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APPLICATION NUMBER:

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MEDICAL REVIEW(S)

CLINICAL REVIEW

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Established Name	Amantadine ER (ADS-5102)
(Proposed) Trade Name	Gocovri [®]
Therapeutic Class	NMDA receptor antagonist
Applicant	Adamas Pharma LLC
Formulation	Capsules, 68.5 and 137 mg. amantadine ER free base
Dosing Regimen	137 mg to 274 mg by mouth once daily at bedtime
Indication	Levodopa-induced dyskinesia
Intended Population	Adult patients with Parkinson's disease and levodopa-induced dyskinesia

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Following assessment of the clinical data, it is the opinion of this reviewer that ADS-5102 (Gocovri[®], amantadine extended release capsules) is a safe and effective treatment for levodopa induced dyskinesia (LID) in patients with Parkinson's disease (PD). It has an adverse event profile consistent with its pharmacological class and its overall risk to benefit ratio is therapeutically acceptable. This application relies upon the 505(b)(2) pathway with Symmetrel[®], an immediate release form of amantadine hydrochloride, as the Reference Listed Drug (NDAs 16020, 16023, 17118, and 18101, Endo Pharmaceuticals).

While drug treatment strategies exist to reduce dyskinesia in PD patients, this would be the first drug approved for this indication.

Reviewer's Comment: Throughout the review cycle discussion was held by the review team as to the most appropriate description of the indication for ADS-5102 for the treatment of the dyskinesia that occurs in patients treated for PD. The rationale for this is that dyskinesia also develops in PD patients treated with dopamine agonist (DA) monotherapy as well as levodopa (LD) monotherapy, albeit less commonly. In addition, most patients are treated with combinations of anti-PD drugs including levodopa and dopamine agonists. As will be seen in this review, only one third of patients in the pivotal trials were treated with LD alone, while 2/3 were treated with some combination of LD, DA, and/or monoamine oxidase B inhibitor(MAOI). To this end, it is recommended that consideration be given to describing the use of ADS-5102 as indicated for the treatment of dyskinesia in patients with Parkinson's disease receiving levodopa-based therapy, with or without concomitant dopaminergic medications.

1.2 Risk Benefit Assessment

Parkinson's disease is a progressive degenerative disorder of the nervous system that affects one in 100 people above age 60. Its pathophysiologic basis is the loss of striatal dopaminergic cells via the toxic effects of abnormal aggregation of the alpha synuclein protein in these neurons. Dopamine is replaced via the oral administration of levodopa, the mainstay of PD pharmacotherapy for the last half century. While levodopa provides good relief of motor symptoms, the benefit from levodopa changes as the illness progresses. Most PD patients will eventually develop the "on-off syndrome." The pharmacodynamic effect of levodopa becomes shorter in duration and the nervous system develops a dyskinetic motor response that, while leaving the patient mobile, may itself become disabling. It is for the treatment of this levodopa-induced dyskinesia (LID) that approval is sought for ADS-5102 by the sponsor.

The efficacy of ADS-5102 was demonstrated in two identically designed randomized trials: Study 301 (US and Canada, n=123) and Study 304 (mostly EU, n=75). Following dose selection based on a Phase 2 study, ADS-5102 340 mg amantadine extended release hydrochloride salt (274 mg free base) or placebo was administered to PD patients with LID after a one week titration using half the dose. Both studies evaluated the patients after 12 weeks of treatment. The primary efficacy outcome was the change in dyskinesia from baseline to Week 12 as measured by the Unified Dyskinesia Rating Scale (UDysRS). The key secondary outcome measure was the change from baseline in ON Time without troublesome dyskinesia based upon the PD Home Diary.

These two studies delivered comparable results. In combined analysis at Week 12, the Least Square (LS) mean change from baseline in UDysRS total score was -7.6 for the placebo group and -17.7 for the ADS-5102 group. Patients in the ADS-5102 group had a greater and statistically significant greater reduction in UDysRS total score (improved dyskinesia) than patients in the placebo group. The LS mean treatment difference was -10.1 (95% CI: -13.8, -6.5; $p < 0.0001$).

As reported by patients in their PD home diaries, the mean duration of ON time without troublesome dyskinesia (ON without dyskinesia + ON with non-troublesome dyskinesia) at baseline was 8.12 hours for the placebo group and 8.48 hours for the ADS-5102 group. At Week 12, the mean ON time without troublesome dyskinesia increased from baseline by 1.37 hours in the placebo group versus 3.80 hours in the ADS-5102 group. The LS mean treatment difference was 2.42 hours (95% CI: 1.48, 3.37; $p < 0.0001$).

The proportion of patients with improvement in their PD syndrome as reflected in the Clinical Global Impression of Change confirmed these results. After 12 weeks of treatment, 15 patients (15.6%) in the placebo group and 57 patients (57.0%) in the ADS-5102 group showed moderate or marked improvement in their overall status. This difference between the treatment groups was statistically significant by categorical analysis.

The clinical safety profile of the RLD is reasonably well established. The safety of ADS-5102 was studied in the randomized, blinded, and placebo-controlled trials as well as in 120 patients with at least one year's exposure. Referencing the labeled safety information for immediate release amantadine, no new or unusual side effects were seen with ADS-5102 treatment. The most commonly observed adverse drug reactions occurring at a frequency of $\geq 10\%$ and greater than placebo were hallucinations, dizziness, dry mouth, peripheral edema, constipation, falls, and orthostatic hypotension. The most common reasons for patients leaving the trials were hallucinations, lightheadedness, dry mouth, blurred vision, constipation, and nausea. If approved, ADS-5102 will be subject to continuing pharmacovigilance on the part of the drug's sponsor and regular analysis of post-marketing safety reports.

On the basis of these findings, the risk to benefit assessment supports the safe and effective use of Gocovri® in the treatment of LID in PD. However, evidence supportive

of the efficacy claim comes from trials only 12 weeks in duration. As a result, the sponsor's claims concerning the maintenance of the anti-dyskinetic effect should be limited to that duration.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No further postmarketing evaluation of risk or mitigation strategy is suggested.

1.4 Recommendations for Postmarket Requirements and Commitments

This review does not recommend any postmarketing requirements or commitments for clinical studies.

2 Introduction and Regulatory Background

Reviewer's Note: For the sake of clarity in referencing submission materials, this review used the milligram dosages of ADS-5102 (Gocovri®) in its hydrochloride salt form as supplied by the sponsor in protocols and study reports throughout the NDA submission. In the labeled Prescribing Information, the 340 mg dose of ADS-5102 as salt will be represented as 274 mg of free base in conformity with current usage standards (as will other doses reflected in the label) and will be supplied as capsules with either 68.5 or 137 mg free base amantadine ER.

2.1 Product Information

The drug substance, amantadine hydrochloride (aminoadamantane hydrochloride, C₁₀H₁₇N HCl, mol weight 187.7), is supplied by MOEHS, Iberica S.L. (letter of authorization to Drug Master File (b) (4))

The drug product is a hard gelatin capsule filled with extended release (b) (4) pellets containing the drug substance. The two dosage strengths of ADS-5102, 85 mg and 170 mg, contain the same (b) (4) pellets and only differ in fill weight, capsule size and appearance. The 85 mg strength is a size '2' hard white gelatin capsule with 'ADAMAS' imprinted on one side and '85' imprinted on other side in black with 3 black radial bands around the body of the capsule. The 170 mg strength is a size '0' hard gelatin light blue capsule with 'ADAMAS' imprinted on one side and '170' imprinted on other side in black with 3 black radial bands around the body of the capsule.

(b) (4)

(b) (4)

Further details on the adequacy of drug composition, synthesis, and control of excipients may be found in the review by the Office of Pharmaceutical Quality.

Figure 1 Schematic of ADS-5102 (b) (4) pellet (source: 2.3P Drug product, p.2)

(b) (4)

The proposed system for commercial delivery include a high-density polyethylene (HDPE) bottle, and a round, white opaque (b) (4) closure with a white induction inner seal. The bottles (different sizes for the two dose strengths) will be filled with 60 capsules which is a 30 day supply. (b) (4) /aluminum push-through blister packs will be created as physician samples.

2.2 Tables of Currently Available Treatments for Proposed Indications

While drug treatment and neurosurgical strategies exist to reduce dyskinesia in PD patients, this would be the first drug approved for this indication. However, immediate release amantadine is available (NDA and multiple ANDAs) with an indication for the treatment of Parkinson's disease.

2.3 Availability of Proposed Active Ingredient in the United States

Amantadine, the drug substance in this product, has been approved for use and marketed in the United States since 1966. The originator, Symmetrel® (Endo Pharmaceuticals NDA 16020 (100 mg capsule), NDA 16023 (50mg/5ml syrup), and NDA18101 (100 mg tablet)) has been discontinued for reasons other than safety by their sponsor.

As listed in the Orange Book, the current reference standards (RS) for amantadine are ANDA 71293 (100mg capsule, Sandoz) and ANDA 76186 (100 mg tablet, USL Pharma) among others for syrup formulations.

2.4 Important Safety Issues With Consideration to Related Drugs

Drugs that interact with the dopaminergic system have a well-known constellation of particular adverse drug reactions. These include sleep attacks, hallucinations, impulse control disorders, and autonomic dysfunction, among others. These are considered in this review in Section 7.3.5 Submission Specific Primary Safety Concerns.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

IND 78671 for the development of amantadine ER was allowed to proceed on August 31, 2007. The following is a summary of relevant information from interactions with the sponsor pertaining to the development of ADS-5102 prior to this NDA submission (indented paragraphs are taken directly from the FDA meeting minutes):

End of Phase 2 Type B Meeting (September 29, 2008)

FDA agreed that the amantadine tablet manufactured by USL Pharmaceutical can be used as the immediate release reference drug product.

(b) (4)
Rather, clinical efficacy studies (b) (4) are needed.

(b) (4)

The Agency believes that the safety of Amantadine ER may be established through the safety data from the proposed (b) (4) clinical trials incorporating the safety data from NDA 17-118 by reference and published data. Safety data from any other clinical trials (efficacy) should be included.

Guidance Written Responses Type C Meeting (December 18, 2013)

(b) (4)

DNP did not find the study acceptable:

Substantial evidence of effectiveness should include documentation of an acceptable duration of the anti-dyskinetic effect of ADS-5102. (b) (4) is insufficient. Clinical

trials for the treatment of motor symptoms in patients with advanced Parkinson's disease are typically 26 weeks in length, with an equivalent open period to provide adequate safety experience. In addition, the clinical meaningfulness of improvement in dyskinesia should be quantified. One example of this would be improvement in on-time without troublesome dyskinesia. In addition, care should be taken to document that these outcomes are not achieved through worsening of the Parkinson motor state as measured by total off-time and the motor score of the UPDRS (Part 3)... (b) (4)

is inadequate to answer the concern as to whether tachyphylaxis develops with continued treatment with amantadine ER.

Specific language to be included in approved labeling would be determined following comprehensive review of the adequate and well- controlled trials submitted in support of the indication.

Additional guidance with regard to suggested pharmacokinetic studies and dosing was offered; this discussion is deferred to the Clinical Pharmacology review.

We cannot agree with your proposed doses and dose regimens in these specific populations before we comprehensively review the totality of the study results, including results from the clinical trials and the PK modeling and simulation.

The amantadine label warns prescribers about the potential for drug accumulation causing life-threatening, irreversible, and unpredictable cardiac adverse reactions and death. High plasma levels of amantadine have also been associated with central nervous system adverse reactions such as delirium, hallucinations, and paranoia. You will need to provide information supporting your proposed dosing regimen for the final commercial amantadine ER product in the elderly and in patients with various categories of renal impairment (e.g., mild, moderate, severe).

DNP agreed that the safety database from approximately 350 subjects/patients (144 healthy volunteers, 211 PD patients) exposed to amantadine ER in the proposed development program would be adequate when examined together with safety data derived from all clinical trials in the development plan, provided the patients were representative of the intended target population. In addition, DNP stated that if there were no new cardiovascular safety concerns identified during clinical trials or during DNP review, a thorough QT study would not be required.

Teleconference; Written Responses Type C Meeting (May 27, 2014)

The sponsor requested clarification with regard to the efficacy outcome and trials necessary to establish efficacy and safety.

The Unified Dyskinesia Rating Scale (UDysRS) is an acceptable primary outcome measure. Because either a reduction dopaminergic medications or their effectiveness lessens dyskinesia, and is usually accompanied by worsening of the motor symptoms of Parkinson's disease, you must show that a reduction in dyskinesia associated with your Amantadine ER product is not accompanied by worsening of motor function. A

reduction in dyskinesia associated with a significant decline in motor function may not benefit patients with Parkinson's disease.

If you plan to describe in the label any of the non-primary endpoints listed, you should use a single hierarchy of endpoints determined by the trial's stated objectives and the clinical relevance and importance of each specific measure independently and in relationship to each other. Any endpoints that are not part of the prespecified hierarchy of primary and key secondary endpoints are exploratory. Information considered for inclusion in the product label, whether it is based on a primary or secondary endpoint, needs to have replication of positive results in a second, independent study.

Because dyskinesia was a new indication for amantadine, DNP reiterated that at least two studies (with one study at least 26 weeks in duration) would be needed to support efficacy. The reasons for this are two-fold: tachyphylaxis of the anti-dyskinetic effect of amantadine has been described in the literature and drug trials for the PD indication have generally been of 26 weeks duration. The sponsor's proposed 52-week open label extension was acceptable but at least 100 patients should have been followed on the highest recommended dose (or higher) for at least one year.

DNP indicated that the 26-week study could be designed using a hierarchical analysis with ordering based on increasing duration on blinded treatment.

One example of this type of hierarchy is that after trial completion the first efficacy analysis is conducted at the 13-week study visit, the second at 18 weeks and the last at 26 weeks. Such an analysis must be prespecified.

The sponsor had completed the aforementioned smaller study and had begun a 13 week trial. DNP offered this possible development pathway:

The Division has concerns that Study ADS-PAR-AM201 was a short duration study with only approximately 20 patients on the targeted dose of Amantadine ER. The study does not address the duration of the treatment effect associated with Amantadine ER in treating patients with a long-term, chronic illness. The Division recommended completing the planned 13-week controlled efficacy study (Study ADS-AMT-PD301) as planned, and a 26-week controlled efficacy study. Patients from both studies could enter the planned open label, long-term safety study. Although the Division raised concerns about Study ADS-PAR-AM201, the decision as to whether it could serve as substantial evidence to support an NDA remains a matter for review.

Pre-NDA Type B Meeting (March 1, 2016)

DNP indicated that, on face and pending full review, Study ADS-AMT-PD301 and Study ADS-PAR-AM201 had the potential to provide evidence of efficacy in support of the intended indication.

Discussion about the duration of treatment was discussed and the sponsor inquired about the possibility of submitting the NDA before the completion of the second pivotal trial. DNP told the sponsor:

The proportion of dropouts in Study ADS-AMT-PD301 may result in a large amount of missing or imputed efficacy data. This could affect the interpretation of the study result, especially if relatively few participants are evaluable at 25 weeks.

Study ADS-AMT-PD304 has the potential to support the effectiveness of ADS-5102 for 13 weeks of continuous treatment. If the completed study report and study datasets for Study ADS-AMT-PD304 are not included in the initial NDA submission, they may not be reviewed during the NDA review cycle. We remind you that all evidence necessary to support approval must be submitted with the original NDA... A complete and adequate safety database is needed at the time of submission.

The structure of SDTM and ADaM datasets, and requirements for the ISE and ISS in the eCTD were discussed. Certain analyses were specified:

Please provide analyses of the MDS-UPDRS Part 3, and Parts 2+3, using the protocol specified analysis for the UPDRS Parts 1+2+3. Provide an analysis for each subscale for the UDysRS. Please ensure that study datasets clearly identify the total scores and change in total scores for each MDS-UPDRS and UDysRS subscale.

You should conduct a sensitivity analysis for patients with implanted deep brain stimulators for the primary and secondary efficacy endpoints.

The ADaM datasets should include a variable that indicates the total score in all instances of rating scale use, in addition to the usual variables for each item in the respective scale.

There was a gap for some patients from the end of the blinded study in which they had participated until subsequent enrollment into the open-label safety study.

The sponsor indicated that for patients enrolled in study ADS-AMT-PD302 that have previously completed the Phase 2/3 study, ADS-PAR-AM201, there is a gap of time of up to 2 years before entering the open-label trial. The Division suggested that all patients in the clinical development program be identified using the SDTM unique subject identifier (USUBJID) and that participants rolling over from ADS-PAR-AM201 to Study ADS-AMT-PD302 that have an exposure gap be flagged in the submitted datasets for ease of identification. In addition, the sponsor clarified that DBS patients were only enrolled in the open-label trial.

With regard to safety, DNP wished to see certain explorations of the safety database:

Provide analyses of events that may reflect worsening Parkinsonism, the presences of an impulse control disorder, psychosis, cardiovascular adverse events, suicidality, and

hypotension. If you have included patients who have implanted deep brain stimulators, provide details and indicate whether any additional programming or lead replacement had taken place during trials and the date of intervention(s). This may be treated as a “concomitant medication” in your datasets.

In creating exposure tables, you should pool patients treated with the highest recommend dose and above (e.g., ≥ 340 mg), then list exposure for remaining dose levels. Please do not calculate exposure by mean dose; instead, use the actual dose patients received during the trial. Please use actual days patients were treated with a specific dose of ADS-5102 for the display of exposure duration, instead of using the mean number of days on treatment. Please indicate clearly the numbers of patients included in the active treatment arm versus the placebo arm in Study ADS- AMT-PD301, and those patients who continued into open-label treatment in ADS-AMT-PD302.

Please report all adverse events by treatment arm in the controlled trial (actual dose). Please provide a flag to identify adverse events that occurred while patients were treated with a titration dose (e.g., 260 mg), and a flag to distinguish these events from adverse events that occurred on maintenance dose.

The Division reiterated the need to be able to trace each adverse event to the dose received by the patient at the time the AE occurred in datasets submitted for review. The sponsor clarified that there are very few patients at the 420 mg dose level in study ADS-PAR-AM201; therefore, these participants would be captured in the ≥ 340 mg dose group. This is acceptable. It was also agreed that an exposure table would show the exposure presented by days at the actual dose, and that a table of AEs by actual dose would be provided in the ISS.

The sponsor submitted sample datasets and further advice was given concerning their structure. In particular the ADSL file for the ISS should be formatted as one subject per line. The sponsor was told that if a subject participated in more than one study, columns and flags should be used to identify these features. Provide separate ISS datasets for double blind trials and open label studies. The Preferred Terms in these datasets should be coded using a single MedDRA version.

Initial Pediatric Study Plan was submitted on November 21, 2014 and agreed upon with DNP. The sponsor indicated their intent to request a full waiver from pediatric studies. Following review, the Pediatric Review Committee granted the waiver (PeRC meeting minutes, August 9, 2017).

2.6 Other Relevant Background Information

Amantadine ER for the treatment of levodopa-induced dyskinesia in PD was granted orphan designation 13-4132 on April 9, 2015.

Following initial review of the sponsor's proposal, the NDA submission was denied priority designation. This application presents a new dosage form for amantadine, a drug substance previously indicated and available for the treatment of PD. It has long been recognized that most treated PD patients develop dyskinesia over time and there are accepted clinical strategies in use to reduce dyskinesia related to the drug treatment of PD.

With agreement from DNP, following review by the Division of Medication Error Prevention and Analysis, the proposed proprietary name, Gocovri[®], was deemed acceptable.

Preliminary review of the CMC portion of the application revealed that the proposed established name “(b) (4)” and the labeled capsule strengths, i.e., 85 mg and 170 mg based on content of the hydrochloride salt, are inconsistent with FDA and USP recommendations that the labeled strength be expressed in terms of the parent acid or base for drug products formulated with a salt unless justified otherwise as described in USP <1121>. The sponsor was notified by email on February 10, 2017 to change the established name from “amantadine hcl” to “amantadine”, and change the presentation of the strength from 85 mg and 170 mg (for the hydrochloride salt) to 68.5 mg and 137 mg (for amantadine free base).

While this will be important for accurate labeling of the drug, for the sake of clarity in this review and to be consistent with all documents and data submitted by the sponsor, this conversion to free base mg is deferred to labeling and Prescribing Information.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The clinical sections of the application were provided in full at the time of the original submission through the FDA eCTD gateway. The 120 day Safety Update provided the safety experience of all patients still actively taking drug during that period. All appropriate information needed to adequately review the data and insure its transparency and traceability to source records was provided. Data submitted electronically adhered to appropriate CDISC SDTM and ADaM data standards. MedDRA 17.0 was used code adverse events (AEs). The application of Dictionary Derived Definitions for verbatim descriptions of AEs was reviewed for all events and prominent splitting of similar events using different Preferred Terms was found. As noted in the relevant sections of the review below, these were edited in collaboration with the Cross Discipline Team Leader.

As supported in Sections 3.2 and 3.3, below, there is no indication that this application in support of ADS-5102 lacked integrity.

3.2 Compliance with Good Clinical Practices

All studies in the development program for ADS-5102 were performed under IND 78671. The applicant has provided attestation that the clinical studies in the development program were conducted in accordance with federal regulations governing the protection of human subjects (21 CFR part 50), Institutional Review Boards (21 CFR part 56), and the obligations of clinical investigators (21 CFR 312.50 to 312.70) in accordance with good clinical practice (GCP). No persons debarred under 21 CFR 306 were associated with this application. Audits were performed by the sponsor and FDA also performed inspections as noted in the table below.

Table 1 Sponsor audits for covered studies and FDA BIMO Inspections

GCP / ICH E6 Audits	Function	Sponsor Inspection	FDA BIMO Inspection
Adamas Pharma, LLC	Sponsor		4/17, NAI
Study 301			
(b) (4)	Clinical trial support	(b) (4)	
(b) (4)	Clinical trial support	(b) (4)	
(b) (4)	Interactive response technology	(b) (4)	
(b) (4)	CRO	(b) (4)	
(b) (4)	CRO	(b) (4)	
Paul Nasieda	Clinical site #1 (N=12)	8/14	
Daniel Truong	Clinical site #21 (N=10)	1/15	
Keith Hull	Clinical site #4 (N=6)	4/15	4/17, NAI
Richard Singer	Clinical site #39 (N=5)	7/15	
Maureen Leehey	Clinical site #16 (N=4)	10/15	
Pinky Agarwal	Clinical site #7 (N=6)		4/17, NAI
Study 304			
(b) (4)	Clinical trial support	(b) (4)	
(b) (4)	CRO	(b) (4)	
(b) (4)	Interactive response technology	(b) (4)	
Theresa Zesiewicz	Clinical site #59 (N=4)	3/16	
Jaime Kulisevsky	Clinical site #69 (N=2)	2/16	
Reinhard Ehret	Clinical site #79 (N=6)	3/16	
Jean-Philippe Azulay	Clinical site #89 (N=6)	3/16	5/17, NAI
Claudia Trenkwaller	Clinical site #76 (N=6)		3/17, NAI

All sites passed the sponsor's audits. On FDA inspection, one site (Trenkwaller #76) was noted to have protocol violations involving two patients who did not have sufficient dyskinesia at baseline to qualify for enrollment. Nevertheless adherence to GCP and

the data generated by the site were verified. The investigator was aware of the protocol violations. (This was unlikely to have had any falsely positive effect on the outcome of the study as these patients did not demonstrate improvement over minor dyskinesia at baseline.)

One investigator (Nausieda) participated in Study 301 (site #1, n=12), Study 304 (site #1, n=4) and open label Study 302 (n=15). This clinical site was closed due to the investigator's retirement in September, 2015. Throughout his career, Dr. Nausieda was a distinguished Parkinson's disease clinical investigator in the US. His site had been audited by the sponsor and there has been previous satisfactory FDA inspection of his site for a different application. The clinical review team did not have additional concerns about the data generated at that site. Isaacson, (Study 301 site #2, n=5; Study 304 site #2, n=4) also underwent previous satisfactory FDA inspection for other applications and was therefore not chosen for inspection in this submission.

3.3 Financial Disclosures

The applicant has adequately disclosed financial interests and arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*. In this application, the covered clinical studies that provide substantial evidence of effectiveness are Study 301 and Study 304. The Clinical Investigator Financial Disclosure Forms for these studies may be found in [Appendix 9.4](#) of this review.

The sponsor provided a full listing of all investigators and sub-investigators and using Form 3454 submitted appropriate information concerning disclosable financial interests and arrangements as described in 21 CFR § 54.4(a)(3).

The only reportable arrangement were for Studies 301 and 302; (b) (6)
Principal Investigator (Study 301 (b) (6)) was given \$31,611.47 in consulting fees (training supervision). As required, this was documented on Form 3455, submitted by the sponsor for this individual.

Taken as a whole, the design of the pivotal studies minimized bias due to randomized, blinded, and objective endpoints, and the clinical investigator with financial issues provided minimal contribution to study data when the data are considered in totality.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The Office of Pharmaceutical Quality indicates that from a quality perspective the application, which was amended during the review process, provides adequate

information to ensure that the applicant can consistently manufacture a product that is suitable for use by the intended patients.

The OPQ risk assessment indicates that a warning should be included in product labeling about the risk for alcohol related dose dumping. Otherwise, assay, stability, content uniformity, microbial limits, bead size for sprinkles, and dissolution all have an acceptable risk assessment.

4.2 Clinical Microbiology

Not applicable to this submission.

4.3 Nonclinical Pharmacology/Toxicology

The pharmacology and toxicology reviewer indicated that from a non-clinical perspective no issues were identified for this well-established moiety and its drug product and that, with recommended labeling, is it approvable.

Recommendations for changes from the RLD label include that comparisons to the recommended human dose (RHD) should be based upon the Gocovri[®] RHD of 274 mg (free base) daily. The label should also reflect that there are adequate nonclinical data to support the claim that amantadine is a weak NMDA receptor antagonist. The sponsor also submitted 3 publications relevant to reproductive and developmental toxicology and it is recommended that the label describe the findings of these citations.

4.4 Clinical Pharmacology

The clinical pharmacology investigations provided in this NDA submission include [five Phase 1 pharmacokinetic studies](#) (relative bioavailability, bioequivalence, food effect, single ascending dose, and multiple ascending dose studies). In addition, PK simulations were performed to optimize dosing in patients with renal function impairment.

Review of the submission by the Office of Clinical Pharmacology (OCP), resulted in the following recommendations:

- The steady state exposures for ADS-5102 ($C_{max,ss}$, $AUC_{0-24,ss}$) following the administration of the sponsor's ER formulated product and the reference listed drug (immediate release formulation) were found to meet standards for bioequivalence, based upon a relative bioavailability study.
- The starting dose of ADS-5102 is 170 gm (salt) at orally bedtime for one week followed by a maintenance dose of 340 mg nightly.
- ADS-5102 may be taken with or without food. It may be sprinkled on a small amount of soft food (e.g. apple sauce) but should be swallowed without chewing.
- Concomitant use of alcohol should be avoided.
- No dose adjustment is required for hepatic impairment.

- Dosing recommendations for renal impairment:
 - o No dosage adjustment is necessary for subjects for mild renal impairment
 - o Reduce daily dose by half, both the initial starting daily dose (68.5 mg free base) and also daily maintenance dose (137 mg free base) for moderately renally impaired subjects
 - o Reduce to a daily dose to 68.5 mg (starting and maintenance dose) in severely renally impaired subjects
 - o Use should be avoided in patients with End Stage Renal Disease (ESRD) whether on dialysis or otherwise.

Reviewer's comment: While ADS-5102 meets the specification for bioequivalence to the reference standard, the sponsor has declined the indication for parkinsonism. The smallest dose capsule to be marketed is the 170 mg salt (68.5 free base) capsule. It may not be possible to start at smaller doses as required by impaired renal function. It is probably not reliable to consider having the patient open the capsule and parsing the amount of sprinkles inside to approximate a smaller dose. Further Clinical Pharmacology recommendations will be needed for labeling in this regard.

4.4.1 Mechanism of Action

The pharmacology and toxicology review offers this assessment of the putative action of amantadine:

The mechanism by which amantadine exerts efficacy in the treatment of levodopa-induced dyskinesia is unknown. Amantadine is a weak uncompetitive antagonist of the NMDA receptor. Amantadine has not been shown to possess direct anticholinergic activity in animal studies; however, it exhibits anticholinergic-like side effects such as dry mouth, urinary retention, and constipation in humans. Amantadine may have direct and indirect effects on dopamine neurons; it exerts dopaminergic-like side effects such as hallucinations and dizziness in humans.

4.4.2 Pharmacodynamics

The relationship between ADS-5102 dose and efficacy was evaluated in the Phase 2/3 dose-ranging study (Study 201, described in [Section 5.3.1](#), below.) An analysis of dose response was performed across the four treatment groups (placebo and ADS-5102 salt: 260 mg, 340 mg, and 420 mg) for change from baseline to Week 8 in Unified Dyskinesia Rating Scale (UDysRS). An analysis of covariance model was used, with treatment group as a factor and baseline value as a covariate. The relationship between UDysRS scores at Week 8 and ADS-5102 plasma concentrations at Week 6 was assessed. There was a high inter-individual variation seen in the plasma concentration across the dose range of 260 to 420 mg and, as a result, a plasma concentration-response relationship was not able to be defined.

