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A Short-Term, Multicenter, Placebo-Controlled, Randomized Withdrawal Study of a Metabotropic Glutamate 2/3 Receptor Agonist Using an Electronic Patient-Reported Outcome Device in Patients With Schizophrenia

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Abstract: This 6-week, multicenter, randomized withdrawal, placebo-controlled trial sought to determine whether symptoms of physical dependence occur after abrupt cessation of pomaglumetad methionil (LY2140023 monohydrate), a metabotropic glutamate 2/3 receptor agonist, in patients with schizophrenia. Eligible outpatients, 18 to 65 years old who required a modification or initiation of antipsychotic medication received 4 weeks of pomaglumetad methionil during open-label treatment and then were randomized, double-blind, to continue pomaglumetad methionil or receive placebo for 2 weeks. The primary outcome compared results of the 3-day moving mean of the total score on the Discontinuation Symptom Checklist-Modified Rickels for pomaglumetad methionil-treated patients with those on placebo during the randomized withdrawal phase. An electronic patient-reported outcome (ePRO) device was used daily to record these results. During the withdrawal phase, 103 patients were randomized, and 98 patients completed the trial. There was no statistically significant evidence of withdrawal symptoms associated with placebo compared with pomaglumetad methionil continuation as measured by Discontinuation Symptom Checklist-Modified Rickels ($P = 0.170$). The results are supported by secondary analyses with the clinician-rated, Clinical Institute Withdrawal Assessment of Alcohol Scale Revised, which showed no statistically significant differences between treatment groups. Using the ePRO device, 82.5% of the patients achieved 75% to 100% of compliance. No discontinuations due to worsening of schizophrenia, serious adverse events, deaths, or seizures were reported during either phase of the study. These findings suggest that there is no evidence of withdrawal symptoms associated with the abrupt discontinuation of pomaglumetad methionil and that an ePRO device can be successfully used in a multicenter schizophrenia trial.

Key Words: schizophrenia, electronic patient-reported outcome, pomaglumetad methionil, withdrawal symptoms, mGluR2/3 agonist

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Schizophrenia is a complex and chronic mental health disease that affects nearly 1% of the total adult population, with more than 2 million Americans having this disease a year.

Patients experience unusual and/or disturbed thoughts, hallucinations, delusions, and lack of emotion and energy. The most prescribed medications for the treatment of schizophrenia are second-generation antipsychotics that primarily work as antagonists of the dopamine-2 receptor.[1] Pomaglumetad methionil (LY2140023 monohydrate),[2] a metabotropic glutamate 2/3 receptor (mGluR2/3) agonist, was recently in development as a monotherapy for acutely ill patients with schizophrenia and as an adjunctive treatment for partially remitted patients with schizophrenia who had prominent negative symptoms.

Efficacy of pomaglumetad methionil was demonstrated compared with placebo in a 4-week phase 2 trial in patients with schizophrenia.[2] Unfortunately, the development program for schizophrenia was discontinued when the compound failed to further demonstrate efficacy in studies that were assessing efficacy in schizophrenia either as a monotherapy in patients with acute psychotic exacerbation or as an add-on therapy in patients with prominent negative symptoms.[3,4] Although the efficacy of pomaglumetad methionil in schizophrenia has not been clearly demonstrated as a monotherapy treatment for patients with schizophrenia, a genetic association was discovered between non-Hispanic white patients with schizophrenia carrying the minor allele for the serotonin 2A receptor gene (*HTR2A*) single-nucleotide polymorphism, rs7330461, and response to treatment with pomaglumetad methionil.[5] A significantly greater response to treatment was observed in patients carrying T-alleles for rs7330461 in *HTR2A* compared with A/A homozygotes. This association was subsequently replicated in 2 additional clinical trials [6,7] and suggests that there is potential efficacy of pomaglumetad methionil in a subpopulation defined by a genetic biomarker. Further investigation is required to fully understand the functional basis for the association between *HTR2A* rs7330461 and response to treatment with pomaglumetad methionil.

