ADS-5102 Increased ON Time Without Troublesome Dyskinesia Throughout Waking Hours in the EASED Study

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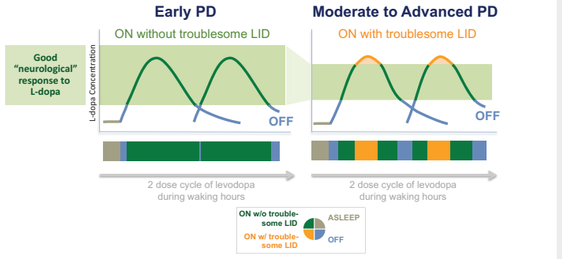
Background

- For the past 30 years, drugs aimed at improving motor complications have increased ON time without troublesome dyskinesia primarily through the reduction in OFF time. No agents have increased ON time without troublesome dyskinesia by reducing the duration and/or severity of dyskinesia. There is currently no approved medication for the treatment of levodopa-induced dyskinesia (LID).

Figure 1. Development of Troublesome LID and OFF Episodes During Chronic Treatment of PD
(Figure depicts a 2-dose cycle of levodopa)



- ADS-5102 is an extended release formulation of amantadine HCl being developed for the treatment of LID. Administered once daily at bedtime, ADS-5102 is designed to deliver its primary treatment effect when the complications of levodopa treatment are at their worst, and potentially reduce the known adverse events of immediate-release amantadine when the patient is asleep.
- In a recent publication (Pahwa, 2015), results from the Phase 2/3 EASED study (NCT 01397422), a multicenter, randomized, double-blind study of 83 subjects with PD, demonstrated that ADS-5102 340 mg once daily at bedtime reduced the disability and functional impact of LID as measured by the Unified Dyskinesia Rating Scale as well as by PD home diaries. (Study eligibility required at least 1 hour of troublesome LID between 9 am and 4 pm on baseline diaries.)
- ADS-5102 was generally well tolerated and reported adverse event terms were consistent with PD and the known amantadine safety profile.
- Diary results were reported as time spent in each diary state during 24 hours. This new analysis provides a time profile of the diary states, synchronized to subject WAKE-UP time.

Objectives

- To describe the time profile of motor complications throughout the day for PD patients with troublesome dyskinesia.
- To determine the impact of ADS-5102 on troublesome dyskinesia throughout the day.

Methods

- EASED study subjects completed 2 consecutive 24-hour PD home diaries at Baseline and every 2 weeks, indicating time (in half-hour intervals over each 24 hours) spent ASLEEP, OFF, ON without dyskinesia, ON with non-troublesome dyskinesia and ON with troublesome dyskinesia. Each diary covered a 5:30 am to 5:30 am 24-hour time period. If a subject's WAKE-UP time was later than 6 am, a full 24-hour cycle of post-awakening data could not be captured. We collected at least 17 hours of post-awakening data for all subjects.
- A post hoc analysis of the diary data utilized a pre-defined per protocol analysis population (a subset of the mITT population that completed 8 weeks of study treatment and provided Week 8 efficacy assessments).
- This post hoc analysis compares the percentage of placebo versus ADS-5102 treated subjects (all 3 dose levels) experiencing each PD diary state throughout the day, in half-hour intervals, at Baseline and at Week 8. Because diary results from the earlier mITT analysis were similar for the 3 dose levels of ADS-5102, the ADS-5102 subjects were pooled for this analysis.

Results

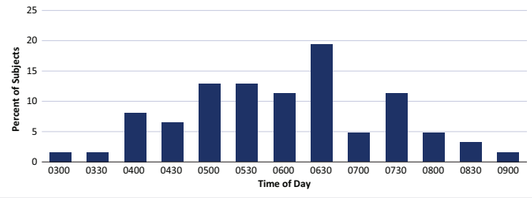
- The per protocol population included 63 subjects; 1 subject who did not contribute 2 consecutive valid diaries at baseline was excluded from the analysis.

Table 1. Demographics and Baseline Characteristics

		Placebo (N=20)	Combined ADS-5102 (N=42)
Age (yrs), Mean (SD)		65.4 (9.1)	64.6 (9.0)
Sex	Male	13 (65.0)	20 (47.6)
Ethnicity	Not Hispanic or Latino	19 (95.0)	39 (92.9)
Race	White	18 (90.0)	38 (90.5)
Time Since PD Diagnosis (yrs), Mean (SD)		9.8 (6.4)	8.9 (3.4)
Duration of Levodopa Treatment (yrs), Mean (SD)		8.2 (6.1)	7.23 (3.7)
Daily Levodopa Dose (mg), Mean (SD)		778.8 (435.1)	686.3 (334.9)
Duration of LID (yrs), Mean (SD)		3.96 (3.98)	3.39 (2.4)
Baseline UDysRS, Total, Mean (SD)		39.2 (18.1)	40.8 (12.4)

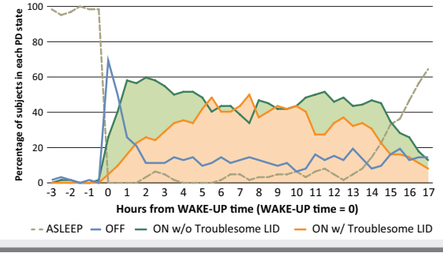
- Diary data completeness in the EASED study was excellent, with 100% and 97% of PD diaries considered valid (no more than four 30 minute intervals of missing or illegible data) at baseline and Week 8, respectively; data missing from valid diaries were imputed using pre-specified algorithms.
- This diary data set was synchronized according to each subject's WAKE-UP time. The WAKE-UP time for each subject was defined as the beginning of the first 2 hour period of awake time (4 consecutive half-hour intervals not recorded as ASLEEP) starting no earlier than 3 am.

