renal Disease [MDRD] calculation)
22. Inability to swallow oral capsules, or a history of gastrointestinal malabsorption that would preclude the use of oral medication
23. If female, is pregnant or lactating
24. 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 screening 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.
25. Received live attenuated influenza vaccine within 2 weeks prior to randomization or planning to receive live attenuated influenza vaccine during the duration of the study (amantadine may interfere with the efficacy of live attenuated vaccine)
26. Current treatment with medications that may affect urinary pH: carbonic anhydrase inhibitors, sodium bicarbonate, urinary acidification agents, quinine, quinidine, triamterene, or trimethoprim
27. Treatment with an investigational drug or device within 30 days prior to screening
28. Treatment with an investigational biologic within 6 months or 5 half-lives, whichever is longer, prior to screening
29. Current participation in another clinical trial
30. Prior or current participation in an Adamas clinical trial
31. Planned elective surgery, with the exception of minor dermatological procedures, during study participation

Investigational Product, Dosage and Mode of Administration:

All subjects are to continue their current (prior to screening visit) MS medications and regimens, without change, for the duration of their study participation, to the extent compatible with good neurological care.

Consented subjects who complete screening and the Single-Blind Placebo Run-In Period and meet study eligibility criteria will be randomized with equal probability to 1 of 3 treatment groups: placebo, 137 mg ADS-5102, or 274 mg ADS-5102.

ADS-5102 (amantadine ER capsules) will be administered orally, as 2 capsules once daily at bedtime for the 12-week Double-Blind Treatment Period.

The dosing regimens for the 2 active treatment arms are:

- 137 mg/d (1 x 137 mg capsule + 1 placebo capsule) for 12 weeks for the 137 mg ADS-5102 group
- 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 + 1x 68.5 mg capsule) for 1 week, followed by 274 mg/d (2 x 137 mg capsules) for 10 weeks for the 274 mg ADS-5102 group

Reference Therapy, Dosage and Mode of Administration:

Placebo capsules (indistinguishable from ADS-5102 capsules) will be administered orally as 2 capsules once daily at bedtime for the 4-week Single-Blind Placebo Run-In Period for all subjects and for the 12-week Double-Blind Treatment Period for subjects randomized to the placebo arm.

Duration of Treatment: Maximum duration of subject participation is up to approximately 21 weeks and will include a 3-week (maximum) screening period, 4-week Single-Blind Placebo Run-In Period, a 12-week Double-Blind Treatment Period for all subjects, and a 2-week post-treatment safety follow-up period for subjects who choose not to participate in the OLE study.

Criteria for Evaluation:

Primary Efficacy Measure: T25FW (measured in seconds but calculated to a feet/sec measurement)

Secondary Efficacy Measures: TUG (seconds), 2MWT (meters), and MSWS-12

Safety Measures: Adverse events (AEs), clinical laboratory evaluations (hematology, clinical chemistry, urinalysis, serum pregnancy tests for females of child bearing potential), vital signs, and Columbia-Suicide Severity Rating Scale (C-SSRS)

Statistical Methods:

Primary Efficacy Endpoint and Sample Size Determination:

The primary efficacy endpoint is the proportion of responders in each treatment group (see definition details below).

Based on the results from the Phase 2 study, responder rates of 24% and 33% were observed at Week 4 for subjects treated with placebo and 274 mg ADS-5102, respectively, in the modified intent-to-treat (MITT) analysis set. In this study, it is anticipated that the placebo response rate at Week 16 will be no greater than 20% and response rate among subjects treated with 274 mg or 137 mg ADS-5102 will be at least 33%. Using these estimates, 180 randomized subjects per active treatment group and placebo will be needed for the test of differences in proportions (Farrington-Manning approach for the Miettimen-Nurminen [MN] test.) to have 80% power at the 2-sided 5% significance level to detect this 13% difference favoring ADS-5102. Assuming a 5% dropout rate during the 4-week placebo run-in period, 570 subjects will be enrolled in the study to randomize 540.

For this sample size of 180 randomized subjects per group, power will be at least 80% to detect treatment differences (ADS-5102 versus placebo) of -2.7 seconds and 5.0 meters in the changes from baseline at Week 16 in the TUG test and 2MWT when the standard deviation of the changes from baseline is no greater than 6.0 sec and 14.9 meters, respectively, and the dropout rate is not greater than 20%.

Analysis Sets:

The safety analysis set will include all randomized subjects who receive at least one dose of double-blind study drug and will be analyzed according to the treatment actually received.

The intent-to-treat (ITT) analysis set will include all randomized subjects who receive at least one dose of study drug, and will be analyzed according to the randomized treatment assignment. This population will be used for the efficacy analyses including the analyses of primary and key secondary endpoints.

The per-protocol (PP) analysis set will include all randomized and dosed subjects who provide Week 16 efficacy data and do not have any major protocol deviations that could confound this assessment. This population will also be used for efficacy analyses.

Efficacy Analyses

Primary Efficacy: The primary efficacy endpoint is the proportion of responders in the 274 mg ADS-5102 treatment group relative to the placebo group, where a responder is defined as a subject who has a ≥ 20% increase from Baseline to Week 16 in walking speed measured using the T25FW (average of two measurements 5 minutes apart). This analysis will be done using the ITT analyses set. Subjects who fail to have an increase of at least 20% at Week 16 in the T25FW (feet/seconds) will be considered non-responders. Subjects who do not have an observation at Week 16 for whatever reason will be considered to have an indeterminate outcome and will also be included in the denominators, effectively counting them as non-responders for the purpose of treatment comparisons. However, tabulations of each response category will be provided. For this endpoint, baseline will be defined as the average walking speed (feet/seconds) from the T25FW at Weeks 0 and 2 (prior to randomization).

The objective of the primary efficacy analysis is to test for superiority of the 274 mg ADS-5102 group compared to the placebo group in terms of the difference (active minus placebo) in the proportion of responders at Week 16 using the ITT analysis set. This test of proportions will be done using the MN test at the 2-sided 5% level. Both the 2-sided p-value and the 95% confidence interval (CI) for the difference will be obtained. Superiority will be concluded if the lower limit of the 95% CI is greater than zero (equivalently 2-sided p-value < 0.05).

Key Secondary Efficacy: Provided superiority of 274 mg ADS-5102 versus placebo is shown in the primary analysis, the key secondary objectives will be evaluated using a gatekeeping strategy to control the overall Type I error rate at 5%. Using this approach, the following research hypotheses will be evaluated sequentially in the order given using the ITT analyses set: (1) superiority of 274 mg ADS-5102 compared to placebo in mean change from baseline at Week 16 in the T25FW (feet/second) test; (2) superiority of 274 mg ADS-5102 compared to placebo in mean change from baseline at Week 16 in the TUG (sec) test; (3) superiority of 274 mg ADS-5102 compared to placebo in mean change from baseline at Week 16 in the 2MWT (m); (4) superiority of 137 mg ADS-5102 compared to placebo in terms of the proportion of T25FW responders at Week 16; (5) superiority of 137 mg ADS-5102 compared to placebo in mean change from baseline at Week 16 in the T25FW (feet/second) test; (6) superiority of 137 mg ADS-5102 compared to placebo in mean change from baseline at Week 16 in the TUG test; and (7) superiority of 137 mg ADS-5102 compared to placebo in mean change from baseline at Week 16 in the 2MWT. For each hypothesis, if a non-significant result (p > 0.05) is obtained, no further inferential conclusions will be drawn and any statistically significant result will be declared supportive of efficacy only.

The test of superiority of 137 mg ADS-5102 versus placebo in terms of the proportion of responders at Week 16 will be done using the same approach as for the primary analyses.

The tests of superiority of 274 mg ADS-5102 and of 137 mg ADS-5102 versus placebo in terms of the mean change from baseline in the T25FW (feet/second), TUG test (sec), and the 2MWT (m) will be done using t-tests derived from the corresponding linear mixed model with repeated measurement (MMRM) model with the change from baseline (i.e. T25FW, TUG, or 2MWT) as the dependent variable and fixed effects of treatment group, study week, and treatment by study week interaction. The baseline value will be included as a covariate and an unstructured variance-covariance matrix will be used for the within-subject residual variability. For the T25FW, TUG test, and the 2MWT, baseline will be the average of Weeks 0 and 2 (prior to randomization).

Secondary Supportive Endpoints: Each active dose will be compared to placebo in terms of the mean change from baseline at each study visit in the T25FW (feet/sec), TUG test (sec)and the 2MWT (m). These analyses will be done using the MMRM model described earlier. The T25FW (sec) will be evaluated in a similar manner.

Safety and Tolerability Analyses

Adverse events will be recorded starting from the date/time of first dose during the Single-Blind Placebo Run-In Period through the EOS Visit. The time periods of AE recording will be divided into AEs with onset during the Single-Blind Placebo Run-In Period and AEs during the Double-Blind Treatment Period (i.e., treatment-emergent AEs [TEAEs]). All AEs will be listed by subject and period.

For AEs during double-blind treatment, standard incidence rates will be summarized by treatment group, system organ class (SOC), and preferred term (PT) within SOC in the safety analysis set.

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 will be tabulated by treatment group. 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 treatment group and 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
2,4-DAP	2,4-diaminopyridine
4-AP	4-aminopyridine
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
ECG	Electrocardiogram
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
ITT	Intent-to-treat
IUD	Intrauterine device
IWRS	Interactive web response system

Table 1: Abbreviations and Specialist Terms (Continued)

MDRD	Modification of Diet in Renal Disease
MI	Myocardial infarction
MMRM	Mixed model repeated measurement
MN	Miettimen-Nurminen
MS	Multiple sclerosis
MSWS-12	Multiple Sclerosis Walking Scale-12
OLE	Open-label extension
PD	Parkinson's disease
PI	Principal Investigator
PP	Per-protocol
REB	Research ethics board
SAE	Serious 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

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., 2013; 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 on the percent change in walking speed from baseline was observed and a greater proportion of ADS-5102-treated participants experienced a ≥ 20% improvement. Trends suggesting benefit, which did not reach statistical significance, were observed for the Timed Up and Go (TUG) test, and less so on the 2-Minute Walk Test (2MWT). 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, is, therefore, to confirm the efficacy, safety, and tolerability of ADS-5102 as a treatment to improve walking in the patients with MS that was suggested in the Phase 2 study.

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 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

Two dosages of ADS-5102 are being tested in Study ADS-AMT-MS301, 137 mg/d and 274 mg/d, to adequately characterize the dose-response curve.

The 274 mg dose was selected because this was the dose that was tested in the Phase 2 study, Study ADS-AMT-MS201, and showed a statistically significant effect on walking speed in the T25FW test. Additionally, the 274 mg dose showed a clearly positive trend toward significance in the TUG test in the Phase 2 study. With respect to the safety and tolerability of the 274 mg dose, the overall AE profile and the AE-related dropout rate observed in Study ADS-AMT-MS201 support entering Phase 3 in MS, with the preliminary expectation that acceptable safety and tolerability will be confirmed. The AE profile was qualitatively similar to the AE profile discernible from the published studies of amantadine IR in MS (Canadian MS Research Group 1987; Chiba et al., 1992; Krupp et al., 1995; Ashtari et al., 2009; Berger, 2011) and to the AE profile observed in the clinical studies of ADS-5102 in PD, as reflected in the GOCOVRI™ prescribing information.

Although the 137 mg dose was not evaluated as a separate treatment arm in the Phase 2 study, the data suggest that this dose may confer some effect on walking speed. A separation in the least squared (LS) mean walking speeds between the ADS-5102 and placebo groups was evident at the first post-baseline T25FW test, which was performed after 2 weeks of dosing. As the first 2 weeks of dosing constituted a 1-step titration, with subjects in the active-therapy arm receiving ADS-5102 at 137 mg/d for the first week, it is plausible that the time spent at the 137 mg dose could have contributed to the efficacy signal at study Week 2. The low dropout rates during the first week of dosing suggest that the 137 mg dose is tolerable. Even if the 137 mg dose of ADS-5102 should prove to be only minimally effective, it could still provide a valuable alternative to patients who may be intolerant of a higher dose of amantadine.

5.5. Dosing Regimen and Titration

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 12-week Double-Blind Treatment Period of the study includes a 2-step, forced titration phase for subjects randomized to the 274 mg/d ADS-5102 arm of the study, followed by a maintenance phase of approximately 10 weeks. 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. Subjects randomized to the 137 mg/d arm will undergo a sham titration, but will, in fact, be continuing on a daily dose of 137 mg/d throughout the titration and maintenance periods. Similarly, subjects randomized to the placebo arm of the study will undergo a sham titration, but

will, in fact, be continuing on placebo throughout the titration and maintenance periods. The sham titrations are included to preserve blinding. No down-titration will be permitted.

Although it is anticipated that the slow absorption of the ER formulation will facilitate the ability of patients to tolerate higher dose of amantadine than historically reported as use in MS, the titration phase is being included for the 274 mg dose to further ensure its tolerability. When a 1-step forced titration, from 137 to 274 mg, was employed in Adamas' clinical studies of ADS-5102 in PD, premature discontinuation rates were still higher during the earlier, as compared to the later, times on-study. Moving from a 1-step to a 2-step titration should serve to further limit early discontinuation of study drug.

5.6. Rationale for ADS-AMT-MS301 Study Design

The overall objectives of this Phase 3 study are to establish the efficacy of ADS-5102, an ER form of amantadine, in improving walking performance, and to characterize its safety and tolerability at a dosage of 137 or 274 mg/d, administered once daily at bedtime, in MS patients with walking impairment. A multicenter, 3-arm, randomized, placebo-controlled, double-blind, parallel-group study, incorporating a Single-Blind Placebo Run-In Period prior to randomization and forced up-titration for the high-dose group, is an appropriate design to accomplish these objectives.

