CVL-231 as a Novel Positive Allosteric Modulator Targeting M4 Muscarinic Receptors: Results From a Phase 1b Trial in Patients With Schizophrenia

John H. Krystal, MD, PhD; John M. Kane, MD, PhD;1,2,3 Christoph U. Correll, MD, PhD;4,5; David F. Walling, PhD;5,6 Matthew Leoni, MD, MBA;7 Sidhar Duvvuri, PhD;5,8 Shrinal Patel, PharmD;9; Hh Chang, PhD;5,8 Philip Iredale, MPH;10; Stacey Versavel, PhD;11 Pamela Perry, MS;12 Raymond Sanchez, MD;4 John Renge, PhD;5,13
1Yale Department of Psychiatry, Yale School of Medicine, New Haven, CT, USA; 2Department of Psychiatry, Zucker Hillside Hospital, Glen Oaks, NY, USA; 3Department of Psychiatry and Molecular Medicine, The Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY, USA; 4Department of Child and Adolescent Psychiatry, Charité University Medicine, Berlin, Germany; 5CNS Network, LLC, Garden Grove, CA, USA; 6Cerevel Therapeutics, Cambridge, MA, USA

Presenting Author: Matthew Leoni; matthew.leoni@cerevel.com

OBJECTIVE

To describe the safety, tolerability, and pharmacodynamics (PD) of emraclidine 30 mg once daily (QD) and emraclidine 20 mg twice daily (BID) in patients with acute schizophrenia.

INTRODUCTION

Previous studies have indicated that M4 muscarinic receptor activation is a promising therapeutic approach for the treatment of schizophrenia; however, the muscarinic agents investigated in clinical studies to date are associated with unwanted side effects that are likely related to nonselective pharmacology.14,15 Emraclidine (previously known as CVL-231) is a novel, brain-penetrant, highly selective M4 muscarinic allosteric modulator being investigated for the treatment of schizophrenia.

The current presentation includes data from Part B of a 2-part, phase 1b, multiple-ascending-dose trial of emraclidine in patients with schizophrenia.

METHODS

This was a 2-part, randomized, placebo-controlled phase 1b study (NCT04308072).

Part A consisted of a multiple-ascending-dose study in patients with stable schizophrenia, using the highest doses of emraclidine established in Part A, the safety, tolerability, and PD of emraclidine in participants with acute schizophrenia were investigated in Part B.

In Part B, adults aged ≥15 years with a primary diagnosis of schizophrenia (per the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition [DSM-5], confirmed by the Mini International Neuropsychiatric Interview at screening, were eligible for the study.

The nonclinical criteria for inclusion in Part B included Positive and Negative Syndrome Scale (PANSS) scores of ≤28; Global Impression of Severity of Symptoms Scale (GSS) scores of ≤4; a history of relapse and/or symptoms 3 months prior to screening; no need for antipsychotic treatment within 14 days for the current episode of schizophrenia; and a history of at least 1 hospitalization at least 4 times.

Key exclusion criteria for inclusion in Part B included a current diagnosis other than schizophrenia, history of refusals to antipsychotic treatment, hospitalization within 14 days for the current episode of schizophrenia, and presentation with a first episode of schizophrenia.

Participants in Part B were randomized 1:1:1 to 6 weeks of treatment with emraclidine 30 mg QD, emraclidine 20 mg BID, or placebo.

RESULTS

PARTICIPANTS

In Part B of the study, 81 participants were randomized and treated; most participants were male (73%) and Black (69%). All participants had been hospitalized at least once; 33% of participants had been hospitalized at least 4 times. The mean (standard deviation) age was 30 (11) years; 30% of participants had been hospitalized at least 4 times; 33% of participants had been hospitalized at least 10 times. The mean (SD) PASI score was 52 (18).7

SAFETY AND TOLERABILITY

The incidence of AEs was similar between emraclidine and placebo groups, with the most commonly reported AE being headache (Table; there were no deaths in the study).

Safety AEs included 1 instance each of COVID-19 (emraclidine 20 mg BID), accidental overdose (emraclidine 30 mg QD), and exacerbation of schizophrenia (emraclidine 30 mg QD); none of the serious AEs were considered treatment related.