The present study was conducted to investigate the potential of an mGluR2/3 agonist to produce signs and symptoms suggestive of physical dependence when abruptly discontinued after an acute treatment trial in patients with schizophrenia. Pomaglumetad methionil binds specifically only to mGluR2/3 subtypes as a receptor agonist. The mGluR2/3 receptors function as autoreceptors that, when stimulated by endogenous glutamate, are able to diminish the activity of cortical pyramidal neurons. A nonclinical physical dependence/withdrawal study was performed in monkeys based on their metabolic similarities to humans. The nonclinical study evaluated physical dependence/withdrawal in 2 groups of monkeys: 1 group received chronic doses of pomaglumetad methionil, and the other received ketamine (a positive control). After 3 weeks of administration, both groups were withdrawn from treatment. Monitoring of behavioral and physiological parameters was performed throughout both treatment and withdrawal periods. Overall, in the pomaglumetad methionil group, the shift and frequency of clinical signs were unremarkable.

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However, ketamine-treated animals did show a shift of behavior during the randomized withdrawal phase, especially in activity levels and, to a lesser degree, in repetitive movements. In summary, results indicate that withdrawal symptoms were not observed after discontinuation of pomaglumetad methionil treatment but were observed after withdrawal of the glutamatergic agent ketamine, an N-methyl-D-aspartate antagonist (Eli Lilly and Company, LLC, data on file).

A randomized withdrawal study was conducted to evaluate potential for dependence in humans by assessing symptoms of withdrawal after abrupt discontinuation of pomaglumetad methionil. The primary assessment was measured and recorded by an electronic patient-reported outcome (ePRO) device. Responses were compared for patients who underwent double-blind randomization with either continued pomaglumetad methionil treatment or with placebo.

MATERIALS AND METHODS

Patient Selection

Patients were male or female outpatients, 18 to 65 years old (inclusive) at study entry, with a diagnosis of schizophrenia as defined in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (*DSM-IV-TR*) and confirmed by the structured clinical interview for *DSM-IV-TR* Disorders. Eligibility was contingent upon patients requiring a modification or initiation of antipsychotic medication, as indicated by their clinical psychiatric status and/or treatment tolerability as an outpatient.

Patients were ineligible if they had been hospitalized for an exacerbation of symptoms of schizophrenia with a discharge date within 2 months of screening or if they had a score of greater than 4 on the Clinical Global Impression-Severity (CGI-S) at screening. Additional exclusion criteria included any comorbid axis I disorder according to *DSM-IV-TR* criteria, diagnosis of substance abuse or dependence according to the *DSM-IV-TR* criteria within 6 months of study entry, diagnosis of substance-induced psychosis according to *DSM-IV-TR* criteria within 7 days of study entry or at any time during the study, current suicidal ideation, a history of significant suicidal ideation or previous suicide attempt that causes present concern, treatment (at the time of study entry) with a depot formulation of an antipsychotic medication, treatment with clozapine during the month before study entry or at doses greater than 200 mg daily within 12 months of study entry, or had seizure disorder or electroconvulsive therapy. In addition, patients were excluded for a diagnosis of Parkinson disease, dementia-related psychosis, or any related disorders. Patients with a CGI-S score of greater than 4 at the time of randomization were allowed to continue treatment with pomaglumetad methionil but were not included in the primary analysis.

Patients were required to be willing and capable of using a handheld, electronic diary (ie, the ePRO device) to enter daily symptom scores. Patients began filling out the Discontinuation Symptom Checklist-Modified Rickels (DSCMR) 1 week before randomization, using the ePRO device to record their answers. If they did not complete the DSCMR using the ePRO device as instructed, on the last 3 days of week 4 during the open-label phase, patients were discontinued before randomization.

Benzodiazepine Use

Limited use of anxiolytics (benzodiazepines) or sedative hypnotics to treat anxiety or insomnia was permitted during all phases of the study, as clinically indicated. Concurrent use of multiple benzodiazepines or sedative hypnotics was discouraged. Benzodiazepine dosage was not to exceed 3-mg lorazepam equivalents per day at any time during the study with the recommendation to use the smallest dose possible. Benzodiazepines were not administered 8 hours before psychiatric evaluations and were only taken episodically (as needed) and not as a standing dose.

