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RESEARCH ARTICLE

Randomized, Placebo-Controlled Trial of ADS-5102 (Amantadine) Extended-Release Capsules for Levodopa-Induced Dyskinesia in Parkinson's Disease (EASE LID 3)

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ABSTRACT: Background: The treatment of levodopa-induced dyskinesia in Parkinson's disease (PD) is an unmet need with no approved drug therapy.
Objective: The purpose of this study was to investigate the efficacy and safety of 274 mg ADS-5102 (amantadine) extended-release capsules (equivalent to 340-mg amantadine HCl) for levodopa-induced dyskinesia in a randomized controlled trial.
Methods: PD patients with ≥1 hour of troublesome dyskinesia and at least mild functional impact were randomized to placebo or ADS-5102 once daily at bedtime for 13 weeks. The primary efficacy analysis was based on change from baseline to week 12 on the Unified Dyskinesia Rating Scale total score in the modified intent-to-treat population. OFF time was a key secondary measure.
Results: At week 12, least-squares mean change in the Unified Dyskinesia Rating Scale was −20.7 (standard error 2.2) for ADS-5102 (n = 37) and –6.3 (standard error 2.1) for placebo (n = 38; treatment difference −14.4, 95% confidence interval −20.4 to −8.3, $P < .0001$), indicating improvement in levodopa-induced dyskinesia. OFF time decreased 0.5 hours (standard error 0.3) for ADS-5102 from a baseline mean of 2.6 hours and increased 0.6 hours (standard error 0.3) for placebo from a baseline mean of 2.0 hours (treatment difference −1.1 hours, 95% confidence interval −2.0 to −0.2, $P = .0199$). The most common adverse events (ADS-5102 versus placebo) included dry mouth (13.5% versus 2.6%), nausea (13.5% versus 2.6%), decreased appetite (10.8% versus 0%), insomnia (10.8% versus 0%), orthostatic hypotension (10.8% versus 0%), constipation (8.1% versus 0%), falls (8.1% versus 5.3%), and visual hallucinations (8.1% versus 5.3%). Adverse events led to treatment discontinuation in 19% versus 8%, respectively.
Conclusion: ADS-5102 274 mg is an oral pharmacotherapy demonstrating a significant decrease in levodopa-

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EASE LID 3 principal investigators are listed in the Acknowledgments.

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induced dyskinesia and improving OFF time.

Key Words: Parkinson's disease; amantadine; Unified Dyskinesia Rating Scale; levodopa-induced dyskinesia; randomized controlled trial

Levodopa-induced dyskinesia (LID) is a significant treatment-limiting adverse effect of levodopa therapy that results in the suboptimal management of Parkinson's disease (PD). As PD progresses, patients experience diminished duration of benefit from each levodopa dose, termed *wearing-off*, and motor fluctuations with OFF time between doses. In addition, chronic levodopa treatment often leads to the development of dyskinesia. In patients treated with levodopa, dyskinesia can occur in approximately 50% of patients by 5 years and nearly 90% of patients by approximately 10 years of treatment.[1] LID is associated with impaired activities of daily living, decreased health-related quality of life, increased risk of falls, increased health care utilization, and increased caregiver burden.[2-5]

Many patients on levodopa experience both wearing-off and dyskinesia. LID may be managed by modifying the patient's levodopa dose by either decreasing each dose or fractionating the total daily dose.[6] A monoamine oxidase type B inhibitor, dopamine agonist, or catechol-*O*-methyltransferase inhibitor can be used to treat the underlying PD but may exacerbate dyskinesia.[7] A critical objective in reducing OFF time is to avoid a simultaneous increase in dyskinesia. As there is no approved drug therapy for LID, physicians and patients are faced with a trade-off between ON time with dyskinesia, or greater OFF time without dyskinesia. Patient research shows a strong preference for avoiding the uncomfortable or painful OFF state.[3] If a drug could reduce both OFF time and dyskinesia, it would be a major advance in therapeutics. So far, no drug has been proven to accomplish this goal.

