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 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
- Wearing OFF can be reduced by increasing the frequency of levodopa or by adding other adjunctive 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
- The only approved, acute 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 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 subgroup results of a phase 2 study (CTH105) that examined the safety, tolerability and efficacy of APL-130277 in PD patients

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
- Patients were instructed to take their last dose of levodopa no later than 10 PM the night prior and present 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 where 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
- Change in MDS-UPDRS Part III and assessment of OFF/ON state were conducted pre-dose and at 15, 30, 45, 60 and 90 min after APL-130277 administration
- Plasma apomorphine levels were evaluated pre-dose and at 10, 20, 30, 45, 60 and 90 min after APL-130277 administration
- Three sites participated in pharmacokinetic analyses

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
- The key secondary endpoint was the change in MDS-UPDRS Part III over time following APL-130277 administration
- Pharmacokinetic endpoints: Cmax, Tmax, $t_{1/2}$, AUC
- 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

RESULTS

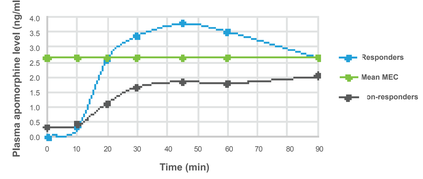
- A total of 19 patients were dosed with APL-130277
  - 8 patients had pharmacokinetic analyses
- Baseline demographics of 8 patients with pharmacokinetic analyses are summarized in Table 1

Table 1: Baseline demographics

Mean age	61 (54–67)
Male: Female	6:2
Modified Hoehn & Yahr	1.9 (1–2)
Mean # of daily OFF episodes	4.25 (2–7)
Mean daily levodopa dose (mg)	913 (500–1400)
Mean # levodopa doses per day	5.5 (3–7)

- Of the 19 total patients dosed with APL-130277, 15 achieved a full ON response
  - All patients turned fully ON 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 2 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 and for the 2 Non-responders (did not achieve a full ON) at 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 2.64 ng/ml (range 0.56–5.37), defined as the minimum efficacious concentration (MEC)
- Average concentrations reached this level between 10 and 20 min and were maintained over this level through 90 min
- Mean apomorphine concentrations for the Non-responders did not meet the minimum efficacious concentration threshold at all doses tested

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



- Figures 3 and 4 present mean change and percent change in MDS-UPDRS Part III from pre-dose to 15, 30, 45, 60 and 90 min post-dose for Responders (at the dose they turned full ON) versus Non-responders (at all doses)
- Responders had large, clinically meaningful UPDRS Part III changes at all time-points while the Non-responders had little motor improvement, but not enough to convert from OFF to ON

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

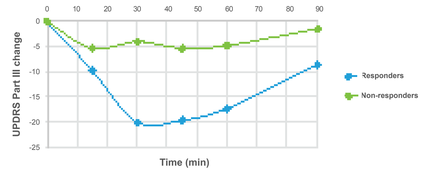
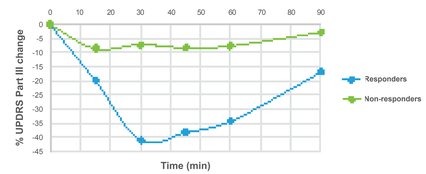


Figure 4: Percent MDS-UPDRS Part III change for Responders vs. Non-responders



- Of the 8 patients with pharmacokinetic analyses:
  - 6 (75%) had an AE
  - 5 (63%) had a related AE (Adverse Drug Reaction, Table 2)
  - 6 (75%) had a mild AE
  - None had a moderate AE
  - 1 (13%) had a severe AE (somnolence)
  - None had a serious AE
  - None discontinued due to AE

Table 2: Overview of Adverse Drug Reactions (ADRs)

	Number of patients N (%), N=8
Any ADR	5 (63)
Serious ADR	0
Mild ADR	5 (63)
Moderate ADR	0
Severe ADR	1 (13)

- Table 3 presents the most common ADRs, timing of ADRs related to dosing and apomorphine concentration at the time of the ADR
- ADRs were almost all mild and known dopaminergic events associated with dopamine agonists
- There appeared to be no clear correlation with plasma apomorphine levels and ADRs
- There were no AEs of local irritation

Table 3: Most common Adverse Drug Reactions

Preferred term	N(%), N=8	Mean time after dosing (min)	Mean apomorphine [ng/ml]	Mean APL dose (mg)
Dizziness	3(38)	23	0.94	16.7
Yawning	3(38)	73	3.52	18.3
Somnolence	1(13)	92	0.51	15
Orthostatic hypotension	1(13)	101	1.54	10
Nervousness	1(13)	54	1.98	10
Upper airway cough syndrome	1(13)	35	2.05	15

CONCLUSIONS

- Sublingual APL-130277 can rapidly convert a patient from the OFF to the ON state
- On average, a minimum efficacious apomorphine concentration of 2.64 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 efficacious concentration was reached in 10-20 min and levels were maintained above this threshold through 90 min after dosing
- Plasma levels above the minimum efficacious concentration 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 efficacious concentration
- Plasma 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 ADRs 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
- Phase 3 studies are planned to further evaluate the efficacy, safety, tolerability and pharmacokinetics of APL-130277

REFERENCES

1. Aquino C, Fox S. Clinical spectrum of levodopa-induced complications. Movement Disorders. 2015;30: 80-89.
2. Rizos A, Martinez-martin P, Odin P, et al. Characterizing motor and non-motor aspects of early-morning off periods in Parkinson's disease: an international multicenter study. Parkinsonism and Related Disorders. 2014;20:1231-1235.
3. Chapuis S, Ouchchane L, Metz O, et al. Impact of motor complications of Parkinson's disease on the quality of life. Movement Disorders. 2005;20:224-230.
4. Apokyn USPI, US WorldMeds, LLC. Louisville, KY, 2014.
5. Laar T, van der Geest R, Danhof M, et al. Stepwise intravenous infusion of apomorphine to determine the therapeutic window in patients with Parkinson's disease. Clinical Neuropharmacology. 1998;21:152-158.

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