

# Ulotaront, a Trace Amine-Associated Receptor 1/Serotonin 5-HT<sub>1A</sub> Agonist, in Patients With Parkinson Disease Psychosis

## A Pilot Study

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## Abstract

### Background and Objectives

Ulotaront (SEP-363856) is a trace amine-associated receptor 1 agonist with 5-HT<sub>1A</sub> receptor agonist activity currently in phase 3 clinical development for the treatment of schizophrenia. In this exploratory, flexibly dosed study, ulotaront was evaluated for the treatment of Parkinson disease psychosis (PDP).

### Methods

Patients with PDP requiring antipsychotic therapy were randomized, double-blind to ulotaront (25, 50, or 75 mg/d) or placebo. Mixed Model for Repeated Measures was used to assess change from baseline in the Scale for the Assessment of Positive Symptoms for Parkinson Disease (SAPS-PD) at 6 weeks (primary end point).

### Results

The efficacy analysis sample comprised 38 patients (ulotaront, n = 24; placebo, n = 14). SAPS-PD total scores were numerically reduced in ulotaront-treated vs placebo-treated patients from week 1 to week 6: Least squares mean (95% confidence interval) difference in change from baseline at week 6 was -1.1 (-6.5, 4.3, *p* = 0.681). PDP symptom complete remission (≥100% improvement [reduction] from baseline in SAPS-PD total score) was observed in 25% of ulotaront-treated vs 0% of placebo-treated patients. SAPS-PD and Neuropsychiatric Inventory hallucinations subscales were numerically reduced vs placebo, and SAPS-PD total scores were reduced in patients with greater cognitive impairment (baseline Mini-Mental State Examination [MMSE] scores ≤24). Ulotaront improved Scales for Outcomes in Parkinson Disease Sleep Scale – Daytime Sleepiness scores (*p* = 0.022). There was no worsening of Unified Parkinson Disease Rating Scale Part III motor score, MMSE, or vital signs. Adverse events (≥10%) with ulotaront vs placebo included hallucinations (24% vs 14%), confusional state (20% vs 14%), dizziness (16% vs 7%), nausea (12% vs 7%), and falls (12% vs 21%).

### Discussion

In this exploratory pilot study, ulotaront may decrease PDP symptoms without worsening motor function, particularly in patients with cognitive impairment.

### MORE ONLINE

#### Class of Evidence

Criteria for rating therapeutic and diagnostic studies

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Parkinson's Disease and Movement Disorders Center of Boca Raton (SHI), FL; JEM Research Institute (MG), Lake Worth, FL; University of Kansas (RP), Kansas City; University of Miami Health System (CS), FL; The Movement Disorder Clinic of Oklahoma (KK), Tulsa; The Lockwood Group (MP), Stamford, CT; and Sunovion Pharmaceuticals Inc. (YZ, DC, KSK, BN), Marlborough, MA.

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## Trial Registration Information

ClinicalTrials.gov identifier: NCT02969369; submitted: November 17, 2016; study start date: December 31, 2016.

## Classification of Evidence

This Class II study was an exploratory pilot study that was underpowered to detect a statistically significant difference between ulotaront and placebo in the treatment of patients with Parkinson disease psychosis without worsening motor function.

The overall incidence of Parkinson disease psychosis (PDP) is ~30% in patients with Parkinson disease (PD) but increases to ~60% as PD progresses.<sup>1,2</sup> PDP is associated with greater functional impairment and mortality for the patient and increased caregiver burden, hospitalizations, and risk of nursing home placement.<sup>3-5</sup>

Treatment approaches for PDP have relied on reducing the dose of dopaminergic therapies used to treat PD or adding antipsychotics that block or do not block dopamine-D<sub>2</sub> receptors; however, reducing dopaminergic therapies or adding on dopamine-blocking therapies may worsen PD symptoms.<sup>6-8</sup> Pimavanserin (NUPLAZID, Acadia Pharmaceuticals Inc., San Diego, CA), a selective serotonin 5-HT<sub>2A</sub> inverse agonist, is currently the only United States Food and Drug Administration (FDA)-approved PDP treatment.<sup>9</sup> Pimavanserin is effective in reducing PDP symptoms without worsening motor parkinsonism<sup>6,10</sup>; however, improvement may be delayed by several weeks, and only 13.7% of patients showed complete resolution of PDP symptoms in a phase 3 trial.<sup>11</sup> D<sub>2</sub>-blocking antipsychotics can worsen motor parkinsonism and are not approved for the treatment of PDP symptoms but can be effective. Only 2 of these D<sub>2</sub>-blocking antipsychotics do not typically worsen motor parkinsonism and therefore have been used off label. For example, clozapine is effective, but its use is limited by serious safety concerns and the need for frequent blood monitoring.<sup>6,12,13</sup> Quetiapine has not demonstrated efficacy in placebo-controlled studies, and dosing can be limited by somnolence and orthostatic hypotension.<sup>7,14-16</sup> Safe and effective therapies approved for the treatment of PDP that do not worsen motor parkinsonism therefore continue to remain a significant unmet need.

Ulotaront (SEP-363856) is a trace amine-associated receptor 1 (TAAR1) agonist with 5-HT<sub>1A</sub> agonist activity currently in phase 3 clinical trials, with FDA breakthrough therapy designation, for the treatment of schizophrenia.<sup>17</sup> Unlike most currently approved antipsychotic drugs, ulotaront does not exert its efficacy by blockade of dopamine D<sub>2</sub> or serotonin 5-HT<sub>2A</sub> receptors.<sup>18</sup> In preclinical studies, TAAR1 agonists, including ulotaront, have demonstrated broad efficacy in animal models of schizophrenia (relating to positive and negative symptoms), depression, and anxiety.<sup>18-21</sup> Given its modulatory effects on monoaminergic and glutamatergic neurotransmission, TAAR1 has emerged as a promising therapeutic target for several neuropsychiatric disorders.<sup>20,21</sup> In particular, TAAR1 agonists may represent a new pharmacologic class for the treatment of schizophrenia and other

psychoses due to TAAR1-mediated regulation of dopaminergic circuitry.<sup>20</sup>

The efficacy and safety of ulotaront treatment was investigated in a 4-week phase 2, randomized, placebo-controlled study of patients with an acute exacerbation of schizophrenia.<sup>22</sup> In this study, ulotaront was observed to be efficacious vs placebo as measured by significant improvement in Positive and Negative Syndrome Scale (PANSS) scores after 4 weeks of treatment.<sup>22</sup> Ulotaront treatment was also found to be safe and well tolerated with an incidence of extrapyramidal symptoms similar to placebo (ulotaront, 3.3%; placebo, 3.2%).<sup>22</sup> This present exploratory study evaluated the efficacy, safety, and tolerability of ulotaront vs placebo in patients with a clinical diagnosis of PDP. The primary objective of this pilot study was to evaluate whether treatment with ulotaront improved symptoms of psychosis in patients with Parkinson-associated psychosis.

