EMPOWERing the Next Generation: A Phase 2 Program to Evaluate Emraclidine, a Selective M4 Positive Allosteric Modulator (PAM), for the Treatment of Schizophrenia

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CONCLUSION

- The EMPOWER program aims to establish the efficacy, safety, tolerability, and appropriate dose range of emraclidine in the treatment of schizophrenia

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REFERENCES: 1. Krystal et al. *Lancet.* 2022;400:2210-2220. **2.** Kay et al. *Schizophr Bull.* 1987;13:261-276.

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INTRODUCTION

- Emraclidine is a novel, highly selective positive allosteric modulator of M4 muscarinic acetylcholine receptors currently in development for the treatment of schizophrenia and Alzheimer's disease psychosis
- By selectively activating M4, emraclidine may reduce excess dopamine signaling in the striatum, potentially leading to a reduction in psychotic symptoms
- In a phase 1b trial, emraclidine significantly reduced total Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression-Severity (CGI-S) scores over 6 weeks of treatment, with a favorable safety profile and minimal side effects.[1] Additional studies in larger cohorts are ongoing, and are needed to confirm the efficacy, safety, and tolerability of emraclidine for the treatment of schizophrenia

OBJECTIVE

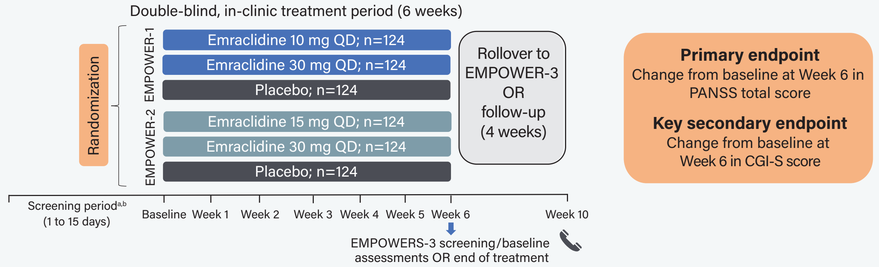
- To present detailed study designs for the EMPOWER program, which includes three phase 2 trials designed to evaluate the efficacy, safety, tolerability, and dose range of once-daily emraclidine for the treatment of schizophrenia

TRIAL DESIGN

EMPOWER-1 AND EMPOWER-2

- EMPOWER-1 and EMPOWER-2 are two adequately powered, multicenter, randomized, double-blind, placebo-controlled, parallel group, 6-week inpatient trials of emraclidine monotherapy (10 mg, 15 mg, and 30 mg once daily [QD]) (**Figure 1**)

Figure 1. EMPOWER-1 and EMPOWER-2 Study Design



Primary endpoint
Change from baseline at Week 6 in PANSS total score

Key secondary endpoint
Change from baseline at Week 6 in CGI-S score

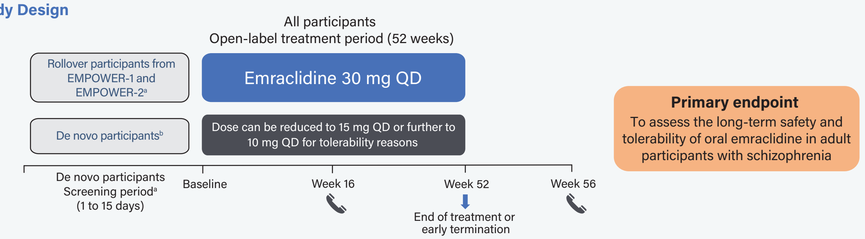
Key inclusion criteria	Key exclusion criteria
• Male and female participants, aged 18-65 years • Primary diagnosis of schizophrenia per DSM-5, as confirmed by the MINI for Psychotic Disorders • CGI-S ≥4 (moderately to severely ill) • PANSS total score between 85 and 120 • An acute exacerbation or relapse of psychotic symptoms requiring hospitalization	• Current DSM-5 diagnosis other than schizophrenia • Schizophrenia considered resistant/refractory to antipsychotic treatment • Time from initial onset of schizophrenia <2 years based on prior records or participant self-reporting • Reduction in PANSS total score of ≥20% between screening and baseline • History of tardive dyskinesia or extrapyramidal symptoms that require medication

