Signal Detection and Diagnostic Uncertainty in Bipolar Depression Clinical Trials: Drug Response vs. Placebo Response

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SUBMISSION DETAILS

What is the Methodological Question Being Addressed? Does enrollment of subjects with low diagnostic confidence contribute to poor signal detention?

Introduction Eligibility criteria for clinical trials testing treatments for subjects with major depressive episodes typically require that subjects meet both the DSM diagnostic criteria for MDE and exceed a threshold score on a depression severity scale such as the Hamilton depression rating scale (HAM-D) or the Montgomery Asberg depression rating scale (MADRS).
These diagnostic and severity assessment techniques should produce congruent results. Notably, the 10 items of the MADRS roughly map into eight of the DSM-5's nine criteria for Major Depressive Episode. All MADRS items are scored a 0 to 6 scale. An item scored ≥ 4 represent clear-cut clinically significant pathology. The DSM-5 MDE criteria requires ≥ 5 symptoms most of the day nearly every day. Since the MADRS only covers 8 of the 9 criteria, we expect that subjects with a confident diagnosis of MDE will have a confirmatory MADRS with least four items scored ≥ 4 ,

Methods A post hoc analysis was conducted using data from a double blind RCT in which subjects meeting DSM 5 criteria for with Bipolar depression were randomized to receive monotherapy with lurasidone 20-60 mg/day (N=161), lurasidone 80-120 mg/day (N=162) or placebo (N=162). The primary and key secondary study endpoints in that study were changes from baseline to week 6 on MADRS and Clinical Global Impression Bipolar Version, Severity of Illness (CGI-BP-S-depression), respectively.

We defined high diagnostic confidence as scoring in the clinically significant range on at least 4 MADRS items at both the screening and pre-treatment baseline visits. Low diagnostic confidence was defined as not meeting the high confidence criteria.

Results A total of 320 (66%) of patients meets the criteria for high diagnostic confidence.
High diagnostic confidence was associated with a significantly higher drug-placebo difference. in MADRS total change score at week 6 ($P<0.05$, statistical interaction test). We found a placebo-corrected effect size of 0.64 (lurasidone -16.15 vs. placebo -10.34, n=320) in the high diagnostic confidence group compared to 0.17 in the low confidence group (lurasidone -13.66 vs. placebo -12.13, n=165).
Furthermore, the placebo-corrected effect size for improvement of CGI-BP-S (depression) from baseline to week 6 endpoint was 0.72 (-1.79 for Active vs.- 0.99 in the high diagnostic confidence group compared to 0.17 in the low confidence group (-1.71 for Active vs. -1.52 for placebo), indicating significant moderating effect by diagnostic confidence ($P < 0.05$, diagnostic confidence by treatment interaction effect at week 6).

Conclusion This post hoc analysis suggests that limiting enrollment to subjects with high diagnostic confidence can increase the detectable treatment effect size. We observed subjects with high diagnostic confidence have both increased response to active drug, and a reduced response to placebo. Our findings have implications for patient selection to improve the likelihood of detecting a treatment signal in bipolar depression trials and perhaps other indications.

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Keywords

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Guidelines I have read and understand the Poster Guidelines

Disclosures if applicable Gary Sachs is a Full Time Employee of Signant Health
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