## Methods

### Patients

This was a phase 2 multicenter, randomized, parallel-group, placebo-controlled study in adults 55 years or older with a clinical diagnosis of PDP (ClinicalTrials.gov identifier: NCT02969369). Eligibility criteria included idiopathic PD consistent with United Kingdom PD Society Brain Bank criteria<sup>23</sup> ≥1 year and psychotic symptoms that developed after PD diagnosis, were present for ≥1 month, occurred at least weekly in the month before screening, and were severe enough to warrant treatment with antipsychotics. Patients had a combined score of ≥6 or an individual score of ≥4 on the Neuropsychiatric Inventory (NPI)<sup>24</sup> item A (delusions) and/or item B (hallucinations) at screening (visit 1) and baseline (visit 3). Patients were on stable doses of dopaminergic and other therapies for PD motor symptoms for ≥1 month before screening and during the trial. Patients had a Mini-Mental State Examination (MMSE) score of >16 points of 30, and a caregiver was required at study visits.

Patients were excluded if they did not meet the above PDP diagnosis criteria. In addition, patients were also excluded if they experienced lack of efficacy in response to adequate doses of ≥2 antipsychotic drugs ≤1 year of screening or had prior surgical treatment for PD, stroke, or other uncontrolled neurologic illness <6 months before baseline, suicidal ideations at screening or baseline, or any clinically significant medical condition or chronic disease that would limit the patient's ability to participate in the study.

## Classification of Evidence

The primary research question was to evaluate whether ulotaront has the potential to reduce the frequency and severity of hallucinations and delusions in patients with PDP. This study provides Class II evidence that, for patients with PDP, flexibly dosed ulotaront may decrease symptoms of psychosis without worsening motor function.

## Standard Protocol Approvals, Registrations, and Patient Consents

In compliance with the Declaration of Helsinki, patients provided written informed consent. The study was approved by independent ethics committees or institutional review boards at each participating study site. Caregivers also provided consent for the patient to participate in the study as well as consent for collection of caregiver data as related to the assessment of the patient's neuropsychiatric status (measured by the NPI).

## Study Design

This study, conducted at 27 clinical sites in the United States between December 31, 2016, and April 20, 2020, evaluated the efficacy, safety, and tolerability of double-blind ulotaront flexibly dosed at 25, 50, or 75 mg/d in patients with PDP. As illustrated in eFigure 1 ([links.lww.com/CPJ/A440](https://links.lww.com/CPJ/A440)), the study consisted of a screening/washout period (14–28 days before double-blind treatment) and a double-blind treatment period (6 weeks). During screening/washout, any antipsychotic or centrally acting anticholinergic medications were tapered and stopped. Prior treatment with antipsychotic agents was discontinued  $\geq 5$  half-lives before performing the NPI and MMSE screening assessments. Based on previous study experience,<sup>25</sup> a 2-week nonpharmacologic placebo lead-in period consisting of brief psychosocial therapy adapted for PD was initially included during screening to reduce placebo response but was subsequently removed to alleviate patient and caregiver burden.

At baseline (day 1), patients who had successfully completed the screening/washout period were randomly assigned through interactive voice/web response system in a 2:1 ratio to ulotaront or placebo. The randomization schedule was generated by a nonstudy biostatistician. All study staff and patients remained blinded to treatment assignment from the time of randomization until database lock and unblinding by keeping randomization data strictly confidential and concealing study drugs with identical packaging, labeling, and appearance. Double-blind study drug was taken in-clinic at baseline and on visit days when the patient uptitrated. Subsequent doses starting the day after were taken at bedtime. Patients randomized to ulotaront received 25 mg/d for 1 week (days 1–7). If there were no safety or tolerability issues, they were uptitrated to 50 mg/d at week 2 and 75 mg/d at week 3. Patients still receiving 25 mg/d had their dose uptitrated to 50 mg/d at week 3 unless there were safety and tolerability concerns. Uptitration was not allowed after week 5. Dose reductions to 50 mg/d or 25 mg/d were allowed by 1 dose level at any time for reasons of safety and tolerability. Patients who completed the double-blind treatment period could continue into a 12-week open-label extension.

Assessments were done at screening, baseline, and weekly study visits (see Table 1 for score ranges of assessment scales). The primary outcome was change in Scale for the Assessment of Positive Symptoms for Parkinson Disease (SAPS-PD)<sup>26</sup> total score from baseline to week 6 (day 43). The SAPS-PD includes 9 items scored 0–5, with 7 items assessing individual symptoms, a global hallucinations item, and a global delusions item. SAPS-PD was evaluated by remote, centralized, blinded raters who had been trained and calibrated. Other secondary efficacy end points at week 6 included the proportion of patients who achieved a reduction on the total SAPS-PD score by  $\geq 30\%$ ,  $\geq 50\%$ , and  $\geq 100\%$  and change from baseline in SAPS-PD hallucinations and delusions subscale scores; Clinical Global Impression of Severity (CGI-S)<sup>27</sup> score, NPI hallucinations and delusions score, and the Scales for Outcomes in Parkinson Disease Sleep Scale – Daytime Sleepiness (SCOPA-DS) and Nighttime Sleep (SCOPA-NS) assessments.<sup>28</sup> The NPI and CGI-S were performed by trained staff at the site who were blinded to the SAPS-PD scores. Safety assessments included adverse events (AE), serious AEs, AEs resulting in discontinuation, and deaths. MMSE scores were also assessed. The Unified Parkinson Disease Rating Scale (UPDRS) Part III<sup>29</sup> motor score was conducted to assess the effect of treatment with ulotaront on motor symptoms of PD. Additional safety measures included ECG, vital signs, laboratory assessments, and suicidal ideations as measured by the Columbia-Suicide Severity Rating Scale. Patients were assessed for orthostatic hypotension based on prespecified criteria, defined as a decrease of  $\geq 20$  mm Hg in systolic blood pressure or  $\geq 10$  mm Hg in diastolic blood pressure. Orthostatic tachycardia was also assessed.

## Statistical Analysis

This pilot trial was designed as an exploratory study and therefore not powered to detect any particular treatment difference. Sample size was determined based on practical considerations. The safety population included all patients who were randomized and received  $\geq 1$  dose of study drug during the double-blind treatment period. The modified intent-to-treat (mITT) population was defined as all patients who were randomized, received  $\geq 1$  dose of study drug, and had a baseline and  $\geq 1$  postbaseline SAPS-PD, NPI, or CGI-S assessment during the double-blind treatment period. The mITT population was the primary population for efficacy analyses. For selected efficacy measures, such as the primary and secondary end points, including SAPS-PD, NPI, CGI-S, and MMSE scores, change from baseline was assessed using a mixed model for repeated measures (MMRM) method. The linear MMRM included fixed factors for treatment, visit (weeks 2, 3, 5, and 6, as a categorical variable), and treatment-by-visit interaction and included baseline SAPS-PD total score as a covariate. Subject was included in the model as a random effect. An unstructured covariance matrix was used for the within-subject correlation, and the Kenward-Rogers approximation was used to calculate the denominator degrees of freedom for testing. Other measures, including SCOPA-DS, SCOPA-NS, and UPDRS Part III scores, were assessed by analysis of covariance model with treatment as a fixed effect and baseline scores as a covariate. All

