

ADS-AMT-PD301

EFFICACY AND SAFETY OF ADS-5102 (AMANTADINE HCL) EXTENDED RELEASE CAPSULES FOR THE TREATMENT OF LEVODOPA INDUCED DYSKINESIA IN PARKINSON'S DISEASE PATIENTS (EASE LID STUDY)

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

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

Telephone: +1 (510) 450-3500

Facsimile: +1 (510) 428-0519

Medical Monitor: Mary Jean Stempien, MD, FACP


Document Date: 31 March 2015

Version: Amendment 2


CONFIDENTIAL THIS DOCUMENT IS CONFIDENTIAL AND CONTAINS PROPRIETARY
INFORMATION OF ADAMAS PHARMACEUTICALS, INC., WHICH MAY NOT BE DISCLOSED
WITHOUT EXPRESS PRIOR WRITTEN PERMISSION OF ADAMAS PHARMACEUTICALS, INC.

APPROVALS

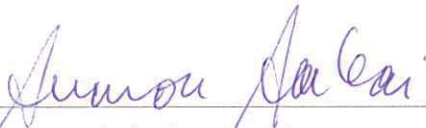
Reviewed and Approved by:



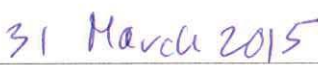
Mary Jean Stempien, MD, FACP
Medical Monitor
Adamas Pharmaceuticals, Inc.



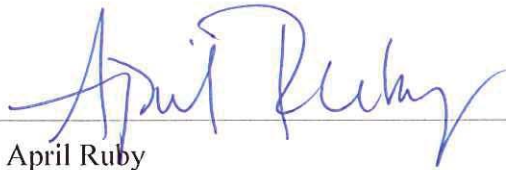
Date




Sharon Sakai, Ph.D., RAC
Vice President, Regulatory Affairs
Adamas Pharmaceuticals, Inc.



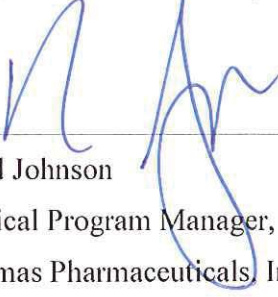
Date




April Ruby
Sr. Director, Clinical Operations
Adamas Pharmaceuticals, Inc.



Date



Reed Johnson
Clinical Program Manager, Clinical Operations
Adamas Pharmaceuticals, Inc.



Date

1. SYNOPSIS

Name of Sponsor/Company: Adamas Pharmaceuticals, Inc.	
Name of Investigational Product: ADS-5102 (amantadine HCl) Extended Release Capsules	
Name of Active Ingredient: Amantadine Hydrochloride	
Title of Study: Efficacy and Safety of ADS-5102 (amantadine HCl) Extended Release Capsules for the Treatment of Levodopa Induced Dyskinesia in Parkinson's Disease Patients (EASE LID Study)	
Study center(s): Approximately 55 sites worldwide	
Study Duration: Approximately 23 months (from randomization of first subject to last subject completion).	Phase of development: 3
<p>Objectives:</p> <p>Primary:</p> <ul style="list-style-type: none"> To evaluate the efficacy of ADS-5102 oral capsules, an extended release formulation of amantadine, at a dose level of 340 mg, dosed once nightly at bedtime, for the treatment of levodopa induced dyskinesia (LID) in subjects with Parkinson's disease (PD) <p>Secondary:</p> <ul style="list-style-type: none"> To evaluate the safety and tolerability of ADS-5102 in this study population 	
<p>Study Design:</p> <p>This is a multi-center, randomized, double-blind, placebo-controlled, 2-arm, parallel group study of ADS-5102 in subjects with PD who have LID.</p> <p>All subjects will have received a stable regimen of antiparkinson's medications for at least 30 days prior to screening, including a levodopa preparation administered not less than three times daily, and be willing to continue the same doses and regimens for the duration of their study participation.</p> <p>Consented subjects who complete screening and meet study eligibility criteria will be centrally randomized in a 1:1 ratio to one of 2 treatment groups: placebo or active (340 mg ADS-5102).</p> <p>Study medications will be administered as 2 capsules once nightly at bedtime (if possible, no earlier than 9 pm) for 25 weeks.</p> <p>Subjects who are randomized to placebo will receive placebo throughout the 25 week treatment period, in a double-blind fashion.</p>	

Subjects who are randomized to active treatment will receive ADS-5102 throughout the 25 week treatment period. Active treatment will start with 170 mg ADS-5102 during Week 1, followed by 23 weeks of 340 mg ADS-5102, and end with 170 mg ADS-5102 during Week 25, in a double-blind fashion.

Following completion of Visit 2 (Baseline/Day 1/Week 0) subjects will return to the clinic after 1, 2, 4, 8, 12, 18, 24, and 25 weeks of dosing.

Subjects who complete 25 weeks of dosing will have the option of transitioning directly to an open-label extension study, ADS-AMT-PD302.

Subjects who decline participation in the open-label extension study will have a final safety follow-up visit at Week 26, 1 week following the completion of dosing, which will include a pregnancy test, if appropriate.

Subjects who withdraw from the study before Week 25 will have an early termination visit that includes safety follow-up and efficacy assessments, if appropriate. In addition, subjects who discontinue study drug after Week 4 should receive a reduced dose for one additional week, either 170 mg ADS-5102 or placebo, in a double-blind fashion before stopping study drug. The additional week of dosing at a reduced dose will not be needed for subjects who discontinue study drug before Week 4.

Subjects who prematurely discontinue from study drug after Week 12, but continue to follow the study protocol procedures, including efficacy assessments, will have the option of transitioning directly into the open-label extension study after their Week 25 visit, as long as the reason for discontinuation of study drug was not due to an adverse event judged to be related to study drug.

A detailed study design schematic can be found in [Appendix B](#).

Study visits and assessments will be scheduled and conducted within the time window of 9 am through 4 pm. All study visits for an individual subject should be scheduled at approximately the same time of day. Efficacy assessments should be conducted when the subject is ON and experiencing their typical dyskinesia and at least 30 minutes following a subject's regularly scheduled levodopa dose. The efficacy measurements for each subject should be performed by the same rater, if possible.

During the screening period, potential subjects and any involved caregivers or study partners will be trained on the proper completion of 24-hour PD home diaries. Following successful completion of training, a set of two consecutive 24-hour diaries (48 hours total) will be completed prior to Visit 2 (Baseline/Day 1/Week 0), serving as the baseline diary score, and repeated prior to selected study visits.

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

Methodology:**Primary Efficacy Analysis:**

The primary efficacy analysis will be completed in the modified intent to treat (MITT) population, which will include all randomized and dosed subjects who provide at least one post-baseline efficacy assessment. The primary efficacy analysis will be completed using a linear mixed model with the change from baseline in the UDysRS score as the dependent variable. The model will include fixed effects for treatment group, week (five levels: 2, 8, 12, 18, and 24), and the interaction between treatment group and week. The baseline value of the UDysRS will be included as a covariate and the unstructured covariance model will be used. The primary analysis will compare the active (340 mg ADS-5102) group to the placebo group at Week 12 using a two-sided test at the 5% level of significance.

Key Secondary Analyses:

The following key secondary analyses will be conducted using a hierarchical procedure ([Westfall and Krishen, 2001](#)) to control the overall level of significance, in the order shown below:

- 340 mg ADS-5102 vs. placebo for UDysRS at Week 24
- 340 mg ADS-5102 vs. placebo for ON Time without troublesome dyskinesia at Week 12
- 340 mg ADS-5102 vs. placebo for ON Time without troublesome dyskinesia at Week 24
- 340 mg ADS-5102 vs. placebo for OFF Time at Week 12
- 340 mg ADS-5102 vs. placebo for OFF Time at Week 24

The above hypotheses will be tested using two-sided tests at the 5% level of significance, but a specified comparison will only be considered to be confirmatory if the primary efficacy analysis and all previously conducted key secondary analyses are statistically significant ($p < 0.05$).

Other Secondary Analyses:

Quantitative secondary endpoints will also be analyzed using linear mixed models for repeated measurements. Using the same model as for the primary analysis, comparisons between active and placebo will also be made at Weeks 2, 8, 12, 18, and 24. In addition, the primary efficacy analysis will be repeated for the per-protocol population, a subset of the efficacy analysis population who complete 12 weeks of study treatment and provide Week 12 efficacy assessments. A per protocol analysis will also be repeated for a subset of the efficacy analysis population who complete 24 weeks of study treatment and provide Week 24 efficacy assessments. All secondary analyses will be performed using two-sided tests at the 5% level of significance.

Safety Analyses:

The safety analysis population will include all randomized subjects who receive at least one dose of study drug. Safety endpoints will be summarized by treatment group (ADS-5102 or

placebo) from the time of first dose and include all available safety data. No formal statistical testing will be done.

All AE data will be listed and will be summarized by system organ class, preferred term, and treatment group. Quantitative safety variables (e.g., vital signs and clinical laboratory tests) will be summarized at each visit by treatment group and changes from baseline will be summarized by treatment group at selected visits.

Sample Size Justification:

In the previous phase 2/3 study, ADS-PAR-AM201, the estimates of the standard deviation (SD) of the UDysRS total score change from baseline to Week 8 across the four treatment groups ranged from 10.8 to 14.1 units and the estimated treatment difference between the 340 mg group and the placebo group was 11.3 units. Assuming an SD of 14 units, and based on the use of a two-sided test at the 5% level of significance, a sample size of 92 subjects (46 per group) provides 90% power to detect a treatment difference of 9.5 units. In order to account for a potential dropout rate of up to 20%, the planned sample size is 120 subjects (60 per group). The overall dropout rate will be monitored in a blinded fashion and the sample size may be adjusted if the dropout rate is different from our estimates.

Number of subjects (planned): Approximately 120 (approximately 60 in placebo group, 60 in active group)

Diagnosis and eligibility criteria for inclusion:

INCLUSION CRITERIA:

1. Signed a current IRB/REB/IEC-approved informed consent form
2. Male or female subjects between 30 and 85 years of age, inclusive
3. Ambulatory or ambulatory-aided (e.g. walker or cane) ability while ON, such that the subject can complete study assessments
4. Knowledgeable and reliable caregiver/study partner, if appropriate, to accompany the subject to study visits and assist in completion of study instruments, as needed and allowed
5. Following diary training, the subject is willing and able to understand and complete the 24-hour PD home diary (caregiver/study partner assistance allowed)
6. Parkinson's disease, per UK Parkinson's Disease Society (UKPDS) Brain Bank Clinical Diagnostic Criteria (see [Appendix C](#))

7. On a stable regimen of antiparkinson's medications for at least 30 days prior to screening, including a levodopa preparation administered not less than three times daily, and willing to continue the same doses and regimens during study participation
8. A score of at least 2 on part IV, item 4.2 (functional impact of dyskinesias) of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS), at screening and at Baseline/Day 1/Week 0
9. Using the 2 consecutive 24-hour PD home diaries completed just prior to Baseline/Day 1/Week 0, at least 2 half-hour time periods between 9 am to 4 pm of each 24-hour period are indicated as "ON with troublesome dyskinesia"
10. Any other current and allowed prescription/non-prescription medications and/or nutritional supplements taken regularly must have been at a stable dose and regimen for at least 30 days prior to screening, and subject must be willing to continue the same doses and regimens during study participation (this criterion does not apply to medications that are being taken pre-study only on an as-needed basis)
11. If taking an antidepressant, must be on a stable dose for at least 30 days prior to study entry

EXCLUSION CRITERIA:

1. History of exclusively diphasic, off state, myoclonic, dystonic, or akathetic dyskinesia without peak dose dyskinesia
2. History of neurosurgical intervention related to Parkinson's disease (e.g. deep brain stimulation)
3. History of other neurological disease that, in the opinion of the investigator, would affect motor function or cognition, including, but not limited to Alzheimer's dementia, Huntington's disease, Lewy body dementia, frontotemporal dementia, corticobasal degeneration, progressive supranuclear palsy, multiple system atrophy, motor or sensory dysfunction secondary to stroke or brain trauma, or multi-infarct dementia with lacunae
4. History of clinically significant hallucinations (visual, auditory, or any other type) due to levodopa, dopamine agonist, underlying PD or other/unknown cause, within 1 year prior to screening
5. History of sensory impairments (e.g., hearing, vision) that, in the opinion of the investigator, would impair the subject's ability to complete study assessments, or presence of untreated angle closure glaucoma
6. History of alcohol or substance dependence or abuse within 2 years prior to screening
7. History of seizures within 2 years prior to screening
8. History of stroke or TIA within 2 years prior to screening

9. History of myocardial infarction, or NYHA Functional Classification of Heart Failure Class 3 or 4 within 2 years prior to screening (see [Appendix D](#))
10. Any clinically significant ECG abnormalities, including any findings of abnormal ventricular conduction or rhythm other than isolated PVCs or first degree AV block
11. 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 or *in situ* cervical cancer
12. Presence of cognitive impairment, as evidenced by a Mini-Mental Status Examination (MMSE) score of less than 24 during screening
13. Hoehn and Yahr Stage 5
14. Presence of an acute or chronic major psychiatric disorder (e.g., Major Depressive Disorder) or symptom (e.g., hallucinations, agitation, paranoia, suicidal ideation) 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
15. 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
16. Any of the following laboratory test results at screening:
 - Hemoglobin < 10 g/dL
 - WBC < 3.0 x 10⁹/L
 - Neutrophils < 1.5 x 10⁹/L
 - Lymphocytes < 0.5 x 10⁹/L
 - Platelets < 100 x 10⁹/L
 - Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) > 2 times the upper limit of normal
17. Estimated GFR < 50 mL/min/1.73m² (calculated using Modification of Diet in Renal Disease (MDRD))
18. Inability to swallow oral capsules, or a history of gastrointestinal malabsorption that would preclude the use of oral medication
19. If female, is pregnant or lactating
20. If a sexually active female, is not surgically sterile or at least 2 years postmenopausal, 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

21. Use of amantadine within 30 days prior to screening, or documented inability to tolerate or lack of response to prior amantadine treatment for LID, or history of suicidal ideation or suicide attempt during prior amantadine use
22. Use of rimantadine for influenza prophylaxis within 30 days prior to screening
23. History of hypersensitivity or allergic reaction to amantadine, rimantadine, or memantine, or to any of the excipients used in the study medication capsules (see [Section 8.7](#))
24. Received live attenuated influenza vaccine within 2 weeks prior to randomization (amantadine may interfere with the efficacy of live attenuated vaccine)
25. Current treatment with carbonic anhydrase inhibitors, sodium bicarbonate, urinary acidification agents, or quinine, quinidine, triamterene, or trimethoprim
26. Current treatment with apomorphine. Subjects who are able to appropriately discontinue at least 30 days prior to screening will be eligible for screening
27. Current treatment with medications that act primarily by blocking dopamine receptors and current treatment with medications that prolong the QT interval and have a known risk of torsades de pointes (see [Appendix E](#)). Subjects who are able to appropriately discontinue these agents at least 60 days prior to screening will be eligible for screening
28. Treatment with an investigational drug or device within 30 days prior to screening
29. Treatment with an investigational biologic within 6 months prior to screening
30. Current participation in another interventional clinical trial
31. Prior participation in the ADS-PAR-AM201 (EASED study)
32. Planned elective surgery during study participation

Investigational product, dosage, mode of administration, and dosing regimen:

All subjects will continue their current PD medications and regimens, without changes, during the study drug dosing period.

Consented subjects who meet eligibility criteria will be randomly assigned in a 1:1 ratio to one of 2 treatments: placebo or active (340 mg ADS-5102).

Study medication will be administered as 2 capsules once nightly at bedtime (and if possible, no earlier than 9 pm), for 25 weeks.

Treatment A (Placebo): Placebo, administered as two placebo capsules for 25 weeks.

Treatment B (Active): An initial dose of 170 mg ADS-5102, administered as 2 capsules (1 capsule of 170 mg ADS-5102 and 1 capsule of placebo) for 1 week, then 340 mg ADS-5102, administered as 2 capsules of 170 mg ADS-5102 for 23 weeks, ending with 170 mg ADS-5102, administered as 2 capsules (1 capsule of 170 mg ADS-5102 and 1 capsule of placebo) during Week 25.

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

Subjects who discontinue study drug after Week 4 should receive a reduced dose for one additional week, either 170 mg ADS-5102 or placebo, in a double-blind fashion before stopping study drug. The additional week of dosing at a reduced dose will not be needed for subjects who discontinue study drug before Week 4.

Subjects whose estimated GFR falls below 50 mL/min/1.73m² (and ≥ 30 mL/min/1.73m²), confirmed by repeat testing, while on study should discontinue study drug after receiving a reduced dose of either 170 mg ADS-5102 or placebo, in a double-blind fashion, for one additional week. The additional week of dosing at a reduced dose will not be needed if the decrease in estimated GFR occurs before Week 4.

Subjects whose estimated GFR falls below 30 mL/min/1.73m², confirmed by repeat testing, while on study should discontinue study drug (without the additional week at a reduced dose).

Subjects who discontinue study medication will be encouraged to complete the remaining study visits. If the subject decides to withdraw from the study, they will have an early termination visit that includes safety follow-up and efficacy assessments, if appropriate.

Duration of treatment: Maximum duration of subject participation can be up to 29 weeks and will include a 3 week (maximum) screening period, 25 week treatment period, and a 1 week safety follow-up period at Week 26 (for subjects who do not transition to open-label extension study).

Criteria for evaluation:

Efficacy:

Primary Outcome Measure: Change from baseline to Week 12 in the Unified Dyskinesia Rating Scale (UDysRS) total score.

This scale has four parts, and a total possible score of 104:

- I. Historical Disability (patient perceptions) of On-Dyskinesia impact
- II. Historical Disability (patient perceptions) of Off-Dystonia impact
- III. Objective Impairment (dyskinesia severity, anatomic distribution, and type, based on 4 observed activities)
- IV. Objective Disability based on Part III activities

Key Secondary Outcome Measures:

Change from baseline to Week 24 in the following:

- Unified Dyskinesia Rating Scale (UDysRS) total score

Change from baseline to Week 12 and change from baseline to Week 24 in each of the following:

- ON time without troublesome dyskinesia (ON time without dyskinesia plus ON time with non-troublesome dyskinesia), based on a standardized PD home diary
- OFF time, based on a standardized PD home diary

Other Secondary Outcome Measures: Change from baseline to Week 12 and change from baseline to Week 24 in each of the following:

- ON time with troublesome dyskinesia, based on a standardized PD home diary
- Total time with dyskinesia (non-troublesome and troublesome), based on a standardized PD home diary
- Unified Parkinson's Disease Rating Scale (MDS-UPDRS), Part IV, Part IV, item 4.1 (time spent with dyskinesias), and Part IV, item 4.2 (functional impact of dyskinesias)
- UDysRS Total Objective Score (Parts III and IV)
- Unified Parkinson's Disease Rating Scale (MDS-UPDRS), individual and combined scores (Parts I, II, III)
- Clinician's Global Impression of Change in overall PD symptoms, determined by a question completed by the investigator

Change from baseline to Week 8 in the following:

- UDysRS total score

Safety: The following safety assessments will be performed during the study:

- AEs
- Safety-related study drug discontinuations
- Vital signs
- Safety laboratory tests

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

TABLE OF CONTENTS

APPROVALS	1
1. SYNOPSIS	2
2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES	11
3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS.....	16
4. INTRODUCTION	19
4.1. Product Rationale.....	20
4.2. Dose and Dose Regimen Justification	20
4.3. Summary Pharmacokinetic Information for Extended Release Amantadine Formulations	21
4.3.1. Single Dose Studies	21
4.3.2. Effect of Food on Bioavailability of Amantadine ER	22
4.3.3. Relative Bioavailability of Amantadine ER vs. Amantadine IR at Steady State	22
4.4. Summary Safety Information for Extended Release Amantadine Formulations	22
4.5. Rationale for ADS-AMT-PD301 Study Design	23
4.6. Population to be Studied.....	23
5. TRIAL OBJECTIVES AND PURPOSE.....	23
5.1. Primary Objective	23
5.2. Secondary Objectives	23
5.3. Primary Outcome Measure	23
5.4. Key Secondary Outcome Measures	24
5.5. Other Secondary Outcome Measures	24
6. INVESTIGATIONAL PLAN.....	24
6.1. Overall Study Design.....	24
6.2. Number of Subjects	26
6.3. Treatment Assignment.....	26
6.4. Dose Adjustment Criteria	26
6.5. Criteria for Study Termination	26

6.6.	Duration of Subject Participation	26
6.7.	Estimated Study Duration.....	26
7.	SELECTION AND WITHDRAWAL OF SUBJECTS.....	27
7.1.	Subject Inclusion Criteria	27
7.2.	Subject Exclusion Criteria	27
7.3.	Subject Withdrawal Criteria	29
7.4.	Subject Enrollment	30
7.5.	Discontinuation of Study Medication.....	30
8.	STUDY DRUG MATERIALS AND MANAGEMENT	31
8.1.	Study Drug.....	31
8.2.	Study Drug Packaging and Labeling	31
8.3.	Study Drug Storage.....	32
8.4.	Administration	32
8.5.	Study Drug Accountability	32
8.6.	Study Drug Handling and Disposal	33
8.7.	Prohibited Medications and Restrictions.....	33
8.8.	Concomitant Medications.....	33
8.9.	Treatment Compliance.....	34
8.10.	Randomization and Blinding	34
9.	ASSESSMENT OF EFFICACY	35
10.	ASSESSMENT OF SAFETY.....	37
10.1.	Physical Examination Assessments Relating to Safety	37
10.2.	Clinical Laboratory Tests	38
10.3.	Demographic/Medical History	39
10.4.	Total Blood Volume Collected.....	39
11.	EVALUATIONS BY VISIT	39
11.1.	Screening/Day -21 to -1	39
11.2.	Treatment Period	40
11.3.	Baseline/Day 1/Week 0	40
11.4.	Week 1 +/- 1 Day (End of Week 1).....	41
11.5.	Week 2 +/- 1 Day (End of Week 2).....	42
11.6.	Week 4 +/- 1 Day (End of Week 4).....	42

