Background

- Levodopa-induced dyskinesia (LID) is a dose-limiting adverse effect of Parkinson’s disease (PD) treatment, characterized by disabling, and negative impact on quality of life. There is currently no approved treatment for LID.
- Amantadine has multiple mechanisms of action, including acting as an NMDA receptor antagonist, and as a mild dopamine agonist. Amantadine has shown activity in several preclinical and clinical studies.

Methods

- Randomized, double-blind, placebo-controlled, parallel-group study conducted at 31 U.S. clinical trial sites (NCT 03745723).
- Consented and eligible PD patients with troublesome LID were randomized in a 1:1:1 ratio to one of three doses of ADS-5102 (200 mg, 140 mg, 420 mg), dosed once-nightly for 8 weeks.
- The primary efficacy analysis was performed using the last observation carried forward (LOCF) approach, followed by dose increases at one week intervals (140 mg, then 420 mg), depending on treatment assignment.

Objectives

- Investigate the safety, efficacy, and tolerability of once-nightly administration of 3 dose levels of ADS-5102 for LID in PD.

Results

- The demographics and baseline characteristics appeared to be balanced across treatment groups.

Table 1. Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Age (Mean, SD)</th>
<th>MDS-UPDRS Combined Score (parts I, II and III)</th>
<th>MDS-UPDRS Total Objective Score (III, IV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>73.7 ± 5.1</td>
<td>44.7 ± 8.4</td>
<td>44.7 ± 8.4</td>
</tr>
<tr>
<td>ADS-5102 200 mg</td>
<td>74.3 ± 5.5</td>
<td>45.2 ± 8.3</td>
<td>45.2 ± 8.3</td>
</tr>
<tr>
<td>ADS-5102 140 mg</td>
<td>74.2 ± 5.5</td>
<td>45.2 ± 8.4</td>
<td>45.2 ± 8.4</td>
</tr>
<tr>
<td>ADS-5102 420 mg</td>
<td>73.8 ± 5.2</td>
<td>44.7 ± 8.2</td>
<td>44.7 ± 8.2</td>
</tr>
</tbody>
</table>

- ADS-5102 is being investigated at daily dose strengths between 1.3 and 2.1-fold higher than those typically used for immediate-release amantadine.

Additional Efficacy Analyses

- The results of analyses of additional efficacy outcome measures, including PD home diary measures (ON Time without troublesome dyskinesia, ON Time with OFF with Troublesome Dyskinesia), MDS-Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) combined score (parts I, II, and III), and MDS-Unified Dyskinesia Rating Scale (UDysRS) Total Score were consistent with Parkinson’s disease and the known amantadine safety profile.

Safety Results

- The safety population included all 83 randomized and treated subjects.
- Treatment emergent AEs were common in all treatment groups, and most were mild to moderate in severity. Serious drug-related AEs were:
  - 260 mg (2 patients: visual ideation); 420 mg (3 patients: confusional state, hallucinations, dizziness, muscle spasms, peripheral edema); 420 mg (5 subjects: balance disorder, hallucinations, psychiatric disorders, hyperammonemia, increased hepatic enzymes, dry mouth, constipation).

Conclusions

- The study met its primary endpoint: Both the 340 mg and 420 mg ADS-5102 doses significantly reduced LID as measured by the change to UDysRS Total Score over 8 weeks versus placebo (p=0.005 and p=0.003, respectively).
- ADS-5102 significantly reduced Troublesome Dyskinesia at the 200 mg, 340 mg and 420 mg dose levels as measured by the change to UDysRS Total Score over 8 weeks versus placebo (p=0.048, p=0.04, and p=0.004, respectively, consistent with changes observed in the PD home diary). ADS-5102 resulted in statistically significant improvements in the functional impact of dyskinesias at the 200 mg, 340 mg, and 420 mg dose levels by MDS-UPDRS part IV (4.2) (p=0.016, p=0.002, and p=0.001, respectively).
- Treatment with ADS-5102 did not result in clinical worsening of PD as measured by the MDS-UPDRS combined score (parts I, II, and III).

- ADS-5102 was generally well tolerated and reported adverse event terms were consistent with Parkinson’s disease and the known amantadine safety profile.

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References

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