Table. Summary of Adverse Events

<table>
<thead>
<tr>
<th>AEs, n (%)</th>
<th>Placebo n=22</th>
<th>Emraclidine 30 mg QD n=27</th>
<th>Emraclidine 20 mg BID n=25</th>
<th>All emraclidine n=52</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total AEs</td>
<td>16 (72%)</td>
<td>15 (56%)</td>
<td>15 (60%)</td>
<td>36 (69%)</td>
</tr>
<tr>
<td>Headache</td>
<td>7 (32%)</td>
<td>6 (22%)</td>
<td>3 (12%)</td>
<td>16 (31%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (18%)</td>
<td>4 (15%)</td>
<td>4 (16%)</td>
<td>12 (23%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2 (9%)</td>
<td>2 (7%)</td>
<td>2 (8%)</td>
<td>6 (11%)</td>
</tr>
<tr>
<td>Back pain</td>
<td>1 (5%)</td>
<td>2 (7%)</td>
<td>1 (4%)</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Blood CPK increased</td>
<td>0 (0%)</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (5%)</td>
<td>1 (4%)</td>
<td>0 (0%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>1 (5%)</td>
<td>1 (4%)</td>
<td>0 (0%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>1 (5%)</td>
<td>3 (11%)</td>
<td>5 (20%)</td>
<td>9 (17%)</td>
</tr>
</tbody>
</table>

*Nominal P < 0.05 over placebo.

Pharmacodynamics

Clinically meaningful reductions in PANSS total scores from baseline vs placebo were observed in both the emraclidine 30-mg QD dose (LSM change from baseline, 18.5% difference vs placebo, -1.7; nominal P = 0.013, Figure 2A) and the 20-mg BID dose (LSM change from baseline, -17.3; difference vs placebo, -11.3; nominal P = 0.007).

A greater proportion of participants receiving emraclidine had ≥20% reductions in PANSS total scores compared with placebo over 6 weeks (Figure 2B). The reductions in PANSS scores over time observed in participants receiving emraclidine compared with placebo were reduced in the corresponding PANSS positive, negative, and general psychopathology subscales through Week 6 (Figure 2C).

Improvements in CGI-S scores over time were observed in both emraclidine treatment groups relative to placebo (Figure 3A). CGI-S score LSE reductions (15.2%, 17.4%, 18.4%, and 14.2%) were observed at Weeks 2, 3, 4, and 5, respectively.

A greater proportion of participants receiving emraclidine had ≥20% improvement in CGI-S scores compared with placebo in Week 6 (Figure 3B). Blood pressure and heart rate were measured daily 2 hours after the morning dose and 2 hours after the evening dose during the treatment period. To reduce the variability of data, the weekly averages of the daily assessments after Day 1 were used as the basis of analysis. Linear MMWR was used to compare each active treatment to placebo, with treatment, study week, and the interaction between treatment and study week as fixed effects, baseline as a covariate, and subject within study week as a repeated measure with an unstructured covariance matrix. Least-squares means (LSM) of difference between each dose and placebo were derived from the model. The evening dose for the 30-mg QD group was a blinded placebo.

Extrapyramidal symptoms were assessed using the Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), and the Simpson-Angus Scale (SAS); all three of these assessments are rating scales in which higher values indicate the absence of symptoms, and increasing values reflect increasing severity.

SAS scores were measured using the Columbia-Suicide Severity Rating Scale (C-SRQ), which included assessments in suicidal ideation (with a subscale ranging from 1 [Wish to be dead] to 10 [Completed suicide]), suicidal behavior, and self-injurious behavior without suicidal intent; the “Baseline/Screening” version of the C-SRQ was used as screening and a “Since Last Visit” version was administered at each visit.

Figure 1. Change from baseline in mean systolic blood pressure, change from baseline in mean diastolic blood pressure, and change from baseline in heart rate 2 hours following administration of morning dose.

Figure 2. (A) Change in total PANSS scores from baseline over time, (B) proportion of participants with 20%, 30%, and 50% reductions in PANSS total scores by Week 6, and (C) changes in PANSS subscores over time.

Figure 3. (A) Change in CGI-S scores from baseline to Week 6, and (B) proportion of participants with ≥20%, ≥30%, and ≥50% improvement in CGI-S scores by Week 6.

CONCLUSIONS

Emraclidine demonstrated a favorable safety profile with a comparable incidence of AEs compared with placebo, no serious AEs associated with treatment, and no evidence of extrapyramidal symptoms, metabolic, gastrointestinal, extrapyramidal effects, suicidal ideation, or weight gain compared with placebo.

Moderate asymptomatic increases in systolic and diastolic blood pressure and heart rate observed at treatment initiation decreased over time and were not clinically meaningful by the end of the study treatment.

Both emraclidine 30-mg QD and 20-mg BID groups demonstrated significant improvements in PANSS total scores compared with placebo over 6 weeks of treatment, with meaningful differences observed in the positive, negative, and general psychopathology subscales.

Consistent with improvements in PANSS scores, CGI-S scores also improved over 6 weeks in the emraclidine treatment groups compared with placebo.

Collectively, these results support the continued investigation of emraclidine as a novel, once-daily treatment for schizophrenia with a potentially favorable side effect profile without the need for titration.

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REFERENCES