11.7.	Week 8 +/- 1 Day (End of Week 8).....	43
11.8.	Week 12 +/- 1 Day (End of Week 12).....	43
11.9.	Week 18 +/- 1 Day (End of Week 18).....	44
11.10.	Week 24 +/- 1 Day (End of Week 24).....	45
11.11.	Week 25 +/- 1 Day (End of Week 25).....	45
11.12.	Early Termination Visit.....	45
11.13.	Safety Follow Up Visit (Week 26).....	46
12.	ADVERSE AND SERIOUS ADVERSE EVENTS.....	46
12.1.	Definition of Adverse Events.....	46
12.1.1.	Adverse Event (AE).....	47
12.1.2.	Severity of Adverse Events.....	49
12.1.3.	Follow-up of Adverse Events and Serious Adverse Events.....	49
12.1.4.	Serious Adverse Event (SAE).....	49
12.1.4.1.	Clarification of SAE Definition.....	50
12.1.4.2.	Clarification of Subject Deaths.....	50
12.2.	Relationship to Study Drug.....	51
12.3.	Recording Adverse Events.....	51
12.4.	Reporting Adverse Events.....	52
12.4.1.	Post-Study Reporting Requirements.....	52
12.4.2.	Investigator Reporting Responsibility.....	52
12.4.3.	Pregnancy.....	53
13.	STATISTICS.....	53
13.1.	Statistical Analyses.....	53
13.1.1.	Sample Size Determination.....	53
13.1.2.	Analysis Populations.....	53
13.1.2.1.	Efficacy Populations.....	53
13.1.3.	Handling of Missing Data.....	54
13.1.4.	Safety and Tolerability.....	54
13.1.5.	Demographics and Baseline Characteristics.....	55
13.1.6.	Prior and Concomitant Medications.....	55
13.1.7.	Completion of the Study and Withdrawals.....	55
13.1.8.	Protocol Deviations.....	55

14.	STUDY CONDUCT.....	55
14.1.	Study Monitoring.....	55
14.2.	Audits and Inspections.....	56
14.3.	Subject Confidentiality	56
14.4.	Case Report Forms	56
14.5.	Retention and Availability of Records	57
15.	QUALITY CONTROL AND QUALITY ASSURANCE	57
16.	ETHICS	57
16.1.	Ethics Review	57
16.2.	Ethical Conduct of the Study.....	58
16.3.	Written Informed Consent	58
16.4.	Changes in the Conduct of the Study or Planned Analyses.....	59
16.5.	Emergency Contact with Investigator	59
17.	INFORMATION DISCLOSURE AND INVENTIONS.....	59
17.1.	Ownership.....	59
17.2.	Confidentiality	59
18.	PUBLICATION POLICY	60
19.	LIST OF REFERENCES.....	61
20.	APPENDICES	65
APPENDIX A.	SCHEDULE OF EVENTS.....	66
APPENDIX B.	STUDY DESIGN SCHEMATIC	68
APPENDIX C.	UK PARKINSON'S DISEASE SOCIETY (UKPDS) BRAIN BANK CLINICAL DIAGNOSTIC CRITERIA.....	69
APPENDIX D.	NYHA FUNCTIONAL CLASSIFICATION.....	70
APPENDIX E.	PROHIBITED MEDICATIONS	71

LIST OF TABLES

Table 1: Abbreviations.....16

Table 2: Clinical Formulations for Study ADS-AMT-PD301.....31

Table 3: Randomization Groups for Study ADS-AMT-PD30132

Table 4: Efficacy Assessments35

Table 5: Physical Examination Assessments Relating to Safety37

Table 6: Clinical Laboratory and Other Assessments:38

LIST OF FIGURES

Figure 1: Pharmacokinetic Modeling of Steady-state Concentrations for ADS-5102 vs
Approved Doses of Amantadine IR.....21

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations are used in this study protocol.

Table 1: Abbreviations

Abbreviation	Explanation
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the curve
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
C	Concentration
C _{max}	observed maximum concentration
C _{min}	observed minimum concentration
CGI-C	Clinician Global Impression of Change
CHF	congestive heart failure
CNS	central nervous system
CRF	Case Report Form (paper and/or electronic)
dL	Deciliter
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
ER	extended release
ET	Early Termination
FDA	Food and Drug Administration (United States)
g	Grams
GCP	Good Clinical Practice
GGT	γ -glutamyltransferase
IB	Investigator's Brochure
ICF	informed consent form

Table 1: Abbreviations (Continued)

ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IR	Immediate release
IRB	Institutional Review Board
IUD	intra-uterine device
LID	Levodopa Induced Dyskinesia
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MDRD	Modification Of Diet In Renal Disease
MDS-UPDRS	Movement Disorder Society-Unified Parkinson's Disease Rating Scale
MI	Myocardial Infarction
MITT	Modified Intent-To-Treat
MMSE	Mini Mental Status Examination
NF	National Formulary
NMDA	N-Methyl D-Aspartate
NYHA	New York Heart Association
PD	Parkinson's Disease
PI	Principal Investigator
PP	Per Protocol
PVC	Premature Ventricular Contractions
RBC	Red Blood Cell(s)
REB	Research Ethics Board
SAE	Serious Adverse Event
SD	Standard Deviation
TIA	Transient Ischemic Attack
t _{max}	Time Of Observed Maximum Concentration
UA	Urinalysis
UDysRS	Unified Dyskinesia Rating Scale

Table 1: Abbreviations (Continued)

UK PDS	UK Parkinson's Disease Society
US/USA	United States (Of America)
USP	United States Pharmacopeia
WBC	White Blood Cell(s); Leukocyte(s)
WHO	World Health Organization

4. INTRODUCTION

Parkinson's disease is a chronic, progressive disorder with prominent motor signs including tremors, rigidity, bradykinesia and postural instability. Levodopa is the most commonly prescribed and effective drug treatment for symptomatic relief in PD; however, chronic treatment with levodopa often results in the emergence of dose-limiting motor side-effects, including abnormal involuntary movements known as LID. With continued levodopa treatment, and as PD progresses, LID can become severely disabling and has been associated with a decrease in the quality of life (Encarnacion et al., 2008). There are currently no medications approved for the treatment of LID, thus there is a significant unmet medical need for new treatments for this condition.

Dyskinesia can be an adverse effect of all dopaminergic therapies, but mostly related to the use of levodopa (Del Sorbo et al., 2008). LID can be diagnosed by the characteristics of the exhibited movement and time to onset relative to daily administration of levodopa. The most common type of LID is referred to as “peak-dose dyskinesia” and usually consists of stereotypical choreic or ballistic movements involving the head, trunk, and/or limbs. Movement disorder specialists have developed rating scales to evaluate dyskinesia for purposes of clinical diagnosis and clinical trial investigation (Goetz et al., 2008; Colosimo et al., 2010; Goetz et al., 2013).

The incidence of LID reported in the literature, including reports of individual studies, varies widely (Duvoisin, 1974; Parkinson Study Group, 1989; Parkinson Study Group, 1996; Thanvi et al., 2007). Based on published studies utilizing a Medicare beneficiaries' database, IMS prescribing data, and demographic studies presented in the peer-reviewed literature, we have estimated a prevalence of approximately 140,000 Parkinson's patients with LID.

The underlying cause of LID is unknown, but the pulsatile administration of levodopa treatment and the degree of denervation in the striatum appear to influence its development (Del Sorbo et al., 2008). Other factors that have been associated with a higher incidence and severity of LID include early age of onset of PD, longer duration of levodopa treatment, levodopa total exposure, female gender, and genetic factors. The preferential use of dopamine agonists in the treatment of early disease and the careful management of pulsatile effects of levodopa therapy can delay but not eliminate the development of LID. A reduction in dyskinesia symptoms can sometimes be accomplished by modification of antiparkinson's dopaminergic medications, which is often accompanied by worsening of the motor symptoms of Parkinson's disease. It is important to demonstrate in the clinical trial setting that a reduction in dyskinesia is not accompanied by worsening of motor function.

Amantadine IR, which is approved for the treatment of PD, is used off-label by movement disorder specialists and other neurologists to treat LID in patients with PD. A number of literature reports suggest amantadine is effective for the treatment of LID (Verhagen et al., 1998; Verhagen et al., 1999; Luginer et al., 2000; Snow et al., 2000; Paci et al., 2001; Thomas et al., 2004; da Silva-Junior et al., 2005; Sawada et al., 2010; Wolf et al., 2010; Goetz et al., 2013).

Despite amantadine's reported utility in the treatment of LID, until recently, the drug was not extensively studied in well-controlled clinical trials that meet evidence-based clinical or regulatory standards of acceptance, nor was the optimal dose for this indication established. The

majority of patients with PD tolerate 200 mg/day of the amantadine IR formulation; however, the available literature on amantadine for the treatment of LID indicates that higher doses of amantadine produce a greater reduction in LID symptoms (Verhagen et al., 1998; Luginger et al., 2000). However, the increased frequency of adverse events (AEs) at higher doses, in particular central nervous system (CNS) events and sleep disturbances, limits the routine use of amantadine IR at doses of 300 mg/day or higher (Tyrrell et al., 1965; Jackson et al., 1967; Hayden et al., 1981).

4.1. Product Rationale

The pharmacologic rationale for a formulation that slows the release of amantadine is based upon the nature and timing of amantadine IR CNS side effects relative to dosing as well as observations with other CNS active drugs. Symmetrel (amantadine HCl IR tablet) has a short t_{max} of 2-4 hours (Aoki et al., 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 (Hayden, 1981; Jackson et al., 1967). These side effects may explain why amantadine is usually administered in divided doses, despite a 16 hour half-life, which would typically support once daily dosing. Moreover, the CNS effects are particularly disruptive late in the day or evening (following a second or third amantadine dose) as the patient is trying to sleep (Tyrrell et al., 1965; Jackson et al., 1967).

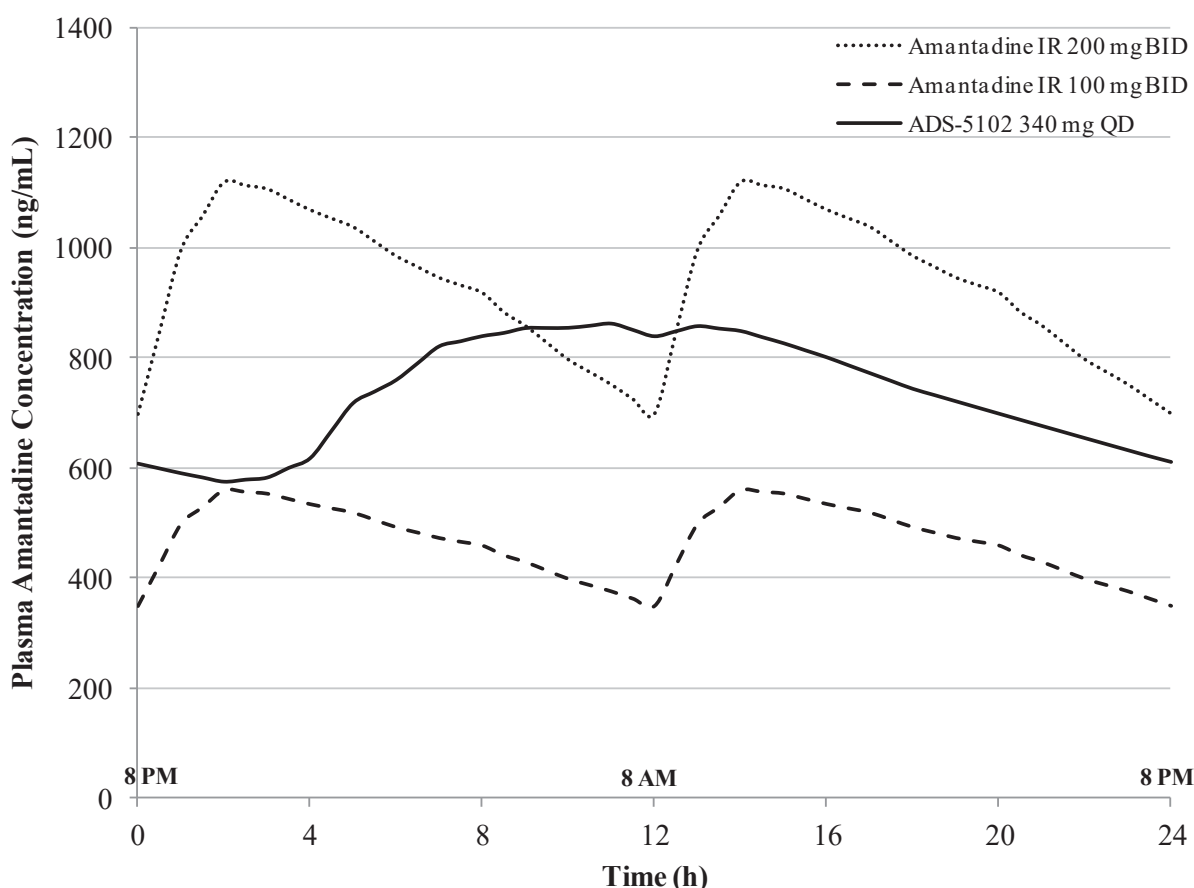
In addition to amantadine, there are other CNS active stimulant drugs, such as methylphenidate and cocaine that have high blood brain permeability (CNS penetrants), and exhibit a short t_{max} . By modifying the PK profile of these drugs to change the initial release characteristics, the type and timing of the CNS effects can be modulated (Volkow et al., 1998; Swanson et al., 2002; Spencer et al., 2006). Hence, the pharmacologic rationale for improved tolerability of an extended-release formulation of amantadine is that the reduction in the rate of rise in plasma concentration may reduce the CNS adverse effects that can occur shortly after dosing, without compromising concentration-dependent efficacy.

4.2. Dose and Dose Regimen Justification

The proposed dose of amantadine HCl in ADS-5102 is 340 mg, to be taken once nightly at bedtime. The t_{max} for ADS-5102 is expected to occur at 12 to 14 hours post dose. ADS-5102 is designed to achieve maximal concentrations in the early morning through mid-day, when LID tends to be troublesome, and lower concentrations in the evening, potentially reducing the negative impact of amantadine on sleep. This pharmacokinetic profile could enable higher daily doses to be tolerated with a once-nightly ER preparation than can be tolerated with an IR formulation. The once-nightly dosing regimen may also provide enhanced convenience and improve compliance.

The labeled dose of Symmetrel for initiating treatment of PD is 100 mg given twice daily. The label also allows for an increase of up to 400 mg daily in divided doses for patients whose responses are not optimal with 200 mg daily. Figure 1 shows pharmacokinetic modeling of the steady state exposure for the ADS-5102 formulation compared to the approved doses of amantadine IR. Profiles were generated from Adamas clinical data in healthy volunteers (NPI-5103-C101).

Figure 1: Pharmacokinetic Modeling of Steady-state Concentrations for ADS-5102 vs. Approved Doses of Amantadine IR



ADS-5102 administered as 340 mg once nightly results in a PK profile that provides higher exposures than possible with 100 mg bid amantadine IR, and yet remains within those approved in the Symmetrel package insert. As seen in Figure 1, the C_{max} of the recommended dose of ADS-5102 remains below that of the 200 mg amantadine IR bid. The minimal concentration after dosing with ADS-5102 remains above the C_{max} from a 100 mg dose of amantadine IR.

4.3. Summary Pharmacokinetic Information for Extended Release Amantadine Formulations

4.3.1. Single Dose Studies

In a single-dose trial, the PK performance of 3 amantadine ER formulations [labeled A, B (ADS-5101), and C (ADS-5102)] was studied in healthy volunteers (Study No. NPI-5103-C-101). The study demonstrated that all 3 ER amantadine formulations had lower C_{max} and longer t_{max} compared to IR amantadine. Relative bioavailability (based on AUC_{0-inf}) of amantadine ER formulations A, B, and C compared to IR amantadine was 85.3%, 94.6%, and 88.5%, respectively.

4.3.2. Effect of Food on Bioavailability of Amantadine ER

Two single-dose crossover studies (study NPI-5101-FE-103 and study ADS-5101-106) established the lack of effect of food on pharmacokinetics and one study demonstrated that administering the ADS-5101 capsule contents sprinkled on applesauce (Study NPI-5101-FE-106) does not affect the bioavailability of amantadine.

When study medication was administered after a standard meal, absorption of amantadine was faster, with slightly higher peak concentration and 1 hour earlier median t_{max} value as compared with the reference fasted treatment. The 90% CIs of the ratio of the least squares geometric mean for C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$ fell within the 80.00% to 125.00% interval for each test treatment (fed and sprinkled) relative to the reference treatment (fasted condition). The results from these studies support dosing recommendations that amantadine ER can be administered with food and can be sprinkled on applesauce.

Steady state pharmacokinetic data are not available for ADS-5102. One of the objectives of this study is to measure steady state amantadine concentrations at the three dose levels.

4.3.3. Relative Bioavailability of Amantadine ER vs. Amantadine IR at Steady State

Two multiple dose studies were conducted with similar study designs: NPI-5101-MD-104 which studied a daily dose of 200 mg (two 100 mg ADS-5101 capsules administered once daily), and ADS-5101-105 which used a dose of 220 mg (two 110 mg ADS-5101 capsules administered once daily). Both studies were 2-treatment, 2-period crossover, single and multiple-dose PK studies comparing once-daily ADS-5101 and twice-daily amantadine IR (2 x 100 mg) in healthy adults under fasting conditions. In each trial, a single dose of the reference (2 x 100 mg amantadine IR) and test (200 mg or 220 mg ADS-5101) substance was administered, followed by 48 hours of plasma sampling to characterize the single dose pharmacokinetic profile. The subjects were then administered 7 days of study drugs (amantadine IR, 100 mg bid or ADS-5101, 200 or 220 mg qd), and the steady state pharmacokinetic profile was assessed. Following a seven day washout, the subjects were crossed over to the alternate test regimens.

Similar PK results were observed on Day 1 and on Day 9. These studies suggest linear kinetics over time for both the IR and ER formulations.

4.4. Summary Safety Information for Extended Release Amantadine Formulations

The safety of amantadine ER formulation has been examined in approximately 120 healthy subjects in the five single dose Phase 1 studies and 61 patients in one repeated dose Phase 2/3 efficacy study.

In the Phase 1 studies in healthy volunteers, the most frequently occurring adverse events reported with the ER formulations of amantadine were headache, fatigue, and dizziness, occurring in 5-10% of subjects. The majority of adverse events were categorized as mild. There were no serious adverse events in any of the trials to date, and no deaths were reported. No meaningful trends were observed for serum chemistry, hematology, or urinalysis results.

In the Phase 2/3 safety and efficacy study conducted in 83 patients with PD, most frequently reported adverse events were constipation, dizziness, dry mouth and hallucinations. Most of these AEs were mild to moderate. Five patients had serious adverse events, and no deaths were reported. No meaningful trends were observed for serum chemistry, hematology, or urinalysis results.

In all the amantadine ER studies, the reported adverse events were generally consistent with the known safety profile of amantadine.

For additional information please refer to the Investigator's Brochure.

4.5. Rationale for ADS-AMT-PD301 Study Design

The objectives of the trial are to confirm efficacy shown in a previously completed Phase 2/3 study, ADS-PAR-AM201, and to collect additional safety data in this population. A randomized, placebo-controlled, parallel-group design is appropriate for this trial.

4.6. Population to be Studied

Subjects with Parkinson's disease who are experiencing troublesome levodopa induced dyskinesia will be randomized into the study.

5. TRIAL OBJECTIVES AND PURPOSE

5.1. Primary Objective

To evaluate the efficacy of ADS-5102 oral capsules, an extended release formulation of amantadine, at a dose of 340 mg once nightly for the treatment of levodopa induced dyskinesia (LID) in subjects with Parkinson's disease (PD).

5.2. Secondary Objectives

To evaluate the safety and tolerability of ADS-5102 in this study population.

