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Safety, Tolerability, and Pharmacokinetics of Mevidalen (LY3154207), a Centrally Acting Dopamine D1 Receptor–Positive Allosteric Modulator, in Patients With Parkinson Disease

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Abstract

Mevidalen (LY3154207) is a positive allosteric modulator of the dopamine D1 receptor that enhances the affinity of dopamine for the D1 receptor. The safety, tolerability, motor effects, and pharmacokinetics of mevidalen were studied in patients with Parkinson disease. Mevidalen or placebo was given once daily for 14 days to 2 cohorts of patients (cohort 1, 75 mg; cohort 2, titration from 15 to 75 mg). For both cohorts, the median time to maximum concentration for mevidalen plasma concentration was about 2 hours, the apparent steady-state clearance was 20–25 L/h, and mevidalen plasma concentrations were similar between the 1st and 14th administration in cohort 1, indicating minimal accumulation upon repeated dosing. Mevidalen was well tolerated, and most treatment-emergent adverse events were mild. Blood pressure and pulse rate increased when taking mevidalen, but there was considerable overlap with patients taking placebo, and vital signs normalized with repeated dosing. In the Movement Disorder Society–United Parkinson's Disease Rating Scale, all patients taking mevidalen showed a better motor examination sub-score on day 6 compared to only some patients in the placebo group. These data support examining mevidalen for symptomatic treatment of patients with Parkinson disease and Lewy body dementia.

Keywords

D1PAM, dopamine, LY3154207, mevidalen, Parkinson disease, pharmacokinetics, safety, tolerability

Motor impairments in Parkinson disease (PD) are associated with progressive dopaminergic neuronal loss in the substantia nigra. The class of dopamine receptors, namely D1-like (D1, D5) and D2-like (D2, D3, D4) receptors has signaling properties that are mediated through G protein–coupled receptors.[1] The D1 and D2 receptors are the major subtypes of dopamine receptors[2] with the D1 receptors having the highest density and distribution compared to other dopamine receptors in the brain.[3] The D1 dopamine receptors are more abundant than the D2 receptors in the prefrontal cortex of the brain, which is an important area for higher cognitive function.[4] Dopamine D1 receptors are important for reward and higher cognitive functions such as attention, working memory, and executive function.[5–9] Insufficient levels of dopamine are associated with early manifestations of cognitive dysfunction in some patients with PD,[10] and dopaminergic therapies have been shown to improve cognition in PD.[11,12]

Activation of D1 receptors has been shown to improve both cognitive and motor function in preclinical

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models and in patients with schizophrenia, providing support for the use of D1-positive allosteric modulators in the treatment of PD, cognitive impairment in schizophrenia, and Alzheimer disease.[5,7,9,13,14]

The acetylcholinesterase inhibitor rivastigmine provides modest cognitive benefit in PD dementia.[15] However, there are concerns that the use of cholinergic drugs can worsen Parkinsonism.[16] A compound that amplifies the actions of dopamine could have the potential to improve both cognitive and motor symptoms in patients.

Mevidalen (LY3154207) is a selective and orally active D1-positive allosteric modulator with >1000-fold selectivity for the human D1 receptor over other tested targets.[13] Mevidalen increases the extracellular level of acetylcholine in the prefrontal cortex and enhances the affinity of dopamine for the D1 receptor. This amplifies the responses to endogenous and exogenous dopamine, which may improve motor and cognitive symptoms of PD and Lewy body dementias as well as sleepiness, mood, and apathy.[7,9,13] Data from nonclinical studies indicate that mevidalen is orally bioavailable, extensively metabolized, and crosses the blood-brain barrier.[13] A previous phase 1 study of mevidalen in healthy subjects demonstrated no treatment-related serious adverse events, acute dose-related increases in blood pressure (BP) and pulse rate that normalized after repeated dosing, linear plasma pharmacokinetics (PK) following single and repeated dosing, central penetrance via measurements of mevidalen in the cerebrospinal fluid, and evidence of central activating effects.[17]

The current study explored the safety and tolerability of multiple daily dosing of mevidalen in patients with PD. In addition, we assessed the PK profile and the effect of mevidalen on motor function.

Methods

Clinical Trial

This was a multicenter, double-blind, randomized, placebo-controlled, multiple-dose, parallel-group study in patients with PD. The study was performed at sites in the United States (Compass Research, Orlando, Florida; and Compass Research, The Villages, Florida). The study was reviewed and approved by an independent institutional review board (Aspire Institutional Review Board, Santee, California). Written informed consent was obtained from all subjects before study participation. The study was conducted in accordance with the International Council on Harmonization guideline for Good Clinical Practice and the original principles embodied by the Declaration of Helsinki. The study is registered at ClinicalTrials.gov as NCT02562768.

