Erratic Changes in the PANSS are Associated with Greater Placebo Response in a Schizophrenia Negative Symptom Trial – A Post hoc Analysis

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METHODOLOGICAL QUESTION BEING ADDRESSED

- Is the presence of erratic changes in the Marder Negative Factor score associated with placebo response in a schizophrenia negative symptom trial?

INTRODUCTION

- Erratic changes represent unusually large changes in symptom severity across consecutive visits in opposite directions, e.g. large improvement is followed by large worsening
- Erratic changes may be a sign of inconsistent interview technique or poor rating quality
- In the current post-hoc analysis of a single clinical trial in schizophrenia focused on negative symptoms we investigated whether erratic changes in the PANSS Marder negative factor score were associated with the magnitude of placebo response

METHODS

- Placebo arm data from a phase 3, randomized, placebo controlled study in stable patients with persistent, predominant negative symptoms of schizophrenia were used to model the placebo response
- Changes were defined as erratic as follows:
  - The PANSS Marder negative factor score changed by at least 20% from visit to visit
  - These changes occurred at consecutive visits and were in opposite directions
- Using MMRM modelling we assessed the PANSS Marder negative factor score difference in placebo response between subjects with and subjects without erratic changes present

RESULTS

- Data from 512 subjects (162 on placebo) were analyzed
- Erratic changes were identified in 73 subjects (20 on placebo)
- The least square mean placebo change from baseline at the end of treatment in these subjects was -9.13 (SE = 1.03) points vs. -6.56 (SE=0.39) in the non-affected subjects, the difference between these 2 groups statistically significantly different (-2.56, $p < 0.01$) (Figure 1)

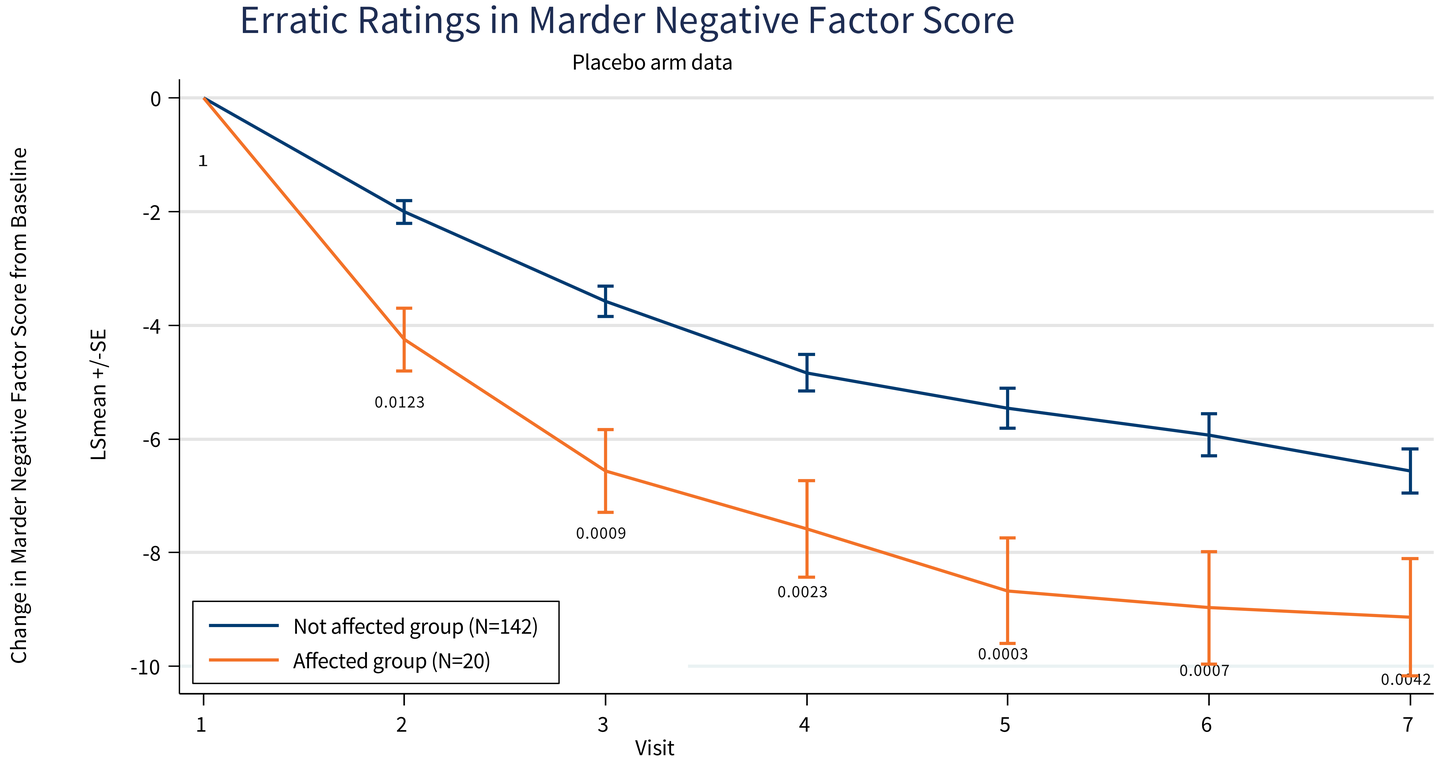

Figure 1: Effect of Presence of Erratic Ratings on Change in Marder Negative Factor Score from Baseline in the Placebo Arm Data.

DISCUSSION

- In this post-hoc analysis subjects with the presence of erratic changes in the Marder negative factor had a significantly higher response to placebo than non-affected subjects
- We used a rather conservative definition of erratic changes where we required the change to be of at least 20% of the Marder negative factor score and it is therefore surprising that there were more than 12% of subjects affected by erratic changes in this negative symptom trial
- Erratic changes in symptom severity may be caused by true symptom severity variations but this is relatively unusual in the intended trial population
- Alternatively, data quality issues such as changes in rater, poor interviewing technique, inconsistent application of scale rules or other aberrant measurement practices at play
- We suggest that erratic ratings should be investigated by review of recorded interviews or worksheets, if available and remediated if appropriate
- Electronic data capture (eCOA) provides a mechanism for rapid assessment and remediation of data quality findings
- The use of centralized, well calibrated raters represents another possible approach to increase data quality in clinical trials
- Replication and further research is needed to better understand the factors affecting the presence of erratic changes and their relationship to placebo response

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