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

Kott, Alan [1]; Lee, Jennifer [2]; Forbes, Andy [2]; Pfister, Stephanie [2]; Ouyang, John [2]; Wang, Xingmei [1]; Daniel, David [1]

[1] Bracket Global, LLC [2] Otsuka Pharmaceutical Development & Commercialization, Inc.

METHODOLOGICAL QUESTION

- Are there markers of rater scoring performance during screening that predict placebo response in clinical trials?

INTRODUCTION

- The presence of PANSS logical inconsistencies during the screening period is associated with an increase in the odds and the incidence rate of the same PANSS logical inconsistencies after randomization (approximately 10 and 7.7 times, respectively (Daniel & Kott, 2016; Kott & Daniel, 2016))
- In the current post-hoc analysis of unblinded data we address the question whether the presence of PANSS logical inconsistencies is associated with a greater magnitude of placebo response

METHODS

- Intent-to-treat data was obtained from two identically designed, phase 3, multicenter, randomized, double-blind, placebo-controlled trials with brexpiprazole in the treatment of adults with acute schizophrenia
- We developed a battery of PANSS logical inconsistencies (implausible PANSS item scores given responses on other items)(Table 1) and identified all visits where at least one such inconsistency occurred

Table 1. List of within PANSS item discrepancies

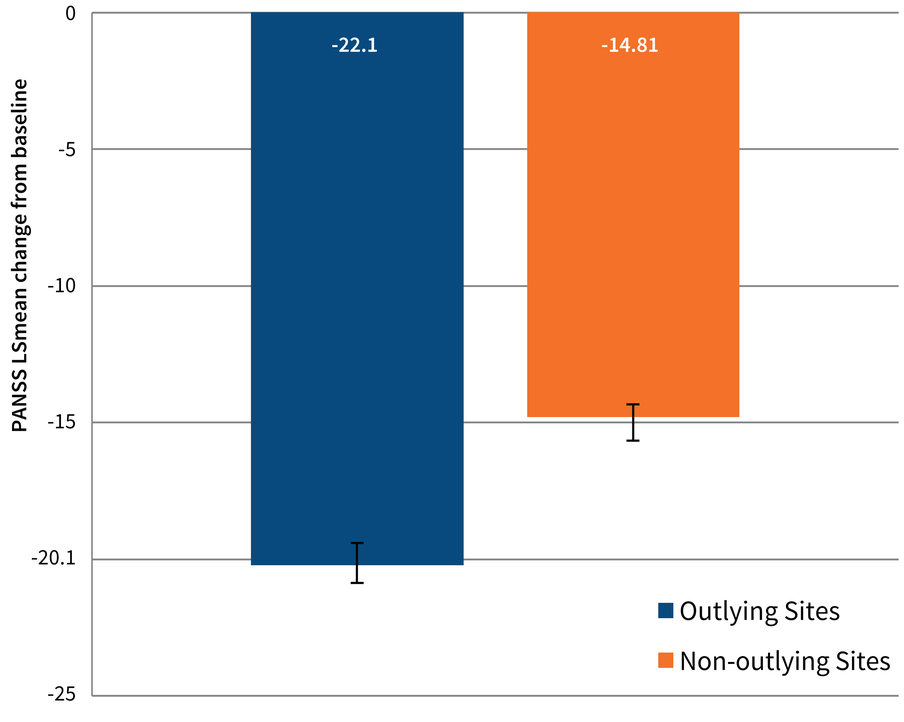
P1 (Delusions) vs. P3 (Hallucinatory behavior)	P1 (Delusions) vs. G1 (Somatic concern)	P1 (Delusions) vs. G9 (Lack of judgment and insight)
P1 (Delusions) vs. P5 (Grandiosity)	P1 (Delusions) vs. G3 (Guilt feelings)	G2 (Anxiety) vs. G12 (Tension)
P1 (Delusions) vs. P6 (Suspiciousness/persecution)	P1 (Delusions) vs. G9 (Unusual thought content)	P4 (Excitement) vs. G7 (Motor retardation)

- Using Fisher's exact test we identified 2 groups of sites: Outlying sites (sites with statistically ($p<=.05$) outlying numbers of PANSS inconsistencies compared to the remaining study data) and Non-outlying sites
- The LSmean change from baseline was derived from a mixed model repeated measures (MMRM) analysis with fixed effect of treatment, visit, treatment visit interaction, baseline value, and baseline visit interaction as covariate for each treatment arm and site group
- Using mixed model repeated measures (MMRM) analysis with fixed effect of treatment, visit, treatment visit interaction, baseline value, subgroup treatment visit three-way interaction, subgroup treatment visit two-way interactions and baseline visit interaction as covariate, and with a compound-symmetry variance-covariance matrix structure the LSmean difference between the outlying and non-outlying sites for placebo arm was computed

RESULTS

- Data coming from 1076 subjects (358 on placebo) were analysed
- Using the Fisher's exact test we identified 25 sites out of 123 sites (20.3%) to be significantly different compared to the study in the number of PANSS inconsistent ratings
- The LSmean change at week 6 for the placebo treatment arm was estimated to be -20.09 (SE=1.58) points for the outlying-sites and -14.81(SE=0.90) for the non-outlying sites, respectively (Figure 1)
- The LSmean difference in the placebo treatment arm between the 2 groups of sites was estimated to be -5.12 points at week 6 (p=0.0049) favouring the outlying sites

Figure 1: Placebo LSmean change from baseline at week 6 for Outlying and Non-outlying sites on within PANSS inconsistencies.
N = 358 subjects on placebo



DISCUSSION

- In this post-hoc analysis sites with outlying number of within 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 hypothesize that the presence of these inconsistencies is indicative of other, likely more serious issues (lack of scale or indication knowledge, data tampering, data manipulation, …) that ultimately translate in the increased response to placebo
- Additional analyses are necessary to understand the relationship between the increased response to placebo and the presence of PANSS logical inconsistencies
- Prior research indicates strong association between the presence of post-baseline PANSS inconsistencies with the presence of the same inconsistencies in the screening period
- This allows sponsors to identify sites at the greatest risk early and to intervene in a timely fashion, preferably before too many subjects get randomized into the study
- Intelligent eCOA solutions can be used to prevent randomization of affected subjects before root cause of the inconsistencies is elicited and rectified

REFERENCES

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