Study Design

The study was conducted in accordance with all applicable regulatory and Good Clinical Practice guidelines and followed the ethical principles originating in the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines and the International Conference on Harmonization Guideline for Good Clinical Practice.[8] All subjects signed an informed consent document before participation in the studies.

This was a short-term (6-week), multicenter, placebo-controlled, randomized withdrawal study comparing pomaglumetad methionil with placebo in the treatment for outpatients with schizophrenia. Patients were enrolled (assigned to therapy) from October 2011 to September 2012 at 13 sites in the United States (n = 11) and Greece (n = 2).

The study included a screening and antipsychotic drug-taper phase (7 days between screening and week 1), an open-label treatment phase (weeks 1–4), and a double-blind randomized withdrawal phase (weeks 5–6). There were a total of 12 clinic visits, one at the beginning of each week as well as midweek during weeks 1, 3, 4, and 5, approximately 3 to 4 days after the initial visit in that week.

Open-label treatment with pomaglumetad methionil began at the first visit of week 1. Patients who completed the open-label phase, had a CGI-S score of 4 or lower, and were compliant with use of the ePRO device were randomized in a 1:1 ratio to pomaglumetad methionil or placebo for the double-blind, randomized withdrawal phase. The timing of randomization was blinded to patients and investigators and occurred at the end of week 4.

Patient symptoms were assessed at every visit by a physician using the CGI-S scale. Safety assessments made throughout the study included treatment-emergent adverse events (TEAEs); extrapyramidal symptoms, as evaluated using the Barnes Akathisia Scale, Simpson-Angus Scale, and Abnormal Involuntary Movement Scale; laboratory tests; vital signs; electrocardiograms; neurological examination; and solicited questioning regarding suicide-related adverse events (behavior and ideation) using the Columbia-Suicide Severity Rating Scale.

Pomaglumetad methionil (40 or 80 mg) supplied as 40-mg tablets and identical-appearing placebo tablets were given orally, twice daily, with or without food. The dose of pomaglumetad methionil was adjustable from 40 mg twice daily to 80 mg twice daily after 1 week of treatment, as clinically warranted. A decrease to 40 mg twice daily was permitted, as clinically indicated, if tolerability issues arose at the higher dose. The dose level at randomization remained constant throughout the double-blind withdrawal phase.

Patient compliance with taking study medication was defined as taking 80% or greater and 120% or less of the pomaglumetad methionil dose prescribed for that interval. Significant noncompliance was defined as missing greater than 6 consecutive doses of study medication or greater than 9 cumulative doses during the study. A missed dose was failing to take 1 or more tablets at an individual time point. Compliance was assessed at each visit, and significantly noncompliant patients were discontinued from the study.

Evaluation of Drug Withdrawal Symptoms

The primary outcome was the DSCMR, which compared patients treated with pomaglumetad methionil versus those treated

TABLE 1. Discontinuation Symptom Checklist-Modified Rickels

During the Past 24 Hours, did you Experience:	
1. Headaches	16. Lack of pleasure
2. Trouble sleeping	17. Happiness
3. Irritability	18. Lack of interest/motivation
4. Nausea	19. Craving for study medication
5. Sensitivity to smells/tastes	20. Restlessness
6. Loss of appetite	21. Difficulty thinking or paying attention
7. Vomiting	22. Poor coordination
8. Anxiety/nervousness	23. Tremors
9. Sweating	24. Sensitivity to sound or changes in your hearing
10. Constipation	25. Faintness/lightheadedness
11. Diarrhea	26. Sensitivity to touch
12. Sadness	27. Muscle aches
13. Sleepiness	28. Weakness
14. Sensitivity to light	29. Unusual feelings/sensations
15. Fatigue	30. Sensitivity to pain

The measure for the primary outcome was the DSCMR, which is a 30-item, patient-rated scale that assesses symptoms daily to identify potential drug withdrawal. Each item was rated on a 0-to-3 scale (0, not at all; 1, mild; 2, moderate; and 3, severe) and entered, by the patient, daily during the course of 2 weeks in a handheld device. The checklist is shown.

with placebo during the double-blind, randomized withdrawal phase. The modified checklist was adapted by Lilly in 2011 from the Physician Withdrawal Checklist, a validated measure of drug withdrawal symptoms, with permission from the author of the original scale.[9] Patients reported scores on the DSCMR daily, beginning at the week before randomization and throughout the randomized withdrawal phase. Treatment groups were compared by the maximum of the 3-day moving mean of the patient's total score on the DSCMR.