Subjects

Patients with a clinical diagnosis of idiopathic PD (stages of 1 to 4 on the Hoehn and Yahr [H/Y] Staging Scale)[18] with a minimum disease duration of 1 year and a body mass index of 18.0 kg/m^2 to 35.0 kg/m^2, inclusive, were enrolled. The patient's motor symptoms were assessed before enrollment and those on a stable dose of anti-Parkinson medications for at least 4 weeks before screening were included. Patients were excluded from the study if they had any medical conditions, screening test results, concomitant medication use, or prior clinical trial experience that made them unsuitable according to the exclusion criteria (had a significant history of or current cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematologic, or neurologic disorders capable of significantly altering the absorption, metabolism, or elimination of drugs or constituting a risk when taking the study medication or interfering with the interpretation of study data).

Study Design

Patients were randomly assigned to one of two cohorts. Patients in cohort 1 received 75 mg mevidalen once daily, and cohort 2 received titrated doses of 15 mg on days 1 to 3, 30 mg on days 4 to 6, and 75 mg on days 7 to 14. In each cohort, a total of 12 patients were evaluated. Of the 12 patients, 8 were assigned to mevidalen and 4 were assigned to placebo. Before each dose administration, patients fasted overnight for at least 8 hours, after which mevidalen or placebo was given orally. On days 1, 2, 7, and 14, patients remained fasted for 4 hours after dosing. For all other days, patients remained fasted for ≈1 hour after dosing. Placebo capsules were identical to mevidalen capsules.

Safety Assessments and Analyses

Safety parameters assessed included treatment-emergent adverse events (TEAEs), vital signs, safety laboratory parameters, ambulatory blood pressure monitoring (ABPM), and electrocardiogram (ECG) parameters. The TEAEs were defined as events that began on or after the date of the study drug administration and up to 30 days thereafter. The adverse events were coded according to the Medical Dictionary for Regulatory Activities version 17.1. The effect of repeated dosing with mevidalen on BP and pulse rate was assessed in patients using ABPM. Measurements were taken continuously over a 24-hour period on days 1, 2, 7, and 14 in cohort 1, and on days 1, 4, 7, and 14 in cohort 2. For each ABPM parameter, the change from baseline was analyzed using a mixed-model repeated-measures (MMRM) analysis, and the least square (LS) means and 90% confidence intervals were reported. Baseline was defined as the mean of the recordings at the –1- and –2-hour time points before dosing on day 1.

Table 1. Summary of Demographic and Other Baseline Characteristics

Characteristics		Placebo (N = 8)	Cohort 1[a] (N = 9)	Cohort 2[b] (N = 8)	Overall (N = 25)
Age, y	Mean (SD)	71.1 (8.2)	65.3 (7.9)	70.4 (5.2)	68.8 (7.5)
Sex	Male, n (%)	6 (75.0)	8 (88.9)	4 (50.0)	18 (72.0)
Ethnicity	Hispanic/Latino, n (%)	1 (12.5)	0 (0)	1 (12.5)	2 (8.0)
	Not Hispanic/Latino, n (%)	7 (87.5)	9 (100.0)	7 (87.5)	23 (92.0)
Race	Black or African American, n (%)	1 (12.5)	1 (11.1)	1 (12.5)	3 (12.0)
	White, n (%)	7 (87.5)	8 (88.9)	7 (87.5)	22 (88.0)
Site	001, n (%)	2 (25.0)	2 (22.2)	0 (0)	4 (16.0)
	002, n (%)	6 (75.0)	7 (77.8)	8 (100.0)	21 (84.0)
Weight, kg	Mean (SD)	78.8 (14.3)	95.2 (13.9)	74.5 (15.9)	83.3 (16.8)
Height (cm)	Mean (SD)	174.6 (8.6)	176.8 (5.3)	168.4 (11.1)	173.4 (8.9)
BMI, kg/m^2	Mean (SD)	25.7 (3.3)	30.4 (4.1)	26.1 (3.3)	27.5 (4.1)
MDS-UPDRS, Part III	Mean (SD)	25.3 (12.2)	30.9 (12.2)	34.8 (7.4)	NC
PDCRS	Mean (SD)	91.8 (8.1)	84.6 (21.6)	91.8 (10.0)	NC
Hoehn and Yahr stage, n	Stage 1	0	1	1	2
	Stage 2	7	4	4	15
	Stage 3	1	4	3	8

BMI, body mass index; MDS-UPDRS, Movement Disorder Society–Unified Parkinson Disease Rating Scale; NC, not calculated; PDCRS, Parkinson's Disease Cognitive Rating Scale; SD, standard deviation.
Motor examination subscore (0-72) refers to the sum of assessment scores referenced in part III of the MDS-UPDRS Scale.
[a] 75 mg mevidalen once daily for 14 consecutive days.
[b] 15 mg mevidalen on days 1 to 3, 30 mg on days 4 to 6, and 75 mg on days 7 to 14.

The primary contrasts of interest were each mevidalen dose level vs placebo on each day. Supine vital signs were taken regularly before dosing and up to 12 hours after dosing on days 1, 2, 7, and 14.

