ADS-AMT-PD302

OPEN-LABEL SAFETY STUDY OF ADS-5102 (AMANTADINE HCL) EXTENDED RELEASE CAPSULES FOR THE TREATMENT OF LEVODOPA INDUCED DYSKINESIA

US IND Number: 78,671

EudraCT Number: 2014-003739-20

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

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1. SYNOPSIS

<table>
<tr><td colspan="2">Name of Sponsor/Company: Adamas Pharmaceuticals, Inc.</td></tr>
<tr><td colspan="2">Name of Investigational Product: ADS-5102 (amantadine HCl) Extended Release Capsules</td></tr>
<tr><td colspan="2">Name of Active Ingredient: Amantadine hydrochloride</td></tr>
<tr><td colspan="2">Title of Study: Open-Label Safety Study of ADS-5102 (amantadine HCl) Extended Release Capsules for the Treatment of Levodopa Induced Dyskinesia</td></tr>
<tr><td colspan="2">Study center(s): Approximately 90 sites worldwide</td></tr>
<tr><td>Study Duration: Approximately 37 months (from enrollment of first subject to last subject completion [LSLV])</td><td>Phase of development: 3</td></tr>
<tr><td colspan="2">Objectives:
Primary:
• To evaluate the safety and tolerability of ADS-5102 oral capsules, an extended release formulation of amantadine, administered at a dose of 340 mg once nightly at bedtime for the treatment of levodopa induced dyskinesia (LID) in subjects with Parkinson’s disease (PD).
Secondary:
• To evaluate duration of ADS-5102 effect on dyskinesia as assessed by the Unified Parkinson’s Disease Rating Scale (MDS-UPDRS), Part IV.
• To evaluate clinical progression of Parkinson’s disease as assessed by MDS-UPDRS, Combined Score, Parts I, II, and III.
Study Design:
This study will be offered to subjects who are described by one of the following 3 groups:
• Group 1 (current Adamas LID study subjects): Subjects who are participating in Adamas efficacy studies evaluating ADS-5102 in LID and choose to immediately transition into ADS-AMT-PD302 without a time gap;
• Group 2 (previous Adamas LID study subjects): Subjects who have previously participated in Adamas efficacy studies evaluating ADS-5102 in LID and will enter ADS-AMT-PD302 after a time gap;
• Group 3 (non Adamas LID study subjects with prior DBS): Subjects who would have been deemed ineligible for participation in previous or current Adamas efficacy studies due to having undergone deep brain stimulation.</td></tr>
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Detailed inclusion/exclusion criteria and a schedule of events are described in this protocol Section 7 and Appendix A, respectively for each of these groups:

- Current Adamas LID study subjects (Group 1) should have their Screening Visit (Visit 1), including consent, for the ADS-AMT-PD302 study occur at the same visit as the final efficacy visit for the previous Adamas efficacy study, as outlined in the previous protocol. Subsequently, they should also have their Baseline Visit (Visit 2) for the ADS-AMT-PD302 study occur during the final study visit (not including any safety follow up visit) of the previous Adamas efficacy study visit, as outlined in the previous protocol.
- Previous Adamas LID study subjects (Group 2) and Non Adamas LID study subjects with prior DBS (Group 3) will not have overlapping visits with any previous protocol.

A study design schematic for study entry differences between these groups can be found in Appendix B.

Consented subjects who complete screening (Visit 1) and meet study eligibility criteria will have a baseline visit (Visit 2) and receive 1 week of 170 mg ADS-5102 (1 capsule) nightly at bedtime, followed by 340 mg ADS-5102 (2 capsules) nightly at bedtime for up to 99 additional weeks. The final week (Week 101) of dosing will be at the reduced dose of 170 mg ADS-5102 (1 capsule) nightly at bedtime.

Subjects will be enrolled into the study at Visit 2 (Week 0, Baseline) and return to the clinic after 4, 8, 16, 28, 40, 52, 64, 76, 88, and 100 weeks dosing. Subjects will receive a telephone reminder at the end of Week 1 to increase their dose to two capsules nightly at bedtime. At the Week 100 visit, subjects will be instructed to reduce their dose for 1 week, taking 1 capsule nightly at bedtime.

An efficacy assessment using the MDS-UPDRS will be completed at all study visits, beginning with the Screening Visit, with the exception of the Baseline/Week 0, Week 4, and Safety Follow Up visit. A safety follow-up visit will occur approximately 2 weeks following the completion of treatment. Women of childbearing potential will also have a pregnancy test performed at the early termination visit or 2 weeks following the completion of treatment at the final safety follow up visit.

Subjects who discontinue study drug before Week 101 will have an early termination visit that includes MDS-UPDRS assessments and safety follow-up.

Subjects who discontinue study drug after Week 4 should receive a reduced dose of 170 mg ADS-5102 for one additional week. The additional week of dosing at a reduced dose will not be needed for subjects who discontinue study drug before Week 4.

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

Methodology:
The safety analysis population will include all enrolled subjects who receive at least one dose of study drug. Safety data will be summarized 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 analysis group, as well as for all analysis groups combined. Quantitative safety variables (e.g., vital signs and clinical laboratory tests) will be summarized at each visit by analysis group, as well as for all analysis groups combined and changes from baseline will be summarized by analysis group at selected visits.

The efficacy analysis population will include all enrolled subjects who receive at least one dose of study drug and provide at least one post-enrollment MDS-UPDRS assessment.

MDS-UPDRS, Part IV and Combined Score, Parts I, II, and III data will be summarized across study visits and include all available data. The baseline MDS-UPDRS scores for a subject will be their MDS-UPDRS scores from the Screening Visit.

Sample Size Justification:

It is expected that a study size of up to 250 subjects and duration of treatment up to 101 weeks will support the goal of 100 subjects completing one year of treatment.

Number of subjects (planned): Up to 250

Diagnosis and eligibility criteria for inclusion:

Group 1: Current Adamas LID study subjects:

Below are the eligibility criteria for subjects who are continuing directly into ADS-AMT-PD302 without a time gap between their Adamas LID efficacy study and ADS-AMT-PD302:

INCLUSION CRITERIA:

1. Signed a current IRB/REB/IEC-approved informed consent form;
2. Completed study visits per protocol in a previous Adamas efficacy study;
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 assessments, as needed and allowed;
5. History of peak dose dyskinesia that might benefit from specific dyskinesia treatment in the judgment of the subject and clinical investigator;
6. On a stable regimen of antiparkinson's medications, including a levodopa preparation administered not less than three times daily.

