ABSTRACT

Introduction: OFF episodes negatively impact quality of life in patients with Parkinson’s disease (PD). There remains a need for an acute, effective, noninvasive treatment.

Background: APL-130277 is a sublingually administered apomorphine oral strip.

Methods: The authors conducted a phase 2, open-label, proof-of-concept study. Patients presented to clinic in the morning in the practically defined OFF state and were dosed with APL-130277 10 mg. Assessments of OFF or ON state and MDS-UPDRS part III were conducted predose and at 15, 30, 45, 60, and 90 minutes. If a full ON was not achieved within 3 hours, the dose was increased in 5 mg increments until a full ON was achieved or to a maximum dose of 30 mg. Patients could be dosed up to two times a day over 3 days. Patients were pretreated with trimethobenzamide for 3 days, which was continued during the study.

Results: Of 19 patients, 15 (78.9%) achieved a full ON response. All 15 achieved a full ON response within 30 minutes and 6 of the 15 patients (40.0%) achieved a full ON response within 15 minutes. The mean (SD) duration of ON was 50 (19.4) minutes. Of the 15 patients, 9 (60.0%) remained fully ON for ≥90 minutes. There were no discontinuations as a result of an adverse event. The most common adverse events were dizziness (36.8%), somnolence (31.6%), and nausea (21.1%).

Conclusion: This was the first study of a new sublingual apomorphine formulation in PD patients. In this open-label study, APL-130277 appeared to provide a convenient, rapid,
Chronic treatment of Parkinson’s disease (PD) with levodopa is commonly associated with the development of OFF episodes\(^1\) that can manifest as predictable wearing OFF, morning akinesia, delayed ON, No-ON, or rapid ON/OFF fluctuations. These motor fluctuations can be either predictable or unpredictable. The mechanisms by which response fluctuations occur are only partially understood but are thought to include presynaptic neuronal degeneration leading to a lack of controlled storage and release of levodopa-derived dopamine, postsynaptic changes in dopamine receptor sensitivity and number, and pharmacokinetic and pharmacodynamic effects of intermittently administered short-acting dopaminergic agents.\(^2,3\) Fluctuations in plasma levels of levodopa occur as a result of the short half-life of levodopa and the unpredictable variability of gastric emptying and intestinal absorption.

Approximately 40% of patients with PD experience motor fluctuations or dyskinesia after 4 to 6 years of levodopa therapy, with close to 90% of patients experiencing these symptoms after 9 or more years of treatment.\(^4\) One study evaluating the effect of quality of life in patients with motor fluctuations versus those without demonstrated that in a population with a mean of approximately 9 years since diagnosis, 66% had motor fluctuations, with 79% of these patients having predictable wearing OFF, 59% having morning akinesia, 50% having ON/OFF fluctuations, and 36% having unpredictable OFFs. Each of these types of OFF episodes was associated with a significant impairment in quality of life as assessed by the 39-parkinson’s disease questionnaire (PDQ)-39.\(^4\)

Wearing-off motor fluctuations can be treated by increasing the dose or frequency of levodopa, by adding adjunctive medications (eg, Monoamine oxidase B (MAO-B) inhibitors, Catechol-O-methyltransferase (COMT) inhibitors, dopamine agonists), or by switching to a longer acting levodopa formulation (carbidopa/levodopa/entacapone, carbidopa and levodopa extended release). However, the benefit of oral medication manipulation is limited.\(^5\) Notably, it has been demonstrated that approximately two thirds of OFF time is from “waiting to turn ON” rather than end-of-dose wearing OFF. Treatment for “waiting to turn ON” (including delayed ON, No-ON) as well as for unpredictable OFFs (sudden OFF and rapid ON/OFF) is limited.\(^6\) The only approved therapy for the acute, intermittent treatment of OFF episodes is apomorphine injected subcutaneously.\(^7\) Although efficacious, subcutaneous apomorphine is not widely used, possibly because of its parenteral administration, potential inconvenience, and difficulty of use. There remains an unmet need for an easy-to-administer, safe and effective, on-demand, rapid, reliable, “turning ON” medication for PD patients.