4.4.3 Pharmacokinetics

OCP, in their review of the sponsor's submission determined that following oral administration of the ER formulation, the median T_{max} for plasma amantadine was around 12 hours and the steady-state concentrations were achieved four days after the dose initiation. The steady-state exposures (AUC_{0-Tau}) were 20-30% higher than after single dosing (accumulation ratio ~1.2-1.3-fold). Mean plasma amantadine elimination half-life was approximately 16 hours. Renal clearance is the predominant elimination pathway for amantadine and it is excreted unchanged. Based on in vitro studies it does not appear to interact with cytochrome P enzymes

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Clinical Pharmacology Studies

Table 2 Phase 1 ADS-5102 Studies (source: 2.5 Clinical Overview, p 12-13)

Clinical Study Report	Study Design	Number of Subjects	Dose and Regimen	Study Objectives	Status
NPI-5103-C-101	Single dose, open-label, randomized crossover, 4-treatment, 4-period study	20 Healthy volunteers	100 mg amantadine ER capsules (Formulations A, B, and C [ADS-5102]) 100 mg amantadine IR tablets	To compare the single dose PK of three amantadine ER formulations, including ADS-5102 (Formulation C), with amantadine IR	Completed; Formulation C selected for development; 88.5% BA relative to IR
ADS-AMT-PK110	Single dose, open-label, 3-treatment crossover study	30 Healthy volunteers	85 mg ADS-5102 capsule 170 mg ADS-5102 capsule 2 x 170 mg ADS-5102 capsules	To evaluate whether single dose PK is proportional to dose following ADS-5102 85 mg, 170 mg, and 340 mg (2 x 170 mg)	Completed; dose-proportionality established
ADS-AMT-PK111	Multiple-dose, open-label, 2-treatment, 2-period crossover study	24 Healthy volunteers	Single dose phase: 170 mg ADS-5102 capsules compared to 200 mg amantadine IR tablets Steady state phase: 170 mg ADS-5102 capsules administered once daily for 8 days 100 mg amantadine IR tablets administered twice daily (2 x 100 mg) for 8 days	To compare the single dose and steady state PK of ADS-5102 once daily to amantadine IR administered twice daily	Completed; ADS-5102 single dose and steady state relative BA compared to IR of 93% and 100%, respectively

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Clinical Study Report	Study Design	Number of Subjects	Dose and Regimen	Study Objectives	Status
ADS-AMT-PK112	Single dose, open-label, 2-treatment crossover study	42 Healthy volunteers	340 mg (2 x 170 mg) ADS-5102 capsule manufactured at Catalent 340 mg (2 x 140 mg and 1 x 60 mg) ADS-5102 capsule manufactured at (b) (4)	To establish bioequivalence of ADS-5102 manufactured at Catalent and (b) (4)	Completed; bioequivalence established
ADS-AMT-PK113	Single dose, open-label, 3-treatment crossover study	36 Healthy volunteers	170 mg ADS-5102 capsule administered under fasting condition 170 mg ADS-5102 administered following a meal (fed condition) 170 mg ADS-5102 capsule administered as capsule contents sprinkled on 30 mL applesauce under fasting condition	To evaluate the relative BA of ADS-5102 administered with a high fat meal and under fasted state To evaluate the relative BA of ADS-5102 when the capsule contents are administered sprinkled on applesauce and from an intact capsule in the fasted state	Completed; lack of food effect and BE of sprinkle established

BA = bioavailability; BE = bioequivalence; ER = extended release; IR = immediate release; PK = pharmacokinetics

Clinical studies in the PD LID population

Table 3 Phase 2 and 3 studies in PD LID (source: 2.5 Clinical Overview, p 14-15)

Clinical Study Report Phase Site Location	Study Design	Dose and Regimen	No. of Subjects/ Gender, Age	Efficacy/Safety Measures
ADS-PAR-AM201 (Phase 2/3) US	Multicenter, randomized, double-blind, placebo-controlled, 4-arm, parallel-group efficacy and safety study to evaluate 3 dose levels	Placebo 260 mg ADS-5102 340 mg ADS-5102 420 mg ADS-5102 Once daily at bedtime 260 mg for first week, then 340 mg for 1 week, then 420 mg as appropriate Treatment duration: 8 weeks	83 (22 placebo, 61 ADS-5102, including 21 at 340 mg) 54% male 46% female Mean 66 years (range 36-84)	<u>Efficacy:</u> UDysRS total score (Week 8 primary); FSS; ON time without troublesome dyskinesia; OFF time; ON time with troublesome dyskinesia; total time with dyskinesia; MDS-UPDRS, Part IV; MDS-UPDRS, Part IV, Items 4.1 and 4.2; UDysRS total objective score (Parts III and IV); MDS-UPDRS individual and combined scores (Parts I, II, and III); CGI-C; PDQ-39 <u>Pharmacokinetics:</u> sampling at Days 1 (Baseline, prior to dosing), 8, 15, 29, and 43 <u>Safety:</u> AEs, physical examination, vital signs, laboratory evaluations
ADS-AMT-PD301 (Phase 3) US, Canada	Multicenter, randomized, double-blind, placebo-controlled, 2-arm, parallel-group efficacy and safety study	Placebo 340 mg ADS-5102 Once daily at bedtime 170 mg for first week, then 340 mg Treatment duration: 25 weeks	123 treated (safety population; 60 placebo, 63 ADS-5102) 58.5% male 31.5% female Mean 64.7 years (range 34-82)	<u>Efficacy:</u> UDysRS total score (Week 12 primary); ON time without troublesome dyskinesia; OFF time; ON time with troublesome dyskinesia; total time with dyskinesia; MDS-UPDRS, Part IV; MDS-UPDRS, Part IV, items 4.1 and 4.2; UDysRS total objective score (Parts III and IV); MDS-UPDRS individual and combined scores (Parts I, II, and III); CGI-C <u>Safety:</u> AEs, physical examination, vital signs, laboratory evaluations

Clinical Study Report Phase Site Location	Study Design	Dose and Regimen	No. of Subjects/ Gender, Age	Efficacy/Safety Measures
ADS-AMT-PD304 (Phase 3) Austria, France, Germany, Spain, US	Multicenter, randomized, double-blind, placebo-controlled, 2-arm, parallel-group efficacy and safety study	Placebo 340 mg ADS-5102 Once daily at bedtime 170 mg for first week, then 340 mg Treatment duration: 13 weeks	75 treated (safety population; 38 placebo: 37 ADS-5102) 52.0% male 48.0% female Mean 64.8 years (range 42-80)	<u>Efficacy:</u> UDysRS total score (Week 12 primary); ON time with troublesome dyskinesia; total time with dyskinesia; MDS-UPDRS, Part IV; MDS-UPDRS, Part IV, items 4.1 and 4.2; UDysRS total objective score (Parts III and IV); MDS-UPDRS individual and combined scores (Parts I, II, and III); CGI-C <u>Safety:</u> AEs, physical examination, vital signs, laboratory evaluations
ADS-AMT-PD302 (Phase 3) Austria, France, Germany, Spain, US	Multicenter, open-label safety study	340 mg ADS-5102 Once daily at bedtime 170 mg for first week, then 340 mg Treatment duration: up to 101 weeks	223 58.7% male 41.3% female Mean 63.7 years (range 32-82)	<u>Efficacy:</u> MDS-UPDRS, Part IV; MDS-UPDRS, Part IV, items 4.1 and 4.2 <u>Safety:</u> AEs, physical examination, vital signs, laboratory evaluations

CGI-C = Clinician's Global Impression of Change; FSS = Fatigue Severity Scale; MDS-UPDRS = Movement Disorder Society-Unified Parkinson's Disease Rating Scale; PDQ-39 = Health-related Quality of Life 39-item; UDysRS = Unified Dyskinesia Rating Scale

5.2 Review Strategy and Brief Outline of Clinical Studies

The sponsor has completed 5 clinical pharmacology studies in healthy volunteers (4 single dose and 1 multiple dose studies). While these Phase 1 studies are reviewed for safety events in Section 7 of this review, the descriptions of the studies and analyses of their results may be found in the reviews performed by my colleagues in related review disciplines.

Three efficacy studies in PD patients with levodopa induced dyskinesia have been completed and a long term open label safety study is ongoing. These four studies comprise the entirety of the clinical development program. Patients eligible for enrollment in these 4 studies had a diagnosis of PD, were receiving a levodopa preparation administered not less than 3 times daily, were on stable doses of all other anti-Parkinson medications, and had LID. Participants could be between 30 and 85 years of age. The study populations were intended to be similar to the anticipated population of patients who will use the marketed product.

The four clinical studies were used to review the safety and efficacy of ADS-5102:

Phase 2/3 Study ADS-PAR-AM201: Extended Release Amantadine Safety and Efficacy Study in Levodopa-Induced Dyskinesia (US, 31 clinical sites).

- Study 201 evaluated the treatment of 83 PD patients with LID with placebo or ADS-5102 at 260, 340, or 420 mg once daily at bedtime for 8 weeks of blinded

treatment. During the first week of treatment all participants that were randomized to the ADS-5102 groups received a daily dose of 260 mg, which was increased to 340 mg at the end of Week 1 for the higher dose groups and then to 420 mg at the end of Week 2 for the highest dose group.

- ADS-5102 340 mg dose selected for Phase 3 studies.
- Primary efficacy outcome: UDysRS at Week 8 visit.

Reviewer's Comment: In Study 201, of 83 patients enrolled only 21 were on 340 mg/d of ADS-5102, the dose intended for marketing. In addition, the duration of maintenance treatment was 7 weeks. While this study served to find an optimum dose for the pivotal studies, it does not provide useful efficacy data of an evidentiary quality. This study will be described briefly in Section 5 with an emphasis on review of the safety findings in Section 7.

Phase 3 Study ADS-AMT-PD301: Efficacy and Safety of ADS-5102 (amantadine HCl) Extended Release Capsules for the Treatment of Levodopa Induced Dyskinesia in Parkinson's Disease Patients (US and Canada, 42 clinical sites)

Phase 3 Study ADS-AMT-PD304: ADS-5102 (amantadine HCl) Extended Release Efficacy and Safety Study in Parkinson's Disease Patients with Levodopa-Induced Dyskinesia (US, Germany, France, Spain, and Austria, 32 clinical sites)

- Studies 301 and 304 are similarly structured blinded, randomized, placebo-controlled pivotal trials in support of efficacy. PD patients with LID randomized to ADS-5102 received a daily dose of 170 mg ADS-5102 during Week 1, followed by 340 mg ADS-5102 in the maintenance period, and ending with 170 mg ADS-5102 during the last week of treatment.
- Both studies used the UDysRS change from baseline and "on" time without troublesome dyskinesia at 12 weeks as the efficacy outcome measures.
- Study 301 (n=123) and Study 304 (n=75) originally differed with regard to the duration of maintenance treatment: 24 and 12 weeks, respectively. However, Study 301 was ended prematurely when the last enrolled patient reached the Week 12 visit.

Reviewer's Comment: These two trials constitute the adequate and well controlled studies performed to support efficacy and safety for registration purposes.

Study ADS-AMT-PD302: Open-Label Safety Study of ADS-5102 (amantadine HCl) Extended Release Capsules for the Treatment of Levodopa Induced Dyskinesia (EASE LID 2 Study)

- This ongoing open-label safety extension study has 223 participants at 67 clinical sites in US, Germany, France, Spain, and Austria. There are 3 distinct groups of patients enrolled in this study:
 - o Patients who completed an efficacy study evaluating ADS-5102 in LID and chose to immediately transition into Study 302 without a time gap (this group contains trial participants who were on either active drug or placebo).

- o Patients who completed a previous efficacy study but entered Study 302 with a time gap between the end of their last trial and starting Study 302.
- o Patients who were previously ineligible to enroll in an efficacy study due to having undergone deep brain stimulation (DBS) for the treatment of their PD (an exclusion criterion).

In this review, these trials will be labeled as **Study 201, 301, 304 and 302**, respectively.

The approach to this review of efficacy and safety is straight forward. In addition to presenting both the sponsor's and the statistical reviewer's assessment of efficacy, I shall review the safety findings of the double blind trials (Studies 201, 301, and 304). In order to give an overall assessment of the safety of ADS-5102 in this PD population, the safety experience from these studies will be presented in integrated fashion in Section 7 of this review.

Reviewer's comment: Open-label Study 302 will be evaluated as supportive of the safety of ADS-5102 for chronic use in the PD population. Despite being unblinded, Study 302 might also have provided additional support of effectiveness over a longer term of use by employing the same efficacy outcome as the double blind trials, the UDysRS. Unfortunately, the sponsor eliminated this measure by protocol amendment shortly after the study commenced, substituting instead single items 4.1 and 4.2 of the MDS-UPDRS. These UPDRS Part IV severity ratings are not linked to descriptive anchors that are used to improve reproducibility from interview data and information collected in the patient's PD diary. Past internal consultation with the Clinical Outcomes Assessment Staff (formerly Study Endpoints and Labeling Development Team) concluded that UPDRS Part IV cannot provide sufficient information to adequately assess a treatment benefit for the target population. The UDysRS, an instrument that rates patient performance or LID symptom severity using multiple items within domains such as activities of daily living, symptom severity, or motor performance, is considered more likely to demonstrate a clinically meaningful change in LID associated with study medication.

Reviewer's note: Study 302, open-label extension study, was the only study ongoing at the time of NDA submission. The data cut-off date for the NDA submission was July 1, 2016 and the 120 day Safety Update cut-off date was December 2, 2016.

The tabulations and calculations in this review are performed by the reviewer using JMP 11.1 and JMP Clinical 6 software on the Sponsor supplied datasets conforming to CDISC SDTM and ADaM standards. Adverse event analysis used MAED software in addition. Any table or figure taken from the Sponsor's submission is referenced as such in the table or figure caption; the rest are created by me.

5.3 Discussion of Clinical Studies

Reviewer's Note: *The Unified Dyskinesia Rating Scale (UDysRS) is the metric used as the primary measure of effectiveness in this application. For the reader's convenience, the scale is presented in its entirety in [Appendix 9.4](#). The PD Home Diary, completed by the patient or caregiver was a key secondary outcome measure as efficacy must include the ability to reduce the amount of dyskinesia considered troublesome to the patient. The diary may be found in [Appendix 9.5](#). The efficacy assessments used for the clinical studies in this application are summarized in the sponsor's table:*

Table 4 Studies 201, 301, 304 and 302: Efficacy assessment by visit (source, 2.7.3. Summary of Clinical Safety, p 20)

Measure	Phase 2/3 ADS-PAR- AM201	Phase 3 Efficacy ADS-AMT- PD301	Phase 3 Efficacy ADS-AMT- PD304	Open-label Safety ADS-AMT- PD302
UDysRS	Day 1 (Baseline) and Weeks 2, 4, and 8 (or ET)	Day 1 (Baseline) and Weeks 2, 8, 12, 18, and 24 (or ET)	Day 1 (Baseline) and Weeks 2, 4, 8, and 12 (or ET)	Not applicable
PD home diary ^a	Day 1 (Baseline) and Weeks 2, 4, 6, and 8 (or ET)	Day 1 (Baseline) and Weeks 2, 8, 12, 18, and 24 (or ET)	Day 1 (Baseline) and Weeks 2, 4, 8, and 12 (or ET)	Not applicable
MDS-UPDRS (Parts I to IV except where noted otherwise)	Screening (Part IV, item 4.2), Day 1 (Baseline) and Weeks 2 (only Part IV), 4, and 8 (or ET)	Screening (Part IV, item 4.2), Day 1 (Baseline) and Weeks 2, 8, 12, 18, and 24 (or ET)	Screening (Part IV, item 4.2), Day 1 (Baseline) and Weeks 2, 4, 8, and 12 (or ET)	Screening, Weeks 8, 16, 28, 40, 52, 64, 76, 88, and 100 (or ET)
CGI-C	Weeks 2, 4, and 8 (or ET)	Weeks 2, 8, 12, 18, and 24 (or ET)	Weeks 2, 4, 8, and 12 (or ET)	Not applicable

^a A set of 2 consecutive 24-hour PD home diaries (48 hours total) were completed during Screening and prior to each specified visit.

5.3.1 Study ADS-PAR-AM201: Extended Release Amantadine Safety and Efficacy Study in Levodopa-Induced Dyskinesia

Study Design

Trial Design, Overview, and Objective

Study 201 was a small study designed to find the optimal dose for Gocovri® in treating LID. It evaluated 3 dose levels taken by mouth once at bedtime. Secondary objectives

were to evaluate safety and tolerability, especially with regard to fatigue. In addition, steady state concentrations of amantadine were also evaluated.

Amendments to the study also reflect the tightening of study procedures for the evaluation of the patient and provide the sponsor with data concerning the final efficacy measures to be used. These were made after the study commenced. The SAP was finalized after the last participant completed the trial.

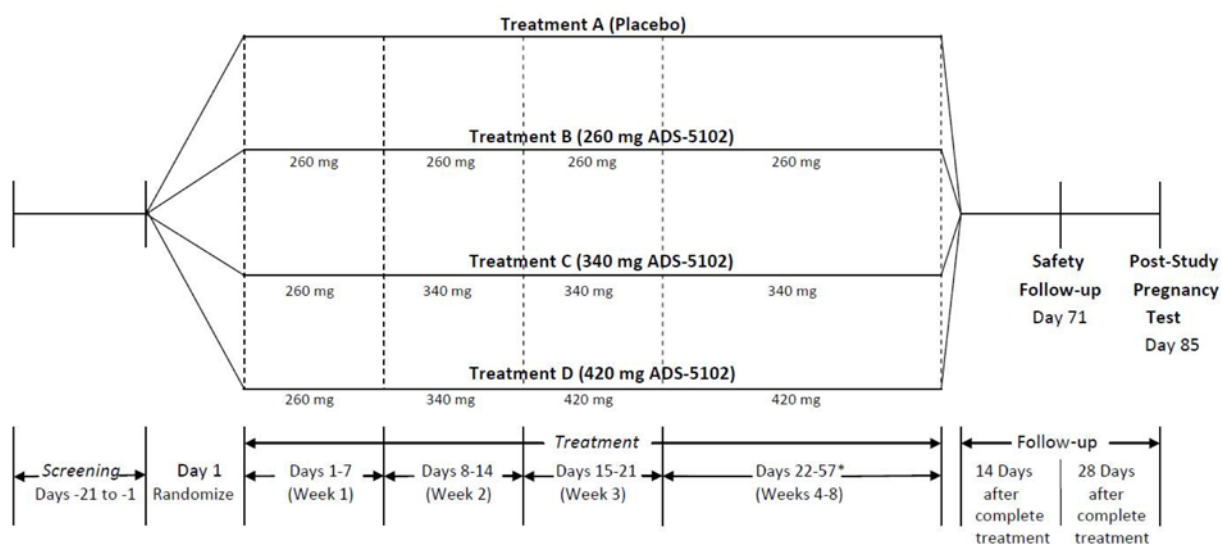
Reviewer's comment: As an 8 week study it was too short to provide substantial support of efficacy and the size of each arm was also too small to provide good support for safety. As a Phase 2 study designed to find which dose to use in Phase 3, it served well. The results of this trial also resulted in the selection of different primary and key secondary endpoints in the pivotal trials.

This is a multi-center, randomized, double-blind, placebo-controlled, 4-arm parallel group study of ADS-5102 in subjects with PD who have LID. All participants had to be on stable doses of anti-Parkinson's medications, including any levodopa preparation dosed at least three times daily, for at least 30 days prior to screening, and their current PD medications and dose regimens had to continue unchanged during the course of the study.

Consented subjects who completed screening and met study eligibility criteria were randomized in a 1:1:1:1 ratio to receive one of 4 treatments: 260 mg, 340 mg, or 420 mg of ADS-5102 or placebo once daily at bedtime. Randomization was to be stratified by the Fatigue Severity Score (FSS >4 or ≤4) at baseline to achieve balance for fatigue among treatment groups (fatigue was a key secondary outcome measure).

Patients who were assigned to placebo or 260 mg ADS-5102 received the same daily dose throughout the entire 8-week dosing period. Subjects who were randomized to 340 mg ADS-5102 or 420 mg ADS-5102 received, in double-blind fashion, escalating doses titrated in one week steps to their assigned dose.

Figure 2 Study 201 Design schematic (sponsor's protocol, p. 214)



Key Inclusion and Exclusion Criteria

Eligible patients with PD fulfilled the United Kingdom Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria. They had to have a score of at least 2 on Part IV, Item 4.2 (functional impact of dyskinesia) of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) at screening and at Day 1 (baseline). In addition, the patient, using the 48-hour PD home diaries completed just prior to Day 1 (baseline), had to have at least 2 half-hour time periods between 10 am and 4 pm of each 24-hour period recorded as "ON with troublesome dyskinesia." PD drug regimens had to be stable for 30 days prior to screening and able to remain unchanged during the study. (Antidepressant medication had to be stable for 60 days prior to entry).

Patients were excluded for prior PD-related surgical intervention, cognitive decline suggesting dementia, atypical Parkinson syndromes (e.g.: MSA, PSP, etc.), PD drug-related psychosis, Mini-Mental State Exam (MMSE) < 24, orthostatic hypotension, abnormal ECG of clinical importance, and reasons pertaining to general medical health.

Study Treatments

Dose selection had been determined by prior pharmacokinetic modeling of the product to the reference standard. All subjects were to continue their concurrent PD medication regimens without change during the study drug dosing period. Study medication was administered as 3 capsules once daily, taken at night (no earlier than 9 pm), for 8 weeks:

- Treatment A: Placebo, administered as three placebo capsules
- Treatment B: 260 mg ADS-5102, administered as two 60 mg capsules and one

140 mg capsule

- Treatment C: 340 mg ADS-5102, administered as one 60 mg capsule and two 140 mg capsules
- Assignment to Treatment 140 mg capsules
- Treatment D: 420 mg ADS-5102, administered as three 140 mg capsules

Dose escalation if needed by treatment arm was performed as follows:

Table 5 Study 201 Treatment arms and study periods (source: sponsor's protocol)

Treatment	Dosing Days 1-7 (Week 1)	Dosing Days 8-14 (Week 2)	Dosing Days 15-56 (Weeks 3-8)
A	Placebo	Placebo	Placebo
B	260 mg ADS-5102	260 mg ADS-5102	260 mg ADS-5102
C	260 mg ADS-5102	340 mg ADS-5102	340 mg ADS-5102
D	260 mg ADS-5102	340 mg ADS-5102	420 mg ADS-5102

Dose Modification and Discontinuation

No dose modification was permitted. Patients who were unable to tolerate their assigned study drug assignment were discontinued and followed for safety for 14 days following completion of treatment.

Administrative Structure

The study was conducted at 31 US clinical sites with IRB approval. The sponsor used a clinical research organization to perform study monitoring, rater training, and data management. An interactive web system was used to randomize and assign blinded treatments. Contract clinical laboratories were used to analyze blood. An electronic CRF system was used to record data.

Procedures and Schedule of Events

Figure 3 Study 201 Schedule of events (sponsor's protocol, p. 211)

	Screening	Dosing							Safety Follow-up (a)
Visit	1	2	3	4	5 (c)	6	7	8 (ET)	9 (EOS)
Day	-21 to -1	1	8 (±1)	15 (±1)	22 (±2)	29 (±1)	43 (±1)	57 (±1)	71 (±3)
Informed consent	✓								
Eligibility Criteria	✓	✓							
Demographics	✓								
Medical History	✓								
Medication History	✓	✓							
Concomitant Medications		✓	✓	✓	✓	✓	✓	✓	✓
Complete Physical Exam (d)	✓							✓	
Targeted Physical Exam (e)		✓				✓			✓
Height and Weight (f)	✓			✓				✓	
Vital Signs (g)	✓	✓	✓	✓		✓	✓	✓	✓
12-lead ECG	✓								
Hematology (h)	✓			✓				✓	
Serum Chemistry (i)	✓			✓				✓	
Urinalysis (j)	✓							✓	
Serum Pregnancy Test (if applicable)	✓	✓ (k)						✓	
MMSE	✓								
Randomization		✓							
Dispense Study Drug (blister pack)		✓	✓	✓		✓	✓		
Collect returned blister packs & assess compliance			✓	✓		✓	✓	✓	
PD Home Diary Concordance Testing	✓ (l)								
Dispense PD Home Diaries (m)	✓	✓ (n)	✓	✓		✓	✓		
Review PD Home Diaries		✓ (n)		✓		✓	✓	✓	
UDysRS		✓		✓		✓		✓	
MDS-UPDRS (all 4 Parts, unless specified otherwise)	✓ (o)	✓		✓ (p)		✓		✓	
PDQ-39		✓				✓		✓	
FSS		✓		✓		✓		✓	
CGI-C		✓ (q)		✓		✓		✓	
PK Sampling		✓ (r)	✓	✓		✓	✓	✓ (s)	
Study Drug dosing, once daily at night (Days 1 – 56)		✓						✓	
Adverse Events (t)		✓	✓	✓	✓	✓	✓	✓	✓

Treatment Compliance

Drug logs recording dispensing were maintained at each clinical site. Used and unused blister cards were counted and used to evaluate compliance.

Participant Completion, Discontinuation, or Withdrawal

Adverse event evaluation and reporting was defined by protocol. There were no predefined exit criteria for the study aside from withdrawal of consent or an adverse event requiring this.

Study Endpoints

Assessments were performed at Baseline (Day1), Day 15, Day 29, and Day 57 (or at early termination).

Primary:

Change from baseline to Week 8 in the Unified Dyskinesia Rating Scale (UDysRS) total score.

Key Secondary:

Change from baseline to Week 8 in the Fatigue Severity Scale (FSS) score

Other Secondary Measures:

Change from baseline to Week 8 in the following (in order of priority):

- Unified Parkinson's Disease Rating Scale (MDS-UPDRS), combined score (Parts I, II and III)
- Total Objective Score (III, IV) of the UDysRS
- ON time without troublesome dyskinesia (ON without dyskinesia plus ON with non-troublesome dyskinesia), based on a standardized PD home diary
- ON time with troublesome dyskinesia, based on a standardized PD home diary
- Total ON time with dyskinesia (non-troublesome and troublesome), based on a standardized PD home diary
- MDS-UPDRS, part IV, items 4.1 (time spent with dyskinesia) and 4.2 (functional impact of dyskinesia)
- MDS-UPDRS, individual part scores (I, II, III, and IV)
- Clinician's Global Impression of Change in overall PD symptoms
- Health-related Quality of Life as measured by the PDQ-39

Safety assessments included the collection of AEs, reasons for drug discontinuation, vital signs and clinical laboratory tests. Samples were also taken for pharmacokinetic analysis.

Statistical Analysis Plan

The Statistical Analysis Plan (Version 1.0) was finalized May 6, 2013.

Missing data for efficacy assessments was imputed using the Last Observation Carried Forward method. Missing data for safety measures was not subject to imputation.

In general, the primary and secondary endpoints used the same statistical analysis method. The primary efficacy variable is change from baseline in total UDysRS score at Week 8. An analysis of covariance model was used that combines the features of both regression and analysis of variance by including treatment as a factor and baseline value as a covariate for the primary efficacy variable.

Key secondary analyses, including dose-response, were performed in the following hierarchy:

- 420 mg ADS-5102 dose group vs. placebo for UDysRS
- 420 mg ADS-5102 dose group vs. placebo for FSS
- 340 mg ADS-5102 dose group vs. placebo for FSS
- 260 mg ADS-5102 dose group vs. placebo for UDysRS
- 260 mg ADS-5102 dose group vs. placebo for FSS

Reviewer's comment: The SAP was finalized 3 weeks after completion of the last enrolled patient.

Protocol Amendments

Original protocol: March 15, 2011
First patient enrolled: August 3, 2011
Last patient completed: April 15, 2013

Amendment 1: October 26, 2011

- Increased the number of clinical trial sites to 30
 - Assessments timed to occur between 9AM and 2PM to coincide with maximum drug plasma concentration.
 - Lack of previous response to amantadine for other PD symptoms is not exclusionary.
 - Documented lack of tolerance to amantadine or lack of dyskinesia response to amantadine is exclusionary.
 - Amantadine plasma level results by patient not provided to the sponsor until after the database is locked.
 - CGI should reflect the totality of the PD state.
 - SAEs will be unblinded only if medically necessary (to avoid unnecessary unblinding in anticipation of a substantial AE rate)
 - Apomorphine added to prohibited medications list.
- In response to FDA advice:
- Revised hierarchical order of secondary outcome measures
 - “On” time assessment will come from the home diary

Amendment 2: February 13, 2012

- Increased the number of clinical trial sites to 40
- Assessment window changed to 10 AM to 4 PM to allow for assessment of patients with troublesome dyskinesia later in the day.
- Duration of study increased to adjust for enrollment rate.
- If PD diaries not satisfactorily completed, patient and caregiver should be retrained and complete new diaries.

Reviewer's comment: Most of these items were protocol clarifications or procedural in nature; it is unlikely they could bias the outcome of the trial even though these were issued after its start.

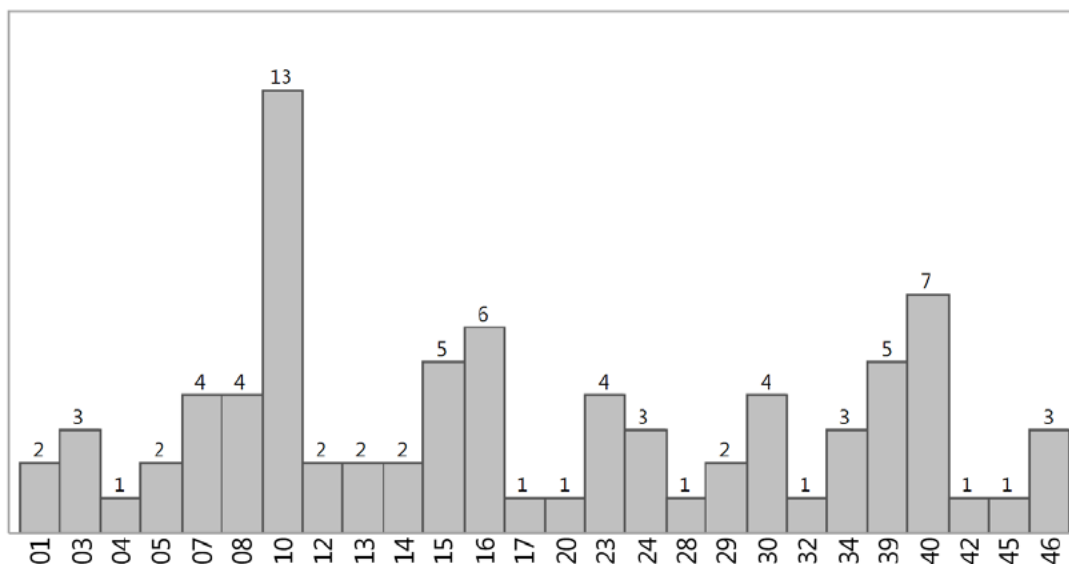
Study Results

Patient Disposition

Enrollment by site reveals that a quarter of the patients were enrolled by two sites 10 and 40. The sponsor had difficulty enrolling the study and had to expand the number of sites (including site 40) by protocol amendment. Both clinical sites are managed by

experienced PD investigators with large movement disorders practices. Site 10 (Isaacson) has been audited by FDA twice before as a large enroller with satisfactory adherence to GCP in other Phase 3 trials.