As part of the tolerability assessment, the Movement Disorder Society–United Parkinson's Disease Rating Scale (MDS-UPDRS),[19] parts III (motor examination) and IV (motor complications), were used to assess any impact of mevidalen on motor signs as well as potential worsening of motor complications in patients with PD. Assessments were done on days –1 (day before the start of dosing), day 6 (day 6 of dosing), day 15 (the first day off treatment), and at follow-up. Part III scores individual motor exam items from 0 (normal) to 4 (severe) in 18 categories, while part IV measures severity and duration of motor complications from 0 (none) to 4 (severe/frequent) across 6 categories, respectively. Changes from baseline (day –1) to day 6 and day 15 for part III and part IV were used to assess the impact of mevidalen on motor signs and motor complications. Data were summarized by treatment and time, and change from baseline data were given with baseline defined as day –1.

Pharmacokinetic Assessments and Analyses

Blood was collected before dosing and 0.5, 1, 2, 3, 4, 5, 6, 8, 12, and 24 hours after dosing on dosing days 1, 7, and 14 to measure plasma concentrations of mevidalen. In addition, samples were collected at 1, 2, 4, 8, 12, and 24 hours after dosing on day 2, as well as before dosing and 4 hours after dosing on days 3, 5, 8, 10, and 12. Mevidalen PK parameters were calculated using standard noncompartmental methods of analysis. The primary parameters for analysis were maximum plasma concentration (C_{max}), time to maximum concentration (t_{max}), area under the concentration-time curve during the dosing interval (AUC_{τ}), and apparent steady-state clearance (CL_{ss}/F). The accumulation ratio based on $AUC_{\tau\ Day\ 14}/AUC\tau_{\ Day\ 1}$ and $C_{max,\ Day\ 14}/C_{max,\ Day\ 1}$ was calculated for cohort 1 only because this cohort had the same dose of 75 mg administered on both day 1 and day 14.

Details on sample preparation and bioanalysis have been reported previously.[17]

Results

Patient Demographics and Patient Disposition

A total of 25 patients (18 males and seven females between the ages of 55 and 81 years) with PD were recruited to participate in the study. Patient demographics are presented in Table 1. The majority of PD patients were H/Y stage 2 (n = 15), followed by H/Y stage 3 (n = 8) and H/Y stage 1 (n = 2). Most patients randomized to this study were White (88%). With the exception of one patient, all other patients were on standard of care treatment for PD, primarily carbidopa/levodopa.

Table 2. Summary of Treatment-Emergent Adverse Events by Treatment in Order of Frequency (All Causes)

	Number of Adverse Events (Number of Subjects With Adverse Events)[a]				
	Placebo (N = 8)	Mevidalen 15 mg (N = 8)	Mevidalen 30 mg (N = 8)	Mevidalen 75 mg (N = 17)	All (N = 25)
Headache		2 (2)		1 (1)	3 (3)
Cough		1 (1)		1 (1)	2 (2)
Constipation[b]	2 (1)				2 (1)
Nausea				2 (1)	2 (1)
Vomiting				2 (1)	2 (1)
Abdominal pain upper[b]				1 (1)	1 (1)
Anemia		1 (1)			1 (1)
Dermatitis contact		1 (1)		1 (1)	1 (1)
Dizziness				1 (1)	1 (1)
Ecchymosis				1 (1)	1 (1)
Fatigue				1 (1)	1 (1)
Hallucination, visual[b]				1 (1)	1 (1)
Headache[b]				1 (1)	
Hypoesthesia[b]				1 (1)	1 (1)
Medical device site reaction[b]	1 (1)				1 (1)
Nasal congestion				1 (1)	1 (1)
Palpitations			1 (1)		1 (1)
Preexisting condition improved[b]				1 (1)	1 (1)
Rectal hemorrhage			1 (1)		1 (1)
Toothache	1 (1)				1 (1)
Tremor[b]	1 (1)				1 (1)

Medical Dictionary for Regulatory Activities version 18.0.
[a] Adverse events with a change of severity are counted only 1 time at the highest severity.
[b] Events related to study treatment.

All of the 25 patients who entered the study were randomly assigned to mevidalen (17 patients) or placebo (8 patients) for 14 days. Of these patients, 24 completed the study, and 1 discontinued from the study. In cohort 1, 1 patient was withdrawn from the study after dosing with mevidalen (75 mg) for 1 day due to a preexisting medical condition (uncontrolled hypertension). Data from this patient were included in the safety data analysis. This patient was replaced with an additional patient who was also dosed with mevidalen (75 mg) and successfully completed the study.

Safety and Tolerability

No deaths or other serious adverse events occurred during the study. One patient with preexisting uncontrolled hypertension was withdrawn from the study on day 1 after dosing with 75 mg of mevidalen after experiencing hypertension.