Assessment time points are planned for the last day of the indicated week (eg, Day 7, 14, 21), with a ±2-day window. Participants will be contacted via telephone or other means of communication to check on their status at Week 10. [a]Participants will be admitted to the inpatient facility at the time they sign the ICF and remain in the inpatient facility for the duration of treatment. [b]Extension of screening (up to a maximum of 21 days total) is allowed following discussion and documented approval by the medical monitor prior to the expiration of the screening period. CGI-S, Clinical Global Improvement-Severity; DSM-5, Diagnostic and Statistical Manual of Mental Disorders 5; ICF, informed consent form; MINI, Mini International Neuropsychiatric Interview; PANSS, Positive and Negative Syndrome Scale; QD, once daily.

EMPOWER-3

- EMPOWER-3 is a 52-week, open-label extension trial to assess the long-term safety and tolerability of emraclidine in adult participants with stable schizophrenia (**Figure 2**)

Figure 2. EMPOWER-3 Study Design



Primary endpoint
To assess the long-term safety and tolerability of oral emraclidine in adult participants with schizophrenia

Key inclusion criteria	Key exclusion criteria
Rollover participants • Completed 6 weeks of post-randomization treatment in EMPOWER-1 and EMPOWER-2 • Participants who, in the opinion of the investigator, could potentially benefit from treatment with emraclidine • Outpatient status at last day of treatment period in EMPOWER-1 and EMPOWER-2 **De novo participants** • Male and female participants, aged 18-65 years • Primary diagnosis of schizophrenia per DSM-5, as confirmed by the MINI for Psychotic Disorders • Participants who have been stable on antipsychotic medication for at least one 3-month period in the year prior to screening • Outpatient status at the time of trial	**Rollover participants** • Participants who had a clinically significant medical, surgical, psychiatric, or laboratory/ECG abnormality during EMPOWER-1 and EMPOWER-2 • A "Yes" response to Suicidal Ideation Item 4 or 5 on the C-SSRS at any time point during EMPOWER-1 and EMPOWER-2 • Positive pregnancy test result, or females who are pregnant, breastfeeding, or planning to become pregnant • Systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and orthostatic hypotension (decrease of ≥10 mm Hg in diastolic blood pressure) **De novo participants** • Current DSM-5 diagnosis other than schizophrenia • Schizophrenia considered resistant/refractory to antipsychotic treatment • History of tardive dyskinesia or extrapyramidal symptoms that required medication • A "Yes" response to Suicidal Ideation Item 4 or 5 on the C-SSRS within the past 6 months

Assessment time points are planned for the last day of the indicated week (eg, Day 7, 14, 28), with a ±3-day window. Participants will be contacted via telephone or other means of communication to check on their status at Weeks 16 and 56. [a]For rollover participants, screening for EMPOWER-3 occurs simultaneously with baseline assessments at the Week 6 (Day 45) time point of EMPOWER-1 or EMPOWER-2. For rollover participants, the first dose of IMP for the open-label trial occurs on the day following baseline assessments. [b]Separate screening and baseline visits are required for de novo participants to allow for completion of eligibility assessments and washout of prohibited concomitant medications, if applicable. An extension of screening (up to a maximum of 21 days total) is allowed following discussion and documented approval by the medical monitor prior to the expiration of the screening period. For de novo participants, the first dose of IMP for the open-label trial occurs on the same day as baseline assessments. AIMS, Abnormal Involuntary Movement Scale; C-SSRS, Columbia-Suicide Severity Rating Scale; CGI-S, Clinical Global Impression-Severity; DSM-5, Diagnostic and Statistical Manual of Mental Disorders 5; IMP, investigational medicinal product; MINI, Mini International Psychiatric Interview; QD, once daily.