Figure 4 Study 201 Enrollment by site (source: sponsor's datasets)



The study enrolled 83 patients into the 4 treatment arms:

Table 6 Study 201 Enrollment by treatment arm

Treatment Arm								All
260 mg ADS-5102		340 mg ADS-5102		420 mg ADS-5102		PLACEBO		
N	%	N	%	N	%	N	%	
20	24.1	21	25.3	20	24.1	22	26.5	83

Their disposition was as follows:

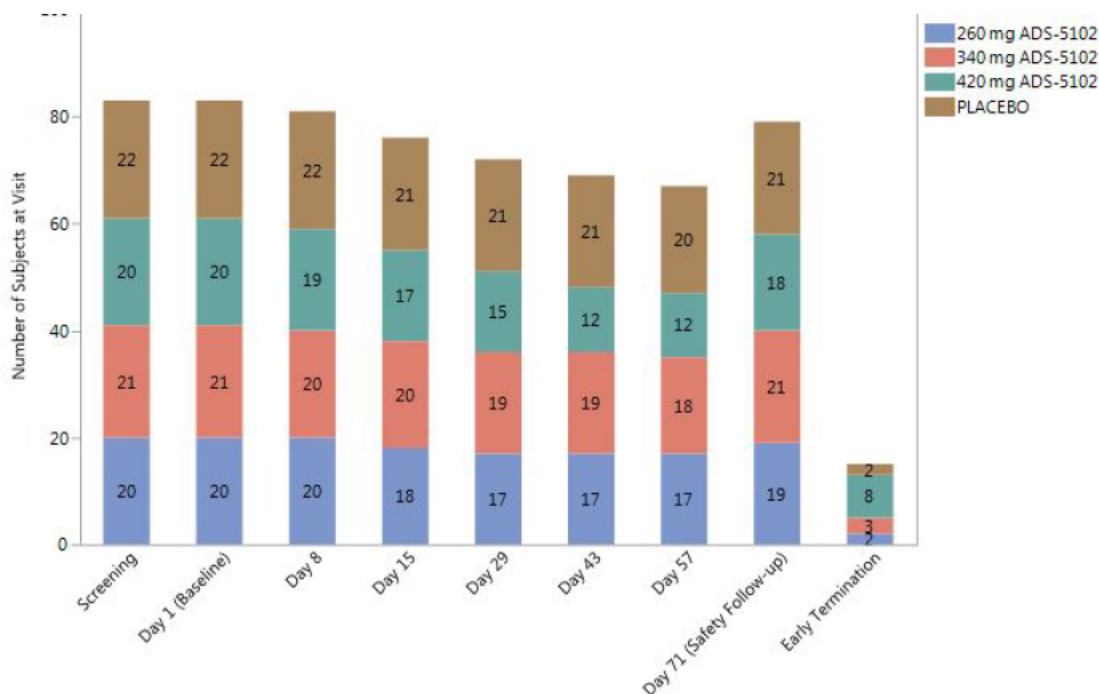
Table 7 Study 201 Disposition of patients by treatment arm (source: CSR, p 57)

Number (%) of Subjects	Placebo (N=22)	260 mg ADS-5102 (N=20)	340 mg ADS-5102 (N=21)	420 mg ADS-5102 (N=20)	All ADS-5102 (N=61)
Randomized	22 (100)	20 (100)	21 (100)	20 (100)	61 (100)
Completed the study ^a	20 (90.9)	17 (85.0)	18 (85.7)	12 (60.0)	47 (77.0)
Withdrawn from study	2 (9.1)	3 (15.0)	3 (14.3)	8 (40.0)	14 (23.0)
Reasons for withdrawal:					
eGFR < 50 mL/min/1.73 m ²	0	0	1 (4.8)	0	1 (1.6)
Intolerable/unacceptable AE	0	3 (15.0)	3 (14.3)	8 (40.0)	14 (23.0)
Other	2 (9.1)	0	0	0	0

Discontinuation:

A most patients completed the study (ADS-5102, 77%; placebo, 91%). In the placebo group, 1 subject withdrew due to a busy work schedule and an unwillingness to continue in the study and 1 subject was withdrawn by the investigator due to increased bradykinesia related to PD. Among subjects treated with ADS-5102, 14 (23.0%) were withdrawn from the study, most in the 420 mg/d dose arm. All 14 subjects had an intolerable or unacceptable AE, discussed in Section 7. In addition, 1 of these had an eGFR value < 50 mL/min/1.73 m², a pre-specified reason for discontinuation of study drug.

Figure 5 Study 201 Patients by visit by treatment arm (source: datasets)



Protocol Violations/Deviations

Deviations from the protocol were reviewed. Four patients on active treatment had violations of inclusion/exclusion criteria: 2 subjects (b) (6) 340 mg, and (b) (6) 420 mg) had insufficient troublesome dyskinesia on the baseline PD home diaries; 1 subject (b) (6) 260 mg) had orthostasis on standing from a seated position; and 1 subject (b) (6) 420 mg) had a history lymphoma that was unknown to the study site at the time the patient was enrolled.

Three patients (all treated with ADS-5102) had a major deviation involving study drug compliance. Patient (b) (6) (340 mg) had “difficulty managing study drug supplies” and did not return unused study drug. Patient (b) (6) (420 mg) was late to a scheduled visit did not have drug for several days. Patient (b) (6) (420 mg) stopped taking study drug due to an AE, and resumed 5 days later.

The remainder of the deviations did not affect study medication or safety. These were summarized by the sponsor as follows:

Table 8 Study 201 Major protocol deviations (source: sponsor's CSR, p 58)

Major Protocol Deviation Category	Placebo (N=22)	260 mg ADS-5102 (N=20)	340 mg ADS-5102 (N=21)	420 mg ADS-5102 (N=20)
No. (%) of subjects with a protocol deviation ^a	1 (4.5)	3 (15.0)	2 (9.5)	5 (25.0)
Assessments/Procedures	1 (4.5)	0	0	1 (5.0)
Concomitant Medications	0	1 (5.0)	0	0
Inclusion/Exclusion Criterion	0	1 (5.0)	1 (4.8)	2 (10.0)
Informed Consent	0	2 (10.0)	0	0
Study Drug Compliance	0	0	1 (4.8)	2 (10.0)

^a Subjects may have contributed more than 1 deviation.

Demographic Characteristics

No significant differences among the treatment arms were found with regard to underlying demographic characteristics (Table 5, below).

Table 9 Study 201 Population demographic features (source: datasets)

Study 201	ADS-5102 260 mg (N=20)		ADS-5102 340 mg (N=21)		ADS-5102 420 mg (N=20)		Placebo (N=22)		ALL (N=83)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Sex										
Male	8	40	13	61.9	10	50	14	63.6	45	54.2
Female	12	60	8	38.1	10	50	8	36.4	38	45.8
Age										
Mean years (SD)	67.5		64.6		66.4		65.5		66	
Median (years)	68		65		69		66		67	
Min, max (years)	50,80		43,80		46,80		36,84		36,84	
Age Group										
< 40 years	0	0	0	0	0	0	1	4.5	1	1.2
40 to 64 years	5	25	10	47.6	7	35	7	31.8	29	34.9
≥ 65 years	15	75	11	52.4	13	65	14	63.6	53	63.9
Race										
White	18		20		17		20		75	90.4
African American	0		1		0		1		2	2.4
Asian	0		0		3		1		4	4.8
American Native	2		0		0		0		2	2.4
Native Hawaiian	0		0		0		0		0	0
Other	0		0		0		0		0	0
Ethnicity										
Hispanic or Latino	2		0		2		1		5	6
Not Hispanic or Latino	18		21		18		21		78	94

Participants had been diagnosed with PD on average 9.5 years earlier (range 1.6 to 26.8 years). They had been on levodopa for an average of 8.1 years (range 0.8 to 26.8 years) with levodopa induced dyskinesia for 3.9 years (range 0.2 to 16.9 years). Most patients (88%) were Hoehn and Yahr Stage 2 or 3. Normal MMSE was required for participation. The average FSS score was 4.7 (range 1.0 to 7.0).

The patients as a group had concomitant medical conditions consistent with the age of the population. Over half the patients had psychiatric histories of anxiety and/ or depression.

The pharmacotherapeutic regimens in use for PD were roughly the same across the study cohorts:

Table 10 Study 201 baseline anti-PD medication in use (source: CSR, p 64)

No. (%) of Subjects Taking Antiparkinson Medication	Placebo (N=22)	260 mg ADS-5102 (N=20)	340 mg ADS-5102 (N=21)	420 mg ADS-5102 (N=20)	Total (N=83)
Levodopa (Sinemet or Stalevo)	22 (100.0)	20 (100.0)	21 (100.0)	20 (100.0)	83 (100.0)
Dopamine Agonist	14 (63.6)	14 (70.0)	10 (47.6)	16 (80.0)	54 (65.1)
MAO-B Inhibitor	14 (63.6)	11 (55.0)	12 (57.1)	12 (60.0)	49 (59.0)
COMT Inhibitor	3 (13.6)	1 (5.0)	6 (28.6)	4 (20.0)	14 (16.9)
Anticholinergic	1 (4.5)	0	0	1 (5.0)	2 (2.4)

COMT = catechol O-methyltransferase; MAO-B = monoamine oxidase B

No rescue medication use was planned for in this trial. Patients had to keep their baseline anti-PD regimen unchanged for the duration of the trial.

Compliance as predefined by the protocol was very good with the exceptions listed among the protocol deviations above.

Efficacy Results

Analyses were performed using an analysis of covariance with imputation of data as described above.

Primary Endpoint

The primary efficacy outcome was a comparison of the total UDysRS score for the three doses and placebo.

This study resulted in the choice of the 340 mg dose for the pivotal trials and demonstrated no addition benefit from the 420 mg dose which was also poorly tolerated by the patients.

Interestingly, this study correctly predicted the clinical effect on the UDysRS total score that was seen in the pivotal Phase 3 trials.

Table 11 Study 201 UDysRS total score change from baseline at Week 8 for the mITT population (source: 2.7.3 Summary of Clinical Efficacy, p 28)

	Placebo (N = 22)	260 mg ADS-5102 (N = 19)	340 mg ADS-5102 (N = 20)	420 mg ADS-5102 (N = 19)
Baseline				
Mean (SD)	39.2 (17.79)	40.2 (13.70)	44.1 (12.30)	41.2 (11.93)
Median (Min, Max)	38.0 (9, 79)	38.0 (19, 67)	42.0 (20, 72)	42.0 (19, 72)
Day 57/Week 8				
Mean (SD)	33.0 (16.35)	28.2 (18.24)	25.4 (17.22)	24.5 (12.32)
Median (Min, Max)	32.0 (10, 71)	20.0 (1, 72)	22.0 (1, 68)	24.0 (6, 53)
Change from Baseline				
Mean (SD)	-6.1 (14.08)	-12.0 (13.20)	-18.8 (10.84)	-16.7 (13.77)
Median (Min, Max)	0.0 (-44, 19)	-13.0 (-42, 12)	-17.0 (-40, -4)	-16.0 (-40, 5)
LS Mean (SE)	-6.7 (2.68)	-12.3 (2.88)	-17.9 (2.82)	-16.7 (2.88)
95% CI	(-12.0, -1.3)	(-18.0, -6.5)	(-23.6, -12.3)	(-22.4, -10.9)
Treatment Difference ^a				
LS Mean	NA	-5.6	-11.3	-10.0
95% CI	NA	(-13.4, 2.2)	(-19.1, -3.5)	(-17.8, -2.2)
P value	NA	0.1595	0.0051	0.0131

P values are based on the comparison between 260 mg ADS-5102 (and respectively 340 mg ADS-5102, 420 mg ADS-5102) vs placebo from the analysis of covariance (ANCOVA) model with change from baseline as the dependent variable, treatment group as a factor, and the baseline value as a covariate and are not adjusted for multiple comparisons. These are unadjusted P values.

^a ADS-5102 minus placebo

Efficacy Results – Secondary and other relevant endpoints

The amount of ON time without troublesome dyskinesia as quantified by the patient or caregiver on the PD Home Diary improved significantly for all test doses at Week 8 when compared to baseline and the placebo treatment arm.

Table 12 Study 201 ON Time without troublesome dyskinesia change from baseline at Week 8 for the mITT population (source: CSR, p75)

ON time without troublesome dyskinesia (hours)	Statistic	Placebo (N=22)	260 mg ADS-5102 (N=19)	340 mg ADS-5102 (N=20)	420 mg ADS-5102 (N=19)
Baseline	n	22	19	20	19
	Mean (SD)	6.9 (3.75)	6.6 (3.95)	7.7 (3.34)	9.0 (3.05)
Day 57/Week 8	n	22	19	20	19
Change from Baseline	LS Mean (SE)	0.9 (0.76)	4.1 (0.82)	3.8 (0.79)	3.6 (0.83)
	95% CI	(-0.6, 2.4)	(2.5, 5.8)	(2.3, 5.4)	(1.9, 5.2)
Treatment Difference ^a	LS Mean	—	3.3	3.0	2.7
	95% CI	—	(1.1, 5.5)	(0.8, 5.2)	(0.5, 5.0)
	p-value	—	0.0040	0.0078	0.0179

P-values are based on the comparison between 260 mg ADS-5102 (and respectively 340 mg ADS-5102, 420 mg ADS-5102) vs. Placebo from the ANCOVA model with change from baseline as the dependent variable, treatment group as a factor, and the baseline value as a covariate.

^a Active minus Placebo

There was no effect of ADS-5102 on the Fatigue Severity Scale at any dose and the 95% CI included 0 for all groups.

The MDS-UPDRS Parts I, II, and III combined score revealed no consistent change for any dose group. At 8 weeks, the Least Square mean treatment differences between the ADS-5102 treatment groups and the placebo group were 1.2 (95% CI: -7.7, 10.1; p = 0.79) for the 260 mg group, -2.2 (95% CI: -11.2, 6.9; p = 0.64) for the 340 mg group, and 1.7 (95% CI: -7.2, 10.6; p = 0.71) for the 420 mg group.

Durability and Persistence of Clinical Effect

Durability of response and persistence of effect could not be evaluated in this brief study.

Safety Results

Safety data from Study 201 is included and assessed in Section 7, the integrated review of safety for the ADS-5102 development program.

5.3.2 Study ADS-AMT-PD301: Efficacy and Safety of ADS-5102 (amantadine HCl) Extended Release Capsules for the Treatment of Levodopa Induced Dyskinesia in Parkinson's Disease Patients

5.3.3 Study ADS-AMT-PD304: ADS-5102 (amantadine HCl) Extended Release Efficacy and Safety Study in Parkinson's Disease Patients with Levodopa-Induced Dyskinesia

Study Design

Trial Design

Basic Design, Overview, and Objective

Studies 301 and 304 are multi-center, randomized, double-blind, placebo-controlled, 2-arm, parallel group studies of ADS-5102 in patients with PD who have LID. The two trials are identical in design and execution except that the duration of treatment is 25 weeks in Study 301 and 13 weeks in Study 304. These are the well-controlled trials that provide the bulk of the evidence in favor of efficacy and safety of ADS-5102.

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

Consented patients who completed screening and met study eligibility criteria were centrally randomized in a 1:1 ratio to one of 2 treatment groups: placebo or active (340 mg ADS-5102). Study medication was administered as 2 capsules once nightly at bedtime (preferably no earlier than 9 pm) for 25 weeks (Study 301) or 13 weeks (Study 304).

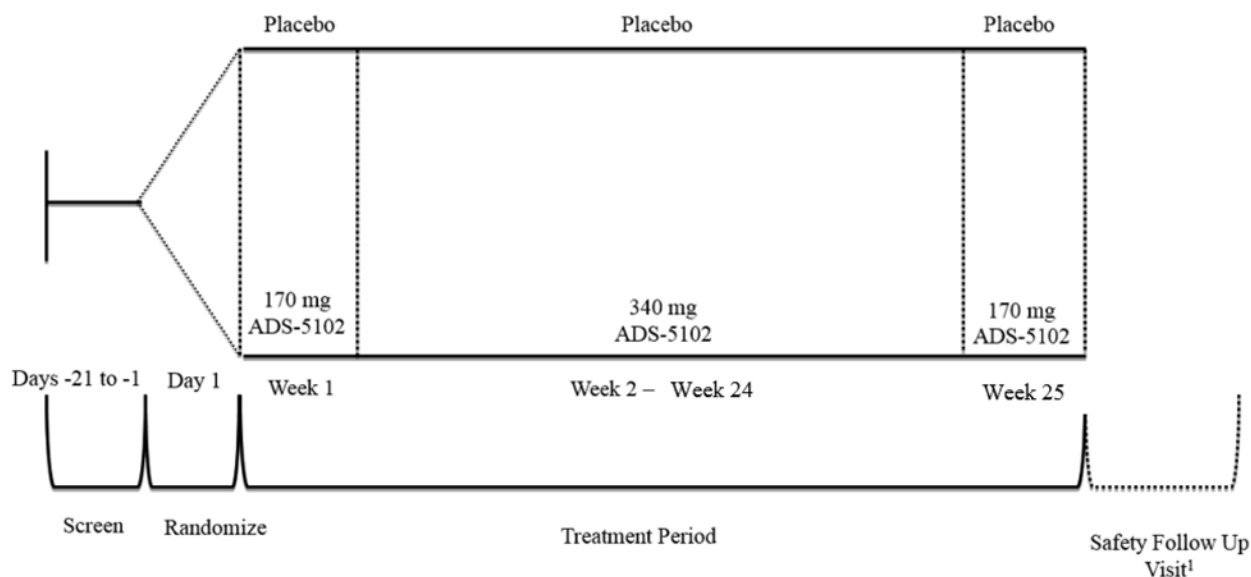
After randomization, the patient is titrated to full dose of ADS-5102 or placebo after 1 week at half dose. The last week is also reduced to half dose. (See the trial schematic below. In the case of Study 304 the treatment period is 13 weeks but the design is otherwise identical. The end-of-study safety visit was only for those participants who chose not to enter the subsequent open-label extension study.)

***Reviewer's Comment:** The study populations were enriched in the sense that a poor response to prior use of amantadine to treat LID was a reason for exclusion. Patients with a history of poor tolerability of prior amantadine use were also excluded.*

The primary outcome measure is the change from baseline to Week 12 in the Unified Dyskinesia Rating Scale (UDysRS) total score. Key secondary outcomes are: ON time without troublesome dyskinesia (ON time without dyskinesia plus ON time with non-troublesome dyskinesia), based on a standardized PD home diary; and OFF time, based on a standardized PD home diary. In addition, improvement in LID could not come at the expense of reduced "on" time or worsening the PD motor status.

For Study 301, the primary and key secondary outcomes are calculated for Week 24 as well.

Figure 6 Study 304 Design schematic (source: protocol, Appendix B)



Choice of Control Group

The control group, PD patients with LID, came from the same pool that received active drug. Participants were parsed using a predetermined randomization scheme.

Diagnostic Criteria

PD patients were diagnosed using UK Parkinson's Disease Society (UKPDS) Brain Bank Clinical Diagnostic Criteria, a standard common to most PD clinical trials.

Key Inclusion and Exclusion Criteria

Customary inclusion and exclusion criteria related to comportment and general health were described. This included the ability to give written informed consent. In addition to having PD, to qualify for enrollment the patient had to fulfill the additional criteria:

- On a stable regimen of anti-Parkinson's medications for at least 30 days prior to screening, including a levodopa preparation administered not less than three times daily, and willing to continue the same doses and regimens during study participation.
- A score of at least 2 on part IV, item 4.2 (functional impact of dyskinesia) of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS), at screening and at randomization baseline.
- Using the 48-hour PD home diaries completed just prior to baseline randomization, at least 2 half-hour time periods between 9 am to 4 pm of each 24-hour period are scored as "ON with troublesome dyskinesia."

- Any prescription or non-prescription medications and/or nutritional supplements taken regularly must have been at a stable dose and regimen for at least 30 days prior to screening.
- If taking an antidepressant, must be on a stable dose for at least 30 days prior to study entry.

Patients were excluded if their dyskinesia was not “peak dose” dyskinesia, if they had had neurosurgical intervention for PD, presence of clinically significant hallucinations or dementia (MMSE less than 24), abnormal electrocardiogram suggesting abnormal ventricular conduction, Hoehn and Yahr Stage 5 (non-ambulatory), or orthostatic hypotension at screening.

Dose Selection and Study Treatments

Dose was selected by Phase 2 dose ranging Study 201. ADS-5102 is supplied as a 170 mg capsule. The study has a one week titration and one week dose reduction of ADS-5102 170 mg nightly at the beginning and end of the study. The dose selected for efficacy and safety evaluation is ADS-5102, 340 mg nightly (two 170 mg capsules) versus matching placebo.

The study drug is packaged in (b) (4) blister cards, each containing a total of 18 capsules to allow for 9 days of dosing (2 capsules per dose, allowing 1 week supply plus 2 extra doses). The number of packages dispensed varied by the planned interval between visits.

Assignment to Treatment and Blinding

Participants are randomized on Day 1 using a centralized randomization system (Interactive Web Response System). Random assignment to treatment arms was on a 1:1 basis. Procedures allowing the unblinding of treatment assignment in the case of emergency were outlined in study procedure manual.

Dose Modification and Discontinuation

No dose modification was considered. Patients discontinuing after more than 4 weeks of drug were tapered off with dose reduction to 170 mg nightly for 1 week (unless the discontinuation was due to an AE).

Administrative Structure

The sponsor assigned a medical monitor to oversee the study. No data safety monitoring board was used. It was the study monitor's role to assess the study's performance and adherence to GCP. Electronic case report forms were used. IRBs and IECs approved the study at individual clinical sites.

Procedures and Schedule of Events

The schedule of events for Studies 301 and 304 are identical except that Study 301, having maintenance drug treatment lasting 24 weeks instead of 12 weeks, adds visits at Weeks 18 and 24 (these are identical to the Week 12 visit in both trials). The final close

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out visit occurs at Week 25 in Study 301 and Week 13 in Study 304, 1 week following a reduction of drug dose reduction to 170 mg/day.

Table 13 Study 304 Schedule of Events (Sponsor's protocol, p. 65)

	Screening	Treatment Period							Early Termination Visit (a)	Safety Follow-up (b)
Visit	1	2	3	4	5	6	7	8		9
Week		0	1	2	4	8	12	13		14
Informed consent	✓									
Eligibility Criteria	✓	✓								
Demographics	✓									
Medical History (j)	✓	✓								
Medication History	✓	✓								
Concomitant Medications		✓	✓	✓	✓	✓	✓	✓	✓	✓
Adverse Events (p)		✓	✓	✓	✓	✓	✓	✓	✓	✓
Complete Physical Exam (c)	✓						✓		✓	
Targeted Physical Exam (d)		✓			✓	✓				✓
Height and Weight (e)	✓				✓		✓		✓	
Vital Signs (f)	✓	✓	✓	✓	✓	✓	✓		✓	✓
Hematology (g)	✓				✓		✓		✓	
Serum chemistry (h)	✓				✓		✓		✓	
Urinalysis (i)	✓				✓		✓		✓	
ECG (12-lead)	✓									
Serum Pregnancy Test (if applicable)	✓						✓ (r)		✓ (q)	✓ (q)
Urine Pregnancy Test (if applicable)		✓			✓	✓				
MMSE	✓									
Randomization		✓								
PD Home Diary Concordance Testing	✓ (k)									
Dispense PD Home Diaries (l)	✓		✓	✓	✓	✓				
Review PD Home Diaries		✓ (m)		✓	✓	✓	✓		✓	
UDysRS		✓		✓	✓	✓	✓		✓ (a)	
MDS-UPDRS (all 4 Parts, unless specified otherwise)	✓ (n)	✓		✓	✓	✓	✓		✓ (a)	
CGI-C		✓ (o)		✓	✓	✓	✓		✓ (a)	
Collect returned blister packs & assess compliance			✓	✓	✓	✓	✓	✓	✓	
Dispense Study Drug (blister pack)		✓	✓	✓	✓	✓	✓			
Study Drug dosing, once nightly at bedtime		✓	✓	✓	✓	✓	✓	✓		

Dietary Instruction and Restriction

No specific dietary regimen was employed in these studies.

Concurrent Medication

Concomitant medication was not specifically addressed in the protocol beyond drugs for PD and specific contraindicated drugs. Prohibited medication (listed in an appendix) included apomorphine, topiramate, dopamine receptor antagonists, drug affecting renal clearance of amantadine, and drugs affecting the QT interval.

Treatment Compliance

Patients were instructed to return all used and unused blister cards of study drug for drug accountability purposes. Drug accountability logs were kept and this responsible staff person documented the amount of study drug received and the amount supplied and/or administered to and returned by participants.

Rescue Medication

No plan for rescue medication was specified.

Participant Completion, Discontinuation, or Withdrawal

Patients could end participation at any time. Reasons include that the patient discontinued study medication and desired to withdraw, or consent is withdrawn, or the sponsor and/or investigator decided to discontinue the patient. The reason is recorded in the case report form. Participants who withdrew are not replaced.

Specific reasons for discontinuation include: estimated glomerular filtration rate (eGFR) falls below 50 mL/min/1.73m², need to take a medication that is excluded or that may interfere with study measurements, intolerable or unacceptable AEs, or a positive pregnancy test.

Study Endpoints

Primary Endpoint

Both Study 301 and Study 304

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

Key Secondary Endpoints

Study 301:

- Change from baseline to Week 24 in the UDysRS total score.
- Change from baseline to Week 12 and change from baseline to Week 24 in each of the following:
 - ON time without troublesome dyskinesia (ON time without dyskinesia plus ON time with non-troublesome dyskinesia), based on a standardized PD home diary
 - OFF time, based on a standardized PD home diary

Study 304:

- Change from baseline to Week 12 in each of the following:
 - ON time without troublesome dyskinesia (ON time without dyskinesia plus ON time with non-troublesome dyskinesia), based on a standardized PD home diary
 - OFF time, based on a standardized PD home diary

Other Secondary Endpoints

The sponsor proposed a number of other secondary endpoints that were sub-scales or otherwise derivative of the Primary and Key Secondary endpoints above. The two exceptions to this were:

- MDS-Unified Parkinson's Disease Rating Scale
- Clinicians Global Impression of Change

The efficacy outcome assessments employed scales commonly used in movement disorders trials. All four of these were used in both trials and assessed at the visits noted below.

Table 14 Study 301 and 304 Efficacy outcome measures by trial visit

Efficacy Assessments	Trial 301	Trial 304
UDysRS	Baseline/Day1/Week 0	Baseline/Day1/Week 0
PD Home Diary	Week 2	Week 2
MDS-UPDRS	Week 8	Week 4
CGI-C	Week 12	Week 8
	Week 18	Week 12 (or end of study)
	Week 24 (or end of study)	

UDysRS

The Unified Dyskinesia Rating Scale evaluates involuntary movements associated with PD. This scale has four parts and a total possible score of 104 (higher score = worse clinical state). There are two primary sections Historical (Parts 1 and 2) and Objective (Part 3 Impairment and Part 4 Disability)

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

PD Home Diary

The diary is used to score five different conditions in 30-minute intervals:

- Asleep,
- OFF,
- ON without dyskinesia,
- ON with non-troublesome dyskinesia,
- ON with troublesome dyskinesia.

During screening, concordance testing was to be performed to evaluate the participant's ability to accurately identify various states and the presence or absence of dyskinesia at different points in time. A set of two consecutive 24-hour PD home diaries (48 hours total) were to be completed during screening period and prior to each specified visit. The consecutive 24-hour diaries are started 3 days before a visit, in case the patient's schedule makes it difficult to complete a diary during the day before a visit.

MDS-UPDRS

Movement Disorder Society-Unified Parkinson's Disease Rating Scale 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).

At screening, only Part IV, item 4.2 (severity of dyskinesia) was administered. At all other visits, Parts I – IV were assessed.

CGI-C

The Clinician Global Impression of Change is a single-item instrument assessing clinician's global impression of change in overall PD symptoms, including but not limited to LID. The CGI-C required the investigator to rate how much the patient's Parkinson's disease had improved or worsened after treatment with study medication relative to the baseline state.

Statistical Analysis Plan

The sponsor provided detailed Statistical Analysis Plans (SAPs) for both pivotal trials. The SAP for Study 301 was finalized approximately a month before the last patient completed the trial. The SAP for Study 304 was finalized one month after the last patient completed. The two SAPs word for word are virtually identical.

Reviewer's comment: Study 301 was stopped by the sponsor due to (b) (4)

“During the conduct of the study, the sponsor decided to stop the study when all randomized subjects had the opportunity to complete the Week 12 study visit and therefore contribute data to the primary efficacy analysis. The number of subjects who contributed data to the Week 24 secondary efficacy analyses was sufficient to assess the durability of effect even with the early study stop (Study 301 CSR page 26).”

The primary efficacy analysis was not changed by protocol amendment but was noted in the final SAP. The need for the sponsor to do this is unclear as Study 304 was completed as planned four months after this early termination. The loss of a sound efficacy evaluation at 24 weeks brings into question the data in support of the persistence of the therapeutic effect. (Studies suggesting tachyphylaxis to the anti-dyskinetic effect of amantadine have been published in the scientific literature). The final 12 weeks of Study 301 could have easily been completed and this would not have changed the submission date for this NDA.

This premature termination changed the statistical analysis of the primary and key secondary outcomes to the same as Study 304. According to the sponsor's last version of the SAP (Version 3.1, page 31):

“As a result of this change, two different linear MMRM models will be utilized for efficacy analyses. All Week 12 analyses of the UDysRS data and PD diary data, including the primary efficacy analysis, will now utilize models that include a categorical effect for time with three levels (Weeks 2, 8, and 12) rather than the planned five levels (Weeks 2, 8, 12, 18, and 24) described in the protocol. Other parameters of these models remain unchanged. The Week 24 analyses of the

UDysRS, PD diary, and the Week 12 and Week 24 analyses of the MDS- UPDRS data will utilize the model with five time points as described in the protocol.”