The DSCMR asks patients to rate the occurrence of 30 symptoms of drug withdrawal, including the occurrence of nausea, vomiting, loss of appetite, anxiety/nervousness, irritability, or craving for study medication (see Table 1). Patients were asked to rate their experience of symptoms during the past 24 hours and enter the results in the ePRO device on each calendar day. Each item was rated on a 0-to-3 scale, as not at all, mild, moderate, or severe, respectively. The total score on the DSCMR was the sum of items 1 through 30 (range, 0–90). The 3-day moving mean was the mean of the scores from that day and the previous 2 days and was calculated each day from the third to the last day of the withdrawal phase. If a total score was missing for any day during the 3-day period, the mean was based on the nonmissing days. If there was no total score for any day of the 3-day period, the mean was considered missing.

The Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar scale),[10] a revision of a scale generally used to quantify severity of alcohol withdrawal syndrome, was also used to monitor symptoms of drug withdrawal and provide concordance with patient-reported outcomes. This 10-item physician-administered scale includes domains/criteria as nausea and vomiting, anxiety, paroxysmal sweats, tactile disturbances, visual disturbances, tremors, agitation, orientation and clouding of sensorium, auditory disturbances, and headache. Each criterion was rated on a scale from 0 to 7, except for orientation and clouding of sensorium, which was rated on a scale from 0 to 4. The total score reflected a sum of scores for all 10 criteria. The CIWA-Ar was administered at randomization and each visit during the randomized withdrawal phase.

Use of ePRO Device

The ePRO refer to any report of patient health status reported directly by the patient, using an electronic instrument/media. In this study, responses to the DSCMR were entered daily by the patient, during the course of 3 weeks (1 week before randomization and 2 weeks during the randomized withdrawal phase), in a handheld digital device (model Treo 650; CRF Health, Plymouth Meeting, PA) and routed electronically to a central database. Extensive site and patient training were conducted, and compliance with data entry was monitored frequently. Compliance was defined as having a complete entry (ie, answering all 30 questions) for the previous 24 hours.

The device did not allow more than 1 response in a calendar day. Every device had time- and date-stamp capability to ensure data integrity; the devices also had the capability to send alerts to patients, reminding them to enter their responses. In addition, investigative sites were able to run reports from the central vendor database, indicating whether patients were completing the checklist as required by the protocol and which patients may require intervention to improve compliance. Furthermore, sites held regular follow-up to monitor patients' use of the tool. Patients were compensated for daily completion of the DSCMR using the ePRO device.

Statistical Analyses

A sample size of approximately 120 patients for the open-label phase ensured that approximately 80 patients were randomized to treatment with pomaglumetad methionil or placebo for the double-blind phase of the study. The sample size of 80 (40 per arm) provided approximately 90% of power to detect a treatment difference, assuming a between-group effect size of 0.75 and 0.05 of alpha level, 2-sided *t* test.

A comparison between the maximum of the 3-day moving means of the total score on the DSCMR during the randomized withdrawal phase for the pomaglumetad methionil- and placebo-treatment groups was performed using an analysis of covariance (ANCOVA) model, with baseline as a covariate and investigative

site, sex, and treatment as fixed effects. The analysis included data from randomized patients with a baseline and at least 1 postbaseline measure. Because each item of the DSCMR represents a different possible discontinuation symptom, if fewer than 90% of the individual items were available for the DSCMR, the total score was considered missing to have the total score as representative of the range of possible discontinuation symptoms.