The duration of the Double-Blind Treatment Period of the study, 12 weeks, should be adequate to demonstrate an effect of ADS-5102 on walking ability, as a positive effect on walking was observed after 4 weeks of treatment in the Phase 2 study. Obtaining serial efficacy measures at multiple timepoints throughout the 12-week duration should indicate whether any observed effect is diminishing, increasing, or holding steady over time. If, as in PD, a positive effect is observed with active study drug early after its initiation, and the effect holds relatively constant through to the last efficacy assessment, then it is likely that the 12-week duration will be assessed to have been adequate to establish the durability of the drug effect over time.

Incorporating into the study design a Single-Blind Placebo Run-In Period for all eligible subjects prior to randomization to their assigned treatment group in the double-blind phase of the study provides several potential advantages over starting double-blind treatment immediately following the initial screening period. By allowing subjects the opportunity to discontinue treatment while only receiving placebo, AEs related to study participation, but not to study drug, per se (e.g., AEs related to anxiety about receiving an experimental therapy), in subjects who might be prone to experiencing such AEs, may be reduced in the safety and tolerability data obtained by study's end and provide a truer reflection of the drug's safety and tolerability profile. Also, it is generally believed that for many outcome measures, the durability of the placebo response diminishes over time. The addition of the pre-randomization placebo run-in period provides additional time for any potential contribution of a placebo response to have decreased by the time of the final efficacy evaluation. Lastly, by performing efficacy assessments during the placebo run-in period, the impact of practice effects on the variability of efficacy measures can be diminished.

The duration of the Single-Blind Placebo Run-In Period, 4 weeks, is considered long enough to permit realization of its potential benefits without being so long as to substantially increase the overall burden of study participation. It is also consistent with the duration of the placebo run-in periods employed in other drug studies in walking impairment in MS (Goodman et al., 2009; Goodman et al., 2010).

As amantadine is not currently known, or widely held, to be a disease modifying treatment for MS, i.e., is generally considered to be a symptomatic therapy, no irreparable harm is considered likely to result from withholding the experimental treatment in the subjects randomized to receive placebo.

5.7. Population to be Studied

Subjects with MS who are experiencing impaired walking will be randomized into the study.

6. TRIAL OBJECTIVES AND PURPOSE

6.1. Primary Objective

- To evaluate the efficacy of 274 mg ADS-5102 in subjects with multiple sclerosis (MS) with walking impairment as measured by the Timed 25-foot Walk (T25FW, feet/second) at Week 16

6.2. Secondary Objectives

6.2.1. Key

- To evaluate the efficacy of 274 mg ADS-5102 in subjects with MS and walking impairment as measured by the T25FW, Timed Up and Go (TUG) test, and the 2-Minute Walk Test (2MWT) at Week 16.
- To evaluate the efficacy of 137 mg ADS-5102 in subjects with MS and walking impairment as measured by the T25FW, the TUG test, and the 2MWT at Week 16.

6.2.2. Supportive

- To evaluate the efficacy of 274 mg ADS-5102 and 137 mg ADS-5102 in subjects with MS and walking impairment as measured by the T25FW, the TUG, and the 2MWT across all study visits.
- To evaluate the efficacy of 274 mg ADS-5102 and 137 mg ADS-5102 in subjects with MS and walking impairment as measured by the Multiple Sclerosis Walking Scale-12 (MSWS-12) in subjects treated with 274 mg ADS-5102 and subjects treated with 137 mg ADS-5102.

6.2.3. Safety

- To evaluate the safety and tolerability of 274 mg and 137 mg of ADS-5102 in subjects with MS and walking impairment.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a multicenter, 3-arm, randomized, placebo-controlled, double-blind, parallel-group study of ADS-5102 (amantadine ER capsules) in MS subjects with walking impairment, incorporating a Single-Blind Placebo Run-In Period prior to randomization, and forced up-titration for the high-dose group.

All subjects will have received a stable regimen of MS medications, both disease modifying and symptomatic, for at least 30 days prior to screening, and will continue the same doses and regimens for the duration of their study participation, to the extent compatible with good neurological care. Subjects will not have used amantadine, dalfampridine, or any 4-AP or 2,4-diaminopyridine (2,4-DAP) preparation within 30 days prior to screening.

Consented subjects who complete the up to 3-week screening period will undergo a 4-week Single-Blind Placebo Run-In Period during which they will administer placebo as 2 capsules once daily at bedtime.

Subjects who complete the Single-Blind Placebo Run-In Period and continue to meet study eligibility criteria will be randomized with equal probability to 1 of 3 treatment groups: placebo or ADS-5102 at a final dosage of either 137 or 274 mg/d (treatment groups are identified by their final dosage). Study drugs will be administered as 2 capsules once daily at bedtime.

Subjects who are randomized to placebo will receive placebo capsules throughout the 12-week Double-Blind Treatment Period, including the 2-week forced titration and 10-week maintenance phases.

Subjects who are randomized to 137 mg of ADS-5102 will receive 137 mg of ADS-5102 throughout the 12-week Double-Blind Treatment Period, including the 2-week forced titration and 10-week maintenance phases.

Subjects who are randomized to 274 mg of ADS-5102 will receive 137 mg for the first week (Week 1 of the forced titration phase of the Double-Blind Treatment Period), 205.5 mg for the second week (Week 2 of the forced titration phase of the Double-Blind Treatment Period), and 274 mg for the remaining 10 weeks of the 12-week Double-Blind Treatment Period.

Subjects will return to the clinic for safety and efficacy assessments at Week 0 and Week 2 prior to randomization and at Weeks 4 (randomization and baseline visit), 6 (only safety), 8, 12, and 16 after randomization. In addition, telephone visits for safety assessments will be conducted at Weeks 5 and 7. Subjects who withdraw from the study before Week 16 will have an early termination visit that includes safety follow-up and efficacy assessments, as appropriate.

Subjects who complete 12 weeks of double-blind treatment (16 weeks total treatment, including placebo run-in) without significant protocol deviations, as assessed by the investigator and the sponsor, will be eligible to enter an optional open-label extension (OLE) study, protocol ADS-AMT-MS303. The Week 16 visit of Study ADS-AMT-MS301 will serve as the first study visit of Study ADS-AMT-MS303 for those subjects who consent to participate.

Subjects who complete 12 weeks of double-blind treatment (16 weeks total treatment, including placebo run-in) but elect not to participate in the OLE study will return to the clinic for a final

post-treatment safety and efficacy assessment 2 weeks after their Week 16 visit (Week 18), i.e., after being off treatment for approximately 2 weeks.

The End of Study (EOS) is defined as when a subject completes the Week 16 visit (if electing to enter the OLE study) or the Safety Follow-Up Visit (if electing not to enter the OLE study).

All study visits and efficacy assessments should be scheduled at approximately the same time of day for an individual subject. To the extent practicable, study visits and efficacy assessments should be scheduled to occur when a subject is not likely to be experiencing acute side effects from a concomitant medication (e.g., flu-like side effects following interferon-beta injection). Efficacy assessments should be conducted in following sequence: MSWS-12; T25FW; TUG; 2MWT. Subjects using an assistive device during the walking assessments at Screening should use the same assistive device for all subsequent walking tests. Each efficacy assessment for an individual should be performed by the same clinical rater, if possible.

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

The schedule of assessments is provided in Appendix A.

7.2. Number of Subjects

Approximately 570 subjects are to be enrolled in the Single-Blind Placebo Run-In Period at approximately 80 study sites to ensure that 540 subjects complete the Single-Blind Placebo Period and are eligible to be randomized into the Double-Blind Treatment Period (approximately 180 enrolled in each treatment group: placebo, 137 mg ADS-5102, and 274 mg ADS-5102).

7.3. Treatment Assignment

Consented subjects who complete screening, meet study eligibility criteria, and complete the Single-Blind Placebo Run-In Period will be randomized with equal probability to 1 of the 3 treatment groups to receive placebo, 137 mg ADS-5102, or 274 mg ADS-5102.

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 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. Study drug may not be down-titrated. This procedure applies to the withholding of study drug throughout the study with the exception of the titration phase of the Double-Blind Treatment Period.

In the special case of study drug being withheld for the evaluation or treatment of an AE occurring during the titration phase of the Double-Blind Treatment Period (i.e., Week 4 to Week 6), the investigator may have the subject do so for up to 3 consecutive days, and is then have the subject resume dosing at same dose level. The subject is to finish the remaining capsules in the blister card (see Section 9.2), i.e., including the 2-dose overage. The subject must return to the clinic to receive his or her next blister pack without missing any additional doses. If, in the judgement of the investigator, study drug needs to be withheld for more than 3 consecutive days the subject is to be permanently discontinued from study drug.

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 21 weeks and will include a 3-week (maximum) screening period, a 4-week Single-Blind Placebo Run-In Period, a 12-week Double-Blind Treatment Period for all subjects (including a 2-week forced up-titration and a 10-week maintenance phase for subjects in the high-dose group), and a 2-week post-treatment safety follow-up period for subjects who choose not to participate in the OLE study.

7.7. Estimated Study Duration

The estimated study duration is approximately 18 months, from randomization of the first subject to the last subject's EOS visit.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Inclusion Criteria

1. Signed a current IRB-approved informed consent form
2. Male or female subjects between 18 and 70 years of age, inclusive, at the time of Screening
3. Confirmed diagnosis of MS according to the 2017 McDonald criteria (Thompson et al., 2017)
4. Current medication regimen must be stable for at least 30 days prior to screening, and subject must be willing to continue the same dosing regimen for the duration of study participation
5. Maximum Expanded Disability Status Scale (EDSS) score during screening of 6.5
6. Sufficient ambulatory ability (ambulatory aids acceptable if used consistently) to complete two trials of the Timed 25-Foot Walk (T25FW) at the screening visit, with the two trials completed within 5 minutes of each other in accordance with the specific instructions provided by the National MS Society Functional Composite Manual
7. Stable physical activity level (inclusive of prescribed physiotherapy) for at least 30 days prior to screening and willing to continue without change for the duration of study participation
8. A score on each of two completed screening T25FW tests between 8 and 45 seconds, inclusive

8.2. Subject Exclusion Criteria

1. Documented inability to tolerate amantadine
2. History of hypersensitivity or allergic reaction to amantadine, rimantadine, or memantine, or to any of the excipients used in the study drug capsules (refer to Table 2)
3. Clinically significant MS relapse with onset less than 30 days prior to screening
4. Presence of neurologic dysfunction or medical condition, the severity of which, in the judgement of the investigator, would preclude the ability to perform walking tests safely
5. Receipt of systemic corticosteroids (intravenous [IV] or oral) or ACTHAR gel within 30 days prior to screening
6. Receipt of dalfampridine (or any 4-aminopyridine or 2,4-diaminopyridine preparation) or amantadine within 30 days prior to screening
7. History of other neurological or medical condition that, in the opinion of the investigator, would affect study outcome assessments
8. History of seizures within 3 years prior to screening
9. History of hallucinations (visual, auditory, or any other type) within 3 years prior to screening
10. History of bipolar disorder, schizophrenia, or psychosis, regardless of treatment

11. For subjects with a history of major depressive disorder, the presence of active depressive symptoms that, in the opinion of the investigator, would affect the subject's ability to complete study assessments, or which would not be in the subject's best interest to participate in the study
12. History of suicide attempt
13. History of suicidal ideation within 3 years of screening, or presence of suicidal ideation at screening, as detected by the Columbia Suicidality Scale (C-SSRS)
14. History of cognitive impairment sufficient, in the clinical judgement of the investigator, to affect the subject's ability to consent or complete study assessments, or to render it not in the subject's best interest to participate in the study
15. History of alcohol or substance dependence or abuse within 2 years prior to screening
16. History of stroke, transient ischemic attack (TIA), or myocardial infarction (MI) within 2 years prior to screening
17. History of cancer within 5 years prior to screening, with the following exceptions: adequately treated non-melanomatous skin cancers, localized bladder cancer, non-metastatic prostate cancer, in situ cervical cancer, or other definitively treated cancer that is considered cured
18. Presence of orthostatic hypotension at screening: a decrease in systolic blood pressure (at least 20 mm Hg) or diastolic blood pressure (at least 10 mm Hg) within 3 minutes of the subject standing up, compared to pressures obtained while sitting
19. Any laboratory test results outside of the central laboratory's normal range at screening that are assessed by the investigator to be clinically significant. Documentation by the investigator of clinical significance or insignificance must accompany out of range laboratory test results at screening
20. Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) screening laboratory results > 2 times the upper limit of normal
21. Estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 (per Modification of Diet in Renal Disease [MDRD] calculation)
22. Inability to swallow oral capsules, or a history of gastrointestinal malabsorption that would preclude the use of oral medication
23. If female, is pregnant or lactating
24. 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 screening 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.
25. Received live attenuated influenza vaccine within 2 weeks prior to randomization or planning to receive live attenuated influenza vaccine during the duration of the study (amantadine may interfere with the efficacy of live attenuated vaccine)

26. Current treatment with medications that may affect urinary pH: carbonic anhydrase inhibitors, sodium bicarbonate, urinary acidification agents, quinine, quinidine, triamterene, or trimethoprim
27. Treatment with an investigational drug or device within 30 days prior to screening
28. Treatment with an investigational biologic within 6 months or 5 half-lives, whichever is longer, prior to screening
29. Current participation in another clinical trial
30. Prior or current participation in an Adamas clinical trial
31. Planned elective surgery, with the exception of minor dermatological procedures, during study participation

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 (see Section 7.4.1)
- 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 encouraged to complete the study. If the subject decides to withdraw from the study, he or she will have an early termination visit that includes efficacy assessments and safety follow-up.

