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

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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[1-3]
- Emraclidine (previously known as CVL-231) is a novel, brain-penetrant, highly selective M4 muscarinic positive allosteric modulator being investigated for the treatment of schizophrenia
- The current presentation includes data from Part B of a two-part, phase 1b, multiple–ascending-dose trial of emraclidine in patients with schizophrenia

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

METHODS

- This was a two-part, randomized, placebo-controlled phase 1b study (NCT04136873)
  - 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
  - Part B was a randomized, double-blind, placebo controlled, parallel-arm study
- In Part B, adults aged ≤55 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
  - Additional inclusion criteria for Part B included Positive and Negative Syndrome Scale (PANSS) scores of ≥80, Clinical Global Impression-Severity of Symptoms Scale (CGI-S) score of ≥4, a history of relapse and/or symptom exacerbation when not receiving antipsychotic medication, and current acute exacerbation or relapse of symptoms with onset within 2 months
  - Key exclusion criteria included a current DSM-5 diagnosis other than schizophrenia, history of refractoriness 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
- The primary objective of Part B of the study was to further characterize the safety and tolerability of target doses selected from the multiple–ascending-dose investigation of emraclidine in Part A in participants with acute schizophrenia; the PD of emraclidine was assessed as an exploratory endpoint
  - PD assessments included the PANSS and the associated Positive, Negative, and General Psychopathology subscales, and the CGI-S
  - The PANSS total score (range, 30-210) is based on the sum of 30 items rated from 1 to 7, with higher scores indicating more severe symptoms
  - The CGI-S scale was administered by the investigator answering the question, "Considering your total clinical experience with this particular population, how ill is the subject at this time?" with responses ranging from 1 (normal, not at all ill) to 7 (among the most extremely ill patients)
  - Changes in PANSS and CGI-S scores from baseline were compared using a Mixed Model for Repeated Measures (MMRM)
- Safety and tolerability were assessed using standard clinical assessments and clinical laboratory tests, including body weight, blood pressure, pulse, electrocardiogram (ECG), and patient reporting of treatment-emergent adverse events (AEs)
  - 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 daily data, the weekly averages of the daily assessments after Day 1 were used as the basis of analysis. A linear MMRM 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 day 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 dose
  - 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 0 indicates the absence of symptoms, and increasing values reflect increasing severity
  - Suicidality was assessed using the Columbia-Suicide Severity Rating Scale (C-SSRS), which includes assessments for subscales for 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-SSRS was used at screening and a "Since Last Visit" version was administered at each visit

RESULTS

PARTICIPANTS

- In Part B of the study, 81 participants were randomized and treated; most participants were male (78%) and Black (69%), and the mean (standard deviation [SD]) age was 40 (9.2) years
- The mean (SD) time since initial disease onset was 19 (10) years and 85% of participants had been hospitalized at least once; 33% of participants had been hospitalized at least 4 times previously
  - The mean (SD) baseline PANSS score was 95 (8.1) and the mean (SD) baseline CGI-S score was 5 (0.6)

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
  - Serious AEs included 1 instance each of COVID-19 (emraclidine 20 mg BID), accidental cocaine overdose (emraclidine 30 mg QD), and exacerbation of schizophrenia (emraclidine 30 mg QD); none of the serious AEs were considered related to the study drug