The Efficacy Population (Modified Intent-to-Treat or MITT) include all randomized participants in each study who receive drug and who have at least one post-baseline assessment of the UDysRS. The MITT population is used for the primary and secondary efficacy analyses comparing the arms to which the patients were assigned.

The Per Protocol Population (PPP) is defined as the subset of the MITT population in each study who had PD with sufficient severity of dyskinesia to enter the study (a score of at least 2 on part IV, item 4.2 of the MDS-UPDRS), had at least an hour of troublesome dyskinesia daily at study entry, completed 12 weeks of study treatment, and provided Week 12 UDysRS efficacy assessments.

Each study's Safety Population includes all patients randomized in the trial who received at least a dose of study drug.

The SAP defined the categories to describe patient disposition, protocol deviations (especially those that eliminate patients from the PPP), and the proposed subgroup analyses and other demographic and baseline descriptions of the study population. Descriptions of the categorizations of adverse events were provided (as in the study protocols).

Reviewer's comment: The sponsor's descriptions of demographics and subgroup and AE analyses closely follow GCP and available FDA guidance and ICH E6 guidelines. These are not repeated here.

Method of Efficacy Analysis for Primary and Key Secondary Outcomes

UDysRS Total Score

The total UDysRS score will be calculated as the sum of all individual subscales after the imputation algorithms (see below) for each subscale are employed. Values range from a minimum of 0 to maximum of 104. The method of analysis was specified by the sponsor (SAP, Version 3.1 page 20)

The primary efficacy analysis will compare the active (340 mg ADS-5102) group to the placebo group at Week 12 using a linear mixed model with repeated measures (MMRM), with the changes from baseline in the UDysRS total score at Weeks 2, 8, and 12 as the dependent variable. The model will include categorical effects for treatment group, visit (three levels corresponding to Weeks 2, 8, and 12), and the interaction between treatment group and visit. The baseline value of the UDysRS total score will be included as a covariate.... Estimates for the LS Means change from Baseline at Week 12 in each treatment arm along with the LS Means treatment difference will be provided with 95% confidence intervals (CIs) using an appropriate contrast from the model.

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

The sponsor also planned additional sensitivity analyses in the PPP and exploratory analyses of the data at various study visits in the MITT population.

PD Home Diary

A set of two consecutive 24-hour PD home diaries (48 hours total) were to be completed during screening and prior to each specified visit. All 24-hour diaries were to be reviewed for evaluability.

- If 4 or fewer 30-minute intervals are marked "Subject did not respond" or were missing on the eCRF, the 24-hour diary will be considered evaluable and will be included in the analysis.
- If more than four 30-minute intervals are marked "Subject did not respond" on the eCRF, the 24-hour diary will be considered un-evaluable and will not be included in the analysis.

The value for "missing intervals" of the evaluable diaries were to be imputed from the prior and subsequent intervals as described below.

All the diary parameters were to be derived in terms of hours and also in percentage of time awake:

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

The average for each of the above categories per 24 hours is determined, and this average is used for all analyses if both diaries are evaluable. If only one diary is evaluable, then it alone will be used for analyses.

The following variables are to be derived using the derived sums for the above mentioned categories:

- $\text{ON time without troublesome dyskinesia} = \text{ON without dyskinesia} + \text{ON with non-troublesome dyskinesia}$
- $\text{Total ON time with dyskinesia} = \text{ON with troublesome dyskinesia} + \text{ON with non-troublesome dyskinesia}$
- $\text{Number of Waking Hours} = 24 - \text{ASLEEP}$

Sponsor's Method for Imputation of Missing Data

UDysRS Total Score

This scale has four parts and a total possible score of 104 from 4 sections.

1. Historical Disability: On-Dyskinesia impact (Subscale Items 1 -11)
2. Historical Disability: Off-Dystonia impact (Subscale Items 12-15)
3. Objective Impairment (Subscale Items 16-22)
4. Objective Disability (Subscale Items 23-26)

Item numbers correspond to the scoring box below:

Figure 7 UDysRS Items for Score Summary

Historical	Score	Objective	Score
1. Time dyskinesia		16. Face	
2. Speech		17. Neck	
3. Chewing/Swallowing		18. Right Hand/arm/shoulder	
4. Eating tasks		19. Left Hand/arm/shoulder	
5. Dressing		20. Trunk	
6. Hygiene		21. Right foot/leg/hip	
7. Handwriting		22. Left foot/leg/hip	
8. Doing hobbies/activities		23. Communication	
9. Walking/balance		24. Drinking	
10. Public/social		25. Dressing	
11 Exciting situations		26. Ambulation (Walking)	
12 Time Off dystonia			
13. Dystonia effects on activities (not pain)			
14. Effect of Pain from dystonia			
15. Dystonia pain severity			
Historical subscore (sum)		Objective subscore (sum)	
Total UDysRS score (Historical + Objective):			

Imputation for Items 1 and 12, percent of hours with of dyskinesia: if missing, scored 0, i.e. no hours with dyskinesia.

Imputation for the other individual items is to average the non-missing items within the respective subscale.

PD Home Diary

If 4 or fewer 30 minute intervals are not available or missing, the value for a missing response interval is imputed by splitting missing interval and assign equal portions of 15 minutes to the responses of the intervals immediately preceding and following.

If a missing response interval occurs at the beginning or end of a 48- hour diary reporting period such that it does not have both preceding and subsequent completed intervals, then the 30 minutes of the missing interval will be assigned to the closest completed (non-missing) interval.

Protocol Amendments

Table 15 Study 301 and 304 conduct and amendment timeline

	Study 301 (24 week)	Study 304 (12 week)
Original protocol	2014 Mar 30	2014 Sep 24
First patient enrolled	2014 May 20	2014 Oct 23
Amendment 1	2014 June 16	2014 Dec 22
Amendment 2	2015 Mar 31	n/a
Last patient completed	2015 Nov 18	2016 Mar 10
Statistical Analysis Plan	2015 Oct 20 (Version 3.1)	2016 April 4 (Version 2.0)

Study 301

Amendment 1

- Increased clinical sites from 45 in North America to 55 worldwide
- Increased the duration of the enrollment period
- The study duration was increased from 13 weeks to 25 weeks (following DNP advice)
 - Treatment period updated from 13 weeks to 25 weeks of treatment in all sections
 - 340 mg ADS-5102 given from Week 2 through Week 24
 - Visits added: Week 18, Week 24, and Week 25 (and assessments adjusted accordingly)
 - Visits removed: Week 13
 - Visits revised: Safety follow up is now 1 week post treatment at Week 26, rather than 2 weeks post treatment at Week 15
- Transition to open label study open to those who discontinue prematurely as long as medications were unchanged.
- Exclusion criteria “lack of response” clarified to mean lack of response of LID to previous amantadine treatment or inability to tolerate amantadine.
- Updated hierarchical analysis to include: Change from Baseline at Week 24 for UDysRS Total Score, ON Time without Troublesome Dyskinesia, and OFF Time.
- Sample size adjusted based on increased dropout rate assumption.
- Outcome criteria revised:
 - o NEW: Change from baseline to Week 24 of the Unified Dyskinesia Rating Scale (UDysRS) total score.
 - o REVISED: Change from baseline to Week 12 & change from baseline to Week 24 in each of the following:
 - ON time without troublesome dyskinesia (ON time without dyskinesia plus ON time with non-troublesome dyskinesia), based on a standardized PD

home diary OFF time, based on a standardized PD home diary

- o REVISED: Change from baseline to Week 12 & change from baseline to Week 24 in each of the following:
 - ON time with troublesome dyskinesia, based on a standardized PD home diary
 - Total time with dyskinesia (non-troublesome and troublesome), based on a standardized PD home diary
 - Unified Parkinson's Disease Rating Scale (MDS-UPDRS), Part IV, Part IV, item 4.1 (time spent with dyskinesia), and item 4.2 (functional impact of dyskinesia)
 - UDysRS Total Objective Score (Parts III and IV)
 - Unified Parkinson's Disease Rating Scale (MDS-UPDRS), individual and combined scores (Parts I, II, III)
 - Clinician's Global Impression of Change in overall PD symptoms, determined by a question completed by the investigator

Amendment 2

Protocol clarifications of some exclusion criteria and adding a list of prohibited drugs that prolong the QT interval.

Study 304

Amendment 1

Protocol clarifications of study procedures, some exclusion criteria, and adding a list of prohibited drugs that prolong the QT interval.

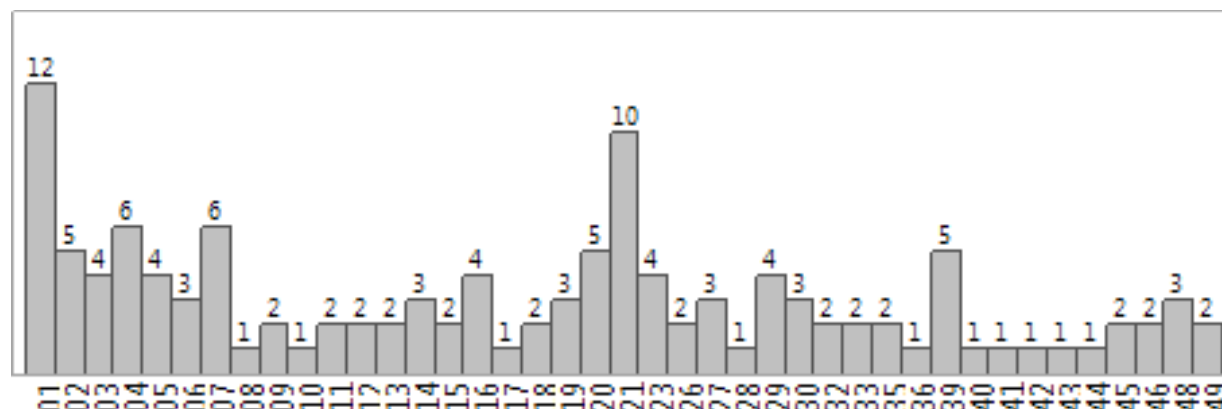
Reviewer's comment: The substantive Amendment 1 for Study 301 was created in response to advice from DNP. Because this was done in the first month of the trial it is unlikely to have altered the integrity of the trial. The protocol for Study 304, having commenced six months after Study 301 also included these modifications without the need for protocol amendment.

Study Results

Patient Disposition

In **Study 301**, patients were screened at 44 clinical sites and randomized at 41 sites (all US except for 1 trial site). The clinical sites randomized 126 patients, 63 in each treatment arm. Three patients randomized to placebo left the study before receiving drug.

Figure 8 Study 301 Enrollments (Safety Population) by Site ID (source: datasets)



In **Study 304**, patients were screened at 39 clinical sites and randomized at 32 sites (US, 11 sites; Germany, 8 sites; France, 7 sites; Spain, 4 sites; Austria, 2 sites). The clinical sites randomized 77 patients, 39 assigned to placebo and 38 to ADS-5102. Two patients who should not have been randomized were removed from the trial, one in each treatment arm. US study sites 1, 2, 4, and 21 participated in both studies.

Figure 9 Study 304 Enrollments (Safety Population) by Site ID (source: datasets)

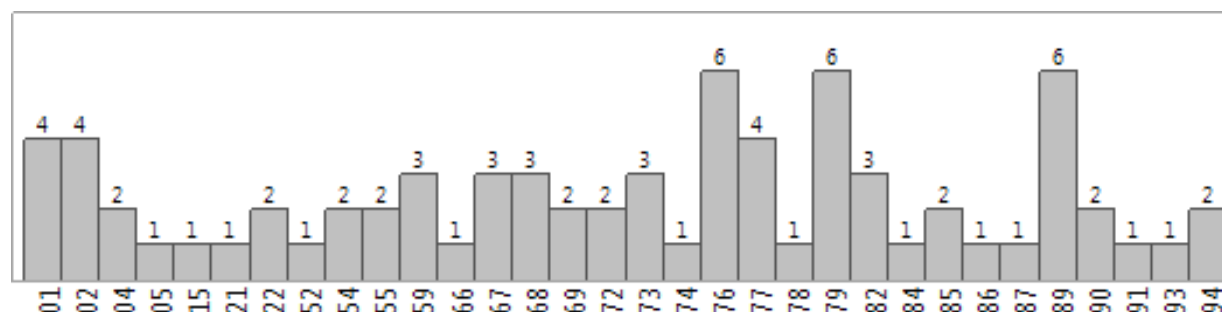


Table 16 Studies 301 and 304 Analysis Populations (source: datasets and CSR)

	Study 301			Study 304		
N (%)	Placebo	ADS-5102	Total	Placebo	ADS-5102	Total
All Randomized	63	63	126	39	38	77
Safety Population	60	63	123	38	37	75
MITT Population	58 (92%)	63 (100%)	121	38 (97%)	37 (97%)	75
PP Population	51 (81%)	47 (75%)	98	32 (82%)	25 (66%)	57

Enrollment and Disposition

The analysis populations for these studies were the result of the following disposition of

all patients screened for both trials. Participants who left the studies (discontinued) are discussed further below.

Figure 10 Study 301 Patient disposition (source: CSR, p. 54)

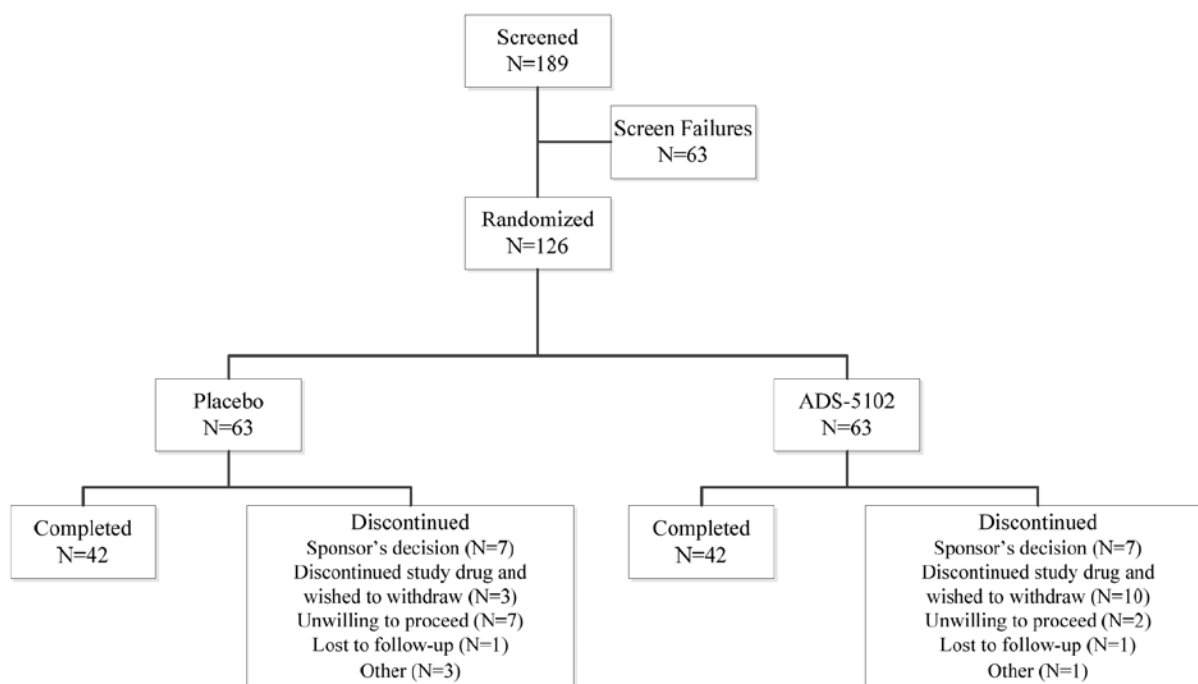


Figure 11 Study 304 Patient disposition (source: CSR p. 54)

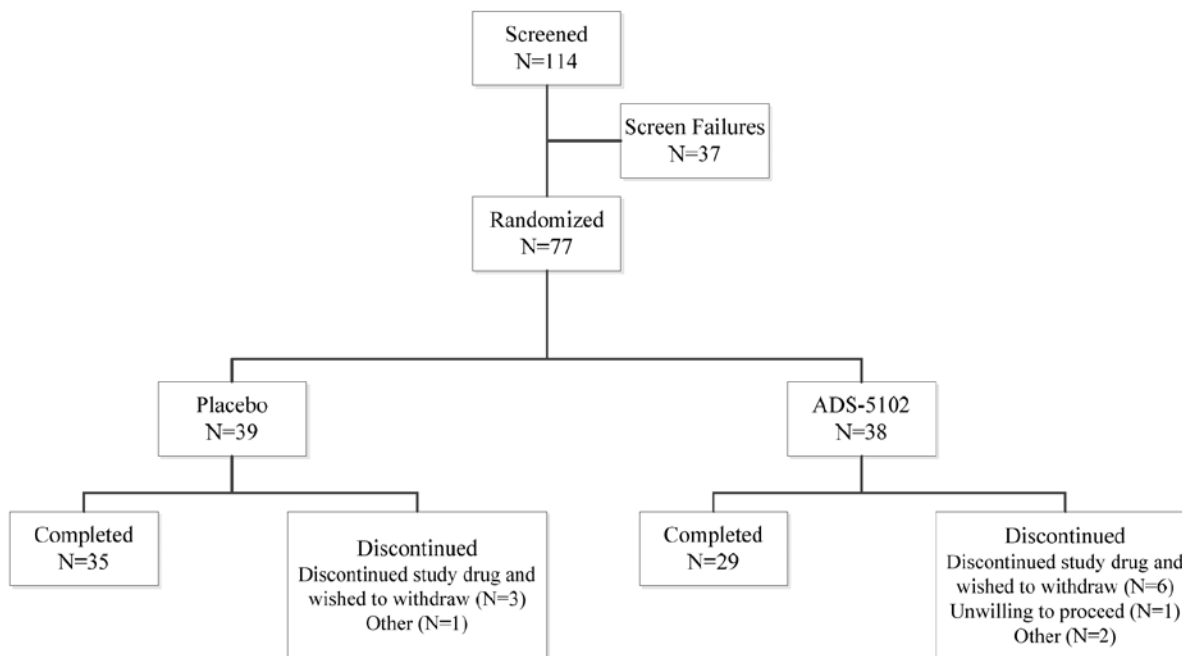
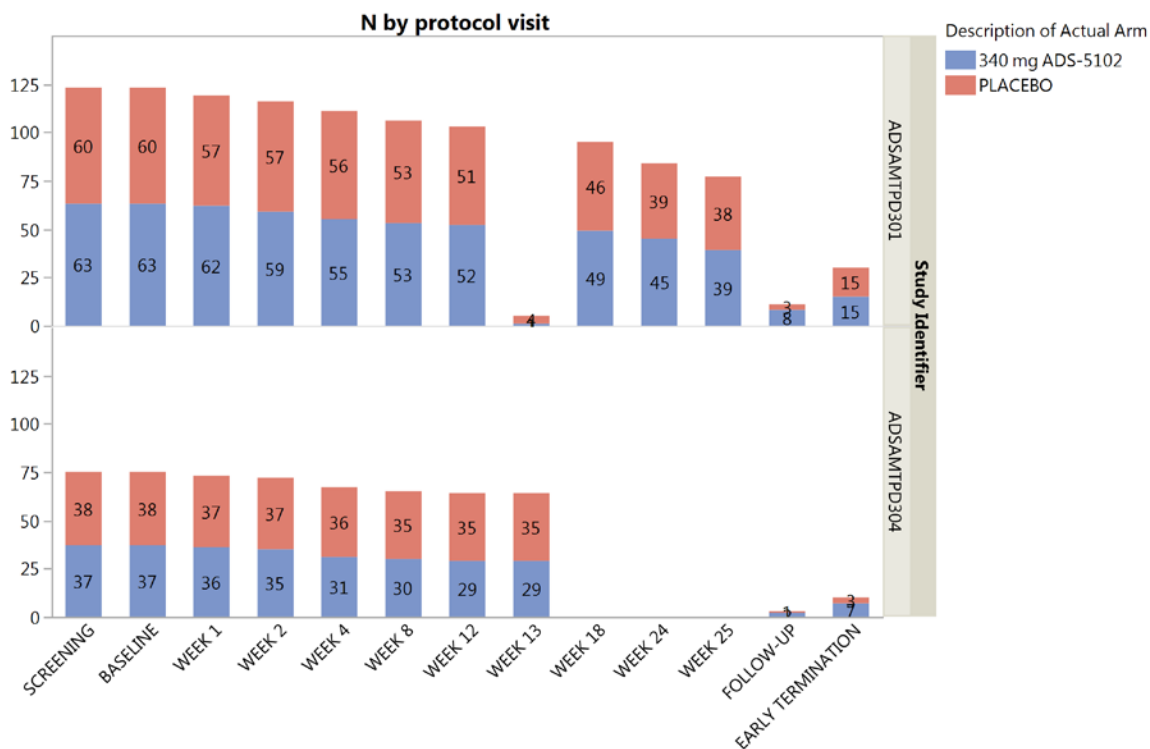


Figure 12 Studies 301 and 304: N reaching each study visit (source: datasets)



In both studies, there were more dropouts in the active treatment arms. The numbers of early termination visits is lower than the number of study discontinuations, suggesting that most dropouts occurred at a regular protocol visit rather than requiring a special visit for evaluation. In Study 301, the number of patients leaving the study after week 12 is artificially higher due to the sponsor terminating that study once the last randomized participant reached the week 12 visit.

Table of Demographic Characteristics

The demographics of the trial populations are fairly uniform between the two pivotal studies. (PD is a disease of middle age that occurs more often in males; the race and ethnic distribution are characteristic of studies in this population.) While there appears to be an imbalance in active drug versus placebo distribution in US and Europe, the overall number in each treatment arm is well balanced in Study 304. This is likely an artifact of the order in which patients were enrolled and assigned to arms by the electronic system.

Table 17 Study 301 and 304 combined demographic analysis (source: datasets)

	Study 301 (N=123)				Study 304 (N=75)				Combined Studies (N=198)			
	ADS-5102 (N=63)		Placebo (N=60)		ADS-5102 (N=37)		Placebo (N=38)		ADS-5102 (N=100)		Placebo (N=98)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Sex												
Male	35	55.6	37	61.7	19	51.4	20	52.6	54	54	57	58.2
Female	28	44.4	23	38.3	18	48.6	18	47.4	46	46	41	41.8
Age												
Mean years (SD)	64		66		65		65		65		64	
Median (years)	64		66		66		65		65		66	
Min, max (years)	34,81		43,82		46,80		42,79		34,81		42,82	
Age Group												
< 40 years	1	1.6	0	0	0	0	0	0	1	1	0	0
40 to 64 years	31	49.2	27	45	16	43.2	15	39.5	47	47	42	42.9
≥ 65 years	31	49.2	33	55	21	56.8	23	60.5	52	52	56	57.1
≥ 75 years	7	11.1	11	18.3	8	21.6	5	13.2	15	15	16	16.3
Race												
White	60		53		36		38		96	96	91	92.9
African American	0		1		0		0		0	0	1	1
Asian	2		3		0		0		2	2	3	3.1
American Native	0		0		0		0		0	0	0	0
Native Hawaiian	1		0		0		0		1	1	0	0
Other	0		3		1		0		1	11	3	3.1
Ethnicity												

Clinical Review
Kenneth Bergmann, MD
NDA 208944
ADS-5102 (Amantadine ER)

Hispanic or Latino	3		9		5		0		8	8	9	9.2
Not Hispanic or Latino	60		51		32		38		92	92	89	90.8
Region												
North America	63		60		15		8		78	78	68	69.4
Europe	0		0		22		30		22	22	30	30.6

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Disease Characteristics:

In order to better judge the efficacy response and side effect profiles, the populations of Studies 301 and 304 were compared with regard to their baseline illness. This is summarized in the following table derived from the sponsors' ISS and ISE datasets.

Table 18 Study 301 and 304 baseline disease characteristics (source: datasets)

	Study 301 (N=123)				Study 304 (N=75)			
* difference between studies - see text	ADS-5102 (N=63)		Placebo (N=60)		ADS-5102 (N=37)		Placebo (N=38)	
	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)
Age at PD Diagnosis (years)	54.9	52.7 - 57.3	57.3	54.9-59.6	54.9	51.8-58.0	54.9	51.8-58.0
Duration of PD (years)*	9.5	8.4-10.5	8.8	7.8-9.9	10.4	8.8-11.9	10.7	9.2-12.2
Baseline MMSE score	28.7	28.3-29.0	28.7	28.4-29.1	29.1	28.6-29.6	28.7	28.2-29.1
Baseline MDS-UPDRS Part 3 (motor score)*	25.9	22.6-29.2	24.6	21.2-28.0	21.2	18.0-24.4	21.4	18.3-24.6
Age at start of levodopa treatment (years)	56.6	54.3-58.8	58.8	57.0-61.6	57.6	54.5-60.8	57.1	54.0-60.2
Duration of levodopa treatment (years)*	7.8	6.9-8.7	6.8	5.9-7.7	7.7	6.2-9.2	8.5	7.1-10.0
Duration of LID (years)	4	3.3-4.7	3.2	2.5-3.9	3.8	2.8-4.7	4	3.0-4.9
Baseline UDysRS score	40.9	37.8-44.0	38.2	35.0-41.3	40.2	36.4-44.1	41.2	37.4-45.0

While the two study populations are roughly equivalent, especially with regard to baseline severity of dyskinesia, analysis of variance revealed that disease duration, severity of PD motor dysfunction, and duration of levodopa treatment differed to a small but statistically significant degree between the studies. By small measure, Study 301 patients had PD disease for a shorter time but with greater motor dysfunction. As is described below the studies had differences in the number of AEs reported and it is unknown if this could have had some influence upon that. The difference in duration of levodopa treatment was driven by the placebo groups and the active treatment arms were identical in length of prior treatment.

Levodopa doses were roughly equivalent between the studies and by protocol did not change over the course of the trials. The sponsor provided a listing of all anti-Parkinson drugs taken by the study participants (next two tables) but did not address how they were used in combination or how they may have affected the efficacy outcome or adverse events.

Table 19 Study 301 Concomitant anti-PD medication (source: CSR)

Table 14: Summary of Concomitant Antiparkinson Medication Usage (Safety Population)

No. (%) of Subjects Taking Antiparkinson Medication	Placebo (N=60)	340 mg ADS-5102 (N=63)	Total (N=123)
Levodopa (Sinemet or Stalevo)	60 (100.0)	63 (100.0)	123 (100.0)
Dopamine Agonists	34 (56.7)	29 (46.0)	63 (51.2)
MAO Inhibitors	24 (40.0)	26 (41.3)	50 (40.7)
COMT Inhibitors	9 (15.0)	7 (11.1)	16 (13.0)
Anticholinergics	3 (5.0)	2 (3.2)	5 (4.1)

COMT = catechol O-methyltransferase; MAO = monoamine oxidase

Source: Study ADS-AMT-PD301, [Table 14.1.10.1](#)

Table 20 Study 304 Concomitant anti-PD medication (source: CSR)

Table 14: Summary of Concomitant Antiparkinson Medication Usage (Safety Population)

No. (%) of Subjects Taking Antiparkinson Medication	Placebo (N=38)	340 mg ADS-5102 (N=37)	Total (N=75)
Levodopa	38 (100.0)	37 (100.0)	75 (100.0)
Dopamine Agonists	25 (65.8)	21 (56.8)	46 (61.3)
MAO Inhibitors	20 (52.6)	17 (45.9)	37 (49.3)
COMT Inhibitors	1 (2.6)	3 (8.1)	4 (5.3)
Anticholinergics	2 (5.3)	0	2 (2.7)

COMT = catechol O-methyltransferase; MAO = monoamine oxidase

Source: Study ADS-AMT-PD304, [Table 14.1.10.1](#)

Combination anti-Parkinson regimens have the potential to increase adverse treatment related events. The numbers of patients by trial and treatment arm were calculated using the sponsors' concomitant medication and demographic ADaM datasets. These combinations are further addressed in the discussion of adverse events.

Table 21 Anti-PD medications by study and treatment (source: sponsor's datasets)

	Actual Arm	PD Treatment			
		LD only	LD + DA	LD + MAOI	LD + DA + MAOI
Study 301	ADS-5102	24	13	14	12
	Placebo	21	15	10	14
Study 304	ADS-5102	11	9	5	12
	Placebo	7	10	7	14

(LD, levodopa; DA, dopamine agonist; MAOI, MAO-B inhibitor. Two patients also were taking LD with a COMT inhibitor. This was counted as LD.)

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

No rescue medication use was specified in the process for Study 301 and 304. The introduction of any PD medication or change in treatment regimen could easily alter the degree to which LID occurs as well as its effect upon the patient's function. For this reason, by protocol, anti-PD drug regimens had to remain stable for the duration of the study. Compliance as determined by monitoring was excellent in both studies. There were 11 events that rose to the level of protocol deviation in the two studies. These are discussed below.

In Study 301, 2 patients in the ADS-5102 group with a concomitant medication deviation (Patients Nos. (b) (6) and (b) (6)) both changed their carbidopa/levodopa dose during the study; the dose was changed on Day 84 for Subject No. (b) (6) due to pharmacy error, and the dose was changed on Day 21 for Subject No. (b) (6) due to an SAE for which the subject discontinued study treatment.

In Study 304, a protocol deviation was reported for patient No. (b) (6) in the ADS-5102 group. The subject had reduced their carbidopa/levodopa dose on Day 3 of the study and discontinued from the study approximately 10 days later due to an AE.

The range of medical conditions and their respective pharmacological treatments in the two studies are usual for a population of this size and demographic.

Protocol Violations/Deviations

The sponsor reported the following classes of "significant" protocol violations (PV) for Studies 301 and 304. The determination of "significant" was not described for either study but examples were given of deviations related to entry criteria, dosing, prohibited concomitant medications, and unblinding. Protocol violations were not collected in the eCRF but determined through another unspecified process.