EXCLUSION CRITERIA:

1. Discontinued study drug in previous Adamas studies due to intolerable or unacceptable AEs considered to be related to ADS-5102;
2. Hoehn and Yahr Stage 5;
3. 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;
4. Estimated GFR < 50 mL/min/1.73m^2 (calculated using Modification of Diet in Renal Disease (MDRD));
5. If female, is pregnant or lactating;
6. 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;
7. Anticipated need for treatment with restricted medication (reference Appendix E);
8. Planned participation in another interventional clinical trial.

Group 2: Previous Adamas LID study subjects

Below are the eligibility criteria for subjects who participated in a previous Adamas efficacy study evaluating ADS-5102 in LID and will enter ADS-AMT-PD302 with a time gap

INCLUSION CRITERIA:

1. Signed a current IRB/REB/IEC-approved informed consent form;
2. Completed study visits in as described per protocol in a previous Adamas efficacy study;
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. Peak dose dyskinesia during Screening that might benefit from specific dyskinesia treatment in the judgment of the subject and clinical investigator OR a history of peak dose dyskinesia that is currently being managed by amantadine treatment;
6. On a stable regimen of antiparkinson's medications at least 30 days prior to screening, including a levodopa preparation administered not less than three times daily;
7. Parkinson's disease, per UK Parkinson's Disease Society (UKPDS) Brain Bank Clinical Diagnostic Criteria (see Appendix C).

EXCLUSION CRITERIA:

1. Discontinued study drug in previous Adamas studies due to intolerable or unacceptable AEs considered to be related to ADS-5102;
2. History of neurosurgical intervention related to Parkinson's disease, with the exception of 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. Current 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;
5. History of alcohol or substance dependence or abuse since completion of participation in previous Adamas trial;
6. History of seizures since completion of participation in previous Adamas trial;
7. History of stroke or TIA since completion of participation in previous Adamas trial;
8. History of myocardial infarction, or NYHA Functional Classification of Heart Failure Class 3 or 4 since completion of participation in previous Adamas trial (see Appendix D);
9. Any clinically significant ECG abnormalities, including any findings of abnormal ventricular conduction or rhythm other than isolated PVCs or first degree AV block;
10. History of cancer since completion of participation in previous Adamas trial, with the following exceptions: adequately treated non-melanomatous skin cancers, localized bladder cancer, non-metastatic prostate cancer or *in situ* cervical cancer;
11. Presence of cognitive impairment, as evidenced by a Mini-Mental Status Examination (MMSE) score of less than 24 during screening;
12. Hoehn and Yahr Stage 5;
13. 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;
14. 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;
15. Any of the following laboratory test results at screening:
    - Hemoglobin < 10 g/dL

- WBC <3.0 x 10^9/L
- Neutrophils <1.5 x 10^9/L
- Lymphocytes < 0.5 x 10^9/L
- Platelets <100 x 10^9/L
- Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) > 2 times the upper limit of normal

16. Estimated GFR < 50 mL/min/1.73m^2 (calculated using Modification of Diet in Renal Disease (MDRD));
17. Inability to swallow oral capsules, or a history of gastrointestinal malabsorption that would preclude the use of oral medication;
18. If female, is pregnant or lactating;
19. 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;
20. Documented inability to tolerate amantadine or history of suicidal ideation or suicide attempt during prior amantadine use;
21. History of hypersensitivity or allergic reaction to amantadine, rimantidine, or memantine, or to any of the excipients used in the study medication capsules (see Section 8.7);
22. Received live attenuated influenza vaccine within 2 weeks prior to enrollment (amantadine may interfere with the efficacy of live attenuated vaccine);
23. Current treatment with carbonic anhydrase inhibitors, sodium bicarbonate, or urinary acidification agents, quinine, quinidine, triamterene, or trimethoprim (see Appendix E);
24. 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;
25. Treatment with an investigational drug (other than ADS-5102) or device within 30 days prior to screening;
26. Treatment with an investigational biologic within 6 months prior to screening;
27. Anticipated need for treatment with restricted medication (see Appendix E);
28. Current or planned participation in another interventional clinical trial.

Group 3: Non Adamas LID study subjects – with prior DBS

Below are the eligibility criteria for subjects who would have been deemed ineligible for participation in previous or current Adamas efficacy studies due to having undergone deep brain stimulation.

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. Subject has undergone a deep brain stimulation procedure prior to start of this study (14 July 2014);
4. Ambulatory or ambulatory-aided (e.g. walker or cane) ability while ON, such that the subject can complete study assessments;
5. 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;
6. Peak dose dyskinesia during Screening that might benefit from specific dyskinesia treatment in the judgment of the subject and clinical investigator OR a history of peak dose dyskinesia that is currently being managed by amantadine treatment;
7. On a stable regimen of antiparkinson's medications at least 30 days prior to screening, including a levodopa preparation administered not less than three times daily;
8. Parkinson's disease, per UK Parkinson's Disease Society (UKPDS) Brain Bank Clinical Diagnostic Criteria (see Appendix C).

EXCLUSION CRITERIA:

1. History of neurosurgical intervention related to Parkinson's disease, with the exception of deep brain stimulation;
2. 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;
3. Current 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;
4. History of alcohol or substance dependence or abuse within 2 years prior to screening;
5. History of seizures within 2 years prior to screening;
6. History of stroke or TIA within 2 years prior to screening;

7. History of myocardial infarction, or NYHA Functional Classification of Heart Failure Class 3 or 4 within 2 years prior to screening (see Appendix D);
8. Any clinically significant ECG abnormalities, including any findings of abnormal ventricular conduction or rhythm other than isolated PVCs or first degree AV block;
9. History of cancer within 5 years of screening, with the following exceptions: adequately treated non-melanomatous skin cancers, localized bladder cancer, non-metastatic prostate cancer or *in situ* cervical cancer;
10. Presence of cognitive impairment, as evidenced by a Mini-Mental Status Examination (MMSE) score of less than 24 during screening;
11. Hoehn and Yahr Stage 5;
12. 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;
13. 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;
14. Any of the following laboratory test results at screening:
    - Hemoglobin < 10 g/dL
    - WBC <3.0 x 10^9/L
    - Neutrophils <1.5 x 10^9/L
    - Lymphocytes < 0.5 x 10^9/L
    - Platelets <100 x 10^9/L
    - Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) > 2 times the upper limit of normal
15. Estimated GFR < 50 mL/min/1.73m^2 (calculated using Modification of Diet in Renal Disease (MDRD));
16. Inability to swallow oral capsules, or a history of gastrointestinal malabsorption that would preclude the use of oral medication;
17. If female, is pregnant or lactating;
18. 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;
19. Documented inability to tolerate amantadine or history of suicidal ideation or suicide attempt during prior amantadine use;

