Further Evaluation of The Pro-Cognitive Effect of KarXT in Acutely Symptomatic Schizophrenia: Consideration of Cognitive Sub-Domains and Methodological Factors

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Methodological Issue Being Addressed Development of a composite cognitive performance score for treatment studies in schizophrenia appears at first to be straightforward, but there are multiple decisions to be made. Some participants may manifest variable performance before randomization while others may have missing data, requiring decisions about which participants should be included and how much data is required to calculate a valid composite. In the MATRICS process, concepts of what constitutes a composite score have changed over time and some commercially available batteries do not include all MATRICS cognitive domains. Further, many cognitive batteries are quite long. Could a shorter form based on a limited number of tests be as sensitive?

Introduction In a phase II trial, KarXT monotherapy improved composite scores on a cognitive battery (d = .50) in acute inpatients with schizophrenia who had clinically significant cognitive impairment at baseline. The investigational drug's (IDs) pro-cognitive effect was replicated (d = .54) in a larger pooled sample of cognitively impaired participants from two similarly designed phase III trials using a different cognitive battery and composite score. Here, we present further analyses of the phase III data to investigate the potential impact of several methodological factors.

Methods In this post-hoc analysis, data were pooled from two phase III (NCT04659161; NCT04738123) 5-week inpatient trials of ID monotherapy in participants experiencing acute psychosis. A 4-subtest CANTAB battery was administered at baseline, week-3, and week-5 as an exploratory measure. The primary composite score was based on one prespecified index from the immediate verbal memory recall, executive functioning, sustained attention, and short-term visual memory subtests; valid scores were required on >/= ¾ subtests. ID effects for each subtest were evaluated in participants with baseline cognitive impairment (N = 137), defined as performing more than 1 SD below healthy norms at baseline. We also examined the impact of screening to baseline practice effects, using a more stringent composite score (i.e., requiring 4/4 valid subtests), adding cognitive indices, and time-of-day effects.

Results Among cognitively impaired participants, ID (N=71) showed significantly greater improvements than placebo (n = 66) on three of the four subtests, with effect sizes (ds = .41-.50) that approached the magnitude of the ID effect on the primary composite (d = .54). Accounting for practice effects did not impact the magnitude of the IDT effect. Further, using a more

stringent/thorough composite score calculation, adding a processing speed index, and restricting analyses to those who completed baseline and endpoint assessments within a 1-hour time window all increased the magnitude of the ID effect (ds = .61 to .70).

Conclusion The ID appeared to have a general benefit across multiple cognitive domains rather than a domain-specific impact. The ID effect was not impacted by practice effects, which were notably absent in the cognitively impaired participants. Further, the ID effect was enhanced when using more rigorous data quality requirements, incorporating more cognitive subdomains, and accounting for time-of-day effects. These findings highlight several methodological sources of noise that can compromise cognitive data quality and impede treatment signal detection; failure to control for these in future studies may result in missing beneficial interventions.

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