Amantadine immediate release (amantadine IR) was approved in the United States as a prophylactic agent against Asian influenza in 1966.[8] In 1969, Schwab and colleagues[9] discovered by serendipity the beneficial effect of amantadine hydrochloride (HCl) on the motor symptoms of PD, but it took more than 30 years to discover its antidyskinetic effect. Relatively short studies have shown an antidyskinetic effect with amantadine IR; however, this effect has not been extensively studied in well-controlled, randomized, long-term clinical trials.[9-12] Despite the same body of trial evidence, there are differing guideline recommendations regarding the use of amantadine in the treatment of levodopa-induced dyskinesia.[13,14] A Cochrane review concluded that there was insufficient evidence to conclude whether amantadine is an effective treatment for LID in patients with PD.[15] American Academy of Neurology guidelines concluded amantadine to be "possibly effective,"[13] whereas a Movement Disorders Society evidence-based review reported that amantadine IR was "efficacious" in the treatment of dyskinesia.[14]

The mechanism of action of amantadine in decreasing LID is not known. Amantadine is an uncompetitive (open-channel) antagonist of the *N*-methyl-D-aspartate (NMDA) receptor (Ki = 10 μM), a type of glutamatergic receptor, and has direct and indirect effects on glutamatergic and dopaminergic signaling.[16-19] Amantadine exhibits predictable anticholinergic (eg, dry mouth, urinary retention, and constipation) and NMDA receptor antagonist activity (eg, hallucinations).[10,20-22]

The safety profile of amantadine has been well characterized.[23,24] Although most patients with PD can tolerate 200 mg daily of amantadine IR (amantadine HCl, equivalent to 162 mg amantadine),[23] the increased frequency of adverse events (AEs) at higher doses,[25] in particular central nervous system events (including sleep disturbances), limits the routine use of amantadine IR at doses of 300 mg/day (equivalent to 243 mg amantadine) or higher. Dosing instructions for amantadine IR in Germany state that patients' last dose of the day should be taken no later than 4:00 in the afternoon.[24]

ADS-5102 (amantadine) extended-release capsules is being developed for the treatment of LID in patients with PD. The pharmacokinetic profile of ADS-5102 has been designed to exhibit an initially slow rate of rise in amantadine levels during sleep and high levels in the morning that are sustained throughout waking hours when patients most need relief from their dyskinesia. This profile enables higher dosing of ADS-5102, which is not interchangeable with amantadine IR on a mg-per-mg basis. The target dose of 274 mg ADS-5102 daily (equivalent to 340 mg amantadine HCl) was selected based on the results of an earlier phase 2/3 dose-ranging study (EASED study).[26] The present study was the second pivotal phase 3 study (prior study, EASE LID study[27]) designed to confirm the efficacy and safety of ADS-5102 274 mg dosed once daily at bedtime for the treatment of LID in patients with PD.

Methods

Study Design and Participants

A phase 3, randomized, double-blind, placebo-controlled study (EASE LID 3 Study, Adamas Pharmaceuticals, Inc., ADS-AMT-PD304) was conducted at 39

sites in the United States and Western Europe (Germany, France, Spain, and Austria). The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. Prior to initiating the study, all participating sites received approval from an institutional review board, research ethics board, or independent ethics committee. Written informed consent was obtained from all study participants before any study-related procedures were performed.

Key inclusion criteria included age between 30 and 85 years, inclusive; diagnosis of PD based on the United Kingdom Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria[28]; score of at least 2 on part IV, item 4.2 (functional impact of dyskinesia) of the Movement Disorder Society–Unified Parkinson's Disease Rating Scale (MDS-UPDRS) at screening and at day 1 (baseline); and at least 2 half-hour time periods between 9:00 AM and 4:00 PM documented as ON time with troublesome dyskinesia on a 24-hour PD patient diary[29] on each of 2 consecutive days just prior to day 1. All antiparkinson medications, including levodopa preparations, were to be unchanged for at least 30 days prior to screening and during study participation. Levodopa preparations had to be administered at least 3 times daily.

Key exclusion criteria included history of dyskinesia that was not caused by dopaminergic stimulation in PD; neurosurgical intervention related to PD; atypical parkinsonism; levodopa- or dopamine-agonist–induced psychosis; cognitive impairment as evidenced by a Mini-Mental State Examination score of less than 24 during screening; estimated glomerular filtration rate <50 mL/min/1.73 m^2; use of amantadine within 30 days prior to screening; documented inability to tolerate or lack of dyskinesia response to prior amantadine treatment; current treatment with apomorphine or dopamine receptor blocking agents; current treatment with medications that prolong the QT interval and have a known risk of torsades de pointes; clinically significant electrocardiographic abnormalities; use of rimantadine; or history of hypersensitivity or allergic reaction to amantadine, rimantadine, or memantine.