**Table 1** Patient Demographics and Clinical Characteristics at Baseline (mITT Population)

	Placebo (n = 14)	Ulotaront (n = 24)	Total (N = 38)
<b>Age, mean (SD), y</b>	71.8 (7.12)	70.0 (7.24)	70.7 (7.15)
≥55 to <65, n (%)	2 (14.3)	5 (20.8)	7 (18.4)
≥65 to <75, n (%)	7 (50.0)	12 (50.0)	19 (50.0)
≥75, n (%)	5 (35.7)	7 (29.2)	12 (31.6)
<b>Sex (male), n (%)</b>	13 (92.9)	20 (83.3)	33 (86.8)
<b>Race, n (%)</b>			
Asian	0	1 (4.2)	1 (2.6)
Native Hawaiian/Pacific Islander	1 (7.1)	0	1 (2.6)
White	12 (85.7)	23 (95.8)	35 (92.1)
Others	1 (7.1)	0	1 (2.6)
<b>Time since onset of PD, mean (SD), y</b>	9.3 (4.36)	8.9 (4.98)	9.0 (4.71)
<b>Time since onset of PDP, mean (SD), y</b>	2.3 (2.36)	2.4 (2.50)	2.4 (2.41)
<5, n (%)	13 (92.9)	22 (91.7)	35 (92.1)
5 to <10, n (%)	1 (7.1)	1 (4.2)	2 (5.3)
10 to <20, n (%)	0	1 (4.2)	1 (2.6)
<b>SAPS-PD total score, mean (SD), range 0–45</b>	14.7 (8.71)	13.1 (6.04)	13.6 (7.02)
<13 median	6 (46.2)	12 (50.0)	18 (48.6)
≥13 median	7 (53.8)	12 (50.0)	19 (51.4)
<b>SAPS-PD hallucinations subscale score, mean (SD), range 0–25<sup>a</sup></b>	12.0 (6.60)	10.5 (4.50)	11.0 (5.29)
<10 median, n (%)	6 (46.2)	8 (33.3)	14 (37.8)
≥10 median, n (%)	7 (53.8)	16 (66.7)	23 (62.2)
<b>SAPS-PD delusions subscale score, mean (SD), range 0–20<sup>b</sup></b>	2.7 (3.95)	2.6 (3.71)	2.6 (3.74)
<0.5 median, n (%)	7 (53.8)	12 (50.0)	19 (51.4)
≥0.5 median, n (%)	6 (46.2)	12 (50.0)	18 (48.6)
<b>CGI-S score, mean (SD), range 0–7</b>	4.1 (1.27)	4.1 (1.05)	4.1 (1.13)
<4, n (%)	5 (35.7)	6 (30.0)	11 (32.4)
≥4, n (%)	9 (64.3)	14 (70.0)	23 (67.6)
<b>NPI (H + D) score, n, range 0–24</b>			
Mean (SD)	8.6 (4.03)	10.8 (5.34)	10.0 (4.96)
<6, n (%)	3 (21.4)	4 (16.7)	7 (18.4)
≥6 to <12, n (%)	7 (50.0)	10 (41.7)	17 (44.7)
≥12, n (%)	4 (28.6)	10 (41.7)	14 (36.8)
<b>NPI hallucinations subscale score, mean (SD), range 0–12</b>	5.1 (2.46)	7.0 (3.26)	6.3 (3.10)
<b>NPI delusions subscale score, mean (SD), range 0–12</b>	3.5 (3.18)	3.8 (4.05)	3.7 (3.71)
<b>MMSE score, mean (SD), range 0–30</b>	24.7 (3.20)	25.1 (4.07)	25.0 (3.73)
≤24, n (%)	7 (50.0)	7 (29.2)	14 (36.8)

Continued

**Table 1** Patient Demographics and Clinical Characteristics at Baseline (mITT Population) (continued)

	Placebo (n = 14)	Ulotaront (n = 24)	Total (N = 38)
≤24, mean (SD)	22.0 (1.15)	19.7 (3.15)	20.9 (2.57)
>24, n (%)	7 (50.0)	17 (70.8)	24 (63.2)
>24, mean (SD)	27.4 (1.90)	27.3 (1.53)	27.3 (1.61)

Abbreviations: CGI-S = Clinical Global Impression of Severity; mITT = modified intent-to-treat; MMSE = Mini-Mental State Examination; NPI = Neuropsychiatric Inventory; NPI (H + D) = Neuropsychiatric Inventory (Hallucinations + Delusions); PD = Parkinson disease; PDP = Parkinson disease psychosis; SAPS-PD = Scale for the Assessment of Positive Symptoms for Parkinson Disease.

<sup>a</sup> The SAPS-PD subscale for hallucinations was defined as the sum of the 4 items for hallucinations and the global hallucination item.

<sup>b</sup> The SAPS-PD subscale for delusions was defined as the sum of the 3 items for delusions and the global delusion item.

statistical analyses were performed using SAS software, version 9.4.

## Data Availability

Access to deidentified participant data will be provided after a research proposal is submitted online (vivli.org) and receives approval from the Independent Review Panel and after a data sharing agreement is in place. Access will be provided for an initial period of 12 months, but an extension can be granted, when justified, for up to an additional 12 months.

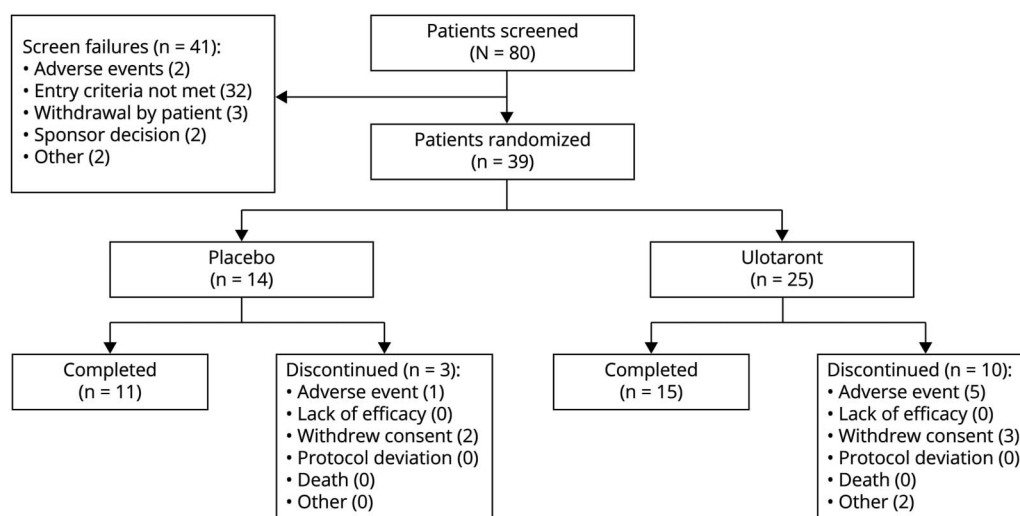
## Results

### Patients

Thirty-nine patients were enrolled, with 25 randomly assigned to ulotaront and 14 to placebo (Figure 1). Of the randomized patients, 15 (60.0%) on ulotaront and 11 (78.6%) on placebo completed double-blind treatment. The most common reason for discontinuation was AEs in the

