improvement of performance on the MATRICS Consensus Cognitive Battery (MCCB) and for ratings on the Schizophrenia Cognition Rating Scale (SCoRS). A detailed examination of factors with the potential to impact the trial results are ongoing (e.g., background antipsychotic medication, treatment adherence, and demographic variables) for purposes of evaluating concluding results and to inform later clinical development programs of any 'red flags' and key lessons learned.

Methods: Two 6-month, randomized, double-blind, placebo-controlled, parallel-dosing, Phase III studies evaluated EVP-6124 versus placebo, as a pro-cognitive treatment in individuals with
schizophrenia on chronic, stable, atypical antipsychotic therapy. Study methodologies were
identical with the exception of geographical participation. A screening period of up to 28 days
occurred as placebo run-in were individuals were assessed for their eligibility based upon pill count compliance over a 14-day period and ability to complete the MCCB cognitive battery. Eligible subjects (total n = 1,520, across both trials) continued their usual antipsychotic regimen and were randomly assigned 1:1:1 on Study Day 1 to receive 1 of 3 double-blind treatments: once-daily EVP-6124 HCl tablets (1 or 2 mg) or placebo for 26 weeks (Study Days 1 to 182). The MCCB battery was completed once during placebo run-in, at baseline, 4, 8, 12, and 26-week study visits.

Results: Robust improvements were observed in both trials on the NeuroCognitive Composite
Score (NCC; all MCCB tests except the MCEIT) and the SCoRS across all treatment groups, from screening through to baseline visit and from baseline through to week 26. However no statistically significant difference between encenicline and placebo emerged using a Mixed Model Repeated Measures change from baseline to week 26 analysis, for either NCC or SCoRS. Although in study EVP-6124-016 there was a small trend for both the 1 and 2mg groups to be greater than placebo for NCC. Encenicline was generally safe and well tolerated with adverse events reported by approximately 50% of the patients; mild constipation was most frequent. Post-hoc analyses (on-going) on pooled data from both trials are examining the effects of adherence on treatment efficacy, site effects (including experience on the part of both assessors and patients), and the impact of various demographic variables (race and geographic location) and treatment (type of anti-psychotic medication).

Conclusions: The results from these two large Phase III studies, showed limited benefit of
encenicline for the treatment of cognitive impairment and related functional deficits in people with schizophrenia. However, a number of valuable observations were obtained from these trials which question whether the Phase III results are less reflective of the true efficacy of encenicline than the phase II studies previously indicated. These include: 1) the importance of accounting for/mitigating non-adherence to treatment, 2) multiple repeated MCCB testing sessions did not plateau learning effects and 3) subjects with greater change in Outcome scores from screening to baseline also showed aberrant changes from baseline to week 26 compared to subjects with smaller changes prior to baseline, inherently reducing signal:noise ratio. Results of additional post-hoc analyses will be discussed to guide and inform the future development of CIAS clinical trials.

32.3 A POST-HOC ANALYSIS EXPLORING PARTICIPANT-LEVEL TRAJECTORIES OF COGNITIVE PERFORMANCE AMONG PATIENTS WITH SCHIZOPHRENIA IN A MULTI-NATIONAL PHASE II TRIAL

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Background: It remains unclear whether the lack of clinical trial success and drug approval for cognitive impairment associated with schizophrenia (CIAS) is due to compounds being ineffective, or whether trial methodology itself has been a limiting factor in successfully demonstrating the efficacy of these agents. Schizophrenia is a heterogeneous disorder and whilst cognitive deficits are a core feature, the profile and degree of neuropsychological impairment can vary across patients. Though most individuals with schizophrenia exhibit some general cognitive impairment compared to antecedent expectations, such as premorbid intelligence, up to a quarter display cognitive performance in the 'normal' range. This may pose a problem for pro-cognitive drug trials in this population given that it potentially inflates baseline scores and reduces the scope to see improvement between treatment and placebo groups. In order to examine this potential issue, we investigated participant-level trajectories of cognitive performance among patients with schizophrenia enrolled in a multi-national, phase II clinical trial.

Methods: We conducted a post-hoc analysis of existing trial data from 463 patients with schizophrenia who participated in a randomized, double-blind, placebo-controlled trial. Patients met established diagnosis for schizophrenia (DSM-5), were clinically stable (non-acute) and had no more than moderate severity ratings on the Positive and Negative Syndrome Scale (PANSS). During the trial, participants completed two different neurocognitive test batteries, the Cambridge Neuropsychological Test Automated Battery (CANTAB) and the MATRICS Consensus Cognitive Battery (MCCB), at 4 separate time points (screening, baseline, week 6 & week 12). Participant data were pooled across placebo and treatment groups to explore trajectories of cognitive performance, at the participant-level, across the course of the study.

Results: Linear mixed model analyses revealed that participants who performed within the 'normal range' at screening on cognitive tasks as measured by CANTAB, continued to perform well at baseline, week 6 and week 12, showing no significant change in their performance. By contrast, participants who performed below the normal range at screening, showed a significant improvement in their test performance across the remainder of the study. When compared in the context of MCCB, those participants who performed a standard deviation (SD) above the MCCB normative mean at screening, were also the participants who performed within the normal range on CANTAB. Approximately 25% of the overall sample were performing within a clinically normal cognitive range at screening.

Conclusions: Substantial variability was evident in cognitive performance among the current sample of patients with schizophrenia. We identified a subsample of patients whose performance fell within a clinically normal range. Cognitive improvement was observed only in those who exhibited a deficit at screening, bringing into question whether the inclusion of unimpaired patients in clinical trials increases the risk of ceiling effects and minimizes chance to see change. Further analyses will determine the interaction between different cognitive trajectories and the treatment arms included in this trial to explore whether there are individuals with a particular cognitive profile who are most likely to respond to treatment. This has potentially important methodological implications in the search to find a drug to treat CIAS.

32.4 A NOVEL TREATMENT FOR COGNITIVE IMPAIRMENT ASSOCIATED WITH SCHIZOPHRENIA BY ENHANCING THE ACTIVITY OF PARVALBUMIN INTERNEURONS

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