Title: Two definitions of early response as predictors of remission in a phase 3 depression program: informing augmentation trial design

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The Methodological Question Being Addressed: Measures of early symptomatic improvement, their relative predictive power for longer-term remission, and the impact on phasic clinical trial designs.

Introduction (Aims): Increasing evidence suggests that clinical course during the first weeks of antidepressant treatment (ADT) is a significant predictor of response and remission up to 8 weeks later (e.g., Papakostas et al, 2006; Szegedi et al, 2009). These findings are useful supplements to existing treatment algorithms as they offer clinicians more confidence in early switching and augmentation. Furthermore, these findings may impact design for trials that include phasic treatment periods (e.g. augmentation trials, maintenance trials) and a need to enrich the randomized sample with only those subjects who are not already on a response course. The current analysis will examine response data from two phase 3 brexpiprazole augmentation trials in major depressive disorder (MDD), and will aim to extend earlier findings by understanding the extent to which early response predicts remission after a full 14 weeks of ADT treatment, applying two different definitions of early response.

Methods: The POLARIS (NCT01360632) and PYXIS (NCT01360645) trials evaluated adjunctive brexpiprazole vs placebo in subjects with MDD who had demonstrated inadequate response to 8 weeks of lead-in monotherapy ADT. Inadequate responders entered the 6-week randomized brexpiprazole vs placebo period. Responders continued their antidepressant treatment for an additional 6 weeks, for a total of 14 weeks of monotherapy ADT. For the current analysis, both trials were pooled to examine only those patients who received 14 weeks of ADT monotherapy. Response (≥ 50% improvement from baseline in MADRS total score) and remission (MADRS ≤ 10) at 14 weeks were evaluated for 1) all subjects who received 14 weeks of monotherapy ADT; 2) those subjects who showed "early improvement" (EI; as defined by Szegedi et al, ≥ 20% improvement from baseline to Week 2); 3) those subjects who showed "early sustained response" (ESR; as defined by Papakostas et al, ≥ 50% improvement from baseline to Week 2 with no subsequent worsening of symptoms in the 8-week lead-in treatment period).

Results: A total of 882 subjects completed 14 weeks of monotherapy ADT. Of those subjects, 542 (61%) were considered responders and 336 (38%) were in remission at Week 14. Both EI and ESR were significantly associated with full remission at Week 14 (EI: $\chi^2 = 14.24$, $p < 0.001$; ESR: $\chi^2 = 29.23$, $p < 0.001$). Odds ratios for EI and ESR were 1.67 and 4.19, respectively.

Conclusions: The current analysis shows that both early improvement and early sustained response were strongly associated with symptomatic remission after 14 weeks of monotherapy ADT, though early sustained response appears to be the stronger predictor. Additional analyses will further elucidate the predictive power of these early symptomatic improvement markers, by examining both clinician-rated and patient-reported outcome measures. These results suggest that trials for adjunctive therapy that

utilize prospective lead-in should consider the predictive value of early response in defining inadequate response to ADT.

References:

1. Papakostas GI, Perlis RH, Scalia MJ, et al. A meta-analysis of early sustained response rates between antidepressants and placebo for the treatment of major depressive disorder. *Journal of Clinical Psychopharmacology.* 2006; 26: 56-60).
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