Table 22 Study 301 Significant protocol violations (Source: CSR, p. 56)

Protocol Deviation Category	Placebo (N=63) n (%)	340 mg ADS-5102 (N=63) n (%)	All (N=126) n (%)
Study procedures/assessments	8 (12.7)	7 (11.1)	15 (11.9)
Study treatment compliance	5 (7.9)	5 (7.9)	10 (7.9)
Inclusion/exclusion criterion	4 (6.3)	3 (4.8)	7 (5.6)
Concomitant medication	1 (1.6)	3 (4.8)	4 (3.2)
Informed consent	1 (1.6)	2 (3.2)	3 (2.4)

Source: Study ADS-AMT-PD301, [Listing 16.2.1.2](#)

Table 23 Study 304 Significant protocol violations (Source: CSR, p. 56)

Protocol Deviation Category	Placebo (N=39) n (%)	340 mg ADS-5102 (N=38) n (%)	All (N=77) n (%)
Inclusion/exclusion criterion	9 (23.1)	6 (15.8)	15 (19.5)
Study procedures/assessments	2 (5.1)	4 (10.5)	6 (7.8)
Study treatment compliance	1 (2.6)	0	1 (1.3)
Concomitant medication	0	1 (2.6)	1 (1.3)

Source: Study ADS-AMT-PD304, [Listing 16.2.1.2](#)

Because of the vagueness of defining deviations, analyses were performed using the DV (and DM) domain datasets for both studies. The following table lists all PV for both Study 301 and 304.

Table 24 Study 301 and 304 protocol deviations (source: sponsor datasets)

Protocol Violation Category	Study 301				Study 304			
	ADS-5102		Placebo		ADS-5102		Placebo	
	Count	%	Count	%	Count	%	Count	%
Concomitant Medication	12	6.7%	7	4.0%	1	1.4%	3	3.0%
Inclusion/exclusion criterion	6	3.4%	7	4.0%	18	27.7%	28	28.0%
Informed Consent Process / Timing	5	2.8%	9	5.2%	0	0.0%	1	1.0%
Inv Oversight	14	7.9%	12	6.9%	3	4.1%	2	2.0%
Inv Record Keeping Source Docs	2	1.1%	3	1.7%	11	15.1%	2	2.0%
Study Procedures/Assessments	65	36.5%	56	32.4%	31	42.5%	37	37.0%
Study Treatment Admin/Dispensing	9	5.1%	9	5.2%	0	0.0%	5	5.0%
Study Treatment Compliance	28	15.7%	33	19.1%	3	4.1%	6	6.0%
Visit Scheduling	30	16.9%	34	19.7%	4	5.5%	14	14.0%
Other GCP Deviation	5	2.8%	3	1.7%	0	0.0%	1	1.0%
Other Protocol Deviation	1	0.6%	0	0.0%	1	1.4%	0	0.0%
Inv Safety Rptg (Reg/Sponsor)	1	0.6%	0	0.0%	0	0.0%	0	0.0%
Data Privacy	0	0.0%	0	0.0%	1	1.4%	1	1.0%
Total	178	100.0%	173	100.0%	73	100.0%	100	100.0%

In Study 301, 351 deviations occurred in 96 patients (ADS-5102 = 47, PBO = 49). In Study 304, 173 deviations occurred in 57 patients (ADS-5102 = 28, PBO = 29). They appear to be randomly distributed between treatment arms in both studies. The differences in type of protocol violation by region are notable, though no national differences are noted among the European sites in Study 304. Notably, only one PV had to do with safety reporting.

European sites had more protocol deviations related to inclusion and exclusion criteria, with North American sites having more deviations related to treatment compliance and study procedures and assessments. The remaining PVs do not have a potential to materially affect the study either in severity or frequency. For example, while medication compliance appeared to be problematic, much of this was due to occasional dropped or skipped pills, failure to return packaging, and so forth. By pre-specified non-compliance criteria, across both trials only three patients crossed that threshold.

On review of violations of inclusion and exclusion criteria for 35 patients, most were inconsequential (out of visit window items, mistakes in using the electronic CRF, omitted laboratory review). Of note, however, 4 patients were taking prohibited medications, (including 2 on amantadine near the baseline visit) and, according to the home PD diaries, nine patients did not have sufficient periods of qualifying ON time with troublesome dyskinesia. However, including these patients in the outcome analysis would not likely result in a Type 1 error or falsely increase degree of effectiveness.

Table 25 Study 301 and 304 Patients violating inclusion criteria: insufficient LID by PD diary (source: sponsor's datasets)

Protocol Violation: "ON time with troublesome dyskinesia" (IC#9)			
USUBJID	Arm	Site	Country
Study 301			
(b) (6)	340 mg ADS-5102	26	USA
	340 mg ADS-5102	48	CAN
	340 mg ADS-5102	22	USA
	340 mg ADS-5102	22	USA
	PLACEBO	74	DEU
	340 mg ADS-5102	76	DEU
	PLACEBO	76	DEU
	PLACEBO	86	FRA
	PLACEBO	94	FRA

On review of PVs related to study assessments, 189 deviations occurred in 90 patients. Again, most were randomly occurring and in a variety of areas such as laboratory procedures (especially urine samples) and out of window visits. A few were related to error in data related to secondary assessment (UPDRS, CGI) data unrelated to the efficacy outcome.

Because PD home diaries are the basis of the efficacy outcome, all violations (69 in 43 patients), were reviewed. Most had to do with elements that, due to their randomness, would not falsely tilt the outcome to effectiveness. These include errors in training, missing or errors in assessments at visits not used in outcome analysis, i.e. not at baseline or 12 weeks. However, 11 patients did have missing diaries either prior to early termination or the Week 12 assessment. These would have resulted in imputation of data for the primary outcome in these patients. An additional patient had one of two baseline diaries missing. These patients are listed in the table below. Given the small number and their occurrence in both treatment arms, they are unlikely to have had an effect on the outcome of the studies.

Table 26 Study 301 and 304 Patients with missing home diaries at final visit (source: sponsor's datasets)

USUBJID	Arm	Home diaries not completed prior to:	Site	Country
Study 301 (b) (6)				
	PLACEBO	Week 2 visit	4	USA
	340 mg ADS-5102	Week 12 visit	19	USA
	PLACEBO	Early Termination visit	29	USA
	340 mg ADS-5102	Early Termination visit	29	USA
	340 mg ADS-5102	Early Termination visit	30	USA
	340 mg ADS-5102	Week 12 visit	35	USA
	PLACEBO	Early Termination visit	39	USA
	340 mg ADS-5102	Early Termination visit	43	USA
	PLACEBO	Early Termination visit	48	CAN
	340 mg ADS-5102	Early Termination visit	4	USA
	PLACEBO	Early Termination visit	94	FRA
	340 mg ADS-5102	Early Termination visit	94	FRA

Efficacy Results

Primary and Key Secondary Endpoints

Studies 301 and 304 were equivalent in design and study population. To ease comparison, the results are presented together. The sponsor performed both individual study and pooled study analyses for both the UDysRS and PD home diary for ON time. The pooled analyses are used here.

Reviewer's note: In Study 301, the rates of missing observations at Week 12 were 15.9% and 10.3% for the 340 mg ADS-5102 group and placebo group, respectively. In Study 304, the rates of missing observations at Week 12 were 21.6% and 7.9% for the 340 mg ADS-5102 group and placebo group, respectively.

Table 27 Studies 301 and 304 Primary and key secondary change from baseline at 12 weeks (source: modified from 2.7.3 Summary of Clinical Efficacy and CSRs)

12 Weeks	mITT population	Primary: UDysRS change from baseline at 12 weeks	Key Secondary: On-time with non-troublesome dyskinesia (change from baseline)
Study 301	Placebo (N=58)	-7.2	0.82 h
	340 mg (N=63)	-17.1	3.56 h
Study 304	Placebo (N=38)	-7.1	2.05 h
	340 mg (N=37)	-21	3.95 h

UDysRS (pooled)

In combined analysis at Week 12, the Least Square mean change from baseline in UDysRS total score was -7.6 for the placebo group and -17.7 for the ADS-5102 group. Patients in the ADS-5102 group had a greater and statistically significant greater reduction in UDysRS total score (improved dyskinesia) than patients in the placebo group. The LS mean treatment difference was -10.1 (95% CI: -13.8, -6.5; $P < 0.0001$).

PD Home Diary (pooled)

At baseline, the mean duration of ON time without troublesome dyskinesia (ON without dyskinesia + ON with non-troublesome dyskinesia), as reported by patients in their PD diaries, was 8.12 hours for the placebo group and 8.48 hours for the ADS-5102 group. At Week 12, the LS mean ON time without troublesome dyskinesia increased from baseline by 1.37 hours in the placebo group versus 3.80 hours in the ADS-5102 group. The LS mean treatment difference was 2.42 hours (95% CI: 1.48, 3.37; $P < 0.0001$).

***Reviewer's comment:** This reviewer did not perform analyses to confirm the efficacy findings submitted to support this application. The Division of Biometrics I statistical reviewer has comprehensively reviewed the datasets, clinical study reports, and the efficacy outcomes. As reported in his Statistical Review and Evaluation, the results for the primary and key secondary efficacy outcome measures provided by the sponsor for the pivotal studies are acceptable and reproducible.*

Efficacy Results – Other secondary endpoints

Clinical Global Impression of Change

Investigators were asked to assess changes from baseline in the subject's clinical status related to overall PD, including but not limited to LID. The results after 12 weeks are in the table below.

Table 28 Studies 301 and 304 Clinical Global Impression of Change at 12 weeks
(source: modified from SCE, p 72)

Response	Phase 3 Efficacy ADS-AMT-PD301		Phase 3 Efficacy ADS-AMT-PD304	
	Placebo (N = 58) n (%)	340 mg ADS-5102 (N = 63) n (%)	Placebo (N = 38) n (%)	340 mg ADS-5102 (N = 37) n (%)
Marked improvement	2 (3.4)	18 (28.6)	0	10 (27.0)
Moderate improvement	9 (15.5)	20 (31.7)	4 (10.5)	9 (24.3)
Minimal improvement	10 (17.2)	13 (20.6)	11 (28.9)	6 (16.2)
No change	25 (43.1)	9 (14.3)	15 (39.5)	8 (21.6)
Minimal worsening	10 (17.2)	2 (3.2)	7 (18.4)	2 (5.4)
Moderate worsening	2 (3.4)	0	1 (2.6)	2 (5.4)
Marked worsening	0	1 (1.6)	0	0

In order to demonstrate movement in the CGIC more clearly, I grouped those with marked or moderate change to differentiate them from those with minimal or no change at 12 weeks.

CGIC at 12 Weeks	Study 301		Study 304	
mITT Population	Placebo (N=58)	340 mg (N=63)	Placebo (N=38)	340 mg (N=37)
Marked or Moderate improvement	11 (19%)	38 (60.3%)	4 (10.5%)	19 (51.4%)
Minimal improvement; No change; Minimal worsening	45 (77.6%)	24 (38.1%)	33 (89.2%)	16 (43.2%)
Marked or Moderate Worsening	2 (3.4%)	1 (1.6%)	1 (2.6%)	2 (5.4%)

In the sponsor's pooled analysis, improvement was defined by combining any positive change in the patient (i.e. minimal, moderate, and marked improvement). After 12 weeks of treatment, 36 patients (37.5%) in the placebo group and 76 patients (76.0%) in the ADS-5102 group were considered by the investigator as showing any improvement in PD symptoms relative to the baseline assessment. Using a more conventional categorization of improvement, 15 patients (15.6%) in the placebo group and 57 patients (57.0%) in the ADS-5102 group showed moderate to marked improvement. In both cases, the difference between the treatment groups was nominally significant using a categorical analysis (Cochran-Mantel-Haenszel test).

MDS-UPDRS

As was discussed above, individual items from this PD rating scale are not useful to evaluate dyskinesia and the sponsor's analysis of a single item to evaluate dyskinesia was not considered in this review. However the combined UPDRS score from Parts 1, 2, and 3 encompassing activities of daily living and a rated motor exam have accepted value as an outcome instrument.

The sponsor reports that in Study 301, there were no significant treatment differences between the ADS-5102 group and the placebo group for changes from baseline in MDS-UPDRS Parts 1, 3, and 3 combined score at Weeks 12 (and at weeks 8 and 24 as well). The Least Square mean treatment difference was -1.1 (95% CI: -6.6, 4.3; $P = 0.6833$) at Week 12. In Study 304, the LS mean treatment difference was -6.5 (95% CI: -12.7, -0.3; $P = 0.0398$) at Week 12.

It is likely that the small size of these studies did not have sufficient power to detect a difference of the magnitude expected over the time course of these studies (a few points).

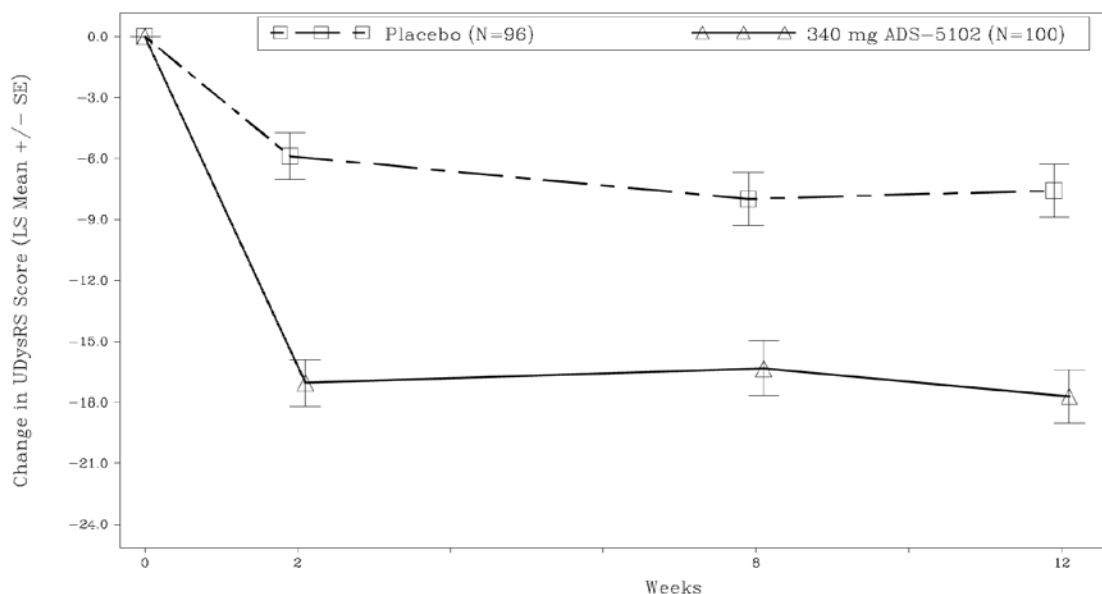
Dose Response

Starting with a forced titration of 170 mg lasting 1 week, all patients in the active arms of these trials were treated with 340 mg ADS-5102. No dose response analysis was performed.

Durability of Response and Persistence of Effect

The sponsor evaluated the primary outcome at visits throughout the pivotal studies.

Figure 13 Studies 301 and 304 pooled mITT population UDysRS score through week 12 (source: ISE p 86)



This was reproduced by the statistical reviewer for each study individually and the effect of ADS-5102 appeared to be sustained over the study period.

Study 301 did have some patients participate in treatment out to week 24 but the trial was stopped when the last enrolled patient reached 12 weeks. As a result, a smaller number of patients reached that milestone: ADS-5102, 39/63 (62%); placebo 38/60 (63%). Despite this the sponsor performed a statistical test using the mITT population and the same methodology as used at the 12 week analysis. Because of the imputation rules for missing data, the remainder of UDysRS results was carried forward from the last prior visit; the rates of missing observations at Week 24 were 33.3% and 36.2% for the 340 mg ADS-5102 group and placebo group, respectively. It is not surprising then that the sponsor's result at 24 weeks is quite similar to that at 12 weeks. (The reader will recall the considerable number of dropouts even by the 12 Week visit). The same is true of the sponsor's evaluation of ON-time without troublesome dyskinesia.

The sponsor performed analyses using the Per Protocol Population but these were not adequate to test the validity of the imputation method used to supply missing data for the chosen statistical analysis method. The statistical reviewer requested post-hoc sensitivity analyses to evaluate the assumptions made for imputing the primary and key secondary endpoints. While some of these sensitivity analyses nominally supported the efficacy outcome at 24 weeks, an analysis performed with the assumption that data are not missing at random and using a multiple imputation method provided a non-significant result for reduction in OFF time. The considerable methodological variables and unknowns acting on the data at Week 24, make it difficult to interpret this result with any certainty. It is also worth recalling that patients who previously had not tolerated or improved on immediate release amantadine were excluded from enrollment in Study 301. This, combined with the smaller number of patients making it to Week 24, calls into question the applicability of the Week 24 result to the general PD population in whom ADS-5102 is likely to be used.

Additional Analyses Conducted on the Individual Trial

The demographic composition of the pivotal trials allowed subgroup analyses for clinical response to ADS-5102 by gender, race, and age (above and below age 65). The statistical reviewer found *"no compelling evidence... that a specific gender, race, age, or geographic region subgroup benefits differently from ADS-5102."*

Safety Results

Safety data from Studies 301 and 304 are included and assessed in Section 7, the integrated review of safety for the ADS-5102 development program.

5.3.4 Study ADS-AMT-PD302: Open-Label Safety Study of ADS-5102 (Amantadine HCl) Extended Release Capsules for the Treatment of Levodopa-Induced Dyskinesia

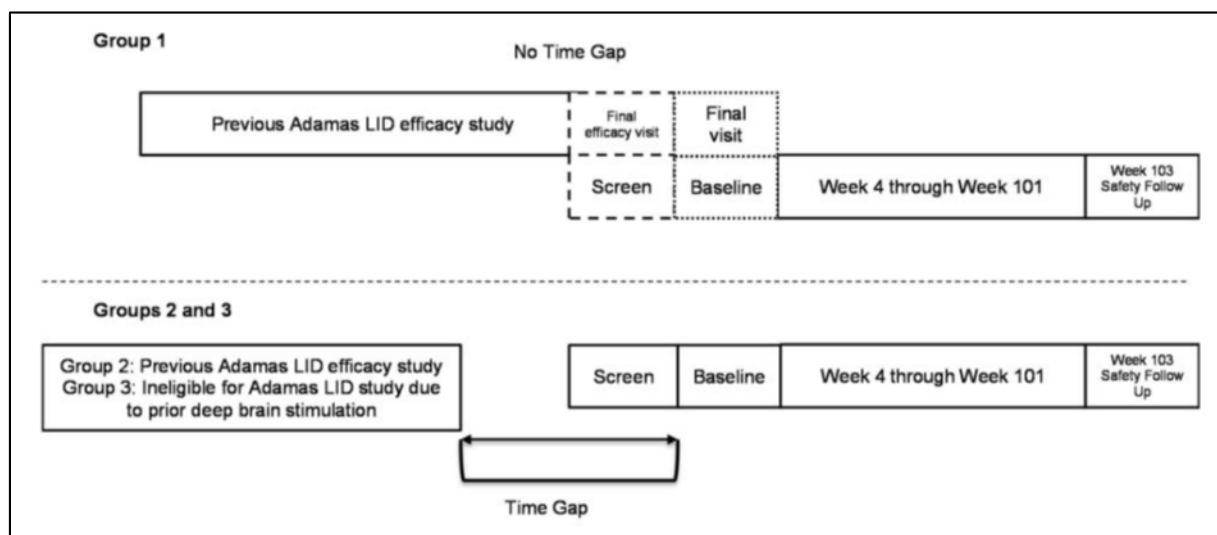
Study Design, Overview, and Objective

The primary objective of this study was to continue to evaluate the safety and tolerability of ADS-5102, 340 mg daily at bedtime in PD patients with LID. The secondary objective was to evaluate the duration of drug effect on LID as measured by the UDysRS total score. (This outcome was changed by protocol amendment to assess the dyskinesia using MDS-UPDRS Part 4 items related to LID).

This study was open to participants who had completed any of the previous randomized, blinded, and placebo-controlled LID studies evaluating ADS-5102, i.e. ADS-PAR-AM201, ADS-AMT-PD301 or ADS-AMT-PD304. This group was further subdivided depending on whether they had received active or placebo drug in one of the prior studies and if they had a time gap (interruption of drug administration) between the end of their prior study and entering Study 302.

In addition, patients previously excluded from the blinded trials solely due to deep brain stimulation (DBS) intervention for PD were allowed to enter this study.

Figure 14 Study 302 Origins of the study population (source: CSR, p 26)



Consented subjects who complete screening (Visit 1) and met study eligibility criteria received 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 102 additional weeks. When terminating the study, if the patient had been on drug for more than one month, the final week of dosing was reduced to 170 mg ADS-5102 (1 capsule) nightly at bedtime.

In the original protocol, patients were enrolled at Visit 2 (Week 0, Baseline) and returned to clinic after 4, 8, 16, 28, 40, and 52 weeks of medication for the first year of the study. (Visits at 64, 76, 88 and 100 weeks of treatment were later added by an amendment that extended the study). Subjects received a telephone reminder at the end of Week 1 to increase their dose during Week 2. At the Week 52 visit, patients were to be instructed to reduce their dose for 1 week, taking 1 capsule nightly at bedtime.

The following safety assessments were to be performed during the study: collection of AEs, safety-related study drug discontinuations, vital signs, and safety laboratory tests.

There was a single treatment regimen:

Table 29 Study 302 treatment regimen (source; protocol)

Treatment	Week 1	Weeks 2 – 52	Week 53
ADS-5102	170 mg ADS-5102 (1x170 mg capsule)	340 mg ADS-5102 (2 x170 mg capsules)	170 mg ADS-5102 (1x170 mg capsule)

In the original protocol, patients were to maintain their same PD regimen unchanged for the first 14 weeks of the study. This was later dropped by protocol amendment and there was no attempt at standardization of PD treatment in this cohort.

Assignment to Treatment

Bottles containing 60 capsules (30 day supply of study drug) of 170 mg ADS-5102 were provided at each study visit to the enrolled patient. The number of bottles provided depended on the next interval between visits.

Procedures and Schedule of Events

The duration of the study was increased by amendment to two years. The schedule of events presented below reflects that amendment.

Table 30 Study 302 Schedule of events through week 52 (source: protocol)

Clinical Review
Kenneth Bergmann, MD
NDA 208944
ADS-5102 (Amantadine ER)

	Screening		Baseline	Open-Label Treatment Period (See next page)						
Visit	1		2	Telephone call (a)	3	4	5	6	7	8
Week			0	1	4	8	16	28	40	52
Groups	1	2 or 3								
Informed consent	✓	✓								
Eligibility Criteria	✓	✓	✓							
Demographics		✓								
Medical History (c)	✓	✓	✓							
Medication History (d)	✓	✓	✓							
Concomitant Medications			✓		✓	✓	✓	✓	✓	✓
Adverse Events (e)					✓	✓	✓	✓	✓	✓
Complete Physical Exam (f)	✓ (g)	✓					✓			✓
Targeted Physical Exam (i)			✓		✓	✓		✓	✓	
Height and Weight (j)	✓ (g)	✓			✓	✓	✓	✓	✓	✓
Vital Signs (k)	✓ (g, h)	✓	✓		✓	✓	✓	✓	✓	✓
Hematology (l)	✓ (g)	✓			✓	✓	✓	✓	✓	✓
Serum chemistry (m)	✓ (g)	✓			✓	✓	✓	✓	✓	✓
Urinalysis (n)	✓ (g)	✓			✓	✓	✓	✓	✓	✓
ECG (12-lead)		✓								
Serum Pregnancy Test (if applicable) (o)	✓	✓								
Urine Pregnancy Test (if applicable) (o)			✓		✓	✓	✓	✓	✓	✓
MMSE	✓	✓								
MDS-UPDRS	✓ (g)	✓				✓	✓	✓	✓	✓
Collect returned bottles & assess compliance					✓	✓	✓	✓	✓	✓
Dispense Study Drug (bottles)			✓ (p)		✓	✓	✓	✓	✓	✓
Study Drug dosing, once nightly at bedtime (Days 1 – 707)			✓		✓	✓	✓	✓	✓	✓

Table 31 Study 302 Schedule of events through week 103 (source: protocol)

Visit	Open-Label Treatment Period (Continued from page 67)				Safety Follow-up (h)	Early Termination Visit
	9	10	11	12	13	
Week	64	76	88	100	103	
Groups						
Informed consent						
Eligibility Criteria						
Demographics						
Medical History (c)						
Medication History (d)						
Concomitant Medications	✓	✓	✓	✓	✓	✓
Adverse Events (e)	✓	✓	✓	✓	✓	✓
Complete Physical Exam (f)				✓		✓
Targeted Physical Exam (i)	✓	✓	✓		✓	
Height and Weight (j)	✓	✓	✓	✓		✓
Vital Signs (k)	✓	✓	✓	✓	✓	✓
Hematology (l)	✓	✓	✓	✓		✓
Serum chemistry (m)	✓	✓	✓	✓		✓
Urinalysis (n)	✓	✓	✓	✓		✓
ECG (12-lead)						
Serum Pregnancy Test (if applicable) (o)					✓	✓
Urine Pregnancy Test (if applicable) (o)	✓	✓	✓	✓		
MMSE						
MDS-UPDRS	✓	✓	✓	✓		✓
Collect returned bottles & assess compliance	✓	✓	✓	✓		✓
Dispense Study Drug (bottles)	✓	✓	✓	✓ (q)		
Study Drug dosing, once nightly at bedtime (Days 1 – 707)	✓	✓	✓	✓		

Concurrent Medication

No specific instructions or limitations were made regarding concurrent medication. By amendment, anti-PD regimens did not have to remain constant during participation.

Treatment Compliance

Patients were instructed to return all used and unused blister cards of study drug for drug accountability purposes. Drug accountability logs were kept and this responsible staff person documented the amount of study drug received and the amount supplied and/or administered to and returned by participants.

Participant Completion, Discontinuation, or Withdrawal

Patients could end participation at any time. Reasons include that the patient discontinued study medication and desired to withdraw, or consent is withdrawn, or the sponsor and or investigator decided to discontinue the patient. The reason was to be recorded in the case report form. Participants who withdrew were not replaced.

Study Endpoints

The study endpoints were:

- AEs
- Safety-related study drug discontinuations
- Vital Signs

- Clinical laboratory tests
- MDS-UPDRS.

Statistical Analysis Plan

No formal statistical testing was planned. Safety was to be performed from the time of first dose through 14 days after the last dose of ADS-5102. All AE data is listed and summarized by system organ class, preferred term, and treatment group. Quantitative safety variables (e.g., vital signs and clinical laboratory tests) were summarized at each visit by treatment group and changes from baseline were summarized by treatment group at selected visits.

Protocol Amendments

Table 32 Study 302 Study milestones and amendments

Study 302 (ongoing)	
Original protocol	2014 Mar 30
First patient enrolled	2014 July 28
Last patient enrolled	2016 March 10
Amendment 1	2014 July 14
Amendment 2	2014 October 7
Amendment 3	2015 January 7
Amendment 4	2015 July 16
Statistical Analysis Plan (Version 1.1)	2015 November 6
NDA data cut-off date	2016 July 1
120 Safety Update cut-off date	2016 December 2

Important or operationally relevant amendment features are as follows.

Amendment 1

Study sites increased from 45 up to 80 clinical sites.

Efficacy assessment changed from UDYSRS to MDS-UPDRS dyskinesia items with Week 4 efficacy assessment dropped.

Patients ineligible for previous studies for the sole reason of DBS allowed.

All Study 201, 301, and 304 patients are eligible to enroll into Study 302.

Need to keep all medication PD unchanged through Week 14 dropped.

Exclusion for prior amantadine use or poor response to amantadine dropped.

Planned N increased to 200.

Amendment 2

Administrative and language revisions made to conform to EU Guidelines for Clinical Trial Application submission.

Amendment 3

Administrative and language updates revisions made in response to Voluntary Harmonization Procedure for the assessment of multinational clinical trial applications.

List of prohibited medications that prolong the QT interval and have a known risk of torsades de pointes added.

Amendment 4

Increased to 90 study sites worldwide and N increased to 250 patients.

Overall study duration increased to 37 months (until last projected patient's completion).

Visits increased to reflect the duration of the ongoing study. i.e.: evaluations at 4, 8, 16, 28, 40, 52, 64, 76, 88, and 100 weeks dosing. Visit procedures added to reflect the increased duration of treatment.

SAP changed to indicate there will be no imputation or sensitivity analysis for missing data.

