Pharmacokinetic-pharmacodynamic Effects of Sublingual Apomorphine (APL-130277) for the Acute Management of OFF Episodes in Parkinson's Disease Patients

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BACKGROUND
- Parkinson's disease (PD) patients suffer from a variety of OFF episodes as the disease progresses.
  - These consist of unpredictable 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 episodes can be reduced by increasing the frequency of levodopa by adding other adjuvant PD medications; however, medication manipulation does not address morning akinesia, delayed ON, no ON or sudden OFF.
- Despite current PD medications, PD patients suffer many OFF episodes daily.

OBJECTIVE
To evaluate the pharmacokinetic-pharmacodynamic effects of APL-130277 on OFF episodes in PD Patients

METHODS
- This was a phase 2, open-label, multi-center, single-arm study.
- The primary efficacy endpoint was the percent of patients turning fully ON following APL-130277 administration.
- Secondary endpoints included efficacy and safety endpoints.
- APL-130277 is a soluble film strip of apomorphine administered sublingually and designed as a "Turning ON" medication to immediately manage OFF episodes by rapidly delivering apomorphine through absorption from the oral cavity mucosa.
- This analysis summarizes the pharmacokinetic-pharmacodynamic effects of sublingual apomorphine (APL-130277) starting with 10 mg. If a full ON, as assessed by clinical criteria, was maintained for at least 30 min, patients could be dosed up to the maximum dose of 30 mg.
- Of the 19 total patients dosed with APL-130277, 15 achieved a full ON response within 30 min, and approximately half within 15 min.
- Mean ON duration was 52 min.
- Of the 4 Non-responders, 2 were dosed incorrectly and were dosed up to the maximum dose of 30 mg.
- Of the 8 patients with pharmacokinetic analyses, 6 achieved a full ON response (Responders).
- All turned fully ON within 30 min and 2 within 15 min.
- Mean apomorphine concentration for the 6 responders at the dose they achieved a full ON for the 2 Non-responders (did not achieve a full ON on all doses tested (10, 15, 20, 25 and 30 mg)) are presented in Figure 2.
- The mean apomorphine concentration when Responders went from OFF to full ON was 2.04 ng/ml (range 0.96–3.77), defined as the minimum effective concentration (MEC).
- The mean apomorphine concentration for the Non-responders did not reach the minimum effective concentration threshold at all doses tested.

RESULTS
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CONCLUSIONS
- APL-130277 can rapidly convert a patient from the OFF to the ON state.
- On average, a minimum effective apomorphine concentration of 2.04 ng/ml was needed to turn a patient fully ON, lower than what has previously been reported with apomorphine.
- Of those patients who turned fully ON after APL-130277 administration, the minimum effective concentration was reached in 10–20 min and levels were maintained above this threshold for 30 min after dosing.
- The data above show the minimum effective concentration threshold translated into sustained improvement in motor function and ON time.
- Patients who did not turn ON following APL-130277 administration did not reach the minimum effective concentration.
- Thicker concentrations related to a full ON may be lower than those needed for a full ON with subcutaneous apomorphine.
- APL-130277 was safe and well-tolerated; almost all AEs were mild and occurred within 2 hours of dosing.
- APL-130277 appears to be a safe and effective treatment for the on-demand management of OFF episodes in PD patients.

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REFERENCES

Figure 1: APL-130277 sublingual apomorphine strip

Figure 2: Mean plasma apomorphine concentration for Responders vs. Non-responders

Table 1: Baseline demographics

Table 2: Number of patients N (%), N=8

Table 3: Most common Adverse Reactions

Figure 3: MDS-UPDRS Part III changes for Responders vs. Non-responders

Figure 4: Percent MDS-UPDRS Part III change for Responders vs. Non-responders