Of the 25 patients with PD who participated in the study and received daily doses of mevidalen or placebo, 14 patients reported a total of 26 TEAEs (all causes), of which 9 were considered related to the study treatment (Table 2) by the investigators. The most commonly reported ($\geq$2 occurrences) TEAE deemed related to the study treatment was constipation. Both occurrences of constipation were in a single patient in the placebo group. The TEAEs were largely mild in severity (Table 3), except for a few incidences of moderate severity TEAEs that were reported for both mevidalen and placebo.

For vital signs (Figure 1A), increases of a greater magnitude were observed in cohorts 1 and 2 compared to placebo at several time points. On day 1, an increase in systolic BP of $>$10 mm Hg compared to baseline was seen at 8 hours after dosing (change from baseline [standard error (SE)]: 11.4 [5.1] mm Hg) in cohort 1 and at 2 hours after dosing (14.9 [6.2] mm Hg) in cohort 2. On day 7, an increase in systolic BP was seen at 4 hours after dosing (10.9 [3.4] mm Hg) in cohort 2. For all other time points, the change from baseline was $\leq$10 mm Hg. For diastolic BP, an increase of $>$5 mm Hg was seen on day 1 at 1 hour (change from baseline [SE]: 5.8 [1.1] mm Hg) and 2 hours (5.1 [2.4] mm Hg) after dosing in cohort 2. For all other time points the change from baseline was $\leq$5 mm Hg. For pulse rate, an increase of $>$10 beats per minute (bpm) was seen on day 1 at 8 hours (change from baseline [SE] 13.9 [2.9] bpm), and 12 hours (15.0 [2.2] bpm) after dosing in cohort 1. For all other time points, the change from baseline was $\leq$10 bpm. A total of eight measurements met the criteria for an orthostatic drop in either systolic BP (drop of $\geq$20 mm Hg) or diastolic BP (drop of $\geq$10 mm Hg) from six patients

Table 3. Severity of Treatment-Emergent Adverse Events in Patients With Parkinson Disease

	Placebo (N = 8)	Cohort 1[a] (N = 9)	Cohort 2[b] (N = 8)	Overall (N = 25)
Subjects with ≥1 TEAE, n (%)	3 (37.5)	6 (66.7)	5 (62.5)	14 (56.0)
Number of TEAEs	5	14	7	26
Mild	4	13	6	23
Moderate	1	1	1	3

TEAEs, treatment-emergent adverse events.
[a] 75 mg mevidalen once daily for 14 consecutive days.
[b] 15 mg mevidalen on days 1 to 3, 30 mg on days 4 to 6, and 75 mg on days 7 to 14.