5.3. Primary Outcome Measure

The primary outcome measure is the change from baseline to Week 12 in the Unified Dyskinesia Rating Scale (UDysRS) total score. This scale has four parts, and a total possible score of 104:

- I. Historical Disability (patient perceptions) of On-Dyskinesia impact
- II. Historical Disability (patient perceptions) of Off-Dystonia impact
- III. Objective Impairment (dyskinesia severity, anatomic distribution, and type, based on 4 observed activities)
- IV. Objective Disability based on Part III activities

5.4. Key Secondary Outcome Measures

Change from baseline to Week 24 in the following:

- Unified Dyskinesia Rating Scale (UDysRS) total score

Change from baseline to Week 12 and change from baseline to Week 24 in each of the following:

- ON time without troublesome dyskinesia (ON time without dyskinesia plus ON time with non-troublesome dyskinesia), based on a standardized PD home diary
- OFF time, based on a standardized PD home diary

5.5. Other Secondary Outcome Measures

Change from baseline to Week 12 and change from baseline to Week 24 in each of the following:

- ON time with troublesome dyskinesia, based on a standardized PD home diary
- Total time with dyskinesia (non-troublesome and troublesome), based on a standardized PD home diary
- Unified Parkinson's Disease Rating Scale (MDS-UPDRS), Part IV, Part IV, item 4.1 (time spent with dyskinesias), and Part IV, item 4.2 (functional impact of dyskinesias)
- UDysRS Total Objective Score (Parts III and IV)
- Unified Parkinson's Disease Rating Scale (MDS-UPDRS), individual and combined scores (Parts I, II, III)
- Clinician's Global Impression of Change in overall PD symptoms, determined by a question completed by the investigator

Change from baseline to Week 8 in the following:

- UDysRS total score

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

This is a multi-center, randomized, double-blind, placebo-controlled, 2-arm, parallel group study of ADS-5102 in subjects with PD who have LID.

All subjects will have received a stable regimen of antiparkinson's medications for at least 30 days prior to screening, including a levodopa preparation administered not less than three times daily, and be willing to continue the same doses and regimens for the duration of their study participation.

Consented subjects who complete screening and meet study eligibility criteria will be randomized in a 1:1 ratio to receive one of 2 treatments: placebo or active (340 mg ADS-5102).

Study medications will be administered as 2 capsules once nightly at bedtime (if possible, no earlier than 9 pm) for 25 weeks.

Subjects who are randomized to placebo will receive placebo throughout the 25 week treatment period, in a double-blind fashion.

Subjects who are randomized to active treatment will receive ADS-5102 throughout the 25 week treatment period. Active treatment will start with 170 mg ADS-5102 during Week 1, followed by 23 weeks of 340 mg ADS-5102, and end with 170 mg ADS-5102 during Week 25, in a double-blind fashion.

Following completion of Visit 2 (Baseline/Day 1/Week 0), subjects will return to the clinic after 1, 2, 4, 8, 12, 18, 24, and 25 weeks of dosing.

Subjects who complete 25 weeks of dosing will have the option of transitioning directly to an open-label extension study, ADS-AMT-PD302.

Subjects who decline participation in the open-label extension study will have a final safety follow-up visit at Week 26, 1 week following the completion of dosing, which will include a pregnancy test, if appropriate.

Subjects who withdraw from the study before Week 25 will have an early termination visit that includes safety follow-up and efficacy assessments, if appropriate. In addition, subjects who discontinue study drug after Week 4 should receive a reduced dose for one additional week, either 170 mg ADS-5102 or placebo, in a double-blind fashion before stopping study drug. The additional week of dosing at a reduced dose will not be needed for subjects who discontinue study drug before Week 4.

Subjects who prematurely discontinued from study drug after Week 12, but continue to follow the study protocol procedures, including efficacy assessments, will have the option of transitioning directly into the open-label extension study after their Week 25 visit, as long as the reason for discontinuation of study drug was not due to an adverse event.

A detailed study design schematic can be found in [Appendix B](#).

Study visits and assessments will be scheduled and conducted within the time window of 9 am through 4 pm. All study visits for an individual subject should be scheduled at approximately the same time of day. Efficacy assessments should be conducted when the subject is ON and experiencing their typical dyskinesia and at least 30 minutes following a subject's regularly scheduled levodopa dose. The efficacy measurements for each subject should be performed by the same rater, if possible.

During the screening period, potential subjects and any involved caregivers or study partners, will be trained on the proper completion of 24-hour PD home diaries. Following successful completion of training, a set of two consecutive 24-hour diaries (48 hours total) will be completed prior to Visit 2 (Baseline/Day 1/Week 0, serving as the baseline diary score, and repeated prior to selected study visits.

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

6.2. Number of Subjects

Approximately 120 (60 in placebo group, and 60 subjects in the active group) will be randomized at approximately 55 sites worldwide.

6.3. Treatment Assignment

Consented subjects who complete screening and meet study eligibility criteria will be centrally randomized in a 1:1 ratio to receive one of 2 treatment groups: placebo or active (340 mg ADS-5102)

6.4. Dose Adjustment Criteria

Subjects who discontinue study drug after Week 4 should receive a reduced dose for one additional week, either 170 mg ADS-5102 or placebo, in a double-blind fashion before stopping study drug. The additional week of dosing at a reduced dose will not be needed for subjects who discontinue study drug before Week 4.

Subjects whose estimated GFR falls below 50 mL/min/1.73m² (and ≥ 30 mL/min/1.73m²), confirmed by repeat testing, while on study should discontinue study drug after receiving a reduced dose of either 170 mg ADS-5102 or placebo, in a double-blind fashion, for one additional week. The additional week of dosing at a reduced dose will not be needed if the decrease in estimated GFR occurs before Week 4.

Subjects whose estimated GFR falls below 30 mL/min/1.73m², confirmed by repeat testing, while on study should discontinue study drug (without the additional week at a reduced dose).

6.5. Criteria for Study Termination

The Sponsor reserves the right to discontinue the trial at any time; reasons will be provided in the event of this happening. The Principal Investigator 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 IRB/REC/IEC in writing of the trial's completion or early termination and provide a copy of the notification to the Sponsor.

6.6. Duration of Subject Participation

Maximum duration of subject participation can be up to 29 weeks and will include a 3 week (maximum) screening period, 25 week treatment period, and a 1 week safety follow-up period (for subjects who do not transition to open-label extension study).

6.7. Estimated Study Duration

Approximately 23 months (from enrollment of first subject to last subject completion)

7. SELECTION AND WITHDRAWAL OF SUBJECTS

7.1. Subject Inclusion Criteria

1. Signed a current IRB/REC/IEC-approved informed consent form
2. Male or female subjects between 30 and 85 years of age, inclusive
3. Ambulatory or ambulatory-aided (e.g. walker or cane) ability while ON, such that the subject can complete study assessments
4. Knowledgeable and reliable caregiver/study partner, if appropriate, to accompany the subject to study visits and assist in completion of study instruments, as needed and allowed
5. Following diary training, the subject is willing and able to understand and complete the 24-hour PD home diary (caregiver/study partner assistance allowed)
6. Parkinson's disease, per UK Parkinson's Disease Society (UKPDS) Brain Bank Clinical Diagnostic Criteria ([Appendix C](#))
7. On a stable regimen of antiparkinson's medications for at least 30 days prior to screening, including a levodopa preparation administered not less than three times daily, and willing to continue the same doses and regimens during study participation
8. A score of at least 2 on part IV, item 4.2 (functional impact of dyskinesias) of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS), at screening and at Baseline/Day 1/Week 0
9. Using the 48-hour PD home diaries completed just prior to Baseline/Day 1/Week 0 (baseline), at least 2 half-hour time periods between 9 am to 4 pm of each 24-hour period are indicated as "ON with troublesome dyskinesia"
10. Any other current and allowed prescription/non-prescription medications and/or nutritional supplements taken regularly must have been at a stable dose and regimen for at least 30 days prior to screening, and subject must be willing to continue the same doses and regimens during study participation (this criterion does not apply to medications that are being taken pre-study only on an as-needed basis)
11. If taking an antidepressant, must be on a stable dose for at least 30 days prior to study entry

7.2. Subject Exclusion Criteria

1. History of exclusively diphasic, off state, myoclonic, dystonic, or akathetic dyskinesia without peak dose dyskinesia
2. History of neurosurgical intervention related to Parkinson's disease (e.g. deep brain stimulation)
3. History of other neurological disease that, in the opinion of the investigator, would affect motor function or cognition, including, but not limited to Alzheimer's dementia,

- Huntington's disease, Lewy body dementia, frontotemporal dementia, corticobasal degeneration, progressive supranuclear palsy, multiple system atrophy, motor or sensory dysfunction secondary to stroke or brain trauma, or multi-infarct dementia with lacunae
4. History of clinically significant hallucinations (visual, auditory, or any other type) due to levodopa, dopamine agonist, underlying PD or other/unknown cause, within 1 year prior to screening
 5. History of sensory impairments (e.g., hearing, vision) that, in the opinion of the investigator, would impair the subject's ability to complete study assessments, or presence of untreated angle closure glaucoma
 6. History of alcohol or substance dependence or abuse within 2 years prior to screening
 7. History of seizures within 2 years prior to screening
 8. History of stroke or TIA within 2 years prior to screening
 9. History of myocardial infarction, or NYHA Functional Classification of Heart Failure Class 3 or 4 within 2 years prior to screening (see [Appendix D](#))
 10. Any clinically significant ECG abnormalities, including any findings of abnormal ventricular conduction or rhythm other than isolated PVCs or first degree AV block
 11. 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 or in situ cervical cancer
 12. Presence of cognitive impairment, as evidenced by a Mini-Mental Status Examination (MMSE) score of less than 24 during screening
 13. Hoehn and Yahr Stage 5
 14. Presence of an acute or chronic major psychiatric disorder (e.g., Major Depressive Disorder) or symptom (e.g., hallucinations, agitation, paranoia, suicidal ideation) 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
 15. 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
 16. Any of the following
 - Hemoglobin < 10 g/dL
 - WBC < 3.0 x 10⁹/L
 - Neutrophils < 1.5 x 10⁹/L
 - Lymphocytes < 0.5 x 10⁹/L
 - Platelets < 100 x 10⁹/L

- Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) > 2 times the upper limit of normal
17. Estimated GFR < 50 mL/min/1.73m² (calculated using Modification of Diet in Renal Disease (MDRD))
 18. Inability to swallow oral capsules, or a history of gastrointestinal malabsorption that would preclude the use of oral medication
 19. If female is pregnant or lactating
 20. If a sexually active female is not surgically sterile or at least 2 years postmenopausal, 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
 21. Use of amantadine within 30 days prior to screening, or documented inability to tolerate or lack of response to prior amantadine treatment for LID, or history of suicidal ideation or suicide attempt during prior amantadine use
 22. Use of rimantadine for influenza prophylaxis within 30 days prior to screening
 23. History of hypersensitivity or allergic reaction to amantadine, rimantadine, or memantine, or to any of the excipients used in the study medication capsules (see [Section 8.7](#))
 24. Received live attenuated influenza vaccine within 2 weeks prior to randomization (amantadine may interfere with the efficacy of live attenuated vaccine)
 25. Current treatment with carbonic anhydrase inhibitors, sodium bicarbonate, or urinary acidification agents, quinine, quinidine, triamterene, or trimethoprim
 26. Current treatment with apomorphine. Subjects who are able to appropriately discontinue at least 30 days prior to screening will be eligible for screening
 27. Current treatment with medications that act primarily by blocking dopamine receptors and current treatment with medications that prolong the QT interval and have a known risk of torsades de pointes (see [Appendix E](#)). Subjects who are able to appropriately discontinue these agents at least 60 days prior to screening will be eligible for screening
 28. Treatment with an investigational drug or device within 30 days prior to screening
 29. Treatment with an investigational biologic within 6 months prior to screening
 30. Current participation in another clinical trial
 31. Prior participation in the ADS-PAR-AM201 (EASED study)
 32. Planned elective surgery during study participation

7.3. 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 medication (see [Section 7.5](#)) and wishes to withdraw

CONFIDENTIAL and PROPRIETARY

- 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.

7.4. Subject Enrollment

All subjects must sign and date an IRB/REB/IEC-approved ICF before any study procedures, including screening procedures are performed. During screening, the investigator or designee is to assess the need and requirements for a caregiver and/or study partner during the course of the study, and to assure the commitment of the person(s) so designated. It is preferable that the involved caregiver remains consistent during study participation; however, if circumstances require that the involved caregiver changes, he/she must undergo appropriate training prior to assisting the subject in completion of study assessments.

Subjects will be considered enrolled into the study after they have signed the ICF, have met all study mandated inclusion/exclusion criteria, and have been randomized.

7.5. Discontinuation of Study Medication

Subjects who discontinue study drug after Week 4 should receive a reduced dose for one additional week, either 170 mg ADS-5102 or placebo, in a double-blind fashion before stopping study drug. The additional week of dosing at a reduced dose will not be needed for subjects who discontinue study drug before Week 4.

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

- Estimated glomerular filtration rate (eGFR) falls below 50 mL/min/1.73m², confirmed by repeat testing.
 - NOTE:
 - Subjects whose eGFR falls below 30 mL/min/1.73m², confirmed by repeat testing, while on study should discontinue study drug without the additional week at a reduced dose.
- Need to take a medication that is excluded or that may interfere with study measurements

- Intolerable or unacceptable AEs
- Positive pregnancy test

Subjects who discontinue study medication will be encouraged to complete the remaining study visits. If the subject decides to withdraw from the study, they will have an early termination visit that includes efficacy assessments and safety follow-up.

8. STUDY DRUG MATERIALS AND MANAGEMENT

8.1. Study Drug

The clinical supplies will include 170 mg ADS-5102 capsules and matching placebo capsules. All capsules provided during the study are indistinguishable in size and appearance.

Amantadine Hydrochloride 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-PD301

	Placebo	ADS-5102 170 mg
Formulation	Microcrystalline cellulose pellets in an oral capsule	Extended release coated pellets of amantadine HCl in an oral capsule
Dose Strength	Not applicable	170 mg amantadine HCl per capsule
Description	White to off-white pellets filled in blue/blue colored hard gelatin capsule, size 0.	White to off-white pellets filled in blue/blue colored hard gelatin capsule, size 0.
Excipients	Microcrystalline cellulose, NF Magnesium stearate, NF	Microcrystalline cellulose, NF Hypromellose, USP Copovidone, NF Talc, USP Ethyl cellulose, NF Povidone, USP Medium chain triglycerides, USP Magnesium stearate, NF

8.2. Study Drug Packaging and Labeling

The study drug will be packaged in child-resistant blister cards, each containing a total of 18 capsules to allow for 9 days of dosing (2 capsules per dose, allowing 1 week supply plus 2 extra doses). One blister card will be dispensed to each subject on Day 1, Week 1, and Week 24, if necessary. Two blister cards will be dispensed to each subject on Week 2. Four blister cards

will be dispensed to each subject on Week 4 and Week 8. Six blister cards will be dispensed to each subject on Week 12 and Week 18.

All blister cards will be labeled with, at a minimum, the protocol number, route of administration, number of capsules to be administered, lot number, expiration date, storage conditions, Sponsor's name and address, and applicable investigational drug caution statements.

8.3. Study Drug Storage

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

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

8.4. Administration

Table 3: Randomization Groups for Study ADS-AMT-PD301

Randomization Groups	Week 1	Week 2 – Week 24	Week 25
Placebo	Placebo (2 x placebo capsules)	Placebo (2 x placebo capsules)	Placebo (2 x placebo capsules)
Active (ADS-5102)	170 mg ADS-5102 (1 x placebo capsule & 1 x 170 mg capsule)	340 mg ADS-5102 (2 x 170 mg capsules)	170 mg ADS-5102 (1 x placebo capsule & 1 x 170 mg capsule)

Each dose will be administered as 2 oral capsules once nightly at bedtime (if possible, no earlier than 9 pm).

Capsules are to be swallowed intact, and can be taken with any nonalcoholic beverage, and with or without food. Dosing will continue through Week 25.

8.5. 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

CONFIDENTIAL and PROPRIETARY

- 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.

8.6. 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.

8.7. Prohibited Medications and Restrictions

A list of medications prohibited prior to study entry is provided in [Appendix E](#).

In addition, the following medications are prohibited during study participation:

- Use of amantadine (other than provided study drug) during study participation
- Live attenuated influenza vaccine during study participation
- While taking study drug, it is recommended as a general safety precaution when evaluating a CNS-active agent that subjects who wish to consume alcohol should do so only in moderation.

No new medications should be initiated during study participation, unless there is an urgent medical need. If this occurs, please inform the Medical Monitor.

8.8. 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 must be on a stable regimen of antiparkinson's medications for at least 30 days prior to screening, including any levodopa preparation dosed at least three times daily, and current PD medications and dose regimens will remain unchanged during the placebo-controlled, double-blind period of the study.

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).

8.9. Treatment Compliance

Blister cards containing a 1-week supply of study drug will be dispensed on Day 1, Week 1, and Week 24, a 2-week supply of study drug will be dispensed at the Week 2 visit, a 4-week supply will be provided at Week 4 and Week 8, and a 6-week supply will be provided at Week 12 and Week 18.

Subjects will be instructed to return all used/unused blister cards at the next study visit (i.e., Weeks 1, 2, 4, 8, 12, 18, 24, 25 or ET), when the designated study site staff will review the number of returned capsules to assess subject compliance.

8.10. Randomization and Blinding

A subject is considered randomized at Day 1, 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.

Consented subjects meeting all eligibility criteria will be randomly assigned in a 1:1 ratio to one of 2 treatment groups, active (ADS-5102) or placebo.

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 Principal Investigator 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.

9. ASSESSMENT OF EFFICACY

Evaluations relating to efficacy to be performed during the study are described in Table 4.

Table 4: Efficacy Assessments

Assessment	Study Visit	Description
PD home diary	Baseline/Day1/Week 0 Week 2 Week 8 Week 12 Week 18 Week 24 (or ET)	<p>The diary will be used to score five different conditions in 30-minute intervals: Asleep, OFF, ON without dyskinesia, ON with non-troublesome dyskinesia, ON with troublesome dyskinesia.</p> <p>During screening, concordance testing will be performed to evaluate the subject's ability to accurately identify various states and the presence or absence of dyskinesia at different points in time.</p> <p>A set of two consecutive 24-hour PD home diaries (48 hours total) will be completed during screening and prior to each specified visit. The consecutive 24-hour diaries may be started 3 days before a visit, if the subject's schedule makes it difficult to complete a diary during the day before a visit. The schedule for diary completion should be determined in advance for each subject.</p>
UDysRS	Baseline/Day1/Week 0 Week 2 Week 8 Week 12 Week 18 Week 24 (or ET)	<p>The UDysRS evaluates involuntary movements associated with PD.</p> <p>This scale has four parts, and a total possible score of 104:</p> <ul style="list-style-type: none"> I. Historical Disability (patient perceptions) of On-Dyskinesia impact II. Historical Disability (patient perceptions) of Off-Dystonia impact III. Objective Impairment (dyskinesia severity, anatomic distribution, and type, based on 4 observed activities) IV. Objective Disability based on Part III activities
MDS-UPDRS	Screening Baseline/Day1/Week 0 Week 2 Week 8 Week 12 Week 18 Week 24 (or ET)	<p>The MDS-UPDRS has 4 parts: Part I (non-motor experiences of daily living), Part II (motor experiences of daily living), Part III (motor examination), and Part IV (motor complications).</p> <p>At screening, only Part IV, item 4.2 will be administered. At all other visits, Parts I – IV will be administered.</p>

Table 4: Efficacy Assessments (Continued)

Assessment	Study Visit	Description
CGI-C	Baseline/Day1/Week 0* Week 2 Week 8 Week 12 Week 18 Week 24 (or ET)	<p>The CGI-C is a single-item instrument assessing clinician's global impression of change in overall PD symptoms, including but not limited to LID.</p> <p>The CGI-C requires the investigator to rate how much the subject's Parkinson's disease has improved or worsened after treatment with study medication relative to the baseline state.</p> <p>*In order to allow a future assessment of the CGI-C, the CGI-C rater should record notes about the subject's baseline clinical status related to overall PD, in their source documents.</p>

10. ASSESSMENT OF SAFETY

10.1. Physical Examination Assessments Relating to Safety

Physical examinations relating to safety to be performed during the study are described in Table 5.

Table 5: Physical Examination Assessments Relating to Safety

Assessment	Study Visit	Description
Complete Physical Examination	Screening Week 12 Week 24 (or ET)	Physical examination including: skin, head-neck, eyes-ears-nose-throat, lungs-chest, heart, abdomen, extremities.
Targeted Physical Examination	Baseline/Day 1/Week 0 Week 4 Week 8 Week 18 Safety Follow Up Visit	Physical examination including: skin, lungs-chest, heart, abdomen, extremities.
Weight and height	Screening Week 4 Week 12 Week 18 Week 24 (or ET)	Height will be measured at screening only and recorded in centimeters. 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 during the study, using the same set of weighing scales when possible.
Vital Signs	Screening Baseline/Day 1/Week 0 Week 1 Week 2 Week 4 Week 8 Week 12 Week 18 Week 24 (or ET) Safety Follow Up Visit	Systolic and diastolic blood pressures, heart rate, should be recorded after the subject has been seated quietly for at least 5 minutes. Body temperature will be obtained at screening, Day 1, and at the safety follow up visit. Blood pressure, respiratory rate and heart rate 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.
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.

10.2. Clinical Laboratory Tests

The clinical laboratory and other tests relating to safety to be performed during the study are described in Table 6.

