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

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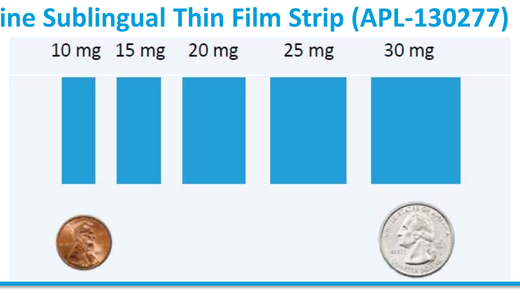
BACKGROUND

- Up to 2/3rds of Parkinson's disease (PD) patients suffer from OFF episodes including:
  - Wearing OFF
  - Morning akinesia
  - Delayed/no-ON and sudden OFF
- OFF episodes in PD have a significant negative impact on quality of life of patients
- APL-130277 is a soluble, sublingual film strip of apomorphine (Figure 1)

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



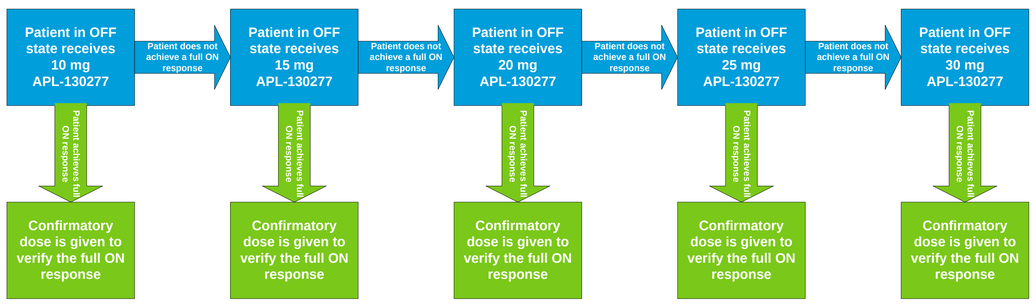
OBJECTIVE

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 usual morning dose of LD and other PD meds
- Patients confirmed to be OFF were dosed with APL-130277, starting at 10 mg (Fig. 2)
- APL-130277 was administered sublingually and allowed to dissolve over 2 minutes

Figure 2: Study Design



- Patients could be dosed up to two times/day over 3 days
- Pre-treatment with trimethobenzamide (anti-emetic) was started 3 days 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

Patients

- Clinical diagnosis of PD (H&Y state 1-3 in ON state); no atypical/secondary forms
- ≥1 OFF episode/day and ≥ 2 hours 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 days of dosing Day 1

Efficacy Endpoints (Presented in Poster 2.089)

- Primary efficacy endpoint: % 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)

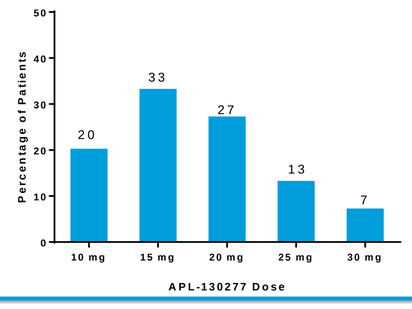
RESULTS

Table 1: Demographic and Baseline Characteristics

Characteristic	N=19 (dosed with APL-130277
Age, years (range)	61.5 (48-79)
Male:Female	14 (73.7%) to 5 (26.3%)
Modified Hoehn & Yahr, mean (range)	2.2 (1-3)
# of daily OFF episodes, mean (range)	3.9 (1-7)
# of PD medication classes, mean (range)	3 (1-5)
Daily levodopa dose, mean (range)	776 mg (100-2100)
# of levodopa doses per day, mean (range)	5.4 (1-12)

RESULTS (continued)

Figure 3: APL-130277 Dose Distribution at First Full ON (Responders)



19 Patients received 77 doses of APL-130277

Mean Dose: 18.4 mg

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)**

*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

No patient discontinued from the study due to an AE

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

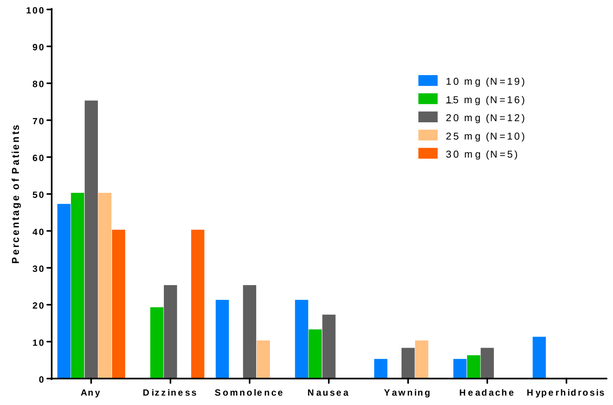
Preferred Term N=19	Any AE n (%)	Mild AE n (%)	Moderate AE n (%)	Severe AE n (%)	Related* AE n (%)
Dizziness	7 (36.8)	7 (36.8)	0	0	5 (26.3)
Somnolence	6 (31.6)	3 (15.8)	3 (15.8)	1 (5.3)	5 (26.3)
Nausea	4 (21.1)	4 (21.1)	1 (5.3)	0	4 (21.1)
Yawning	3 (15.8)	3 (15.8)	0	0	3 (15.8)
Headache	2 (10.5)	2 (10.5)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

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

Safety population

The most common AEs were dizziness, somnolence, nausea and yawning

Figure 4: Most Common AEs by Dose



No apparent dose-response relationship with AEs was observed

- 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 events
- 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 to moderate and known dopaminergic AEs
  - Adaptation of dopaminergic AEs (i.e. nausea) appears to occur during dose titration
- No subject discontinued due to AE
- No apparent dose-response relationship with AEs was observed
- Phase 3 studies have been initiated

ACKNOWELDGEMENTS

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