20. History of hypersensitivity or allergic reaction to amantadine, rimantidine, or memantine, or to any of the excipients used in the study medication capsules (see Section 8.7);
21. Received live attenuated influenza vaccine within 2 weeks prior to enrollment (amantadine may interfere with the efficacy of live attenuated vaccine);
22. Current treatment with carbonic anhydrase inhibitors, sodium bicarbonate, or urinary acidification agents, quinine, quinidine, triamterene, or trimethoprim (see Appendix E);
23. 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;
24. Treatment with an investigational drug (other than ADS-5102) or device within 30 days prior to screening;
25. Treatment with an investigational biologic within 6 months prior to screening;
26. Anticipated need for treatment with restricted medication (see Appendix E);
27. Current or planned participation in another interventional clinical trial.

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

Subjects will be allowed to change their PD medications as needed and record updates on the Concomitant Medications case report forms. Use of amantadine (other than provided study drug) is not allowed during study participation.

Treatment	Week 1	Weeks 2 – 100	Week 101
ADS-5102	170 mg ADS-5102 (1 x 170 mg capsule)	340 mg ADS-5102 (2 x 170 mg capsules)	170 mg ADS-5102 (1 x 170 mg capsule)

Capsules are to be swallowed intact, and can be taken with any nonalcoholic beverage, and with or without food. Dosing will continue through Week 101.

Subjects whose estimated GFR falls below 50 mL/min/1.73m^2 (but is ≥30 mL/min/1.73m^2), confirmed by repeat testing, should discontinue study drug after receiving a reduced dose of 170 mg ADS-5102 for one additional week. 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 30 mL/min/1.73m^2, confirmed by repeat testing, at any time during the study should discontinue study drug (without the additional week of dosing at a reduced dose).

Subjects who discontinue study drug will have an early termination visit that includes efficacy assessments and safety follow-up.

Duration of treatment: Duration of subject participation will be up to 105 weeks and will include a 2-week (maximum) screening period and up to 101 weeks of open-label treatment, followed by a safety follow-up visit 2 weeks after completion of treatment.

Criteria for evaluation:

Efficacy:

The following efficacy assessment will be performed during the study:

- Unified Parkinson's Disease Rating Scale (MDS-UPDRS)

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

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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
CHF	congestive heart failure
CNS	central nervous system
CRF	Case Report Form (paper and/or electronic)
DBS	Deep brain stimulation
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
ICH	International Conference on Harmonisation

Table 1: Abbreviations (Continued)

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
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.

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; Luginger 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., 1964; Jackson et al., 1967; Hayden et al., 1981).

4.1. Product Rationale

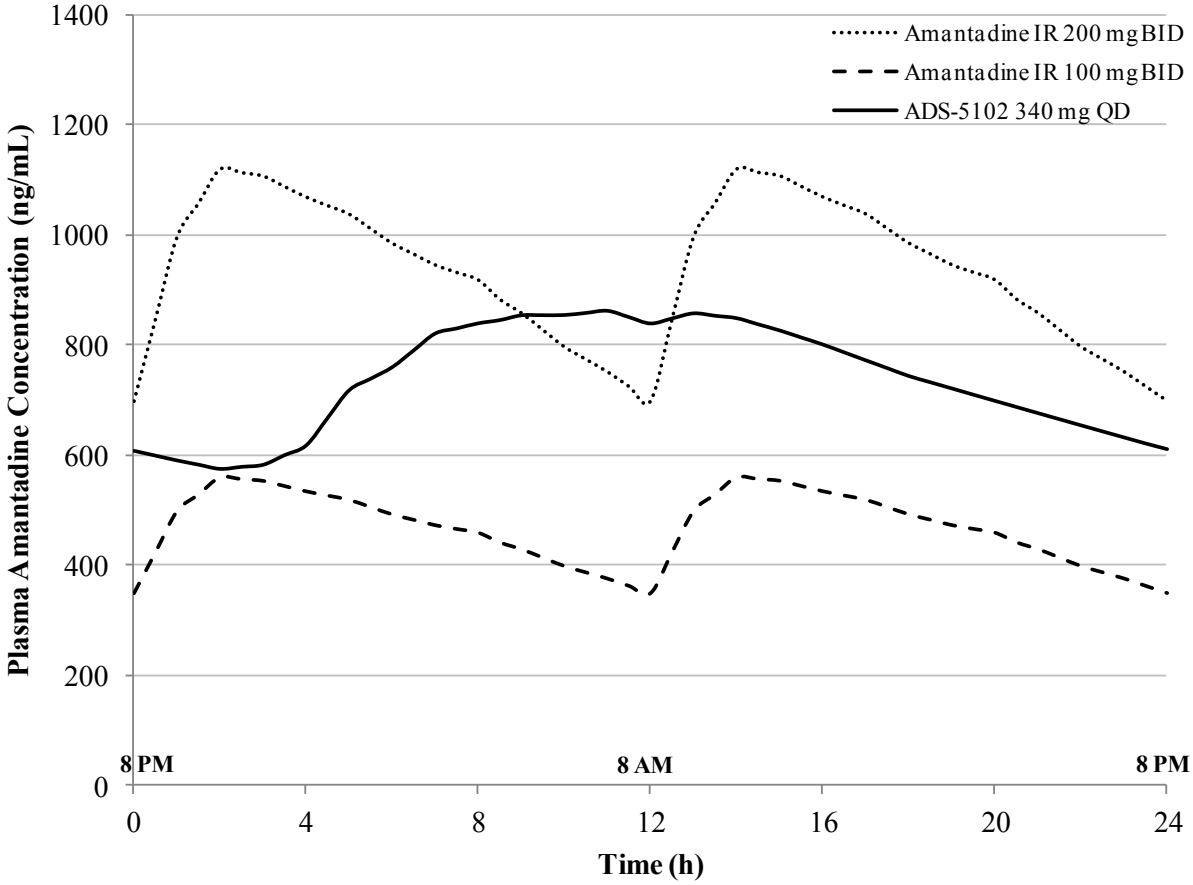
The pharmacologic rationale for a formulation that slows the release of amantadine is based upon the nature and timing of amantadine IR CNS side effects relative to dosing as well as observations with other CNS active drugs. Symmetrel (amantadine HCl IR tablet) has a short t_{max} of 2-4 hours (Aoki 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., 1964; 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 tmax compared to IR amantadine. Relative bioavailability (based on $AUC_{0\text{-}inf}$) 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-PD302 Study Design

