Minimum MDS-UPDRS Part III Change Needed to Convert a Parkinson's Disease Patient From the OFF to full ON State with Sublingual Apomorphine (APL-130277)

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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 strip (APL-130277)

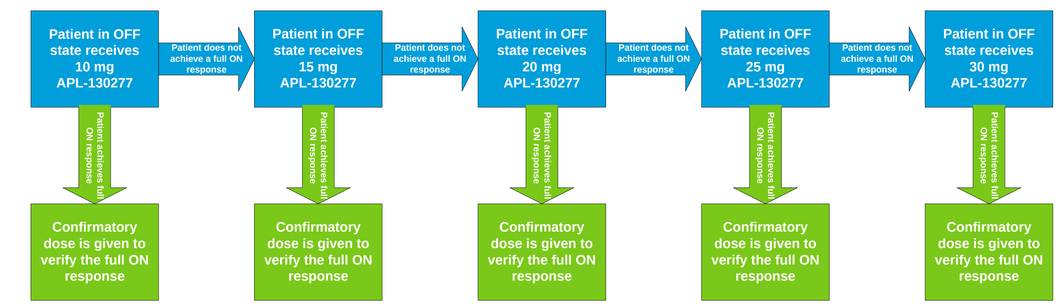
OBJECTIVE

To evaluate the minimum change on the MDS-UPDRS-Part III to convert a PD patient from OFF to full ON

METHODS

- Open-label, single-arm, Phase 2 study
- Patients took last dose of levodopa (LD) no later than 10 PM prior to presenting 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 (Figure 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 2.086)

- Primary efficacy endpoint: % of patients turning fully ON as confirmed by the Investigator following an APL-130277 administration
- Secondary endpoints:
  - Change and % change in MDS-UPDRS-III over time
  - % of patients fully ON at each time point
  - % of patients with a 5 and 10 point MDS-UPDRS Part III improvement following the first full ON dose for Responders or last dose for non-responders

Safety Assessments/Endpoints (Presented in 2.089)

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)

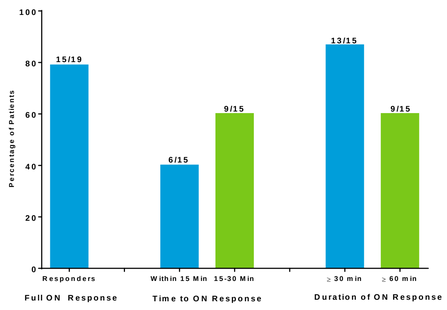
RESULTS

Table 1: Demographic and Baseline Characteristics

Characteristics	All Patients (N=19)	Responders ≤15 minutes (N=6)	Responders > 15 but ≤ 30 min (N=9)	Non Responders (N=4)
Male:Female	14 (73.7%):5 (26.3%)	3 (50%):3 (50%)	8 (89%):1 (11%)	3 (75%):1 (25%)
Modified H & Y, mean (range)	2.2 (1-3)	1.8 (1 - 2)	2.3 (2 - 3)	2.3 (2 - 3)
# of daily OFF episodes, mean (range)	3.9 (1-7)	3 (1 - 5)	4.6 (2 - 7)	3.8 (3 - 4)
# of PD medication classes, mean (range)	3 (1-5)	2.8 (2 - 4)	3 (1 - 5)	3.3 (2 - 4)
Daily levodopa dose, mean (range)	776.3 (100-2100)	783.3 (100 - 2100)	811.1 (250 - 1450)	687.5 (450 - 1200)
# of levodopa doses/day, mean (range)	5.4 (1-12)	5.5 (1 - 12)	5.4 (4 - 7)	4.8 (3 - 6)

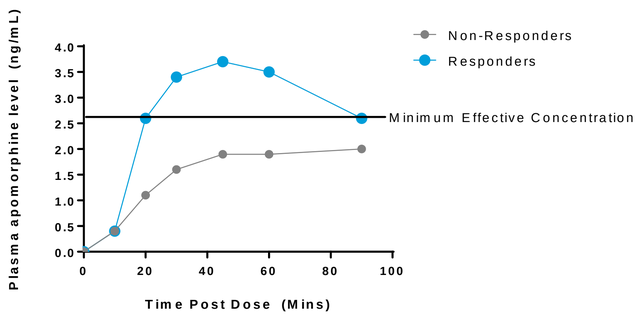
RESULTS (continued)

Figure 3: Responders, Time to Response and Duration of Response



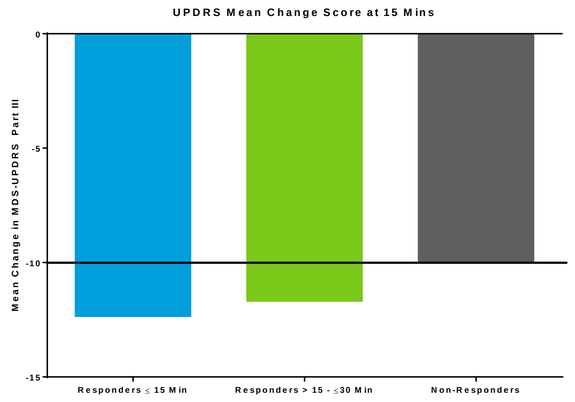
Mean ON duration: 50 minutes

Figure 4: Pharmacokinetics/Pharmacodynamics: Mean Plasma Apomorphine Concentration



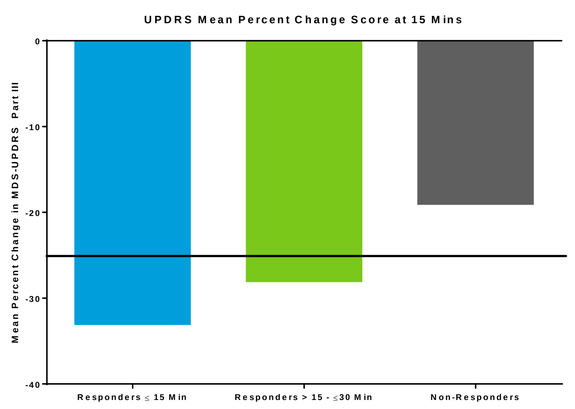
Mean apomorphine concentration when Responders went from OFF to full ON: 2.64 ng/mL (range 0.56-5.37)

Figure 5: Minimum MDS-UPDRS Part III to Turn Full ON (Mean Change)



Mean Change in MDS-UPDRS Part III needed to turn PD patient from OFF to full ON: > 10 points

Figure 6: Minimum MDS-UPDRS Part III to Turn Full ON (Mean Percent Change)



Mean % Change in MDS-UPDRS Part III needed to turn PD patient from OFF to full ON: 25%

CONCLUSIONS

An improvement of over 10 points or a 25% change in the MDS-UPDRS-Part III is needed to turn a PD patient from OFF to full ON

ACKNOWELDGEMENTS

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

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