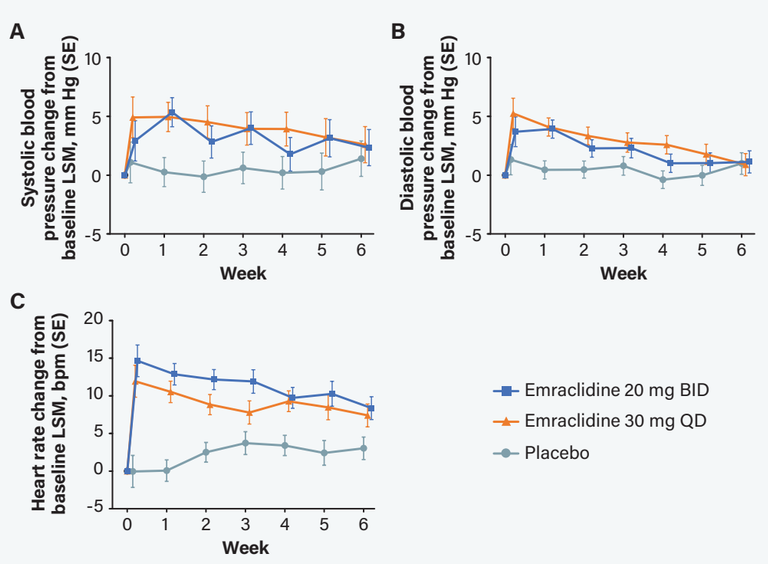
Table. Summary of Adverse Events

	Placebo n=27	Emraclidine 30 mg QD n=27	Emraclidine 20 mg BID n=27	All emraclidine n=54
AEs, n (%)	14 (52)	14 (52)	15 (56)	29 (54)
AEs related to study drug	10 (37)	7 (26)	12 (44)	19 (35)
Serious AEs	0 (0)	2 (7)	1 (4)	3 (6)
AEs leading to study discontinuation	0 (0)	2 (7)	1 (4)	3 (6)
AEs in ≥5% of all emraclidine				
Headache	7 (26)	8 (30)	7 (26)	15 (28)
Nausea	1 (4)	2 (7)	2 (7)	4 (7)
Weight increased	2 (7)	1 (4)	2 (7)	3 (6)
Back pain	1 (4)	2 (7)	1 (4)	3 (6)
Blood CPK increased	0 (0)	1 (4)	2 (7)	3 (6)
Dizziness	0 (0)	1 (4)	2 (7)	3 (6)
Dry mouth	0 (0)	3 (11)	0 (0)	3 (6)
Somnolence	0 (0)	1 (4)	2 (7)	3 (6)

AE, adverse event; BID, twice daily; CPK, creatine phosphokinase; QD, once daily.

- Gastrointestinal AEs were reported with comparable frequencies across treatment groups (placebo, 15%; emraclidine 30 mg QD, 19%; emraclidine 20 mg BID, 7%)
- Weight change from baseline to Day 42 was comparable across all treatment groups; the mean (SD) change from baseline for placebo, emraclidine 30 mg QD, and emraclidine 20 mg BID groups was 1.6 (4.0) kg, 1.4 (4.3) kg, and 1.7 (3.1) kg
- No meaningful trends were observed in mean changes from baseline in glucose or other lipid parameters
- Modest, asymptomatic increases in LSM changes from baseline in supine systolic and diastolic blood pressure and heart rate observed upon treatment initiation in the emraclidine treatment groups decreased over time (**Figure 1**)
  - The Week 6 average mean change from baseline relative to placebo following the morning dose of emraclidine in systolic blood pressure was 1.2 mm Hg and 0.9 mm Hg for the 30-mg QD and 20-mg BID dose, respectively, and the average mean change from baseline relative to placebo in diastolic blood pressure was -0.1 mm Hg and 0.1 mm Hg for the 30-mg QD and 20-mg BID dose, respectively; similar changes were observed for the Week 6 average mean change from baseline relative to placebo for the evening dose
  - Week 6 average mean differences from placebo in LSM supine heart rate following the morning dose for the 30-mg QD and 20-mg BID emraclidine dosing groups were 4.4 bpm and 5.3 bpm, respectively, with similar results following the evening dose
- There was no indication of any effect of study treatment on extrapyramidal symptoms based on results from the SAS, AIMS, and BARS assessments
  - Most participants had scores of 0 on all 3 assessments at baseline and all postbaseline visits; no participants had any score greater than 1 at any postbaseline timepoint
- No meaningful changes were observed in suicidality as assessed by the C-SSRS