Randomization and Blinding

Eligible patients were randomized on day 1 in a 1:1 ratio to receive placebo or ADS-5102. ADS-5102 and placebo capsules and packaging were identical in appearance. The randomization list was generated and validated by Pharmaceutical Product Development, LLC (Wilmington, North Carolina). Randomization was accomplished through an interactive web-based response system managed by Endpoint Clinical (San Francisco, California), which also allowed for unblinding of treatment assignment if necessary for patient safety. All patients, study-site personnel, raters, sponsor, and contract research organization staff were blinded to treatment assignment. Data analyzers were blinded until after the database was locked.

Procedures

Prequalified raters completed training and were certified to administer efficacy scales. Rater training utilized the MDS teaching modules for the Unified Dyskinesia Rating Scale (UDysRS) and MDS-UPDRS. If possible, the same rater conducted efficacy assessments for a patient at least 30 minutes following the patient's regularly scheduled levodopa dose, and when the patient was ON (PD medications providing good effect on motor symptoms) and experiencing typical dyskinesia. There were up to 9 visits (Screening, Baseline, weeks 1, 2, 4, 8, 12, 13, and safety follow-up visits) in this study. Study visits and assessments were scheduled between 9:00 AM and 4:00 PM, and all study visits for an individual participant were to be scheduled at approximately the same time of day. Doses and regimens of antiparkinson medications were maintained without changes during study participation.

During screening (up to 3 weeks prior to baseline), written informed consent was obtained, training and concordance testing for the PD home diary was completed, and study eligibility criteria were assessed. A set of two 24-hour PD home diaries was distributed for completion just prior to the scheduled baseline visit. During the baseline visit (week 0, day 1), study eligibility was confirmed and patients were randomized to ADS-5102 or placebo.

In addition, the following efficacy assessments were completed: UDysRS, review of completed PD home diaries, MDS-UPDRS, and baseline notes to allow future assessment of the Clinician's Global Impression of Change (CGI-C).

During the first week of dosing, patients randomized to ADS-5102 received a daily ADS-5102 dose of 137 mg (one ADS-5102–containing capsule and one placebo capsule, identical in appearance). During weeks 2 through 12, the daily ADS-5102 dose was 274 mg, administered as two 137-mg capsules. During the last week of dosing, the dose was reduced to 137 mg daily. Patients randomized to placebo received 2 placebo capsules for 13 weeks. Individuals who discontinued the study drug were encouraged to continue study participation and complete all study visits.

The UDysRS, MDS-UPDRS, CGI-C, and standard safety assessments were performed at weeks 2, 4, 8, and 12. The PD home diaries were completed prior to each of these visits. A final safety follow-up visit occurred approximately 7 days following treatment completion unless a patient elected to enroll directly into a companion open-label safety study (NCT02202551).[30]

Outcomes

The primary outcome measure was the change from baseline to week 12 in the UDysRS total score. Key secondary outcome measures included the change from baseline to week 12 in ON time without troublesome dyskinesia (ON time without dyskinesia plus ON time with non-troublesome dyskinesia) and OFF time. Other secondary measures included change from baseline to week 12 in MDS-UPDRS, ON time with troublesome dyskinesia, total ON time with dyskinesia (non-troublesome plus troublesome), and the CGI-C. Safety assessments included AEs, reasons for discontinuation, physical examinations, vital signs, and clinical laboratory testing.

Statistical Analyses

The sample size was estimated based on the previous phase 2/3 study,[26] which suggested that 36 patients per group would provide 90% power to detect a treatment difference between the ADS-5102 and placebo groups of 11.5 units (standard deviation 14) with an α level of 0.05 and a potential dropout rate of up to 10%.

The primary efficacy analysis compared the active (274 mg ADS-5102) group with the placebo group at week 12 using a linear mixed model with repeated measures with the changes from baseline in the UDysRS total score at weeks 2, 4, 8, and 12 as the dependent variable. The model included categorical effects for treatment group, visit (4 levels corresponding to weeks 2, 4, 8, and 12), and the interaction between treatment group and visit. The baseline UDysRS total score was included as a covariate. Estimates for the least squares mean change from baseline at week 12 in each treatment arm along with the least squares mean treatment difference were provided with 95% confidence intervals (CIs) using an appropriate contrast from the model.

