Logical inconsistencies among PANSS items are associated with greater placebo response in acute schizophrenia trials – a post-hoc analysis

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Methodological Question Being Addressed: Are there markers of rater scoring performance during screening that predict placebo response in clinical trials?

Introduction: We have previously identified (Kott & Daniel, 2016) a significant association between the presence of post-baseline logical inconsistencies in the PANSS with the presence of the same inconsistencies at screening and baseline. In the current post-hoc analysis of unblinded data we address the question whether the presence of PANSS logical inconsistencies has an effect on the magnitude of placebo response.

Methods: Placebo arm data combined from 2 identically designed phase 3, randomized, placebo controlled, acute schizophrenia trials were used to model the placebo response. We developed a battery of PANSS logical inconsistencies (implausible PANSS item scores given responses on other items) and identified all visits where at least one such inconsistency occurred. Using Fisher's exact test we identified sites that had an outlying number of PANSS inconsistencies (outlying sites) and using MMRM modelling we assessed the difference in placebo response between the outlying and non-outlying sites from baseline to end of treatment.

Results: Data from 1076 subjects (358 on placebo) were analyzed. We have identified 25 out of 123 sites to be significantly different compared to the study in the number of PANSS inconsistent ratings. The least square mean placebo change from baseline at the sites identified as outlying was -20.0 (SE = 1.58) points while at the non-outlying sites the LSmean change was -14.81(SE = 0.90), the difference between these 2 groups was -5.12 (p=0.0049).

Discussion: In this post-hoc analysis sites with outlying numbers of PANSS logical inconsistencies had a significantly higher response to placebo than non-outlying sites. This finding is to an extent surprising as the inconsistencies themselves are unlikely to cause such a difference in the response to placebo. We therefore hypothesize that the presence of PANSS logical inconsistencies in the data may be indicative of other, likely more serious issues that ultimately translate in the increased response to placebo. While more research is needed to understand these underlying problems better, the fact that the post-baseline inconsistencies are highly associated with the presence of inconsistencies in the screening period allows sponsors to identify sites at the greatest risk early and to intervene in a timely fashion before too many subjects get randomized into the study. It as well allows implementation of intelligent eCOA solutions that would prevent randomization of affected subjects before the root cause of the inconsistencies is elicited.

References:

Kott, Alan; Daniel, David G. (2016): Early Indicators of Poor Data Quality in Schizophrenia Clinical Trials. Poster presentation at the 2016 International Society for CNS Clinical Trials and Methodology (ISCTM) Spring Conference, 16-18 February, Washington, D.C., USA.