This study is designed to further investigate the safety and tolerability profile of ADS-5102 oral capsules, an extended release formulation of amantadine, administered at a dose of 340 mg once nightly at bedtime for the treatment of levodopa induced dyskinesia (LID) in subjects with Parkinson's disease (PD). Additionally, this study will evaluate duration of ADS-5102 effect on dyskinesia as assessed by Unified Parkinson's Disease Rating Scale (MDS-UPDRS), Part IV, as well as evaluate clinical progression of Parkinson's disease as assessed by MDS-UPDRS, Combined Score, Parts I, II, and III.

4.6. Population to be Studied

This study will be offered to subjects who are described by one of the following 3 groups:

- Group 1 (current Adamas LID study subjects): Subjects who are participating in Adamas efficacy studies evaluating ADS-5102 in LID and choose to immediately transition into ADS-AMT-PD302 without a time gap;
- Group 2 (previous Adamas LID study subjects): Subjects who have participated in previous Adamas efficacy studies evaluating ADS-5102 in LID and will enter ADS-AMT-PD302 with a time gap;
- Group 3 (non Adamas LID study subjects with prior DBS): Subjects who would have been deemed ineligible for participation in previous Adamas efficacy studies due to having undergone deep brain stimulation.

5. TRIAL OBJECTIVES AND PURPOSE

5.1. Primary Objective

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

5.2. Secondary Objectives

To evaluate duration of ADS-5102 effect on dyskinesia as assessed by the Unified Parkinson's Disease Rating Scale (MDS-UPDRS), Part IV.

To evaluate clinical progression of Parkinson's disease as assessed by MDS-UPDRS, Combined Score, Parts I, II, and III.

5.3. Safety Outcome Assessments

The following safety assessments will be performed during the study:

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

5.4. Efficacy Outcome Assessments

The following efficacy assessment will be performed during the study:

- Unified Parkinson's Disease Rating Scale (MDS-UPDRS)

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

This study will be offered to subjects who are described by one of the following 3 groups:

- Group 1 (current Adamas LID study subjects): Subjects who are participating in Adamas efficacy studies evaluating ADS-5102 in LID and choose to immediately transition into ADS-AMT-PD302 without a time gap;
- Group 2 (previous Adamas LID study subjects): Subjects who have participated in previous Adamas efficacy studies evaluating ADS-5102 in LID and will enter ADS-AMT-PD302 with a time gap;
- Group 3 (non Adamas LID study subjects with prior DBS): Subjects who would have been deemed ineligible for participation in previous Adamas efficacy studies due to having undergone deep brain stimulation.

Detailed inclusion/exclusion criteria and a schedule of events are described in this protocol Section 7 and Appendix A, respectively, for each of these groups.

- Current Adamas LID study subjects (Group 1) should have their Screening Visit (Visit 1), including consent, for the ADS-AMT-PD302 study occur at the same visit as the final efficacy visit for the previous Adamas efficacy study, as outlined in the previous protocol. Subsequently, they should also have their Baseline Visit (Visit 2) for the ADS-AMT-PD302 study occurs during the final study visit (not including any safety follow up visit) of the previous Adamas efficacy study visit, as outlined in the previous protocol.
- Previous Adamas LID study subjects (Group 2) and Non Adamas LID study subjects with prior DBS (Group 3) will not have overlapping visits with any previous protocol.

A study design schematic for study entry differences between these groups can be found in Appendix B.

Consented subjects who complete screening (Visit 1) and meet study eligibility criteria will have a baseline visit and receive 1 week of 170 mg ADS-5102 (1 capsule) nightly at bedtime, followed by 340 mg ADS-5102 (2 capsules) nightly at bedtime for up to 99 additional weeks. The final week (Week 101) of dosing will be at the reduced dose of 170 mg ADS-5102(1 capsule) nightly at bedtime.

Subjects will be enrolled into the study at Visit 2 (Week 0, Baseline) and return to the clinic after 4, 8, 16, 28, 40, 52, 64, 76, 88 and 100weeks dosing. Subjects will receive a telephone reminder at the end of Week 1 to increase their dose during Week 2. At the Week 100 visit, subjects will be instructed to reduce their dose for 1 week, taking 1 capsule nightly at bedtime. The amount of available unused drug will be assessed during the Week 100 visit, and if a subject needs an additional bottle dispensed to cover 1 week of a reduced dose, they should be provided with a new bottle.

An efficacy assessment using the MDS-UPDRS will be completed at all study visits, beginning with the Screening Visit, with the exception of the Baseline/Week 0 visit & Week 4 visit. A safety follow-up visit will occur approximately 2 weeks following the completion of treatment. Women of childbearing potential will also have a pregnancy test performed at the early termination visit or 2 weeks following the completion of treatment at the safety follow up visit.

Subjects who discontinue study drug before Week 101 will have an early termination visit that includes MDS-UPDRS assessments and safety follow-up.

Subjects who discontinue study drug after Week 4 should receive a reduced dose of 170 mg ADS-5102 for one additional week. The additional week of dosing at a reduced dose will not be needed for subjects who discontinue study drug before Week 4.

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

6.2. Number of Subjects

Up to 250 (all active) will be enrolled at approximately 90 sites worldwide.

6.3. Treatment Assignment

All enrolled subjects will receive active treatment (ADS-5102).