The following key secondary analyses were conducted using a fixed-sequence hierarchical procedure to control the overall level of significance, in the order shown below:

- 274 mg ADS-5102 versus placebo for ON time without troublesome dyskinesia at week 12
- 274 mg ADS-5102 versus placebo for OFF time at week 12.

The week 12 secondary analyses in this list were performed using linear mixed model with repeated measures models.

The hypotheses were tested using 2-sided tests at the 5% level of significance, but a specified comparison was considered confirmatory only if the primary efficacy analysis and all previously conducted key secondary analyses were statistically significant ($P < .05$).

The modified intent-to-treat population (mITT) was the prespecified efficacy analysis population and included all randomized patients who were dosed and who provided at least 1 post-baseline assessment of the UDysRS. The safety population included all randomized patients who received at least 1 dose of study drug. Prespecified directions for the handling of individual missing data values related to each efficacy outcome measure were included in the Statistical Analysis Plan. The software package SAS (version 9.4; SAS Institute, Cary, North Carolina) was used for analysis. A data monitoring committee was not used for this trial.

This study is registered with ClinicalTrials.gov, number NCT02274766.

Results

Between October 16, 2014, and December 9, 2015, 114 patients were screened and 77 patients were randomized (Fig. 1). The most common reason for screen failure was that the patient did not report at least 2 half-hour time periods of ON time with troublesome dyskinesia. The mITT and safety populations included 75 patients. Two patients were inadvertently randomized but never dosed. A week 12 visit (primary efficacy endpoint) was completed by 83% of randomized patients. The most common reason for study drug discontinuation was AEs. No unblinding of the treatment assignment was necessary during the study. Demographics and baseline characteristics of the mITT population are shown in Table 1. The treatment groups were balanced at study entry for patient demographics.

The primary efficacy analysis demonstrated a significantly greater reduction in UDysRS total score (improvement in dyskinesia) in the ADS-5102 group when compared with placebo at week 12 (least squares mean treatment difference −14.4 [95% CI −20.4 to −8.3], $P < .0001$; Table 2). Changes in UDysRS total scores at all study visits for ADS-5102 and placebo groups are shown in Figure 2A. The treatment effect of ADS-5102 on UDysRS total score was consistent across the following subgroups: sex, age, baseline renal function, body mass index, dyskinesia severity, baseline OFF time, and baseline levodopa dose (Supplemental Fig. 1).

The historical (patient-reported duration and impact) and objective (rater assessment of impairment and disability) UDysRS scores showed a significantly greater improvement in the ADS-5102 group when compared with placebo at 12 weeks (Table 2). The key secondary PD diary endpoints (ON time without troublesome dyskinesia and OFF time) also showed significant improvements in the ADS-5102 group (Table 2). Changes in PD diary endpoints at all study visits for ADS-5102 and placebo groups are shown in Figure 2B.