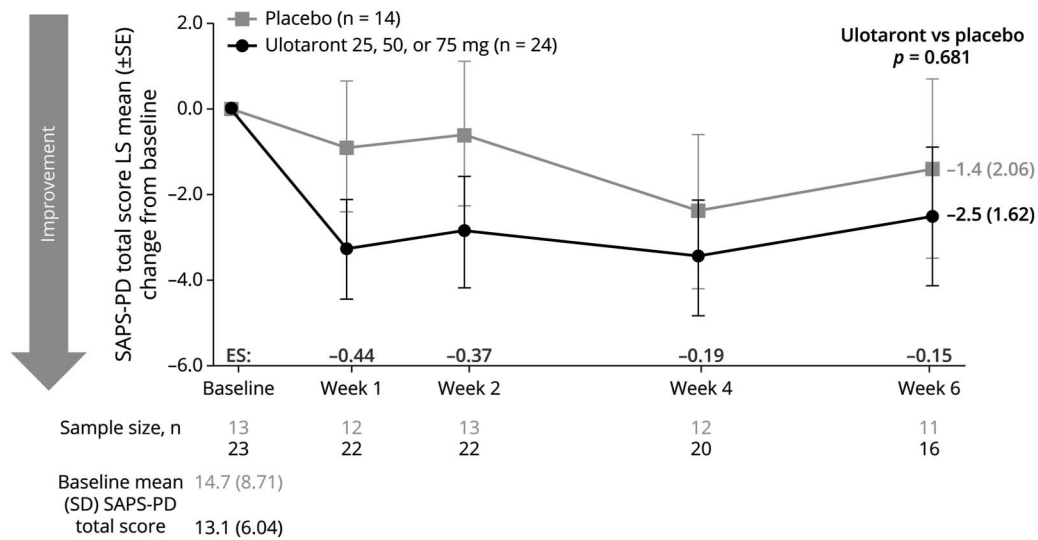
ulotaront group and study withdrawal in the placebo group. Before screening, 7 (17.9%) were on pimavanserin and 6 (15.4%) were on quetiapine; other antipsychotic agents were used in <10% of patients. One patient who was randomized to and received ulotaront was excluded from the mITT efficacy analysis because of not having a postbaseline efficacy assessment. Of the 24 patients in the ulotaront group and 14 in the placebo group in the mITT population, 13 (54.2%) on ulotaront and 7 (50.0%) on placebo underwent the 2-week placebo lead-in period before this period was removed from the study design.

Table 1 shows the baseline demographics and clinical characteristics for the mITT population. The mean (range) time since onset of PD was 9.0 years (2.4–20.7) and was 2.4 years (0.1–11.9) since onset of PDP. Overall, baseline SAPS-PD, NPI, and CGI-S scores indicate that the patient population on average experienced moderate psychosis, with predominantly hallucinations vs delusions (Table 1). Cognitive impairment

**Figure 1** Patient Disposition

One patient randomized to the ulotaront group was not included in the modified intent-to-treat efficacy analysis owing to not having a baseline or ≥1 postbaseline efficacy measurement in SAPS-PD total, NPI, or CGI-S scores. One patient in the placebo group discontinued because of adverse events of rash and hypertension; 5 patients in the ulotaront group discontinued because of adverse events of abdominal pain in a patient on 25 mg, gait disturbance, confusional state, and hallucinations each in 1 patient on 50 mg and hallucinations in 1 patient on 75 mg. CGI-S = Clinical Global Impression of Severity; NPI = Neuropsychiatric Inventory; SAPS-PD = Scale for the Assessment of Positive Symptoms for Parkinson Disease.

**Figure 2** Change From Baseline in SAPS-PD Total Scores (mITT Population)

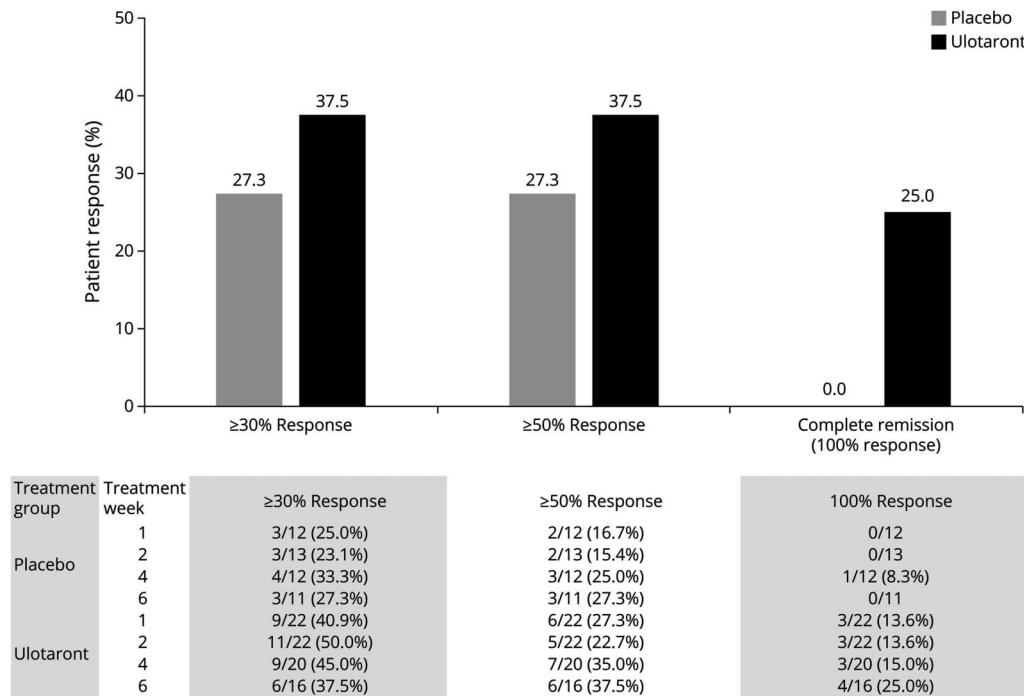


The mITT population includes all patients who received  $\geq 1$  dose and had a SAPS-PD assessment at baseline and  $\geq 1$  postbaseline. ES = effect size; LS = least squares; mITT = modified intent-to-treat; SAPS-PD = Scale for the Assessment of Positive Symptoms for Parkinson Disease; SE = standard error.

(MMSE score  $\leq 24$ ) was present in 14 patients (36.8%) at baseline. There were no notable differences at baseline between treatment groups across the measured scales. The extensive medical comorbidity of study patients is summarized in eTable 1 ([links.lww.com/CPJ/A440](https://links.lww.com/CPJ/A440)).