Study Results

Patient Disposition

Study 302 had reached full enrollment at the time of the original NDA submission with 223 patients. The 120-day Safety Update contained no new patients. The origins of patients in Study 302 are as follows:

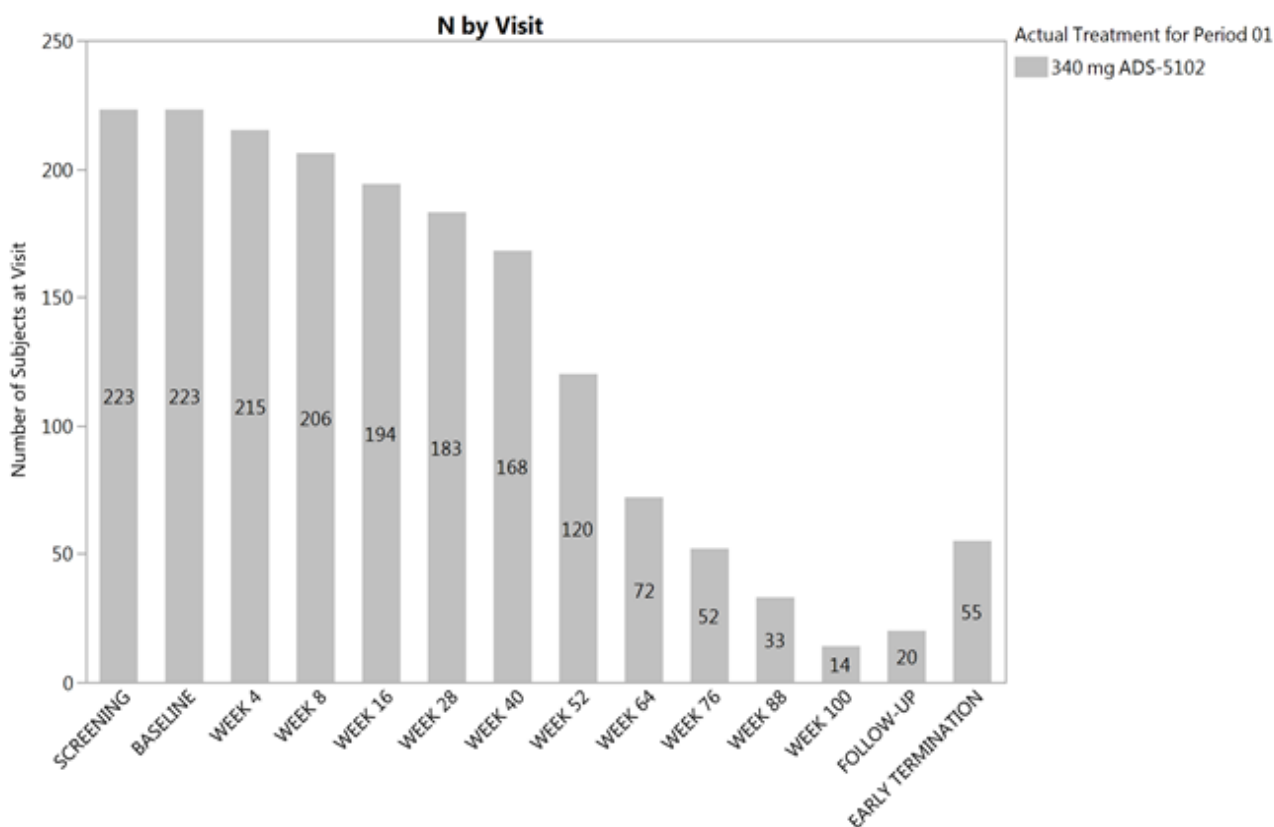
Table 33 Studies contributing to Study 302 enrollment (source: datasets)

Study 302 patients	N=223	%
Study of origin:		
Study 201 Active 260 mg	7	3.1
Study 201 Active 340 mg	4	1.8
Study 201 Active 420 mg	3	1.3
Study 201 Placebo	3	1.3
Study 301 Active	38	17
Study 301 Placebo	47	21.1
Study 304 Active	26	11.7
Study 304 Placebo	34	15.2
DBS Patient	61	27.1

Reviewer's comment: This study population includes 19 patients who had a gap between ending active drug in one study and beginning Study 302. That will be considered when discussing ADS-5102 exposure in the development program in Section 7.

The numbers of patients tallied by visit up to the 120 day safety cut-off date is illustrated in the following graph:

Figure 15 Study 302 patients by visit at 120 day data cut-off (source: datasets)



The dispositions of the patients are listed in the table below from the sponsor's 2.7.4 Summary of Clinical Safety update (p 9). Interim Analysis 1 (IA1) is up to the cut-off date at the time of NDA submission and IA2 is up to the cut-off date for the Safety Update. At the time of the NDA submission, 53 patients had left the study; by the time of the safety update, 10 additional patients had withdrawn.

Table 34 Study 302 Patient disposition as the time of the 120-day Safety Update

	Interim Analysis 1 (N = 223)	Interim Analysis 2 (N = 223)
Subjects enrolled in the study, n	223	223
Subjects who completed the study, n (%)	0	13 (5.8)
Subjects who withdrew from the study, n (%)	53 (23.8)	63 (28.3)
Subjects ongoing, n (%)	170 (76.2)	147 (65.9)
Primary reason for discontinuation of study drug		
Adverse event, n (%)	28 (12.6)	30 (13.5)
Subject unwilling to proceed, n (%)	9 (4.0)	10 (4.5)
Subject needed medication that was excluded or that may have interfered with study measurements, n (%)	3 (1.3)	4 (1.8) ^a
Subject consent was withdrawn, n (%)	2 (0.9)	4 (1.8)
Subject lost to follow-up, n (%)	2 (0.9)	2 (0.9)
Estimated glomerular filtration rate (eGFR) decreased to less than 50 mL/min/1.73 m ²	0	1 (0.4) ^b
Other, n (%)	10 (4.5)	12 (5.4)

^a The additional subject in IA2 is Subject (b) (6). In IA1, the reason for study drug discontinuation for this subject was reported as "other: domperidone."

^b One additional subject (b) (6), who is shown as ongoing in this table, discontinued study drug due to decreased GFR as reported on the AE CRF.

Protocol Violations/Deviations

There were 409 protocol violations among 141 patients but the great majority would have no impact upon the safety of the patient in this open label study. The most significant of these consisted of missed doses of medication, failure to reduce the dose of ADS-5102 for a week prior to discontinuing, or taking a prohibited medication (domperidone and citalopram). Because this study did not provide efficacy data of quality, the many violations related to assessments and out of window visits were not of significance.

There were few violations related to lab assessments and none concerning adverse events reporting.

Table 35 Study 302 Protocol violations (source: datasets)

Non-GCP related	Visit scheduling	61
	Treatment compliance	74
	Study administration	26
	Study assessments	128
	Informed consent	5
	Inclusion / exclusion criteria	9
	Concomitant medication	13
	Other	8
GCP related	Control of study treatment supplies	2
	Medical care	1
	Source document record keeping	21
	Investigational oversight	26
	Informed consent process	31
	Data privacy	2
	Other GCP violation	2

Table of Demographic Characteristics

Demographics reflect those of the trials originating the patients in this follow-on study. The DBS group is somewhat younger on average as would be expected for this neurosurgical intervention.

Table 36 Study 302 Demographic distribution (source: datasets)

Study 302	All (N=223)		DBS Group (N=61)
	n	(%)	n
Sex			
Male	131	58.7	41
Female	92	41.3	20
Age			
Mean years (SD)	63.7		60.2
Median (years)	65		62
Min, max (years)	32,82		32,76
Age Group			
< 40 years	3	1.4	
40 to 64 years	106	47.5	39
≥ 65 years	114	51.1	22
Race			
White	208	93.2	54
African American	2	0.9	1
Asian	8	3.6	4
American Native	0		0
Native Hawaiian	0		0
Other	5	2.2	2
Ethnicity			
Hispanic or Latino	20	9	5
Not Hispanic or Latino	203	91	56

Treatment compliance based upon drug accountability was good (93% by protocol criteria).

Efficacy Results

No efficacy results were submitted. The only clinical measure performed was the MDS-UPDRS and this was not formally analyzed by the sponsor. Looking at the combined scores for UPDRS Parts I, II, and III for all 223 participants, at baseline the mean was 46.9 (SD 19.01). There was little change from baseline over the first year of the study, but only 120 patients contributed scores at 52 weeks. Given the open design and lack of controls, one can make little of this finding.

Safety Results

Safety data from Study 302 is included and assessed in Section 7, the integrated review of safety for the ADS-5102 development program.

6 Review of Efficacy

An integrated review of efficacy was not created for this report. The evidentiary support for efficacy in reducing levodopa induced dyskinesia in PD patients comes from the two identical pivotal trials, Studies 301 and 304. Their results are discussed in the combined [Sections 5.3.2 and 5.3.3](#) above.

7 Review of Safety

Safety Summary

An adequate safety database was submitted for this extended release amantadine product seeking approval via the 505(b)(2) regulatory pathway. No new, novel, or unexpected adverse drug reactions were reported or discovered in this safety review.

7.1 Methods

This review of safety analyzes the data obtained from the safety populations of all trials in the ADS-5102 development program. Adverse events were coded using MedDRA 17.0. The emphasis of this review is on the patients who received the dose intended for label: 340 mg daily. Adverse event information is assessed for potential causality to the investigational drug, especially where it is possible to do so in the context of controlled comparison groups. Deaths, serious adverse events, and severity of adverse events are reviewed for all studies. Dropouts are reviewed whether they were considered by the sponsor as related to adverse events or not.

Pivotal Phase 3 Studies 301 and 304 are considered equivalent from the point of view of design, dosing, exposure and study. These provide blinded and controlled data obtained from the PD population for whom ADS 5102 is commercially intended. The relationship of AEs to baseline PD treatment regimens is also considered.

Phase 2/3 Study 201, while blinded and placebo-controlled, also studied doses not intended for marketing and for a shorter duration of time. Study 302 provides open-label safety data of longer term exposure to ADS-5102. This study also provides some experience in the DBS-treated PD population that was excluded from the randomized controlled trials. Adverse events occurring in these latter two studies are of interest if they are unusual, serious or particularly severe.

Reviewer's Comment: The datasets for adverse events submitted by the sponsor have been reviewed and edited in collaboration with the Cross-Discipline Team Leader due to inaccuracies caused by the use of Preferred terms that did not describe the event well (e.g. dizziness for orthostatic hypotension) and the splitting of adverse event into multiple subcategories resulting in an artificially low occurrence of related phenomena and on occasion over counting of patients in whom the events occurred. Examples of

this that were especially prominent include AEs related to depression, hallucination, and bodily injury likely related to falls.

As the review progressed, discrepancies in data also developed in the assessment of the duration of drug exposure. While the sponsor was told to update relevant datasets at the time of the 120 day Safety Update, the values in most datasets did not extend past the NDA submission date. The only ISS datasets that were updated at 120 days were the visits (VS), demographics (DM) and adverse event (AE) datasets.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Studies 301, 304, 201, and 304 are reviewed for safety in this section. Studies 301 and 304 are pooled for evaluation.

Reviewer's note: Phase 1 clinical pharmacology studies were performed in 152 healthy volunteers. In these five brief trials the sponsor reports no serious adverse events, adverse events of particular severity, or deaths. Perusal of the events by the reviewer reveals a hand fracture that likely would have been considered an SAE, but not likely caused by drug. No unusual adverse events (i.e. known to have occurred with amantadine use) were noted. The most common AEs were nausea, headache and dizziness. These studies are not considered further in this safety review.

The AE tables presented in this section are based upon revised and edited SDTM AE and ADaM ADAE datasets. The tables are formatted for use in the label: adverse reactions reported in greater than ^(b)₍₄₎ of patients treated with ADS-5102. Because of the small numbers of patients in the ADS-5102 development program, making this percentage smaller draws in adverse events previously described for the reference standard and eliminates unrelated events occurring in just one or two patients.

7.1.2 Categorization of Adverse Events

The protocols for all studies contributing patients to the safety database adhered closely to Good Clinical Practices with regard to defining, categorizing, evaluating and reporting of adverse events. Definitions were provided for assessing the severity and significance of adverse events. The considerations regarding the relationship of an AE to the study drug are outlined in the protocol but review of the evaluation of patients withdrawing from trials prematurely suggests that there are considerable individual variations in investigator judgments in this regard.

At times, the interpretation and coding of the verbatim description of adverse events resulted in splitting Preferred Terms into different AEs or even SOC. For example, vomiting, nausea, and retching were all assigned as different AEs. Another example especially pertinent to amantadine included illusions, auditory hallucinations, and visual hallucinations being individually coded when they represent the same pathophysiological event. While orthostatic hypotension was reported as an adverse

event, dizziness was as well. Virtually all AEs with the PT dizziness had a verbatim description involving lightheadedness. The net effect of this coding strategy was to both artificially inflate the numbers of patients affected by assigning more than one event to a single individual while also reducing the frequency of any given adverse event.

These occurrences were collaboratively edited by the reviewer and the Cross Discipline Team Leader. Specific examples are considered below in Section 7.3.5 Submission Specific Primary Safety Concerns.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Studies 301 and 304 are equivalent in design, dose, and AE reporting and are pooled for review.

7.2 Adequacy of Safety Assessments

All relevant safety evaluations were performed in all studies for this 505(b)(2) application. Amantadine has been marketed since 1973 and used extensively in the clinical population studied in this application. No special investigations of drug safety were necessary. Screening for suicidality was not performed in this development program but a history of suicidal ideation was criteria for exclusion.

As part of the initial evaluation of the adequacy of adverse event ascertainment, an analysis of the numbers of adverse events and their relationship to the site and study population was performed for both Study 301 and Study 304.

Clinical sites entered from 1 to 12 patients (3 on average). The number of AEs reported per randomized patient by site ranged from 0 to 12 AEs/patient (mean of 3.2, 95%CI 2.6, 3.8).

Comparison of Study 301 to 304 indicates that there was a trend toward reporting fewer numbers of AEs / randomized patient in the latter study (ANOVA, $p=0.059$):

Table 37 Studies 301 and 304 AEs reported per randomized patient (source: datasets)

Study	Mean AE/N	Std Error	Lower 95%	Upper 95%
301	3.7	0.4	2.9	4.5
304	2.5	0.5	1.6	3.5

Within Study 304, there were no differences in the numbers of AEs per randomized patient by individual country (Austria, France, Germany, Spain and US).

Table 38 Study 304 AEs per randomized patient reported by country (source: datasets)

Country	Mean AE/N	Std Error	Lower 95%	Upper 95%
AUT	4.5	2.4	-0.2	9.2
DEU	2.2	1.0	0.3	4.1
ESP	2.7	1.2	0.3	5.0
FRA	2.8	1.1	0.7	4.9
US-301	3.7	0.4	2.9	4.5
US-304	2.3	0.8	0.7	3.9

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The demographics of the safety population are presented above in Section 5. Links to these tables are here:

Table 9 Study 201 Population demographic features (source: datasets)

Table 17 Study 301 and 304 combined demographic analysis (source: datasets)

Table 36 Study 302 Demographic distribution (source: datasets)

The demographic features of the PD population with dyskinesia are virtually identical among Studies 201, 301 and 304, and Study 302 is a subset of the two pivotal studies.

The safety population reviewed here (any patients receiving a single dose of ADS-5102, exclusive of the Phase 1 studies as noted above) consists of groups from the blinded and open label studies.

Table 39 Safety population from blinded studies (source: datasets)

	ADS-5102 260 mg	ADS-5102 340 mg	ADS-5102 420 mg	Placebo
Study 201				
All	20	21	20	22
Male	8	13	10	14
Female	12	8	10	8
Study 301				
All		63		60
Male		35		37
Female		28		23
Study 304				
All		37		38
Male		19		20
Female		18		18
All	20	121	20	120
Male	8	67	10	71
Female	12	54	10	49
All dose strengths	N = 161	Male = 85 (52.8%)	Female = 76 (47.2%)	

Open label extension Study 302 enrolled patients from the double blind studies in the table above. It was populated by patients originating from the following treatment groups with a group of DBS treated patients recruited separately. The demographic features of the patients in Study 302 may be found at this link:

Table 36 Study 302 Demographic distribution (source: datasets)

Table 40 Origins of the open-label Study 302 cohort (source: datasets)

Study 302 patients	N=223	%
Study of origin:		
Study 201 Active 260 mg	7	3.1
Study 201 Active 340 mg	4	1.8
Study 201 Active 420 mg	3	1.3
Study 201 Placebo*	3	1.3
Study 301 Active	38	17
Study 301 Placebo*	47	21.1
Study 304 Active	26	11.7
Study 304 Placebo*	34	15.2
DBS Patients*	61	27.1
Total	223	100
* Patients not previously exposed to ADS-5102	145	65%

The ADS-5102 development program safety population is a total of 306 PD patients.

The calculation of the total drug exposure is complicated by the fact that 26 patients had a gap in treatment between the ending of their participation in a double blind trial and their rollover into open label treatment. In this case, the prior shorter exposure to ADS-5102 in the double blinded trial is ignored in the exposure calculation. This applied to 19 patients (14 of whom had received active treatment in Study 201), with the others having been in placebo treatment arms.

The tables below show the cumulative exposure for individual Studies 301, 304 and 302, followed by the combined continuous exposure for the three studies.

Table 41 Studies 301 and 304 Exposure to ADS-5102 (source: EX datasets)

Study 301 and 304	Description of Actual Arm	
	340 mg ADS-5102	PLACEBO
Cumulative exposure to treatment (Subject Years)	4.263	4.458
Duration of study treatment (Weeks)		
Number of Subjects	100	98
Mean (SD)	15.6(0.8)	16.6(0.7)

Study 301 and 304	Description of Actual Arm	
	340 mg ADS-5102	PLACEBO
Median	13	13
Min : Max	1:25	1:25
Duration of study treatment by category [n(%)]		
Missing duration	0(0%)	0(0%)
1-4 Weeks	16(16%)	7(7.1%)
5-8 Weeks	5(5%)	4(4.1%)
9-12 Weeks	6(6%)	10(10.2%)
13-16 Weeks	28(28%)	30(30.6%)
17-20 Weeks	6(6%)	10(10.2%)
21-24 Weeks	34(34%)	30(30.6%)
25-28 Weeks	5(5%)	7(7.1%)

Table 42 Study 302 patients with prior gaps in treatment (source: datasets)

USUBJID	STUDY	ARM	Rx gap (days)
ADSAMTPD301	Study 301	340 mg ADS-5102	7
ADSAMTPD301	Study 301	340 mg ADS-5102	34
ADSAMTPD301	Study 301	340 mg ADS-5102	76
ADSAMTPD304	Study 304	340 mg ADS-5102	6
ADSAMTPD304	Study 304	340 mg ADS-5102	2
ADS-PAR-AM201-	Study 201	420 mg ADS-5102	987
ADS-PAR-AM201-	Study 201	260 mg ADS-5102	707
ADS-PAR-AM201-	Study 201	260 mg ADS-5102	971
ADS-PAR-AM201-	Study 201	340 mg ADS-5102	1086
ADS-PAR-AM201-	Study 201	340 mg ADS-5102	912
ADS-PAR-AM201-	Study 201	260 mg ADS-5102	784
ADS-PAR-AM201-	Study 201	260 mg ADS-5102	796
ADS-PAR-AM201-	Study 201	420 mg ADS-5102	1274
ADS-PAR-AM201-	Study 201	420 mg ADS-5102	584
ADS-PAR-AM201-	Study 201	260 mg ADS-5102	843
ADS-PAR-AM201-	Study 201	260 mg ADS-5102	788
ADS-PAR-AM201-	Study 201	340 mg ADS-5102	640
ADS-PAR-AM201-	Study 201	340 mg ADS-5102	593
ADS-PAR-AM201-	Study 201	260 mg ADS-5102	766

The populations of Studies 301, 304 and 302 that had treatment without a gap between studies results in the cumulative exposure table below. It does not include the exposure of the 61 patients in Study 201 who had 8 weeks or less treatment with ADS-5102. (All of these patients would have had a time gap prior to being able to entering Study 302.)

There were 132 patients in the safety population with an exposure of 1 year or longer to ADS-5102 340 mg daily.

Table 43 Studies 301, 304 and 302 cumulative exposure (source: datasets)

Studies 301, 304 and 302	< 3 months	< 6 months	< 9 months	< 12 months	< 18 months	< 24 months	> 24 months	TOTAL
All patients	23	10	17	41	91	30	11	223
Sex								
Male	13	6	12	20	57	16	7	131
Female	10	4	5	21	34	14	4	92
Race								
Asian	1	1	1		4	1		8
Black or AA		1			1			2
White	22	8	14	40	85	28	11	208
Other			2	1	1	1		5
Age								
< 65	8	2	9	22	47	14	7	109
65 to 74	11	6	6	14	36	12	4	89
75 or greater	4	2	2	5	8	4		25

7.2.2 Explorations for Dose Response

The development program for ADS-5102 studied the efficacy and safety of a single dose of 340 mg at bedtime, administered as a forced titration after a one week of 170 mg at bedtime. No exploration of dose response was performed.

7.2.4 Routine Clinical Testing

Routine clinical testing consisting of physical and neurological examinations and clinical laboratory tests were performed at entry and exit in trials as well as regular intervals during all studies.

VS were taken in the seated position at every visit but the patient was only checked for orthostasis at the screening visit (exclusion criteria). Electrocardiography was only performed as a screening measure.

Hematology parameters included 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.

Routine serum chemistry parameters included alkaline phosphatase, albumin, blood urea nitrogen, calcium, carbon dioxide, chloride, creatinine, γ-glutamyltransferase, glucose, inorganic phosphorus, potassium, alanine aminotransferase, lactate dehydrogenase, aspartate aminotransferase, sodium, total bilirubin, and total protein.

Urinalysis by dipsticks: leukocytes, specific gravity, pH, protein, ketones, glucose, nitrite, blood, urobilinogen, and bilirubin.

7.3 Major Safety Results

7.3.1 Deaths

Six deaths occurred during the ADS-5102 development program. There was one death in Study 301 two weeks after the patient stopped study drug (340 mg/d); the remainder occurring in the open-label Study 302 while taking 340 mg daily. Following review of the narratives, none are likely to be a direct result of drug treatment.

Table 44 Deaths in the ADS-5102 development program

ISS Number	USUBJID	Sex	Age	Day	Cause
Study 301					
14-1-003	(b) (6)	F	75	167	Hospice care following failure to thrive. Died two weeks after drug cessation. Extensive medical history including stent and pacemaker, aortic bypass, arrhythmia, peripheral vascular disease.
Study 304					
02-2-503		F	73	99	MRSA pneumonia following repair of arm fracture with metal implants.
21-2-006		M	65	55	Myocardial infarction (diabetes, hypertension, chronic kidney disease, obesity)
16-2-002		M	74	416	Volvulus with antibiotics followed by C. difficile
89-2-505		F	79	190	Out of hospital cardiac arrest.
21-2-010		F	63	507	Sepsis, disseminated intravascular coagulopathy
76-2-508		F	69	406	Sepsis of unknown etiology. Extensive medical history with cholelithiasis

7.3.2 Nonfatal Serious Adverse Events

In **Study 201**, seven SAEs occurred in 5 patients, most in the 420 mg arm. According to the sponsor, none withdrew from the study as a result and none were considered a result of the study drug. Given the increase in falls as an AE of ADS-5102, the patient suffering the subdural hematoma could have been an event possibly related to drug. The patient with the psychotic episode had had study drug discontinued at the start of the skin hypersensitivity reaction. The brief psychotic event occurred when the patient was hospitalized 11 days later and resolved in 2 days. In patient AM201 (b) (6) the pneumonia and altered mental state were coincident and resolved together.

Table 45 Study 201 Nonfatal serious adverse events (source: datasets)

USUBJID	Age	Sex	Arm	Study Day	Body System	Preferred Term	Adverse Event
ADS-PAR-AM201	(b) (6) 80	F	420 mg	16	Infections and infestations	Urinary tract infection	COMPLICATED UTI
ADS-PAR-AM201	79	M	260 mg	69	Infections and infestations	Lobar pneumonia	RIGHT MIDDLE LOBE PNEUMONIA
ADS-PAR-AM201	79	M	260 mg	69	Psychiatric disorders	Mental status changes	ALTERED MENTAL STATUS
ADS-PAR-AM201	75	F	420 mg	50	Immune system disorders	Hypersensitivity	ALLERGIC REACTION (skin)
ADS-PAR-AM201	75	F	420 mg	51	Psychiatric disorders	Psychotic disorder	PSYCHOSIS
ADS-PAR-AM201	59	M	420 mg	69	Infections and infestations	Cellulitis	CELLULITIS OF LEFT LOWER EXTREMITY
ADS-PAR-AM201	70	M	420 mg	38	Injury, poisoning and procedural complications	Subdural haematoma	SUBDURAL HEMATOMA

In **Study 301**, 10 SAEs occurred in 10 patients on 340 mg ADS-5102. (Three additional patients in the placebo group had SAEs: two hip fractures and cellulitis). According to the sponsor, none were considered a result of the study drug. Following my review of the narratives, none are likely to be a direct result of drug treatment. While the AE dataset indicates no one withdrew from the study as a result of an SAE, some patients did discontinue drug following their event, e.g.:

- Patient (b) (6) died following her SAE unrelated to study drug.
- Patient (b) (6) was discharged to an assisted living facility following her fracture and discontinued drug 2 months later.
- Patient (b) (6) had worsening of her underlying PD and was hospitalized for worsening tremor. She discontinued drug a month later.
- Patient PD301-(b) (6) discontinued drug due to muscle weakness.

Table 46 Study 301 Nonfatal serious adverse events (source: datasets)

Unique Subject Identifier	Age	Sex	Study Day	Body System	Preferred Term	Adverse Event
ADSAMTPD301	61	F	21	Injury, poisoning and procedural complications	Humerus fracture	PROXIMAL HUMERUS FRACTURE OF LUE
ADSAMTPD301	61	F	57	Nervous system disorders	On and off phenomenon	SEVERE OFF PERIOD DUE TO MISSED DOSE OF CARBIDOPA/LEVODOPA
ADSAMTPD301	75	F	76	Injury, poisoning and procedural complications	Hip fracture	RIGHT HIP FRACTURE
ADSAMTPD301	75	F	167	Nervous system disorders	Encephalopathy	ENCEPHALOPATHY DUE TO ALPRAZOLAM WITHDRAWAL
ADSAMTPD301	73	M	140	Nervous system disorders	Presyncope	PRESYNCOPE (MOBITZ TYPE II HEART BLOCK)
ADSAMTPD301	63	F	53	Infections and infestations	Cellulitis	CELLULITIS, RIGHT LOWER LEG
ADSAMTPD301	63	F	91	Injury, poisoning and procedural complications	Subdural haematoma	SUBDURAL HEMATOMA
ADSAMTPD301	81	M	59	Gastrointestinal disorders	Small intestinal obstruction	SMALL BOWEL OBSTRUCTION
ADSAMTPD301	74	F	170	Gastrointestinal disorders	Constipation	WORSENING OF CONSTIPATION
ADSAMTPD301	78	F	15	Musculoskeletal and connective tissue disorders	Muscular weakness	INCREASED LOWER EXTREMITY WEAKNESS

In **Study 304**, four patients, all on active drug, had seven SAEs. Patient (b) (6)'s adverse event with constipation and urinary retention was considered related to study drug but the patient continued and completed the study. Patient (b) (6) had a pre-study history of alcoholism and undisclosed prior history of suicidal ideation and purchase of a gun. Study drug had been stopped 3 days prior to a self-inflicted gunshot wound. She was withdrawn from the study. The other SAEs were unrelated to study drug.

Table 47 Study 304 Nonfatal serious adverse events (source: datasets)

Unique Subject Identifier	Age	Sex	Study Day	Body System	Preferred Term	Adverse Event
(b) (6)	46	F	53	Psychiatric disorders	Suicide attempt	SELF INFLICTED GUN SHOT WOUND (SUICIDE ATTEMPT)
(b) (6)	46	F	55	Cardiac disorders	Cardio-respiratory arrest	CARDIO-RESPIRATORY ARREST
(b) (6)	67	F	16	Nervous system disorders	Transient ischaemic attack	TRANSIENT ISCHEMIC ATTACK
(b) (6)	67	F	20	Nervous system disorders	Dysaesthesia	DYSESTHESIA IN THE TOES OF THE RIGHT FOOT
(b) (6)	77	F	33	Injury, poisoning and procedural complications	Laceration	HEAD LACERATION
(b) (6)	63	M	30	Gastrointestinal disorders	Constipation	ACUTE CONSTIPATION
(b) (6)	63	M	30	Renal and urinary disorders	Urinary retention	ACUTE URINARY RETENTION

In **Study 302**, 37 SAEs were reported for 27 participants in the original NDA submission and 11 more patients were added at the time of the 120 day safety update. Investigators assessed Patient (b) (6) (urinary tract infection) and Patient (b) (6) (suicidal ideation) as being related to drug.

In the table below, patients who withdrew from the study as a result of their SAE are highlighted in grey. Additionally, drug was interrupted for six.