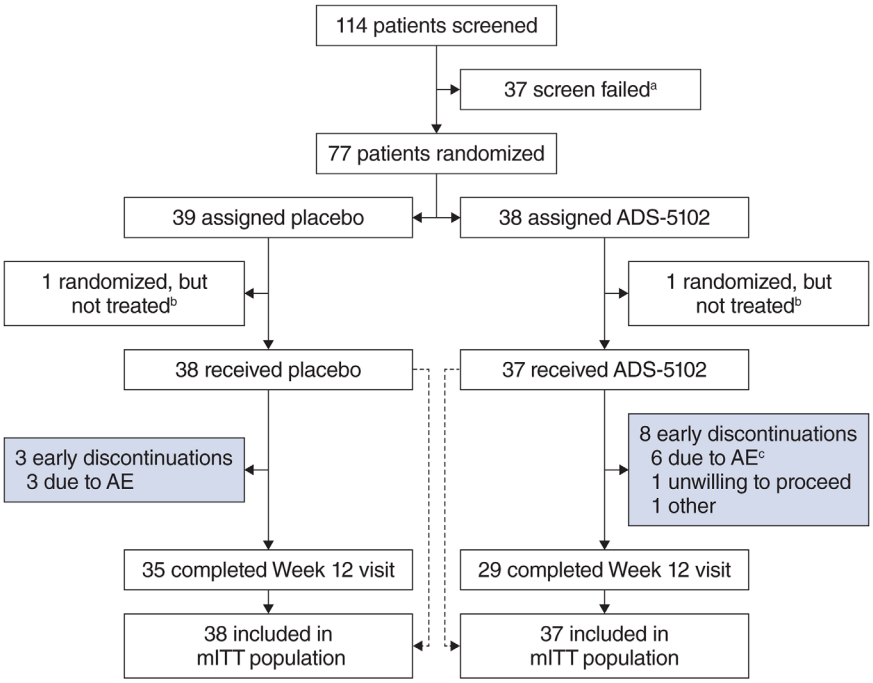

FIG. 1. Trial profile. [a]The most common reason for screen failure was that the patient did not report at least two half-hour time periods of ON with troublesome dyskinesia at baseline. [b]Two participants, randomized to ADS-5102 and placebo, respectively, were randomized in error and did not receive study drug. [c]One additional patient discontinued study drug as a result of AEs but continued the study. AE, adverse event; mITT, modified intent-to-treat. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1. Baseline demographics and PD characteristics (modified intent-to-treat population)

	Placebo, n = 38	ADS-5102, n = 37
Age, y	64.9 (9.1)	64.7 (9.7)
Sex, male	20 (52.6)	19 (51.4)
Race, white	38 (100.0)	36 (97.3)
Baseline levodopa (any preparation), dose (mg)	635.8 (446.7)	671.9 (465.7)
Duration of LID, y	4.0 (2.6)	3.8 (3.2)
Years since PD diagnosis	10.7 (4.3)	10.4 (5.1)
Mini-Mental State Examination	28.7 (1.4)	29.1 (1.6)
Hoehn and Yahr (while ON)	2.4 (0.6)	2.1 (0.6)
UDysRS, total (max possible score: 104)	41.2 (10.3)	40.2 (13.1)
PD home diary		
ON time with troublesome dyskinesia, h	6.0 (3.4)	4.7 (2.5)
ON time without troublesome dyskinesia, h	7.8 (3.2)	8.8 (2.5)
OFF time, h	2.0 (1.7)	2.6 (2.0)
Participants with OFF time at baseline	35 (84.2)	29 (86.5)
MDS-UPDRS (while ON)		
Part I (max possible score: 52)	9.9 (4.9)	11.3 (59)
Part II (max possible score: 52)	14.8 (6.1)	14.1 (6.2)
Part III (max possible score: 132)	21.4 (10.2)	21.2 (9.2)
Combined score (Parts I–III) (max possible score: 236)	46.1 (17.0)	46.6 (14.8)
Part IV (max possible score: 24)	11.1 (2.4)	9.8 (2.8)
Part IV, item 4.1, time spent with dyskinesia	2.8 (0.9)	2.2 (0.8)
Part IV, item 4.2, functional impact of dyskinesia	2.5 (0.5)	2.5 (0.6)
Concomitant medication use at baseline		
Dopamine agonist	25 (65.8)	21 (56.8)
MAO inhibitor	20 (52.6)	17 (45.9)
COMT inhibitor	1 (2.6)	3 (8.1)
Anticholinergic	2 (5.3)	0 (0.0)

Data are mean (standard deviation) or n (%). COMT, catechol-*O*-methyltransferase; LID, levodopa-induced dyskinesia; MAO, monoamine oxidase; MDS-UPDRS, Movement Disorder Society–Unified Parkinson's Disease Rating Scale; PD, Parkinson's disease; UDysRS, Unified Dyskinesia Rating Scale.