OUTCOMES

- The EMPOWER program objectives and endpoints are presented in the **Table**
- The Positive and Negative Syndrome Scale (PANSS) is comprised of Positive, Negative, and General Psychopathology subscales containing 30 symptom constructs, with scores ranging from 1 (absence of symptoms) to 7 (extremely severe symptoms)[2]; the PANSS total score ranges from 30 to 210
- The CGI-S will be used by the investigator by answering the question, "Considering your total clinical experience with this particular population, how ill is the participant at this time?" with scores ranging from 1 (normal, not ill) to 7 (among the most extremely ill)
- Across all EMPOWER trials, participant quality of life will be assessed using the Short Form-6 Dimensions (SF-6D), a 6-dimension (physical functioning, role participation, social functioning, bodily pain, mental health, and vitality) classification paired with an algorithm to generate a continuous index for health
- In EMPOWER-3, the effect of treatment on work productivity and regular activities will be evaluated using the Work Productivity and Activity Impairment (WPAI) questionnaire in schizophrenia, a 6-question assessment that evaluates absenteeism, presenteeism, and impairment in unpaid activity because of health over a recall period of 7 days

Table. Key Objectives and Endpoints

EMPOWER-1 and EMPOWER-2	EMPOWER-3
PRIMARY OBJECTIVE • To evaluate the efficacy of 2 fixed oral doses (EMPOWER-1, 10 mg QD and 30 mg QD; EMPOWER-2, 15 mg and 30 mg QD) of emraclidine in adult participants with schizophrenia experiencing an acute exacerbation of psychosis **Primary endpoint** • Change from baseline at Week 6 in the PANSS total score **Secondary endpoints** • Change from baseline at Week 6 in the CGI-S score • Change from baseline at all time points in PANSS total score and CGI-S score • Percentage of responders at Week 6 (responders defined as ≥30% reduction from baseline in PANSS total score) **Exploratory endpoints** • CGI-I at Weeks 3 and 6, change from baseline at all time points in PANSS positive, negative, and general psychopathology subscale scores and PANSS Marder Factor scores **SECONDARY OBJECTIVE** • To evaluate the safety and tolerability of emraclidine by assessing treatment-emergent adverse events **EXPLORATORY OBJECTIVE** • To evaluate quality of life (SF-6D) and cognition (BACS) following fixed oral doses of emraclidine in adult participants with schizophrenia experiencing an acute exacerbation of psychosis	**PRIMARY OBJECTIVE** • To assess the long-term safety and tolerability of oral emraclidine in adult participants with schizophrenia **Primary endpoints** • Treatment-emergent adverse events • Clinically significant changes in vital sign measurements, body weight, physical and neurological examination results, ECG assessments, clinical laboratory assessments, and metabolic parameters • Clinically significant findings in suicidality assessed using the C-SSRS • Extrapyramidal symptoms evaluated using the change from baseline in SAS, AIMS, and BARS assessments **EXPLORATORY OBJECTIVES** • To evaluate the effect of emraclidine on symptoms of schizophrenia (PANSS and PANSS subscales, CGI-S, CGI-I), quality of life (SF-6D), work productivity, and regular activities (WPAI) over 52 weeks

AIMS, Abnormal Involuntary Movement Scale; BACS, Brief Assessment of Cognition in Schizophrenia; BARS, Barnes Akathisia Rating Scale; CGI-I, Clinical Global Impression-Improvement; CGI-S, Clinical Global Impression-Severity; C-SSRS, Columbia-Suicide Severity Rating Scale; ECG, electrocardiogram; PANSS, Positive and Negative Syndrome Scale; QD, once daily; SAS, Simpson Angus Scale; SF-6D, Short Form-6 Dimensions; WPAI, Work Productivity and Activity Impairment.