Pharmacokinetics, Safety and Tolerability of High-dose Sub-lingually Administered APL-130277 in Healthy Volunteers

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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
- OFF time can be reduced by increasing the frequency of levodopa or by adding other adjunctive PD medications but, despite these manipulations, most PD patients suffer many OFF episodes daily as these changes to not address morning akinesia, delayed or No-ON or sudden OFF
- The only approved, acute, intermittent treatment of OFF episodes is subcutaneous (sc) apomorphine (Apokyn® in the US, APO-go® in the EU), 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, a soluble film strip of apomorphine administered sublingually is designed to immediately manage OFF episodes by rapidly delivering apomorphine through absorption from the oral cavity mucosa
- This Phase 1 Study examined the pharmacokinetic effects and safety of a higher dose of apomorphine delivered sub-lingually in health volunteers

OBJECTIVE

To evaluate the pharmacokinetics, safety and tolerability of sublingually administered APL-130277 25 mg in healthy volunteers

METHODS

- This was a single-center, Phase 1, study in healthy volunteers that assessed the single dose pharmacokinetics, safety and tolerability of APL-130277 25 mg (Figure 1) conducted in Penang, Malaysia
- The study was initially planned as a crossover study compared to 4 mg of subcutaneous apomorphine, however the 3 mg dose of subcutaneous apomorphine in the previous study (CTH103) resulted in a severe AE of seizure and the IRB would not allow for higher dosing of subcutaneous apomorphine in healthy volunteers
- Subjects were dosed with APL film strip on the underside of the tongue with the drug layer facing the bottom of the tongue
- Subjects were pre-medicated with 3 days of domperidone, which was continued during treatment

Figure 1: APL-130277 sublingual apomorphine strip

Patients

- Main inclusion criteria
  - Healthy male volunteers
  - Aged 21–60 inclusive
  - Body Mass Index (BMI) of 18–28 kg/m^2
- Main exclusion criteria
  - Any history or presence of significant cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, ophthalmologic or psychiatric disease.
  - A family history (immediate family) of Parkinson's disease
  - Use of tobacco or nicotine-containing products within 2 weeks before dosing of study
  - Cankers, mouth sores or chronic dry mouth

Endpoints

- Efficacy:
  - Blood samples were collected for measurement of plasma APL-130277 concentration pre-dosing, and in regular intervals up to 4 hours post dosing
  - Pharmacokinetic parameters, calculated from the APL-130277 plasma concentration profiles included: $AUC_{0\text{-}24h}$, $AUC_{0\text{-}4h}$, $AUC_{0\text{-}\infty}$, C_{max}, t_{max}, λ_z, M_{RT}, $t_{1/2}$, V_{ss}/F, and C1/F
- Safety:
  - Treatment Emergent Adverse Events, physical examination findings, vital signs, 12-lead electrocardiogram (ECG) measurements, and clinical laboratory tests (hematology, chemistry and urinalysis) were analyzed

RESULTS

- A total of 13 subjects were randomized in the study with 11 receiving APL-130277 and 2 receiving placebo strip
- Baseline demographics are presented in Table 1

Table 1: Baseline demographics

	Cohort 1 (n=13)
Age (years)	26.0
Weight (kg)	68.3
Height (inches)	66.8
BMI (kg/m^2)	23.5
Ethnicity (Malay:Chinese)	68:32 %

Pharmacokinetics

- Mean Concentration-Time Curve for APL-130277 25 mg is presented in Figure 2 and pharmacokinetic parameters are presented in Table 2
  - It took approximately 8 minutes to reach the minimum efficacious concentration of apomorphine (typically around 3 ng/ml)
  - Concentrations were maintained over the minimum efficacious concentration for over 2 and a half hours
  - Apomorphine exposure was slightly lower than dose proportional as the dose was raised from 15 mg (as studied in CTH103) to 25 mg; however, the shortfall in exposure was not large and fell within one standard deviation of the mean values

Figure 2: Plasma concentration-time curve for APL-130277 25 mg

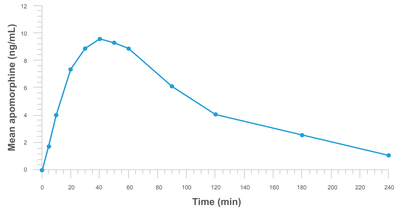


Table 2: Mean pharmacokinetics of APL-130277 25 mg

Dose	C_{max} (ng/ml)	T_{max} (min)	$T_{1/2}$ (min)	AUCLast (min*ng/ml)	AUCinf (min*ng/ml)
APL-130277 25 mg	11.2	41.5	62.2	1102	1204

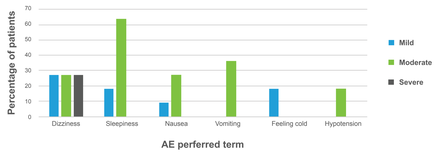
Safety

- Incidence of adverse events (AE) in > 1 subject with APL-130277 25 mg is presented in Table 3
- Adverse events were known adverse events associated with dopaminergic medications
- 1 of the 2 placebo subjects had a mild AE of dizziness
- AEs were mostly mild to moderate in severity, except for dizziness, which was reported as severe in three subjects and recovered without sequela (Figure 3)
- No serious AEs occurred
- There were no clinically significant changes in laboratory values or ECG

Table 3: Incidence of adverse events with APL-130277 25 mg

Type of AE	N(%) N=11
Any AE	11(100)
Related AE	11(100)
Dizziness	9(82)
Sleepiness	9(82)
Nausea	4(36)
Vomiting	4(36)
Feeling cold	2(18)
Hypotension	2(18)

Figure 3: Incidence of AEs by severity



CONCLUSIONS

- APL-130277 25 mg administered sublingually demonstrates a favorable PK profile to support a rapid and sustained effect for acute relief of OFF episodes in PD patients
- Time to reach a minimum efficacious plasma concentration was achieved in under 10 minutes and apomorphine levels were maintained above this concentration for over 2.5 hours
- Although dopaminergic AEs were relatively high in healthy volunteers, these are expected to be lower in PD patients already on dopaminergic medications and with impaired dopamine production
- APL-130277 may offer an easy to administer, rapid, on-demand treatment of OFF episodes in PD patients

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

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