Table 6: Clinical Laboratory and Other Assessments:

Assessment	Study Visit	Description
Hematology	Screening Week 4 Week 12 Week 18 Week 24 (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, platelet count. Hematology will be conducted by a central laboratory.
Serum Chemistry	Screening Week 4 Week 12 Week 18 Week 24 (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 ^a , γ -glutamyltransferase, glucose, inorganic phosphorus, potassium, alanine aminotransferase, lactate dehydrogenase, aspartate aminotransferase, sodium, total bilirubin, and total protein.
Urinalysis	Screening Week 4 Week 12 Week 18 Week 24 (or ET)	UA 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 24* Safety Follow Up Visit (or ET)	Serum pregnancy test will be performed for all female subjects of childbearing potential. *For individuals directly rolling into the long term extension study, there will be a serum pregnancy test at Week 24, as part of the Screening Visit for ADS-AMT-PD302 and serve as the final pregnancy test for ADS-AMT-PD301.
Urine pregnancy test (if applicable)	Baseline/Day1/Week 0 Week 4 Week 8 Week 12 Week 18	Urine pregnancy test will be performed for all female subjects of childbearing potential.

^aEstimated glomerular filtration rate (eGFR) will be calculated by the central laboratory using MDRD.

10.3. Demographic/Medical History

A complete medical history (including PD history, mental health history, alcohol and drug use) will be obtained from the subject at the Screening Visit and recorded on the appropriate CRF. The medical history and other enrollment criteria will be reviewed and updated at the Baseline/Day 1/Week 0 visit to determine continued eligibility for the study.

10.4. Total Blood Volume Collected

The estimated total blood volume collected throughout the study (for clinical laboratory tests) is expected to be approximately 75 mL for safety serum chemistry and hematology laboratory evaluations.

11. EVALUATIONS BY VISIT

A schedule of study evaluations is provided in [Appendix A](#).

11.1. Screening/Day -21 to -1

During screening, potential subjects for the study will be fully informed about the nature of the study and possible adverse events (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 Day 1. 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;
- Record demographic information;
- Medical history with an emphasis on the subject's Parkinson's disease and movement disorders, including dyskinesia 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 CHF; and history of cancer;

- Record medications currently taken or taken in the previous 30 days for Parkinson's Disease, including dyskinesia and medications currently taken for any condition;
- Complete physical examination;
- Obtain subject weight in kilograms and height in centimeters;
- Vital signs (blood pressure, respiratory rate, heart rate, 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 female subjects of childbearing potential;
- Mini-Mental Status Examination (MMSE);
- Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) (Part IV, item 4.2 only);
- Instruct and train the subject and any involved caregiver/study partner, if appropriate, on the proper completion of the PD home diary. During training, subjects will need to demonstrate ability to properly complete a set of PD home diaries and concordance testing will be performed to evaluate the subject's ability to accurately identify various states and the presence or absence of dyskinesia at different points in time;
- Following successful completion of training and concordance testing, subjects will be instructed to complete a set of two consecutive 24-hour diaries prior to the next visit. The consecutive 24-hour diaries may be started 3 days before a visit, if the subject's schedule (e.g., travel requirements) makes it difficult to complete the diary the day before a visit. The schedule for diary completion should be determined in advance of each visit for each subject.

Full details on diary training will be provided in the study manual.

11.2. Treatment Period

The treatment period will be a maximum of 25 weeks.

11.3. Baseline/Day 1/Week 0

The following procedures will be performed on Baseline/Day 1/Week 0:

- Review completed subject diaries (PD home diary);
 - NOTE: If the subject has not satisfactorily completed the PD home diary, the subject and caregiver/study partner, if appropriate, should be re-trained on proper completion of the diary. The subject should be provided with an additional set of diaries and instructed to complete the diaries and return for an additional visit for

review. The subject should proceed through the remainder of Day 1 assessments (including randomization) only after the subject satisfactorily completed the baseline set of PD home diaries;

- Review inclusion/exclusion criteria and determine subject eligibility;
- Medical history with an emphasis on the subject's Parkinson's disease and movement disorders, including dyskinesia 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 CHF; and history of cancer;
- Record medications currently taken for any condition or discontinued since Screening;
- Targeted physical examination;
- Vital signs (blood pressure, respiratory rate, heart rate and temperature);
- Unified Dyskinesia Rating Scale (UDysRS);
- MDS-UPDRS (all 4 parts);
- In order to allow a future assessment of the CGI-C, the CGI-C rater should record notes about the subject's baseline clinical status related to overall PD, in their source documents;
- Urine sample for urine pregnancy test in female subjects of childbearing potential;
- Randomize the subject to treatment via the interactive system and dispense study medication (1-week supply specific for Week 1 [Days 1-7]).

11.4. Week 1 +/- 1 Day (End of Week 1)

The following procedures will be performed:

- Assess and record concomitant medications;
- Assess and record Adverse Events;
- Vital signs (blood pressure, respiratory rate, heart rate);
- Subjects will be provided with PD home diary and instructed to complete a set of two consecutive 24-hour diaries prior to the next visit. The consecutive 24-hour diaries may be started 3 days before a visit, if the subject's schedule (e.g., travel requirements) makes it difficult to complete the diary the day before a visit. The schedule for diary completion should be determined in advance of each visit for each subject;
- Collect used/unused blister cards and evaluate compliance;
- Dispense study medication (1-week supply specific for Week 2 [Days 8-14]).

11.5. Week 2 +/- 1 Day (End of Week 2)

The following procedures will be performed:

- Assess and record concomitant medications;
- Assess and record Adverse Events;
- Vital signs (blood pressure, respiratory rate, heart rate);
- Review subject diaries (PD home diary);
- Unified Dyskinesia Rating Scale (UDysRS);
- MDS-UPDRS (all parts);
- Clinician's Global Impression of Change (CGI-C);
- Collect used/unused blister cards and evaluate compliance;
- Dispense study medication (2-week supply specific for Weeks 3 and 4 [Days 15-28]).

11.6. Week 4 +/- 1 Day (End of Week 4)

The following procedures will be performed:

- Assess and record concomitant medications;
- Assess and record Adverse Events;
- Targeted physical examination;
- Obtain subject weight in kilograms;
- Vital signs (blood pressure, respiratory rate, heart rate);
- Blood sample for central laboratory analysis including hematology, serum chemistry, and eGFR;
- Urinalysis;
- Urine sample for urine pregnancy test in female subjects of childbearing potential;
- Subjects will be provided with PD home diary and instructed to complete a set of two consecutive 24-hour diaries prior to the next visit. The consecutive 24-hour diaries may be started 3 days before a visit, if the subject's schedule (e.g., travel requirements) makes it difficult to complete the diary the day before a visit. The schedule for diary completion should be determined in advance of each visit for each subject;
- Collect used/unused blister cards and evaluate compliance;
- Dispense study medication (4-week supply specific for Week 5 through Week 8 [Days 29-56]).

11.7. Week 8 +/- 1 Day (End of Week 8)

The following procedures will be performed:

- Assess and record concomitant medications;
- Assess and record Adverse Events;
- Targeted physical examination;
- Vital signs (blood pressure, respiratory rate, heart rate);
- Review subject diaries (PD home diary);
- Unified Dyskinesia Rating Scale (UDysRS);
- MDS-UPDRS (all 4 parts);
- Clinician's Global Impression of Change (CGI-C);
- Urine sample for urine pregnancy test in female subjects of childbearing potential;
- Subjects will be provided with PD home diary and instructed to complete a set of two consecutive 24-hour diaries prior to the next visit. The consecutive 24-hour diaries may be started 3 days before a visit, if the subject's schedule (e.g., travel requirements) makes it difficult to complete the diary the day before a visit. The schedule for diary completion should be determined in advance of each visit for each subject;
- Collect used/unused blister cards and evaluate compliance;
- Dispense study medication (4-week supply specific for Week 9 through Week 12 [Days 57-84]).

11.8. Week 12 +/- 1 Day (End of Week 12)

The following procedures will be performed:

- Assess and record concomitant medications;
- Assess and record Adverse Events;
- Complete physical examination;
- Obtain subject weight in kilograms;
- Vital signs (blood pressure, respiratory rate, heart rate);
- Blood sample for central laboratory analysis including hematology, serum chemistry, and eGFR;
- Urinalysis;
- Urine sample for urine pregnancy test in female subjects of childbearing potential;
- Review subject diaries (PD home diary);

- Unified Dyskinesia Rating Scale (UDysRS);
- MDS-UPDRS (all 4 parts);
- Clinician's Global Impression of Change (CGI-C);
- Subjects will be provided with PD home diary and instructed to complete a set of two consecutive 24-hour diaries prior to the next visit. The consecutive 24-hour diaries may be started 3 days before a visit, if the subject's schedule (e.g., travel requirements) makes it difficult to complete the diary the day before a visit. The schedule for diary completion should be determined in advance of each visit for each subject;
- Collect used/unused blister cards and evaluate compliance;
- Dispense study medication (6-week supply specific for Week 13 through Week 18 [Days 85-126]).

11.9. Week 18 +/- 1 Day (End of Week 18)

The following procedures will be performed:

- Assess and record concomitant medications;
- Assess and record Adverse Events;
- Targeted physical examination;
- Obtain subject weight in kilograms;
- Vital signs (blood pressure, respiratory rate, heart rate);
- Blood sample for central laboratory analysis including hematology, serum chemistry, and eGFR;
- Urinalysis;
- Urine sample for urine pregnancy test in female subjects of childbearing potential;
- Review subject diaries (PD home diary);
- Unified Dyskinesia Rating Scale (UDysRS);
- MDS-UPDRS (all 4 parts);
- Clinician's Global Impression of Change (CGI-C);
- Subjects will be provided with PD home diary and instructed to complete a set of two consecutive 24-hour diaries prior to the next visit. The consecutive 24-hour diaries may be started 3 days before a visit, if the subject's schedule (e.g., travel requirements) makes it difficult to complete the diary the day before a visit. The schedule for diary completion should be determined in advance of each visit for each subject;
- Collect used/unused blister cards and evaluate compliance;

- Dispense study medication (6-week supply specific for Week 19 through Week 24 [Days 127-168]).

11.10. Week 24 +/- 1 Day (End of Week 24)

The following procedures will be performed:

- Assess and record concomitant medications;
- Assess and record Adverse Events;
- Complete physical examination;
- Obtain subject weight in kilograms;
- Vital signs (blood pressure, respiratory rate, heart rate);
- Blood sample for central laboratory analysis including hematology, serum chemistry, and eGFR;
- For individuals directly rolling into the long term extension study, there will be a serum pregnancy test at Week 24, as part of the Screening Visit for ADS-AMT-PD302 and serve as the final pregnancy test for ADS-AMT-PD301;
- Urinalysis;
- Review subject diaries (PD home diary);
- Unified Dyskinesia Rating Scale (UDysRS);
- MDS-UPDRS (all 4 parts);
- Clinician's Global Impression of Change (CGI-C);
- Collect used/unused blister cards and evaluate compliance;
- Dispense study medication (1-week supply specific for Week 25 [Days 169-175]).

11.11. Week 25 +/- 1 Day (End of Week 25)

The following procedures will be performed:

- Assess and record concomitant medications;
- Assess and record Adverse Events;
- Collect used/unused blister cards and evaluate compliance.

11.12. Early Termination Visit

The following procedures will be performed at the early termination visit:

- Assess and record concomitant medications;
- Assess and record Adverse Events;
- Complete physical examination;

- Obtain subject weight in kilograms;
- Vital signs (blood pressure, respiratory rate, heart rate);
- Blood sample for central laboratory analysis including hematology, serum chemistry, and eGFR;
- Urinalysis;
- Review subject diaries (PD home diary), if available;
- Unified Dyskinesia Rating Scale (UDysRS), if ET visit is prior to Week 24;
- MDS-UPDRS (all 4 parts), if ET visit is prior to Week 24;
- Clinician's Global Impression of Change (CGI-C), if ET visit is prior to Week 24;
- Collect used/unused blister cards and evaluate compliance;
- A blood sample for a serum pregnancy test will be collected for subjects who are of child-bearing potential.

11.13. Safety Follow Up Visit (Week 26)

NOTE: Visit is only applicable for subjects who complete the Week 25 visit and decline participation in the open-label extension study.

The following procedures will be performed at the safety follow up visit:

- Assess and record concomitant medications;
- Assess and record Adverse Events;
- Targeted physical examination;
- Vital signs (blood pressure, respiratory rate, heart rate);
- A blood sample for a serum pregnancy test will be collected for subjects who are of child-bearing potential.

12. ADVERSE AND SERIOUS ADVERSE EVENTS

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, whichever occurs first.

12.1. Definition of Adverse Events

An adverse event (AE) is any untoward medical occurrence 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.

12.1.1. Adverse Event (AE)

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.

Any AE (i.e., a new event or an exacerbation of a pre-existing condition) with an onset date after study drug administration up to and including the designated follow-up safety visit should be recorded as an AE on the CRF. All AEs must be recorded on the AE CRF regardless of the severity or relationship to study medication. 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.

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);
- situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social, and/or convenience admissions);
- overdose of either study drug or concomitant medication without any signs or symptoms.

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.

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 12.1.2](#)), causality to study

drug ([Section 12.2](#)), whether an SAE or not ([Section 12.1.4](#)), and action taken (i.e., no action taken; study medication interrupted; study medication 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.

12.1.2. Severity of Adverse Events

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

- **Mild:** 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 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" (see [Section 12.1.4](#)). 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**.

12.1.3. 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.

12.1.4. Serious Adverse Event (SAE)

A **serious adverse event** (SAE) is any AE occurring at any dose that:

- 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.

12.1.4.1. 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 12.1.2](#)); 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.

12.1.4.2. 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.

12.2. Relationship to Study Drug

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.

12.3. Recording Adverse Events

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 that is deemed clinically significant or is associated with signs and/or symptoms must be recorded as an AE (and additionally as an SAE if it meets the criteria of being serious; see [Section 12.1.4](#)), 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.

12.4. Reporting Adverse Events

The Sponsor has requirements for reporting SAEs to both the local regulatory authority and other regulatory agencies about 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 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 IRB/REB/IECs.

12.4.1. Post-Study Reporting Requirements

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 (or Week 25 for subjects that directly enroll into the open label extension study), 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.

12.4.2. Investigator Reporting Responsibility

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/REB/IEC and keep a copy in their files.

12.4.3. 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 Investigator will be required to complete a Pregnancy Information Form and fax the information to the Sponsor or designee.

13. STATISTICS

13.1. Statistical Analyses

13.1.1. Sample Size Determination

In the previous phase 2/3 study, ADS-PAR-AM201, the estimates of the standard deviation (SD) of the UDysRS total score change from baseline to Week 8 across the four treatment groups ranged from 10.8 to 14.1 units and the estimated treatment difference between the 340 mg group and the placebo group was 11.3 units. Assuming an SD of 14 units, and based on the use of a two-sided test at the 5% level of significance, a sample size of 92 subjects (46 per group) provides 90% power to detect a treatment difference of 9.5 units. In order to account for a potential dropout rate of up to 20%, the planned sample size is 120 subjects (60 per group). The overall dropout rate will be monitored in a blinded fashion and the sample size may be adjusted if the dropout rate is different from our estimates.

13.1.2. Analysis Populations

13.1.2.1. Efficacy Populations

The modified intent to treat population (MITT) will include all randomized subjects who are dosed, and provide at least one post-baseline assessment of the UDysRS. The MITT population will be used for the primary efficacy analysis, as well as for all secondary efficacy analyses. In all analyses and summaries based on the MITT population, subjects will be included in the treatment group to which they were randomized.

The per-protocol population will be the subset of the MITT population who complete 12 weeks of study treatment and provide Week 12 efficacy assessments. Supportive analyses of the primary endpoint, as well as the secondary efficacy endpoints, will be completed in the per-protocol population.

The safety population will include all subjects randomized in the trial who received a dose of study medication. In all safety analyses, subjects will be included in the treatment group based on the treatment received.

13.1.2.1.1. Primary Efficacy Analysis

The primary efficacy analysis will be completed using a linear mixed model with the change from baseline in the UDysRS score as the dependent variable. The model will include fixed

effects for treatment group, week (five levels: 2, 8, 12, 18, and 24), and the interaction between treatment group and week. The baseline value of the UDysRS will be included as a covariate and the unstructured covariance model will be used. The primary analysis will compare the active (340 mg ADS-5102) group to the placebo group at Week 12 using a two-sided test at the 5% level of significance.

13.1.2.1.2. Key Secondary Efficacy Analyses

The following key secondary analyses will be conducted using a hierarchical procedure ([Westfall and Krishen, 2001](#)) to control the overall level of significance, in the order shown below:

- 340 mg ADS-5102 vs. placebo for UDysRS at Week 24
- 340 mg ADS-5102 vs. placebo for ON Time without troublesome dyskinesia at Week 12
- 340 mg ADS-5102 vs. placebo for ON Time without troublesome dyskinesia at Week 24
- 340 mg ADS-5102 vs. placebo for OFF Time at Week 12
- 340 mg ADS-5102 vs. placebo for OFF Time at Week 24

The above hypotheses will be tested using two-sided tests at the 5% level of significance, but a specified comparison will only be considered to be confirmatory if the primary efficacy analysis and all previously conducted key secondary analyses are statistically significant ($p < 0.05$).

13.1.2.1.3. Other Secondary Efficacy Analysis

Quantitative secondary endpoints will also be analyzed using linear mixed models for repeated measurements. Using the same model as for the primary analysis, comparisons between active and placebo will also be made at Weeks 2, 8, 12, 18, and 24. In addition, the primary efficacy analysis will be repeated for the per-protocol population, a subset of the efficacy analysis population who complete 12 weeks of study treatment and provide Week 12 efficacy assessments. A per protocol analysis will also be repeated for a subset of the efficacy analysis population who complete 24 weeks of study treatment and provide Week 24 efficacy assessments. All secondary analyses will be performed using two-sided tests at the 5% level of significance.

13.1.3. Handling of Missing Data

For the primary analysis, as well as for all other analyses completed using linear mixed models for repeated measurements, the available data from each subject will be used. Additional sensitivity analyses will be completed to investigate the effects of missing data. These will be described in the statistical analysis plan.

13.1.4. Safety and Tolerability

The safety analysis population will include all randomized subjects who receive at least one dose of study drug. Safety endpoints will be summarized by treatment group (ADS-5102 or placebo)

from the time of first dose and include all available safety data. No formal statistical testing will be done.

All AE data will be listed and will be summarized by system organ class, preferred term, and treatment group. Quantitative safety variables (e.g., vital signs and clinical laboratory tests) will be summarized at each visit by treatment group and changes from baseline will be summarized by treatment group at selected visits.

13.1.5. 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 MITT and Safety populations.

13.1.6. 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.

13.1.7. 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 medication discontinuations will be summarized in a similar fashion.

13.1.8. Protocol Deviations

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

14. STUDY CONDUCT

14.1. 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.

In accordance with International Committee on Harmonisation (ICH) Good Clinical Practice (GCP) and the Sponsor audit plans, this study may be selected for an audit. Inspection of site facilities (e.g., pharmacy, drug storage areas, laboratories, etc.) and review of study-related records may occur in order to evaluate the trial conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements. The investigator is to notify the Sponsor immediately if contacted by a regulatory agency for audit of documents related to this study.

14.2. 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 a 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 guidelines of the International Conference on Harmonization, and any applicable regulatory requirements. The investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

14.3. Subject Confidentiality

The Investigator must ensure that each subject's anonymity is maintained as described below. On the Clinical Assessment Forms or other study related documents, subjects must be identified by no more than their initials, date of birth, and a 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/REB/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.

14.4. Case Report Forms

Electronic Case Report Forms (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.

14.5. Retention and Availability of Records

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, Informed Consent Forms, and adequate records for the receipt and disposition of all study medications, 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.

15. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit. Please see [Section 14.2](#) for more details regarding the audit process.

16. ETHICS

16.1. Ethics Review

The Principal Investigator must obtain IRB/REB/IEC approval for the investigation. Initial IRB/REB/IEC approval, and all materials approved by the IRB for this study including the patient consent form 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 governing the protection of human subjects (21 CFR 50), Institutional Review Boards (IRB), Research Ethics Boards (REB) or Independent Ethics Committees (IEC) (21 CFR 56), the obligations of clinical investigators (21 CFR 312), and ICH GCP guidelines.

The Sponsor expects the Principal Investigator 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 Principal Investigator 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 Principal Investigator is also responsible for the following interactions with the IRB/REB/IEC:

- Obtaining IRB/REB/IEC 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 medication reported by the Sponsor, as required.

16.2. Ethical Conduct of the Study

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

16.3. 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 16.4](#)) 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 Informed Consent must comply with all applicable US Code of Federal Regulations (21 CFR 50), and ICH Good Clinical Practice guidelines. It should also include any additional information required by local laws relating to institutional review. A statement that subject

medical records must be available for investigations into SAEs must be included in the ICF. It should also include any additional information required by local laws relating to institutional review.

16.4. 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.

16.5. Emergency Contact with Investigator

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

17. INFORMATION DISCLOSURE AND INVENTIONS

17.1. 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, which 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.

17.2. 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:

1. Information that becomes publicly available through no fault of the Investigator or site staff;
2. Information that it is necessary to disclose in confidence to an IRB/REB/IEC solely for the evaluation of the study;
3. Information that it is necessary to disclose in order to provide appropriate medical care to a study subject;
4. Study results that may be published as described in [Section 18](#).

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

18. 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.