APL-130277 is a sublingually administered apomorphine film strip in clinical development that is being investigated for the treatment of both predictable and unpredictable OFF episodes. It consists of a thin film bilayer designed to maximize apomorphine drug delivery while optimizing film disintegration and buccal tissue compatibility. The first layer is the apomorphine drug layer, designed to ensure drug stability, rapid drug diffusion, and maximal bioavailability. The second layer is a separate buffer layer designed to rapidly and completely neutralize acid generation following drug absorption while enhancing drug permeability. Thus, APL-130277 is designed as a “turning ON” medication to acutely manage OFF episodes by rapidly delivering apomorphine from the oral cavity mucosa without inducing local skin or mucosal irritation or reactions. We conducted a phase 2, open-label, proof-of-concept study to assess safety, tolerability, and efficacy, and to determine the effective doses of APL-130277 needed to convert PD patients from the OFF to the ON state. This was the first study of this new apomorphine sublingual formulation in PD patients.

**Methods**

**Study Design**

This was a phase 2, multicenter, open-label, single-arm study conducted at 4 sites in the United States. Patients were instructed to take their last dose of levodopa no later than 10 PM the night prior and present to

![FIG. 1. APL-130277 sublingual apomorphine oral strip. Figure depicts the size of the APL-130277 sublingual apomorphine oral strip. The 10-mg APL-130277 sublingual strip is smaller than a U.S. penny, whereas the 30-mg APL-130277 sublingual strip is approximately the size of a U.S. quarter.](image-url)
the clinic in the morning without taking their usual morning dose of levodopa and other PD medications. Patients could be brought to the clinic by a caregiver or family member if needed. Patients confirmed to be in the OFF state were dosed with APL-130277 10 mg (Fig. 1) and evaluated for 90 minutes. Patients were instructed to drink a glass of water immediately prior to dosing. Patients were then dosed by study staff members who placed the APL-130277 strip in the sublingual space with the drug layer facing toward the bottom of the tongue, and the patient was asked not to swallow for 2 minutes. If a full ON, as assessed by the investigator, was not achieved within 3 hours, the next higher dose was administered. Patients could be dosed up to two times a day for 3 days. The dose was increased in 5-mg increments until a full ON was achieved to a maximum dose of 30 mg. If a patient achieved a full ON response, they received a subsequent confirmatory administration of the same dose to assess reproducibility. Once they received the confirmatory dose (or failed to achieve a full ON response to the maximum dose) the patient received no further doses of APL-130277 and the study was completed. All patients were pretreated with trimethobenzamide for 3 days prior to initiation of APL-130277 and continued on this treatment throughout the study.

Patients

Key inclusion criteria included >18 years of age, diagnosis of PD consistent with the U.K. Parkinson’s Disease Society Brain Bank Criteria, ingestion of stable doses of levodopa ± stable doses of other adjunctive PD therapies for at least 4 weeks, predictable morning OFF on awakening and at least one OFF episode per day with a total daily OFF time of ≥2 hours, and Hoehn-Yahr stage I to III in the ON state. Key exclusion criteria included atypical or secondary parkinsonism and past treatment with any form of apomorphine within 30 days of dosing day 1.

Assessments

MDS-UPDRS part III and assessment of OFF/ON state were conducted by trained investigators at predose and at 15, 30, 45, 60, and 90 minutes after each APL-130277 administration. Investigators used their clinical judgment and familiarity with each individual patient’s levodopa response to assess their ON and OFF states. Adverse events (AEs) were obtained at each visit and coded using the Medical Dictionary for Regulatory Activities and tabulated by preferred term.

Statistical Analysis

The primary efficacy endpoint was the percentage of patients turning fully ON following an APL-130277 administration. Secondary efficacy endpoints were the absolute change and percent change in MDS-UPDRS part III, percent of patients fully ON at each time point, and percent of patients with 5- and 10-point improvements in MDS-UPDRS part III scores following administration of APL-130277. The primary and secondary endpoints were analyzed using data from the first full ON for responders and the last dose tested for nonresponders. Additional efficacy endpoints included MDS-UPDRS part III over time for each dose that provided a full ON response (includes first full ON and confirmatory ONs for responders and last dose tested for nonresponders). Safety endpoints included adverse events (AEs), serious AEs, electrocardiogram, vital signs (including orthostatic blood pressure [BP]), clinical laboratory values and oral examination.