9. STUDY DRUG MATERIALS AND MANAGEMENT

9.1. Study Drug

The clinical supplies will include 137 mg and 68.5 mg ADS-5102 capsules and matching placebo capsules. All capsules provided during the study are indistinguishable in size and appearance.

Amantadine is designated generically as amantadine hydrochloride and chemically as 1-adamantanamine hydrochloride.

The clinical formulations are shown in the table below.

Table 2: Clinical Formulations for Study ADS-AMT-MS301

	Placebo	**ADS-5102** **137 mg and 68.5 mg**
Formulation	Microcrystalline cellulose pellets in an oral capsule	Extended release coated pellets of amantadine in an oral capsule
Dose Strength	Not applicable	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.	White to off-white pellets filled in white opaque/white opaque colored hard gelatin capsule, size 0.
Excipients	Microcrystalline cellulose, NF/EP Magnesium stearate, USP/NF/EP	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, each containing a total of 36 capsules (2 capsules per dose, allowing a 2-week supply plus 2 extra doses per week). All blister wallets 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 25ºC (77ºF) 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

Table 3: Randomization Groups for Study ADS-AMT-MS301

TREATMENT GROUP			
	274 mg ADS-5102	**137 mg ADS-5102**	**Placebo**
Single-Blind Placebo Run-In Period			
Week 0 to Week 4	2 x placebo capsules	2 x placebo capsules	2 x placebo capsules
Double-Blind Treatment Period, Forced Titration Phase			
Week 4 to Week 5	1 x 137 mg ADS-5102 capsule 1 x placebo capsule	1 x 137 mg ADS-5102 capsule 1 x placebo capsule	2 x placebo capsules
Week 5 to Week 6	1 x 137 mg ADS-5102 capsule 1 x 68.5 mg ADS-5102 capsule	1 x 137 mg ADS-5102 capsule 1 x placebo capsule	2 x placebo capsules
Double-Blind Treatment Period, Maintenance Phase			
Week 6 to Week 16	2 x 137 mg ADS-5102 capsule	1 x 137 mg ADS-5102 capsule 1 x placebo capsule	2 x placebo capsules

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 16.

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
- Dalfampridine, or any formulations of 4-AP (or 2,4-DAP)
- Live attenuated influenza vaccine
- Medications that may affect urinary pH: carbonic anhydrase inhibitors, sodium bicarbonate, urinary acidification agents, quinine, quinidine, triamterene, or trimethoprim

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, it is recommended as a general safety precaution when evaluating a CNS-active agent that subjects should avoid alcohol consumption.

No new medications should be initiated during the course of the study, except as deemed necessary by the investigator to treat an AE. No new MS medications should be initiated during study participation, unless there is an urgent medical need. If this occurs, please inform the Medical Monitor.

9.8. Concomitant Medications

Information regarding medications taken by the subject within 30 days prior to the screening visit and 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.

All subjects will have received a stable regimen of MS medications for at least 30 days prior to screening, and will continue the same doses and regimens for the duration of their study participation. Subjects will not have used amantadine, dalfampridine, or any 4-AP or 2,4-DAP preparation within 30 days prior to screening.

Any other current and allowed prescription/non-prescription medications and/or nutritional supplements must have been at a stable dose and frequency for at least 30 days prior to screening, and subjects must be willing to continue those doses and regimens during the placebo-controlled, double-blind period of the study. (This criterion does not apply to medications that are taken on an as-needed basis only).

9.9. Treatment Compliance

Subjects will be instructed to return all used/unused blister cards 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

A subject is considered randomized at Baseline/Week 0, when the site confirms the randomization event via a centralized randomization system (interactive web response system [IWRS]). Complete instructions on the use of the system are provided in the IWRS manual.

Following completion of the 4-week Single-Blind Placebo Run-in Period, consented subjects meeting all eligibility criteria will be randomly assigned in equal probability to 1 of 3 treatment groups: placebo, 137 mg ADS-5102, or 274 mg ADS-5102.

The identity of the treatment assigned to individual subjects can be revealed in an emergency only. Details of the process to be followed are provided in the study and IWRS manuals. The PI is responsible for ensuring that the instructions on how to request unblinding of treatment are stored safely, that their location is known, and that access is readily available to the relevant staff in case of an emergency.

A subject's treatment assignment should only be unblinded when knowledge of the treatment is essential for the safety of the subject. Unblinding for any other reason will be considered a protocol deviation.

10. ASSESSMENT OF EFFICACY

Evaluations relating to efficacy to be performed during the study are described in the following table. Full details on how efficacy assessments are to be performed will be provided in the study manual.

Table 4: Efficacy Assessments

Assessment	Study Visit	Description
Timed 25-Foot Walk (T25FW)	Screening Week 0, Week 2 Baseline/Week 4 Week 8 Week 12 Week 16 (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)	Week 0, Week 2 Baseline/Week 4 Week 8 Week 12 Week 16 (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)	Week 0, Week 2 Baseline/Week 4 Week 8 Week 12 Week 16 (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)	Week 0, Week 2 Baseline/Week 4 Week 8 Week 12 Week 16 (or ET) Safety Follow-Up	The MSWS-12 is a 12-item walking scale that is a measure of subject-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

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 5: Physical Examination Assessments Relating to Safety

Assessment	Study Visit	Description
Complete physical examination	Screening Week 16 (or ET)	Physical examination including: skin, head-neck, eyes-ears-nose-throat, lungs-chest, heart, abdomen, extremities.
Symptom-directed physical examination, as needed	Baseline/Week 4 Week 8 Week 12 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.
Height	Screening	Height will be measured at screening only and recorded in centimeters.
Weight	Screening Week 16 (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	Screening Week 0, Week 2 Baseline/Week 4 Week 8 Week 12 Week 16 (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. During screening only, 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.
Electrocardiogram (ECG)	Screening	A 12-lead ECG (25 or 50 mm/sec) with a 10-second rhythm strip will be recorded after the subject has rested supine or semi-recumbent for at least 5 minutes.

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, as described above.

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 6: Clinical Laboratory and Other Assessments

Assessment	Study Visit	Description
Hematology	Screening Week 16 (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. Hematology will be conducted by a central laboratory.
Serum Chemistry	Screening Week 16 (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, lactate dehydrogenase, aspartate aminotransferase, sodium, total bilirubin, and total protein.
Urinalysis	Screening Week 16 (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)	Screening Week 16 (or ET) Safety Follow-Up	Serum pregnancy test will be performed for all female subjects of childbearing potential.
Urine pregnancy test (if applicable)	Week 0, Week 2 Baseline/Week 4	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 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 separately.

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: www.jointcommission.org/sea_issue_56/.

Subjects should be 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.

Study visits should occur on the day scheduled. There is a (+/-) 2 day window for Visit 3 through Visit 18.

12.1. Screening/Day -21 to -1

During screening, 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 screening visit must be conducted within 21 days prior to the Week 0 visit. Potential study subjects will be evaluated for entry into the study according to the stated inclusion and exclusion criteria. Individuals who are identified during this screening as not eligible for study enrollment need not complete all screening procedures. The reason for ineligible status is to be documented.

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
- Confirm commitment of caregiver and/or study partner, if applicable
- Review inclusion/exclusion criteria and evaluate initial subject eligibility
  - Administer the EDSS (administration instructions and forms will be provided separately)
  - Administer the screening T25FW (administration instructions and forms will be provided in the study manual)
- 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 (e.g., hallucinations, agitation, paranoia, suicidal ideation), history of seizures, stroke or TIA; history of MI or congestive heart failure (CHF); and history of cancer
- Record all medications currently taken or taken in the previous 30 days
- Complete physical examination
- Obtain subject weight in kilograms and height in centimeters
- Vital signs (blood pressure, respiratory rate, heart rate, and temperature), including assessment of orthostatic hypotension
- Blood sample for central laboratory analysis including hematology, serum chemistry and eGFR
- ECG (12-lead)
- Urinalysis
- Blood sample for serum pregnancy test in females of childbearing potential.
- Administer the C-SSRS (administration instructions and forms will be provided in the study manual)

Full details on how individual efficacy assessments are to be performed will be provided in the study manual.

12.2. Single-Blind Placebo Run-In Period/Week 0 to Week 2

The following procedures will be performed at the Week 0 and Week 2 visits:

- Review inclusion/exclusion criteria and assess continued subject eligibility
- 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
- Efficacy assessments
- C-SSRS
- Dispense placebo (4-week supply) for eligible subjects (Week 0 only)
- Collect used/unused blister cards and evaluate compliance (Week 2 only)

12.3. Baseline/Week 4

- Review inclusion/exclusion criteria and determine subject eligibility
- Assess and record any changes in concomitant medications since screening
- Assess and record AEs

- Symptom-direct 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
- Efficacy assessments (see Section 10)
- C-SSRS
- Collect used/unused blister cards and evaluate compliance
- Randomize the subject to treatment via the interactive system
- Dispense double-blind study drug (2-week supply)

12.4. Double-Blind Treatment Period: Telephone Visits at Weeks 5 and 7

- Review dosing instructions
- Assess and record any changes in concomitant medications since screening
- Assess and record AEs

12.5. Double-Blind Treatment Period: Week 6 Visit

- Assess and record concomitant medications
- Assess and record AEs
- C-SSRS
- Collect used/unused blister cards and evaluate compliance
- Dispense double-blind study drug (2-week supply)

12.6. Double-Blind Treatment Period: Week 8 Visit

- Assess and record concomitant medications
- Assess and record AEs
- Symptom-direct physical examination, as needed
- Vital signs (blood pressure, respiratory rate, heart rate, and temperature)
- Efficacy assessments
- C-SSRS
- Collect used/unused blister cards and evaluate compliance
- Dispense double-blind study drug (4-week supply)

12.7. Double-Blind Treatment Period: Week 12 Visit

- Assess and record concomitant medications
- Assess and record AEs
- Symptom-direct physical examination, as needed
- Vital signs (blood pressure, respiratory rate, heart rate, and temperature)
- Efficacy assessments
- C-SSRS
- Collect used/unused blister cards and evaluate compliance
- Dispense double-blind study drug (4-week supply)

12.8. Double-Blind Treatment Period: Week 16 Visit

- Assess and record concomitant medications
- Assess and record AEs
- Complete physical exam
- Vital signs (blood pressure, respiratory rate, heart rate, and temperature)
- Obtain subject weight in kilograms
- Blood sample for central laboratory analysis including hematology, serum chemistry, and eGFR
- Urinalysis
- Blood sample for serum pregnancy test in females of childbearing potential
- Efficacy assessments
- C-SSRS
- Collect used/unused blister cards and evaluate compliance

12.9. Early Termination Visit

- Assess and record concomitant medications
- Assess and record AEs
- Complete physical examination
- Blood sample for central laboratory analysis including hematology, serum chemistry, and eGFR
- Urinalysis
- Vital signs (blood pressure, respiratory rate, heart rate, and temperature)
- Obtain subject weight in kilograms
- Blood sample for serum pregnancy test in females of childbearing potential

- Efficacy assessments
- C-SSRS
- Collect used/unused blister cards 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)

12.10. Safety Follow-Up/End of Study Visit

This will be the final post-treatment safety and efficacy visit for subjects who complete 12 weeks of double-blind treatment but elect not to participate in the OLE study. Subjects will return to the clinic 2 weeks after their Week 16 visit (Week 18), i.e., 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)
- Efficacy assessments
- Blood sample for serum pregnancy test in females of childbearing potential
- C-SSRS

12.11. 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 (e.g., 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 (i.e., signs or symptoms associated with lack of efficacy will generally be considered to reflect underlying disease, rather than AEs);

  - 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 (e.g., 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 CRF(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 (i.e., 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 (e.g., "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 (i.e., 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, i.e., 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 (e.g., 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 (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. If an investigator is uncertain as to whether an SAE has occurred, the investigator should contact the Medical Monitor.

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 (e.g., 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 (e.g., death as a passenger in an automobile accident);
- A clearly more likely alternative explanation for the AE is present (e.g., 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 (i.e., 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, 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 are designated as treatment-emergent adverse events (TEAEs) to distinguish these from AEs occurring after enrollment, but before treatment. For the purposes of this trial, AEs occurring during the Single-Blind Placebo Rin-in Period will be recorded, but will not be considered TEAEs.

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 (e.g., clinical chemistry, hematology) or findings on other assessments (e.g., 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.

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 (e.g., 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. Primary Efficacy Endpoint and Sample Size Determination

The primary efficacy endpoint is the proportion of responders in each treatment group (see definition details below).

Based on the results from the Phase 2 study, responder rates of 24% and 33% were observed at Week 4 for subjects treated with placebo and 274 mg ADS-5102, respectively, in the modified intent-to-treat (MITT) analysis set. In the present study, it is anticipated that the placebo response rate at Week 16 will be no greater than 20% and the response rate among subjects treated with 274 mg or 137 mg ADS-5102 will be at least 33%. Using these estimates, 180 randomized subjects per active treatment group and placebo group will be needed for the test of differences in proportions (Farrington-Manning approach for the Miettimen-Nurminen [MN] test) to have 80% power at the 2-sided 5% significance level to detect this 13% difference favoring ADS-5102. Assuming a 5% dropout rate during the 4-week Single-Blind Placebo Run-In Period, 570 subjects will be enrolled in the study to randomize 540.