The symptoms of withdrawal as measured by the CIWA-Ar total score were calculated by adding the individual items. The change from baseline for the total score and the individual items to all postbaseline visits during the randomization phase was assessed using a mixed-model repeated measures (MMRM) analysis. The model included the fixed, categorical effects of treatment, sex, investigative site, visit, and Treatment × Visit interaction as well as the continuous, fixed covariates of baseline and Baseline × Visit interaction. The within-patient errors were modeled using an unstructured covariance matrix. The baseline CIWA-Ar total score and the individual items were presented and analyzed with a single factor analysis of variance model with a fixed effect of treatment.

Type III tests for the least-squares (LS) means were used for the statistical comparison using generalized linear models (ie, MMRM, analysis of variance, ANCOVA). Significance tests were based on LS means and type III tests at a 2-sided 0.05-alpha level.

The incidence rates of TEAEs were analyzed by Fisher exact test to compare randomized treatment groups.

The proportion of patients who were compliant with their treatment during the open-label phase was summarized. In addition, the proportion of patients who were compliant during the double-blind randomized withdrawal phase was compared between treatment groups using Fisher exact test.

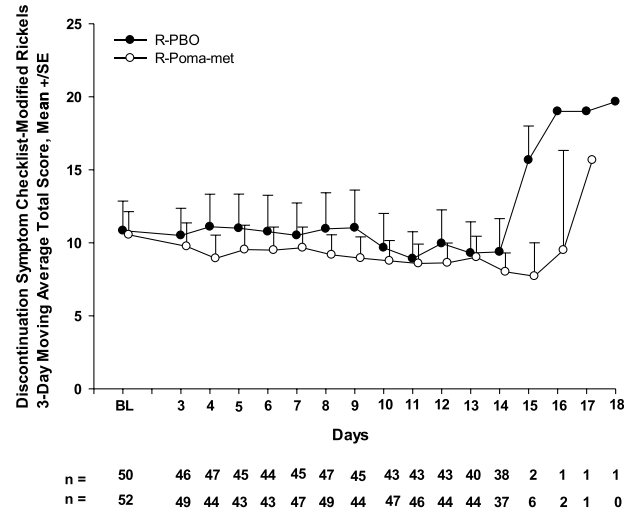

FIGURE 1. Plot of the 3-day moving mean of the DSCMR total score by day and treatment in patients who entered the randomized withdrawal phase. Baseline is defined as the 3-day mean of the patient's total score at the time of randomization. The 3 days include baseline visit date, baseline visit date – 1, and baseline visit date – 2. Day X = [mean DSCMR assessment date on day X, DSCMR assessment date on day (X – 1), DSCMR assessment date on day (X– 2)]. BL indicates baseline; R-PBO, randomized to placebo; R-Poma-met, randomized to pomaglumetad methionil.

RESULTS

Baseline Characteristics and Disposition

Of the 174 patients who entered the study and participated in the antipsychotic drug-taper phase, 123 entered the open-label treatment phase and received at least 1 dose of study drug (United States, 107 patients; Greece, 16 patients); 103 patients were assigned to the randomized withdrawal phase, and 98 patients completed the study. No patient had a CGI-S score of greater than 4 at the end of the open-label phase, so all patients in the withdrawal phase were randomized.

Of the 103 randomized patients, the mean (SD) age was 42.7 (11.4) years, and most of the patients were men (72.8%). Most patients were black or African American (66.0%), followed by white (29.1%). Most randomized patients had paranoid-type schizophrenia (n = 91, 88.3%). There were no statistically significant differences between treatment groups with respect to the baseline characteristics.

During the randomized withdrawal phase, reasons for early discontinuation among patients in the placebo group were sponsor decision (n = 1), subject decision-consent withdrawn (n = 1), and subject moving or moved (n = 1). Among patients in the pomaglumetad methionil group, the only reason for early discontinuation was adverse events (n = 2). There were no statistically significant differences between the treatment groups with respect to reasons for early discontinuation ($P = 0.496$).

Primary Safety Outcome

An ANCOVA of the maximum of the 3-day moving mean of the total score on the DSCMR during the randomized withdrawal phase of the study showed no difference between the placebo and pomaglumetad methionil treatment groups with respect to worsening of withdrawal symptoms. The LS mean was −1.73, with a confidence interval of (−4.22, 0.76) and a P value of 0.170. The 3-day moving mean of the DSCMR by day and by treatment during the randomized withdrawal phase is presented in Figure 1.