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

19. LIST OF REFERENCES

- Aoki F, Sitar D. Amantadine kinetics in healthy elderly men: implications for influenza prevention. *Clinical Pharmacology Therapeutics*. 1985; 37(2): 137-144.
- Aoki F, Sitar D. Clinical pharmacokinetics of amantadine hydrochloride. *Clinical Pharmacokinetics*. 1988; 14(1): 35-51.
- Aoki F, Sitar D, Ogilvie R. Amantadine kinetics in healthy young subjects after long-term dosing. *Clinical Pharmacology Therapeutics*. 1979; 26(6): 729-736.
- Aoki F, Stiver G, Sitar D, Boudreault A, Ogilvie R. Prophylactic amantadine dose and plasma concentration-effect relationships in healthy adults. *Clinical Pharmacology Therapeutics*. 1985; 37(2): 128-136.
- Berridge M, Apana S, Nagano K, Berridge C, Leisure G, Boswell M. Smoking produces rapid rise of [¹¹C]nicotine in human brain. *Psychopharmacology*. 2010; 209(4): 383-394.
- Blanchet P, Konitsiotis S, Chase T. Amantadine reduces levodopa-induced dyskinesias in parkinsonian monkeys. *Movement Disorders*. 1998; 13(5): 798-802.
- Bleidner W, Harmon J, Hewes W, Lynes T, Hermann E. Absorption, distribution and excretion of amantadine hydrochloride. *J Pharmacology and Experimental Therapeutics*. 1965; 150(3): 484-490.
- Colosimo C, Martinez-Martin P, Fabbrini G, Hauser R, Merello M, Miyasaki J, Poewe W, Sampaio C, Rascol O, Stebbins G, Schrag A, Goetz C. Task force report on scales to assess dyskinesia in Parkinson's disease: Critique and recommendations. *Movement Disorder*. 2010; 25(9): 1131-1142.
- Colosimo C, Merello M, Pontieri F. Amantadine in parkinsonian patients unresponsive to levodopa: a pilot study. *Journal of Neurology*. 1996; 243(5): 422-425.
- da Silva-Junior F, Braga-Neto P, Sueli Monti F, de Bruin V. Amantadine reduces the duration of levodopa-induced dyskinesia: a randomized, double-blind, placebo-controlled study. *Parkinsonism & Related Disorders*. 2005; 11(7): 449-452.
- Dallos V, Heathfield K, Stone P, Allen F. Use of amantadine in Parkinson's disease. Results of a double-blind trial. *British Medical Journal*. 1970; 4(726): 24-26.
- Danzysz W, Parsons C, Kornhuber J, Schmidt W, Quack G. Aminoadamantanes as NMDA receptor antagonists and antiparkinsonian agents- preclinical studies. *Neuroscience and Biobehavioral Reviews*. 1997; 21(4):455-468.
- Del Sorbo F, Albanese A. Levodopa-induced dyskinesias and their management. *J Neurol*. 2008; 255 Suppl 4: 32-41.
- Dorsey E, Constantinescu R, Thompson J, Biglan K, Holloway R, Kieburtz K, Marshall F, Ravina B, Schifitto G, Siderowf A, Tanner C. Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. *Neurology*. 2007; 68(5): 384-386.

- Duvoisin, R. Hyperkinetic reactions with L-DOPA. In: Yahr, MD, ed. *Current Concepts in the Treatment of Parkinsonism*. New York, NY: Raven Press; 1974: 203-210.
- Encarnacion E, Hauser R. Levodopa-induced dyskinesias in Parkinson's disease: etiology, impact on quality of life, and treatments. *European Neurology*. 2008; 60(2): 57-66.
- Fox S, Lang A, FRCPC, Brotchie J. Translation of nondopaminergic treatments for levodopa-induced dyskinesia from MPTP-lesioned nonhuman primates to phase IIa clinical studies: keys to success and roads to failure. *Movement Disorder*. 2006; 21(10): 1578-1594.
- Goetz C, Fahn S, Martinez-Martin P, Poewe W, Sampaio C, Stebbins G, Stern M, Tilley B, Dodel R, Dubois B, Holloway R, Jankovic J, Kulisevsky J, Lang A, Lees A, Leurgans S, LeWitt P, Nyenhuis D, Olanow C, Rascol O, Schrag A, Teresi J, van Hilten J, LaPelle N. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Process, format, and clinimetric testing plan. *Movement Disorder*. 2007; 22(1): 41-47.
- Goetz C, Nutt J, Stebbins G. The Unified Dyskinesia Rating Scale: Presentation and Clinimetric Profile. *Movement Disorders*. 2008a; 23(16): 2398-2403.
- Goetz C, Stebbins G, Chung K, Hauser R, Miyasaki J, Nicholas A, Poewe W, Seppi K, Rascol O, Stacy M, Nutt J, Tanner C, Urkowitz A, Joglin J, Ge S. Which Dyskinesia Scale Best Detects Treatment Response? *Movement Disorder*. 2012b; 28(3): 341-346.
- Hauser R, Deckers F, Leher P. Parkinson's disease home diary: further validation and implications for clinical trials. *Movement Disorder*. 2004; 19(12): 1409-1413.
- Hauser R, Friedlander J, Zesiewicz T, Adler C, Seeberger L, O'Brien C, Molho E, Factor S. A home diary to assess functional status in patients with Parkinson's disease with motor fluctuations and dyskinesia. *Clinical Neuropharmacology*. 2000; 23(2): 75-81.
- Hayden F, Gwaltney J, Van De Castle R, Adams K, Giordani B. Comparative toxicity of amantadine hydrochloride and rimantadine hydrochloride in healthy adults. *Antimicrobial Agents and Chemotherapy*. 1981; 19(2): 226-233.
- Hayden F, Minocha A., Spyker D., and Hoffman H. Comparative Single-Dose Pharmacokinetics of Amantadine Hydrochloride and Rimantadine Hydrochloride in Young and Elderly Adults. *Antimicrobial Agents and Chemotherapy*. 1985; 28(2): 216-221.
- Hughes A, Daniel S, Kilford L, Lees A. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J. Neurology, Neurosurgery, and Psychiatry*. 1992; 55(3): 181-184.
- Jackson G, Stanley E, Lee Muldoon R. Chemoprophylaxis of viral respiratory diseases. *Bulletin Pan Am Health Org*. 1967; 147: 595-603.
- Luginger E, Wenning G, Bosch S, Poewe W. Beneficial effects of amantadine on L-dopa-induced dyskinesias in Parkinson's disease. *Movement Disorders*. 2000; 15(5): 873-878.
- Paci C, Thomas A, Onofri M. Amantadine for dyskinesia in patients affected by severe Parkinson's disease. *Neurological Sciences*. 2001; 22(1): 75-76.

Parkes J, Zilkha K, Marsden P, Baxter R. Amantadine dosage in treatment of Parkinson's disease. *Lancet*. 1970; 1(7657): 1130-1133.

Parkinson's Study Group. DATATOP: A Multicenter Controlled Clinical Trial in Early Parkinson's Disease. *Arch Neurol*. 1989; 46: 1052-1060.

Parkinson's Study Group. Impact of Deprenyl and Tocopherol Treatment on Parkinson's Disease in DATATOP Patients Requiring Levodopa. *Ann Neurol*. 1996; 39:37-45.

Sawada H, Oeda T, Kuno S, Nomoto M, Yamamoto K, Yamamoto M, Hisanaga K, Kawamura T. Amantadine for Dyskinesia in Parkinson's Disease: A Randomized Controlled Trial. *PLOS ONE*. 2010; 5(2):1-7.

Schwab R, Poskanzer D, England A, Young R. Amantadine in Parkinson's disease. Review of more than two years' experience. *JAMA*. 1972; 222(7): 792-795.

Shram M, Sathyan G, Khanna S, Tudor I, Nah R, Thippawong J, Sellers E. Evaluation of the abuse potential of extended release hydromorphone versus immediate release hydromorphone. *J. Clinical Psychopharmacology*. 2010; 30(1): 25-33.

Snow B, Macdonald L, Mcauley D, Wallis W. The effect of amantadine on levodopa-induced dyskinesias in Parkinson's disease: a double-blind, placebo-controlled study. *Clinical Neuropharmacology*. 2000; 23(2): 82-85.

Spencer T, Biederman J, Ciccone P, Madras B, Dougherty D, Bonab A, Livni E, Parasrampura D, Fischman A. PET study examining pharmacokinetics, detection and likeability, and dopamine transporter receptor occupancy of short- and long-acting oral methylphenidate. *Am J Psychiatry*. 2006; 163(3): 387-395.

Swanson T, Volkow N. Pharmacokinetic and pharmacodynamic properties of stimulants: implications for the design of new treatments for ADHD. *Behav Brain Res*. 2002; 130(1-2): 73-78.

Thanvi B, Lo N, Robinson T. Levodopa-induced dyskinesia in Parkinson's disease: clinical features, pathogenesis, prevention and treatment. *PostGradMed Journal*. 2007; 83:384-388.

Thomas A, Iacono D, Luciano A, Armellino K, Di Iorio A, Onofri M. Duration of amantadine benefit on dyskinesia of severe Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry*. 2004; 75(1): 141-143.

Tyrrell D, Bynoe M, Hoorn B. Studies on the antiviral activity of 1-adamantanamine. *British Journal of Experimental Pathology*. 1964; 46(4): 370-375.

Verhagen-Metman L, del Dotto P, Blanchet P, van den Munckhof P, Chase T. Blockade of glutamatergic transmission as treatment for dyskinesias and motor fluctuations in Parkinson's disease. *Amino Acids*. 1998; 14(1-3): 75-82.

Verhagen-Metman, Del Dotto P, Van Den Muckhof, Fang J, Mouradian M, Chase T. Amantadine as treatment for dyskinesias and motor fluctuations in Parkinson's disease. *Neurology*. 1998; 50(5): 1323-1326.

Verhagen-Metman, Del Dotto P, LePoole K, Konitsiotis S, Fang J, Chase T. Amantadine for levodopa-induced dyskinesias: a 1-year follow-up study. *Arch Neurol*. 1999; 56(11): 1383-1386.

Vernier V, Harmon J, Stump J, Lynes T, Marvel J, Smith D. The toxicologic and pharmacologic properties of amantadine hydrochloride. *Toxicol Appl Pharmacol*. 1969; 15(3): 642-665.

Volkow N, Ding Y, Fowler J, Wang G. Cocaine addiction: hypothesis derived from imaging studies with PET. *J. Addictive Diseases*. 1996; 15(4): 55-71.

Volkow N, Wang G, Fowler J, Gatley S, Logan J, Ding Y, Hitzemann R, Pappas N. Dopamine transporter occupancies in the human brain induced by therapeutic doses of oral methylphenidate. *Am J Psychiatry*. 1998; 155(10): 1325-1331.

Westfall P, Krishen A. Optimally weighted, fixed sequence and gatekeeper multiple testing procedures. *J. Statistical Planning and Inference*. 2001; 99: 25-40.

Wolf E, Seppi K, Katzenschlager R, Hochschorner G, Ransmayr G, Schwingenschuh P, Ott E, Kloiber I, Haubenberger D, Auff E, Poewe W. Long-term antidyskinetic efficacy of amantadine in Parkinson's disease. *Movement Disorder*. 2010; 25(10): 1357-1363.

20. APPENDICES

APPENDIX A. SCHEDULE OF EVENTS

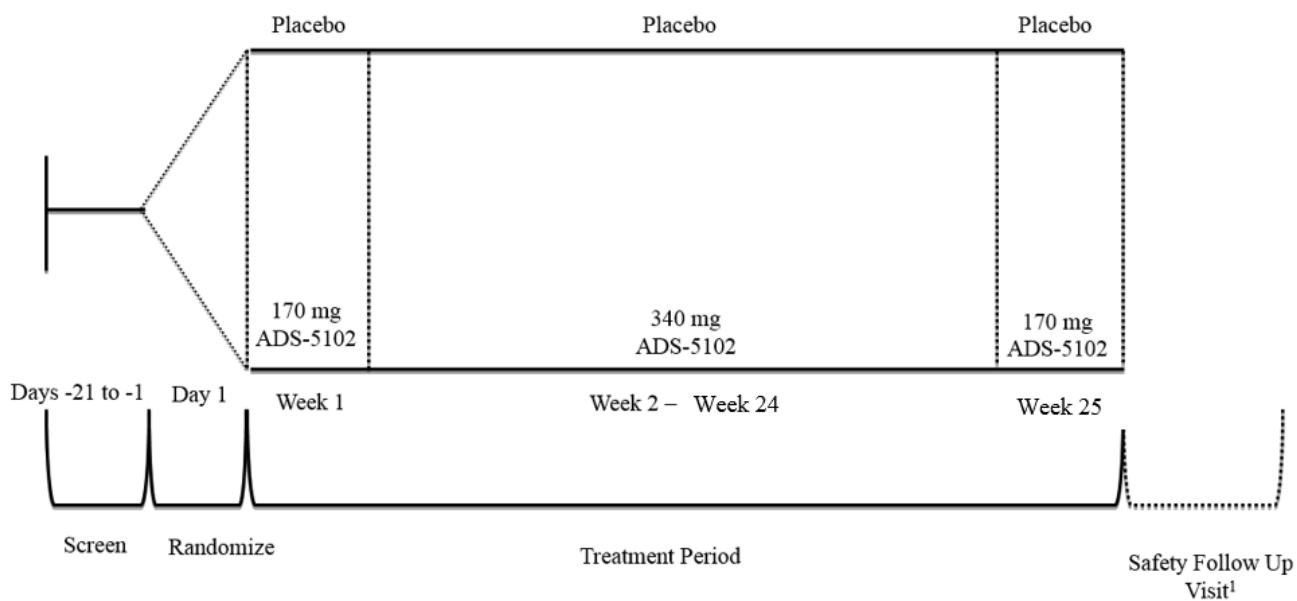
Visit	Screening	Treatment Period										Safety Follow Up Visit (a)	Early Termination Visit (b)
		1	2	3	4	5	6	7	8	9	10		
Week		0	1	2	4	8	12	18	24	25	26		
Informed consent	✓												
Eligibility Criteria	✓	✓											
Demographics	✓												
Medical History (j)	✓	✓											
Medication History	✓	✓											
Concomitant Medications		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Adverse Events (p)		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Complete Physical Exam (c)	✓						✓		✓			✓	
Targeted Physical Exam (d)		✓			✓	✓		✓			✓		
Height and Weight (e)	✓				✓		✓	✓	✓			✓	
Vital Signs (f)	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	
Hematology (g)	✓				✓		✓	✓	✓			✓	
Serum chemistry (h)	✓				✓		✓	✓	✓			✓	
Urinalysis (i)	✓				✓		✓	✓	✓			✓	
ECG (12-lead)	✓												
Serum Pregnancy Test (if applicable)	✓								✓ (r)		✓ (q)	✓ (q)	
Urine Pregnancy Test (if applicable)		✓			✓	✓	✓	✓					
MMSE	✓												
Randomization		✓											
PD Home Diary Concordance Testing	✓ (k)												
Dispense PD Home Diaries (l)	✓		✓		✓	✓	✓	✓					
Review PD Home Diaries		✓ (m)		✓		✓	✓	✓	✓			✓	
UDysRS		✓		✓		✓	✓	✓	✓			✓ (b)	
MDS-UPDRS (all 4 Parts, unless specified otherwise)	✓ (n)	✓		✓		✓	✓	✓	✓			✓ (b)	
CGI-C		✓ (o)		✓		✓	✓	✓	✓			✓ (b)	
Collect returned blister packs & assess compliance			✓	✓	✓	✓	✓	✓	✓	✓		✓	
Dispense Study Drug (blister pack)		✓	✓	✓	✓	✓	✓	✓	✓				
Study Drug dosing, once nightly at bedtime (Days 1 – 175)		✓	✓	✓	✓	✓	✓	✓	✓	✓			

Footnotes for Schedule of Events

- a. Safety follow up visit will be performed at Week 26, 1 week following dosing, only for subjects that complete the Week 25 visit and decline participation in the open-label extension study.
- b. Subjects that early discontinue after Week 24 visit do not need to have efficacy assessments performed at their early termination visit.
- c. Complete PE to include: skin, head-neck, eyes-ears-nose-throat, lungs-chest, heart, abdomen, extremities, neurological.
- d. Targeted PE to include: skin, lungs-chest, heart, abdomen, extremities.
- e. Height (in centimeters) will be measured at Screening only. Weight (in kilograms) will be measured at Screening and on Week 4, Week 12, Week 18, and Week 24. Subjects may be weighed in their undergarments, or in light clothing (no jackets or shoes). Measuring weight must be done consistently during the study, using the same set of weighing scales when possible.
- f. Vital signs obtained after the subject has been sitting for at least 5 minutes. Body temperature will be obtained at screening, Day 1, and at the final follow up visit. Blood pressure, respiratory rate and heart rate will be measured once each day assessed. During screening only, after the seated blood pressure has been obtained, the blood pressure 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 BP assessments (sitting/standing) should be obtained, and the results of the last attempt should be reported.
- g. Hematology consists of hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), red blood cell count (RBC), white blood cell (WBC) count, WBC differential (absolute), and numerical platelet count.
- h. Serum chemistry (fasting not required) consists of alkaline phosphatase, albumin, blood urea nitrogen, calcium, carbon dioxide, chloride, creatinine (MDRD formula for eGFR, to be done by the central laboratory), γ -glutamyltransferase, glucose, inorganic phosphorus, potassium, alanine aminotransferase, lactate dehydrogenase, aspartate aminotransferase, sodium, total bilirubin, and total protein.
- i. Urinalysis will be performed locally 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 at the central laboratory.
- j. A complete medical history (including PD history, mental health history, alcohol and drug use) will be obtained from the subject at the Screening Visit and recorded on the appropriate CRF. The medical history and other enrollment criteria will be reviewed and updated at the Baseline/Day 1 visit to determine continued eligibility for the study.
- k. During concordance testing, the subject and the approved Home Diary Reviewer will concurrently (and independently) evaluate the subject's motor states and rate every 30 minutes during concordance testing. The duration of concordance testing will be at least 2 hours (4 half-hour periods); However, the session may be extended to 3 or 4 hours or be repeated, if necessary, in a second 2, 3, or 4 hour session prior to the baseline visit. Successfully completed concordance testing worksheets must document at least one concordant half-hour period with dyskinesia and at least 75% concordance for ON and OFF states.
- l. During screening, potential subjects and caregivers or study partners, if appropriate, will be trained on the proper completion of 24-hour PD home diaries. Following completion of training, a set of two consecutive 24-hour diaries will be completed prior to Visit 2 (Baseline/Day 1/Week 0), serving as the baseline diary score and then prior to visits on Week 2, 8, 12, 18, 24 (or ET). The consecutive 24-hour diaries may be started 3 days before a visit, if the subject's schedule (e.g., travel requirements) makes it difficult to complete the diary the day before a visit. The schedule for diary completion should be determined in advance for each visit for each subject.
- m. If the subject has not satisfactorily completed the PD home diary, the subject and caregiver/study partner, if appropriate, should be re-trained on proper completion of the diary. The subject should be provided with an additional set of diaries and instructed to complete the diaries and return for an additional visit for review. The subject should proceed through the remainder of Day 1 assessments (including randomization) only after the subject satisfactorily completed the set of training diaries.
- n. MDS-UPDRS Part IV, item 4.2 only at screening. Note: In accordance with Inclusion Criterion #8, a score of at least 2 on part IV, item 4.2 (functional impact of dyskinesia) of the MDS-UPDRS is required at screening and at Day 1 (baseline).
- o. The CGI-C requires the investigator to rate how much the subject's Parkinson's disease has improved or worsened after treatment with study medication relative to the baseline state. In order to allow a future assessment of the CGI-C, the CGI-C rater should record notes about the subject's baseline clinical status related to overall PD, in their source documents.
- p. Adverse events will be recorded from the time of the first dose of study drug. Any subject with an ongoing AE will be followed until the AE is resolved, returns to baseline or deemed stable by the investigator.
- q. Post-study pregnancy testing in women of childbearing potential will occur at the final safety follow up visit or early termination visit.
- r. For individuals directly rolling into the long term extension study, there will be a serum pregnancy test at Week 24, as part of the Screening Visit for ADS-AMT-PD302 and serve as the final pregnancy test for ADS-AMT-PD301.

CONFIDENTIAL and PROPRIETARY

APPENDIX B. STUDY DESIGN SCHEMATIC



¹ Applicable only for subjects who complete 25 weeks of treatment and decline participation in the open-label extension

APPENDIX C. UK PARKINSON'S DISEASE SOCIETY (UKPDS) BRAIN BANK CLINICAL DIAGNOSTIC CRITERIA

Step 1. Diagnosis of Parkinsonian Syndrome

- Bradykinesia
- At least one of the following
 - muscular rigidity
 - 4-6 Hz rest tremor
 - postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction

Step 2. Exclusion criteria for PD

- history of repeated strokes with stepwise progression of parkinsonian features
- history of repeated definite encephalitis
- oculogyric crises
- neuroleptic treatment at onset of symptoms
- more than one affected relative
- sustained remission
- strictly unilateral features after 3 years
- supranuclear gaze palsy
- cerebellar signs
- early severe autonomic involvement
- early severe dementia with disturbances of memory, language, and praxis
- Babinski sign
- presence of cerebral tumor or communication hydrocephalus on imaging study
- negative response to large doses of levodopa in absence of malabsorption
- MPTP exposure

Step 3. Supportive prospective positive criteria for Parkinson's disease

Three or more required for diagnosis of definite Parkinson's disease in combination with step one

- unilateral onset
- rest tremor present
- progressive disorder
- persistent asymmetry affecting side of onset most
- excellent response (70-100%) to levodopa
- severe levodopa induced chorea
- levodopa response for 5 years or more
- clinical course of 10 years or more

APPENDIX D. NYHA FUNCTIONAL CLASSIFICATION

The New York Heart Association (NYHA) Functional Classification provides a simple way of classifying the extent of heart failure. It places patients in one of four categories based on how much they are limited during physical activity; the limitations/symptoms are in regards to normal breathing and varying degrees in shortness of breath and or angina pain:

NYHA Class Symptoms

- I No symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.
- II Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
- III Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m).