Efficacy data were analyzed in the modified intention-to-treat (mITT) population, which included patients who were dosed with APL-130277 and received at least 1 postdose motor evaluation (all 19 patients). Sensitivity analyses were performed for responders (15 patients who turned fully ON following an APL-130277 administration) and the per protocol population (included only the 15 patients who completed the study with no protocol violations). The per protocol analysis set excluded 3 patients who were erroneously instructed to swallow the oral strip instead of allowing it to dissolve sublingually and 1 patient who was dosed in an OFF state following administration of their first dose of PD medications. The safety analysis set included all 19 patients treated with APL-130277. The percentage of patients ON at any time point and at each time point for first full ON as well as MDS-UPDRS part III absolute and percentage change at first full ON dose were tested using a paired t test. For MDS-UPDRS part III assessments, missing data were imputed using Last Observation Carried Forward. Because this was a phase 2 learning study, no formal sample size calculation was performed.

Protocol Approval, Trial Registration, and Patient Consent

The protocol and all patient materials were approved by independent ethics committees at each of the 4 institutions. All patients provided institutional review board-approved informed consent, and the study was conducted according to the Declaration of Helsinki. The study was performed between August 2014 and November 2014 and is registered on Clinicaltrials.gov (NCT02228590).

Results

Patients

A total of 20 patients were enrolled in the study (Fig. 2). Of the 20 patients, 19 were dosed with APL-130277 and completed the study. One patient withdrew consent prior to receiving the first dose. Of the
19 patients dosed with APL-130277, the baseline mean age was 61.5 years (SD 8.7), the mean baseline MDS-UPDRS part III OFF score was 42.8 (SD 15.7), mean number of daily OFF episodes was 3.9 (SD 1.5), and the mean number of classes of oral PD medications was 3 (SD 1.1; Supplemental Table 1). Fourteen patients were men and 5 were women.

**Efficacy**

A full ON response was achieved by 15 of 19 patients dosed (78.9%) in the mITT population (primary endpoint), whereas 13 of 15 patients (86.7%) achieved a full ON response in the per protocol population. All 15 responders (100.0%) achieved a full ON response within 30 minutes from the time of administration, and 6 of 15 (40.0%) achieved a full ON response within 15 minutes. The mean duration of ON time was 50 (SD 19.4) minutes. Of the 15 responders, 13 (86.7%) remained ON for at least 30 minutes, and 9 of 15 (60.0%) remained fully on for 90 minutes after dosing.

Figure 3 presents the percentage of patients achieving a full ON at various time points using data from the first full ON for responders and the last dose tested for nonresponders. Of the 15 responders, 3 (20.0%) turned fully ON with 10 mg of APL-130277, 5 (33.3%) with 15 mg, 4 (26.7%) with 20 mg, 2 (13.3%) with 25 mg, and 1 (6.7%) with 30 mg. A total of 4 patients (21.1%) did not achieve a full ON response following administration of APL-130277. Of these patients, 2 were dosed incorrectly (told to swallow APL-130277 immediately instead of keeping it sublingual for 2 minutes), and 2 were dosed to the maximum of 30 mg without experiencing a full ON response. There were no qualitative differences in baseline demographics in these 4 nonresponders when compared with those who responded.

Regarding reproducibility of response, of the 15 patients who achieved a full ON response to a dose of APL-130277, 14 received a confirmatory dose at the same dosage and 1 did not as per protocol because they achieved a full ON response at the last dosing of 30 mg. Of the 14 other patients who achieved a full ON response and received a confirmatory dose at the same dosage, 13 (92.9%) again achieved a full ON response and 1 (7.1%) did not.