Table 48 Study 302 Serious adverse events (source: datasets)

Unique Subject Identifier	Age	Sex	Study Days	Body System	Preferred Term	Adverse Event
(b) (6)	63	F	246	Musculoskeletal and connective tissue disorders	Arthralgia	WORSENING RIGHT KNEE PAIN
	73	F	45	Injury, poisoning and procedural complications	Wrist fracture	LEFT WRIST FRACTURE
	73	F	96	Infections and infestations	Staphylococcal sepsis	MRSA BACTEREMIA, PRESUMABLY DUE TO INFECTED HARDWARE
	73	F	96	Infections and infestations	Pneumonia	PNEUMONIA
	73	F	96	Respiratory, thoracic and mediastinal disorders	Respiratory distress	RESPIRATORY DISTRESS SECONDARY TO PNEUMONIA
	69	M	141	Psychiatric disorders	Mental status changes	ALTERED MENTAL STATUS
	75	M	329	Injury, poisoning and procedural complications	Hip fracture	COMMINUTED INTERTROCHANTERIC RIGHT HIP FRACTURE
	82	M	54	Infections and infestations	Urinary tract infection	PERSISTENT URINARY TRACT INFECTION
	65	M	69	Musculoskeletal and connective tissue disorders	Osteonecrosis	AVASCULAR NECROSIS OF RIGHT PATELLA
	65	M	178	Infections and infestations	Arthritis bacterial	SEPTIC RIGHT KNEE REQUIRING RIGHT TOTAL KNEE ARTHROPLASTY
	56	M	147	Cardiac disorders	Angina pectoris	CARDIAC CHEST PAIN (ETIOLOGY UNKNOWN)
	64	F	58	Musculoskeletal and connective tissue disorders	Osteoarthritis	WORSENING RIGHT KNEE DEGENERATIVE DISEASE
	67	M	92	Reproductive system and breast disorders	Benign prostatic hyperplasia	WORSENING OF BPH
	67	M	179	Infections and infestations	Cellulitis	CELLULITIS-RIGHT LEG
	73	M	41	General disorders and administration site	Adverse drug reaction	ADVERSE DRUG REACTION TO MELATONIN AND STOOL

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				condition		SOFTENER
(b) (6)	73	M	147	Gastrointestinal disorders	Volvulus	SIGMOID VOLVULUS
	73	M	416	Infections and infestations	Clostridium difficile sepsis	C. DIFF SEPSIS
	73	M	416	Gastrointestinal disorders	Colonic pseudo-obstruction	OGLIVE SYNDROME
	72	F	146	Injury, poisoning and procedural complications	Laceration	LEFT KNEE LACERATION
	62	M	146	Gastrointestinal disorders	Constipation	SLOW TRANSIT CONSTIPATION
	65	M	55	Cardiac disorders	Myocardial infarction	HEART ATTACK
	77	M	471	Injury, poisoning and procedural complications	Hip fracture	LEFT HIP FRACTURE
	75	F	229	Injury, poisoning and procedural complications	Femur fracture	LEFT INTERTROCHANTERIC FEMUR FRACTURE
	57	F	171	Infections and infestations	Sepsis	SEPSIS
	68	M	248	Nervous system disorders	Encephalopathy	ENCEPHALOPATHY
	68	M	299	Blood and lymphatic system disorders	Lymphadenopathy	LYMPHADENOPATHY
	69	M	14	Gastrointestinal disorders	Intestinal obstruction	INTESTINAL OBSTRUCTION
	61	M	78	Psychiatric disorders	Suicide attempt	ATTEMPTED SUICIDE
	61	M	78	Respiratory, thoracic and mediastinal disorders	Respiratory arrest	RESPIRATORY ARREST
	64	M	270	Musculoskeletal and connective tissue disorders	Rhabdomyolysis	RHABDOMYOLYSIS
	62	F	141	Injury, poisoning and procedural complications	Traumatic fracture	RIGHT TIBIAL FRACTURE- MOTOR VEHICLE ACCIDENT
	68	F	447	Injury, poisoning and procedural complications	Ankle fracture	BROKEN ANKLE (L)
	50	M	295	Psychiatric disorders	Anxiety	WORSENING ANXIETY
	50	M	440	Psychiatric disorders	Suicidal ideation	SUICIDAL IDEATION WITH INTENT FOR SELF HARM
	72	F	212	Injury, poisoning and procedural complications	Fall	DYSFUNCTION OF DEEP BRAIN STIMULATION DEVICE WITH INCREASED DISPOSI
	72	F	247	Ear and labyrinth disorders	Vertigo positional	BENIGN PAROXYSMAL POSITIONAL VERTIGO

(b) (6)	69	F	253	Injury, poisoning and procedural complications	Forearm fracture	FOREARM FRACTURE LEFT
	34	M	201	Vascular disorders	Venous thrombosis	THROMBOSIS OF THE VENA SAPHENA MAGNA IN THE THIGH AND LOWER LEG LEF
	62	M	266	Nervous system disorders	Parkinson's disease	PARKINSONISM AGGRAVATION
	76	M	5	Gastrointestinal disorders	Volvulus	RECURRENT SIGMOID VOLVULUS
	76	F	579	Injury, poisoning and procedural complications	Ankle fracture	FRACTURED RIGHT ANKLE
	69	F	405	Infections and infestations	Gastroenteritis viral	DEHYDRATION DUE TO STOMACH FLU
	77	F	142	Injury, poisoning and procedural complications	Rib fracture	RIBS FRACTURE
	77	F	233	Injury, poisoning and procedural complications	Fall	WORSENING OF MOTOR SYMPTOMS WITH INCREASED DISPOSITION TO FALLS
	77	F	282	Nervous system disorders	Parkinson's disease	WORSENING OF PARKINSON'S DISEASE
	62	F	295	Cardiac disorders	Coronary artery disease	ANGINA PECTORIS CORONARY VASCULAR DISEASE
	78	F	297	Infections and infestations	Herpes zoster	STRONG PAIN DUE TO HERPES ZOSTER
	74	M	86	Injury, poisoning and procedural complications	Traumatic fracture	TRAUMATIC SERIAL RIB FRACTURES
	74	M	90	Respiratory, thoracic and mediastinal disorders	Haemothorax	HEMOTHORAX
	68	M	433	Nervous system disorders	On and off phenomenon	WORSENING MOTOR FLUCTUATIONS RELATED TO PD
	79	F	190	Cardiac disorders	Cardiac arrest	CARDIAC ARREST
	66	M	174	Gastrointestinal disorders	Inguinal hernia	INGUINAL HERNIA

7.3.3 Dropouts and/or Discontinuations

Study discontinuations due to deaths and SAEs are discussed in sections above. This section surveys the remainder of patients who left their study prematurely. Study 201 dropouts were noted above. Most were in the 420 mg/d dose and were due to side effects. The categorization of dropouts and discontinuations in made by the sponsor for the remaining studies is illustrated in the table below.

Table 49 Studies 301, 304 and 302 dropouts and discontinuations (source: modified sponsor's CSR tables)

Discontinuations	Study 301		Study 304		Study 302 (OL)
	ADS-5102	Placebo	ADS-5102	Placebo	ADS-5102
N randomized	63	63	38	39	223
Completed the study	42	42	29	35	(13) ongoing
Total withdrawn from the study	21 (33.3%)	21 (33.3%)	9 (23.7%)	4 (10.3%)	63 (28.3%)
Reason:					
Sponsor's decision (study stopped)	7	7			
Patient stopped drug and withdrew	10	3	6	3	
Patient was "unwilling to proceed" or "withdrew consent"	2	7	1	0	14
Adverse event					31
Lost to follow up	1	1			2
Other	1	3	2	1	12
Needed medication not allowed in study (e.g. domperidone)					4

The sponsor's DM and ADSL datasets call this categorization into question. One aspect of the table above is notable: the absence of discontinuations due to adverse events in the pivotal studies.

In Study 301 and 304, ADSL demographic datasets have two columns regarding study completion, COMPLRS (Completer Population Exclusion Reason) and CMPTRTRS (Reason for Treatment Discontinuation). In COMPLRS, 55 patients in the pivotal trials were flagged as non-completer (consistent with the above table) with 59 patients in CMPTRTRS listing reasons for stopping drug. (4 patients stopped drug but continued with their study visits; in the DM datasets, they were flagged as completers but "adverse event" was entered in columns marking the reason for stopping drug.) Of these 59 patients, 27 (55.5%) show "adverse event" as the reason for non-completion (20 taking ADS-5102 and 7 receiving placebo). The 20 patients on ADS-5102 had 112 adverse events, (7 severe, 43 moderate and 62 mild). The severe adverse events occurred in 5 patients: two with hallucinations and one each with orthostatic hypotension, worsening depression and leg weakness. The common AEs by head count were visual hallucinations (6), dry mouth (5), blurred vision (3), constipation (3), and nausea (3). The dates of the adverse events correspond to the date of last drug treatment.

Most of the adverse events leading to discontinuation in Study 302 were experienced by those participants who had not previously taken ADS-5101 (i.e. placebo and DBS patients). The Study 302 cohort was, in some sense, enriched via patients' participation in a previous study (see Table 32, above). This participation would likely have previously reduced the numbers of those patients who might be more susceptible to an adverse event in the extension study.

7.3.4 Significant Adverse Events

The sponsor defined AEs as “any untoward medical occurrence” regardless of whether it is considered a result of the investigational medicine. For it to be considered severe, the AE should produce incapacitation of significant impairment of functioning and is a definite health hazard.

The sponsor reported that of 223 patients in Study 302, 196 suffered an AE and of these 45 patients (23%) were considered to have a severe AE. The AE was considered to be drug related in just 10 of these.

At the time of the original NDA submission the sponsor reported in the ISS severe AE occurring in more than 1% of patients taking ADS-5102 safety population (n=306). (Splitting of AEs is in evidence; there is no pathophysiological reason to parse hallucinations into visual and auditory.)

Table 50 Severe AEs in $\geq 1\%$ of the safety population (source: SCS, p 51)

Preferred Term	Number (%) of Subjects			
	Placebo (N = 120)	340 mg ADS-5102 (N = 276)	≥ 340 mg ADS-5102 (N = 293)	ADS-5102 (N = 306)
No. of subjects with any severe AE	9 (7.5)	53 (19.2)	60 (20.5)	61 (19.9)
Fall	1 (0.8)	9 (3.3)	10 (3.4)	10 (3.3)
Hallucination (Pooled) ^a	0	7 (2.5)	8 (2.7)	8 (2.6)
Visual hallucination	0	7 (2.5)	8 (2.7)	8 (2.6)
Auditory hallucination	0	1 (0.4)	1 (0.3)	1 (0.3)
Constipation	0	4 (1.4)	5 (1.7)	5 (1.6)
Urinary retention	0	3 (1.1)	3 (1.0)	3 (1.0)

Inspection of the AE datasets of Studies 301 and 304, confirms this assessment, with one potential exception: bodily injury likely resulting from falls. This is elaborated upon in the next section.

7.3.5 Submission Specific Primary Safety Concerns

The following adverse drug reactions of potential seriousness have been known to occur with the use of dopaminergic agents in the treatment of PD. Some have previously been described in the label of the reference standard, amantadine.

Sleepiness, somnolence, and fatigue:

No sudden onset of sleepiness was described as an adverse event in Studies 301 and 304; two patients had an AE of “sleep attack” in the open label Study 302.

The Dictionary-Derived terms in the AE dataset (AEDECOD) that were used to describe sleepiness and fatigue may result in splitting of a related phenomenon. Somnolence, sleep disorder, fatigue, lethargy, malaise, and asthenia all appeared as Preferred Terms. When analyzed separately, the following fairly equal distribution is seen in the table below. However, when all are combined into a single category of somnolence and fatigue, they represent 10 ADS-5102 patients (9.9%) versus 3 placebo patients (2.94%), a three-fold difference.

Table 51 Studies 301 and 304 Head count of preferred terms related to sleepiness and fatigue (source: datasets)

AEBODSYS	AEDECOD	ADS-5102 (N=100)	ADS-5102 %	Placebo (N=98)	Placebo %
General disorders and administration site conditions	Asthenia	2	2.0	2	2.0
General disorders and administration site conditions	Fatigue	2	2.0	1	1.0
Nervous system disorders	Lethargy	1	1.0		
General disorders and administration site conditions	Malaise	2	2.0		
Psychiatric disorders	Sleep disorder	1	1.0		
Nervous system disorders	Somnolence	2	2.0		

Psychiatric adverse events

The Dictionary-Derived terms in the AE dataset (AEDECOD) that were used to describe events in the Psychiatry disorders SOC resulted in splitting of a related phenomenon. Terms related to depression included: affect lability, depressed mood, depression, and mood altered. Terms related to anxiety included: agitation, anxiety, generalized anxiety disorder, nervousness, and restlessness. Suicidality included both ideation and attempt. (There was no systematic monitoring for suicidality in this development program.) A usual head-count analysis of the original dataset reveals the following distribution:

Table 52 Studies 301 and 304 Head count of preferred terms related to depression and anxiety (source: datasets)

AEDECOD	ADS-5102 (N=100)	ADS-5102 %	Placebo (N=98)	Placebo %
Affect lability	1	1.0		
Agitation	1	1.0	1	1.0
Anxiety	7	6.9	2	2.0
Depressed mood	2	2.0		
Depression	4	4.0	1	1.0
Generalised anxiety disorder			1	1.0
Mood altered	1	1.0		
Nervousness	1	1.0		
Restlessness			1	1.0
Suicidal ideation	1	1.0		
Suicide attempt	1	1.0		

However, joining these terms into general categories of depression and anxiety reveals that the categories suggest a considerably higher risk for psychiatric adverse events in the ADS-5102 arm compared to placebo. It is evident that these weren't single patients described by multiple terms but rather different individuals described using different preferred terms that reduced the impact through splitting. Because anxiety, depression and suicidality can occur in a single patient, an analysis combining these terms did reveal some overlap: ADS-5102, n=14 (13.9%) versus placebo, n=5 (4.9%).

Table 53 Studies 301 and 304 Head count of psychiatric preferred terms grouped by anxiety, depression and suicidality (source: datasets)

AEDECOD joined by category	ADS-5102 (N=100)	ADS-5102 %	Placebo (N=98)	Placebo %
Anxiety	9	8.9	4	3.9
Depression	7	6.9	1	1.0
Suicidality	2	2.0	0	0.0

Auditory and visual hallucinations and illusions were reported separately. When joined together 21 patients on ADS-5102 (20.8%) had hallucinations while 3 patients on placebo did as well (2.9%)

One count each of suicidal ideation and suicidal attempt occurred in the open label Study 302.

Postural dizziness and orthostatic hypotension

The Dictionary-Derived terms in the AE dataset (AEDECOD) that were used to describe events potentially related to orthostatic blood pressure were more common in the ADS-5102 treated arms of Studies 301 and 304.

Table 54 Studies 301 and 304 Head count of preferred terms potentially related to orthostatic hypotension (source: datasets)

AEDECOD	ADS-5102 (N=100)	ADS-5102 %	Placebo (N=98)	Placebo %
Dizziness	16	15.8	1	1.0
Orthostatic hypotension	5	5.0	1	1.0
Dizziness postural	3	3.0		
Syncope	2	2.0		
Hypotension	2	2.0		
Presyncope	1	1.0		

When combining PTs these together, it becomes evident that they represent individual patients, not patients who have had multiple similar events coded by different PTs. (Almost all PTs coded “dizziness” had verbatim descriptions of “lightheadedness.”)

Table 55 Studies 301 and 304 Head count of preferred terms potentially related to orthostasis joined (source: datasets)

AEDECOD	ADS-5102 (N=100)	ADS-5102 %	Placebo (N=98)	Placebo %
Dizziness	25	24.8	2	2.0

Falls and trauma

Individual Instances of falls and trauma revealed the following head count suggesting that the two groups of adverse events occur more commonly with ADS-5102 treatment and that these phenomena might be linked.

Table 56 Studies 301 and 304 Head count of preferred terms related to falls and trauma (source: datasets)

AEDECOD	ADS-5102 (N=100)	ADS-5102 %	Placebo (N=98)	Placebo %
Fall	13	12.9	7	6.9
Contusion	6	5.9	1	1.0
Gait disturbance	3	3.0		
Laceration	2	2.0	1	1.0
Balance disorder	2	2.0	3	2.9
Traumatic haematoma	1	1.0		
Subdural haematoma	1	1.0		
Sternal fracture	1	1.0		
Muscle strain	1	1.0		
Humerus fracture	1	1.0		
Hip fracture	1	1.0	2	2.0
Facial bones fracture	1	1.0		
Face injury	1	1.0		
Craniocerebral injury	1	1.0		
Skin wound			1	1.0
Ligament sprain			1	1.0
Injury			1	1.0

When the PTs potentially related to falls and trauma are grouped, the results of trauma become more evident in the ADS-5102 treated arms.

Table 57 Studies 301 and 304 Head count of preferred terms potentially related to falls and trauma joined (source: datasets)

AEDECOD	ADS-5102 (N=100)	ADS-5102 %	Placebo (N=98)	Placebo %
Fall	17	16.8	9	8.8
Trauma	15	14.9	7	6.9

Is there an interaction between possible orthostasis and falls and trauma? One of these adverse events groups occurred in 55 patients (ADS-5102, n=27; placebo, n=28). A cross tabulation analysis shows no interaction between the potential AE of orthostasis and the AE of either falls or trauma (one ADS-5102 patient combined orthostasis with trauma; none with falls). On the other hand, falling and trauma occurred individually in 2 and 6 ADS-5102 patients respectively, while 9 patients experienced these together.

Renal dysfunction

Because amantadine is mainly excreted in the urine, the dosage must be reduced in people with any renal dysfunction (creatinine clearance below 60 mL/min) and not used in patients with severe renal impairment with creatinine clearance less than 15 mL/min. Specific recommendations are made in the Clinical Pharmacology review.

Impulse control disorders

There was no systematic screening for impulsiveness. None occurred in Studies 301 and 304 but there were three counts of impulse dyscontrol, one count of pathological gambling and one count of compulsive eating reported as an AE in open label extension Study 302 (all in different patients).

Withdrawal-emergent hyperpyrexia and confusion was not reported as an adverse event in the development program.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most commonly observed adverse reactions occurring at a frequency of $\geq 10\%$ and greater than placebo were hallucination, dizziness, dry mouth, peripheral edema, constipation, fall, and orthostatic hypotension.

Adverse reactions reported for $\geq 3\%$ of patients treated with 340 mg daily in Studies 301 and 304 are pooled in the table below. For the purpose of greater accuracy, visual and auditory hallucinations were combined in this head count. Similarly, orthostatic hypotension, postural dizziness, syncope, pre-syncope and hypotension were grouped together. (The psychiatric AEs are computed as listed in the unedited datasets provided by the sponsor.)

Table 58 Common treatment emergent adverse reactions in Studies 301 and 304 occurring in $\geq 3\%$ of patients and more in ADS-5102 than placebo treated with 340 mg daily (source: AE and DM datasets)

Adverse Reactions	GOCOVRI 274 mg N=100 %	Placebo N=98 %
Psychiatric disorders		
Hallucination	21	3
Anxiety	7	2
Insomnia	6	2
Depression/Depressed mood	6	1
Abnormal dreams	4	2
Confusional state	3	2

Nervous system disorders		
Dizziness	16	1
Headache	6	3
Dystonia	3	1
Gastrointestinal disorders		
Dry mouth	16	1
Constipation	13	3
Nausea	8	3
Vomiting	3	0
General disorders and administration site conditions		
Peripheral edema	15	1
Gait disturbance	3	0
Injury, poisoning and procedural complications		
Fall	13	7
Contusion	6	1
Infections and infestations		
Urinary tract infection	8	5
Skin and subcutaneous tissue disorders		
Livedo reticularis	6	0
Pigmentation disorder	3	0
Metabolism and nutrition disorders		
Decreased appetite	6	1
Vascular disorders		
Orthostatic hypotension	13	1
Eye disorders		
Blurred vision	4	1
Cataract	3	1
Dry eye	3	0
Musculoskeletal and connective tissue disorders		
Joint swelling	3	0
Muscle spasms	3	0
Reproductive system and breast disorders		
Benign prostatic hyperplasia (male patients only: ADS-5102, n=54; placebo, n=57)	6	2
Respiratory, thoracic and mediastinal disorders		
Cough	3	0

Common adverse events occurring in Study 302 are found in the table below. The dataset was edited to combine nausea and vomiting, common psychiatric events, and events suggestive of orthostasis. Events likely due to unrelated intercurrent illness were eliminated.

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Table 59 Study 302 Common adverse events occurring in greater than 2% and not due to intercurrent illness (source: datasets)

AESOC	AEDECOD	Head Count (N=223)	%
Injury, poisoning and procedural complications	Fall	56	25.1
Psychiatric disorders	Hallucination	46	20.6
General disorders and administration site conditions	Oedema peripheral	29	13.0
Gastrointestinal disorders	Constipation	28	12.6
Vascular disorders	Orthostasis	23	10.3
Gastrointestinal disorders	Vomiting or Nausea	22	9.9
Skin and subcutaneous tissue disorders	Livedo reticularis	18	8.1
Gastrointestinal disorders	Dry mouth	16	7.2
Psychiatric disorders	Insomnia	16	7.2
Infections and infestations	Urinary tract infection	15	6.7
Psychiatric disorders	Abnormal dreams	11	4.9
Psychiatric disorders	Depression	9	4.0
Psychiatric disorders	Rapid eye movements sleep abnormal	9	4.0
Nervous system disorders	Parkinson's disease	7	3.1
Renal and urinary disorders	Urinary retention	7	3.1
Injury, poisoning and procedural complications	Contusion	6	2.7
Nervous system disorders	Balance disorder	6	2.7
Nervous system disorders	Cognitive disorder	6	2.7
Psychiatric disorders	Anxiety	6	2.7
Psychiatric disorders	Confusional state	6	2.7
Psychiatric disorders	Sleep disorder	6	2.7
General disorders and administration site conditions	Fatigue	5	2.2

Hallucinations includes Hallucinations visual or auditory, Parkinson's disease related hallucinations

The DBS population (n=61) entered into this open label study had not been in previous ADS-5102 studies and were also analyzed separately. Their adverse events were qualitatively and quantitatively identical to the cohort as a whole. This sub-group accounted for one count of suicidal ideation and one count of sleep attack, but none of the impulse dyscontrol related events.

The sponsor, tallying site investigators' opinion, considered the following events (by headcount for each Preferred Term) in the program's safety population as related to study drug:

Table 60 TEAEs in the safety population (N=306) considered related to ADS-5102 by sponsor (source: ISS, p 52)

Preferred Term	Number (%) of Subjects			
	Placebo (N = 120)	340 mg ADS-5102 (N = 276)	≥ 340 mg ADS-5102 (N = 293)	ADS-5102 (N = 306)
No. of subjects with any study drug-related AEs	28 (23.3)	156 (56.5)	166 (56.7)	175 (57.2)
Hallucination (Pooled) ^a	2 (1.7)	48 (17.4)	51 (17.4)	54 (17.6)
Visual hallucination	2 (1.7)	45 (16.3)	47 (16.0)	49 (16.0)
Auditory hallucination	0	9 (3.3)	9 (3.1)	9 (2.9)
Hallucination	0	3 (1.1)	4 (1.4)	5 (1.6)
Dry mouth	1 (0.8)	32 (11.6)	34 (11.6)	37 (12.1)
Constipation	1 (0.8)	26 (9.4)	29 (9.9)	32 (10.5)
Peripheral edema	2 (1.7)	26 (9.4)	27 (9.2)	28 (9.2)
Dizziness	1 (0.8)	18 (6.5)	19 (6.5)	20 (6.5)
Livedo reticularis	0	18 (6.5)	18 (6.1)	18 (5.9)

7.4.2 Laboratory Findings

All clinical laboratory tests were evaluated for shift from baseline values using the JMP Clinical evaluations module. These results overall were unremarkable with little variation in any laboratory parameter over the course of the individual trials.

No one had a change in renal function over time though one patient was enrolled with baseline abnormal renal function.

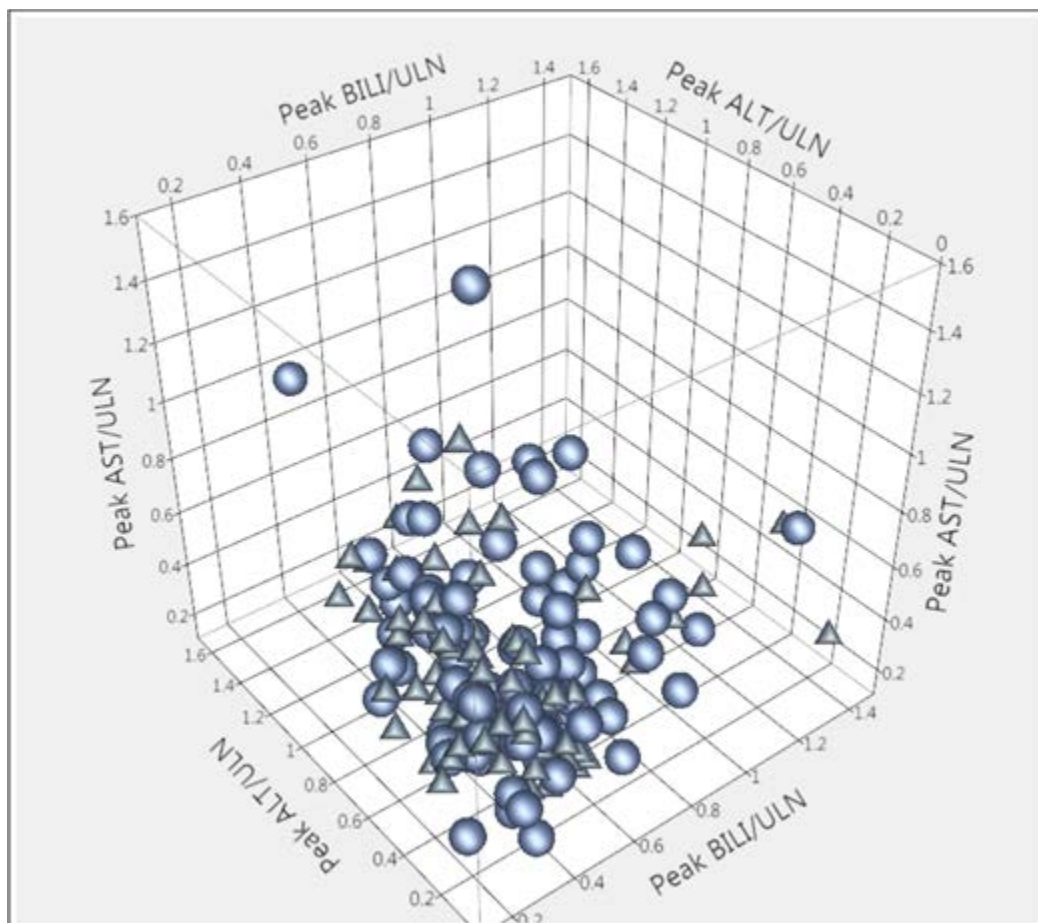
For **Studies 301 and 304** the only finding of note is related to hepatic function. A shift from baseline GGT occurred in 5 patients; four of these were in the active treatment arm.

Figure 16 Study 301 and 304 GGT (all trial samples) shift table (source: LB datasets)

	GGT Baseline					
	Less than 2x ULN		2x and 5x ULN		All	
GGT Trial Mean	Count	%	Count	%	Count	%
Less than 2x ULN	188	94.9%	1	0.5%	189	95.5%
2x and 5x ULN	1	0.5%	3	1.5%	4	2.0%
5x and 10x ULN	0	0.0%	1	0.5%	1	0.5%
Missing	4	2.0%	0	0.0%	4	2.0%
All	193	97.5%	5	2.5%	198	100.0%

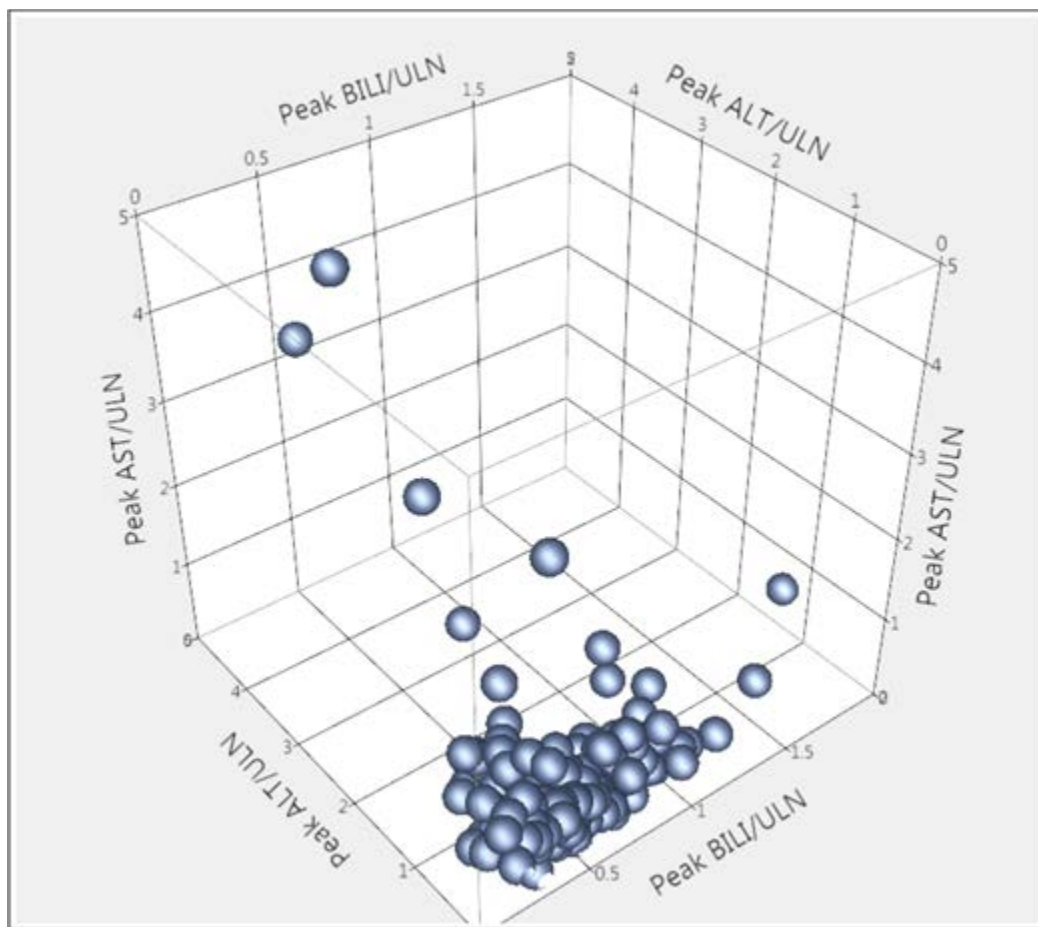
No cases of Hy's law were found in the clinical laboratories. No patient had an elevation above twice the upper limit of normal for any individual hepatic function test: bilirubin, ALT, AST, or ALP. In the representation below, the active arm is represented by spheres.

Figure 17 Study 301 and 304 - Three dimensional representation of change in hepatic enzymes from baseline (source: LB dataset)



In **Study 302** there was also one patient who shifted from baseline and had GGT elevated 5 times the upper limit of normal as an isolated finding. Four other participants had elevated GGT from baseline but did not change further over the course of the study. There were sporadic elevations of ALT or AST in 4 patients and ALP elevation in one. Evaluation for Hy's law revealed no cases.

Figure 18 Study 302 Three dimensional representation of change in hepatic enzymes from baseline (source: LB dataset)



7.4.3 Vital Signs

Orthostasis in blood pressure measurement was evaluated only at the time of screening enrollment. (Significant orthostatic hypotension was an exclusion criterion.) Vital signs were otherwise performed in the sitting position throughout the development program.

Like the clinical laboratory analyses, measures were evaluated by a matched-pairs analysis from the baseline value to trial measurements. A separate analysis was done for each finding. This revealed no shifts of note in diastolic or systolic blood pressure, heart rate, respiratory rate or weight in the development program.

7.4.4 Electrocardiograms (ECGs)

Electrocardiograms were only used at screening visits to determine study eligibility. There were no cardiovascular adverse events that would suggest that the heart or vascular system is a target of specific organ toxicity.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

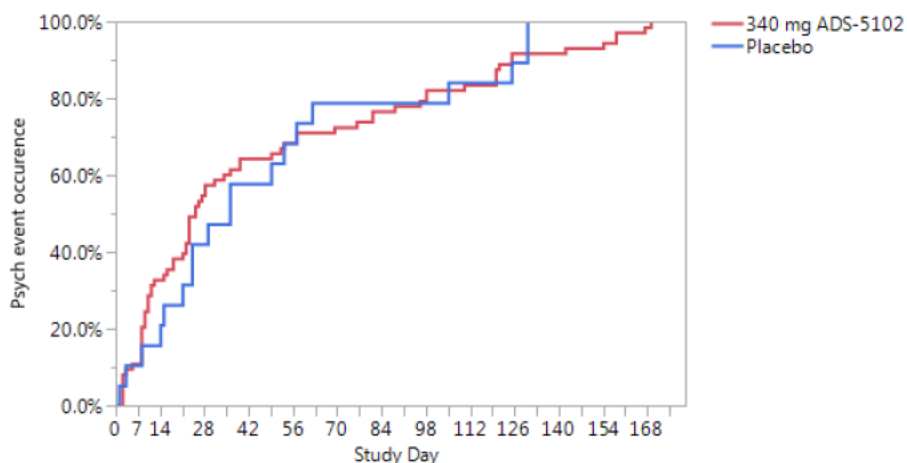
A single dose was studied in the development program.

