Poster #: 337

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

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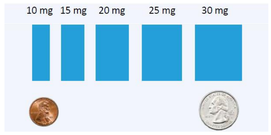
BACKGROUND

Up to 2/3rds of Parkinson's disease (PD) patients suffer from OFF episodes

OFF episodes in PD have a significant negative impact on QoL of patients

APL-130277 (Figure 1) is a soluble, sublingual film strip of apomorphine that provides a rapid time to ON (Presented in Poster 335)

Figure 1: Apomorphine Sublingual Thin Film Strip (APL-130277)



OBJECTIVE

Evaluate the safety of APL-130277 in patients with PD and OFF episodes

METHODS

- Open-label, single-arm, Phase 2 study
- Patients took their last dose of levodopa (LD) no later than 10 PM the night prior and presented to clinic in a.m. without taking any PD meds
- If OFF, patients were dosed with APL-130277, starting at 10 mg (Figure 2)
- APL-130277 administered sublingually and allowed to dissolve over 2 mins
- Patients could be dosed up to 2 times/d over 3 d
- Pre-treatment with trimethobenzamide (anti-emetic) was started 3 d prior to initiation of APL-130277 and was continued during its dosing
- MDS-UPDRS Part III and assessment of OFF/ON were conducted pre-dose and at 15, 30, 45, 60 and 90 mins after APL-130277 administration

APL-130277 Dosing (Figure 2)

- On dosing Day 1, patients who were in an OFF state received 10 mg APL-130277. If the patient did not turn ON within 3 hours of dosing the patient then received 15 mg of APL-130277.
- On dosing Day 2, patients who turned ON with either 10 or 15 mg of APL-130277 received the same dose. Patients who had not turned ON with 15 mg of APL-130277 received 20 mg of APL-130277. If the patient did not turn ON within 3 hours of dosing the patient then received 25 mg of APL-130277.
- On dosing Day 3, patients who turned on with either 20 or 25 mg of APL-103277 received the same dose. Patients who had not turned ON with 25 mg of APL-130277 received 30 mg of APL-130277.
- Dosing days were not required to be sequential, but all dosing had to be completed within 7 days.

Patients

- Diagnosis of PD (H&Y state 1-3 in ON state); no atypical/secondary forms
- >1 OFF episode/d and > 2 hrs of daily OFF time
- Predictable OFF episodes upon awakening prior to receiving AM dose of LD
- May not have received any form of apomorphine within 30 d of dosing Day 1

Primary Efficacy Endpoint (Presented in Poster 335)

- % of patients turning fully ON as confirmed by the Investigator following an APL-130277 administration

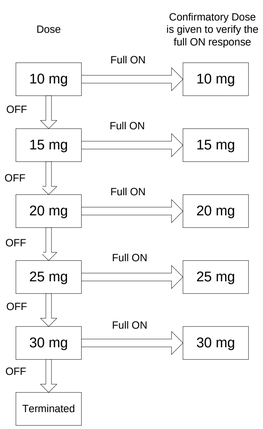
Safety Assessments/Endpoints

- Adverse events (AEs)
- ECG, vital signs (including orthostatic BP) and clinical lab values were evaluated

Data Analyses: according to 3 datasets

- Modified Intention to Treat (mITT) – includes 19 patients dosed
- Responders – includes 15 patients who turned fully ON post APL-130277 treatment
- Per Protocol (PP) – includes 15 patients with no protocol dosing violations
- (excludes 3 patients who were improperly instructed to swallow the strip and 1 patient who was dosed in an OFF state following administration of their first dose of PD meds)

