Safety of Sublingual Apomorphine (APL-130277) for the Treatment of OFF Episodes in Patients with Parkinson's Disease

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BACKGROUND

• Parkinson's disease (PD) patients suffer from a variety of predictable and unpredictable OFF episodes throughout the disease duration
• These consist of predictable wearing OFF, morning akinesia, delayed or No-ON or sudden OFF
• Up to 2/3 of all PD patients across all stages of the disease experience OFF episodes, which have a significant negative impact on quality of life
• OFF time can be reduced by increasing the frequency of levodopa or by adding other adjunctive PD medications but, despite these manipulations, most PD patients suffer many OFF episodes daily
• The only approved, acute, intermittent treatment of OFF episodes is subcutaneous apomorphine (Apokyn® in the US), which is very efficacious but has significant limitations due to the parenteral nature of administration
• More convenient, on-demand, medications for the management of OFF episodes would be beneficial

OBJECTIVE

The primary objective of the study was to evaluate the efficacy, tolerability and safety of single treatments of APL-130277 in 19 patients with PD

METHODS

• This was a Phase 2, open-label, single-arm study
• Patients were instructed to take their last dose of levodopa no days prior to initiation of APL-130277, which was continued to immediately manage OFF episodes by rapidly delivering apomorphine through absorption from the oral cavity mucosa
• This Phase 2 Study examined the effects of APL-130277 in PD patients with OFF episodes

RESULTS

• A total of 19 patients were dosed with APL-130277
• Baseline demographics are summarized in Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>57.0</td>
<td>10.5</td>
<td></td>
</tr>
<tr>
<td>Sex (female)</td>
<td>57.9</td>
<td></td>
<td></td>
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<tr>
<td>Disease duration (years)</td>
<td>13.8</td>
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• Efficacy data is presented as a separate poster at the American Neurological Association 2015 Annual Meeting
• Of the 19 patients dosed, 15 (79%) turned fully ON following APL-130277 administration
• On average, there was a large, robust, clinically meaningful improvement in the MDS-UPDRS Part III at 15, 40, 60, and 90 minutes after dosing
• 19 subjects received a total of 77 doses of APL-130277, at doses ranging from 10–30 mg
• A summary of adverse events are presented in Table 2

| Adverse Event | N (%)
|---------------|---------|
| Nausea | 4 (21.1)
| Headache | 4 (21.1)
| Dizziness | 3 (15.8)
| Nausea | 3 (15.8)
| Hyperhidrosis | 1 (5.3)
| Yawning | 1 (5.3)

• Only 1 patient (5%) had an AE of orthostatic hypotension (mild)
• 4/19 patients experienced AEs of nausea with APL-130277
• There were no AEs of oral mucosal irritation
• No subjects discontinued due to AE

• Rates of AEs were comparable to other dopamine agonists and some (nausea/vomiting, orthostatic hypotension) occurred lower than that seen with the apomorphine injection
• Adaptation of dopaminergic AEs (i.e. nausea) appears to occur during dose titration

CONCLUSIONS

• Sublingual APL-130277 rapidly converts PD patients from the morning OFF state to the ON state
• APL-130277 was safe and well tolerated in this Phase 2 study
• The most common AEs were mild to moderate and known dopaminergic AEs
• Rates of AEs were comparable to other dopamine agonists and some (nausea/vomiting, orthostatic hypotension) occurred lower than that seen with the apomorphine injection
• Adaptation of dopaminergic AEs (i.e. nausea) appears to occur during dose titration
• Only 1 patient (5%) experienced symptomatic orthostatic hypotension and there were no AEs of oral mucosal irritation
• APL-130277 appears to be a safe and effective, easy to administer medication for the acute, on-demand management of OFF episodes in PD patients
• Phase 3 studies are being initiated to further evaluate the efficacy, safety, tolerability of APL-130277 in PD patients

ACKNOWLEDGEMENTS

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REFERENCES