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 2/3rds 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 are needed
- APL-130277, a soluble film strip of apomorphine, is a "turning ON" medication administered sublingually designed 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

OBJECTIVE

To 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 later than 10 PM the night prior and presented to the clinic in the morning without taking their usual morning dose of levodopa and other PD medications
- Those patients confirmed to be in the OFF state were then dosed with APL-130277 (Figure 1), starting with 10 mg. If a full ON, as assessed by the Investigator and patient, was not achieved, the dose was increased in 5 mg increments until a full ON was achieved, to a maximum dose of 30 mg.
- Patients could be dosed up to two times a day over 3 days
- If a patient achieved a full ON response, they received a subsequent confirmatory dose to verify the full ON response
- All patients were pretreated with trimethobenzamide for 3 days prior to initiation of APL-130277, which was continued during dosing
- Change in MDS-UPDRS Part III and assessment of OFF/ON were conducted pre-dose and at 15, 30, 45, 60 and 90 minutes after APL-130277 administration

Figure 1: APL-130277 sublingual apomorphine strip

Patients

- Main inclusion criteria
  - Clinical diagnosis of idiopathic Parkinson's disease
  - At least one OFF episode per day and ≥ 2 hours of daily OFF time
  - Experience predictable OFF episodes upon awakening prior to receiving morning dose of levodopa
  - Hoehn and Yahr stage I–III in the ON state
- Main exclusion criteria
  - Atypical or secondary Parkinsonism
  - Past treatment with any form of apomorphine within 30 days of dosing Day 1

Efficacy & safety endpoints

- The primary efficacy endpoint was the percent of patients turning fully ON following APL-130277 administration
- Secondary endpoints included the change and percent change in MDS-UPDRS Part III over time, percent of patients fully ON at each time point, percent of patients with a 5 and 10 point MDS-UPDRS Part III improvement at first full ON dose for Responders or last dose for non-responders
- Adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities (MedDRA) and were tabulated by MedDRA preferred term (PT).
- ECG, vital signs (including orthostatic blood pressure) and clinical laboratory values were evaluated
- All 19 patients dosed in the Intention to treat population are included in the safety dataset

RESULTS

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

Table 1: Baseline demographics

Mean age	61.5 (48-79)
Male: Female	14 (73.7%): 5 (26.3%)
Modified Hoehn & Yahr	2.2 (1-3)
Mean # of daily OFF episodes	3.9 (1-7)
Mean # PD medications classes	3 (1-5)
Mean daily levodopa dose (mg)	837 (100-1500)
Mean # levodopa doses per day	5.3 (1-12)

- Efficacy data is presented as a separate poster at the 19th International Congress of Parkinson's Disease and Movement Disorders (abstract # 233)
  - 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, 30, 45, 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:

Table 2: Overview of adverse events with APL-130277

N = 19	N (%)
Any AE	13 (68.4)
Mild AE	13 (68.4)
Moderate AE	4 (21.1)
Severe AE	2 (10.5)
Any related AE	11 (57.9)
Any serious AE	1 (5.3)

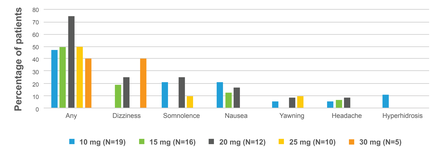
- One patient had serious AE of dysphagia, which was deemed not related to APL-130277 by the Investigator and the Sponsor
- The most common adverse events were dizziness, somnolence, nausea and yawning (Table 3)

Table 3: Most common AEs with APL-130277 (occurring in >1 patient)

Preferred term	Any AE	Mild AE	Moderate AE	Severe AE	Related AE
N=19	N (%)	N (%)	N (%)	N (%)	N (%)
Dizziness	7 (36.8)	7 (36.8)	0	0	5 (26.3)
Somnolence	6 (31.6)	3 (15.8)	3 (15.8)	1 (5.3)	5 (26.3)
Nausea	4 (21.1)	4 (21.1)	1 (5.3)	0	4 (21.1)
Yawning	3 (15.8)	3 (15.8)	0	0	3 (15.8)
Headache	2 (10.5)	2 (10.5)	0	0	1 (5.3)
Hyperhidrosis	2 (10.5)	2 (10.5)	0	0	2 (10.5)

- Only 1 patient (5%) had an AE of orthostatic hypotension (mild)
- There were no AEs of dyskinesia
- 4/19 patients experienced AEs of nausea with APL-130277
  - AEs of nausea occurred following 8 of 77 total APL doses (10%)
    - 6 AEs were mild
    - 2 AEs were moderate
  - AEs occurred after the first dose for all 4 patients
  - Onset was typically between 15–40 minutes after dosing
  - 3 of the 4 patients received higher doses of APL (up to 30 mg) on subsequent days without further AEs of nausea
  - Only 1 of the 4 patients with nausea experienced an AE of vomiting (mild in severity)
  - 1 of the 4 patients had a medical history of intermittent nausea
  - AEs of nausea were not seen with APL doses of 25 or 30 mg
- There was no apparent dose-response relationship with AEs (Table 4)
- There were no AEs of oral mucosal irritation
- No subjects discontinued due to AE
- There were no clinically meaningful changes in ECG or laboratory analysis

Figure 2: Most common AEs by dose



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
- No subjects discontinued due to AE
- 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

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APL-130277 is currently an investigational product in some countries, including the United States.

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