Comfortable only at rest.

- IV Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

APPENDIX E. PROHIBITED MEDICATIONS

apomorphine

mucuna pruriens

topiramate

Agents that act primarily via dopamine receptor antagonism

Phenothiazine derivatives, including those used as antiemetics:

- chlorpromazine (generic, Thorazine)
- thioridazine (generic, Mellaril)
- trifluoperazine (generic)
- perphenazine (generic)
- fluphenazine (generic, Prolixin)
- prochlorperazine (generic, Compazine)
- thiethylperazine (generic)
- promethazine

Thiothixene (generic, Navane)

Haloperidol (generic, Haldol)

Droperidol

Pimozide

Molindone

Agents that may affect the renal clearance of amantadine

Carbonic anhydrase inhibitors (topical use permitted):

- acetazolamide
- dichlorphenamide
- methazolamide

Urinary acidification agents:

- potassium acid phosphate (any K-Phos product)

Sodium Bicarbonate

Quinine

Quinidine

Trimethoprim

Triamterene

Agents that prolong the QT interval and have a known risk of torsades de pointes:

amiodarone	ibutilide
amitriptyline	levofloxacin
anagrelide	levomethadyl
astemizole	lidoflazine
azithromycin	loratidine
bepiridil	mesoridazine
budipine	methadone
chloroquine	moxifloxacin
chlorpromazine	ondansetron
citalopram	pentamidine
cisapride	pimozide
clarithromycin	probucol
cotrimoxazole	procainamide
disopyramide	quinidine
dofetilide	sertindole
domperidone	sevoflurane
droperidol	sotalol
erythromycin	sparfloxacin
escitalopram	sulpiride
flecainide	terfenadine
fluconazole	terodiline
fluoxetine	thioridazine
halofantrine	vandetanib
haloperidol	

Adamas Pharmaceuticals, Inc.

ADS-AMT-PD301

***EFFICACY AND SAFETY OF ADS-5102 (AMANTADINE HCL)
EXTENDED RELEASE CAPSULES FOR THE TREATMENT OF
LEVODOPA INDUCED DYSKINESIA IN PARKINSON'S DISEASE
PATIENTS
(EASE LID STUDY)***

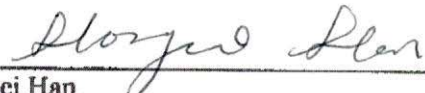
20OCT2015

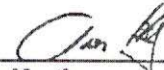
Statistical Analysis Plan

Version 3.1


Prepared by:

PPD On Behalf of
Adamas Pharmaceuticals, Inc.
*1900 Powell Street, Suite 750
Emeryville, CA 94608*

Issued by:  Date: 10/29/2015
Hongmei Han
Lead Biostatistician, Biostatistics
PPD

Reviewed by:  Date: 10/29/2015
Andrew Hartley
Senior Statistical Reviewer, Biostatistics
PPD

Upon Review of this document, including table, listing, and figure shells, the undersigned approves the statistical analysis plan. The analysis methods and data presentation are acceptable, and the table, listing and figure production can begin.

Approved by:  Date: 10/20/2015
Natalie McClure
Sr. Vice President, Product Development
Adamas Pharmaceuticals, Inc.

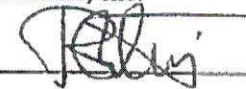
Approved by:  Date: 10/20/2015
Rajiv Patni
Chief Medical Officer
Adamas Pharmaceuticals, Inc.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS.....	5
1. INTRODUCTION.....	6
2. STUDY OBJECTIVES.....	7
3. INVESTIGATIONAL PLAN	7
3.1. OVERALL STUDY DESIGN AND PLAN	7
3.2. STUDY ENDPOINTS	8
3.3. TREATMENTS.....	9
3.4. DOSE ADJUSTMENT	9
4. GENERAL STATISTICAL CONSIDERATIONS	10
4.1. REPORTING CONVENTIONS	10
4.1.1. <i>Visit Windows</i>	10
4.1.2. <i>Calculation Using Dates</i>	11
4.1.3. <i>Definitions of Study Day 1 and Baseline</i>	11
4.2. SAMPLE SIZE	12
4.3. RANDOMIZATION, STRATIFICATION, AND BLINDING	12
4.4. ANALYSIS SETS	12
4.4.1. <i>All Randomized</i>	12
4.4.2. <i>Modified Intent-to-Treat (MITT)</i>	13
4.4.3. <i>Per Protocol (PP)</i>	13
4.4.4. <i>Safety</i>	13
5. SUBJECT DISPOSITION	13
5.1. PROTOCOL DEVIATIONS	14
6. DEMOGRAPHICS, MEDICAL HISTORY AND BASELINE CHARACTERISTICS.....	14
6.1. DEMOGRAPHICS AND BASELINE CHARACTERISTICS	14
6.2. MEDICAL HISTORY	14
6.2.1. <i>General Medical History</i>	14
6.2.2. <i>Parkinson’s Disease-Specific Medical History</i>	15
6.3. INCLUSION AND EXCLUSION CRITERIA	15
6.4. PARKINSON’S DISEASE-RELATED BASELINE CHARACTERISTICS	16
6.5. PHYSICAL EXAMINATION	16
7. TREATMENTS AND MEDICATIONS.....	16
7.1. PRIOR AND CONCOMITANT MEDICATIONS.....	16
7.2. STUDY TREATMENT.....	17
7.2.1. <i>Duration of Exposure</i>	17
7.2.2. <i>Treatment Compliance</i>	17
8. EFFICACY ANALYSIS.....	18

8.1.	PRIMARY EFFICACY ENDPOINT.....	18
	<i>UDysRS total score</i>	19
	8.1.1. <i>Primary Efficacy Analysis</i>	20
	8.1.2. <i>Assumption Evaluation</i>	21
	8.1.3. <i>Other Analyses of Primary Efficacy Endpoint</i>	21
8.2.	SECONDARY EFFICACY ENDPOINTS	22
	8.2.1. <i>PD Home Diary</i>	22
	8.2.2. <i>UDysRS total objective score</i>	23
	8.2.3. <i>MDS-UPDRS</i>	23
	8.2.4. <i>Clinician’s Global Impression of Change scale (CGI-C)</i>	24
8.3.	KEY SECONDARY ANALYSES.....	25
8.4.	OTHER SECONDARY ANALYSES	25
8.5.	SUBGROUP ANALYSIS.....	26
9.	SAFETY ANALYSIS.....	26
9.1.	ADVERSE EVENTS.....	26
	9.1.1. <i>Incidence of Adverse Events</i>	27
	9.1.2. <i>Causality of Adverse Events due to Study Drug</i>	27
	9.1.3. <i>Intensity of Adverse Events</i>	27
	9.1.4. <i>Serious Adverse Events</i>	28
	9.1.5. <i>Adverse Events Leading to Treatment Discontinuation</i>	28
	9.1.6. <i>Adverse Events Leading to Death</i>	28
	9.1.7. <i>Adverse Events of Special Interest</i>	28
9.2.	CLINICAL LABORATORY EVALUATIONS	29
	9.2.1. <i>Hematology</i>	29
	9.2.2. <i>Serum Chemistry</i>	29
	9.2.3. <i>Urinalysis</i>	30
	9.2.4. <i>Serum and Urine Pregnancy Tests</i>	30
9.3.	VITAL SIGN MEASUREMENTS	30
9.4.	PHYSICAL EXAMINATION	30
10.	CHANGES IN THE ANALYSES PLANNED IN THE PROTOCOL	31
11.	REFERENCES.....	32
12.	APPENDICES	33
	12.1. SCHEDULE OF EVENTS.....	34
	12.2. STUDY DESIGN SCHEMATIC	37

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse Event
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CGI-C	Clinician’s Global Impression of Change
CI	Confidence Interval
CNS	Central Nervous System
CSR	Clinical Study Report
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EOS	End-of-study
ET	Early Termination
HEENT	Head, eyes, ears, nose, and throat
ICH	International Conference on Harmonisation
LS	Least Square
LID	Levodopa–Induced Dyskinesia
LOCF	Last Observation Carried Forward
IR	Immediate Release
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MDS-UPDRS	Movement Disorder Society–Unified Parkinson’s Disease Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified Intent–To–Treat
MMSE	Mini-Mental Status Examination
PD	Parkinson’s Disease
PP	Per Protocol
PT	Preferred Term
RBC	Red Blood Cell(s)
SAE	Serious Adverse Event
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
UDysRS	Unified Dyskinesia Rating Scale
WBC	White Blood Cell(s); leukocyte(s)
WHO	World Health Organization

1. Introduction

Parkinson's disease (PD) is a chronic, progressive disorder with prominent motor signs including tremors, rigidity, bradykinesia and postural instability. Levodopa is the most commonly prescribed and effective drug treatment for symptomatic relief in PD; however, chronic treatment with levodopa often results in the emergence of dose-limiting motor side-effects, including abnormal involuntary movements known as levodopa-induced dyskinesia (LID). With continued levodopa treatment, and as PD progresses, LID can become severely disabling and has been associated with a decrease in quality of life (Encarnacion et al. 2008).

Levodopa-induced dyskinesia (LID) is an adverse effect of all dopaminergic therapies, but mostly related to the use of levodopa. The most common type of LID is referred to as "peak-dose dyskinesia" and usually consists of stereotypical choreic or ballistic movements involving the head, trunk, and limbs. Movement disorder specialists have developed rating scales to evaluate dyskinesia for purposes of clinical diagnosis and clinical trial investigation (Goetz, Nutt et al. 2008; Colosimo, Martinez-Martin et al. 2010; Goetz et al. 2013).

Amantadine immediate-release (IR), which is approved for treatment of PD, is used off-label by movement disorder specialists and other neurologists to treat LID in patients with PD. A number of literature reports suggest amantadine is effective for the treatment of LID. Despite amantadine's reported utility in the treatment of LID, until recently, the drug was not extensively studied in well-controlled clinical trials that meet evidence-based clinical or regulatory standards of acceptance, nor was the optimal dose for this indication established. The majority of patients with PD tolerate 200 mg/day of the amantadine IR formulation. It has been reported that higher doses of amantadine produce a greater reduction in LID symptoms (Verhagen et al. 1998; Luginer et al. 2000). However, the increased frequency of adverse events (AEs) at higher doses, in particular central nervous system (CNS) events and sleep disturbances, limits the routine use of amantadine IR at doses of 300 mg/day or higher (Jackson et al. 1967; Hayden et al. 1981).

The pharmacologic rationale for a formulation that slows the release of amantadine is based upon the nature and timing of amantadine IR CNS side effects relative to dosing as well as observations with other CNS active drugs. Symmetrel (amantadine HCl IR tablet) has a short t_{max} of 2-4 hours (Aoki et al. 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.

Hence, the pharmacologic rationale for improved tolerability of an extended-release formulation of amantadine is that the reduction in the rate of rise in plasma concentration may reduce the CNS adverse effects that can occur shortly after dosing, without compromising concentration-dependent efficacy.

ADS-5102 is an extended release formulation of amantadine HCl. The proposed daily dose of ADS-5102 is 170 mg during the first week of dosing, and 340 mg thereafter, each dose to be taken once nightly at bedtime. The efficacy and safety of this ADS-5102 regimen is being investigated in this study.

2. Study Objectives

Primary Objective

- To evaluate the efficacy of ADS-5102 oral capsules, an extended release formulation of amantadine, at a dose of 340 mg once nightly at bedtime for the treatment of LID in subjects with PD.

Secondary Objective

- To evaluate the safety and tolerability of ADS-5102 in this study population.

3. Investigational Plan

3.1. Overall Study Design and Plan

This is a multi-center, randomized, double-blind, placebo-controlled, 2-arm, parallel group study of ADS-5102 in subjects with PD who have LID. All subjects will have received a stable regimen of antiparkinson's medications for at least 30 days prior to screening; including a levodopa preparation administered not less than three times daily. Current PD medications and dose regimens will continue unchanged during study participation.

Consented subjects meeting all study eligibility criteria will be randomized in a 1:1 ratio to one of 2 treatment groups: placebo or active (340 mg ADS-5102). Study drug will be administered as 2 capsules once nightly at bedtime (if possible, no earlier than 9 pm) for 25 weeks. Following completion of Visit 2 (Baseline/Day 1/Week 0), subjects will return to the clinic after 1, 2, 4, 8, 12, 18, 24 and 25 weeks of dosing.

Subjects who complete 25 weeks of dosing will have the option of transitioning directly to an open-label extension study, ADS-AMT-PD302.

Subjects who prematurely discontinue from study drug after Week 12, but continue to follow the study protocol procedures, including efficacy assessments, will have the option of transitioning directly into the open-label extension study after their Week 25 visit, as long as the reason for discontinuation of study drug was not due to an adverse event judged to be related to study drug.

Subjects who decline participation in the open-label extension study will have a final safety follow-up visit at Week 26, 1 week following the completion of dosing.

This SAP is based on Amendment 2 of the protocol, dated 31 March 2015.

3.2. Study Endpoints

Primary Endpoint

The primary endpoint is the change from baseline to Week 12 in the Unified Dyskinesia Rating Scale (UDysRS) total score.

Key Secondary Endpoints

Change from baseline to Week 24 in the following:

- UDysRS total score

Change from baseline to Week 12 and change from baseline to Week 24 in each of the following:

- ON time without troublesome dyskinesia (ON time without dyskinesia plus ON time with non-troublesome dyskinesia), based on a standardized PD home diary
- OFF time, based on a standardized PD home diary

Other Secondary Endpoints

Change from baseline to Week 12 and change from baseline to Week 24 in each of the following:

- ON time with troublesome dyskinesia, based on a standardized PD home diary
- Total time with dyskinesia (non-troublesome and troublesome), based on a standardized PD home diary
- Unified Parkinson's Disease Rating Scale (MDS-UPDRS), Part IV
- Unified Parkinson's Disease Rating Scale (MDS-UPDRS), Item 4.1 (time spent with dyskinesias) and Item 4.2 (functional impact of dyskinesias) in Part IV
- UDysRS Total Objective Score (Parts III and IV)
- Unified Parkinson's Disease Rating Scale (MDS-UPDRS), individual and combined scores (Parts I, II, III)
- Clinician's Global Impression of Change (CGI-C) in overall PD symptoms, determined by a question completed by the investigator

Change from baseline to Week 8 in the following:

- UDysRS total score

3.3. Treatments

Study treatments consist of an oral formulation of amantadine HCl (ADS-5102) and a placebo control. ADS-5102 is formulated as extended release coated pellets of 170 mg amantadine HCl in oral capsule form. Study drug will be administered as 2 capsules once nightly at bedtime (and, if possible, no earlier than 9 pm), for 25 weeks. Both active drug and placebo will be administered in double-blind fashion; the capsules will be indistinguishable in size and appearance.

For the active group, a dose of 170 mg ADS-5102 will be administered as 2 capsules (1 capsule of 170 mg ADS-5102 and 1 capsule of placebo) during Week 1. During Week 2 through Week 24, a dose of 340 mg ADS-5102 will be administered as 2 capsules, each containing 170 mg ADS-5102. There will be a reduction in dose to 170 mg ADS-5102 administered as 2 capsules (1 capsule of 170 mg ADS-5102 and 1 capsule of placebo) during Week 25.

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

3.4. Dose Adjustment

Subjects who discontinue study drug after Week 4 should receive a reduced dose for 1 additional week, either 170 mg ADS-5102 or placebo, in a double-blind fashion before stopping study drug. The additional week of dosing at a reduced dose will not be needed for subjects who discontinue study drug before Week 4.

Subjects whose estimated Glomerular Filtration Rate (eGFR) falls below 50 mL/min/1.73m² (and ≥ 30 mL/min/1.73m²), confirmed by repeat testing, while on study should discontinue study drug after receiving a reduced dose of either 170 mg ADS-5102 or placebo, in a double-blind fashion, for 1 additional week. The additional week of dosing at a reduced dose will not be needed if the decrease in estimated GFR occurs before Week 4.

Subjects whose estimated GFR falls below 30 mL/min/1.73m², confirmed by repeat testing, while on study should discontinue study drug (without the additional week at a reduced dose).

On a case by case basis, and following discussion with the principal investigator, a study subject unable to tolerate the full dose of study drug (340 mg ADS-5102 or placebo) may be allowed to continue in the study if willing and able to tolerate a reduced dose (170 mg ADS-5102 or placebo).

4. General Statistical Considerations

4.1. 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 (eg, age groups), regardless of whether data were present in each category, unless otherwise specified. For other categorical data (eg, AEs and medications), only categories with non-zero frequencies will be presented.

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.”). For analysis tables repeated over multiple analysis sets, if the analysis sets are the same with the same allocations of patients to columns (treatment arms), then 1 of the analysis tables will merely refer to the other table.

4.1.1. Visit Windows

A visit window method, as described in Table 1a (safety) and Table 1b (efficacy), will be applied to assign visits to safety and efficacy data across the study. If a subject has multiple assessments within a visit window, the value closest to the target day for that visit will be selected for the visit. If there are two values which are equidistant in terms of time then the later value will be

selected. The study day for visit post start of treatment is defined as the difference between the date of assessment and the start of treatment plus 1

Table 1a: Visit Window Method - Safety

Timepoint	Week	Target Day	Window Start Day, Inclusive	Window End Day, Inclusive
Day 8	Week 1	8	2	11
Day 15	Week 2	15	12	22
Day 29	Week 4	29	23	43
Day 57	Week 8	57	44	71
Day 85	Week 12	85	72	106
Day 127	Week 18	127	107	148
Day 169	Week 24	169	149	183

Table 1b: Visit Window Method - Efficacy

Timepoint	Week	Target Day	Window Start Day, Inclusive	Window End Day, Inclusive
Day 15	Week 2	15	2	36
Day 57	Week 8	57	37	71
Day 85	Week 12	85	72	106
Day 127	Week 18	127	107	148
Day 169	Week 24	169	149	183

4.1.2. Calculation Using Dates

The following conventions will be used to calculate study day for reporting purposes:

- Study Day = date of measurement – randomization date +1, if date of measurement is on or after the randomization date.
- Study Day = date of measurement – randomization date, if date of measurement is prior to the randomization date.

4.1.3. Definitions of Study Day 1 and Baseline

Study Day 1 is defined as the date of randomization. Subjects should receive double-blind study drug on the date of randomization and presumably take the first dose at bedtime on the same day. No Day 0 is defined. Negative study days indicate observations were obtained during the baseline/screening period.

Baseline is defined as the last observation on or before Day 1.

4.2. Sample Size

In the previous phase 2/3 study, ADS-PAR-AM201, the estimates of the SD of the UDysRS total score change from baseline to Week 8 across the four treatment groups ranged from 10.8 to 14.1 units and the estimated treatment difference between the 340 mg group and the placebo group was 11.3 units. Assuming an SD of 14 units, and based on the use of a two-sided test at the 5% level of significance, a sample size of 92 subjects (46 per group) provides 90% power to detect a treatment difference of 9.5 units. In order to account for a potential dropout rate of up to 20%, the planned sample size is 120 subjects (60 per group). The overall dropout rate will be monitored in a blinded fashion and the sample size may be adjusted if the dropout rate differs from estimates. If the SD is as large as 15.4 (10% larger), then 112 subjects (56 per group) are needed to provide 90% power.

4.3. Randomization, Stratification, and Blinding

A subject is considered randomized at Day 1 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.

Consented subjects meeting all eligibility criteria will be randomly assigned in a 1:1 ratio to one of 2 treatment groups: active (ADS-5102) or placebo.

The identity of the treatment assigned to individual subjects can be revealed only in an emergency. Details of the process to be followed are provided in the study and IWRS manuals. The Principal Investigator 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.

4.4. Analysis Sets

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 analysis population 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.

4.4.1. All Randomized

The All Randomized population includes every randomized subject.

4.4.2. Modified Intent-to-Treat (MITT)

The modified intent to treat (MITT) population will include all randomized subjects who are dosed and who provided at least one post-baseline assessment of the UDysRS. The MITT population will be used for the primary efficacy analysis, as well as for all secondary efficacy analyses. In all analyses and summaries based on the MITT population, subjects will be included in the treatment group to which they were randomized.

4.4.3. Per Protocol (PP)

The per-protocol population will be the subset of the MITT population who met inclusion criteria 6, 8, 9, completed 12 weeks of study treatment, and provided Week 12 UDysRS efficacy assessments. Supportive analyses of the primary endpoint, as well as the secondary efficacy endpoints, will be completed in the PP population.

4.4.4. Safety

The safety population will include all subjects randomized in the trial who received at least a dose of study drug. It will be used for all safety analyses. In these analyses, subjects will be analyzed according to the treatment received most often.

5. Subject Disposition

Subject disposition, using all randomized subjects, will be summarized using a frequency table by treatment groups and overall for follow-up visits. This summary table will include the number and percentage of subjects in each of the analysis sets along with completion status.