Treatment and ePRO Compliance

Patient compliance with study medication was assessed at each visit. Overall, 86.2% of the patients were compliant during the open-label phase, and approximately 96% of the patients across treatment groups were compliant during the randomized withdrawal phase (pomaglumetad methionil, 96.0%; placebo, 96.2%). There were no statistically significant differences between treatment groups in overall treatment compliance or in treatment compliance at week-6 visits.

Compliance with use of the ePRO device, defined as having a complete entry on each calendar day for the previous 24-hour period, was good. There was 1 of the 123 patients enrolled in the open-label phase who was discontinued from the study because of inability or unwillingness to complete the DSCMR on the last 3 days of the initial week using the ePRO device. Of the patients who entered the randomized withdrawal phase, 82.5% (85/103) were between 75% and 100% compliant, and all patients adhered to the instructions by completing the ePRO for at least some portion of the 2 weeks.

Other Safety Outcomes: CIWA-Ar

There were no statistically significant differences in mean changes from baseline in the CIWA-Ar total score during the randomized withdrawal phase when the pomaglumetad methionil group was compared with the placebo group (Table 2). The pomaglumetad methionil group was associated with a statistically significantly (LS mean [SE], P value) higher mean change from baseline for nausea and vomiting compared with the placebo group at week 5 (0.3 [0.1], $P = 0.011$) and mid-week 5 (0.2 [0.1], $P = 0.011$).

TABLE 2. Analysis of CIWA-Ar Total Score

			Change From Baseline			R-Pomaglumetad Methionil vs R-Placebo		
	Treatment	n	LS Mean (*P**)	SE	95% CI	LS Mean (*P*†)	SE	95% CI
Mid-week 4	R-placebo	50	−0.7 (0.041)	0.3	(−1.4, −0.0)	0.8 (0.109)	0.5	(−0.2, 1.7)
	R-pomaglumetad methionil	53	0.0 (0.882)	0.3	(−0.6, 0.7)			
Week 5	R-placebo	49	−0.9 (0.004)	0.3	(−1.4, −0.3)	0.4 (0.372)	0.4	(−0.4, 1.1)
	R-pomaglumetad methionil	52	−0.8 (0.003)	0.3	(−1.4, −0.3)			
Mid-week 5	R-placebo	47	−0.8 (0.003)	0.3	(−1.4, −0.3)	0.2 (0.555)	0.4	(−0.5, 0.9)
	R-pomaglumetad methionil	51	−0.6 (0.023)	0.3	(−1.1, −0.1)			
Week 6	R-placebo	47	−0.4 (0.207)	0.3	(−1.0, 0.2)	−0.1 (0.806)	0.4	(−1.0, 0.7)
	R-pomaglumetad methionil	51	−0.5 (0.105)	0.3	(−1.1, 0.1)			

Repeated measure analysis of change from baseline to each postbaseline visit (MMRM), in patients who entered the randomized withdrawal phase.

Baseline is the last nonmissing CIWA-Ar assessment of the total score during the first visit of weeks 3 to 4.

Model: change from baseline = baseline + treatment + gender + pooled investigative site + visit + (Baseline × Visit) + (Treatment × Visit); covariance structure = unstructured.

*Within-group *P* values are from *t* tests of LS mean.

†*P* values are from type 3 sums of squares.

CI indicates confidence interval; N, number of patients in this analysis set with baseline and a result at a given visit within each treatment group; R, randomized.

Adverse Events

There were no deaths or serious adverse events during this study. During the open-label phase, 5 patients (4.1%) discontinued because of adverse events (ie, anxiety, fatigue, headache, insomnia, and schizophrenia). During the randomized withdrawal phase, no patients in the placebo group and 2 patients in the pomaglumetad methionil group (3.8%) discontinued because of adverse events (electrocardiogram QT interval [period from the beginning of the QRS complex to the end of the T wave on an electrocardiogram] and increased hepatic enzyme). There were no statistically significant differences between treatment groups in the incidence of adverse events leading to discontinuation.