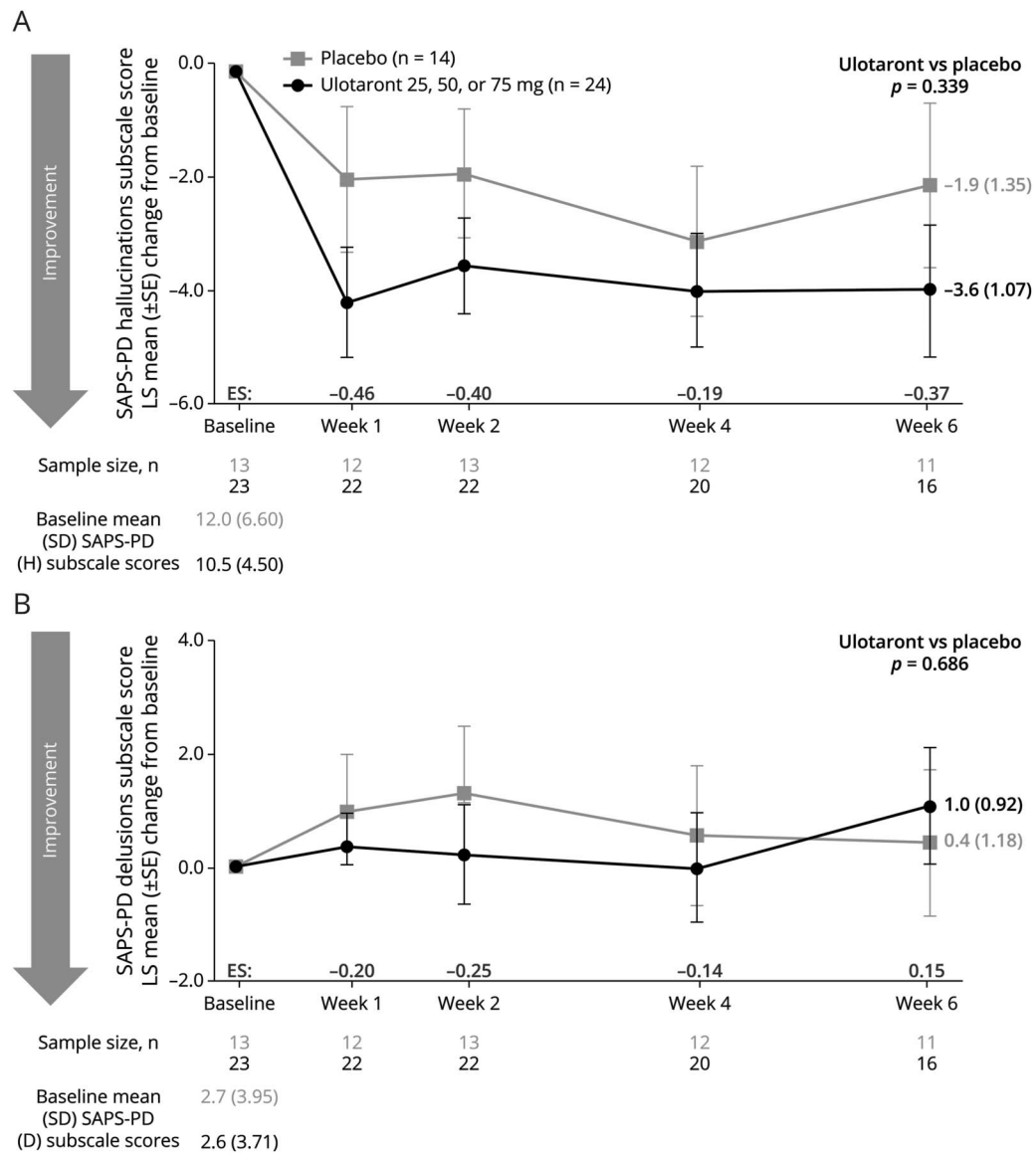
The mean (range) duration of exposure during the double-blind treatment period was 32.1 days (2–43) for ulotaront (mean dose: 47.5 mg) and 37.4 days (9–45) for placebo. All patients received 25 mg at baseline. In the ulotaront group, 16 of 24 patients (66.7%) were uptitrated to 50 mg after 1 week of

**Figure 3** Percentage Improvement in SAPS-PD Total Scores at Week 6 (mITT Population)



The mITT population includes all patients who received  $\geq 1$  dose and had a SAPS-PD assessment at baseline and  $\geq 1$  postbaseline. Categories are not mutually exclusive; a  $\geq 50\%$  responder is also included in the  $\geq 30\%$  responder category. mITT = modified intent-to-treat; SAPS-PD = Scale for the Assessment of Positive Symptoms for Parkinson Disease.

**Figure 4** Change From Baseline in SAPS-PD Hallucinations (A) and Delusions (B) Subscale Scores (mITT Population)



The mITT population includes all patients who received  $\geq 1$  dose and had a SAPS-PD assessment at baseline and  $\geq 1$  postbaseline. D = delusions; ES = effect size; H = hallucinations; LS = least squares; mITT = modified intent-to-treat; SAPS-PD, = Scale for the Assessment of Positive Symptoms for Parkinson Disease; SE = standard error.