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

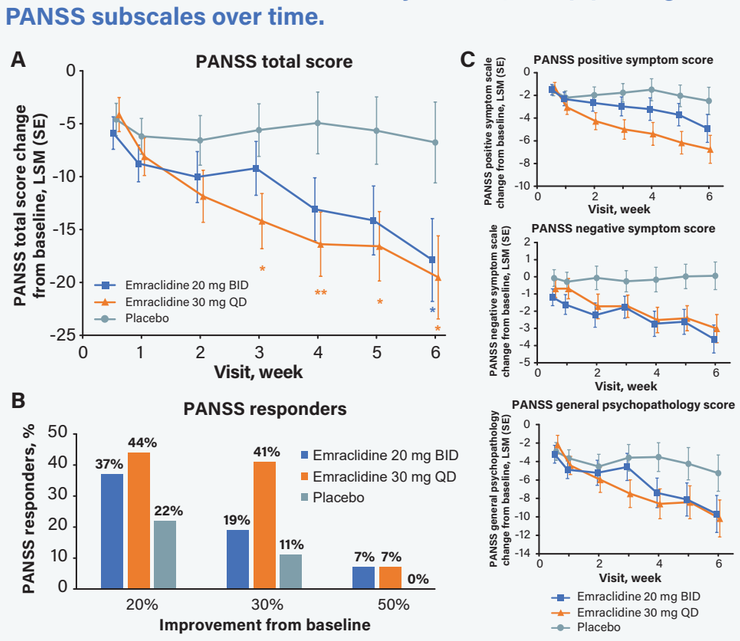


BID, twice daily; bpm, beats per minute; LSM, least-squares mean, QD, once daily; SE, standard error of the mean.

PHARMACODYNAMICS

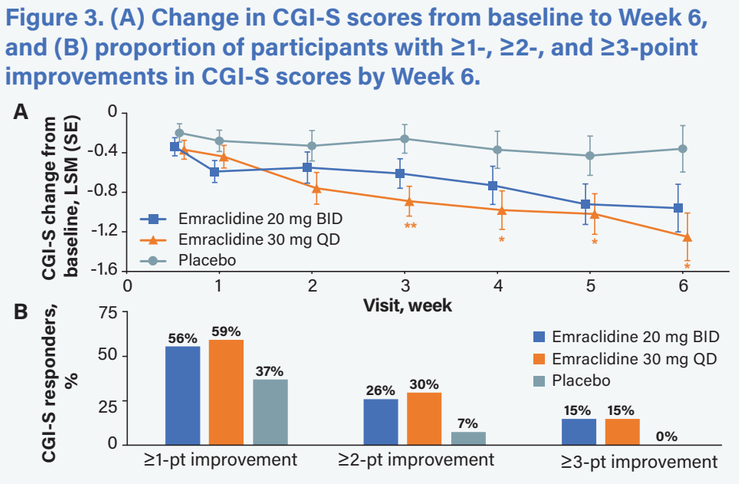
- Clinically meaningful reductions in PANSS total scores from baseline vs placebo were observed in both the emraclidine 30-mg QD dose (LSM change from baseline, 19.5; difference vs placebo, -12.7; nominal *P*=0.023; **Figure 2A**) and the 20-mg BID dose (LSM change from baseline, -17.9; difference vs placebo, -11.1; nominal *P*=0.047)
  - A greater proportion of participants receiving emraclidine had ≥20% reductions in PANSS total scores by Week 6 (**Figure 2B**) compared with placebo
  - The reductions in PANSS scores over time observed in participants receiving emraclidine compared with placebo were accompanied by reductions 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 LSM reductions (SE) from baseline for the placebo, emraclidine 30-mg QD, and 20-mg BID groups at Day 42 were 0.36 (0.24), 1.25 (0.24), and 0.96 (0.24) points, respectively
  - Significant reductions in CGI-S scores compared with placebo were observed by Week 3 in the emraclidine 30-mg QD group (LSM change from baseline, -0.89; difference vs placebo, -0.63; nominal *P*=0.003) and sustained through Week 6 (LSM difference vs placebo, -0.89; nominal *P*=0.01)
  - A greater proportion of participants receiving emraclidine had ≥1-point improvements in CGI-S scores by Week 6 compared with placebo (**Figure 3B**)

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 subscales over time.



BID, twice daily; LSM, least-squares mean; PANSS, Positive and Negative Syndrome Scale; QD, once daily; SE, standard error of the mean. *Nominal *P*<0.05 over placebo. **Nominal *P*<0.01 over placebo.

Figure 3. (A) Change in CGI-S scores from baseline to Week 6, and (B) proportion of participants with ≥1-, ≥2-, and ≥3-point improvements in CGI-S scores by Week 6.



BID, twice daily; CGI-S, Clinical Global Impressions Scale; LSM, least-squares mean; QD, once daily; SE, standard error of the mean. *Nominal *P*<0.05 over placebo. **Nominal *P*<0.01 over placebo.

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 effects, gastrointestinal effects, suicidal ideation, or weight gain compared with placebo
- Modest, 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 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 PANSS 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: 1. Bodick et al. *Arch Neurol*. 1997;54:465-473. **2.** Brannan et al. *N Engl J Med*. 2021;384:717-726. **3.** Shekhar et al. *Am J Psychiatry*. 2008;165:1033-1039.