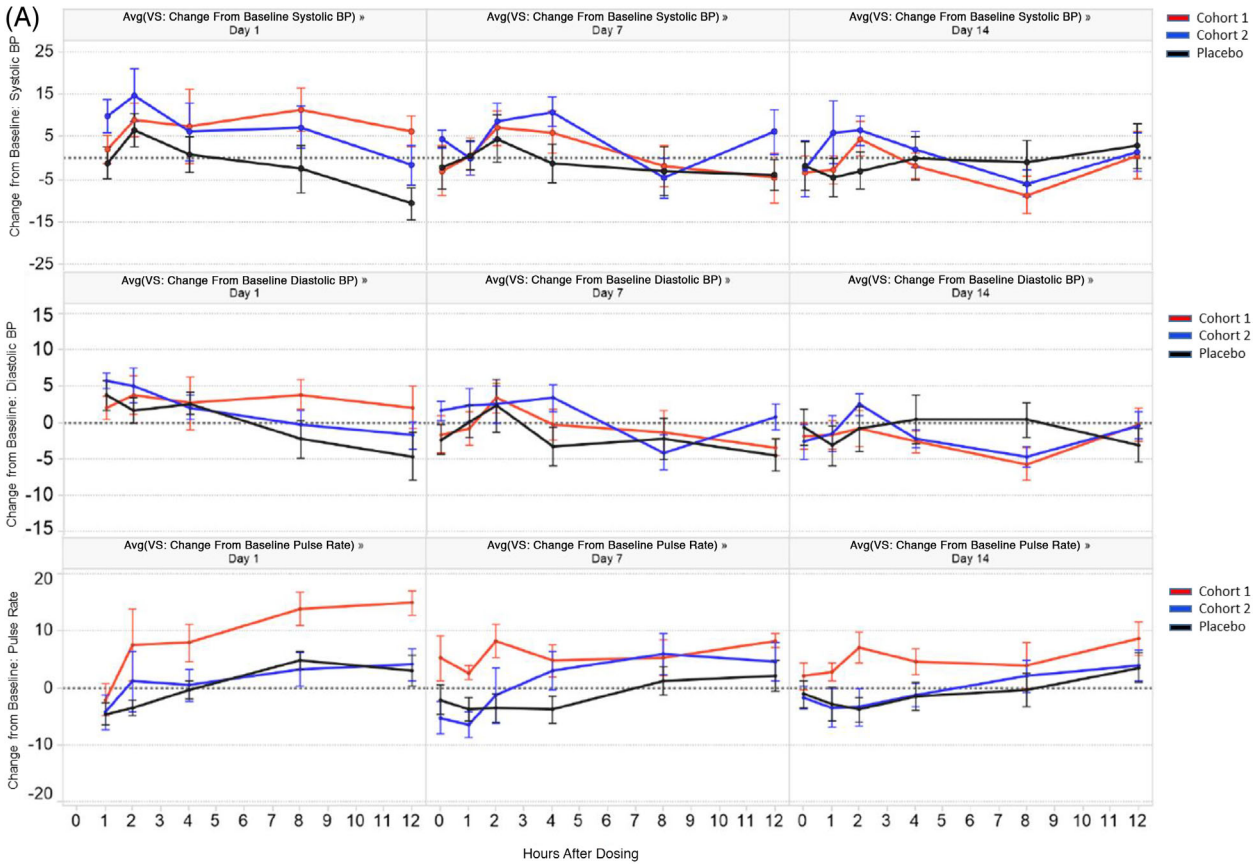

Figure 1. (A) Change from baseline in vital signs. Data shown as mean ± 1 standard error. Cohort 1: 75 mg mevidalen once daily for 14 consecutive days. Cohort 2: 15 mg mevidalen on days 1 to 3, 30 mg on days 4 to 6, and 75 mg on days 7 to 14. (B) Change from baseline in ABPM. Data shown as mean ± 1 standard error. Cohort 1: 75 mg mevidalen once daily for 14 consecutive days. Cohort 2: 15 mg mevidalen on days 1 to 3, 30 mg on days 4 to 6, and 75 mg on days 7 to 14. ABPM, ambulatory blood pressure monitoring; Avg, average; BP, blood pressure; VS, vital signs.

(1 dosed with placebo, 5 with mevidalen), and there was no trend in the orthostatic BP data observed over time.

Using ABPM (Figure 1B), similar to vital signs, increases of a greater magnitude were observed in cohorts 1 and 2 compared to placebo at several time points. On day 1, an increase in mean hourly systolic BP of >10 mm Hg was seen in cohort 1 between 3 hours and 8 hours after dosing (maximum change from baseline [SE], 5 hours (16.1 [3.4] mm Hg) after dosing) and at 3 hours (10.8 [3.6] mm Hg) after dosing in cohort 2. The mean hourly systolic BP change was ≤10 mm Hg at all other time points. For mean hourly diastolic BP, an increase of >5 mm Hg was seen on day 1 at 3 hours (change from baseline [SE], 5.4 [2.3] mm Hg) and 4 hours (5.4 [1.6] mm Hg) after dosing in the placebo group and at 5 hours (6.1 [2.5] mm Hg) after dosing in cohort 1. The mean hourly diastolic BP change was ≤5 mm Hg at all other time points.

