T141

CVL-231 as a Novel Positive Allosteric Modulator of Cholinergic M4 Receptors for the Treatment of Schizophrenia: Results From an Early Proof-of-Concept Study in Patients With Schizophrenia

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CONCLUSIONS

- The safety profile of CVL-231 was favorable, with comparable incidence of AEs compared with placebo, no serious AEs associated with treatment, and no evidence of extrapyramidal symptoms, metabolic effects, gastrointestinal effects, or weight gain compared with placebo
- CVL-231 exhibited comparable exposures at once-daily or twice-daily dosing, supporting the utility of a once-daily dosing paradigm
- Both CVL-231 30 mg QD and 20 mg BID demonstrated significant reductions in the PANSS total score compared with placebo over 6 weeks of treatment
  - Meaningful differences were also observed in the positive, negative, and general psychopathology PANSS subscales in both CVL-231 groups relative to placebo
- Overall, these data support the potential of CVL-231 as a novel, once-daily treatment without titration for schizophrenia with potentially reduced side effect burden compared with commonly used antipsychotics

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REFERENCES: 1. Rummel-Kluge et al. *Schizophr Res*. 2010;123:225-233. **2.** Huhn et al. *Lancet*. 2019;394:939-951. **3.** Shekhar et al. *Am J Psychiatry*. 2008;165:1033-1039. **4.** Brannon et al. *N Engl J Med*. 2021;384:717-726.

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INTRODUCTION

- Currently used antipsychotic medications for schizophrenia are associated with undesirable side effects including extrapyramidal motor symptoms, metabolic effects, and weight gain[1,2]
  - Preclinical and clinical data have suggested that muscarinic acetylcholine receptor M4 activators can effectively modulate symptoms of psychosis in schizophrenia, but these agents were associated with gastrointestinal side effects and nonspecific pharmacology[3,4]
- CVL-231 is a novel, brain-penetrant, highly selective M4 muscarinic positive allosteric modulator being developed for the treatment of schizophrenia
- The current presentation includes data from Part B of a two-part, phase 1b, multiple–ascending-dose trial in patients with schizophrenia

OBJECTIVE

- To assess the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics of CVL-231 30 mg once daily (QD) and 20 mg twice daily (BID) in patients with schizophrenia who are experiencing acute exacerbation of psychosis

METHODS

- This study was a two-part, randomized, placebo-controlled phase 1b study (NCT04136873)
  - The safety, tolerability, PK, and pharmacodynamics of CVL-231 in participants with acute schizophrenia were investigated in Part B at 30-mg QD and 20-mg BID doses based on the safety and tolerability data from Part A of the study
  - Part B was a randomized, double-blind, placebo-controlled, parallel-arm study
- 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
  - Inclusion criteria for Part B included Positive and Negative Syndrome Scale (PANSS) total score ≥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 or failure to respond to clozapine/response to clozapine only, hospitalization >14 days for the current episode of schizophrenia, and presentation with a first episode of schizophrenia
- Planned enrollment in Part B was approximately 75 participants randomized 1:1:1 to CVL-231 30 mg QD, CVL-231 20 mg BID, or placebo; participants received treatment for 6 weeks
- 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 CVL-231 in Part A in participants with acute schizophrenia; the PK of CVL-231 was assessed as a secondary endpoint
  - Exploratory pharmacodynamic assessment included the PANSS and the associated Positive, Negative, and General Psychopathology subscales; 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
  - Changes in PANSS scores from baseline were compared using a mixed model for repeated measures
- Plasma concentrations of CVL-231 were analyzed with a validated liquid chromatography with tandem mass spectrophotometry method; PK parameters were estimated using noncompartmental methods
- Safety and tolerability were assessed through standard clinical assessments, including body weight, blood pressure, pulse, electrocardiogram (ECG), and patient reporting of adverse events (AEs)
  - Extrapyramidal symptoms were assessed using the Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), and the Simpson-Angus Scale (SAS)
  - Suicidality was assessed using the Columbia-Suicide Severity Rating Scale (C-SSRS)

RESULTS

PARTICIPANT DISPOSITION AND BASELINE CHARACTERISTICS

- 81 participants were randomized and treated in Part B
  - 6 participants discontinued from the trial in each treatment group; 63 participants completed the study
- The majority of participants were male (78%) and Black (69%); the mean age was 40 years
  - The mean time since initial disease onset was 19 years; 85% of participants had been hospitalized at least once
  - The mean baseline PANSS total score was 95; baseline demographic and disease characteristics were distributed evenly across treatment groups

SAFETY

- The frequency of AEs was similar across all treatment groups (**Table 1**)
  - Most AEs were mild to moderate in severity, with headache as the most frequently reported AE; there were no deaths in the study
  - The incidence of nausea and other gastrointestinal AEs was low and similar across all treatment groups
  - Serious AEs included 1 instance each of COVID-19 (CVL-231 20 mg BID), accidental cocaine overdose (CVL-231 30 mg QD), and exacerbation of schizophrenia (CVL-231 30 mg QD); none of the serious AEs were considered related to the study drug
- Modest, asymptomatic increases from baseline relative to placebo were observed in mean supine systolic and diastolic blood pressure and heart rate in both CVL-231 groups with initiation of treatment; mean blood pressure and heart rate measures trended downward for both CVL-231 groups over the treatment period, such that by week 6, there was no clinically meaningful increase in mean blood pressure and heart rate compared with placebo
- The percentage of participants who had an increase in body weight of ≥7% from baseline to day 42 was similar across treatment groups (19%, 15%, and 14% in the placebo, CVL-231 30-mg QD, and CVL-231 20-mg BID groups, respectively)
- There were no clinically meaningful or consistent changes from baseline in laboratory parameters or ECG results
- There was no indication of any effect of treatment on extrapyramidal symptoms or suicidality based on AIMS, BARS, SAS, and C-SSRS assessments