7.5.2 Time Dependency for Adverse Events

The time to the development of adverse events was investigated in the double blind safety population. The system organ classes with the greatest number of adverse events were psychiatric disorders (92 events), nervous system disorders (72 events), and gastrointestinal disorders (74 events). These systems provided sufficient numbers of events for analysis. Using failure plots to model the time to occurrence in days to the first adverse event for a given Preferred Term for each patient, no statistically significant pattern of time dependency is revealed when active drug and placebo are compared. However, in each SOC, the median time to the adverse event was shorter and events more numerous in the active drug arm. Both Log-Rank and Wilcoxon signed-rank tests were used for analysis.

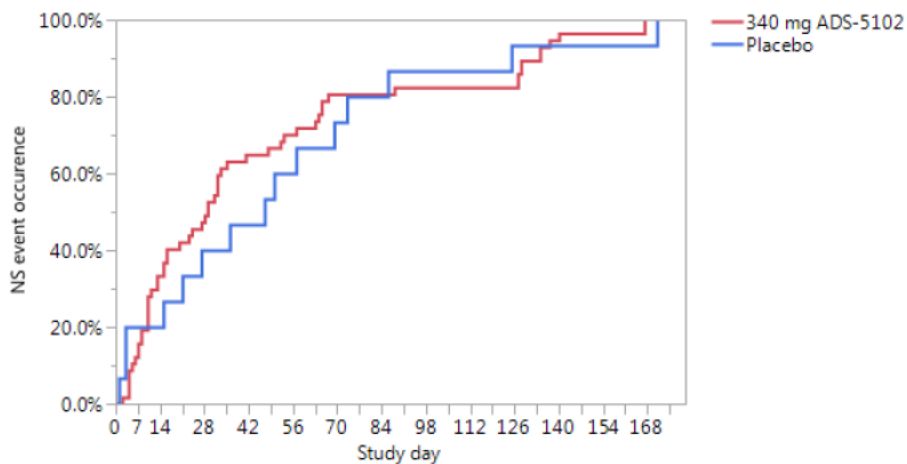
Figure 19 Studies 301 and 304 time dependency for common TEAEs by System Organ Class (source: datasets)

Psychiatric Disorders



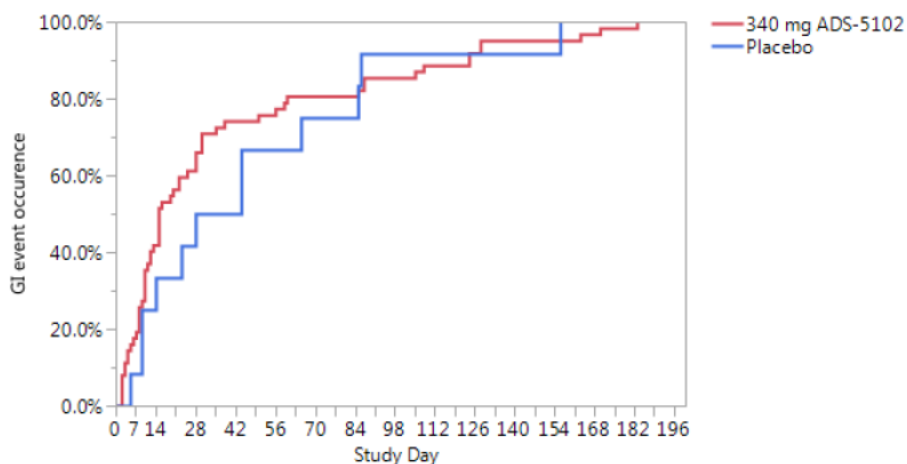
Psychiatric Group	Events	Median Time	Lower 95%	Upper 95%	25% Failures	75% Failures
340 mg ADS-5102	73	25	18	36	10	81
Placebo	19	36	15	57	15	62
Combined	92	25.5	22	36	10	78.5

Nervous System Disorders



NS Group	Events	Median Time	Lower 95%	Upper 95%	25% Failures	75% Failures
340 mg ADS-5102	57	29	15	35	10	64
Placebo	15	47	3	69	15	73
Combined	72	30	20	41	10	65

Gastrointestinal Disorders



GI Group	Events	Median Time	Lower 95%	Upper 95%	25% Failures	75% Failures
340 mg ADS-5102	62	15	11	28	8	50
Placebo	12	36	9	85	11.5	75
Combined	74	17.5	13	28	9	56

After Preferred Terms were edited to eliminate splitting, time (days) until the appearance of the most common drug treatment emergent adverse events were analyzed:

Table 61 Studies 301 and 304 Time (days) to emergence of common TEAEs (source: datasets)

Preferred Term	Event Count	Median Time	Lower 95%	Upper 95%	25% Failures	75% Failures
Anxiety and Depression	14	69	8	125	11	125
Constipation	17	28	10	50	15	50
Dry mouth	16	10.5	8	15	8.5	15
Fall	21	33	14	91	14	92
Hallucination	26	28	18	57	16	76
Livedo reticularis	7	84	69	147	71	147
Nausea and Vomiting	12	24.5	2	108	8	84
Oedema peripheral	24	80.5	67	124	64.5	137
Orthostatic hypotension	29	29	10	39	10	52

Autonomic side-effects (constipation, dry mouth, nausea and vomiting, and orthostasis) consistently appeared on average in the first month of treatment. Livedo reticularis and peripheral edema occurred after more chronic therapy, consistent with their more prevalent appearance in the open label extension Study 302.

7.5.3 Drug-Demographic Interactions

Age and gender subgroup analyses were performed for treatment emergent adverse events in Studies 301 and 304. The lack of ethnic and racial diversity in the blinded trials made that analysis not meaningful.

While there appeared to be disparities in some adverse events between men and women, those differences were quantitative, not qualitative and their significance is unclear. Given the small sample, it was not possible to control for differences in demographic features, geographic location (European sites tended to report fewer adverse events), concomitant medications and disease state.

Adverse reactions reported more frequently in women treated with ADS-5102 (n=46) compared to men (n=54) were: auditory or visual hallucinations, dry mouth, falls, constipation, nausea, urinary tract infection, depression and decreased appetite. Men (n=54) reported the following adverse reactions more frequently: dizziness, peripheral edema, anxiety, headache, insomnia, orthostatic hypotension, and gait disturbance.

While the differences are quantitatively small, patients age 65 or older suffered more events related to hallucinations, gait disturbance and falls, orthostatic hypotension, and livedo reticularis.

Table 62 Studies 301 and 304 Common TEAEs by gender (source: datasets)

AEDECOD	ADS-5102 Female (N=46)	ADS-5102 Female %	ADS-5102 Male (N=54)	ADS-5102 Male %	Female > Male
Dizziness	5	11	11	20	
Hallucination	11	24	10	19	x
Oedema peripheral	5	11	10	19	
Dry mouth	10	22	6	11	x
Fall	7	15	6	11	x
Constipation	7	15	6	11	x
Anxiety	1	2	6	11	
Headache	2	4	4	7	
Insomnia	2	4	4	7	
Orthostatic hypotension	1	2	4	7	
Urinary tract infection	5	11	3	6	x
Depression	3	7	3	6	x
Back pain	1	2	3	6	
Benign prostatic hyperplasia	0	0	3	6	
Gait disturbance	0	0	3	6	
Nausea	6	13	2	4	x
Contusion	4	9	2	4	x
Decreased appetite	4	9	2	4	x
Vision blurred	2	4	2	4	
Nasopharyngitis	1	2	2	4	
Confusional state	1	2	2	4	
Upper respiratory tract infection	1	2	2	4	
Cough	1	2	2	4	
Dizziness postural	1	2	2	4	

Table 63 Studies 301 and 304 Common TEAEs by age above and below 65 years
(source: datasets)

AEDECOD	ADS-5102 (N=52) ≥ Age 65	ADS-5102 ≥ Age 65 %	ADS-5102 (N=48) < Age 65	ADS-5102 < Age 65 %	More in Age ≥ 65
Hallucination	16	31	5	10	x
Fall	9	17	4	8	x
Oedema peripheral	8	15	7	15	
Dry mouth	6	12	10	21	
Dizziness	5	10	11	23	
Constipation	4	8	9	19	
Nausea	4	8	4	8	
Contusion	4	8	2	4	x
Livedo reticularis	4	8	2	4	x
Orthostatic hypotension	4	8	1	2	x
Urinary tract infection	3	6	5	10	
Back pain	2	4	2	4	
Insomnia	2	4	4	8	
Decreased appetite	2	4	4	8	
Depression	2	4	4	8	
Abnormal dreams	2	4	2	4	
Vision blurred	2	4	2	4	
Dizziness postural	2	4	1	2	x
Gait disturbance	2	4	1	2	x
Benign prostatic hyperplasia	2	4	1	2	x
Cataract	2	4	1	2	x

7.5.5 Drug-Drug Interactions

The clinical treatment of PD is characterized by polypharmacy with different classes of dopaminergic drugs commonly used in combination. Whether this contributes to the occurrence of adverse events was investigated. The combinations of treatments used in Studies 301 and 304 were as follows:

Table 64 Studies 301 and 304 (N=198) PD treatment regimens in use (source: CM datasets)

	Arm	PD Treatment				
		Levodopa (LD) only*	LD + any CM	LD + DA	LD + MAOI	LD + DA + MAOI
Study 301	ADS-5102	24	39	13	14	12
	Placebo	21	39	15	10	14
Study 304	ADS-5102	11	26	9	5	12
	Placebo	7	31	10	7	14
Total	ADS-5102	35	65	22	19	24
	Placebo	28	70	25	17	28
* includes all levodopa containing products						
CM = all concomitant PD medication; DA = dopamine agonists; MAOI = monoamine oxidase B inhibitors						

Analysis using individual combinations of PD treatment regimens (the three columns to the right in the table above) resulted in numbers too small to be meaningful. However the most common adverse drug reactions (hallucination, dizziness, dry mouth, peripheral edema, constipation, and falls) remained at the top of the list in all groups.

Reducing the cohort into two groups (treated by levodopa alone or levodopa in combination with other adjunctive agents), revealed that there was no obvious difference between the drug regimens with the exception that ADS_5102 appeared to uniformly increase adverse drug reactions over placebo, regardless of other PD therapy.

Table 65 Studies 301 and 304 Common adverse events by concomitant PD treatment (source: datasets)

AEDECOD	ADS-5102 (LD)	% ADS-5102 (LD)	ADS-5102 (LD+CM)	% ADS-5102 (LD+CM)	PLACEBO (LD)	% PLACEBO (LD)	PLACEBO (LD+CM)	% PLACEBO (LD+CM)
N	35		65		28		70	
Dizziness	6	17.1	10	15.4	1	3.6		
Dry mouth	5	14.3	11	16.9			1	1.4
Hallucination, visual	5	14.3	13	20.0			3	4.3
Oedema peripheral	5	14.3	10	15.4	1	3.6		
Anxiety	4	11.4	3	4.6	2	7.1		
Constipation	4	11.4	9	13.8	2	7.1	1	1.4
Back pain	3	8.6	1	1.5	4	14.3	2	2.9
Contusion	3	8.6	3	4.6			1	1.4
Decreased appetite	3	8.6	3	4.6			1	1.4
Depression	3	8.6	1	1.5			1	1.4
Fall	3	8.6	10	15.4	2	7.1	5	7.1
Hallucination, auditory	3	8.6	3	4.6				
Livedo reticularis	3	8.6	3	4.6				
Urinary tract infection	3	8.6	5	7.7	1	3.6	4	5.7
Abnormal dreams	2	5.7	2	3.1	1	3.6	1	1.4
Headache	2	5.7	4	6.2			3	4.3
Joint swelling	2	5.7	1	1.5				
Nausea	2	5.7	6	9.2			3	4.3
Orthostatic hypotension	2	5.7	3	4.6			1	1.4

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The sponsor has submitted an analysis of the habituation and abuse potential of amantadine consistent with that proposed by FDA guidance. This included searches of the FDA Adverse Event Reporting System and other public drug abuse databases. No evidence was found to suggest that amantadine is a drug of abuse.

However, the disproportionality analysis, while not revealing of terms related to abuse, dependence, or overdose, did identify dopamine dysregulation syndrome as exceeding the background rate. This is difficult to interpret because of the concomitant use of other anti-Parkinson drugs (levodopa and dopamine agonists) clearly associated with that syndrome.

The current prescribing information for amantadine states that it
“...should not be discontinued abruptly in patients with Parkinson’s disease since a few patients have experienced a Parkinsonian crisis, i.e., a sudden marked clinical deterioration, when this medication was suddenly stopped. The dose of anticholinergic drugs or of SYMMETREL should be reduced if atropine-like effects appear when these drugs are used concurrently. Abrupt discontinuation may also precipitate delirium,

agitation, delusions, hallucinations, paranoid reaction, stupor, anxiety, depression and slurred speech.”

As a result, by protocol, dose tapering for 1 week at half dose was used in any patient in Studies 301, 304, and 302 who was exposed to ADS-5102 (or placebo) for longer than 4 weeks. No adverse events suggesting abuse, dependence, or withdrawal were reported.

An internal review was also performed by the Division of Pharmacovigilance I (February 9, 2017) and they are in agreement with the sponsor's assessment. Review by the Controlled Substance Staff (July 24, 2017) also concluded that abuse liability is not supported by the available data and recommended that ADS-5102 not be scheduled under the Control Substance Act. Section 9.0, Abuse and Dependence, was not recommended for labeling.

8 Postmarket Experience

ADS-5102 is not currently marketed in any country.

9 Appendices

9.1 Literature Review/References

None.

9.2 Labeling Recommendations

The Prescribing Information for ADS-5102 is derived from that of the reference standard for this 505(b)(2) application. Describing the safe and effective use of Gocovri® has been the subject of collaborative effort between FDA and the sponsor throughout the review cycle. The safety information found in the label of the reference standard is updated with regard to this specific drug product. Qualitatively adverse events appear to be no different for ADS-5102, but the drug substance is an old product and the methods of obtaining treatment emergent adverse events were unlikely to be equivalent to those in this development program. Importantly, no new novel or previously undescribed adverse events have occurred in the ADS-5102 development program.

This review used the dosages of Gocovri® in its salt form as supplied by the sponsor in protocols and study reports throughout the development program. In the labeled Prescribing Information, the 340 mg dose of ADS-5102 as salt will be represented as 274 mg of free base in conformity with current usage standards.

9.3 Advisory Committee Meeting

No advisory committee input was sought for this 505(b)(2) application.

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9.4 Studies 301 and 304 Clinical Investigator Financial Disclosure

Financial Disclosure for Covered Clinical Study:
Study ADS-AMT-PD301: Efficacy and Safety of ADS-5102 (amantadine HCl) Extended Release Capsules for the Treatment of Levodopa Induced Dyskinesia in Parkinson's Disease Patients

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: <u>41 PIs and 164 subinvestigators</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>None</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>1</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>n/a</u> Significant payments of other sorts: <u>1</u> (b) (6) Proprietary interest in the product tested held by investigator: <u>n/a</u> Significant equity interest held by investigator in sponsor of covered study: <u>n/a</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>205</u>		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

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Financial Disclosure for Covered Clinical Study:
Study ADS-AMT-PD304: ADS-5102 (amantadine HCl) Extended Release Efficacy and Safety Study in Parkinson's Disease Patients with Levodopa-Induced Dyskinesia

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: <u>32 PIs and 144 subinvestigators</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>n/a</u> Significant payments of other sorts: <u>n/a</u> Proprietary interest in the product tested held by investigator: <u>n/a</u> Significant equity interest held by investigator in sponsor of covered study: <u>n/a</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>176</u>		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

9.5 Unified Dyskinesia Rating Scale (UDysRS)

The UDysRS has two primary sections, Historical and Objective. Each of these, in turn, has two parts: Part 1 (On Dyskinesia), Part 2 (Off Dystonia), Part 3 (Impairment), and Part 4 (Disability). The Historical section rates the impact of the last week. The impact of Parkinson's disease (stiffness, slowness and shaking) is specifically excluded from the rating system. In full form, instructions are provided for the completion of each section for the rater (either patient or caregiver).

Score Summary

Historical	Score	Objective	Score
1. Time dyskinesia		16. Face	
2. Speech		17. Neck	
3. Chewing/Swallowing		18. Right Hand/arm/shoulder	
4. Eating tasks		19. Left Hand/arm/shoulder	
5. Dressing		20. Trunk	
6. Hygiene		21. Right foot/leg/hip	
7. Handwriting		22. Left foot/leg/hip	
8. Doing hobbies/activities		23. Communication	
9. Walking/balance		24. Drinking	
10. Public/social		25. Dressing	
11. Exciting situations		26. Ambulation	
12. Time Off dystonia			
13. Dystonia effects on activities (not pain)			
14. Effect of Pain from dystonia			
15. Dystonia pain severity			
Historical sub-score (sum)		Objective sub-score (sum)	
Total UDysRS score (Historical + Objective):			

Part 1 (A) Time spent with on-dyskinesia

0 Normal	No dyskinesia	1. Total Hours On: 2, Total Hours of on-Dyskinesia % On-Dyskinesia = $((2/1)*100$	
1 Slight	<25% of on-time		
2 Mild	25-50% of on-time		
3 Moderate	51-75% of on-time		
4 Severe	>75% of on-time		

Part 1 (B) Patient Dyskinesia Questionnaire

2. SPEECH: Over the past week, when your Parkinson's disease medications were working, did jerking or twisting movements called on-dyskinesias usually cause problems with your speech? Consider only effects of dyskinesias, not problems caused by Parkinson's disease. 0: Normal: Not at all, no problems. 1: Slight: Dyskinesias were present, but they did not interfere with my speech. 2: Mild: Dyskinesias caused a few problems with my speech and people asked me to repeat myself occasionally. 3: Moderate: Dyskinesias caused enough problems that I tried to avoid talking when I had on-dyskinesias. 4: Severe: When I had dyskinesias, most or all of my speech could not be understood.	Score _____
3. CHEWING AND SWALLOWING: Over the past week, when your Parkinson's disease medications were working, did jerking or twisting movements called on-dyskinesias usually cause problems swallowing pills or eating meals? Did you need your pills cut or crushed or your meals to be made soft, chopped or blended to avoid choking? Consider only effects of dyskinesias, not problems caused by Parkinson's disease. 0: Normal: Not at all, no problems. 1: Slight: Dyskinesias were present, but they did not interfere with my chewing or swallowing. 2: Mild: Dyskinesias caused a few problems with chewing and swallowing and it took me longer to chew or swallow because of on-dyskinesias. 3: Moderate: Dyskinesias caused enough problems that I tried to avoid chewing and swallowing when I had on-dyskinesias. 4: Severe: When I had dyskinesias, I was unable to chew or swallow at all	Score _____
4. EATING TASKS: Over the past week, when your Parkinson's disease medications were working, did jerking or twisting movements called on-dyskinesias usually cause troubles handling your food and using eating utensils? For example, did you have trouble handling finger foods or using forks, knives, spoons, chopsticks? Consider only effects of dyskinesias, not problems caused by Parkinson's disease. 0: Normal: Not at all, no problems. 1: Slight: Dyskinesias were present, but they did not interfere with my eating. 2: Mild: Dyskinesias caused a few problems with eating and it took me longer to eat because of on-dyskinesias. 3: Moderate: Dyskinesias caused enough problems that I tried to avoid eating when I had on-dyskinesias. 4: Severe: When I had dyskinesias, I needed help for most or all eating tasks.	Score _____
5. DRESSING: Over the past week, when your Parkinson's disease medications were working, did jerking or twisting movements called on-dyskinesias usually cause problems with your dressing? For example, did you need help with buttoning, using zippers, putting on or taking off your clothes or jewelry? Consider only effects of dyskinesias, not problems caused by Parkinson's disease. 0: Normal: Not at all, no problems. 1: Slight: Dyskinesias were present but they did not interfere with dressing tasks.	Score _____

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2: Mild: Dyskinesias caused a few problems with dressing and it took me longer to get dressed because of on-dyskinesias. 3: Moderate: Dyskinesias caused enough problems that I tried to avoid getting dressed when I had on-dyskinesias. 4: Severe: When I had dyskinesias, I needed help for most or all dressing tasks.	
6. HYGIENE: Over the past week, when your Parkinson's disease medications were working, did jerking or twisting movements called on-dyskinesias usually cause problems with your personal hygiene? For example, did you need help with washing, bathing, shaving, brushing teeth, or combing your hair? Consider only effects of dyskinesias, not problems caused by Parkinson's disease. 0: Normal: Not at all, no problems. 1: Slight: Dyskinesias were present but they did not interfere with hygiene tasks. 2: Mild: Dyskinesias caused a few problems with hygiene tasks and it took me longer to do these activities because of on-dyskinesias. 3: Moderate: Dyskinesias caused enough problems that I tried to avoid doing hygiene tasks when I had on-dyskinesias. 4: Severe: When I had dyskinesias, I needed help for most or all of my hygiene tasks.	Score _____
7. HANDWRITING: Over the past week, when your Parkinson's disease medications were working, did jerking or twisting movements called on-dyskinesias usually cause trouble with your handwriting. Consider only effects of dyskinesias, not problems caused by Parkinson's disease. 0: Normal: Not at all, no problems. 1: Slight: Dyskinesias were present, but they did not interfere with my handwriting. 2: Mild: Dyskinesias caused a few problems with writing and it took me longer to write because of on-dyskinesias. 3: Moderate: Dyskinesias caused enough problems that I tried to avoid writing when I had on-dyskinesias. 4: Severe: When I had dyskinesias, most or all words could not be read.	Score _____
8. DOING HOBBIES AND OTHER ACTIVITIES: Over the past week, when your Parkinson's disease medications were working, did jerking or twisting movements called on-dyskinesias usually cause trouble doing your hobbies or other things that you like to do? Consider only effects of dyskinesias, not problems caused by Parkinson's disease. 0: Normal: Not at all, no problems. 1: Slight: Dyskinesias were present but they did not interfere with these activities. 2: Mild: Dyskinesias caused a few problems with these activities and it took me longer to do them because of on-dyskinesias. 3: Moderate: Dyskinesias caused enough problems that I tried to avoid doing hobbies or other activities when I had on-dyskinesias. 4: Severe: When I had dyskinesias, I was unable to do most or all of these activities.	Score _____
9. WALKING AND BALANCE: Over the past week, when your Parkinson's disease medications were working, did jerking or twisting movements called on-dyskinesias usually cause problems with balance and walking. Consider only effects of dyskinesias, not problems caused by Parkinson's disease. 0: Normal: Not at all, no problems. 1: Slight: Dyskinesias were present but they did not interfere with walking or balance. 2: Mild: Dyskinesias caused a few problems with walking. It took me longer to walk because of on-dyskinesias and I occasionally bumped into things. 3: Moderate: Dyskinesias caused enough problems that I usually used a walking aid (cane, walker) to walk safely without falling. However, I did not usually need the support of another person. I tried to avoid walking when I had on-dyskinesias. 4: Severe: When I had dyskinesias, I could not walk safely without falling.	Score _____
10. PUBLIC AND SOCIAL SETTINGS: Over the past week, when your Parkinson's disease medications were working, did jerking or twisting movements called on-dyskinesias usually cause problems when you were dealing with other people or in public? Consider only effects of dyskinesias, not problems caused by Parkinson's disease. 0: Normal: Not at all, no problem. 1: Slight: Dyskinesias were present but they did not interfere with these activities. 2: Mild: Dyskinesias caused a few problems and I was self-conscious in public but I did not avoid social situations. 3: Moderate: Dyskinesias caused enough problems that I tried to avoid some social situations when I had on-dyskinesias. 4: Severe: When I had dyskinesias, I could not be with people, even friends or family.	Score _____
11. EXCITING OR EMOTIONAL SETTINGS: Over the past week, when your Parkinson's disease medications were working, did jerking or twisting movements called on-dyskinesias usually cause problems during emotional conversations, exciting movies, or other highly stimulating situations. Consider only effects of dyskinesias, not problems caused by Parkinson's disease. 0: Normal: Not at all, no problem. 1: Slight: Dyskinesias were present, but they did not interfere with these activities. 2: Mild: Dyskinesias caused few problems. 3: Moderate: Dyskinesias caused enough problems that I tried to avoid some exciting situations when I had on-dyskinesias. 4: Severe: When I had dyskinesias, I could not stay in exciting situations	Score _____

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Part 2 (A) Off-dystonia completed by rater

12. TIME SPENT WITH OFF-DYSTONIA Over the past week, on a typical day, think about the number of hours of the day when you are stiff and slow, whether this is before you take morning medications, perhaps late in the evening, or during the day when the good effects of medication have worn out. Within these "OFF" times, how many hours or minutes do you have spasms or cramps that we call OFF-dystonia? 0 = Never 1 = Less than 30 minutes a day 2 = Less than 60 minutes a day 3 = Less than 2 hours a day 4 = Greater than 2 hours a day	Score _____
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Part 2 (B) Patient questionnaire

13. EFFECTS OF SPASMS OR CRAMPS CALLED OFF-DYSTONIA <u>SEPARATE FROM PAIN</u> ON ACTIVITIES. During the past week, separate from pain, have spasms or cramps called off- dystonia occurred? 0: Normal: Not at all. 1: Slight: Off-dystonia occurred but it did not interfere with my daily activities. 2: Mild: Off-dystonia caused a few problems and it took me longer to do activities because of off-dystonia. 3: Moderate: Off-dystonia caused enough problems that I avoided doing these activities when I had off-dystonia. 4: Severe: When off-dystonia occurred, I could not do many activities.	Score _____
14. EFFECTS OF PAIN FROM OFF-DYSTONIA ON DAILY ACTIVITIES: On average during this past week, if spasms or cramps called off-dystonia occurred, did <u>pain</u> limit your activities? 0: Normal: Not at all, no pain from off-dystonia. 1: Slight: I had pain from off-dystonia, but it did not limit my activities 2: Mild: Pain from off-dystonia caused a few problems and it took me longer to do activities because of pain from off-dystonia. 3: Moderate: Pain from off-dystonia caused enough problems that I avoided doing these activities when I had pain from off-dystonia. 4: Severe: Because of pain from dystonia, I could not do many activities.	Score _____
15. DYSTONIA PAIN: On average during the past week, how severe was the pain from the spasms or cramps of off-dystonia? 0: Normal: Not painful 1: Slight: Mild ache or discomfort. 2: Mild: Moderate ache and discomfort. 3: Moderate: Severe discomfort. 4: Severe: Excruciating pain.	Score _____

Part 3 Objective evaluation of dyskinesia disability

INTENSITY SCALE: IMPAIRMENT (PART 3)					
0=No dyskinesia					
1=Questionable or mild dyskinesia					
2=Moderate dyskinesia with movements which are not intrusive nor distort voluntary movements					
3=Severe dyskinesia which disturbs but does not prohibit posture or voluntary movements					
4=Incapacitating dyskinesia which prohibits some postures and voluntary movements					
IMPAIRMENT SCORE	Communication	Drinking	Dressing	Ambulation	Highest score
FACE					(16)
NECK					(17)
R ARM/SHOULDER					(18)
L ARM/SHOULDER					(19)
TRUNK					(20)
R LEG/HIP					(21)
L LEG/HIP					(22)

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Part 4 Disability scale

DISABILITY SCALE (PART 4)

<u>Communication</u> 0=No dyskinesia 1=Dyskinesia present but does not impair communication 2=Dyskinesia impairs communication but patient is fully understandable 3=Dyskinesia interferes with communication such that parts of communication cannot be understood but overall content is understandable 4=Dyskinesia interferes with comprehension of overall communication	(23)
<u>Drinking from a cup</u> 0=No dyskinesia observed 1=Dyskinesia present but it does not affect performance of the task 2=Dyskinesia affect the smooth performance but causes no splashing or spilling 3=Dyskinesia affects performance such that patient spills a few drops of water 4=Dyskinesia affects performance such that patient spills more than a few drops or dyskinesia causes coughing or choking	(24)
<u>Dressing</u> 0=No dyskinesia observed 1=Dyskinesia present but does not interfere with or slow dressing 2=Dyskinesia affects smooth performance of task but the performance is at most minimally slowed 3=Dyskinesia interferes and slows performance but it is completed within 60 seconds 4=Dyskinesia precludes completing the task within 60 seconds	(25)
<u>Ambulation</u> 0=No dyskinesia observed 1=Mild dyskinesia present but does not alter normal synchrony or cadence 2=Dyskinesia is present which alters the normal cadence of rising, sitting or walking but does not slow overall performance. 3=Dyskinesia is present which disrupts or distorts arising, sitting or walking. Performance is slowed. Patient is able to rise and walk without imminent danger of falling. 4=Dyskinesia prohibits walking safely without assistance	(26)

9.6 Parkinson's Disease Home Diary

PARKINSON'S DISEASE DIARY					
NAME _____			Date _____		
Instructions: For each half-hour time period place <u>one</u> check mark to indicate your predominant status during most of that period. ON = Time when medication is providing benefit with regard to mobility, slowness, and stiffness. OFF = Time when medication is not providing benefit with regard to mobility, slowness, and stiffness Dyskinesia = Involuntary twisting, turning movements. These movements are an effect of medication and occur during ON time. Non-troublesome dyskinesia does <u>not</u> interfere with function or cause meaningful discomfort. Troublesome dyskinesia interferes with function or causes meaningful discomfort. Tremor is shaking back and forth and is not considered dyskinesia.					
time	asleep	OFF	ON without dyskinesia	ON with <u>non</u> troublesome dyskinesia	ON with troublesome dyskinesia
6:00 AM					
:30					
7:00 AM					
:30					
8:00 AM					
:30					
9:00 AM					
:30					
10:00 AM					
:30					
11:00 AM					
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KENNETH J BERGMANN
08/23/2017

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08/23/2017