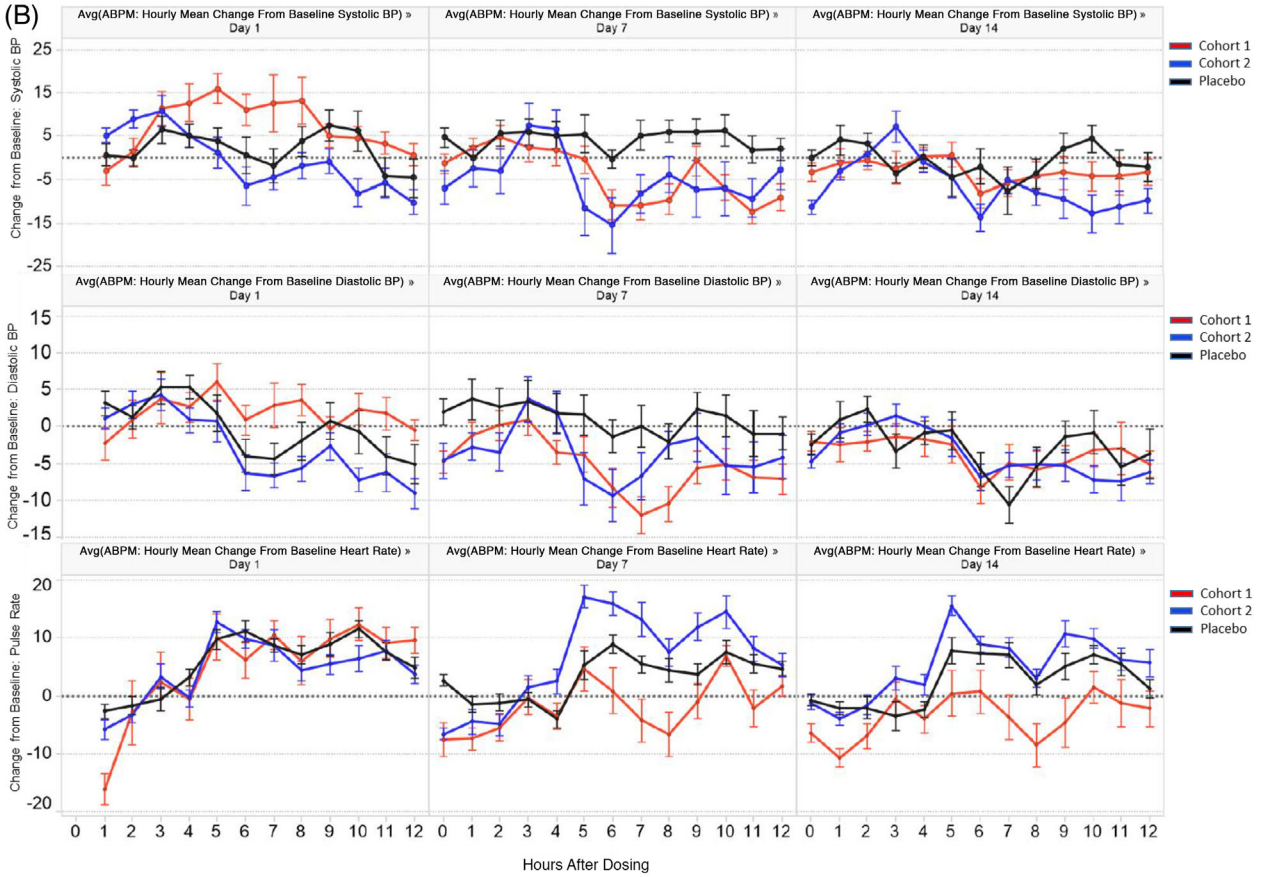

Figure 1. *Continued*

For pulse rate, an increase of >10 bpm was seen on day 1 at 6 hours (change from baseline [SE], 11.3 [1.7] bpm) and 10 hours (11.6 [1.5] bpm) after dosing in the placebo group; at 5 hours (10.2 [3.9] bpm), 7 hours (10.6 [2.5] bpm), 9 hours (10.0 [3.2] bpm), and 10 hours (12.5 [2.8] bpm) in cohort 1; and at 5 hours (12.9 [1.8] bpm), in cohort 2. On day 7, an increase of >10 bpm was seen between 5 hours and 10 hours after dosing in cohort 2 with a maximal change of 17.2 bpm [2.0] at 5 hours. On day 14, an increase >10 bpm was seen at 5 hours (15.6 [1.7] bpm) and 9 hours (10.8 [2.2] bpm) after dosing in cohort 2. There was a trend for decreases in systolic and diastolic BP by day 14 in cohorts 1 and 2.

During the course of the study, there were no clinically significant changes in the 12-lead ECG parameters following multiple doses of mevidalen.

There was no statistically significant difference in the change from baseline to day 6 or day 15 in the MDS-UPDRS motor examination subscore; however, all participants in the mevidalen-treated group showed a better motor examination subscore on day 6, compared to only some patients in the placebo group (Figure 2).

Pharmacokinetics

Figure 3 illustrates the mean plasma mevidalen concentration versus time profiles, and Table 4 provides the PK parameters from cohorts 1 and 2 on days 1, 7 and 14. Across mevidalen administration for 14 consecutive days, the median t_{max} was about 2 hours. The CL_{ss}/F was about 25 L/h for cohort 1 and 20 L/h for cohort 2, and the accumulation ratio was minimal for cohort 1 (Table 4). Intersubject variability was similar across the cohorts on day 14 at 32% for CL_{ss}/F and about 38% for C_{max}.

Discussion

This study assessed the safety, tolerability, motor effects, and PK properties of mevidalen after daily administration for 14 days in patients with PD across two different dose regimens; 75 mg once daily for 14 days, and a dose titration including doses of 15 mg, 30 mg, and 75 mg over 14 days. There were no apparent changes in the laboratory safety data or the ECG data following dosing with mevidalen or placebo. There were no serious adverse events reported in the