Figure 2. Distribution of WAKE-UP Times (Baseline, All Subjects, N=62)



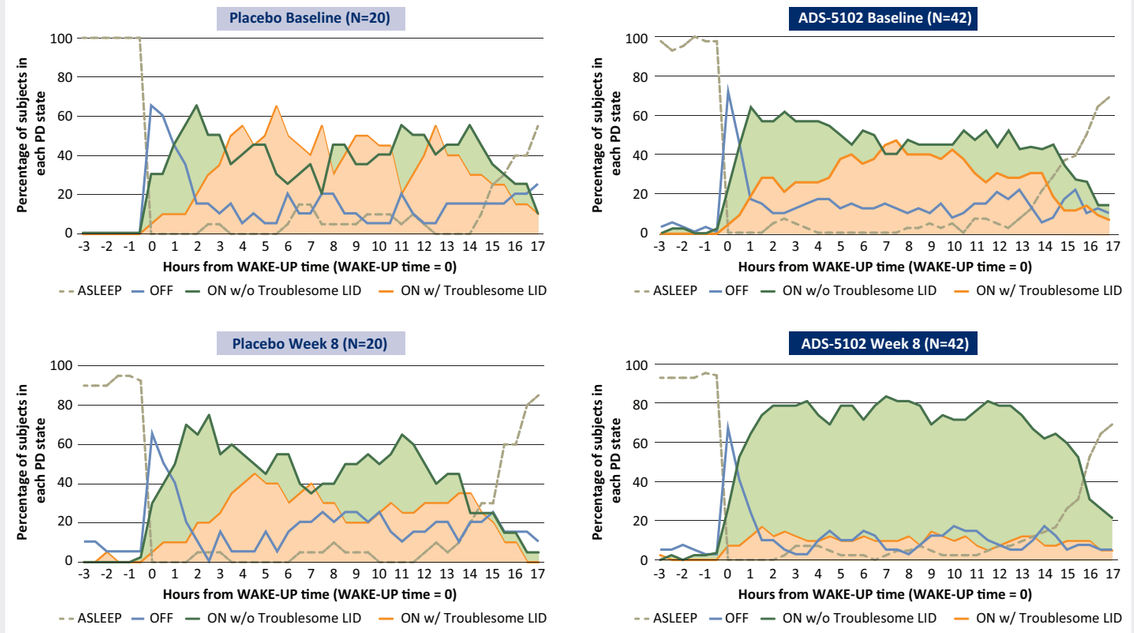
- Baseline WAKE-UP time of subjects ranged from 3 am to 9 am. Because of the variability in WAKE-UP time, synchronization of subjects' diary profiles was important to characterizing the time profile.

Figure 3. Synchronized Time Profile of Motor Complications (Baseline, N=62)



- Within 30 minutes after WAKE-UP, approximately 70% of subjects were in the OFF state; this rapidly diminished over the next hour, presumably reflecting the effect of the first morning dose of levodopa.
- After the early morning OFF time peak, the percentage of subjects in the OFF state was approximately 15% during the remainder of the day.
- The majority of subjects reported what would be considered good ON time (ON without troublesome LID) between 1 and 4 hours post-awakening.
- Troublesome LID was reported throughout the day.

Figure 4. Synchronized Time Profile of Motor Complications, Placebo vs. ADS-5102 (Baseline and Week 8)



- At Week 8, the placebo group showed little change in the time profile, with a modest reduction in the percentage of subjects reporting ON time with trouble-some dyskinesia (along with an increase in subjects without troublesome dyskinesia) compared to Baseline.
- In contrast, at Week 8, ADS-5102 treatment resulted in a pronounced change in the synchronized time profile throughout the morning, afternoon and evening. In contrast to Baseline and Week 8 placebo profiles, the Week 8 ADS-5102 profile was essentially simplified to two diary states: ON without troublesome dyskinesia and ASLEEP.
- The majority of ADS-5102-treated subjects reported ON time without troublesome dyskinesia throughout the waking day, for at least 14 hours post-awakening.

Conclusions

- Synchronized time profile diary analysis elucidated the complex and dynamic pattern of motor complications over the course of a day for PD clinical trial subjects with LID.
- Subjects awaken primarily in the OFF state, followed by ON without troublesome LID, and then by variable episodes of OFF and ON with troublesome LID.
- In this analysis, ADS-5102 treatment improved the quality of ON time by increasing ON time without troublesome LID from morning to late afternoon and evening hours.
- The safety and efficacy of ADS-5102 340 mg, including these diary findings, are being evaluated for the treatment of LID in confirmatory global Phase 3 clinical trials.

Acknowledgements and Disclosures
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Reference: Pahwa R, Tanner CM, Hauser RA, Sethi K, Isaacson S, Truong D, Struck L, Ruby AE, McClure NL, Went GT, Stempien MJ. Amantadine extended release for levodopa-induced dyskinesia in Parkinson's disease (EASED Study). Movement Disorders. 2015 May;30(6):788-95

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