Secondary endpoints included the mean change and mean percent change in MDS-UPDRS part III from predose to postdose at 15, 30, 45, 60, and 90 minutes for all analysis sets at the first full ON dose for
responders and the last dose tested for nonresponders. A significant change compared to predose was observed at all time points with all analysis sets, with a mean maximum change of 18.9 points for the mITT group and 20.5 points for the responders (Fig. 4a). Mean percent change in MDS-UPDRS part III from predose to postdose was approximately 30% at each time point (Fig. 4b), with a maximum improvement of 45.5% for the mITT group and 51.3% for the responder population.

A large percentage of patients had a clinically significant improvement in the MDS-UPDRS part III with their full ON dose (Supplemental Figs. 1a and 1b). In the mITT population, 16 patients (84.2%) had 10-point MDS-UPDRS part III improvement (Supplemental Fig. 1c). A total of 13 patients (68.4%) experienced ≥30% MDS-UPDRS part III improvement, and most achieved this within 30 minutes after dosing with APL-130277 and all within 45 minutes (Supplemental Fig. 1d).

Safety

All 19 patients dosed are included in the safety analysis. They received a total of 77 dose administrations of APL-130277 at doses of 10 to 30 mg. Overall, 13 of 19 (68.4%) patients experienced AEs and 11 of 19 (57.9%) were judged to be treatment related (Tables 1 and 2). Adverse events were transient and most were mild or moderate. Two patients experienced severe AEs (balance disorder and fatigue in 1 patient and apathy and somnolence in another). There was 1 serious AE of dysphagia that was considered not related to APL-130277. There were no discontinuations because of AEs. The most common AEs were dizziness (36.8% of patients, n = 7), somnolence (31.6% of patients, n = 6), and nausea (21.1% of patients, n = 4; Tables 1 and 2). Nausea occurred after the first dose in 4 patients and onset was typically 15 to 40 minutes after dosing. Of the 4 patients, 3 received higher doses of APL-130277 on subsequent days without further AEs of nausea.

Orthostatic hypotension (OH) was reported as an AE in 1 patient (5.3%). In that case, the patient met BP criteria for OH and experienced mild and transient orthostatic symptoms. There were 6 patients (31.6%) who did not meet BP criteria for OH at any time during the study, and 13 (68.4%) who met BP criteria for OH at some point during the study. One patient (5.3%) met BP criteria for OH only at baseline, 5 (26.3%) met BP criteria for OH both before and after APL-130277 administration, and 7 (36.8%) did not meet BP criteria for OH before APL-130277 administration but did meet BP criteria for OH after APL-130277 administration.

There were no reported AEs of dyskinesia. A total of 12 patients (63.2%) were rated on the MDS-UPDRS part III as having dyskinesia during study evaluations. A total of 5 patients (26.3%) were rated as having dyskinesia at either the screening or baseline evaluations (prior to APL-130277) and were not observed to exhibit dyskinesia following APL-130277 administration. There were 6 patients (31.6%) who were rated as having dyskinesia at either the screening or baseline evaluations (prior to APL-130277) who also had dyskinesia following an administration of APL-130277. In addition, there was 1 patient (5.3%) who did not have dyskinesia at screening or baseline who was subsequently rated as having dyskinesia following administration of APL-130277. For this patient, dyskinesia occurred following a 30-mg dose of APL-130277. Notably, the MDS-UPDRS part III dyskinesia item only assesses its presence and does not rate its severity.
There were no clinically meaningful electrocardiogram or laboratory changes.

Discussion

This open-label, proof-of-concept, dose-finding study suggests that APL-130277 can rapidly and effectively convert a patient from the OFF state to the ON state. Approximately 80% of patients (15 of 19) successfully resolved a morning OFF episode, and 2 of 4 who did not respond swallowed the strip, thereby preventing full apomorphine absorption. Patients who responded had a robust and clinically meaningful improvement in motor function as measured by the MDS-UPDRS part III. Almost all responders had ≥10 point MDS-UPDRS part III improvement (mean = 14 points), and 80% of responders effectively turned ON with 1 of the 3 lowest doses of APL-130277 (10, 15, and 20 mg), with only 20% of patients requiring the highest 2 doses (25 or 30 mg). Approximately two-thirds of responders remained fully ON for 90 minutes after dosing and maintained a mean MDS-UPDRS part III improvement of about 10 points or greater. In addition, the response appeared highly reproducible because more than 90% of patients who received a confirmatory dose achieved a full ON response with repeat administration.