TABLE 2. Efficacy results (modified intent-to-treat population)

	LS mean change from baseline to week 12 (SE)			
	Placebo, n = 38	ADS-5102, n = 37	Treatment difference, 95% CI	*P* value
Primary endpoint				
UDysRS total score	−6.3 (2.1)	−20.7 (2.2)	−14.4 (−20.4 to −8.3)	<.0001
Key secondary endpoints				
ON time without troublesome dyskinesia	2.1 (0.5)	4.0 (0.6)	1.9 (0.4 to 3.5)	.0168
OFF time	0.6 (0.3)	−0.5 (0.3)	−1.1 (−2.0 to −0.2)	.0199
Other secondary endpoints				
ON time with troublesome dyskinesia	−2.5 (0.4)	−3.6 (0.5)	−1.1 (−2.4 to 0.2)	.0853
Total time with dyskinesia	−2.7 (0.7)	−4.2 (0.7)	−1.6 (−3.59 to 0.45)	.1254
ASLEEP time	8.1 (1.6)	8.1 (1.6)	n/a	n/a
UDysRS historical score, parts I & II	−4.0 (1.4)	−12.1 (1.5)	−8.1 (−12.1 to −4.1)	.0001
UDysRS objective score, parts III & IV	−2.2 (1.2)	−8.7 (1.3)	−6.5 (−10.1 to −3.0)	.0004
MDS-UPDRS, part IV, motor complications	−1.3 (0.5)	−4.3 (0.5)	−3.0 (−4.5 to −1.6)	<.0001
MDS-UPDRS, part IV, item 4.1, time spent with dyskinesia	−0.6 (0.2)	−0.9 (0.2)	−0.3 (−0.8 to 0.2)	.1929
MDS-UPDRS, Part IV, item 4.2, functional impact of dyskinesia	−0.6 (0.1)	−1.6 (0.2)	−0.9 (−1.4 to −0.5)	<.0001
MDS-UPDRS, combined score, parts I-III	−2.0 (2.1)	−8.4 (2.2)	−6.5 (−12.7 to −0.3)	.0398
Daily levodopa dose (any preparation), mg, mean change from baseline (SD)	0.0 (0.0)	−13.5 (67.3)	n/a	n/a

CI, confidence interval; LS, least squares; MDS-UPDRS, Movement Disorder Society–Unified Parkinson's Disease Rating Scale; n/a, not applicable; SD, standard deviation; SE, standard error; UDysRS, Unified Dyskinesia Rating Scale.

To further characterize the effect of ADS-5102 on patient-reported diary states throughout waking hours, a summary of diary states across waking hours for the study population was generated (Supplemental Fig. 2). The results showed a greater increase in ON time without troublesome dyskinesia (as a result of decreases in both OFF time and ON time with troublesome dyskinesia) throughout waking hours for the ADS-5102–treated patients when compared with placebo-treated patients.

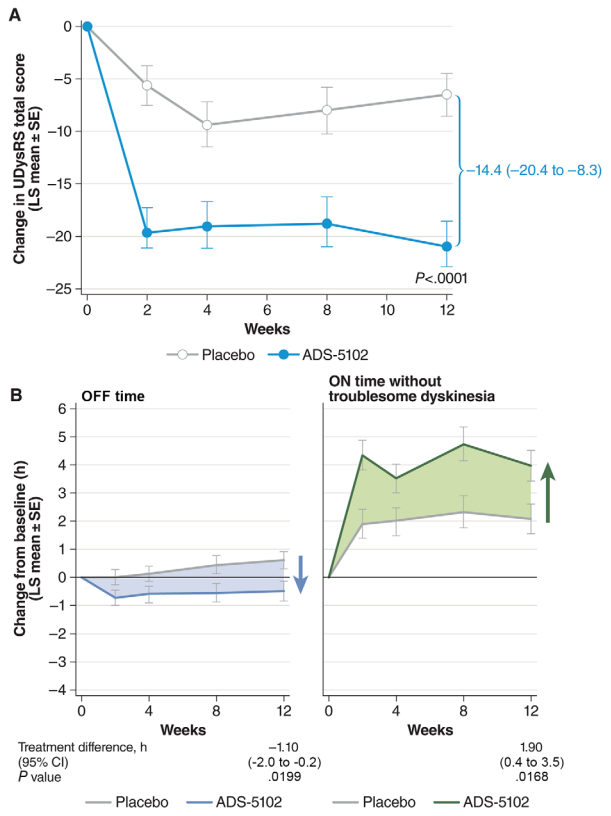

FIG. 2. (**A**) Change in UDysRS over time (mITT population). Range in parentheses indicates 95% confidence interval. (**B**) Change in PD home diary data over time (mITT population). CI, confidence interval; LS, least squares; mITT, modified intent-to-treat; PD, Parkinson's disease; UDysRS, Unified Dyskinesia Rating Scale; SE, standard error.