Table 1. Summary of Adverse Events

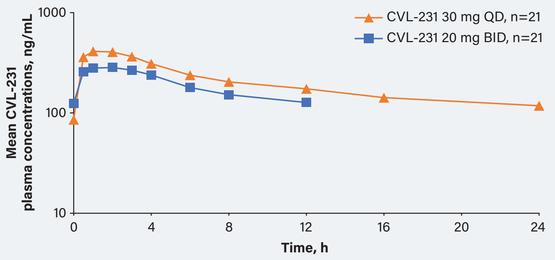
	Placebo n=27	CVL-231 30 mg QD n=27	CVL-231 20 mg BID n=27	All CVL-231 n=54
AEs, n (%)	14 (52)	14 (52)	15 (56)	29 (54)
AEs related to study drug	10 (37)	7 (26)	12 (44)	19 (35)
Serious AEs	0 (0)	2 (7)	1 (4)	3 (6)
AEs leading to study discontinuation	0 (0)	2 (7)	1 (4)	3 (6)
AEs in ≥5% of all CVL-231				
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.

PHARMACOKINETICS

- Steady-state CVL-231 plasma concentration-time profiles are presented in **Figure 1**; CVL-231 exposures were similar across both dose groups

Figure 1. CVL-231 Plasma Concentration Over Time on Day 36

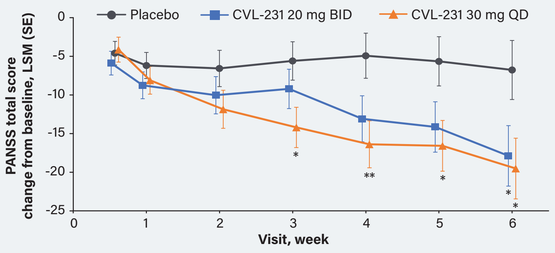


BID, twice daily; QD, once daily.

PHARMACODYNAMICS

- Meaningful reductions in the PANSS total score compared with placebo were observed as early as week 3 of treatment in both CVL-231 dose groups (**Figure 2A**)
  - More participants exhibited reductions of 20% and 30% in PANSS total score in the CVL-231 treatment groups compared with the placebo group; no participants in the placebo group had total PANSS score reductions of 50% (**Figure 2B**)
  - Reductions in the total PANSS score were supported by reductions in the PANSS subscale scores (**Figure 2C**)
  - Reductions in the PANSS total score from baseline to week 6 for both CVL-231 treatment groups were considered statistically significant compared with placebo (**Table 2**)

Figure 2A. Change in Total PANSS Scores From Baseline Over Time



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

Figure 2B. Proportion of Participants With 20%, 30%, and 50% Reductions in PANSS Total Scores by Week 6

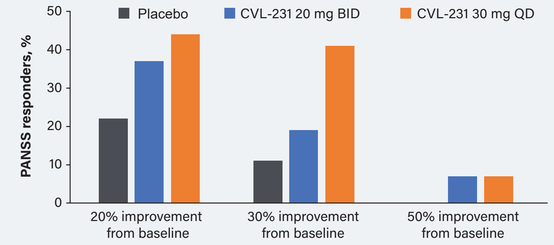
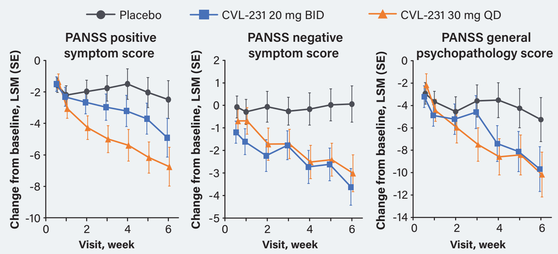


Figure 2C. Changes in PANSS Subscales Over Time



BID, twice daily; LSM, least squares mean; PANSS, Positive and Negative Syndrome Scale; QD, once daily; SE, standard error of the mean.

Table 2. Summary of PANSS Total Score Change From Baseline at Day 21 and Day 42

	Placebo n=27	CVL-231 30 mg QD n=27	CVL-231 20 mg BID n=27	All CVL-231 n=54
Baseline PANSS total score, mean (SD)	93 (8.8)	93 (7.3)	97 (7.9)	95 (7.7)
Day 21 change from baseline				
LSM (SE)	-5.6 (2.49)	-14.20 (2.55)	-9.22 (2.61)	-11.71 (1.82)
LSM difference from placebo	–	-8.61	-3.62	-6.11
95% CI	–	-15.70, -1.51	-10.81, 3.57	-12.26, 0.03
P-value	–	0.018	0.319	0.051
Day 42 change from baseline				
LSM (SE)	-6.77 (3.82)	-19.52 (3.91)	-17.88 (3.93)	-18.70 (2.77)
LSM difference from placebo	–	-12.74	-11.11	-11.93
95% CI	–	-23.66, -1.82	-22.06, -0.15	-21.36, -2.5
P-value	–	0.023	0.047	0.014

BID, twice daily; CI, confidence interval; LSM, least squares mean; PANSS, Positive and Negative Syndrome Scale; QD, once daily; SD, standard deviation; SE, standard error of the LSM. The estimates were based on a mixed-measures repeated model with an unstructured covariance matrix and fixed effects for treatment group, visit, treatment group-by-visit interaction, a random effect for participant, and the baseline value as a covariate. *P*-values are nominal.