6.4. Dose Adjustment Criteria

Subjects who discontinue study drug after Week 4 should receive a reduced dose for one additional week 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/1.73m^2, confirmed by repeat testing,(but is ≥ 30 mL/min/1.73m^2) should discontinue study drug after receiving a reduced dose of 170 mg ADS-5102 for one additional week. 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 30 mL/min/1.73m^2, confirmed by repeat testing, at any time during the 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

Duration of subject participation will be up to 105 weeks and will include a 2-week (maximum) screening period and up to 101 weeks of open-label treatment, followed by a final safety follow-up visit 2 weeks after completion of treatment.

6.7. Estimated Study Duration

Approximately 37 months (from enrollment of first subject to last subject completion of last visit [LSLV]).

7. SELECTION AND WITHDRAWAL OF SUBJECTS

7.1. Subject Inclusion Criteria

7.1.1. Group 1: Current Adamas LID study subjects

Below are the inclusion criteria subjects who are continuing directly into ADS-AMT-PD302 without a time gap between their Adamas LID efficacy study and ADS-AMT-PD302:

1. Signed a current IRB/REB/IEC-approved informed consent form;
2. Completed study visits per protocol in a previous Adamas efficacy study;
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 assessments, as needed and allowed;
5. History of peak dose dyskinesia that might benefit from specific dyskinesia treatment in the judgment of the subject and clinical investigator;
6. On a stable regimen of antiparkinson's medications, including a levodopa preparation administered not less than three times daily.

7.1.2. Group 2: Previous Adamas LID study subjects

Below are the inclusion criteria for subjects who participated in a previous Adamas efficacy study evaluating ADS-5102 in LID and will enter ADS-AMT-PD302 with a time gap:

1. Signed a current IRB/REB/IEC-approved informed consent form;
2. Completed study visits per protocol in a previous Adamas efficacy study;
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. Peak dose dyskinesia during Screening that might benefit from specific dyskinesia treatment in the judgment of the subject and clinical investigator OR a history of peak dose dyskinesia that is currently being managed by amantadine treatment;
6. On a stable regimen of antiparkinson's medications at least 30 days prior to screening, including a levodopa preparation administered not less than three times daily;
7. Parkinson's disease, per UK Parkinson's Disease Society (UKPDS) Brain Bank Clinical Diagnostic Criteria (see Appendix C).

7.1.3. Group 3: Non Adamas LID study subjects – with prior DBS

Below are the inclusion criteria for subjects who would have been deemed ineligible for participation in previous or current Adamas efficacy studies due to having undergone deep brain stimulation:

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. Subject has undergone deep brain stimulation procedure prior to start of this study (14 July 2014);
4. Ambulatory or ambulatory-aided (e.g. walker or cane) ability while ON, such that the subject can complete study assessments;
5. 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;
6. Peak dose dyskinesia during Screening that might benefit from specific dyskinesia treatment in the judgment of the subject and clinical investigator OR a history of peak dose dyskinesia that is currently being managed by amantadine treatment;
7. On a stable regimen of antiparkinson's medications at least 30 days prior to screening, including a levodopa preparation administered not less than three times daily;
8. Parkinson's disease, per UK Parkinson's Disease Society (UKPDS) Brain Bank Clinical Diagnostic Criteria (see Appendix C).

7.2. Subject Exclusion Criteria

7.2.1. Group 1: Current Adamas LID study subjects

Below are the exclusion criteria subjects who are continuing directly into ADS-AMT-PD302 without a time gap between their Adamas LID efficacy study and ADS-AMT-PD302:

1. Discontinued study drug in previous Adamas studies due to intolerable or unacceptable AEs considered to be related to ADS-5102;
2. Hoehn and Yahr Stage 5;
3. 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;
4. Estimated GFR < 50 mL/min/1.73m^2 (calculated using Modification of Diet in Renal Disease (MDRD));
5. If female, is pregnant or lactating;
6. 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;

7. Anticipated need for treatment with restricted medication (reference Appendix E);
8. Planned participation in another interventional clinical trial.

7.2.2. Group 2: Previous Adamas LID study subjects

Below are the exclusion criteria for subjects who participated in a previous Adamas efficacy study evaluating ADS-5102 in LID and will enter ADS-AMT-PD302 with a time gap:

1. Discontinued study drug in previous Adamas studies due to intolerable or unacceptable AEs considered to be related to ADS-5102;
2. History of neurosurgical intervention related to Parkinson's disease, with the exception of 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. Current 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;
5. History of alcohol or substance dependence or abuse since completion of participation in previous Adamas trial;
6. History of seizures since completion of participation in previous Adamas trial;
7. History of stroke or TIA since completion of participation in previous Adamas trial;
8. History of myocardial infarction, or NYHA Functional Classification of Heart Failure Class 3 or 4 since completion of participation in previous Adamas trial (see Appendix D);
9. Any clinically significant ECG abnormalities, including any findings of abnormal ventricular conduction or rhythm other than isolated PVCs or first degree AV block;
10. History of cancer since completion of participation in previous Adamas trial, with the following exceptions: adequately treated non-melanomatous skin cancers, localized bladder cancer, non-metastatic prostate cancer or in situ cervical cancer;
11. Presence of cognitive impairment, as evidenced by a Mini-Mental Status Examination (MMSE) score of less than 24 during screening;
12. Hoehn and Yahr Stage 5;
13. 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;
14. 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;

15. Any of the following laboratory test results at screening:
    - Hemoglobin < 10 g/dL
    - WBC <3.0 x 10^9/L
    - Neutrophils <1.5 x 10^9/L
    - Lymphocytes < 0.5 x 10^9/L
    - Platelets <100 x 10^9/L
    - Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) > 2 times the upper limit of normal;
16. Estimated GFR < 50 mL/min/1.73m^2 (calculated using Modification of Diet in Renal Disease (MDRD));
17. Inability to swallow oral capsules, or a history of gastrointestinal malabsorption that would preclude the use of oral medication;
18. If female, is pregnant or lactating;
19. 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;
20. Documented inability to tolerate amantadine, or history of suicidal ideation or suicide attempt during prior amantadine use;
21. History of hypersensitivity or allergic reaction to amantadine, rimantidine, or memantine, or to any of the excipients used in the study medication capsules (see Section 8.7);
22. Received live attenuated influenza vaccine within 2 weeks prior to enrollment (amantadine may interfere with the efficacy of live attenuated vaccine);
23. Current treatment with carbonic anhydrase inhibitors, sodium bicarbonate, or urinary acidification agents, quinine, quinidine, triamterene, or trimethoprim (see Appendix E);
24. 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;
25. Treatment with an investigational drug (other than ADS-5102) or device within 30 days prior to screening;
26. Treatment with an investigational biologic within 6 months prior to screening;
27. Anticipated need for treatment with restricted medication (see Appendix E);
28. Current or planned participation in another interventional clinical trial.