At week 12, changes in MDS-UPDRS showed a statistically significant treatment effect for ADS-5102 at week 12 for the part II score ($P = .0076$), the combined scores for parts I, II, and III ($P = .0398$), and for the part IV score ($P < .0001$; Table 2). The CGI-C results showed that 19 patients (51%) in the ADS-5102 group and 4 patients (11%) in the placebo group were assessed as moderately or markedly improved in overall PD symptoms, including dyskinesia, at week 12 ($P = .0009$ for overall distribution; Supplemental Table 1).

Overall, AEs were reported for 84% of ADS-5102 patients and 50% of placebo patients. Most patients reported AEs that were mild to moderate in intensity (26 [70%] in ADS-5102 and 17 [45%] in placebo). The most common AEs (≥5% in the ADS-5102 group) were dry mouth, nausea, decreased appetite, insomnia, orthostatic hypotension, constipation, falls, and visual hallucinations (Table 3). Two study drug–related serious AEs (constipation and urinary retention) were reported for 1 patient during the study. One patient treated with ADS-5102 experienced suicidal ideation (assessed by the investigator as related to the study drug), and a second patient attempted suicide (assessed by the investigator as not related to the study drug). Both patients had a history of depression and discontinued the study drug. The patient who

TABLE 3. Adverse events (AEs) overview (safety population)

	Placebo, n = 38	ADS-5102, n = 37
Number (%) of participants with any:		
AEs	19 (50.0)	31 (83.8)
Study drug-related AEs	10 (26.3)	21 (56.8)
Serious AEs	0	4 (10.8)
Study drug-related serious AEs	0	1 (2.7)
Number (%) of participants who permanently discontinued treatment as a result of any:		
AEs	3 (7.9)	7 (18.9)
Study drug-related AEs	2 (5.3)	6 (16.2)
Most common AEs (at least 5% in active arm)		
Dry mouth	1 (2.6)	5 (13.5)
Nausea	1 (2.6)	5 (13.5)
Decreased appetite	0	4 (10.8)
Insomnia	0	4 (10.8)
Orthostatic hypotension	0	4 (10.8)
Constipation	0	3 (8.1)
Fall	2 (5.3)	3 (8.1)
Hallucination, any type	2 (5.3)	3 (8.1)
Hallucination, visual	2 (5.3)	3 (8.1)
Hallucination, auditory	0	1 (2.7)

attempted suicide had stopped the study drug 4 days prior to the attempt. There were no deaths. In general, vital signs and laboratory results remained consistent with baseline values throughout the study.

Of the 37 ADS-5102 patients, 7 (19%) and 3 (8%) of the 38 placebo patients discontinued the study drug because of AEs. In the ADS-5102 group, 5 of these 7 patients discontinued treatment during the first month (16% of ADS-5102 group). The most common AE leading to treatment discontinuation in the ADS-5102 group was visual hallucinations (2 [5.4%]).

Discussion

ADS-5102 is a high-dose, extended-release amantadine administered once daily at bedtime with a slow initial rate of rise in amantadine concentrations and a prolonged T_{max} without exacerbating adverse events. This pharmacokinetic profile provides a peak concentration in the morning with continuous coverage throughout the day to alleviate LID, with high plasma concentrations (approximately 1500 ng/mL) that cannot be achieved with conventional dosing (100 mg bid/tid) with amantadine IR.

This is the second pivotal phase 3 study confirming that ADS-5102 significantly improves dyskinesia in patients with PD.[27] Efficacy of ADS-5102 was demonstrated across multiple outcome measures assessing several aspects of dyskinesia. Bedtime administration of ADS-5102 274 mg (equivalent to 340 mg amantadine HCl) was associated with a clinically significant reduction in the UDysRS total score when compared with placebo. ADS-5102 was also associated with a significant increase in ON time without troublesome dyskinesia. These diary results, along with the marked improvement in CGI-C, support the clinical relevance of the decrease in the UDysRS total score and the reduction in LID. In addition, the antidyskinetic benefit of ADS-5102 was achieved with a significant reduction in OFF time as well as an improvement in MDS-UPDRS scores.[31]

Statistical significance in reducing ON time with troublesome dyskinesia was not met largely because of the placebo response (change from baseline of −2.5 hours). In comparison, the placebo response in the companion EASE LID study[27] was −1.6 hours at week 12. In both studies, the ADS-5102 group had a similar decrease in ON time with troublesome dyskinesia at week 12 (EASE LID: -3.2 hours, EASE LID 3: −3.6 hours).