For this sample size of 180 randomized subjects per group, power will be at least 80% to detect treatment differences (ADS-5102 versus placebo) of -2.7 seconds and 5.0 meters in the changes from baseline at Week 16 in the TUG test and 2MWT when the standard deviation of the changes from baseline is no greater than 6.0 sec and 14.9 meters, respectively, and the dropout rate is not greater than 20%.

14.2. Analysis Sets

The safety analysis set will include all randomized subjects who receive at least one dose of double-blind study drug and will be analyzed according to the treatment actually received.

The intent-to-treat (ITT) analysis set will include all randomized subjects who receive at least one dose of study drug, and will be analyzed according to the randomized treatment assignment. This population will be used for the efficacy analyses including the analyses of primary and key secondary endpoints.

The per-protocol (PP) analysis set will include all randomized and dosed subjects who provide Week 16 efficacy data and do not have any major protocol deviations that could confound this assessment. This population will also be used for efficacy analyses.

14.3. Handling of Missing Data

This will be described in the statistical analysis plan.

14.4. Efficacy Analyses

14.4.1. Primary Efficacy Analyses

The primary efficacy endpoint is the proportion of responders in the 274 mg ADS-5102 treatment group relative to the placebo group, where a responder is defined as a subject who has a $\geq$ 20% increase from Baseline to Week 16 in walking speed measured using the T25FW (average of two measurements 5 minutes apart). This analysis will be done using the ITT analyses set. Subjects who fail to have an increase of at least 20% at Week 16 in the T25FW

(feet/seconds) will be considered non-responders. Subjects who do not have an observation at Week 16 for whatever reason will be considered to have an indeterminate outcome and will also be included in the denominators, effectively counting them as non-responders for the purpose of treatment comparisons. However, tabulations of each response category will be provided. For this endpoint, baseline will be defined as the average walking speed (feet/seconds) from the T25FW at Weeks 0 and 2 (prior to randomization).

The objective of the primary efficacy analysis is to test for superiority of the 274 mg ADS-5102 group compared to the placebo group in terms of the difference (active minus placebo) in the proportion of responders at Week 16 using the ITT analysis set. This test of proportions will be done using the MN test at the 2-sided 5% level. Both the 2-sided p-value and the 95% confidence interval (CI) for the difference will be obtained. Superiority will be concluded if the lower limit of the 95% CI is greater than zero (equivalently 2-sided p-value < 0.05).

14.4.2. Key Secondary Efficacy Analyses

Provided superiority of 274 mg ADS-5102 versus placebo is shown in the primary analysis, the key secondary objectives will be evaluated using a gatekeeping strategy to control the overall Type I error rate at 5%. Using this approach, the following research hypotheses will be evaluated sequentially in the order given using the ITT analyses set: (1) superiority of 274 mg ADS-5102 compared to placebo in mean change from baseline at Week 16 in the T25FW (feet/second) test; (2) superiority of 274 mg ADS-5102 compared to placebo in mean change from baseline at Week 16 in the TUG (sec) test; (3) superiority of 274 mg ADS-5102 compared to placebo in mean change from baseline at Week 16 in the 2MWT (m); (4) superiority of 137 mg ADS-5102 compared to placebo in terms of the proportion of T25FW responders at Week 16; (5) superiority of 137 mg ADS-5102 compared to placebo in mean change from baseline at Week 16 in the T25FW (feet/second) test; (6) superiority of 137 mg ADS-5102 compared to placebo in mean change from baseline at Week 16 in the TUG test; and (7) superiority of 137 mg ADS-5102 compared to placebo in mean change from baseline at Week 16 in the 2MWT. For each hypothesis, if a non-significant result ($p > 0.05$) is obtained, no further inferential conclusions will be drawn and any statistically significant result will be declared supportive of efficacy only.

The test of superiority of 137 mg ADS-5102 versus placebo in terms of the proportion of responders at Week 16 will be done using the same approach as for the primary analyses.

The tests of superiority of 274 mg ADS-5102 and of 137 mg ADS-5102 versus placebo in terms of the mean change from baseline in the T25FW, TUG test, and the 2MWT will be done using t-tests derived from the corresponding linear mixed model with repeated measurement (MMRM) model with the change from baseline (i.e., T25FW, TUG, or 2MWT) as the dependent variable and fixed effects of treatment group, study week, and treatment by study week interaction. The baseline value will be included as a covariate and an unstructured variance-covariance matrix will be used for the within-subject residual variability. For the T25FW, TUG test, and the 2MWT, baseline will be the average of Weeks 0 and 2 (prior to randomization).

14.4.3. Secondary Supportive Analyses

Each active dose will be compared to placebo in terms of the mean change from baseline at each study visit in the T25FW, TUG test, and the 2MWT. These analyses will be done using the MMRM model described earlier. The T25FW (sec) will be evaluated in a similar manner.

For the MSWS-12, the research hypothesis of superiority of 274 mg ADS-5102 compared to placebo in the mean changes from baseline at Week 16 will be evaluated using the pooled Phase 3 studies. Similar evaluations will be done for 137 mg ADS-5102. Details of these analyses will be provided in the SAP for the Integrated Summaries of Efficacy (ISE).

14.5. Safety and Tolerability

Adverse events will be recorded starting from the date/time of first dose during the Single-Blind Placebo Run-In Period through the EOS Visit. The time periods of AE recording will be divided into AEs with onset during the Single-Blind Placebo Run-In Period and AEs during the Double-Blind Treatment Period (i.e., TEAEs). All AEs will be listed by subject and period.

For AEs during double-blind treatment, standard incidence rates will be summarized by treatment group, system organ class (SOC) and preferred term (PT) within SOC in the safety analysis set. This includes all subjects who received at least one dose of double-blind study drug according to the treatment arm actually received.

Incidence of TEAEs will be summarized for:

- All TEAEs
- Investigator-determined treatment-related TEAEs
- TEAEs leading to drug discontinuation
- TEAEs by severity
- Serious TEAEs (SAEs)
- Investigator- determined treatment-related SAEs
- Discontinuation due to SAEs

Clinical laboratory test parameters will be listed for individual subjects and values outside of the reference ranges will be flagged. Descriptive statistics for the mean and mean changes from baseline at each study week will be generated by treatment group. The incidence of potentially clinically significant changes in laboratory parameters will be tabulated by treatment group. 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 treatment group and visit. Results will also be depicted graphically.

14.6. Demographics and Baseline Characteristics

Demographic and baseline characteristics (age at screening, gender, weight, height, BMI, race, ethnicity, medical history, physical examination) will be listed for individual subjects and will be summarized by treatment group. Demographic data and key baseline characteristics will be summarized for the safety population.

14.7. 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 by treatment group.

14.8. Completion of the Study and Withdrawals

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

14.9. 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 (e.g., 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 (e.g., 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 EDC system. 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 GCP 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 GCP 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 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.

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22. APPENDICES

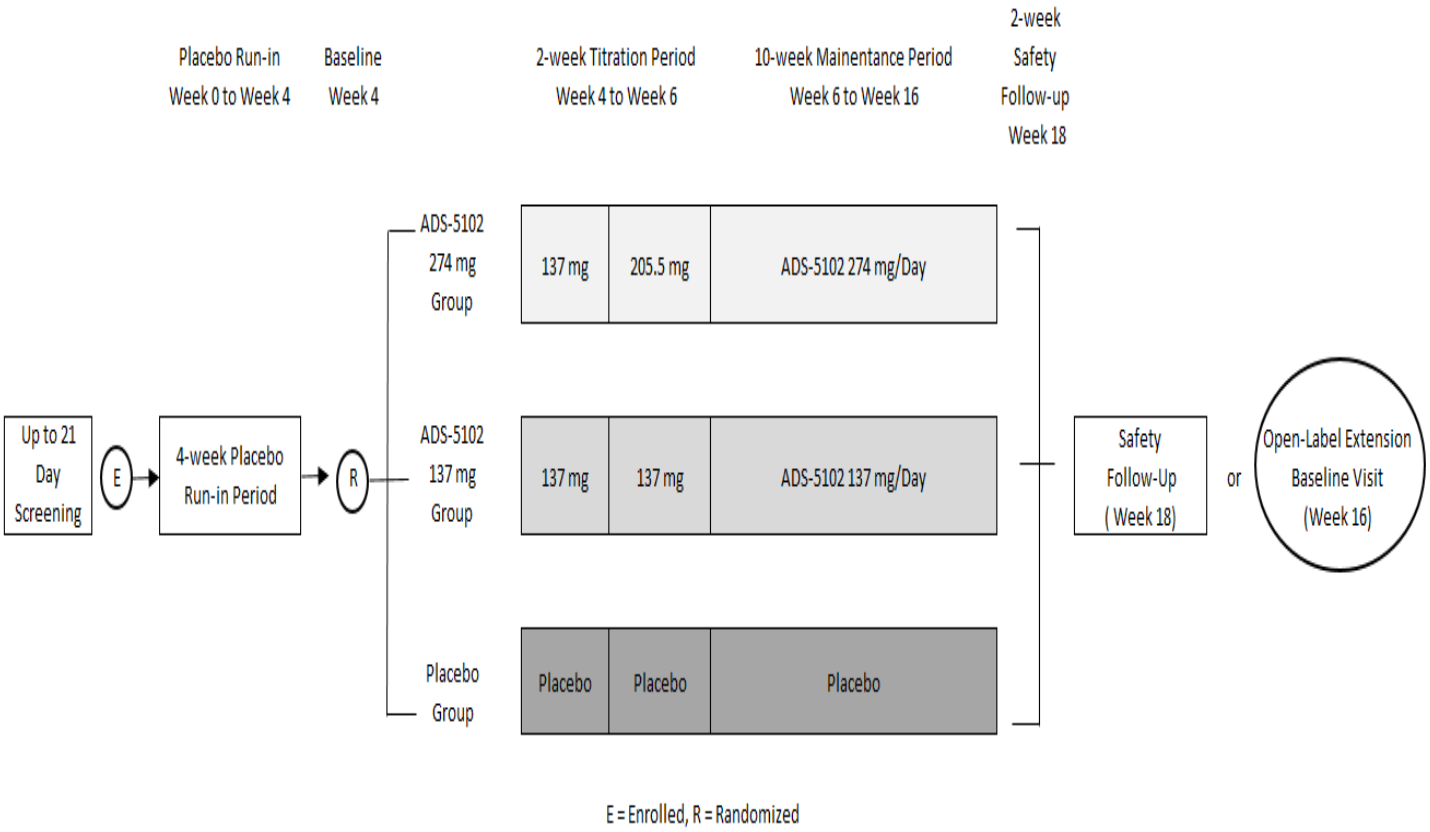
APPENDIX A. SCHEDULE OF EVENTS

	Screening	Single-Blind Placebo Run-In Period [d]		Double Blind Treatment Period[a] (±2 day) [d]					Safety Follow-Up[b] (±2 day)	Early Termination
				Baseline	Maintenance					
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	
Week		**0**	**2**	**4**	**6**	**8**	**12**	**16**	**18**	
Informed consent	✓									
Eligibility criteria	✓	✓	✓	✓						
Demographics	✓									
Medical history	✓									
Medication history	✓									
Concomitant medications	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Adverse events		✓	✓	✓	✓	✓	✓	✓	✓	✓
Complete physical exam	✓							✓		✓
Symptom-directed physical exam, as needed				✓		✓	✓		✓	
Height	✓									
Weight	✓							✓		✓
Vital signs	✓	✓	✓	✓		✓	✓	✓	✓	✓
Hematology	✓							✓		✓
Serum chemistry	✓							✓		✓
Urinalysis	✓							✓		✓
ECG (12-lead)	✓									
Serum pregnancy test (if applicable)	✓							✓	✓	✓
Urine pregnancy test (if applicable)		✓	✓	✓						
Expanded Disability Status Scale (EDSS)	✓									
Timed 25-Foot Walk (T25FW)[c]	✓	✓	✓	✓		✓	✓	✓	✓	✓
Multiple Sclerosis Walking Scale-12 (MSWS-12)[c]		✓	✓	✓		✓	✓	✓	✓	✓
Timed Up and Go (TUG)[c]		✓	✓	✓		✓	✓	✓	✓	✓
2-Minute Walk Test (2MWT)[c]		✓	✓	✓		✓	✓	✓	✓	✓
Columbia-Suicide Severity Rating Scale (C-SSRS)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Randomization				✓						
Collect returned study drug & assess compliance			✓	✓	✓	✓	✓	✓		✓
Dispense study drug		✓	✓	✓	✓	✓	✓			
Study drug dosing, once daily at bedtime		✓	✓	✓	✓	✓	✓	✓		

[a] In addition, telephone visits will be conducted at Weeks 5 and 7 to review dosing instructions and assess and record AEs and any changes in concomitant medications.

[b] For subjects who elect not to enter the open-label extension study
[c] Efficacy assessments include Multiple Sclerosis Walking Scale-12 (MSWS-12), Timed 25-Foot Walk (T25FW), Timed Up and Go (TUG), and 2-Minute Walk Test (2MWT), to be performed in that order
[d] Study visits should occur on the day scheduled. There is a (+/-) 2 day of the visit window from Visit 3 through Visit 18.

APPENDIX B. STUDY DESIGN SCHEMATIC



Adamas Pharmaceuticals, Inc.