All TEAEs were reported by 83 (67.5%) of the 123 patients during the open-label phase. The TEAEs reported in greater than or equal to 3% of the patients were nausea, headache, anxiety, tremor, vomiting, blood creatine phosphokinase increase, agitation, hyperhidrosis, insomnia, somnolence, constipation, dizziness, diarrhea, fatigue, and irritability.

Of the 103 randomized patients, 13 placebo-treated patients (26.0%) and 21 pomaglumetad methionil-treated patients (39.6%) experienced at least 1 TEAE. The difference between treatment groups was not significant ($P = 0.150$). The TEAEs reported in greater than or equal to 3% of the patients in the placebo group were anxiety, headache, nausea, visual impairment, and hearing impairment. Headache, visual impairment, and hearing impairment had 2 or greater times the incidence rate of the pomaglumetad methionil-treatment group. The TEAEs reported in greater than or equal to 3% of the patients in the pomaglumetad methionil group were anxiety, agitation, headache, nausea, blood creatine phosphokinase increase, tremor, visual impairment, hyperhidrosis, upper respiratory tract infection, and vomiting. Agitation, nausea, and blood creatine phosphokinase increase had 2 or greater times the incidence rate of the placebo-treatment group. There were no statistically significant differences between treatment groups in the occurrence of any TEAE.

Benzodiazepine Use

During the open-label phase, 13 patients (10.6%) received benzodiazepines (lorazepam, n = 12, 9.8%; temazepam, n = 1, 0.8%). During the randomized withdrawal phase, 4 patients in the placebo group (8.0%) and 5 patients in the pomaglumetad methionil group (9.4%) received lorazepam; 5 patients in the placebo group (10.0%) and 1 patient in the pomaglumetad methionil group (1.9%) received zolpidem. There were no statistically significant differences between treatment groups with respect to treatment with benzodiazepines ($P = 1.00$) or sedative/hypnotics.

Extrapyramidal Symptoms and Vital Signs

There were no patients with categorical changes in the Simpson-Angus Scale total score for treatment-emergent Parkinsonism at any visit during the open-label and randomized withdrawal phases.

During the open-label phase, there were 5 patients (4.3%) who experienced changes in the Barnes Akathisia Scale global score for treatment-emergent akathisia as recorded at weeks 2 to 4. During the randomized withdrawal phase, 1 patient in the pomaglumetad methionil-treated group (2.0%) experienced akathisia, recorded at mid-week 5. There were no statistically significant differences between treatment groups during the randomized withdrawal phase. Categorical changes in the Abnormal Involuntary Movement Scale of 1-to-7 total score for treatment-emergent dyskinesia were reported by 1 patient (0.8%) during the open-label phase and no patients during the randomized withdrawal phase.

There were no statistically significant differences in most vital signs between treatment groups at any time or at end point for patients who entered the randomized withdrawal phase. The exceptions were at mid-week 5, when the pomaglumetad methionil group was associated with statistically significantly higher mean standing pulse rate compared with the placebo group (6.13 [1.76] beats/min [bpm], $P < 0.001$), higher mean supine pulse rate (3.57 [1.78] bpm, $P = 0.048$), and higher mean orthostatic pulse rate (2.68 [1.31] bpm, $P = 0.044$).

DISCUSSION

This was a short-term, multicenter, placebo-controlled, phase 3, randomized withdrawal study of pomaglumetad methionil (flexibly dosed at 40 or 80 mg twice daily) in patients with schizophrenia. This mGluR2/3 agonist exhibits a different mechanism of action than currently available antipsychotics, and it is

unknown whether there is a potential for withdrawal or physical dependence. This study was intended to determine whether pomaglumetad methionil is likely to produce signs and symptoms suggestive of physical dependence when discontinued abruptly after an acute treatment trial in patients with schizophrenia. No statistically significant evidence of withdrawal symptoms associated with pomaglumetad methionil was found as measured by DSCMR. This finding was supported by the secondary analyses of the clinician-rated scale for monitoring drug withdrawal, CIWA-Ar.