The most common AEs with ADS-5102 treatment are largely predicated by its NMDA receptor antagonist activity (eg, hallucinations) and anticholinergic activity (eg, dry mouth and constipation). Most AEs were of mild to moderate intensity, transient, and did not result in treatment discontinuation. The most common reason for discontinuation of treatment was visual hallucinations (n = 2). Participants with a major psychiatric disorder, including suicidal ideation, were excluded from participation in the study. Of the participants, 2 (both in the ADS-5102 group) had AEs related to suicidal attempt or ideation (1 each); both participants had a prestudy history of depression, and 1 participant had an undisclosed history of suicidal ideation. Patients should be monitored during treatment for the development of depressed mood, depression, and changes in behavior or thinking that are not typical for the patient and for suicidal ideation or behavior. Orthostatic hypotension may manifest as dizziness or result in falls. Risk factors for falls in patients with PD include prior history of falls, disease severity, gait abnormalities, and cognitive impairment.[32] Precautions should be taken to reduce the risk of falls. Although incidences of AEs such as hallucinations, orthostatic hypotension, and falls were increased in the ADS-5102 group, these events represented mostly reversible morbidity, were generally mild to moderate in nature, and most did not result in study drug discontinuation. ADS-5102 has a manageable safety profile.

In the study, the rate of visual hallucination in the ADS-5102 group was lower than that reported in the previous phase 3 study[27] (24% vs 8%). This does not appear to be explained by baseline PD duration, LID duration or severity, or age, as both studies had similar baseline demographics. However, participants randomized to ADS-5102 in the current study reported a lower mean baseline levodopa dose (672 mg vs 906 mg) and a greater prevalence of dopamine agonists

(57% vs 46%) and monoamine oxidase inhibitor use (46% vs 41%) compared with patients who received ADS-5102 in the previous phase 3 study. Use of anticholinergics was low in both study populations (<5% of total participants).

Goetz and colleagues[33] reported a placebo-corrected reduction in the UDysRS total score of −6.6 points after 8 weeks of treatment with amantadine IR (mean dose: 229 mg of amantadine per day). In the EASE LID 3 study, which did not include a direct comparison with amantadine IR, ADS-5102 treatment at 274 mg resulted in a placebo-corrected −14.4-point decrease in UDysRS total score after 12 weeks.[33] However, any conclusions regarding the relative efficacy and safety of ADS-5102 and amantadine IR would require a direct comparison of these agents in a randomized trial, and no such direct comparison exists. Based on results from this pivotal phase 3 study, and the first pivotal phase 3 study (EASE LID),[27] there is substantial evidence that 274 mg of ADS-5102 administered at bedtime is an effective dosage for the treatment of dyskinesia. Long-term safety of this ADS-5102 regimen is currently being evaluated in an open-label safety study (ClinicalTrials.gov identifier: NCT02202551).[30] Future research efforts should establish the minimal clinically important difference for the UDysRS. In addition, studies that address converting treatment from amantadine IR to ADS-5102 may be useful.

There is no approved drug therapy for LID. DBS (Activa, Medtronic, Minneapolis, Minnesota; Brio, St. Jude Medical, St. Paul, Minnesota) is currently the only approved treatment for reducing symptoms of advanced levodopa-responsive PD that are not adequately controlled. There remains an unmet need for an approved pharmacotherapy that treats dyskinesia without compromising underlying PD control and has a manageable safety profile.[27] Of note, 60 patients who continue to experience dyskinesia despite undergoing DBS have been enrolled in an ongoing ADS-5102 open-label safety study.[30]

The effect of ADS-5102 reducing both dyskinesia and OFF time has now been confirmed in 2 phase 3 controlled studies. These data support ADS-5102 as an adjunctive therapy to levodopa for the treatment of dyskinesia and OFF in PD patients with LID. In addition, 95% of patients who completed this study continued into a 2-year extension study that will allow further evaluation of the long-term efficacy and safety of ADS-5102 in this patient population. ■

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Supporting Data

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