7.2.3. Group 3: Non Adamas LID Study Subjects – with prior DBS

Below are the exclusion criteria for subjects who would have been deemed ineligible for participation in previous or current Adamas efficacy studies due to having undergone deep brain stimulation:

1. History of neurosurgical intervention related to Parkinson's disease, with the exception of deep brain stimulation;
2. 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;
3. Current 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;
4. History of alcohol or substance dependence or abuse within 2 years prior to screening;
5. History of seizures within 2 years prior to screening;
6. History of stroke or TIA within 2 years prior to screening
7. History of myocardial infarction, or NYHA Functional Classification of Heart Failure Class 3 or 4 within 2 years prior to screening (see Appendix D);
8. Any clinically significant ECG abnormalities, including any findings of abnormal ventricular conduction or rhythm other than isolated PVCs or first degree AV block;
9. History of cancer within 5 years of screening, with the following exceptions: adequately treated non-melanomatous skin cancers, localized bladder cancer, non-metastatic prostate cancer or in situ cervical cancer;
10. Presence of cognitive impairment, as evidenced by a Mini-Mental Status Examination (MMSE) score of less than 24 during screening;
11. Hoehn and Yahr Stage 5;
12. 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;
13. 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;
14. Any of the following laboratory test results at screening:
    - Hemoglobin < 10 g/dL
    - WBC $<3.0 \times 10^9$/L
    - Neutrophils $<1.5 \times 10^9$/L

- Lymphocytes < 0.5 x 10^9/L
- Platelets <100 x 10^9/L
- Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) > 2 times the upper limit of normal;

15. Estimated GFR < 50 mL/min/1.73m^2 (calculated using Modification of Diet in Renal Disease (MDRD));
16. Inability to swallow oral capsules, or a history of gastrointestinal malabsorption that would preclude the use of oral medication;
17. If female, is pregnant or lactating;
18. 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;
19. Documented inability to tolerate amantadine, or history of suicidal ideation or suicide attempt during prior amantadine use;
20. History of hypersensitivity or allergic reaction to amantadine, rimantidine, or memantine, or to any of the excipients used in the study medication capsules (see Section 8.7);
21. Received live attenuated influenza vaccine within 2 weeks prior to enrollment (amantadine may interfere with the efficacy of live attenuated vaccine);
22. Current treatment with carbonic anhydrase inhibitors, sodium bicarbonate, or urinary acidification agents, quinine, quinidine, triamterene, or trimethoprim (See Appendix E);
23. 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;
24. Treatment with an investigational drug (other than ADS-5102) or device within 30 days prior to screening;
25. Treatment with an investigational biologic within 6 months prior to screening;
26. Anticipated need for treatment with restricted medication (see Appendix E);
27. Current or planned participation in another interventional clinical trial.

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);
- 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 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 are enrolled at Visit 2 (Week 0, Baseline).

7.5. Discontinuation of Study Medication

Subjects who discontinue study drug after Week 4 should receive a reduced dose for one additional week of ADS-5102 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/1.73m^2, confirmed by repeat testing. (see Section 6.4)

  NOTE:

  – Subjects whose eGFR falls below 30 mL/min/1.73m^2 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

If the subject decides to discontinue study drug, 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.

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

The clinical formulation is shown in Table 2.

Table 2: Clinical Formulation for Study ADS-AMT-PD302

	ADS-5102 **170 mg**
Formulation	Extended release coated pellets of amantadine HCl in an oral capsule
Dose Strength	170 mg amantadine HCl per capsule
Description	White to off-white pellets filled in blue/blue colored hard gelatin capsule, size 0.
Excipients	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

Bottles containing 60 capsules (30 day supply of study drug) of 170 mg ADS-5102 will be provided at each study visit once enrolled. The number of bottles provided will depend on the visit. One bottle will be dispensed on Day 1 and Week 4. Two bottles will be dispensed on Week 8, and three bottles will be dispensed at Week 16, Week 28, Week 40, Week 52, Week 64, Week 76, and Week 88.

The amount of available unused drug will be assessed during the Week 100 visit, and if a subject needs an additional bottle dispensed to cover 1 week of a reduced dose, they should be provided with a new bottle.

All bottles will be labeled with, at a minimum, the protocol number, route of administration, number of capsules to be administered, lot number, storage conditions, Sponsor's name and address, and the applicable investigational drug caution statements and will be compliant with the "EU Guidelines for Good Manufacturing Practice Medicinal Products for Human and Veterinary Use Annex 13. Investigational Medicinal Products".

8.3. Study Drug Storage

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

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

8.4. Administration

Table 3: Treatment Schedule for Study ADS-AMT-PD302

Treatment	Week 1	Week 2 – Week 100	Week 101
ADS-5102	170 mg ADS-5102 (1 x 170 mg capsule)	340 mg ADS-5102 (2 x 170 mg capsules)	170 mg ADS-5102 (1 x 170 mg capsule)

Each dose will be administered as 1 or 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 101.

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
- Any product accidentally or deliberately destroyed
- Current quantity of total study drug supply

Subjects will be instructed to return all used and unused bottles (with unused capsules) of study drug for drug accountability purposes. All used and unused bottles (with unused capsules) 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, as well as during study participation, 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

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.

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. (This criterion does not apply to medications that are taken on an as-needed basis only).

8.9. Treatment Compliance

One bottle containing a 30 day supply of study drug will be dispensed on Day 1 and Week 4. Two bottles will be dispensed on Week 8, and three bottles will be dispensed at Week 16, Week 28, Week 40, Week 52, Week 64, Week 76, and Week 88.

The amount of available unused drug will be assessed during the Week 100 visit, and if a subject needs an additional bottle dispensed to cover 1 week of a reduced dose, they should be provided with a new bottle.

Subjects will be instructed to return all used/unused bottles at the next study visit (i.e. Weeks 4, 8, etc or ET), when the designated study site staff will review the number of returned capsules to assess subject compliance.