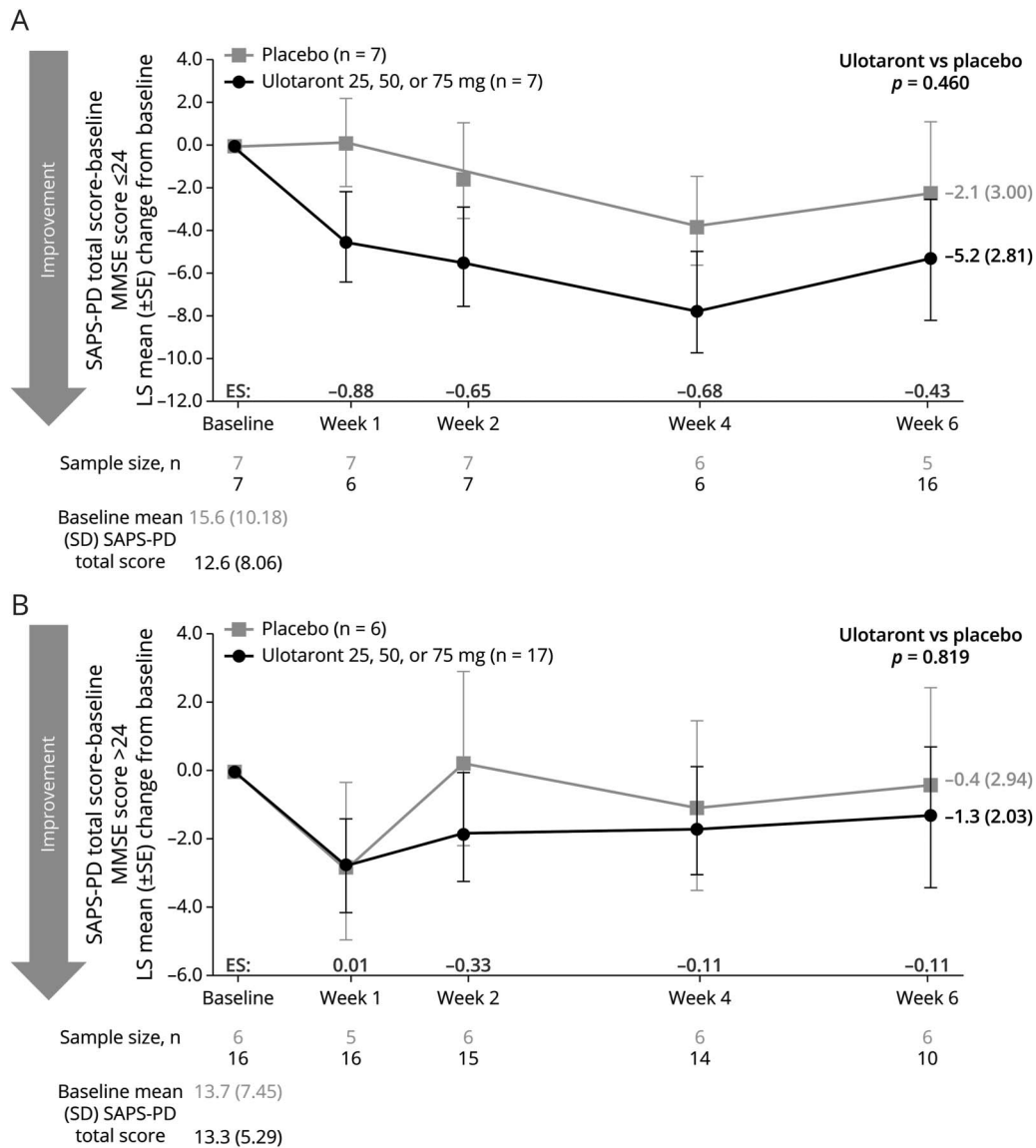
treatment, 11 of 22 (50.0%) were uptitrated to 75 mg after 2 weeks, and 13 of 22 (59.1%) were on 75 mg by 4 weeks of treatment. Dose exposure was similar for those patients receiving the placebo equivalent. Among the 22 patients in the ulotaront group at week 4, 4 (18.2%) were on 50 mg, 13 (59.1%) were on 75 mg, 4 (18.2%) discontinued (1 on 50 mg, 3 on 75 mg), and data were missing for 1 patient (4.5%). Among the 13 patients in the placebo group at week 4, 2 (15.4%) were on 25 mg, 2 (15.4%) were on 50 mg, 8 (61.5%) were on 75 mg, and 1 (7.7%) discontinued on 50 mg.

### Efficacy

Figure 2 illustrates the least squares (LS) mean change from baseline in SAPS-PD for ulotaront and placebo groups through week 6. The LS mean 95% confidence interval (CI)

difference between ulotaront and placebo in change from baseline at week 6 was  $-1.1$  ( $-6.5, 4.3, p = 0.681$ ), favoring ulotaront, but the difference was not statistically significant. Reduction in SAPS-PD total scores was observed as early as 1 week postdose when all patients were receiving 25 mg ulotaront and was maintained through week 6. SAPS-PD responders were defined as patients with  $\geq 30\%$ ,  $\geq 50\%$ , and  $\geq 100\%$  improvement (reduction) from baseline, respectively, in SAPS-PD total scores at weeks 1 through 6 (figure 3, table inset). A greater percentage of ulotaront-treated patients achieved  $\geq 30\%$  and  $\geq 50\%$  response at all weeks compared with placebo-treated patients. Complete remission of symptoms (i.e., 100% response) was observed in 4 of 16 patients (25.0%) in the ulotaront group compared with 0 of 11 patients in the placebo group at week 6 (Figure 3).

**Figure 5** Change From Baseline in SAPS-PD Total Scores for Patients by Baseline MMSE Score  $\leq 24$  (A) and MMSE Score  $>24$  (B) (mITT Population)



The mITT population includes all patients who received  $\geq 1$  dose and had a SAPS-PD assessment at baseline and  $\geq 1$  postbaseline. ES = effect size; LS = least squares; mITT = modified intent-to-treat; MMSE = Mini-Mental State Examination; SAPS-PD = Scale for the Assessment of Positive Symptoms for Parkinson Disease; SE = standard error.

Figure 4 illustrates the LS mean (standard error [SE]) change from baseline in SAPS-PD hallucinations (Figure 4A) and delusions (Figure 4B) subscores through week 6. LS mean (95% CI) difference between ulotaront and placebo in change from baseline at week 6 was  $-1.7$  ( $-5.2, 1.9, p = 0.339$ ) for SAPS-PD hallucinations subscore, favoring ulotaront, but the difference was not statistically significant. A numerical difference between ulotaront and placebo was observed as early as 1 week postdose. The LS mean (95% CI) difference between ulotaront and placebo in change from baseline at week 6 was  $0.6$  ( $-2.4, 3.7, p = 0.686$ ) for SAPS-PD delusions subscore. The results for NPI hallucinations subscore were similar to SAPS-PD hallucinations subscore as follows: The LS mean (95% CI) difference in change from baseline at week 6 was  $-1.8$  ( $-4.3, 0.8, p = 0.167$ ). There

were no differences between ulotaront and placebo groups in the change from baseline at week 6 in NPI hallucinations and delusions, NPI delusions subscale, or CGI-S scores.

Studies have suggested that patients with PDP and cognitive impairments may show greater response than the overall PDP population to treatment for psychotic symptoms.<sup>6,30,31</sup> To assess the effects of ulotaront in patients with PDP and cognitive impairment, a prespecified analysis was done in patients with an MMSE score  $\leq 24$  (indicative of greater cognitive impairment) and patients with an MMSE score  $>24$  (Figure 5, A and B). The LS mean (95% CI) difference in change from baseline in SAPS-PD total score at week 6 for patients with a baseline MMSE score  $\leq 24$  was  $-3.1$  ( $-11.5, 5.3, p = 0.460$ ). Reduction in SAPS-PD



**Table 2** Adverse Events in  $\geq 2$  Patients at Any Dose<sup>a</sup> of Ulotaront (Safety Population)

System organ class/preferred term, n (%)	Ulotaront 25 mg (n = 11)	Ulotaront 50 mg (n = 9)	Ulotaront 75 mg (n = 10)	Placebo (n = 12)
<b>Any adverse event</b>	11 (100.0)	9 (100.0)	10 (100.0)	12 (100.0)
<b>Nausea</b>	2 (18.2)	1 (11.1)	0	1 (8.3)
<b>Fall</b>	0	3 (33.3)	1 (10.0)	3 (25.0)
<b>Dizziness</b>	2 (18.2)	4 (44.4)	0	1 (8.3)
<b>Somnolence</b>	2 (18.2)	1 (11.1)	1 (10.0)	0
<b>Confusional state</b>	1 (9.1)	1 (11.1)	3 (30.0)	2 (16.7)
<b>Hallucinations</b>	2 (18.2)	3 (33.3)	2 (20.0)	2 (16.7)
<b>Insomnia</b>	0	2 (22.2)	0	1 (8.3)

<sup>a</sup> Dose used at the time of onset of adverse event.

total score for the ulotaront group was observed at week 1 postdose and maintained throughout the 6-week treatment period (Figure 5A). For patients with an MMSE score  $>24$ , no consistent reduction in SAPS-PD total scores was observed throughout the 6-week treatment period (Figure 5B). The LS mean (95% CI) difference in change from baseline at week 6 was  $-0.8$  ( $-8.1, 6.5, p = 0.819$ ).