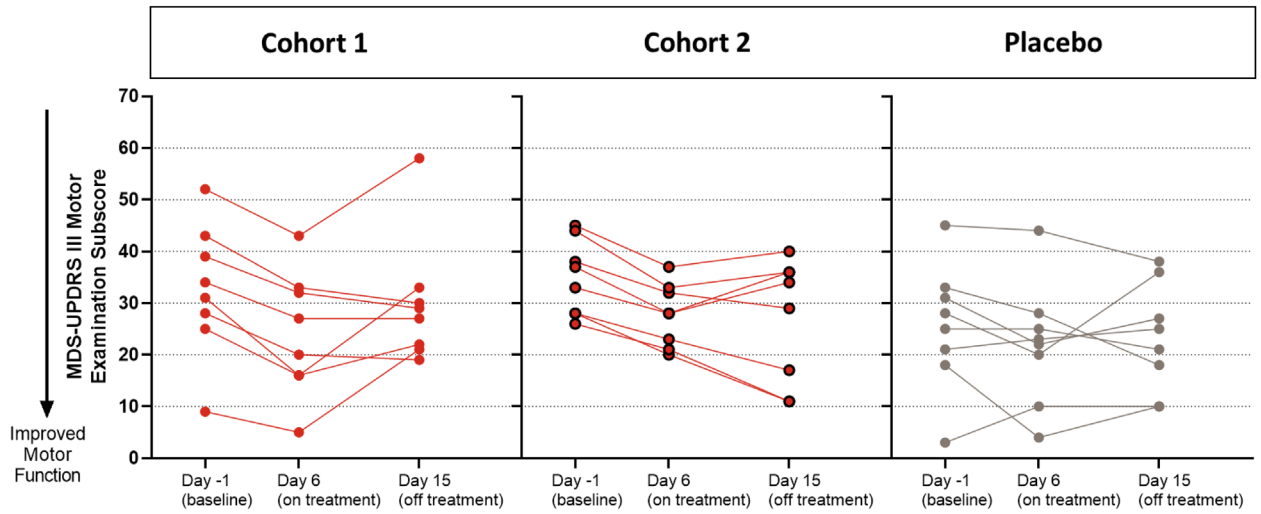

Figure 2. Movement Disorder Society–United Parkinson's Disease Rating Scale (MDS-UPDRS) Part III – Motor function as a measure of tolerability outcome. To evaluate drug tolerability, patients were tested at days −1, 6, and 15 of the study using the MDS-UPDRS motor examination. Line graphs show the individual subscores for part III of the MDS-UPDRS for patients at baseline (day −1), during treatment (day 6), and after cessation of treatment (day 15). Lines connect points for single patients. Two mevidalen-treated patients in cohort 2 were tested on day 16 rather than day 15. One mevidalen-treated patient in cohort 1 discontinued before the day 6 MDS-UPDRS measurement and is not included in the figure. Cohort 1: 75 mg mevidalen once daily for 14 consecutive days. Cohort 2: 15 mg mevidalen on days 1 to 3, 30 mg on days 4 to 6, and 75 mg on days 7 to 14. MDS-UPDRS, Movement Disorder Society–United Parkinson's Disease Rating Scale.

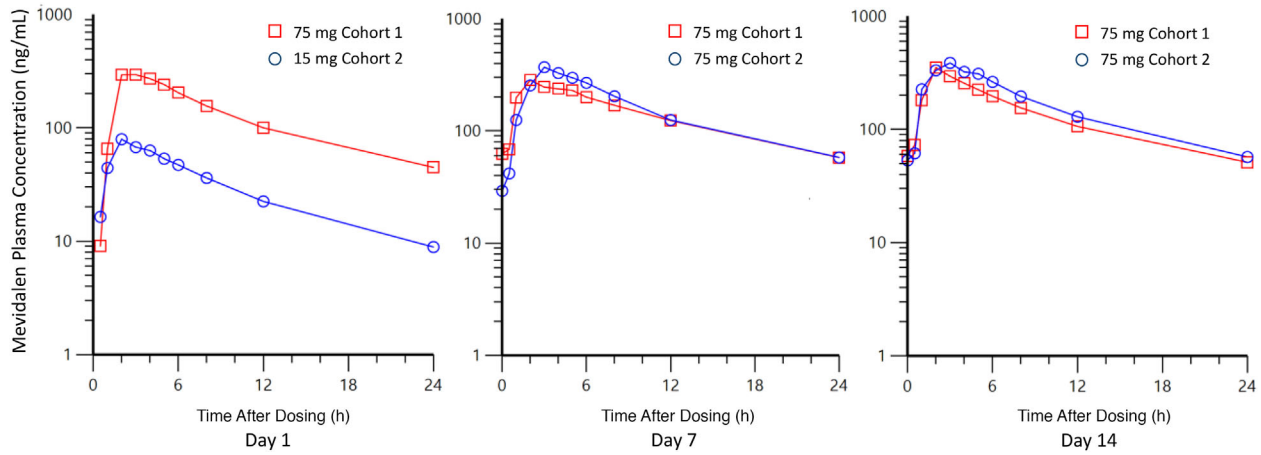

Figure 3. Mevidalen plasma concentration vs time profiles in patients with Parkinson disease. Mevidalen plasma concentrations are expressed as arithmetic mean. Patients in cohort 1 received 75 mg of mevidalen once daily for 14 consecutive days, and cohort 2 received titrated doses of 15 mg on days 1 to 3, 30 mg on days 4 to 6, and 75 mg on days 7 to 14. Left panel shows the PK profile following the initial administration of mevidalen on day 1, and the middle and right panels show the PK profile following the 7th and 14th daily administration of mevidalen, respectively. h, hour; PK, pharmacokinetics.

study. The number of TEAEs were largely mild in severity. The most commonly reported TEAE that was related to study treatment was constipation (placebo group). In a prior evaluation in healthy subjects, the most commonly reported TEAEs with mevidalen were insomnia, dizziness, nervousness, palpitations, and nausea.[17] It is unknown if this difference in TEAEs between healthy subjects and patients with PD is related to the patient population or a factor of a smaller sample size. However, differences in baseline dopaminergic tone between healthy volunteers and patients with PD, and that the patients with PD were stable on their standard dopaminergic therapy, could play a role.