One of the main limitations of this study is its open-label design. Both patients and investigators knew that an active drug was being administered, and this could have inflated efficacy results, although both the patient and the investigator had to agree that the patient was fully ON. Similarly, AEs may also be overreported or underreported in open-label studies. Another limitation is that the sample size included only 19 patients. However, previous pivotal trials with subcutaneous apomorphine only enrolled 17 and 29 patients. It should also be noted that administration was only performed in the clinic in the practically defined OFF state, and APL-130277 was not studied in the at-home setting without clinician supervision or during the day between levodopa doses. However, this was a proof-of-concept study. A larger, longer term, double-blind, placebo-controlled, phase 3 study is ongoing that includes patient self-administration in the morning and through the day (clinicaltrials.gov: NCT02469090) in addition to a long-term, open-label safety and efficacy study (clinicaltrials.gov: NCT02542696).

In our study, time to full ON was calculated based on the assessment of clinical status at 15, 30, 45, and 90 minutes postdose. Of the responders, 40% turned fully ON by 15 minutes, and the other 60% of responders turned fully ON between 15 and 30 minutes. This resulted in a calculated mean time to full ON of approximately 24 minutes, but this is likely to be overinflated because some patients turned ON before 15 minutes and others before the 30-minute time point. However, even calculating time to full ON in this way, the result is comparable to that seen with an injection of subcutaneous apomorphine in the APO202 and APO301 studies as well as the interim analysis from the AM-IMPAKT study.10,11

Although 4 patients did not respond to APL-130277, 2 of these 4 patients were dosed incorrectly and were mistakenly instructed to swallow the strip. It is well documented that if apomorphine is taken orally, it is quickly sulfonated, undergoes extensive first-pass metabolism, and has minimal bioavailability. For the other 2 patients who did not turn ON following APL-130277 administration at the highest dose tested (30 mg), there was some benefit observed in UPDRS scores,

### Table 1. Overview of adverse events (AEs; N = 19)

| Category          | N (%)   |
|-------------------|---------|
| Any AEs           | 13 (68.4) |
| Any related AEs   | 11 (57.9) |
| Mild AEs          | 13 (68.4) |
| Moderate AEs      | 4 (21.1)  |
| Severe AEs        | 2 (10.5)  |
| Serious AEs       | 1 (5.3)   |

![FIG. 4. Mean absolute and percent MDS-UPDRS part III change over time following APL-130277 administration. Significant improvements in motor function as measured by the MDS-UPDRS part III (a: absolute change; b: percent change) were seen at 15, 30, 45, 60, and 90 minutes after dosing with APL-130277 for all analysis sets. The change with standard error (SE) is represented in each of the graphs. mITT, modified intent-to-treat; min, minutes.](image-url)
which may suggest the need for a higher apomorphine dose. One patient who swallowed the strip did turn fully ON but the duration of ON was only 15 minutes, and this may have been the result of limited apomorphine absorption or a placebo response.

APL-130277 was safe and generally well tolerated. Importantly, there were no discontinuations because of AEs. The most common AEs observed were known dopaminergic AEs. In the current study, nausea was experienced by approximately 21% of patients, occurred within 40 minutes of dosing, and was transient. Only 1 patient had associated emesis. This rate and severity of nausea is similar to what has been reported with other dopamine agonists and some levodopa preparations.5,7,13–17 Although patients were pre-treated with trimethobenzamide, it may only be needed for a few weeks as is the case with subcutaneous apomorphine,18 and studies evaluating APL-130277 with mucosal irritation associated with sublingual dosing. This open-label, proof-of-concept study supports the hypothesis that APL-130277 alone can rapidly and predictably convert a PD patient from the practically defined OFF state to a full ON state. A double-blind, double-dummy study. Lancet Neurol 2014;13(2):141–149.

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### Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site.