Improvement was observed in SCOPA-DS scores for patients receiving ulotaront. The LS mean (95% CI) difference in change from baseline at week 6 was  $-2.7$  ( $-4.9, 0.4, p = 0.022$ ). Conversely, no improvement was observed in change from baseline at week 6 for SCOPA-NS scores.

To assess whether treatment with ulotaront has an effect on motor symptoms of PD, UPDRS Part III motor scores were measured at baseline and postbaseline study visits. The mean (SD) baseline UPDRS Part III scores were 33.4 (10.28) and 35.9 (13.12) for ulotaront and placebo groups, respectively. Treatment with ulotaront did not worsen UPDRS Part III motor scores. No consistent changes were observed in LS mean (SE) change from baseline in UPDRS Part III scores for ulotaront and placebo groups through week 6 (eFigure 2, [links.lww.com/CPJ/A440](https://links.lww.com/CPJ/A440)). Treatment with ulotaront also did not affect MMSE scores.

## Safety

Overall, 18 patients (72.0%) in the ulotaront group experienced 65 AEs and 12 patients (85.7%) in the placebo group experienced 32 AEs. Two patients (8.0%) in the ulotaront group experienced a serious AE (SAE). One patient, receiving ulotaront 75 mg at the time of the SAE, experienced a right femoral neck subcapital hip fracture with arthroplasty (spontaneous) on day 21 which required hospitalization. The second patient, receiving ulotaront 50 mg at the time of the SAE, experienced an altered mental state on day 33 which required hospitalization; the altered mental state was judged to be “not related to study drug” and resolved on day 37. No patients in the placebo group experienced serious AEs. Five patients (20.0%) in the ulotaront

group each experienced 1 AE that resulted in discontinuation. One patient (7.1%) in the placebo group experienced 2 AEs that resulted in discontinuation (additional details are included in Figure 1). No deaths were reported. Most AEs were mild or moderate in severity. Four patients in the ulotaront group experienced 8 AEs that were rated severe: 1 patient receiving ulotaront 75 mg experienced auditory hallucinations and confusional state, and 1 patient receiving ulotaront 75 mg experienced disorganized speech; 1 patient receiving ulotaront 50 mg experienced auditory hallucinations, and 1 patient receiving ulotaront 50 mg experienced hypotension (reported as 3 separate events). No patients in the placebo group experienced an AE rated as severe.

AEs by dose at the time of event onset are shown in Table 2. The most common AEs ( $\geq 10\%$ ) for ulotaront vs placebo included hallucinations (24% vs 14%), confusional state (20% vs 14%), dizziness (16% vs 7%), nausea (12% vs 7%), falls (12% vs 21%), and fatigue (8% vs 14%). Overall, the incidence of neuropsychiatric AEs was higher in the ulotaront 50-mg and 75-mg dose groups compared with the 25-mg dose group. The incidence of confusional state was highest in patients receiving 75 mg ulotaront. Overall, the incidence of patients meeting predefined orthostatic hypotension criteria at baseline and postbaseline was similar in the ulotaront group compared with placebo. At baseline, 11 patients (44.0%) in the ulotaront group and 6 patients (42.9%) in the placebo group met criteria. At postbaseline, 13 patients (52.0%) in the ulotaront group and 11 patients (78.6%) in the placebo group met criteria. No patients in either treatment group met predefined criteria for orthostatic tachycardia either at baseline or postbaseline. There were no clinically meaningful changes in ECG parameters, laboratory values, or the Columbia-Suicide Severity Rating Scale over the course of the study.

## Discussion

This exploratory pilot study investigated the effects of flexibly dosed ulotaront, a TAAR1/5-HT<sub>1A</sub> agonist with antipsychotic-like

activity for the treatment of PDP. Although not powered to demonstrate statistically significant treatment differences, a nonsignificant trend of greater improvement was observed for ulotaront treatment compared with placebo for most outcomes. Ulotaront treatment resulted in a numerically greater reduction in psychotic symptoms as measured by the SAPS-PD as early as week 1, when all patients were on the 25-mg dose, suggesting response may occur soon after initiation of treatment and at a relatively low dose. Symptom improvement was maintained up to week 6, the last time point measured, suggesting responses may be durable. The mean change in SAPS-PD total score at week 6 in the ulotaront-treated group was  $-2.5$  (see Figure 2). This result may have, in part, been confounded by a placebo response, which occurred between weeks 3 and 5; a strong placebo response has been reported in previous PDP trials.<sup>10</sup> However, it is noteworthy that complete remission occurred by week 6 in 25% of ulotaront-treated patients in comparison with 0% in the placebo group. Further evidence supporting the possible efficacy of ulotaront include decreased scores on the SAPS-PD hallucinations subscale, on the total SAPS-PD scale in patients with cognitive impairment, and on the NPI hallucinations subscale. The lack of a possible treatment effect on the SAPS-PD delusions subscale may reflect the relatively low baseline SAPS-PD delusions subscale scores.

PDP is present in up to 60% of patients with PD<sup>25,32-35</sup> and incidence is 4-fold higher with the onset of cognitive impairment (i.e., patients with PD dementia).<sup>36</sup> In an analysis of a phase 3 study evaluating pimavanserin vs placebo in patients with PDP with and without cognitive impairment, pimavanserin was superior to placebo as measured by LS mean change from baseline in SAPS-PD scores for both the cognitively impaired (MMSE score 21–24,  $p = 0.002$ ) and unimpaired (MMSE score  $\geq 25$ ,  $p = 0.046$ ) groups.<sup>37</sup> In addition, in a prespecified subgroup analysis of pimavanserin in patients with Alzheimer disease psychosis and moderate-to-severe psychosis (NPI Nursing Home version score  $\geq 12$ ) at baseline, improvement in psychosis was demonstrated by separation between pimavanserin and placebo at week 6 (LS mean difference,  $-4.43$  [95% CI,  $-7.81, -1.04$ ]).<sup>38</sup> Although preliminary, findings from this study are consistent with the results of pimavanserin studies in patients with PDP and Alzheimer disease psychosis. In the current study, the subgroup of ulotaront-treated patients with greater cognitive impairment (MMSE score  $\leq 24$ ) showed numerically greater reductions in SAPS-PD total scores compared with placebo-treated patients throughout the course of the 6-week study. Of note, the separation between ulotaront and placebo in SAPS-PD total scores at week 6 was numerically greater for patients with cognitive impairment (LS mean difference,  $-3.1$  [95% CI,  $-11.5, 5.3$ ]) compared with all ulotaront-treated patients (LS mean difference,  $-1.1$  [95% CI,  $-6.5, 4.3$ ]) and with the subgroup of patients without cognitive impairment (LS mean difference,  $-0.8$  [95% CI,  $-8.1, 6.5$ ]). Taken together, these results suggest that ulotaront may be particularly beneficial in patients with cognitive impairment.<sup>25,39,40</sup>