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

05Dec2019

Statistical Analysis Plan

Version 2.0

Prepared by:

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List of Abbreviations

Abbreviation	Explanation
2MWT	2-Minute Walk Test
2,4-DAP	2,4-diaminopyridine
4-AP	4-aminopyridine
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
bpm	Beats per Minute
BUN	Blood Urea Nitrogen
CH	Clinically High
CI	Confidence interval
CL	Clinically Low
cm	centimeters
CRF	Case report form (paper and/or electronic)
C-SSRS	Columbia-Suicide Severity Rating Scale
CTMS	Clinical Trial Management System
DMT	Disease Modifying Therapy
ECG	Electrocardiogram
EDSS	Expanded Disability Status Scale
eGFR	Estimated glomerular filtration rate

Abbreviation	Explanation
EOS	End of study
ER	Extended Release
ET	Early termination
HCl	Hydrochloride
HEENT	Head, Eyes, Ears, Nose, and Throat
ICH	International Conference on Harmonization
ITT	Intent-to-treat
IV	Intravenous
IWRS	Interactive web response system
kg	Kilograms
LDH	Lactate Dehydrogenase
LLN	Lower Limit of Normal
m	Meters
MAR	Missing at Random
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mg/d	Milligrams per day
MI	Multiple Imputation
MITT	Modified intent to treat
mL/min	Milliliters per minute

Abbreviation	Explanation
mmHg	Millimeters of Mercury
MMRM	Mixed model repeated measurement
MN	Miettinen-Nurminen
MS	Multiple sclerosis
MSWS-12	Multiple Sclerosis Walking Scale-12
N/A	Not Applicable
NMAR	Not Missing at Random
OLE	Open-label extension
PCS	Potentially clinically significant
PP	Per-protocol
PT	Preferred Term
RBC	Red Blood Cell
s, sec	Seconds
SAP	Statistical Analysis Plan
SI	International Standard
SOC	System organ class
T25FW	Timed 25-Foot Walk
TEAE	Treatment-emergent adverse event
TUG	Timed Up and Go
ULN	Upper Limit of Normal
WBC	White blood cell(s); leukocyte(s)
WHO	World Health Organization

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1. Introduction

This statistical analysis plan (SAP) is based upon Section 14 (Statistics) of the Protocol dated 28 February 2018 / Amendment 1.0 and is prepared in compliance with International Conference on Harmonization (ICH) E9. Furthermore, this SAP describes the analyses and data presentations for the final analysis of data collected for Study ADS-AMT-MS301.

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).

2. Objectives

2.1. Primary

To evaluate the efficacy of 274 mg ADS-5102 in subjects with multiple sclerosis (MS) with walking impairment as measured by the Timed 25-foot Walk (T25FW, feet/second) at Week 16.

2.2. Secondary

2.2.1. Key

- To evaluate the efficacy of 274 mg ADS-5102 in subjects with MS and walking impairment as measured by the Timed Up and Go (TUG) test (s), and the 2-Minute Walk Test (2MWT) (m) at Week 16.
- To evaluate the efficacy of 137 mg ADS-5102 in subjects with MS and walking impairment as measured by the T25FW (feet/second), the TUG test (s), and the 2MWT (m) at Week 16.

2.2.2. Supportive

- To evaluate the efficacy of 274 mg ADS-5102 and 137 mg ADS-5102 in subjects with MS and walking impairment as measured by the T25FW (s), the TUG (s), and the 2MWT (m) across all study visits.
- To evaluate the efficacy of 274 mg ADS-5102 and 137 mg ADS-5102 in subjects with MS and walking impairment as measured by the Multiple Sclerosis Walking Scale-12 (MSWS-12) in subjects treated with 274 mg ADS-5102 and subjects treated with 137 mg ADS-5102.

2.2.3. Safety

- To evaluate the safety and tolerability of 274 mg and 137 mg of ADS-5102 in subjects with MS and walking impairment.

3. Investigational Plan

3.1. Overall Study Design and Plan

This is a multicenter, 3-arm, randomized, placebo-controlled, double-blind, parallel-group study of ADS-5102 (amantadine ER capsules) in MS subjects with walking impairment, incorporating a Single-Blind Placebo Run-In Period prior to randomization, and forced up-titration for the high-dose group.

All subjects will have received a stable regimen of MS medications, both disease modifying and symptomatic, for at least 30 days prior to screening, and will continue the same doses and regimens for the duration of their study participation, to the extent compatible with good neurological care. Subjects will not have used amantadine, dalfampridine, or any 4-AP or 2,4 diaminopyridine (2,4-DAP) preparation within 30 days prior to screening.

Consented subjects who complete the up to 3-week screening period will undergo a 4-week Single-Blind Placebo Run-In Period during which they will take their dose of 2 placebo capsules once daily at bedtime.

Subjects who complete the Single-Blind Placebo Run-In Period and continue to meet study eligibility criteria will be randomized with equal probability to 1 of 3 treatment groups: placebo or ADS-5102 at a final dosage of either 137 or 274 mg/d (treatment groups are identified by their final dosage). Study drug will be administered as 2 capsules once daily at bedtime.

Subjects who are randomized to placebo will receive placebo capsules throughout the 12-week Double-Blind Treatment Period, including the 2-week forced titration and 10-week maintenance phases.

Subjects who are randomized to 274 mg of ADS-5102 will receive 137 mg for the first week (Week 1 of the forced titration phase of the Double-Blind Treatment Period), 205.5 mg for the second week (Week 2 of the forced titration phase of the Double-Blind Treatment Period), and 274 mg for the remaining 10 weeks of the 12-week Double-Blind Treatment Period.

Subjects will return to the clinic for safety and efficacy assessments at Week 0 and Week 2 prior to randomization and at Weeks 4 (randomization and baseline visit), 6 (only safety), 8, 12, and 16 after randomization. In addition, telephone visits for safety assessments will be conducted at Weeks 5 and 7. Subjects who withdraw from the study before Week 16 will have an early termination visit that includes safety follow-up and efficacy assessments, as appropriate.

Subjects who complete 12 weeks of double-blind treatment (16 weeks total treatment, including placebo run-in) without significant protocol deviations, as assessed by the investigator and the sponsor, will be eligible to enter an optional open-label extension (OLE) study, protocol ADS-AMT-MS303. The Week 16 visit of Study ADS-AMT-MS301 will serve as the first study visit of Study ADS-AMT-MS303 for those subjects who consent to participate.

Subjects who complete 12 weeks of double-blind treatment (16 weeks total treatment, including placebo run-in) but elect not to participate in the OLE study will return to the clinic for a final

post-treatment safety and efficacy assessment 2 weeks after their Week 16 visit (Week 18), i.e., after being off treatment for approximately 2 weeks.

The End of Study (EOS) is defined as when a subject completes the Week 16 visit (if electing to enter the OLE study) or the Safety Follow-Up Visit (Week 18) (if electing not to enter the OLE study).

All study visits and efficacy assessments should be scheduled at approximately the same time of day for an individual subject. To the extent practicable, study visits and efficacy assessments should be scheduled to occur when a subject is not likely to be experiencing acute side effects from a concomitant medication (e.g., flu-like side effects following interferon-beta injection). Efficacy assessments should be conducted in the following sequence: MSWS-12; T25FW; TUG; 2MWT. Subjects using an assistive device during the walking assessments at Screening should use the same assistive device for all subsequent walking tests. Each efficacy assessment for an individual should be performed by the same clinical rater, if possible.

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

The schedule of assessments is provided in Appendix 14.1.

3.2. Study Endpoints

3.2.1. Primary

The primary efficacy endpoint is the proportion of responders in each treatment group, where a responder is defined as a subject who has a ≥20% increase from Baseline to Week 16 in walking speed measured using the T25FW (average of two measurements 5 minutes apart), in the Intent-to-Treat (ITT) analyses set. Subjects who do not have a Week 16 assessment will be classified as having an indeterminate outcome and will be included in the denominator (i.e., they will be treated as de-facto non-responders). If a subject has not completed two walking tests, then the result for the one T25FW will be used.

3.2.2. Secondary

3.2.2.1. Key

The key secondary endpoints listed below will be used for comparisons between treatment groups for which inferential statistics, with appropriate control of the Type I error rate, will be used.

- The mean change from baseline at Week 16 in the T25FW (feet/second)
- The mean change from baseline at Week 16 in the TUG (s)
- The mean change from baseline at Week 16 in the 2MWT (m)

3.2.2.2. Supportive

The following endpoints will be used for supportive comparisons among treatment groups.

- Mean changes from baseline in the T25FW (feet/second) at Weeks 8 and 12
- Mean changes from baseline in the T25FW (s) at Weeks 8, 12 and 16
- Mean changes from baseline in the TUG (s) at Weeks 8 and 12
- Mean changes from baseline in the 2MWT (m) at Weeks 8 and 12

3.2.2.3. Safety

Safety endpoints will include incidence of subjects with adverse events data, potentially clinically significant changes in laboratory data, and changes in the Columbia-Suicide Severity Rating Scale (C-SSRS) data.

4. Treatments

Study treatments consist of an oral formulation of extended release (ER) amantadine HCl (ADS-5102) and a placebo control. The clinical supplies will include 137 mg and 68.5 mg ADS-5102 capsules and matching placebo capsules. All capsules provided during the study are indistinguishable in size and appearance.

The dosing regimens for the 2 active treatment arms are:

- 137 mg/d (1 x 137 mg capsule + 1 placebo capsule) for 12 weeks for the 137 mg ADS-5102 group
- 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 10 weeks for the 274 mg ADS-5102 group

Placebo capsules will be administered orally as 2 capsules once daily at bedtime for the 4-week Single-Blind Placebo Run-In Period for all subjects and for the 12-week Double-Blind Treatment Period for subjects randomized to the placebo arm.

4.1. Dose Adjustment/Modifications

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. These subjects should be encouraged to complete study visits per the protocol.

Dose Adjustment for Adverse Events

Study drug may only be withheld for the evaluation or treatment of an 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. Study drug may not be down-

titrated. This procedure applies to the withholding of study drug throughout the study with the exception of the titration phase of the Double-Blind Treatment Period.

In the special case of study drug being withheld for the evaluation or treatment of an AE occurring during the titration phase of the Double-Blind Treatment Period (i.e., Week 4 to Week 6), 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. The subject is to finish the remaining capsules in the blister card, i.e., including the 2-dose overage. The subject must return to the clinic to receive his or her next blister pack without missing any additional doses. If, in the judgement of the investigator, study drug needs to be withheld for more than 3 consecutive days, the subject is to be permanently discontinued from study drug.

5. General Statistical Considerations

5.1. Randomization, Stratification, and Blinding

A subject is considered randomized at Baseline/Week 4, when the site confirms the randomization event via a centralized randomization system (interactive web response system [IWRS]).

Following completion of the 4-week Single-Blind Placebo Run-in Period, consented subjects who continue to meet eligibility criteria will be randomly assigned in equal probability to 1 of 3 treatment groups: placebo, 137 mg ADS-5102, or 274 mg ADS 5102. No stratifications are being utilized in the randomization design.

The identity of the treatment assigned to individual subjects can be revealed in an emergency only. A subject's treatment assignment should only be unblinded when knowledge of treatment is essential for the safety of the subject. Emergency unblinding will be considered a major protocol deviation.

5.2. Sample Size

Based on the results from the Phase 2 study, responder rates of 24% and 33% were observed at Week 4 for subjects treated with placebo and 274 mg ADS-5102, respectively, in the modified intent-to-treat (MITT) analysis set. In the present study, it is anticipated that the placebo response rate at Week 16 will be no greater than 20% and the response rate among subjects treated with 274 mg or 137 mg ADS-5102 will be at least 33%. Using these estimates, 180 randomized subjects per active treatment group and placebo group will be needed for the test of differences in proportions (Farrington-Manning approach for the Miettinen-Nurminen [MN] test) to have 80% power at the 2-sided 5% significance level to detect this 13% difference favoring ADS-5102. Assuming a 5% dropout rate during the 4-week Single-Blind Placebo Run-In Period, 570 subjects will be enrolled in the study to randomize 540.

For this sample size of 180 randomized subjects per group, power will be at least 80% to detect treatment differences (ADS-5102 versus placebo) of -2.7 seconds and 5.0 meters in the changes from baseline at Week 16 in the TUG test and 2MWT when the standard deviations of the

change from baseline are no greater than 6.0 sec and 14.9 meters, respectively, and the dropout rate is not greater than 20%.

5.3. Analysis Set

5.3.1. All Enrolled

The all enrolled set will include all subjects who signed the study informed consent form and entered the placebo run-in period.

5.3.2. Intent-to-Treat (ITT) Set

The intent-to-treat (ITT) analysis set will include all randomized subjects who receive at least one dose of double-blind study drug, and will be analyzed according to the randomized treatment assignment. This population will be used for the efficacy analyses including the analyses of primary and key secondary endpoints.

5.3.3. Per Protocol (PP) Set

The per-protocol (PP) analysis set will include all randomized and dosed subjects who provide Week 16 T25FW data and do not have any major protocol deviations as outlined in Section 6.2 that could confound this assessment. These deviations will be determined prior to unblinding and database lock. This population will also be used for select efficacy analyses. Subjects in the PP set will be analyzed according to the randomized treatment assignment.

5.3.4. Safety Set

The safety analysis set will include all randomized subjects who receive at least one dose of double-blind study drug, and will be analyzed according to the treatment actually received. If there are no treatment misallocations, this population will be identical to the ITT analysis set.

5.4. Baseline

For endpoints based on the T25FW, Baseline will be defined as the average of up to two separate visit averages (each based on up to two measurements taken five minutes apart) collected at Weeks 2 and 4 (prior to randomization). If one of the two T25FW Baselines values is missing, then Baseline will be defined as the last non-missing measurement prior to or on the date of randomization.

For endpoints based on the TUG, 2MWT, and MSWS-12, Baseline will be defined as the average of up to two separate measurements collected at Weeks 2 and 4 (prior to randomization). If one of the two TUG, 2MWT and/or MSWS-12 Baselines values is missing, Baseline will be defined as the last non-missing measurement prior to or on the date of randomization.

