Pharmacokinetics, Safety and Tolerance 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 unpredictable 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. These episodes have a negative impact on quality of life.
- OFF time can be reduced by increasing the frequency of medication dosing, but this can lead to side effects and patient manipulations, most PD patients suffer many OFF episodes daily as these changes to no-ON/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 EEC, 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 designed to immediately manage OFF episodes by rapidly delivering apomorphine through absorption from the oral cavity mucosa.
- This Phase I Study examined the pharmacokinetic effects and safety of apomorphine delivered sublingually versus 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 on 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 on 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 donepezil, which was continued during treatment.

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 apomorphine on consecutive days.
- Baseline demographics for each cohort are presented in Table 1.

CONCLUSIONS

- Sublingually administered APL-130277 reaches therapeutic blood levels comparable to sc apomorphine.
- APL-130277 is a lower Cmax, less variable than Cmax and more rounded Cmax, which translates to less frequent and less severe dopaminergic adverse events compared to sc apomorphine.
- Inpatient, APL-130277 reaches the minimum efficacious plasma threshold comparable to sc apomorphine but remains in the therapeutic window for a longer duration of effect. This results in a longer duration of efficacy while maintaining improved tolerability.
- The percentage of PD patients with adverse events is expected to be lower given that they have improved dopaminergic function compared to healthy volunteers.
- The differences in PK profile with sublingual APL-130277 compared to sc apomorphine should be 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.

REFERENCES


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