A Clinical Trial Inclusion Criteria to Enrich for Patients Presenting with Canonical symptom structure in Bipolar Depression

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What is the Methodological Issue Being Addressed? The methodology introduces the ability to reduce heterogeneity in symptom structure at baseline to improve the measurement certainty of psychiatric symptoms in a clinical trial. The method flips the usual question of “what instrument is best for my study?” to become rather “what symptom presentation is best for my instrument?”

Introduction Clinical drug development in psychiatry is challenging due to heterogeneous patient populations and the uncertainty of measuring neuropsychiatric constructs with symptom rating scales. Here we describe the development and implementation of an enrichment algorithm that identifies canonical versus anomalous symptom presentations, at the individual subject level, based on MADRS ratings obtained at screening and baseline.

Methods Here we describe 1) the development of an algorithm to identify canonical versus anomalous symptom presentations one subject-at-a-time with respect to a four-factor model of MADRS symptoms, using MADRS ratings at screening and baseline, 2) the performance of the algorithm at reducing nondrug-related heterogeneity when applied retrospectively to clinical trials in bipolar depression, and 3) the prospective implementation and performance of the algorithm as an inclusion criteria in a Phase 3 trial of non-racemic amisulpride (SEP-4199) for bipolar depression. Data from 5 randomized, placebo-controlled, phase 3 trials in bipolar I disorder was used (N=2,026 subjects and 15,239 MADRS assessments) retrospectively to develop the algorithm. We developed a novel mathematical formulation we call the variance-covariance difference (VCD) vector to encode individual symptom structure using the 10 items of MADRS from the two sequential assessments. We derived an anomaly score, calculated from each subject’s VCD vector using an isolation forest algorithm to quantify the degree of disparity from the hypothesized canonical item structure. The performance of the method was tested post-hoc with data from a Phase 2 pivotal trial with SEP-4199 and was implemented prospectively a priori in the randomization schema of a Phase 3 pivotal trial.

Results The algorithm reliably identifies a threshold anomaly score above which the psychometric properties of MADRS deteriorate. Cumulative fit indices, as a function of subject’s anomaly score demonstrate that subjects with anomaly scores above 0.425 deteriorate the fit to the 4-factor model. Likewise, in the prospective use of this threshold in (the IVRS of) a Phase 3 study, the enrolled subjects’ canonical symptom structure also produces excellent fits of the 4-factor model, while the subjects with anomalous symptom structure excluded from randomization also do not. Consistent with increasing the certainty of MADRS ratings, subjects with a canonical symptom

structure at baseline demonstrated greater effect sizes post-baseline in a phase 2 placebo-controlled trial of non-racemic amisulpride (SEP-4199) for bipolar depression, analyzed retrospectively. The magnitude of placebo change is -14.3 points from baseline. As previously reported the effect size in the ITT population is statistically significant but with small effect sizes (0.34 and 0.31 for the active dose levels versus placebo in total score change from baseline at Week 6). Here we report that among the subjects who present at baseline with canonical symptom structure, there is less placebo change and greater effect size (0.58 and 0.44).

Conclusion The methodology enhances the analysis and understanding of symptom structures in clinical drug development for psychiatry, particularly within the context of bipolar depression. Our analyses show that the developed algorithm can reduce the symptom structure heterogeneity at baseline and thus improve the measurement certainty of psychiatric symptoms in clinical trials. This novel enrichment method has been prospectively implemented in a Phase 3 clinical study of SEP-4199 and is consistent with regulatory guidelines aimed at increasing the statistical power and lowering patient-burden in clinical trials.

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