For C-SSRS analyses, the questionnaire three-year history data obtained during the Screening visit will be considered Baseline.

For all other endpoints, Baseline is defined as the last non-missing measurement prior to or on the date of randomization.

5.5. Study Completion

Study completion is defined as study participation through the Week 16 Visit and rollover into OLE, or completion of a Safety Follow-Up Visit.

5.6. Study Day

Study Day 1 will correspond with the date of first dose of double-blind study drug. Study day will be calculated as follows:

If the Date of Interest < First Dose Date of Double-Blind Study Drug then,

$$Study\ Day = (Date\ of\ Interest - Date\ of\ Randomization)$$

If the Date of Interest ≥ First Dose Date of Double-Blind Study Drug then,

$$Study\ Day = Date\ of\ Interest - Date\ of\ Randomization + 1$$

For subjects that are never treated with double-blind study drug, study day will not be calculated.

5.7. Standard Conversions

The following conversions will be used:

$1\ Year = 365.25\ days$
$1\ Month = 30\ days$
$1\ Week = 7\ days$

1 Meter = 39.37 inches

5.8. Unscheduled Visits

Data collected at unscheduled visits will be displayed in data listings and used to calculate maximum/minimum values, as applicable, but will not be displayed in summaries presented by study visit.

5.9. Visit Windowing

No programmatic visit windowing will be implemented.

5.10. Significance Level

Unless otherwise specified, all testing of statistical significance will be 2-sided, and a treatment difference resulting in a p-value less than or equal to 0.05 will be considered statistically significant. Similarly, all confidence intervals will be two-sided 95% confidence intervals.

5.11. Data Imputation

Unless otherwise specified, all available efficacy and safety data will be included in data listings and tabulations. Prior to database lock, critical data that are potentially spurious or erroneous will be examined and queried according to standard data management operation procedures.

For the efficacy analyses of responder rates, a subject with missing data will be defined as a non-responder. For all other endpoints, missing data will be treated as missing and no data imputations will be applied, unless otherwise specified. See Section 9.2.1 for sensitivity analyses concerning the missing data assumptions.

5.11.1. Missing/Partial Dates in Concomitant Medications

Concomitant medications with start dates that are completely or partially missing will be analyzed as follows:

- If month and year are known, but day is missing, then impute day to first of the month
- If year is known, but day and month are missing, then 1st of January of the year will be imputed
- If the start date is completely missing, then impute date to first dose date of double-blind study drug
- Should any of the previous concomitant medication start dates created come after the complete medication stop date provided, the medication stop date will be used instead

Concomitant medications with stop dates that are completely or partially missing will be analyzed as follows:

- If "ongoing" is checked, no imputation is necessary
- If month and year are known but day is missing, the last day of the month will be imputed
- If year is known, but day and month are missing,
    - If YYYY < year of last dose of double-blind study drug, then 31st of December will be imputed
    - If YYYY = year of last dose of double-blind study drug, then the last dose date of study drug will be imputed
    - If YYYY > year of last dose of double-blind study drug, then 1st of January will be imputed
- If the stop date is completely missing, then impute date to last dose date of double-blind study drug
- If subject dies, then use death date for concomitant medication stop date. After the imputation, all imputed stop dates will be checked against the corresponding start dates to ensure the stop date does not come before the start date. If the imputed stop date is prior to the start date, then the start date will be used.

5.11.2. Missing/Partial Dates in Adverse Events

Adverse events with start dates that are completely or partially missing will be imputed as follows:

- If month and year are known but day is missing
  - If month and year are the same as month and year of first dose date of double-blind study drug, then impute to first dose date of double-blind study drug
  - If month and year are different than month and year of first dose date of double-blind study drug, then impute to first of the month
- If year is known but day and month are missing
  - If year is same as year of first dose date of double-blind study drug, then first dose date of double-blind study drug will be used instead
  - If year is different than year of first dose date of double-blind study drug, then 1st of January of the year will be imputed
- If the start date is completely missing, then it will be imputed with first dose date of double-blind study drug

5.11.3. Missing/Partial Dates for Multiple Sclerosis Symptom Onset and Diagnosis Date

Multiple sclerosis symptom onset dates and diagnosis dates that are partially missing will be imputed as follows:

- If year is present, but month and day are missing, impute to July 1
- If year and month are present but day is missing, impute to 1st of month
- If year and day are present but month is missing, impute to July
- If year is missing, or date is completely missing – do not impute. Leave as missing

5.11.4. Multiple Sclerosis Walking Scale Imputations

A maximum of three missing items in the twelve-item scale will be allowed. As necessary, any missing value will be imputed as the average of the non-missing items. If more than three of the twelve items have missing responses, no total score will be computed for the given timepoint.

5.11.5. Laboratory Data Imputations

If a lab value is reported using a non-numeric qualifier (e.g., less than [<] a certain value, or greater than [>] a certain value), the given numeric value will be used in the summary statistics, ignoring the non-numeric qualifier. For instance, a value reported as "<200" would be listed as such, but summarized as "200."

5.12. Software Details

All statistical procedures will be performed using SAS® Version 9.3 or higher.

5.13. Reporting Conventions

All tables, listings, figures and any other supportive SAS output will include in the footer explanatory notes that will indicate, at a minimum, the programming source (i.e., name, file path of the SAS program that generates the output), data extraction date, and run date.

Continuous data will be described using descriptive statistics as follows: number of observations (n), mean, median, standard deviation, minimum, and maximum, unless otherwise specified. All minimum and maximum values will be displayed with the same number of decimal places relative to the raw data, the mean and median will be displayed with one additional decimal place, and the standard deviation will be displayed with two additional decimal places.

Categorical data will be summarized by the number and percentage of subjects in each category. The denominator of all percentages will be number of subjects in the population of interest, unless otherwise stated. When count data are presented, the percent will be suppressed when the count is zero in order to draw attention to the non-zero counts. A row denoted "Missing" will be included in count tabulations where necessary to account for dropouts and missing values. Non-zero percentages will be rounded to one decimal place, except 100% will be displayed without any decimal places.

In summary tables for categorical data, all categories will be presented if they are specified on the Case Report Form (CRF), or if categories are ordered intervals (e.g., age groups), regardless of whether data were present in each category, unless otherwise specified. For other categorical data (e.g., AEs and medications), only categories with non-zero frequencies will be presented.

P-values will be rounded to 4 decimal places. P-values that round to 0.0000 will be presented as '<0.0001' and p-values that round to 1.000 will be presented as '>0.9999'. Confidence intervals (CIs) will be presented as 2-sided 95% CIs unless specified differently in specific analysis.

Data will be displayed in all listings sorted by treatment, study site, and subject number concatenated with site number. All summaries will be presented by treatment group, unless otherwise specified.

When no data are available for a table or appendix, an empty page with the title will be produced with suitable text (e.g., "There are no observations for this table/appendix.").

6. Subject Disposition

6.1. Disposition

The all enrolled set will be utilized for a table summarizing the number of subjects included and excluded from each analysis set, along with reasons for exclusion. The summary will be provided by treatment group and overall and will also be provided in a data listing.

The ITT set will be utilized for a table summarizing subjects discontinuing study drug early by treatment group and overall and will include the following information:

- Whether the subject completed treatment through Week 16 (Yes, No)
- As applicable, the reason for premature study drug discontinuation

The ITT set will be utilized for a table summarizing subject study completion status by treatment group and overall and will include the following information:

- Subject completion status (Yes, No)
- Whether the subject consented to participate in the open label extension (Yes, No)
- Reason for early termination

All disposition information will also be provided in data listings.

6.2. Protocol Deviations

Protocol deviations will be recorded within the PPD Clinical Trial Management System (CTMS) and undergo cross-functional team review prior to database lock in order to finalize the PP set. The Deviation Guidance Document contains all potential protocol deviations classified by CTMS subtype. After review, deviations deemed to be of special interest will be classified as significant protocol deviations.

Major protocol deviations are those deviations that may have an impact on the efficacy analysis or the safety of the subject. Major protocol deviations can be related to study inclusion/exclusion criteria, trial conduct, patient management, or patient assessments. Major protocol deviations will be determined by the sponsor and submitted to PPD prior to database lock. Major protocol deviations are a subset of significant deviations.

The number and percentage of subjects with significant protocol deviations will be summarized by treatment group and overall using the ITT set. Subjects will be counted once within each deviation category regardless of how many deviations they have in that category.

All significant protocol deviations will also be provided in a data listing.

A blinded review of the data listings will be conducted prior to database lock to determine the extent to which subjects completed the study according to the protocol. In the event that the blinded data review reveals major protocol deviations that impact interpretation of efficacy assessments, the per-protocol (PP) analysis set may exclude additional subjects. Final decisions regarding subjects to be included in all analysis sets will be made prior to any unblinding of the treatment allocations and database lock.

7. Demographics and Baseline Characteristics

7.1. Demographics

The following demographic information will be summarized for the Safety, ITT, and PP sets by treatment group and overall:

- Age (years), calculated as (informed consent date – birth date + 1) / 365.25
    - No rounding will be performed and only the integer value will be retained
- Categorical Age (<55, ≥55, <65, ≥65)
- Gender (Female, Male)
- Ethnicity (Hispanic or Latino, Not Hispanic and Not Latino)

- Race (White, African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other)
- Height (cm)
- Weight (kg)
- BMI (kg/m^2)
- Categorical BMI (Underweight (<18.5), Normal (18.5 - <25), Overweight (25 - <30), Obese (≥30))
- Expanded Disability Status Scale (EDSS) score at Baseline
- Baseline T25FW (<26.5 s, ≥26.5 s)

Demographic information will also be provided via data listings.

7.2. Medical History

7.2.1. General Medical History

General medical history information will be summarized using the ITT set by system organ class.

MedDRA dictionary Version 21.0 will be used for reporting and will be described in the relevant table and listing footnotes.

General medical history information will also be provided via data listings.

7.2.2. Multiple Sclerosis Disease History

The following multiple sclerosis specific disease information will be summarized for the ITT set by treatment group and overall:

- Type of Multiple Sclerosis (Relapsing Remitting, Secondary Progressive, Progressive with Relapse, Progressive Without Relapse)
- Time Since Symptom Onset (years), calculated as (informed consent date – date + 1) / 365.25
- Time Since Diagnosis (years), calculated as (informed consent date – date + 1) / 365.25
- Corticosteroids (IV or Oral) or ACTHAR Gel Use within 30 days prior to screening (Yes, No)
- Prior Amantadine Use (Yes, No)
- Prior Dalfampridine Use (Yes, No) and Form (Ampyra/Fampyra, 4-Aminopyrimidine, 2-4-Diaminopyrimidine) and reason for stopping (Side Effects, Loss of Efficacy, No Efficacy, Other)

Multiple sclerosis disease history will also be provided via data listings.

7.3. Inclusion and Exclusion Criteria

Inclusion and exclusion violations will be provided via data listings.

8. Treatments and Medications

8.1. Prior and Concomitant Medications

Prior medications are defined as medications with a stop date occurring from 30 days prior to the screening visit up to the day prior to randomization. Concomitant medications are defined as medications taken on or after the date of randomization through the date of last dose of study drug (inclusive) or listed as ongoing. Medications with start and stop dates (or ongoing) which bracket the randomization date will be summarized as both prior and concomitant medications.

All non-study drugs (including prescribed and over the counter medications) taken during the study will be collected on the CRF. All medications will be coded according to the World Health Organization (WHO) Drug Dictionary and summarized using the Anatomical Therapeutic Chemical (ATC) class (Level 2) and preferred term (PT). The WHO Drug Dictionary dated March, 2018 will be used for study reporting and will be detailed in the relevant table and listing footnotes.

Prior medications will be summarized for the Safety set. Medications taken prior to enrollment and prior to randomization will be summarized separately. At each level of summarization, a subject is counted once if he/she reported one or more medications at that level.

Concomitant medications will be recorded beginning with the first dose of study drug and continuing through the last study visit. Concomitant medications will be summarized for the Safety set. At each level of summarization, a subject is counted once if he/she reported one or more medications at that level.

Prior and concomitant medication information will also be provided via data listings.

8.2. Study Treatments

Study drug will be packaged in child-resistant blister wallets, each containing a total of 36 capsules (two capsules per dose, allowing for a two-week supply plus two extra doses per week).

Table 1: Expected Capsules Dispensed and Returned by Visit

Visit	Expected Capsules Dispensed at The Indicated Visit	Expected Capsules Returned at The Next Visit
Week 0	72	16*
Week 2	N/A	N/A
Week 4	36	8
Week 6	36	8
Week 8	72	16
Week 12	72	16
Week 16	0	N/A

* 2 blister wallets containing 36 capsules each are dispensed at Week 0. One is to be collected at Week 2, the other at Week 4

8.2.1. Extent of Exposure

The extent of double-blind study drug exposure will be summarized for the active treatment arms with continuous measures (n, mean, median, standard deviation, minimum, and maximum) and categorical measures (1-7 days, 8-14 days, 15-28 days, 29-56 days, 57-84 days, and >84 days; >= 1 month, >=2 months, and >=3 months) using the Safety set.

Extent of exposure will be calculated as follows:

$$\begin{aligned} &Extent\ of\ exposure\ (days) \\ &= (Date\ of\ Last\ Dose\ of\ Double\ Blind\ Study\ Drug \\ &- Date\ of\ First\ Dose\ of\ Double\ Blind\ Study\ Drug) + 1 \end{aligned}$$

Study drug exposure details for both the Placebo Run-in and Double-Blind Treatment periods will also be provided via data listings.