Patients with PD had increases from baseline in BP and pulse following mevidalen administration. In cohort 1, the 1-hour postdose pulse rate on ABPM was lower than the baseline level on day 1. Although the peak mean was not much different from placebo, this change was confounded by the fact that the predose level in cohort 1 was artificially high for an unknown

Table 4. Mevidalen Plasma Pharmacokinetic Parameters in Patients With Parkinson Disease

	Cohort 1[a]			Cohort 2[b]		
	Day 1 (75 mg)	Day 7 (75 mg)	Day 14 (75 mg)	Day 1 (15 mg)	Day 7 (75 mg)	Day 14 (75 mg)
N	9	8	8	8	8	8
C_{max}, ng/mL	322 (91)	312 (90)	354 (120)	81.9 (26)	392 (120)	425 (158)
t_{max},[c] h	2.00 (2.00-3.00)	2.00 (2.00-5.98)	2.00 (1.87-3.00)	2.00 (1.00-4.08)	3.00 (2.00-5.00)	2.50 (1.00-4.00)
AUC_{τ}, ng • h/mL	2910 (650)	3260 (1130)	3170 (891)	697 (210)	3640 (1160)	3840 (1170)
CL_{ss}/F, L/h	NC	25.7 (9)	25.7 (9)	NC	NC	21.3 (7)
R_A C_{max}	NC	0.97 (0.3)	1.11 (0.4)	NC	NC	NC
R_A AUC_{τ}	NC	1.10 (0.3)	1.08 (0.2)	NC	NC	NC

AUC_{τ}, area under the concentration-time curve during the dosing interval; CL_{ss}/F, apparent steady-state clearance; C_{max}, maximum plasma concentration; NC, not calculated; RA, accumulation ratio (day 14/day 1 or day 7/day 1); t_{max}, time to maximum plasma concentration.
Data are expressed as arithmetic mean (standard deviation) unless noted otherwise.
[a] 75 mg once daily for 14 consecutive days.
[b] 15 mg on days 1 to 3, 30 mg on days 4 to 6, and 75 mg on days 7 to 14.
[c] Median (range).

reason. The 1-hour postdose change based on ABPM was about 16 bpm less than the baseline value, likely due to the high predose baseline. For cohort 2, dose titration helped lessen the mevidalen-evoked increases in BP; however, this was not so apparent for pulse rate. On initiation of 75 mg on day 7, an increase in pulse rate was observed on ABPM that was a greater magnitude compared to day 1, whereas a similar increase was not observed in pulse rate obtained from vital sign assessments. There was some variability when comparing the results from ABPM and vital signs in patients with PD, and the trend for an increase in systolic BP on day 1 appeared more pronounced based on ABPM. The initial increase in systolic and diastolic BP and pulse rate seen with initial administration of mevidalen showed normalization with repeated dosing in patients with PD, but this normalization effect was highly variable. In this report, the overall directional increases in pulse rate and BP, with evidence of normalization after repeated administration of mevidalen are consistent with previous reports of mevidalen in healthy volunteers.[17] Data from cohort 2 suggest that further exploration of titration may be warranted. On the MDS-UPDRS motor subscales, more patients in the mevidalen-treated group showed a better motor examination sub-score compared to patients in the placebo group indicating a signal for better motor function with mevidalen. However, larger-scale efficacy trials would be required to make definitive conclusions about the motor effects of mevidalen in patients with PD. Consistent with preclinical data and mechanism of action, there is a suggestion of possible motoric benefit in patients with PD.[7,13]

The PK properties of mevidalen were reported in patients with PD following once-daily dosing of mevidalen for 14 days, and we have previously reported on the PK profile of mevidalen in healthy subjects.[17] In general, the PK results in patients were consistent with healthy subjects. Across the populations, there was some general concordance with t_{max}, CL_{ss}/F, and accumulation, although the sample size was too small to make any definitive conclusions. Further data collection and analysis are warranted in patients in larger-scale clinical trials to evaluate the effect of physiological and demographic factors on the PK profile of mevidalen.

Conclusions

The results from this study showed that mevidalen was tolerated in patients with PD. The initial increase in systolic and diastolic BP and pulse rate showed normalization with repeated dosing. The study suggests mevidalen could have efficacy for motor symptoms in patients with PD since there was a more consistent improvement on the motor examination subscore in mevidalen-treated patients. Although this study did not show a statistically significant effect on motor symptoms, larger studies in the appropriate population will be necessary to address this question. Overall, the safety, PK, and motor effects support examination of mevidalen for symptomatic treatment of PD and Lewy body dementias.

Acknowledgment

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Conflicts of Interest

D.W., K.M.B., M.P., P.A., and W.K. are employees of Eli Lilly and Company Inc. and may own stock in this company. K.A.S. and M.T. are former employees of Eli Lilly and Company Inc. and may own stock in this company.

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