Background

- Motor complications (dyskinesia and OFF) are associated with fluctuations in concentrations of dopamine, increased extracellular glutamate, and over-activation of the gliature NMDA receptor.

- While amantadine IR has been used to treat dyskinesia, it has been shown to have short-term effect and increased adverse events at higher doses that limit its clinical utility.

- ADS-5102 (amantadine extended release) is a treatment for dyskinesia in patients with Parkinson’s disease (PD).

- It is an uncompetitive NMDA receptor antagonist.

- The maintenance dose is 274 mg amantadine (340 mg amantadine HCl) taken once daily at bedtime.

- It exhibits a slow redistribution in plasma concentration, a delayed T1/2 of 12 hours with sustained high plasma concentrations during waking hours, when dyskinesia and OFF symptoms can be most bothersome.

- Two Phase 3, placebo-controlled clinical studies of 3 and 6 months duration showed that ADS-5102 treatment reduced dyskinesia with a secondary effect of reduced OFF time.

- Previously reported open-label studies exhibited that ADS-5102 treatment effect on dyskinesia and OFF was maintained for up to 88 weeks.

Objectives

- To evaluate the effect of ADS-5102 on motor complications and tolérability in patients who changed from pre-existing IR treatment in the time of study enrollment (baseline) and subsequently switched to ADS-5102.

Study Design and Methods

- In the ongoing open-label safety study (EASE LID 2), conducted at 56 sites in North America and Western Europe (NCT01220351), Parkinson’s patients with dyskinesia requiring treatment (based on clinician’s judgment) received ADS-5102 274 mg once daily at bedtime for up to two years.

- Motor complications were assessed by the Movement Disorders Society-UCLA Parkinson’s Disease Rating Scale (MDS-UPDRS) Report IV (range 0 to 24).

- The MDS-UPDRS, Part IV was summarized for the following three subgroups from baseline through week 84 of the open-label study (EASE LID 2):

  - Previous Active – Patients previously treated with ADS-5102 during a double-blind phase 3 trial who switched without interruption to the open-label study (N=79).
  - Previous Placebo – Patients previously receiving placebo during a double-blind phase 3 trial who switched without interruption to the open-label study (N=79).
  - Previous Amantadine IR – Patients experiencing dyskinesia despite treatment with amantadine IR who switched to open-label ADS-5102 without interruption (N=32).

- The Previous Amantadine IR group did not participate in the Phase 3 controlled trials.

- They either had prior deep brain stimulation (DBS) (N=24) or were participants in the Phase 3/4 ADS-5102 dose finding study (N=4).

- Changes from baseline were analyzed using a mixed model repeated measures (MMRM) approach with categorical effects for subgroup, visit, and the interaction between subgroup and visit.

- The baseline MDS-UPDRS Part IV, at end of study, duration of levodopa treatment, baseline levodopa dose, and duration of dyskinesia were included as continuous covariates.

Patient Disposition

- In total, 32 patients were included in the previous amantadine IR subgroup, 24 patients were post-status DBS (average duration of DBS 4–6 years) and 8 subjects who previously completed the phase 2/3 EASE LID-2 study.

Table 1. Patient Disposition Overview

<table>
<thead>
<tr>
<th>Disposition</th>
<th>Previous Active IR</th>
<th>Previous Placebo</th>
<th>Previous Amantadine IR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligibility</td>
<td>46 (14.6)</td>
<td>48 (16.8)</td>
<td>27 (13.1)</td>
</tr>
<tr>
<td>Completed</td>
<td>3 (4.9)</td>
<td>3 (4.2)</td>
<td>1 (3.1)</td>
</tr>
<tr>
<td>Discontinued</td>
<td>12 (18.7)</td>
<td>28 (15.4)</td>
<td>13 (24.4)</td>
</tr>
<tr>
<td>Reasons for discontinuation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse event</td>
<td>3 (4.9)</td>
<td>4 (6.8)</td>
<td>2 (3.7)</td>
</tr>
<tr>
<td>Consent withdrawn</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Unlikely to succeed</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Lost to follow up</td>
<td>0 (0)</td>
<td>1 (1.6)</td>
<td>1 (3.1)</td>
</tr>
<tr>
<td>Needed to use exclusory medication</td>
<td>0 (0)</td>
<td>3 (5.8)</td>
<td>1 (3.1)</td>
</tr>
<tr>
<td>eGFR less than 50 mL/min/m²</td>
<td>1 (2.0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Other</td>
<td>8 (13.9)</td>
<td>2 (3.2)</td>
<td>3 (9.7)</td>
</tr>
</tbody>
</table>

- These patients were previously enrolled in either EASE US-1 or SABE US.

References


Acknowledgments and Disclosures

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CD

Conclusions

- These open-label data are encouraging and support the premise that higher sustained daytime concentrations of amantadine provided by ADS-5102 (approx. 1000 mg/day) provide a further reduction in dyskinesia and OFF in previously treated amantadine IR patients.

- The effect in dyskinesia and OFF in all subgroups was durable out to 64 weeks.

- Additionally, at the time of the data cut, approximately 25% of patients in each subgroup were able to increase their levodopa dose without compromising dyskinesia control.

- The safety profile in patients who switched from amantadine IR directly to ADS-5102 was consistent with previously reported safety data from the controlled and open-label clinical trials.

- Finally, these data suggest that patients currently being treated with amantadine IR can be switched directly to ADS-5102 without interruption.