8.2.2. Drug Accountability and Treatment Compliance

Treatment compliance in the Placebo Run-In and Double-Blind Treatment Periods will be summarized separately for the Safety set and calculated as follows:

$$Treatment\ compliance\ (capsules, \%) = \left(\frac{A}{P}\right) * 100$$

where

$P = The\ number\ of\ capsules\ prescribed = Number\ of\ days\ dosing\ expected * 2\ Capsules$
$A = The\ actual\ number\ of\ capsules\ taken$

Total number of capsules prescribed will be calculated based on the number of capsules prescribed from Day 1 to the last day of dosing. If the number of capsules returned at a given visit is missing, overall treatment compliance will be missing. Non-compliance is defined as less than 80% or more than 120% non-missing compliance with study drug. Subjects with missing compliance are classified as non-assessable.

Drug accountability and treatment compliance data will also be provided via data listings.

9. Efficacy Analysis

The ITT set will be used for the primary efficacy analysis, as well as for the primary analysis of each secondary endpoint.

9.1. Primary Efficacy Analysis

The primary efficacy endpoint is the proportion of responders in each treatment group as defined in Section 3.2.1.

The objective of the primary efficacy analysis is to compare the 274 mg ADS-5102 group versus the placebo group in terms of the difference (active minus placebo) in the proportion of responders at Week 16 using the ITT analysis set. The Farrrington-Manning test will be used to obtain a 2-sided p-value based on the resulting Z-score. The Miettinen-Nurminen (MN) approach will be used to obtain the 95% confidence interval (CI) for the difference. Superiority will be concluded if the 2-sided p-value is less than 0.05 and the lower limit of the 2-sided 95% CI is greater than 0.00. (Note that this test is effectively a one-sided test at the 0.025 level.)

This test can be expressed mathematically as follows:

$$H_0: d = 0$$
$$H_1: d > 0$$

Where $d = p_1 - p_0$ (i.e. risk difference between the proportion of responders in the 274 mg ADS-5102 group and the proportion of responders in the placebo group).

The primary efficacy analysis will be provided via a summary table.

9.1.1. Sensitivity Analyses

Subjects with missing data will be treated as non-responders for efficacy analyses of responder rates. The following analyses will be performed to assess the impact of missing data:

- The primary efficacy analysis specified in Section 9.1 will be repeated using:
    1. The Per-Protocol Set
    2. Study Completers.
        - Subjects who complete Week 16 treatment and have pertinent Week 16 efficacy data.

9.1.2. Subgroup Analyses

Subgroup analyses for the primary efficacy analysis specified in Section 9.1 will be repeated using the following subgroups:

- Categorical Age
    - <55
    - ≥55
    - <65
    - ≥65
- Gender
    - Female
    - Male
- Race

  - African American
  - White
  - Other (Asian, Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native, Other)
- Categorical BMI
  - Underweight (<18.5)
  - Normal (18.5 - <25)
  - Overweight (25 - <30)
  - Obese (≥30)
- Type of MS
  - Relapsing remitting
  - Secondary progressive
  - Progressive with relapse
  - Progressive without relapse
- Time Since MS diagnosis
  - < Median of enrolled trial population
  - ≥ Median of enrolled trial population
- EDSS Score at Baseline
  - 0 to 3.5 (No to minimal walking limitation)
  - 4 to 5.5 (Walking limitation)
  - 6 to 6.5 (Need for assistive device)
- Use of Assistive Devices During T25FW Test at Baseline
  - Yes / No
- History of Dalfampridine Use
  - Yes / No
- History of Amantadine Use
  - Yes / No
- T2FW Category at Baseline
  - < 26.5 seconds
  - ≥26.5 seconds

The results will be provided via summary tables and also presented graphically in a forest plot.

9.2. Key Secondary Efficacy Analyses

The key secondary endpoints are the mean changes from Baseline between treatment groups at Week 16 for the T25FW (feet/second), TUG (s), and 2MWT (m). These are described in Section 3.2.2.1.

Provided superiority of 274 mg ADS-5102 versus placebo is shown in the primary analysis, the key secondary objectives will be evaluated using a fixed-sequence gatekeeping strategy to control the overall Type I error rate at 5%. Using this approach, the following research hypotheses will be evaluated sequentially in the order given using the ITT analysis set:

1. Superiority of 274mg ADS-5102 compared to placebo in mean change from baseline at Week 16 in the T25FW(feet/second) test

2. Superiority of 274 mg ADS-5102 compared to placebo in mean change from baseline at Week 16 in the TUG (s) test
3. Superiority of 274 mg ADS-5102 compared to placebo in mean change from baseline at Week 16 in the 2MWT (m)
4. Superiority of 137 mg ADS-5102 compared to placebo in terms of the proportion of T25FW responders at Week 16
5. Superiority of 137 mg ADS-5102 compared to placebo in mean change from baseline at Week 16 in the T25FW (feet/second) test
6. Superiority of 137 mg ADS-5102 (s) compared to placebo in mean change from baseline at Week 16 in the TUG test
7. Superiority of 137 mg ADS-5102 compared to placebo in mean change from baseline at Week 16 in the 2MWT(m)

At each step, superiority will be concluded if the 2-sided p-value is less than 0.05 and the lower limit of the 2-sided 95% CI is greater than 0.00, for tests comparing responder rates or mean changes from baseline in 2MWT and T25FW, or the 2-sided 95% CI is less than 0.00, for tests comparing mean changes from baseline in the TUG. If a non-significant result (p-value ≥ 0.05) or a p-value <0.05 is noted but superiority is not shown, no further inferential conclusions will be drawn and any subsequent statistically significant result will be declared supportive of efficacy only. This strategy effectively controls the Type I error rate at the 2.5% level (one-sided) for testing superiority of ADS-5102 versus placebo.

The statistical test of difference between 137 mg ADS-5102 versus placebo in terms of responders at Week 16 (Item 4 above) will be done using the same approach used for the primary analysis.

The hypothesis tests of difference between 274 mg ADS-5102 and of 137 mg ADS-5102 versus placebo in terms of the mean change from baseline in the T25FW, TUG test, and the 2MWT, as described above, will be done using t-tests derived from the corresponding linear mixed model with repeated measurement (MMRM) model with the change from baseline (i.e., T25FW, TUG, or 2MWT) as the dependent variable and fixed effects of treatment group, study week, and treatment by study week interaction. The baseline value will be included as a covariate and an unstructured variance-covariance matrix will be used for the within-subject residual variability. Should the model fail to converge under this assumption, then a compound symmetry covariance structure will be assumed. The Kenward-Rogers method will be used to estimate the denominator degrees of freedom.

All key secondary analyses will be repeated using the PP set.

Least squared mean change from baseline values will be presented graphically by visit and treatment for the T25FW, TUG, and 2MWT.

9.2.1. Sensitivity Analyses

For the analyses of the key secondary variables, mean changes from baseline in T25FW, TUG and 2MWT, the MMRM model (Protocol Section 14.4.2) will be used based on available data

and there will be no imputation of missing values. These analyses effectively assume that the missing observations are missing at random (MAR). For each parameter, two sensitivity analyses will be conducted using a multiple imputation (MI) approach. The first sensitivity analysis will assume the data are MAR and will include additional covariates (Age, Duration of MS) in the imputation step that could be predictive of response and/or the probability of missingness. The second sensitivity analysis will assume the data are not missing at random (NMAR) and missing observations in the ADS-5102 treatment group will be imputed as if they had been obtained in the placebo treatment group.

9.3. Secondary Supportive Efficacy Analyses

The supportive secondary endpoints are the mean changes from Baseline between treatment groups at Weeks 8, 12, and 16 for the T25FW (s) and Weeks 8 and 12 for the T25FW (feet/second), TUG (s), and 2MWT (m). These are described in Section 3.2.2.2.

Each active dose will be compared to placebo in terms of the mean change from baseline at each study visit in the T25FW (both feet/sec and sec), TUG test, and the 2MWT. These analyses will be done using the MMRM model described earlier.

9.4. Other Efficacy Analyses

9.4.1. Multiple Sclerosis Walking Scale -12

Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be provided for the MSWS-12 total score by study visit.

For this scale, each of the twelve items can be answered with five options with 1 meaning no limitation and 5 meaning extreme limitation. The total score is generated and transformed to a 0 to 100 scale by subtracting the minimum score possible (12) from the subject's score, dividing by the maximum score possible minus the minimum possible (60 – 12 = 48), and multiplying the result by 100. Walking improvement on the MSWS-12 is indicated by negative change scores.

9.4.2. Change in Walking Speed using T25FW

The percent change in average walking speed from Baseline to Week 16 using the T25FW will be calculated by treatment group and presented in a summary table. The difference in the percent change in average walking speed between placebo and active drug (137 mg ADS-5102 and 274 mg ADS-5102) will be analyzed. Point estimates, 95% confidence intervals, and p-values will be presented.

10. Safety Analyses

10.1. Adverse Events

Adverse events (AE) will be recorded starting from the date/time of first dose during the Single-Blind Placebo Run-In Period through the End of Study (EOS) Visit. The time periods of AE

recording will be divided into AEs with onset during the Single-Blind Placebo Run-In Period and AEs with onset during the Double-Blind Treatment Period.

A Treatment-Emergent Adverse Event (TEAE) is defined as an adverse event that begins or worsens in severity on or after the date of randomization.

Incidence of TEAEs during the Double-Blind Treatment Period (as well as number and percentage of subjects with TEAEs) will be tabulated according to Medical Dictionary for Regulatory Activities (MedDRA) by system organ class (SOC) and preferred term (PT) and will include the following categories:

- All TEAEs
- Most Commonly Reported TEAEs (≥5% in any treatment group) (by PT only)
- TEAEs by Relatedness to Study Drug
- TEAEs by Severity
- TEAEs Leading to Study Drug Discontinuation
- Serious TEAEs Leading to Study Drug Discontinuation by Relatedness to Study Drug
- Serious TEAEs by Relatedness to Study Drug
- Study Drug-Related Serious TEAEs
- TEAEs of Special Interest

MedDRA dictionary Version 21.0 will be used for reporting and will be described in the relevant table and listing footnotes.

Subjects with the same AE more than once will have that event counted only once within each System organ class (SOC) and Preferred term (PT). Subjects with the same AE more than once will have the maximum intensity of that event counted within each SOC and once within each PT for summaries of severity.

SOCs and PTs within SOC will be presented by descending frequency based on the ADS-5102 274 mg and ADS-5102 137 mg groups combined.

An overall summary AE table will include the numbers and percentages of subjects who had at least one of each of the following: TEAE, serious TEAE, study drug-related TEAE, TEAE leading to study drug discontinuation, serious TEAE leading to study drug discontinuation, study drug-related serious TEAE, AE of special interest, or on-study death.

TEAEs that have missing severity will be classified in table summaries as severe. Similarly, TEAEs that have missing relationship to study drug will be classified in table summaries as related.

All AEs will be listed by subject and period.

The three AE categories listed below are considered adverse events of special interest (AESI):

- Suicidality
- Hallucinations
- Events Potentially Related to Orthostatic Hypotension.

For each of the AESIs listed above, an additional data listing will be provided to include additional information collected in the clinical database for each type of AESI. Death Adverse events resulting in death will be provided in a separate data listing.

10.2. Clinical Laboratory Evaluations

The clinical laboratory assessments relating to safety to be performed include those for Hematology, and Serum Chemistry.

Laboratory assessments for hematology and serum chemistry will be performed by a central laboratory. All summaries will be based on the International System (SI) units provided by the central lab. No unit conversions will be made.

All clinical laboratory measures will be classified using the following alert flags:

- LP - Low Panic
- LT - Low Telephone
- LN - Low Normal
- N – Normal
- HP - High Panic
- HT - High Telephone
- HN - High Normal
- AB - Abnormal

10.2.1. Hematology

The number and percentage of subjects with any potentially clinically significant changes from baseline will be tabulated and summarized by treatment group.

Table 2: Potential Clinical Significance (PCS) for Hematology Parameters

Laboratory Parameter	Flag	Criteria*	
		Observed Value	Change from Baseline
Hemoglobin	High (CH)	> 1.3 × ULN	> 30% Increase from Baseline
	Low (CL)	< 0.8 × LLN	> 20% Decrease from Baseline
Hematocrit	High (CH)	> 1.3 × ULN	> 30% Increase from Baseline
	Low (CL)	< 0.8 × LLN	> 20% Decrease from Baseline
Erythrocyte count (RBC)	High (CH)	> 1.3 × ULN	> 30% Increase from Baseline
	Low (CL)	< 0.8 × LLN	> 20% Decrease from Baseline
Mean corpuscular Volume (MCV)	High (CH)	> 1.15 × ULN	> 15% Increase from Baseline

Laboratory Parameter	Flag	Criteria*	
		Observed Value	Change from Baseline
	Low (CL)	< 0.85 × LLN	> 15% Decrease from Baseline
Mean corpuscular hemoglobin (MCH)	High (CH)	> 1.15 × ULN	> 15% Increase from Baseline
	Low (CL)	< 0.85 × LLN	> 15% Decrease from Baseline
Mean corpuscular hemoglobin concentration (MCHC)	High (CH)	> 1.15 × ULN	> 15% Increase from Baseline
	Low (CL)	< 0.85 × LLN	> 15% Decrease from Baseline
Leukocyte count (WBC)	High (CH)	> 1.6 × ULN	> 100% Increase from Baseline
	Low (CL)	< 0.65 × LLN	> 60% Decrease from Baseline
Neutrophils	High (CH)	> 1.6 × ULN	> 100% Increase from Baseline
	Low (CL)	< 0.65 × LLN	> 75% Decrease from Baseline
Lymphocytes	High (CH)	> 1.5 × ULN	> 100% Increase from Baseline
	Low (CL)	< 0.25 × LLN	> 75% Decrease from Baseline
Eosinophils	High (CH)	> 4.0 × ULN	> 300% Increase from Baseline
	Low (CL)	N/A	N/A
Monocytes	High (CH)	> 4.0 × ULN	> 300% Increase from Baseline
	Low (CL)	N/A	N/A
Basophils	High (CH)	> 4.0 × ULN	> 300% Increase from Baseline
	Low (CL)	N/A	N/A
Platelets	High (CH)	> 1.5 × ULN	> 100% Increase from Baseline
	Low (CL)	< 0.65 × LLN	> 50% Decrease from Baseline

Notes: PCS = potentially clinically significant
CH = high PCS based on criterion value and increase from predose.
CL = low PCS based on criterion value and decrease from predose.
*A postdose value is considered as a PCS value if it meets both criteria for observed value and change from predose.