8.10. Randomization and Blinding

This is an open label study in which all subjects receive active treatment (340 mg ADS-5102), therefore randomization is not necessary.

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
MDS-UPDRS	Screening Week 8 Week 16 Week 28 Week 40 Week 52 Week 64 Week 76 Week 88 Week 100 (or ET)	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)

10. ASSESSMENT OF SAFETY

10.1. Physical Assessments Relating to Safety

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

Table 5: Physical Assessments Relating to Safety

Assessment	Study Visit	Description
Complete Physical Examination	Screening Week 16 Week 52 Week 100 (or ET)	Physical examination including: skin, head-neck, eyes-ears-nose-throat, lungs-chest, heart, abdomen, extremities, neurological.
Targeted Physical Examination	Baseline/Day 1 (Week 0) Week 4 Week 8 Week 28 Week 40 Week 64 Week 76 Week 88 Safety Follow Up Visit	Physical examination including: skin, lungs-chest, heart, abdomen, extremities.
Weight and height	Screening Week 4 Week 8 Week 16 Week 28 Week 40 Week 52 Week 64 Week 76 Week 88 Weel 100 (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.

Table 5: Physical Assessments Relating to Safety (Continued)

Assessment	Study Visit	Description
Vital Signs	Screening Baseline/Day 1 (Week 0) Week 4 Week 8 Week 16 Week 28 Week 40 Week 52 Week 64 Week 76 Week 88 Week 100 (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. 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.
ECG (12-lead)	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. ECGs are only necessary for Group 2 and Group 3 study subjects at the Screening Visit.

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 8 Week 16 Week 28 Week 40 Week 52 Week 64 Week 76 Week 88 Week 100 (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.

Table 6: Clinical Laboratory and Other Assessments (Continued)

Assessment	Study Visit	Description
Serum Chemistry	Screening Week 4 Week 8 Week 16 Week 28 Week 40 Week 52 Week 64 Week 76 Week 88 Week 100 (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 8 Week 16 Week 28 Week 40 Week 52 Week 64 Week 76 Week 88 Week 100 (or ET)	UA will be performed locally using sponsor-supplied dipsticks, including specific gravity, pH, protein, ketones, glucose, nitrite, leukocytes, blood, urobilinogen, and bilirubin. If nitrite, blood, or protein tests are positive, a microscopic examination will be performed at the central laboratory.
Serum pregnancy test (if applicable)	Screening Safety Follow Up Visit (or ET)	Serum pregnancy test will be performed for all female subjects of childbearing potential.
Urine pregnancy test (if applicable)	Baseline/Day1/Week 0 Week 4 Week 8 Week 16 Week 28 Week 40 Week 52 Week 64 Week 76 Week 88 Week 100	Urine pregnancy test will be performed for all female subjects of childbearing potential.

[a] Estimated 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 165 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 -14 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 14 days prior to Day 1.

NOTE: If a subject from a previous Adamas LID study wishes to enroll directly in ADS-AMT-PD302 without a time gap, they should have their Screening Visit (Visit 1), including consent, for the ADS-AMT-PD302 study occur during the final efficacy study visit for the previous Adamas efficacy study, as outlined in the previous protocol.

Per the Schedule of Events in Appendix A, if a subject is directly rolling over to the open label extension, a number of common assessments between the Adamas efficacy study visit and the Screening Visit (ADS-AMT-PD302) only need to be performed once.

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;

- Vital signs (standing blood pressure), assessment of orthostatic hypotension should occur at screening visit and apply only to ADS-AMT-PD302;
- 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), 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;
- ECG (12-lead); NOTE: Only for Group 2 or Group 3 subjects;
- Mini-Mental Status Examination (MMSE).

Assessments that could be shared between the previous Adamas LID efficacy study & Screening (ADS-AMT-PD302):

- MDS-UPDRS;
- Complete physical examination;
- Obtain subject weight in kilograms and height in centimeters;
- Vital signs (sitting blood pressure, respiratory rate, heart rate, temperature);
- Blood sample for central laboratory analysis including hematology, serum chemistry and eGFR;
- Urinalysis;
- Blood sample for serum pregnancy test in female subjects of childbearing potential.

11.2. Treatment Period

The treatment period will be a maximum of 101 weeks.

11.3. Baseline/Day 1/Week 0

NOTE: If a subject from a previous Adamas LID efficacy study wishes to enroll directly in ADS-AMT-PD302 without a time gap, they should have their Baseline Visit (Visit 2) for the ADS-AMT-PD302 study occur on the same day as the final study visit (not including any safety follow up visit) of the previous Adamas efficacy study visit, as outlined in the previous protocol.

The following procedures will be performed:

- 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; other neurological diseases, psychiatric disorders including Major Depressive Disorder or symptom (e.g., hallucinations, agitation, paranoia), 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;
- Urine pregnancy test will be performed for all female subjects of childbearing potential;
- Dispense study medication (4-week supply, 1 bottle of 60 capsules);
- Targeted physical examination;
- Vital signs (blood pressure, respiratory rate, heart rate and temperature).

11.4. 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 Exam;
- Obtain subject weight in kilogram;
- Vital signs (blood pressure, respiratory rate, heart rate);
- Blood sample for central laboratory analysis including hematology, serum chemistry and eGFR;
- Urinalysis;
- Urine pregnancy test will be performed for all female subjects of childbearing potential;
- Collect unused study drug and bottles and evaluate compliance;
- Dispense study medication (4-week supply, 1 bottle of 60 capsules).

11.5. 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 Exam;
- Obtain subject weight in kilogram;
- Vital signs (blood pressure, respiratory rate, heart rate);
- Blood sample for central laboratory analysis including hematology, serum chemistry and eGFR;
- Urinalysis;

- Urine pregnancy test will be performed for all female subjects of childbearing potential;
- MDS-UPDRS;
- Collect unused study drug and bottles and evaluate compliance;
- Dispense study medication (8-week supply, 2 bottles of 60 capsules).

11.6. Week 16 +/- 3 days (End of Week 16)

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 pregnancy test will be performed for all female subjects of childbearing potential;
- MDS-UPDRS;
- Collect unused study drug and bottles and evaluate compliance;
- Dispense study medication (12-week supply, 3 bottles of 60 capsules).