Figure 2: Study Design



RESULTS

Table 1: Demographic and Baseline Characteristics

Characteristic	N=19
Mean Age, mean (range)	61.5 (48—79)
Male: Female, number (%)	14 (73.7%): 5 (26.3%)
Modified Hoehn and Yahr, mean (SD)	2.2 (0.5)
MDS-UPDRS Total Score, mean (SD)	42.8 (15.9)
Mean # of Daily OFF Episodes, mean (range)	3.9 (1–7)
Mean # of PD Medications, mean (range)	3 (1–5)
Mean Daily Levodopa Dose (mg), mean (range)	776 (100–2100)
Mean # of Levodopa Doses Per Day, mean (range)	5.4 (1–12)

Table 2: Overview of Adverse Events with APL-130277

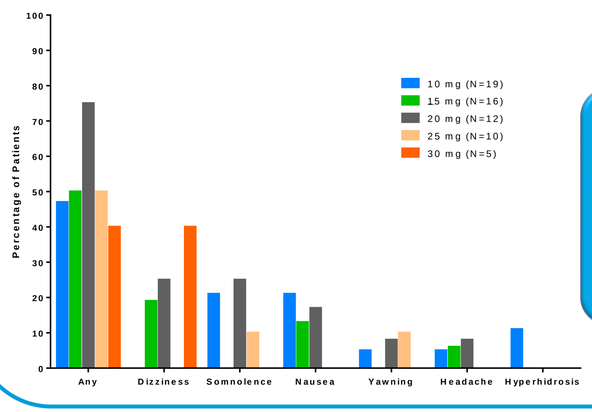
	N=19 n (%)
Any AE	13 (68.4)
Any Related* AE	11 (57.9)
Mild AE	13 (68.4)
Moderate AE	4 (21.1)
Severe AE	2 (10.5)
Serious AE	1 (5.3)**

No subject discontinued from the study due to an AE

*Related AE=an AE deemed certainly, possibly or probably related to APL-130277 by the Investigator
**Deemed unrelated to APL-130277 by the Investigator

Safety population

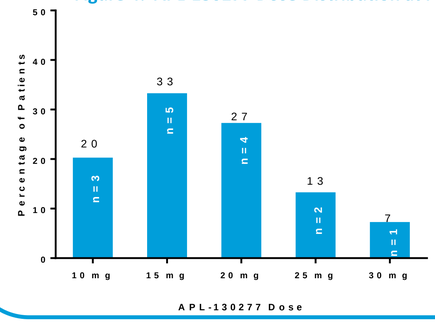
Figure 3: Most Common AEs by Dose



No apparent dose-response relationship with AEs was observed

RESULTS (continued)

Figure 4: APL-130277 Dose Distribution at First Full ON (Responders)



19 Patients received 77 doses of APL-130277

Mean Dose: 18.4 mg

- Nausea occurred in only 4 patients after the first dose; typically 15-40 mins after dosing
  - Occurred with 8 of 77 total APL-130277 dosings (10%)
    - 6 AEs were mild
    - 2 AEs were moderate
  - 3 of 4 patients received higher doses (up to 30 mg) without further nausea
  - 1 of 4 patients experienced vomiting (mild)
  - APL-130277 doses of 25 or 30 mg were not associated with nausea
- Orthostatic hypotension (mild) only occurred in one patient (5%)
- Dyskinesia was not reported as a treatment-related adverse event
- Oral mucosal irritation was not reported
- ECG or laboratory analyses showed no clinically meaningful change

CONCLUSIONS

APL-130277 was generally well-tolerated

- Most common AEs were mild/moderate, known dopaminergic AEs
- Adaptation of dopaminergic AEs occurred during dose titration

No subject discontinued from the study due to an AE

No apparent dose-response relationship with AEs was observed

Phase 3 studies are underway

ACKNOWLEDGEMENTS/DISCLOSURES

This study was supported by Cynapsus Therapeutics. Additionally, the Michael J. Fox Foundation provided a grant in support of the study. BD, TB, and AA are all employees of Cynapsus Therapeutics and hold stock or stock options. SI was an Investigator in the study and received compensation from Cynapsus for research activities.
APL-130277 is currently an investigational product.