A separate table will be presented to show the number (%) of subjects who withdrew from the study and the primary reason for withdrawal, by treatment groups and overall. The primary reasons of withdrawal reported by subjects will be presented in this table. Similarly, the number (%) of subjects who discontinued study drug and the reason for early discontinuation will be summarized in a separate table, by treatment groups and overall. The primary reasons of discontinuation reported by subjects will be presented.

The time to discontinuation of blinded study drug will be analyzed. The time to discontinuation is defined as the number of days from the randomization date to the last dose of blinded study drug. Subjects will be censored if no early study drug discontinuation occurred. The median duration and the associated 95% confidence interval for each treatment arm will be estimated using the Kaplan-Meier method. Kaplan-Meier estimates of the survival function will be calculated and displayed graphically.

A listing will present data concerning subject disposition.

5.1. Protocol Deviations

Subjects having significant protocol deviations will be listed and may be excluded from the PP Population. Categories under which protocol deviators will be reviewed include, but are not limited to, the following:

- poor compliance with study drug (<80%)
- use of prohibited concomitant medications
- violation of inclusion/exclusion criteria
- missing baseline efficacy data

The protocol deviations will be classified into categories and a listing of all subjects with significant protocol deviations will be presented.

6. Demographics, Medical History and Baseline Characteristics

6.1. Demographics and Baseline Characteristics

The following demographic information will be summarized using the MITT population, Safety population, and PP population, by treatment groups and overall.

- Age (years), calculated as (informed consent date – birthdate +1)/365.25
- Age Categories (<65, >=65)
- Sex (male/female)
- Race (White, Black, American Indian/Alaska Native, Native Hawaiian or Other Pacific Islander, Asian, Other)
- Ethnicity (Hispanic or Latino, Non-Hispanic/Non-Latino)
- Height (cm)
- Body Weight (kg)
- Body mass index (BMI), calculated at screening as (weight in kg)/(height in meters)² (kg/m²)
- eGFR provided by the central lab using subject data and MDRD-NKDEP equation

The demographic data will be listed for the Safety population.

6.2. Medical History

6.2.1. General Medical History

Any medical history will be summarized for the Safety population. The table summary will show the number and percentages of subjects with a history for each of the following body systems.

- HEENT
- Dermatological
- Psychiatric
- Neurological
- Cardiovascular
- Respiratory
- Gastrointestinal
- Genitourinary
- Musculoskeletal
- Endocrine
- Hematological
- Allergies
- Immunological
- Renal
- Hepatic
- Other

Medical history including specific details will be listed for the Safety population.

6.2.2. Parkinson's Disease-Specific Medical History

Parkinson's Disease history including the following will be summarized using the MITT population, Safety population, and PP population, by treatment groups and overall.

- Age (years) at PD diagnosis
- Time since PD diagnosis in years
- Age (years) at start of levodopa treatment
- Duration of levodopa treatment in years
- Duration of levodopa-induced dyskinesia in years

For the duration of Parkinson's disease, if only the month and year of diagnosis is available, the 15th day of the indicated month is assumed, and when only the year of diagnosis is available, July 1 of the indicated year is assumed. A similar algorithm is used for age at PD diagnosis, age at start of levodopa treatment, duration of levodopa treatment, and duration of levodopa-induced dyskinesia. Fractional years of duration will be used for the analyses.

Parkinson's Disease history data will be listed for the safety population.

6.3. Inclusion and Exclusion Criteria

The inclusion and exclusion criteria are detailed in Sections 7.1 and 7.2 of the protocol.

6.4. Parkinson's Disease-Related Baseline Characteristics

Parkinson's Disease related baseline characteristics will be summarized using the MITT population, Safety population, and PP population, by treatment groups and overall.

- UDysRS: total score, total objective score
- PD Diary: Time spent on following categories: ON without troublesome dyskinesia, ON with troublesome dyskinesia, Total with dyskinesia, OFF, and Asleep
- MDS-UPDRS: Part I, Part II, Part III, Combined (Parts I, II, and III), Part IV, Part IV item 4.1, Part IV, item 4.2
- MMSE score
- Hoehn and Yahr Stage

6.5. Physical Examination

A table will summarize physical examination results at screening visit by treatment groups and overall for the Safety population. The summary will include the number and percentage of subjects with clinically significant abnormal finding for the following body systems: skin; head, neck; eyes, ears, nose, and throat; lungs, chest; heart; abdomen; extremities, and neurological. Physical examination results will be listed for the safety population.

7. Treatments and Medications

7.1. Prior and Concomitant Medications

Prior medications are defined as medications with a stop date occurring before the first dose date. Concomitant medications are defined as medications with a stop date occurring on or after the first dose date, or listed as ongoing. Medications with start and stop dates (or ongoing) which bracket the first dose 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 most recent World Health Organization (WHO) Drug Dictionary.

Prior and concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) Level and preferred term (PT) by treatment groups and total, for Safety population. At each level of summarization, a subject is counted once if he/she reported one or more medications at that level. The PD prior and concomitant medications will be presented separately.

For the purpose of classifying medications as prior and/or concomitant in summaries, incomplete medication start and stop dates will be imputed as detailed below:

- If year and month are present and day is missing then set start day to last day of month, and set end day to the later of (first day of month, start day)
- If year and day are present and month is missing then set start month to December, and set end month to the later of (January, start month)
- If year is present and month and day are missing then set start month and day to December 31st, and set end month and day to the later of (January 1st, start month and day)
- Completely missing dates will not be imputed

If start date is completely missing and end date is after the first dose, then the medication will be classified as both prior and concomitant. If the end date is missing, then the medication will be classified as ongoing. Medications for which the start and end dates are missing will be classified as prior and concomitant.

Prior and concomitant medications will also be listed, with a flag identifying each prior medication.

A separate table will summarize the levodopa dose at baseline, Week 12, and Week 24 for MITT population, by treatment groups and overall. The change from baseline at Week 12 and Week 24 will be included in the same table.

7.2. Study Treatment

One blister card containing study drug will be dispensed on Day 1, Week 1, and Week 24. Two cards will be dispensed at the Week 2 visit. Four cards will be provided at Weeks 4 and 8. Six cards will be dispensed at Weeks 12 and 18.

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. Number of capsules dispensed, number of capsules returned, and number of missed doses, will be collected in drug accountability pages of CRFs.

7.2.1. Duration of Exposure

Duration of exposure to treatment will be defined below:

Duration of exposure (Days) = (Date of Last Dose – Randomization Date) + 1.

The duration of exposure will be summarized for the Safety population.

7.2.2. Treatment Compliance

Percentage treatment compliance will be calculated for all subjects based on their dosing days (treatment exposure) using the drug accountability data.

Compliance for capsules (%) = $(A/P) \times 100\%$

where:

P = the number of capsules prescribed = number of days dosed in the study x 2 capsules

A = the number of capsules utilized = total number of capsules dispensed – total number of capsules returned

Total number of capsules prescribed will be calculated based on the numbers prescribed from Day 1 to the last day of dosing.

Total number of capsules utilized will be calculated based on the number of capsules utilized from Day 1 to last day of dosing. If, for any visit interval, the numbers of capsules returned are missing, but the subject was able to report “number of missed doses”, the “number of missed doses” data will be used to assume compliance. If, for any visit interval, the number of capsules returned are missing, and the subject is lost to follow up, or cannot report “number of missed doses”, the interval will be disregarded in calculating a subject’s compliance.

The treatment compliance will be summarized for the safety population.

All drug accountability data will be presented in the listing.

8. Efficacy Analysis

The MITT population will be used for the primary efficacy analysis, as well as for the primary analysis of each secondary efficacy endpoint. In all analyses and summaries based on the MITT population, subjects will be included in the treatment group to which they were randomized.

All efficacy analysis statistical tests will be performed using the 2-sided 5% significance level.

All efficacy data will be listed using the Safety population.

8.1. Primary Efficacy Endpoint

Efficacy will be assessed primarily using the UDysRS total score. The UDysRS was developed to evaluate involuntary movements often associated with treated Parkinson’s disease (Goetz, Nutt 2008).

The scoring for the scale is as follows:

Part IA: Historical Disability of On–Dyskinesia impact (Question 1– rater calculation of time with on–dyskinesia, maximum 4 points)

Part IB: Historical Disability of On–Dyskinesia impact (Questions 2 – 11, maximum 40 points)

Part IIA: Historical Disability of Off–Dystonia impact (Question 12 – rater calculation of time with off–dystonia, maximum 4 points)

Part IIB: Historical Disability of Off–Dystonia impact (Questions 13 – 15, maximum 12 points)

Part III: Objective Impairment (dyskinesia severity, anatomical distribution over seven body regions, and type (choreic or dystonic) based on four activities observed (Questions 16 – 22, maximum 28 points)

Part IV: Objective Disability based on Part III activities (Questions 23 – 26, maximum 16 points)

Imputation rules for individual UDysRS subscale items and total scores

The missing items will be imputed applying the methods described below prior to calculating the UDysRS subscales (Parts IB, IIB, III and/or IV) and total scores. If 2 or more individual UDysRS items are missing in one or more of the UDysRS subscales (parts IB, IIB, III and/or IV), the individual subscales will be missing.

Table 2: Imputation rules for individual UDysRS subscale items and total scores

	Subscale (Total) Items	Missing Items	Imputation (Y/N)	Imputation Method
Part IA	1	1	No	Assign a value of 0
Part I B	10	1	Yes	Average of non-missing items within the subscale
Part IIA	1	1	No	Assign a value of 0
Part II B	3	1	Yes	Average of non-missing items within the subscale
Part III	7	1	Yes	Average of non-missing items within the subscale
Part IV	4	1	Yes	Average of non-missing items within the subscale
Total Objective Score (Part III + Part IV)	11	Part III or Part IV	No	Missing
Total UDysRS Score	26	Part I B or Part II B or Part III or Part IV	No	Missing

UDysRS total score

The total UDysRS score will be calculated as the sum of all individual subscales (including Part I A and Part II A) after the imputation algorithms for each subscale are employed. Values will range from a minimum of 0 to maximum of 104.

8.1.1. Primary Efficacy Analysis

The primary efficacy analysis will compare the active (340 mg ADS-5102) group to the placebo group at Week 12 using a linear mixed model with repeated measures (MMRM), with the changes from baseline in the UDysRS total score at Weeks 2, 8, and 12 as the dependent variable. The model will include categorical effects for treatment group, visit (three levels corresponding to Weeks 2, 8, and 12), and the interaction between treatment group and visit. The baseline value of the UDysRS total score will be included as a covariate. An unstructured covariance matrix will be used to model the within-subjects errors. If the model does not converge with an unstructured covariance matrix, then a compound symmetry matrix will be used. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom and adjust the standard errors. The primary analysis will compare the active (340 mg ADS-5102) group to the placebo group at Week 12. Estimates for the LS Means change from Baseline at Week 12 in each treatment arm along with the LS Means treatment difference will be provided with 95% confidence intervals (CIs) using an appropriate contrast from the model.

To implement the primary analysis, the following model will be fitted in SAS PROC MIXED:

$$Y_{ijk} = \mu + \lambda X_{ij} + \alpha_i + d_{ij} + \tau_k + (\alpha\tau)_{ik} + \varepsilon_{ijk}$$

where

Y_{ijk} = Visit k Change from baseline in Total UDysRS score for Subject j in Drug Group i

μ = a constant common to all observations

λ = a fixed coefficient on the covariate (baseline UDysRS total score)

X_{ij} = Covariate for subject j in drug group i

α_j = the main effect parameter of treatment group i

d_{ij} = is a normally distributed random variable corresponding to subject j in drug group i

τ_k = the main effect parameter of Visit k

$(\alpha\tau)_{ik}$ = the interaction parameter corresponding to Drug Group i and Visit k

ε_{ijk} = a normal distributed random error corresponding to subject j in drug group i at visit k

The SAS model that will be used for the primary endpoint analysis will be similar to the one stated below:

```
Proc Mixed Data=All;
Class subject treatment time;
Model CFB = baseline treatment time treatment*time /ddfm=kr;
Repeated time / sub = subject type = UN;
estimate 'trt 0 at W12' intercept 1 baseline &blavg
                    treatment 1 0
                    time 0 0 1
                    treatment*time 0 0 1 0 0 0
                    /e;
estimate 'trt 1 at W12' intercept 1 baseline &blavg
                    treatment 0 1
                    time 0 0 1
```

```
                treatment*time 0 0 0   0 0 1
                /e;
estimate 'trt diff at W12' treatment -1 1
                treatment*time 0 0 -1   0 0 1
                /e;

Run;
```

A line graph will display the UDysRS total score change from baseline by treatment (LS Means \pm SE), over time, based on the above modeling. In addition, the UDysRS total score change from baseline to Week 8 and Week 12 (LS Means \pm SE) will also be displayed in bar graphs.

8.1.2. Assumption Evaluation

The residuals at Week 12 from the primary analysis modeling will be plotted on a quantile-quantile plot.

If there is strong evidence suggesting that the residuals from the model deviate much from normality, then a supplemental analysis using an analysis of covariance (ANCOVA) model for ranked data (Stokes, 2000) will be utilized. This nonparametric ranked ANCOVA will be performed on the MITT population in order to assess the robustness of the primary MMRM analysis.

8.1.3. Other Analyses of Primary Efficacy Endpoint

As additional sensitivity analyses, the following procedures will be applied to the primary efficacy endpoint (change from baseline to Week 12 in UDysRS total score):

- Repeat of the primary efficacy analysis, for the PP population,
- Repeat of the primary efficacy analysis including all of the available data through Week 24 in the model (five levels of visit (Weeks 2, 8, 12, 18, and 24)), for the MITT and PP population,
- Repeat of the primary efficacy analysis including all of the available data through Week 24 in the model, for the subset of the PP population who provide UDysRS total scores at Week 24,
- ANCOVA using change from baseline to Week 12, having applied the last observation carried forward (LOCF) method, for the MITT population,
- Wilcoxon rank sum test using change from baseline to Week 12, having applied LOCF, for the MITT population.

A graph will display the cumulative proportion of subjects who have achieved the level of response over UDysRS change score at Week 12, by treatment group, for the MITT population having applied LOCF.

8.2. Secondary Efficacy Endpoints

8.2.1. PD Home Diary

Each subject will record data to score 5 different conditions in 30-minute intervals: ASLEEP, OFF, ON without dyskinesia, ON with non-troublesome dyskinesia, and ON with troublesome dyskinesia (Hauser, Friedlander, 2000). A set of two consecutive 24-hour PD home diaries (48 hours total) will be completed during screening and prior to each specified visit. The consecutive 24-hour diaries may be started 3 days before a visit, if the subject's schedule makes it difficult to complete a diary during the day before a visit. The schedule for diary completion should be determined in advance for each subject.

All 24-hour diaries will be reviewed for evaluability. If 4 or fewer 30-minute intervals are marked "Subject did not respond" or missing on the eCRF, the 24-hour diary will be considered evaluable and will be included in the analysis. If more than four 30-minute intervals are marked "Subject did not respond" on the eCRF, the 24-hour diary will be considered un-evaluable and will not be included in the analysis. The value for "missing intervals" of the evaluable diaries will be imputed from the prior and subsequent intervals as described below.

Imputation Rules

If 4 or fewer 30 minute intervals are not available or missing, the value for a missing response interval will be imputed by assigning the 30 minutes of each missing interval, in equal portions of 15 minutes each, to the responses of the immediately preceding and subsequent completed (non-missing) intervals. If a missing response interval occurs at the beginning or end of a 48-hour diary reporting period such that it does not have both preceding and subsequent completed intervals, then the 30 minutes of the missing interval will be assigned to the closest completed (non-missing) interval.

If both 24-hour diaries are evaluable for a study visit, data from both diaries may be used to impute missing interval values.

Derived and Transformed Data

All the diary parameters will be derived in terms of hours and also in percentage of time awake.

Absolute Time

The times (in hours) spent

- ASLEEP
- OFF
- ON without dyskinesia
- ON with non-troublesome dyskinesia
- ON with troublesome dyskinesia

will be summed for each one of the two 24 hour diaries. The average for each of the above categories per 24 hours will be determined, and this average will be used for all analyses and

summaries if both diaries are evaluable. If only one diary is evaluable, then this diary will be used for analyses.

In addition, the following variables will be derived using the derived sums for above mentioned categories:

- ON time without troublesome dyskinesia: ON without dyskinesia + ON with non-troublesome dyskinesia
- Total ON time with dyskinesia: ON with troublesome dyskinesia + ON with non-troublesome dyskinesia
- Number of Waking Hours: 24 – ASLEEP

Time as a Percentage of time awake

The times in the following categories will be also calculated, as percentages of time awake, by dividing the each item listed below over the number of Waking Hours.

- ON without troublesome dyskinesia
- ON with troublesome dyskinesia
- Total ON with dyskinesia
- OFF

8.2.2. UDysRS total objective score

The UDysRS total objective Score (III, IV) will be calculated by summing the Part III and Part IV scores. If either Part III or Part IV is missing, the UDysRS total objective score will also be missing.

8.2.3. MDS-UPDRS

The MDS-UPDRS consists of four components: Part I (non-motor experiences of daily living), Part II (motor experiences of daily living), Part III (motor examination), and Part IV (motor complications) (Goetz, Tilley, 2008).

Parts I and II each contain 13 questions measured on a 5-point scale (0–4). Part III contains objective rater assessments of the motor signs of PD measured on a 5-point scale (0–4). Part IV contains 6 questions. Generally for MDS-UPDRS scores and sub-scores, the lower the score, the better. Parts I, II, III and IV consist of the following assessments:

Part I. Non-Motor experiences of daily living

This component (Questions 1.1–1.13, excludes 1.A and 1.6a) includes cognitive impairment, hallucinations and psychosis, depressed mood, anxious mood, apathy, features of dopamine dysregulation syndrome, sleep problems, daytime sleepiness, pain and other sensations, urinary problems, constipation problems, lightheadedness on standing, and fatigue.

Part II. Motor experiences of daily living

This component (Questions 2.1 – 2.13) includes speech, saliva and drooling, swallowing, handwriting, cutting food, dressing, hygiene, turning in bed, falling, freezing, walking, tremor, and sensory complaints.

Part III. Motor examination

This component (Questions 3.1 – 3.18) includes speech, facial expression, rigidity, tremor at rest, finger taps, hand movements, rapid alternating movements, toe taps, leg agility, arising from chair, posture, gait, postural stability, global spontaneity of movement, postural tremor, kinetic tremor, and rest tremor. Responses to questions 3a, 3b, 3c, 3c1 and the Hoehn & Yahr stage are recorded but excluded from the calculation of the Part III score.

Part IV. Motor complications

This component (Questions 4.1 – 4.6) includes time spent with dyskinesia, functional impact of dyskinesia, time spent in OFF state, functional impact of fluctuations, complexity of motor fluctuations, painful OFF-state dystonia.

Imputation Rules

Imputation algorithms similar to those described in Section 8.1 will apply. The threshold of missing items for Part I, II, and III is 1, 1, and 3, respectively. If the number of missing items is within the threshold, the average of the non-missing items within the respective part will be used to impute missing items. If the number of missing items exceeds the threshold, the part total can not be validly calculated and will be missing.

For part IV, if any of the individual questions 4.1-4.6 are missing, then the total Part IV score will be missing.

MDS-UPDRS Combined Score (Parts I, II, and III)

Part I, II, and III scores will be calculated by summing the individual scores, after employing the imputation rules described earlier. The MDS-UPDRS combined score will be calculated by summing the scores for each of Parts I, II and III. Thus imputed data contributing to the score of an individual component will also contribute to the MDS-UPDRS combined score. If one or more components are missing, the MDS-UPDRS combined score will also be missing.

8.2.4. Clinician's Global Impression of Change scale (CGI-C)

The Clinician's Global Impression of Change in overall PD symptoms is determined by a question completed by the investigator and is a 7-point scale that requires the physician to assess how much the subject's illness has improved or worsened relative to the subject's baseline state and is rated as: -3 = Marked Worsening; -2 = Moderate worsening; -1 = Minimal worsening; 0 = no change; 1 = Minimal Improvement; 2 = Moderate Improvement; 3 = Marked Improvement.

8.3. Key Secondary Analyses

The following key secondary analyses will be conducted using a fixed sequence hierarchical procedure (Westfall and Krishen, 2001; Dmitrienko and D'Agostino, 2013) to control the overall level of significance, in the order shown below:

- 340 mg ADS-5102 vs. placebo for UDysRS at Week 24
- 340 mg ADS-5102 vs. placebo for ON Time without troublesome dyskinesia at Week 12
- 340 mg ADS-5102 vs. placebo for ON Time without troublesome dyskinesia at Week 24
- 340 mg ADS-5102 vs. placebo for OFF Time at Week 12
- 340 mg ADS-5102 vs. placebo for OFF Time at Week 24

The Week 12 secondary analyses in this list will be performed using linear MMRM methods, similar to that described in Section 8.1.1. All Week 24 analyses, though, will be performed using linear MMRMs with five levels of visit (Weeks 2, 8, 12, 18, and 24) with the other parameters of these models remaining unchanged.

The above hypotheses will be tested using two-sided tests at the 5% level of significance, but a specified comparison will be considered confirmatory only if the primary efficacy analysis and all previously conducted key secondary analyses are statistically significant ($p < 0.05$).