11.7. Week 28 +/- 3 days (End of Week 28)

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 pregnancy test will be performed for all female subjects of childbearing potential;

- MDS-UPDRS;
- Collect unused study drug and bottles and evaluate compliance;
- Dispense study medication (12-week supply, 3 bottles of 60 capsules).

11.8. Week 40 +/- 3 days (End of Week 40)

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 pregnancy test will be performed for all female subjects of childbearing potential;
- MDS-UPDRS;
- Collect unused study drug and bottles and evaluate compliance;
- Dispense study medication (12-week supply, 3 bottles of 60 capsules).

11.9. Week 52 +/- 3 Days (End of Week 52)

The following procedures will be performed:

- Assess and record concomitant medications;
- Assess and record Adverse Events;
- Complete physical examination including body weight (recorded in kilograms);
- Vital signs (blood pressure, respiratory rate, heart rate);
- Blood sample for central laboratory analysis including hematology, serum chemistry and eGFR;
- Urinalysis;
- Urine pregnancy test will be performed for all female subjects of childbearing potential;
- MDS-UPDRS;
- Collect unused study drug and bottles and evaluate compliance;
- Dispense study medication (12-week supply, 3 bottles of 60 capsules).

11.10. Week 64 +/- 3 Days (End of Week 64)

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 pregnancy test will be performed for all female subjects of childbearing potential;
- MDS-UPDRS;
- Collect unused study drug and bottles and evaluate compliance;
- Dispense study medication (12-week supply, 3 bottles of 60 capsules).

11.11. Week 76 +/- 3 Days (End of Week 76)

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 pregnancy test will be performed for all female subjects of childbearing potential;
- MDS-UPDRS;
- Collect unused study drug and bottles and evaluate compliance;
- Dispense study medication (12-week supply, 3 bottles of 60 capsules).

11.12. Week 88 +/- 3 Days (End of Week 88)

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 pregnancy test will be performed for all female subjects of childbearing potential;
- MDS-UPDRS;
- Collect unused study drug and bottles and evaluate compliance;
- Dispense study medication (12-week supply, 3 bottles of 60 capsules).

11.13. Week 100 +/- 3 Days (End of Week 100)

The following procedures will be performed:

- Assess and record concomitant medications;
- Assess and record Adverse Events;
- Complete physical examination including body weight (recorded in kilograms);
- 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 pregnancy test will be performed for all female subjects of childbearing potential;
- MDS-UPDRS;
- Collect unused study drug and bottles and evaluate compliance;
- Dispense study medication, if necessary.

11.14. Early Termination Visit

The following procedures will be performed:

- Assess and record concomitant medications;
- Assess and record Adverse Events;
- Complete physical examination including body weight (recorded in kilograms);
- Vital signs (blood pressure, respiratory rate, heart rate);
- Blood sample for central laboratory analysis including hematology, serum chemistry and eGFR;
- Urinalysis;
- MDS-UPDRS;
- Blood sample for serum pregnancy test in female subjects of childbearing potential;
- Collect unused study drug and bottles and evaluate compliance.

11.15. Safety Follow Up Visit

The following procedures will be performed:

- Assess and record concomitant medications;
- Assess and record Adverse Events;
- Targeted Physical Exam;
- Vital signs (temperature, blood pressure, respiratory rate, heart rate);
- Blood sample for serum pregnancy test in female subjects of childbearing 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. (Dosing details will be recorded on the appropriate eCRF(s)).

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.

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is any serious adverse event that is considered related to the investigational product, and that is also unexpected. SUSARs qualify for expedited reporting to applicable Health Authorities, Eudravigilance, and IRB/REB/IECs.

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.

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

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, other regulatory agencies, and Eudravigilance 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, 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

It is expected that a study size of up to 250 subjects and duration of treatment up to 101 weeks will support the goal of 100 subjects completing one year of treatment.

13.1.2. Analysis Populations

13.1.2.1. Efficacy Populations

The efficacy analysis population will include all enrolled subjects who receive at least one dose of study drug and provide at least one post-enrollment MDS-UPDRS assessment.

MDS-UPDRS data will be summarized across study visits and include all available data. The baseline MDS-UPDRS scores will be from each subject's Screening Visit.

13.1.3. Handling of Missing Data

Observed data will be summarized. There will be no imputation of missing data.

13.1.4. Safety and Tolerability

The safety analysis population will include all enrolled subjects who receive at least one dose of study drug. Safety data will be summarized 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 analysis group, as well as for all analysis groups combined. Quantitative safety variables (e.g., vital signs and clinical laboratory tests) will be summarized at each visit by analysis group, as well as for all analysis groups combined.

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 analysis group, as well as for all analysis groups combined. Demographic data and key baseline characteristics will be summarized for the Efficacy 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 analysis group, as well as for all analysis groups combined.

13.1.7. Completion of the Study and Withdrawals

Withdrawals and the reason for withdrawal will be tabulated.

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. Subjects will be identified by a unique Subject Identification Number. Study related documents should be kept in strict confidence by the Investigator in compliance with applicable regulations and ICH GCP Guidelines. The Investigator and Institution must permit authorized representatives of regulatory agencies, and the IRB/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 ICH guidelines (Topic E6: Guideline for Good Clinical Practice), the US Code of Federal Regulations (21 CFR), and local ethical and legal requirements that are consistent with the most current version of the Declaration of Helsinki.

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:

- Information that becomes publicly available through no fault of the Investigator or site staff;
- Information that it is necessary to disclose in confidence to an IRB/REB/IEC solely for the evaluation of the study;
- Information that it is necessary to disclose in order to provide appropriate medical care to a study subject;
- 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. 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 Disorder.* 2010; 25(9): 1131-1142.

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.

Del Sorbo F, Albanese A. Levodopa-induced dyskinesias and their management. *J Neurol.* 2008; 255 Suppl 4: 32-41.

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.

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, val 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.

Hayden F, Gwaltney J, Van De Castle R, Adams K, Giordani B. Comparative toxicity of amantadine hydrochloride and rmantadine 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-dopa-induced dyskinesias in Parkinson's disease. *Movement Disorders.* 2000; 15(5): 873-878.

Paci C, Thomas A, Onofrj M. Amantadine for dyskinesia in patients affected by severe Parkinson's disease. *Neurological Sciences.* 2001; 22(1): 75-76.

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.

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, Parasrampuira 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, Onofrj 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.

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.

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