In the development of new central nervous system agents, it is essential to assess the new compound's potential to cause discontinuation symptoms after stopping the medication as part of both short- and long-term treatments.[9] The study was designed so that the duration of the open-label treatment phase enabled sufficient time to bring patients' plasma pomaglumetad methionil to "steady state" (given the molecule's short half-life) and was an adequate period to assess response to treatment. The double-blind, randomized withdrawal phase was sufficient to detect any withdrawal symptoms that might have emerged.

Overall, 7 patients (5.7%) discontinued from the study because of an adverse event, and the adverse events reported are consistent with the safety profile of pomaglumetad methionil.[2,11] Although the incidence of nausea and vomiting in patients during the open-label phase of the study was higher than usual, no patients discontinued because of an adverse event of nausea or vomiting.

The use of concomitant benzodiazepines and sedative hypnotics was controlled by instructing investigators as to which medications could be used and the indications that warranted usage and by limiting treatment duration and quantity of medication that could be dispensed to a patient (as defined in Methods). This measure resulted in limited use of benzodiazepines and sedative hypnotics during the open-label and randomized withdrawal phases of the study. In effect, the use of benzodiazepines and sedative hypnotics likely did not confound the withdrawal results obtained, as there was infrequent use in the pomaglumetad methionil and placebo groups during the randomized withdrawal phase of the study.

A unique feature of this study was the use of electronic diaries (ie, the ePRO device) to maximize the value of the patient-rated scale and to ensure sufficient data for the study's primary objective. The United States Food and Drug Administration may accept the use of such devices for patient-reported data collection and advocates the use of patient-reported outcomes in clinical trials.[12] The quality of the data collected depends on patient understanding of the ePRO device and patient compliance in entering accurate, complete responses each day. This study shows that 1 of the 123 patients enrolled in the open-label phase of the study was discontinued for noncompliance with use of the ePRO device.

Other studies using electronic recording devices with patients with schizophrenia demonstrated the feasibility of routinely collecting meaningful outcomes and incorporated patient-reported assessments into routine care for schizophrenia.[13] Use of smartphone software applications for ambulatory monitoring of psychotic symptoms has also been shown to be feasible and a valid way of assessing psychotic phenomena for research and clinical management purposes.[14]

Awad and Voruganti[15] detected a favorable trend on a number of such outcomes, demonstrating that interest is increasing in including patients' reports in the management of their psychiatric conditions, and indicated that electronic technology should be quickly adopted by the field to bring about patient self-reports through remote electronic means to enable evaluation in real time, enhance recruitment, and reduce cost. Considered together, our results and the results of others[13–15] suggest that the use of an electronic device to collect patient-reported outcomes in patients with schizophrenia is feasible and warrants further investigation.

A limitation of this study is that the DSCMR has not been formally validated in patients with schizophrenia in an independent trial; exploratory analyses were conducted to provide data to support the reliability and validity of the DSCMR scale in patients with schizophrenia. Such analyses performed in this study (data not shown) explored the psychometric properties and demonstrated some support for the primary outcome measure; however, further validation of this scale in patients with schizophrenia is warranted.

In summary, the primary analysis found no statistically significant evidence of physical dependence associated with withdrawal of pomaglumetad methionil. The use of a handheld ePRO device to record potential withdrawal-related symptoms in patients experiencing schizophrenia demonstrated good adherence and compliance and reliable outcomes that were comparable with the physician-rated scale, CIWA-Ar, and the protocol-specified safety parameters.

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AUTHOR DISCLOSURE INFORMATION

All authors are employees of Eli Lilly and Company.

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ERRATUM

Regarding the article: David A. Mrazek, MD, FRC Psych, Joanna M. Biernacka, PhD, Donald E. McAlpine, MD, et al. Treatment Outcomes of Depression: The Pharmacogenomic Research Network Antidepressant Medication Pharmacogenomic Study. *J Clin Psychopharmacol.* 2014;34:313–317.

The authors of this article have sent the following notice to the Journal:

"We regret to inform you that Dr. David Mrazek, one of the authors of this article, tragically passed away after the paper was written but before it was published."

The Editors-in-Chief