Hematology data will also be provided via data listings.

10.2.2. Serum Chemistry

The number and percentage of subjects with any potentially clinically significant changes from baseline will be tabulated and summarized by treatment group.

Table 3: Potential Clinical Significance (PCS) for Serum Chemistry Parameters

Laboratory Parameter	Flag	Criteria*	
		Observed Value	Change from Baseline
Bicarbonate	High (CH)	> 1.3 × ULN	> 40% Increase from Baseline

Laboratory Parameter	Flag	Criteria*	
		Observed Value	Change from Baseline
	Low (CL)	< 0.7 × LLN	> 40% Decrease from Baseline
Sodium	High (CH)	> 1.1 × ULN	> 10% Increase from Baseline
	Low (CL)	< 0.85 × LLN	> 10% Decrease from Baseline
Potassium	High (CH)	> 1.2 × ULN	> 20% Increase from Baseline
	Low (CL)	< 0.8 × LLN	> 20% Decrease from Baseline
Phosphorus	High (CH)	> 3.0 × ULN	> 200% Increase from Baseline
	Low (CL)	< 0.5 × LLN	> 50% Decrease from Baseline
Chloride	High (CH)	> 1.2 × ULN	> 20% Increase from Baseline
	Low (CL)	< 0.8 × LLN	> 20% Decrease from Baseline
Calcium	High (CH)	> 1.3 × ULN	> 30% Increase from Baseline
	Low (CL)	< 0.7 × LLN	> 30% Decrease from Baseline
Alkaline phosphatase (ALP)	High (CH)	> 2.0 × ULN	> 100% Increase from Baseline
	Low (CL)	< 0.5 × LLN	> 80% Decrease from Baseline
Alanine Aminotransferase (ALT)	High (CH)	> 3.0 × ULN	> 200% Increase from Baseline
	Low (CL)	N/A	N/A
Aspartate Aminotransferase (AST)	High (CH)	> 3.0 × ULN	> 200% Increase from Baseline
	Low (CL)	N/A	N/A
Gamma-glutamyl transferase	High (CH)	> 3.0 × ULN	> 200% Increase from Baseline
	Low (CL)	N/A	N/A
Lactate Dehydrogenase (LDH)	High (CH)	> 4.0 × ULN	> 300% Increase from Baseline
	Low (CL)	< 0.4 × LLN	> 60% Decrease from Baseline
Bilirubin, Total	High (CH)	> 2.5 × ULN	> 150% Increase from Baseline
	Low (CL)	N/A	N/A
Glucose, non-fasting	High (CH)	> 3.0 × ULN	> 200% Increase from Baseline
	Low (CL)	< 0.6 × LLN	> 40% Decrease from Baseline
Protein, Total	High (CH)	> 1.5 × ULN	> 50% Increase from Baseline
	Low (CL)	< 0.5 × LLN	> 50% Decrease from Baseline
Albumin	High (CH)	> 1.5 × ULN	> 50% Increase from Baseline
	Low (CL)	< 0.5 × LLN	> 50% Decrease from Baseline
Serum creatinine	High (CH)	> 2.0 × ULN	> 100% Increase from Baseline
	Low (CL)	< 0.3 × LLN	> 100% Decrease from Baseline
Blood Urea Nitrogen (BUN)	High (CH)	> 3.0 × ULN	> 200% Increase from Baseline
	Low (CL)	< 0.2 × LLN	> 100% Decrease from Baseline

Notes: PCS = potentially clinically significant
CH = high PCS based on criterion value and increase from predose.

Laboratory Parameter	Flag	Criteria*	
		Observed Value	Change from Baseline

CL = low PCS based on criterion value and decrease from predose.

*A postdose value is considered as a PCS value if it meets both criteria for observed value and change from predose.

Serum chemistry data will also be provided via data listings.

10.3. Vital Sign Measurements

The number and percentage of subjects with any potentially clinically significant changes from baseline will be tabulated and summarized by treatment group for vital sign parameters including blood pressure and heart rate.

Table 4: Potential Clinical Significance for Vital Signs Parameters

Vital Sign Parameter	Flag	Criteria*	
		Observed Value	*Change from Baseline*
Systolic Blood Pressure (mmHg)	High (CH)	≥ 180 mmHg	Increase of ≥ 20 mmHg
	Low (CL)	≤ 90 mmHg	Decrease of ≥ 20 mmHg
Diastolic Blood Pressure (mmHg)	High (CH)	≥ 105 mmHg	Increase of ≥ 15 mmHg
	Low (CL)	≤ 50 mmHg	Decrease of ≥ 15 mmHg
Heart Rate (bpm)	High (CH)	≥ 120 bpm	Increase of ≥ 15 bpm
	Low (CL)	≤ 50 bpm	Decrease of ≥ 15 bpm

Notes: PCS = potentially clinically significant
CH = high PCS based on criterion value and increase from predose.
CL = low PCS based on criterion value and decrease from predose.
mmHg = Millimeter mercury. bpm = Beat per minute.

*A postdose value is considered as a PCS value if it meets both criteria for observed value and change from predose.

Vital signs data will also be provided via data listings.

10.4. Physical Examination

Complete physical examinations will be performed at Screening and Week 16 (or ET) and symptom-directed examinations will be performed as needed.

Clinically significant abnormal findings will be summarized at Screening and Week 16 (or ET) by body system and overall for each treatment.

All abnormal physical examination data will be provided via data listings.

10.5. C-SSRS

C-SSRS data will be scored using the Columbia-Suicide Severity Rating Scale Score and Data Analysis Guide and the following summaries will be provided:

- Number of subjects with suicidal ideation, suicidal behavior, and self-injurious behavior without suicidal intent during lifetime
- Number of subjects with suicidal ideation, suicidal behavior, and self-injurious behavior without suicidal intent during past three years
- Number of subjects with suicidal ideation, suicidal behavior, and self-injurious behavior without suicidal intent during double-blind treatment period
- Shift-table to demonstrate changes in suicidal ideation scores from baseline during treatment

CSSR-S data will also be provided via data listings.

10.5.1. C-SSRS Outcomes, Endpoints, and Scoring

The following outcomes are C-SSRS categories and have binary responses (yes/no):

- Category 1: Wish to be Dead
- Category 2: Non-specific Active Suicidal Thoughts
- Category 3: Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
- Category 4: Active Suicidal Ideation with Some Intent to Act, without Specific Plan
- Category 5: Active Suicidal Ideation with Specific Plan and Intent
- Category 6: Preparatory Acts or Behavior
- Category 7: Aborted Attempt
- Category 8: Interrupted Attempt
- Category 9: Actual Attempt (non-fatal)
- Category 10: Completed Suicide

Self-injurious behavior without suicidal intent is also a C-SSRS outcome and has a binary response (yes/no).

The following outcome is a numerical score derived from the C-SSRS categories. The score is created at each assessment for each patient and is used for determining treatment emergence.

- **Suicidal Ideation Score:** The maximum suicidal ideation category (1-5 on the CSSRS) present at the assessment. Assign a score of 0 if no ideation is present.

Composite endpoints using the categories described above are defined below.

- **Suicidal Ideation:** A ”yes” answer at any time during treatment to any one of the five suicidal ideation questions (Categories 1-5) on the C-SSRS.
- **Suicidal Behavior:** A ”yes” answer at any time during treatment to any one of the five suicidal behavior questions (Categories 6-10) on the C-SSRS.
- **Suicidal Ideation or Behavior:** A ”yes” answer at any time during treatment to any one of the 10 suicidal ideation or behavior questions (Categories 1-10) on the C-SSRS.

CSSR-S data will also be provided via data listings.

11. Changes from the Protocol in the Planned Analyses

- Section 14.1 of the protocol version amendment 1 states that the primary efficacy endpoint is the proportion of responders in each treatment group, but in Section 14.4.1 this same endpoint is said to be the proportion of responders in the 274 mg ADS-5102 treatment group relative to the placebo group. The definition included in Section 14.4.1 is being used for this analysis.
- Additional details on how the test for superiority will be performed for the primary efficacy analysis and the key secondary endpoints using the sequential gatekeeping strategy have been provided.
- Emergency unblinding will be considered a major protocol deviation.
- The Safety set will include all subjects who receive at least one dose of double-blind study drug.
- Randomization date instead of first treatment with double-blind study drug will be used to determine adverse event treatment emergence.
- Section 14.2 of protocol version amendment 1 states that any missing Week 16 efficacy data will remove a subject from the per-protocol population; the analysis will only use missing T25FW at Week 16 to exclude from that population.
- During the finalization of the protocol, the numbering of the study weeks was revised as shown in the table below.

	Single Blind Placebo Run-in Period			Double Blind Treatment Period
Original numbering	Week -4 (prior to 1rst pbo dose)	Week -2	Week 0 (prior to randomization)	Week 0 to Week 12
Revised numbering	Week 0 (prior to 1rst pbo dose)	Week 2	Week 4 (prior to randomization)	Week 4 to Week 16

12. Changes from the Initial SAP version

12.1. Timed 25-foot Walk Percent Change

The percent change in T25FW will be calculated and descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be provided for the percent change by study visit. Additionally, the MMRM described in section 9.2 will be performed with the percent change from baseline as the dependent variable and fixed effects of treatment group, study week, and treatment by study week interaction.

12.2. Prior Amantadine Use

Prior Amantadine Use (Yes, No), form and reason for stopping (Side Effects, Loss of Efficacy, No Efficacy, Other), dose, and frequency of use will be summarized for the ITT set by treatment group and overall.

12.3. Concomitant Multiple Sclerosis Therapies

Concomitant multiple sclerosis therapies will be recorded beginning with the first dose of study drug and continuing through the last study visit. These medications will be summarized for the Safety set. At each level of summarization, a subject is counted once if he/she reported one or more medications at that level.

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14. Appendices

14.1. Schedule of Events

Schedule of Study Procedures	Screening	Single-Blind Placebo Run-In Period (±2 day)[d]		Double Blind Treatment Period[a] (±2 day)					Safety Follow-Up[b] (±2 day)	Early Termination
				Baseline	Maintenance					
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	
Week		**0**	**2**	**4**	**6**	**8**	**12**	**16**	**18**	
Informed consent	✓									
Eligibility criteria	✓	✓	✓	✓						
Demographics	✓									
Medical history	✓									
Medication history	✓									
Concomitant medications	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Adverse events		✓	✓	✓	✓	✓	✓	✓	✓	✓
Complete physical exam	✓							✓		✓
Symptom-directed physical exam, as needed				✓		✓	✓		✓	
Height	✓									
Weight	✓							✓		✓
Vital signs	✓	✓	✓	✓		✓	✓	✓	✓	✓
Hematology	✓							✓		✓
Serum chemistry	✓							✓		✓
Urinalysis	✓							✓		✓
ECG (12-lead)	✓									
Serum pregnancy test (if applicable)	✓							✓	✓	✓
Urine pregnancy test (if applicable)		✓	✓	✓						
Expanded Disability Status Scale (EDSS)	✓									
Timed 25-Foot Walk (T25FW)[c]	✓	✓	✓	✓		✓	✓	✓	✓	✓
Multiple Sclerosis Walking Scale-12 (MSWS-12)[c]		✓	✓	✓		✓	✓	✓	✓	✓
Timed Up and Go (TUG)[c]		✓	✓	✓		✓	✓	✓	✓	✓
2-Minute Walk Test (2MWT)[c]		✓	✓	✓		✓	✓	✓	✓	✓

Schedule of Study Procedures	Screening	Single-Blind Placebo Run-In Period (±2 day)[d]		Double Blind Treatment Period[a] (±2 day)					Safety Follow-Up[b] (±2 day)	Early Termination
				Baseline	Maintenance					
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	
Week		**0**	**2**	**4**	**6**	**8**	**12**	**16**	**18**	
Columbia-Suicide Severity Rating Scale (C-SSRS)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Randomization				✓						
Collect returned study drug & assess compliance			✓	✓	✓	✓	✓	✓		✓
Dispense study drug		✓	✓	✓	✓	✓	✓			
Study drug dosing, once daily at bedtime		✓	✓	✓	✓	✓	✓	✓		

[a] In addition, telephone visits will be conducted at Weeks 5 and 7 to review dosing instructions and assess and record AEs and any changes in concomitant medications.
[b] For subjects who elect not to enter the open-label extension study
[c] Efficacy assessments include Multiple Sclerosis Walking Scale-12 (MSWS-12), Timed 25-Foot Walk (T25FW), Timed Up and Go (TUG), and 2-Minute Walk Test (2MWT), to be performed in that order
[d] Study visits should occur on the day scheduled. There is a (+/-) 2 day window for Visit 3 through Week 18.

14.2. Study Design Schematic