Pharmacokinetics, Safety and Tolerability of Sublingually Administered APL-130277 Compared to Subcutaneous Apomorphine 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 apomorphine delivered sublingually versus via sc injection

OBJECTIVE

To evaluate the pharmacokinetics, safety and tolerability of 2 doses of sublingually administered APL-130277 compared to sc apomorphine in healthy volunteers

METHODS

- This was a single-center, Phase 1, crossover study in healthy volunteers that assessed the single dose pharmacokinetics, safety and tolerability of APL-130277 (Figure 1) compared to sc apomorphine conducted in Penang, Malaysia
- Cohort 1 was randomly assigned to receive a single dose of APL-130277 10 mg or sc apomorphine 2 mg on the first day and switched to the other treatment the subsequent day
- Cohort 2 was randomly assigned to receive a single dose of APL-130277 15 mg or sc apomorphine 3 mg on the first day and switched to the other treatment the subsequent day
- Subjects were dosed with APL-130277 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
  - Able to tolerate a subcutaneous injection and take sublingual strip of study medication
- 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 and sc apomorphine 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, MRT, $t_{1/2}$, 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

- In cohort 1, 13 subjects were randomly dosed with either APL-130277 and sc apomorphine on consecutive days
- In cohort 2, 14 subjects were randomly dosed with either APL-130277 and sc apomoprhine on consecutive days
- Baseline demographics for each cohort are presented in Table 1

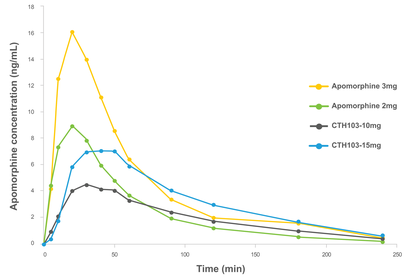
Table 1: Baseline demographics

	Cohort 1 (n=13)	Cohort 2 (n=14)
Age (years)	28.0	26.0
Weight (kg)	66.0	67.8
Height (inches)	65.9	66.4
BMI (kg/m^2)	23.5	23.8
Ethnicity (Malay:Chinese)	10:3	12:2

Pharmacokinetics

- Mean Concentration-Time Curve for APL-130277 compared to sc apomoprhine are presented in Figure 1 and pharmacokinetic parameters in Table 2
  - C_{max} was higher with sc apomoprhine compared to APL-130277
  - There was a less steep rise to C_{max} and a more rounded peak with APL-130277 compared to sc apomorphine
  - Time to reach the minimally efficacious plasma threshold in PD patients (typically around 3 ng/ml) was comparable but slightly longer with APL-130277 versus sc apomorphine
  - Duration over the minimally efficacious plasma threshold was longer with APL-130277 compared to sc apomorphine
  - Subcutaneous apomorphinea resulted in plasma levels above the typical toxicokinetic threshold in PD patients (usually 8.5–10 ng/ml)

Figure 2: Pharmacokinetic profile of APL-130277 versus sc apomorphine



- In cohort 1:
  - The C_{max} geometric least squares means ratio was 53.95% for 10 mg APL-130277 compared to 2 mg sc apomorphine, and the 90% confidence interval was 36.40 to 79.96%.
  - For AUC_{last} and AUC_{inf}, the ratios were 81.15 and 84.92%, respectively, and both 90% confidence intervals included 100% but were not within the generally accepted bounds of 80 – 125% for bioequivalence.
- In cohort 2:
  - Comparative bioavailability revealed that 15 mg APL-130277 produced a C_{max} ratio of geometric least squares means of 47.24% versus the reference and the 90% confidence interval was 37.49 – 59.51%.
  - For AUC_{last} and AUC_{inf} the ratios were 75.24 and 78.19%, respectively, and both 90% confidence intervals were outside (low) of the generally accepted bounds of 80 – 125% for bioequivalence.

Table 2: Mean pharmacokinetics of APL-130277 and sc apomorphine

Dose	C_{max} (ng/ml)	T_{max} (min)	$T_{1/2}$ (min)	AUCLast (min*ng/ml)	AUCinf (min*ng/ml)
APL-130277 10 mg	5.45	34.2	56.5	509	543
SC apomorphine 2 mg	9.78	20.4	42.1	597	612
APL-130277 15 mg	8.02	39.2	54.7	804	854
SC apomorphine 3 mg	16.2	26.7	40.1	996	1022

Safety

- Both APL-130277 and sc apomorphine resulted in known dopaminergic adverse events (AE)
- The incidence and severity of dopaminergic AEs was greater with sc apomorphne compared to APL-130277 (Table 3)
- The total number of adverse events was greater with sc apomorphine compared to APL-130277 (Table 4)
- The only severe adverse event (seizure) occurred following administration of sc apomorphine 3 mg
- There were no clinically meaningful changes in ECG or laboratory values

Table 3: Incidence of adverse events with APL-130277 and subcutaneous apomorphine

Adverse event	APL 10 mg N(%) N=13	SC Apo 2 mg N(%) N=13	APL 15 mg N(%) N=14	SC Apo 3 mg N(%) N=14
Any AE	5(38)	11(85)	13(93)	12(86)
Related AE	5(38)	9(69)	11(79)	12(86)
Moderate AE	2(15)	5(38)	4(29)	11(79)
Sleepiness	0	3(23)	11(79)	10(71)
Nausea	2(15)	4(31)	3(21)	8(57)
Dizziness	3(23)	4(31)	7(50)	7(50)
Vomiting	0	0	2(14)	5(36)
Yawning	0	0	0	3(21)

Table 4: Total number of adverse events with sublingual versus subcutaneous apomorphine

Event	10 mg APL	2 mg sc Apo	15 mg APL	3 mg sc Apo
Total events	5	11	22	46
Dizziness	3	4	6	8
Drowsiness	0	0	0	1
Gastrointestinal hypermotility	0	0	0	1
Giddiness	0	0	0	1
Headache	0	0	0	1
Hypotension	0	0	0	0
Lethargic	0	0	0	2
Muscle weakness upper limb	0	0	0	3
Nausea	2	4		8
Seizure	0	0	0	1
Sleepiness	0	3	11	10
Stomachache	0	0	0	1
Sweating	0	0	0	1
Vomiting	0	0	2	5
Yawning	0	0	0	3

CONCLUSIONS

- Sublingually administered APL-130277 reaches therapeutic blood levels comparable to sc apomorphine
- APL-130277 has a lower C_{max}, less sloped rise to C_{max} and a more rounded C_{max}, which translates to less frequent and less severe dopaminergic adverse events compared to sc apomorphine
- However, APL-130277 reaches the minimum efficacious plasma threshold comparable to sc apomorphine but remains in the therapeutic window for a longer duration of time which can potentially result in a longer duration of effect while maintaining improved tolerability
- The percentage of PD patients with adverse events is expected to be lower given that they have impaired dopaminergic function compared to healthy volunteers
- The differences in PK profile with sublingual APL-130277 compared to sc apomorphine should result in improved tolerability while maintaining the same efficacy known to occur with apomorphine
- 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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