The pathophysiologic basis of PDP is complex and includes disturbances in dopaminergic, serotonergic, and glutamatergic networks associated with PD neurodegeneration.<sup>34,36,41</sup> Upregulation of cortical serotonergic 5-HT<sub>2A</sub> receptors have been reported in patients with psychosis.<sup>41,42</sup> Typical and atypical antipsychotic agents exert their antipsychotic effects through antagonism at D<sub>2</sub> and/or 5-HT<sub>2A</sub> receptors.<sup>43</sup> The use of D<sub>2</sub>-blocking agents in patients with PDP is complicated by their potential to worsen motor symptoms associated with PD; therefore, agents with a different mechanism of action are needed.<sup>30,44</sup> In the current study, improvement in SAPS-PD scores with ulotaront was not associated with worsening of motor symptoms as measured by the UPDRS Part III motor scores. This distinguishes ulotaront from current off-label use of antipsychotic agents for PDP that target the postsynaptic D<sub>2</sub> and 5-HT<sub>2A</sub> receptors (e.g., clozapine, quetiapine).<sup>6,7</sup> The use of clozapine is limited by safety concerns and the need for frequent blood monitoring.<sup>12</sup> Although quetiapine may not worsen motor symptoms as measured by UPDRS Part III, other off-target receptor side effects (e.g., somnolence, orthostatic hypotension) may still occur; there is a lack of placebo-controlled evidence supporting the efficacy and tolerability (i.e., motor symptoms) of quetiapine in PDP.<sup>14,15</sup>

In a clinical trial of patients with an acute exacerbation of schizophrenia, ulotaront, given at doses of 50 mg and 75 mg, resulted in statistically significant improvement in symptoms of schizophrenia compared with placebo, as measured by change in PANSS scores after 4 weeks of treatment.<sup>22</sup> Ulotaront was found to be effective in treating both positive and negative symptoms of schizophrenia and was safe and well-tolerated with no difference vs placebo on assessments of extrapyramidal symptoms.<sup>22</sup> In a 26-week open-label extension study, patients demonstrated continued improvement in PANSS scores, including positive and negative subdomains, with no new safety concerns.<sup>45</sup> Taken together, these findings demonstrate that ulotaront was effective and well-tolerated for the treatment of adults with schizophrenia. In addition, the safety profile of ulotaront is distinct from that of antipsychotics. A recent analysis compared the profile of AEs reported in 1 ulotaront clinical trial with AEs reported in 5 clinical trials of atypical antipsychotics and observed that 42%, 52%, and 60% of patients treated with quetiapine, lurasidone, and olanzapine, respectively, had AEs with preferred terms having antipsychotic class-specific disproportional reporting (as determined by 3-fold to 4-fold or greater reporting in the FDA Adverse Event Reporting System).<sup>46</sup> By comparison, only 23% of ulotaront-treated patients had these class-specific AEs, demonstrating a differentiated safety profile.<sup>46</sup>

Treatment with ulotaront in this study resulted in significant improvement in daytime sleepiness as assessed by SCOPA-DS. Sleep and wakefulness disorders have been reported in  $\sim 90\%$  of patients with PD<sup>47</sup> and excessive daytime sleepiness has been estimated to occur in 20–60% of patients with PD.<sup>48</sup> Concurrent sleep disorders are a significant risk factor for PDP with an odds ratio of 4.6.<sup>2</sup> The results of this study suggest that

ulotaront may improve excessive daytime sleepiness symptoms in patients with PDP.

Overall, the safety profile of ulotaront in this study was consistent with the absence of D<sub>2</sub> receptor blockade.<sup>22</sup> For most AEs, there was no difference in incidence with ulotaront vs placebo. Incidence of CNS effects, hallucinations, confusional state, and dizziness were higher with ulotaront vs placebo and generally higher in patients treated with 75 mg, suggesting treatment may be better tolerated at lower doses in patients with PDP. Importantly, ulotaront treatment did not result in worsening of cognitive function and was not associated with higher incidence of orthostatic hypotension, a common complication in patients with PD.<sup>49</sup>

Several limitations to this study should be noted. This was a small, hypothesis-generating, exploratory pilot study that was not powered to detect any particular differences between treatment groups. As noted in other PDP trials,<sup>10,15</sup> placebo responses were also observed in this study, notably starting at week 3, which may have diminished the effect size at week 6 compared with weeks 1 and 2. A 2-week lead-in period that included brief psychosocial therapy adapted for PD was initially incorporated into the study to reduce the placebo response<sup>10</sup> but subsequently eliminated to diminish patient and caregiver burden. Nonetheless, numerical differences favoring ulotaront were maintained across several scales over the course of the study. As noted for this patient population, delusions were relatively mild at baseline, thereby limiting detection of a possible treatment effect. In contrast to the SAPS-PD, which was assessed by trained central raters, the CGI-S and NPI were assessed by local raters without regular calibration of intra-rater and inter-rater reliability. This may have contributed to the signal detection issues with these assessments.

The results of this 6-week, proof-of-principle study of patients with PDP suggest that ulotaront, a TAAR1/5-HT<sub>1A</sub> agonist with antipsychotic activity, may provide a new treatment option for PDP without worsening motor parkinsonism. Adequately powered trials are warranted to establish the efficacy and safety of ulotaront in PDP.

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### TAKE-HOME POINTS

- This exploratory study investigated the effects of flexibly dosed ulotaront, a TAAR1/5-HT<sub>1A</sub> agonist with antipsychotic-like activity for the treatment of Parkinson disease psychosis.
- Although not powered to demonstrate statistically significant treatment differences, a nonsignificant trend of greater improvement was observed for ulotaront treatment compared with placebo for most outcomes.
- Ulotaront treatment resulted in a numerically greater reduction in psychotic symptoms as measured by the Scale for the Assessment of Positive Symptoms for Parkinson Disease as early as week 1, when all patients were on the 25-mg dose, suggesting that response may occur soon after initiation of treatment and at a relatively low dose.
- Adequately powered trials are warranted to establish the efficacy and safety of ulotaront in Parkinson disease psychosis.

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<b>Mark Goldstein, MD</b>	JEM Research Institute, Lake Worth, FL	Drafting/revision of the manuscript for content, including medical writing for content; approval of the final article
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<b>Carlos Singer, MD</b>	University of Miami Health System, FL	Drafting/revision of the manuscript for content, including medical writing for content; approval of the final article
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<b>Michael Pucci, PhD</b>	The Lockwood Group, Stamford, CT	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data; approval of the final article

## Appendix 1 (continued)

Name	Location	Contribution
<b>Yi Zhang, DrPH</b>	Sunovion Pharmaceuticals Inc., Marlborough, MA	Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; study concept or design; analysis or interpretation of data; approval of the final article
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## Appendix 2 Coinvestigators

Coinvestigators are listed at [links.lww.com/CPJ/A441](https://links.lww.com/CPJ/A441).

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