Pharmacokinetic-pharmacodynamic Effects of Sublingual Apomorphine (APL-130277) for Acute Rescue 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 include off-on fluctuations, “freezing” of gait, and tremor.
• In some cases, the patients seek urgent care and are administered off-label high doses of levodopa for symptomatic relief.
• Parkinson’s disease OFF episodes can be divided into three subtypes: intermittent, partial, and continuous.
• Continuous OFF episodes are the most problematic.
• Continuous OFF episodes can occur at any time of the day, are more frequent, and can last longer than intermittent OFF episodes.

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 before and to 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.
• 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 (Respondents).
• All turned fully ON within 30 min and 2 within 15 min.
• Mean apomorphine concentration for the 6 responders at the dose they achieved their full ON and for the 4 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 Respondents went from OFF to full ON was 2.64 mg (range 0.36–2.37), 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 reach the minimum efficacious concentration (less than 0.51 mg) at all doses tested.

RESULTS

• Of the 15 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 (Respondents).
• All turned fully ON within 30 min and 2 within 15 min.
• Mean apomorphine concentration for the 6 responders at the dose they achieved their full ON and for the 4 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 Respondents went from OFF to full ON was 2.64 mg (range 0.36–2.37), 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 reach the minimum efficacious concentration (less than 0.51 mg) at all doses tested.

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 mg 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 sublingual 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 AEs were mild and occurred within 2 hours of dosing.
• APL-130277 may 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


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