A line graph will display the UDysRS total score change from baseline by treatment (LS Means \pm SE), over time, based on the above modeling. In addition, the UDysRS total score change from baseline to Week 8, Week 12, and Week 24 (LS Means \pm SE) will also be displayed in bar graphs.

8.4. Other Secondary Analyses

As sensitivity analyses, the key secondary MMRMs stipulated in Section 8.3 will be repeated using the PP population. PD diary data which are not covered in Section 8.3 will also be repeated using the PP population.

The other secondary efficacy endpoints, except for the CGI-C, will be analyzed using two sets of MMRMs for the MITT population, similar to that described in Section 8.1.1 (see Table 3 below). Specifically, the Week 12 analyses of the PD diary data and UDysRS data will be performed using linear MMRM methods with 3 levels of visit (Week 2, 8, and 12). The Week 24 analyses of PD diary data, the Week 8 and Week 24 analyses of the UDysRS data, and the Week 12 and Week 24 analyses of the MDS-UPDRS data will utilize the MMRM methods with five levels of visit (Weeks 2, 8, 12, 18, and 24) with the other parameters of these models remaining unchanged.

At each post-baseline visit, the null hypothesis of no association between treatment and CGI-C will be tested using the Cochran–Mantel–Haenszel test, having applied the LOCF method, for the MITT population.

Table 3: Table of Other Secondary Analyses

Instrument	Endpoint	Imputation	Method
PD home diary	ON time with troublesome dyskinesia, based on a standardized PD home diary	No	MMRM
PD home diary	Total time with dyskinesia (non-troublesome and troublesome), based on a standardized PD home diary	No	MMRM
MDS-UPDRS	Part IV; Part IV, item 4.1 (time spent with dyskinesias); Part IV, item 4.2 (functional impact of dyskinesias)	No	MMRM
UDysRS	Total Objective Score (Parts III and IV)	No	MMRM
MDS-UPDRS	Individual and combined scores (Parts I, II, III)	No	MMRM
CGI-C	Clinician Global Impression of Change in overall PD symptoms	LOCF	Cochran-Mantel-Haenszel
UDysRS	Total Score change from baseline to Week 8	No	MMRM

All secondary analyses will be performed using two-sided tests at the 5% level of significance.

For each of Baseline and Weeks 12 and 24, a figure will be generated displaying the percentages of subjects ON without troublesome dyskinesia, ON with troublesome dyskinesia, OFF and ASLEEP, over the time course, based on the PD Diary data, using the PP population. The methods described below will be followed to generate such figures.

This analysis includes PP population subjects who have complete/evaluable diaries (see Section 8.2.1) for both 24 hour periods at Baseline, Week 12, and Week 24. The WAKE-UP time (t=0) will be identified for each subject as the start of the first of 4 consecutive intervals that do not contain “ASLEEP”, beginning at 3:00 AM (the 3:30 AM time interval) from the first 24 hour period. Last, once WAKE-UP time (t=0) is identified, the subject’s day is staggered and the next 17 hours following WAKE-UP time will be plotted by ½ hour intervals against predominant status subjects on across visits and treatment groups.

8.5. Subgroup Analysis

No subgroup analyses are planned.

9. Safety Analysis

Safety endpoints will be summarized by treatment group from the time of first dose and include all available safety data. No formal statistical testing will be done with one exception described under 9.1.7.

9.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence 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.

All AEs collected on the AE eCRF page will be considered treatment–emergent. Partial (Incomplete) AE onset and end dates will be listed as such. Dates of onset for AEs will be imputed as the earliest date compatible with known data. If day is missing, the date will be imputed as the later of (first day of the month given in the partial date, the latest visit in that month + 1 day). Imputed onset dates will be used to calculate the duration in the time to event analysis. Missing or partial AE end dates will not be imputed.

Adverse events will be presented according to the Medical Dictionary for Regulatory Activities (MedDRA[®] version 17.0 or higher), system organ class (SOC), and PT. Each summary will be ordered alphabetically by SOC and PT, and by decreasing frequency of preferred term in the total column (or active treatment arm when total is not present).

Most commonly reported (at least 5% of subjects in active treatment group) AEs will be presented by preferred term, and summarized by treatment group.

For each summary, at each of the SOC and PT levels, a subject will be counted once if s/he reported one or more AEs. Percentages will be calculated out of the number of subjects in the Safety population.

9.1.1. Incidence of Adverse Events

Adverse events will be summarized by treatment group, SOC and PT. In a separate table, same summarization will be presented by age group (<65, >=65).

9.1.2. Causality of Adverse Events due to Study Drug

The investigator will use clinical judgment to assess the causality of each AE/Serious Adverse Event (SAE) due to study drug based on pre-defined criteria. Adverse events will be summarized by this causality.

In the statistical analyses, if a subject experiences multiple occurrences of the same SOC or PT, only the related occurrence (if any exists) will be summarized. If the causality due to the study drug is missing, it will be considered “related”. The imputed values for causality due to study drug will be used for the incidence summary while actual values will be listed.

9.1.3. Intensity of Adverse Events

Adverse events will be summarized by treatment and intensity. In this summary, if a subject reported multiple occurrences of the same AE, only the most intense AE will be presented. AEs

with missing intensity will not be included in the summary table, but will be presented in the data listing with a missing intensity.

9.1.4. Serious Adverse Events

The seriousness of an AE should be assessed by the investigator independently from the intensity of the AE. A SAE is any AE occurring at any dose that:

- 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;
or
- 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.

A listing of SAEs will be presented.

9.1.5. Adverse Events Leading to Treatment Discontinuation

Any AEs collected with an investigational product action taken of “Study drug discontinued” will be summarized.

9.1.6. Adverse Events Leading to Death

Any AEs leading to death will be listed.

9.1.7. Adverse Events of Special Interest

Time to onset of first AE will be analyzed for two event categories: Hallucinations and Neuropsychiatric. The Hallucinations category combines all PTs that contain the term “Hallucination”. The Neuropsychiatric category combines the following SOC: Nervous system disorder and Psychiatric disorder.

The time to onset is defined as the number of days from the first dose of blinded study drug to the onset of the first AE in the category. Subjects will be censored at the latest date known not to have had such AE. The median time to event and the associated 95% confidence interval for each treatment arm will be estimated using the Kaplan-Meier method. Kaplan-Meier estimates of the survival function will be calculated and displayed graphically.

9.2. Clinical Laboratory Evaluations

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

Laboratory assessments for hematology and serum chemistry will be performed by a central laboratory. All summaries will be based on the SI units provided by the central lab, except that, for urobilinogen, mg/dL will be used instead.

Summary tables including actual values and changes from baseline will be presented for clinical laboratory tests with numeric values. If a lab value is reported using a non-numeric qualifier (eg, 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.” All clinical laboratory measures will be classified as Low, Normal, or High, or Normal/Abnormal according to the normal ranges. These categorical data will be summarized in shift tables comparing the results at each scheduled post-baseline visit, and the most abnormal results over the treatment period, with those at the baseline visit.

9.2.1. Hematology

The following hematology measures will be summarized: 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. A listing will present hematology values for Safety population.

9.2.2. Serum Chemistry

The following serum chemistry measures will be summarized: alkaline phosphatase, albumin, blood urea nitrogen, calcium, carbon dioxide, chloride, creatinine, estimated GFR, γ -glutamyltransferase, glucose, inorganic phosphorus, potassium, alanine aminotransferase, lactate dehydrogenase, aspartate aminotransferase, sodium, total bilirubin, and total protein. A listing will present chemistry values for Safety population.

A separate listing will include two estimates of subjects' renal function: 1) eGFR values calculated by the central lab using subject data and the MDRD-NKDEP equation, and 2) eCreatinine Clearance values calculated using subject data and the Cockcroft-Gault equation.

The equation to calculate eCreatinine Clearance values is described as following:

$$\text{eCreatinine Clearance (ml/min/1.73 m}^2\text{)} = \frac{[1.73 \times (140 - \text{age}) \times \text{weight (kg)} \times (0.85 \text{ if female})]}{[\text{Serum creatinine (mg/dL)} \times 72 \times \text{Body Surface Area}]}$$

$$\text{Body Surface Area} = [\text{weight (kg)} \times \text{height (cm)} / 3600]^{1/2}$$

Creatinine in mg/dL is rounded to 1 decimal place prior to applying the Cockcroft-Gault equation.

9.2.3. Urinalysis

The following quantitative urinalysis measures will be summarized: leukocytes, specific gravity and pH. Remaining qualitative category measures will be summarized by count and the percentage: protein, glucose, ketones, nitrite, blood, urobilinogen, and bilirubin. If nitrite, blood, or protein tests are positive, a microscopic examination will be performed, including WBC/high power field (HPF), RBC/HPF. A listing will present urinalysis values for Safety population.

9.2.4. Serum and Urine Pregnancy Tests

Serum and urine pregnancy tests will be performed for all female subjects of childbearing potential, at Screening, Baseline (Day 1), Week 4, Week 8, Week 12, Week 18, and the final safety follow up visit or early termination visit. The data will be listed.

9.3. Vital Sign Measurements

The following vital sign measures will be summarized: systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate. Weight will be summarized in the same table. Change from Baseline will be summarized at Week 12 and Week 24. All vital sign measurement data will be listed for Safety population.

9.4. Physical Examination

Complete physical examinations will be performed at Screening and Weeks 12 and 24 (or ET) while targeted physical examinations will be performed at Baseline (Day 1) and Weeks 4, 8, 18 and the Safety Follow-up Visit.

Clinically significant physical examination findings post-baseline not noted at baseline will be summarized by body system. All data will be listed for Safety population.

10. Changes in the Analyses Planned in the Protocol

This study is being stopped by sponsor decision due to an external competitive development program. When the study stops, all randomized subjects (n=126) will have had the opportunity to complete the Week 12 study visit and contribute Week 12 data to the primary efficacy analysis (change from baseline to Week 12 in the UDysRS total score). Thus, this change will not reduce the sample size for that analysis, or for the analyses of other Week 12 efficacy assessments, as described in the protocol. Furthermore, at least 70 subjects will have contributed data at Week 24 to the Week 24 secondary efficacy analyses, which should provide adequate power.

As a result of this change, two different linear MMRM models will be utilized for efficacy analyses. All Week 12 analyses of the UDysRS data and PD diary data, including the primary efficacy analysis, will now utilize models that include a categorical effect for time with three levels (Weeks 2, 8, and 12) rather than the planned five levels (Weeks 2, 8, 12, 18, and 24) described in the protocol. Other parameters of these models remain unchanged. The Week 24 analyses of the UDysRS, PD diary, and the Week 12 and Week 24 analyses of the MDS-UPDRS data will utilize the model with five time points as described in the protocol. This approach will support a comprehensive interpretation of the efficacy of ADS-5102 on the treatment of dyskinesia.

11. References

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

Colosimo C, Martinez-Martin P, Fabbrini G, Hauser R, Merello M, Miyasaki J, Poewe W, Sampaio C, Rascol O, Stebbins G, Schrag A, Goetz C. Task force report on scales to assess dyskinesia in Parkinson's disease: Critique and recommendations. *Movement Disorders*. 2010; 25(9): 1131-1142.

Dmitrienko A, D'Agostino R. Traditional multiplicity adjustment methods in clinical trials. *Statistics in Medicine*. 2013; 32(29):5172-218.

Encarnacion E, Hauser R. Levodopa-induced dyskinesias in Parkinson's disease: etiology, impact on quality of life, and treatments. *European Neurology*. 2008; 60(2): 57-66.

Goetz C, Nutt J, Stebbins G. The Unified Dyskinesia Rating Scale: Presentation and Clinimetric Profile. *Movement Disorders*. 2008; 23(16): 2398-2403.

Goetz, C. G., et al. (2013). "Which Dyskinesia Scale Best Detects Treatment Response?" *Movement Disorders* 28(3): 341-346.

Goetz, C. G., et al (2015). "Handling Missing Values in the MDS-UPDRS" *Movement Disorders*. 4 FEB 2015, DOI: 10.1002/mds.26153.

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

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

Luginger E, Wenning G, Bosch S, Poewe W. Beneficial effects of amantadine on L-dopainduced dyskinesias in Parkinson's disease. *Movement Disorders*. 2000; 15(5): 873-878.

Stokes, M. E., Davis, C. S., and Koch, G. G. (2000), *Categorical Data Using the SAS System*, Second Edition, Cary, NC: SAS Institute Inc.

Verhagen-Metman, Del Dotto P, Van Den Muckhof, Fang J, Mouradian M, Chase T. Amantadine as treatment for dyskinesias and motor fluctuations in Parkinson's disease. *Neurology*. 1998; 50(5): 1323-1326.

Westfall P, Krishen A. Optimally weighted, fixed sequence and gatekeeper multiple testing procedures. *J. Statistical Planning and Inference*. 2001; 99: 25-40.

12. Appendices

12.1. Schedule of Events

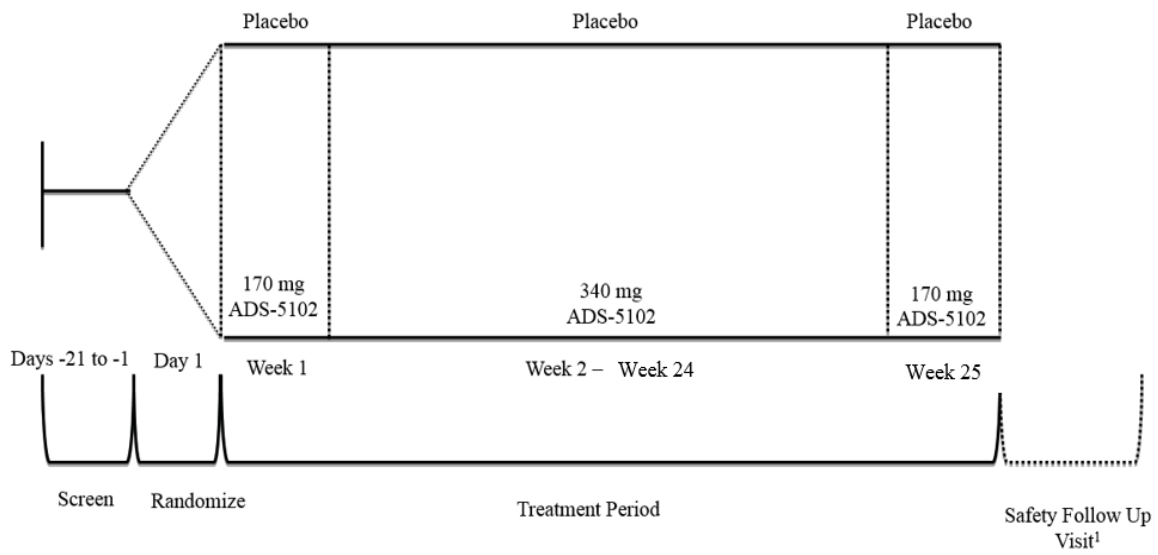
Visit	Screening	Treatment Period										Safety Follow Up	Early Termination Visit (b)
	1	2	3	4	5	6	7	8	9	10	11		
Week		0	1	2	4	8	12	18	24	25	26		
Informed consent	✓												
Eligibility Criteria	✓	✓											
Demographics	✓												
Medical History (j)	✓	✓											
Medication History	✓	✓											
Concomitant Medications		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Adverse Events (p)		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Complete Physical Exam (c)	✓						✓		✓			✓	
Targeted Physical Exam (d)		✓			✓	✓		✓			✓		
Height and Weight (e)	✓				✓		✓	✓	✓			✓	
Vital Signs (f)	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	
Hematology (g)	✓				✓		✓	✓	✓			✓	
Serum chemistry (h)	✓				✓		✓	✓	✓			✓	
Urinalysis (i)	✓				✓		✓	✓	✓			✓	
ECG (12-lead)	✓												
Serum Pregnancy Test (if applicable)	✓								✓ (r)		✓ (q)	✓ (q)	
Urine Pregnancy Test (if applicable)		✓											
MMSE	✓												
Randomization		✓											
PD Home Diary Concordance Testing	✓(k)												
Dispense PD Home Diaries (l)	✓		✓		✓	✓	✓	✓					
Review PD Home Diaries		✓(m)		✓		✓	✓	✓	✓			✓	
UDysRS		✓		✓		✓	✓	✓	✓			✓ (b)	
MDS-UPDRS (all 4 Parts, unless specified otherwise)	✓(n)	✓		✓		✓	✓	✓	✓			✓ (b)	
CGI-C		✓(o)		✓		✓	✓	✓	✓			✓ (b)	
Collect returned blister packs & assess compliance			✓	✓	✓	✓	✓	✓	✓	✓		✓	
Dispense Study Drug (blister pack)		✓	✓	✓	✓	✓	✓	✓	✓				
Study Drug dosing, once nightly at bedtime (Days 1 – 175)		✓	✓	✓	✓	✓	✓	✓	✓	✓			

Footnotes for Schedule of Events

- a. Safety follow up visit will be performed at Week 26, 1 week following dosing, only for subjects that complete the Week 25 visit and decline participation in the open-label extension study.
- b. Subjects that early discontinue after Week 24 visit do not need to have efficacy assessments performed at their early termination visit.
- c. Complete PE to include: skin, head-neck, eyes-ears-nose-throat, lungs-chest, heart, abdomen, extremities, neurological.
- d. Targeted PE to include: skin, lungs-chest, heart, abdomen, extremities.
- e. Height (in centimeters) will be measured at Screening only. Weight (in kilograms) will be measured at Screening and on Week 4, Week 12, Week 18, and Week 24. Subjects may be weighed in their undergarments, or in light clothing (no jackets or shoes). Measuring weight must be done consistently during the study, using the same set of weighing scales when possible.
- f. Vital signs obtained after the subject has been sitting for at least 5 minutes. Body temperature will be obtained at screening, Day 1, and at the final follow up visit. Blood pressure, respiratory rate and heart rate will be measured once each day assessed. During screening only, after the seated blood pressure has been obtained, the blood pressure 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 BP assessments (sitting/standing) should be obtained, and the results of the last attempt should be reported.
- g. Hematology consists of hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), red blood cell count (RBC), white blood cell (WBC) count, WBC differential (absolute), and numerical platelet count.
- h. Serum chemistry (fasting not required) consists of alkaline phosphatase, albumin, blood urea nitrogen, calcium, carbon dioxide, chloride, creatinine (MDRD formula for eGFR, to be done by the central laboratory), γ -glutamyltransferase, glucose, inorganic phosphorus, potassium, alanine aminotransferase, lactate dehydrogenase, aspartate aminotransferase, sodium, total bilirubin, and total protein.
- i. Urinalysis will be performed locally 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 at the central laboratory.
- j. A complete medical history (including PD history, mental health history, alcohol and drug use) will be obtained from the subject at the Screening Visit and recorded on the appropriate CRF. The medical history and other enrollment criteria will be reviewed and updated at the Baseline/Day 1 visit to determine continued eligibility for the study.
- k. During concordance testing, the subject and the approved Home Diary Reviewer will concurrently (and independently) evaluate the subject's motor states and rate every 30 minutes during concordance testing. The duration of concordance testing will be at least 2 hours (4 half-hour periods); However, the session may be extended to 3 or 4 hours or be repeated, if necessary, in a second 2, 3, or 4 hour session prior to the baseline visit. Successfully completed concordance testing worksheets must document at least one concordant half-hour period with dyskinesia and at least 75% concordance for ON and OFF states.
- l. During screening, potential subjects and caregivers or study partners, if appropriate, will be trained on the proper completion of 24-hour PD home diaries. Following completion of training, a set of two consecutive 24-hour diaries will be completed prior to Visit 2 (Baseline/Day 1/Week 0), serving as the baseline diary score and then prior to visits on Week 2, 8, 12, 18, 24 (or ET). The consecutive 24-hour diaries may be started 3 days before a visit, if the subject's schedule (e.g., travel requirements) makes it difficult to complete the diary the day before a visit. The schedule for diary completion should be determined in advance for each visit for each subject.
- m. If the subject has not satisfactorily completed the PD home diary, the subject and caregiver/study partner, if appropriate, should be re-trained on proper completion of the diary. The subject should be provided with an additional set of diaries and instructed to complete the diaries and return for an additional visit for review. The subject should proceed through the remainder of Day 1 assessments (including randomization) only after the subject satisfactorily completed the set of training diaries.
- n. MDS-UPDRS Part IV, item 4.2 only at screening. Note: In accordance with Inclusion Criterion #8, a score of at least 2 on part IV, item 4.2 (functional impact of dyskinesia) of the MDS-UPDRS is required at screening and at Day 1 (baseline).
- o. The CGI-C requires the investigator to rate how much the subject's Parkinson's disease has improved or worsened after treatment with study medication relative to the baseline state. In order to allow a future assessment of the CGI-C, the CGI-C rater should record notes about the subject's baseline clinical status related to overall PD, in their source documents.
- p. Adverse events will be recorded from the time of the first dose of study drug. Any subject with an ongoing AE will be followed until the AE is resolved, returns to baseline or deemed stable by the investigator.

- q. Post-study pregnancy testing in women of childbearing potential will occur at the final safety follow up visit or early termination visit.
- r. For individuals directly rolling into the long term extension study, there will be a serum pregnancy test at Week 24, as part of the Screening Visit for ADS-AMT-PD302 and serve as the final pregnancy test for ADS-AMT-PD301.

12.2. Study Design Schematic



¹ Applicable only for subjects who complete 25 weeks of treatment and decline participation in the open-label extension