

The effect of accumulation of erratic changes in PANSS Negative Factor at research sites on response to placebo and drug placebo separation.

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METHODOLOGICAL QUESTION

Does an increased presence of erratic ratings in the PANSS at sites affect response to placebo and drug placebo difference in negative symptom schizophrenia clinical trials?

INTRODUCTION

- We have previously reported increased response to placebo in subjects with an erratic pattern of symptom changes (Kott, Umbricht, Wang, Daniel; 2017)
- Erratic changes represent unusually large changes in ratings of symptom severity across consecutive visits in opposite directions and may be an indicator of poor rating quality
- We investigated the question if a high rate of erratic ratings at certain sites shows an association with the magnitude of placebo response and drug placebo separation at these sites compared to sites with no signs of unusually high erratic ratings
- This post-hoc analysis was performed in unblinded data originating from three schizophrenia clinical trials of bitopertin focusing on the treatment of negative symptoms

METHODS

- Data from three phase 3, randomized, placebo controlled, negative symptom schizophrenia trial of bitopertin were used to model the placebo response and drug placebo difference
 - Data were analyzed for each protocol separately
- We defined changes as erratic if the PANSS Marder negative factor score changed by at least 20% from visit to visit across a minimum of three consecutive visits and the changes occurred in opposite directions
- We identified sites with a high rate of erratic ratings as those sites where the presence of erratic ratings was statistically significantly above the study mean
- Placebo response and drug placebo difference for each subgroup was derived from a 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 covariates, and with a AR(1) matrix structure. LSMEAN difference between Subgroups for each dose at each visit was computed

RESULTS

- Data from all 3 protocols totaling 1,794 subjects (598 on placebo; 603 on low dose and 593 on high dose of active medication) were analyzed
- Using Fisher's exact test we identified 19/92(21%), 24/96(25%) and 25/105(24%) sites as having significantly higher occurrence of erratic ratings
- Across the 3 protocols at all timepoints the placebo response was significantly higher at the affected than the not affected sites with the exception of week 4 for protocol WN25309 and week 24 for protocol NN25310 where the placebo response at the affected sites was increased at a non-significant level (figure 1)
- At week 24 there were no differences in the drug placebo separation between the two groups in any of the three studies (figure2)

DISCUSSION

- In this post-hoc analysis of unblinded data from bitopertin phase 3 trials with negative results, sites with significantly increased presence of erratic changes in the Marder negative factor had a significantly higher response to placebo than non-affected sites
- While the increased response to placebo at the affected sites did not translate into statistically significant differences in drug placebo separation between the groups in these trials, the occurrence of erratic ratings should still be cause for great concern during the conduct of a study as they most likely represent poor quality of ratings and can increase placebo response
- Accumulated presence of erratic ratings at a site should be investigated further by available means of data quality assurance methodologies, such as review of audio/video recorded interviews, worksheet reviews or data analytics, and remediated where appropriate

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

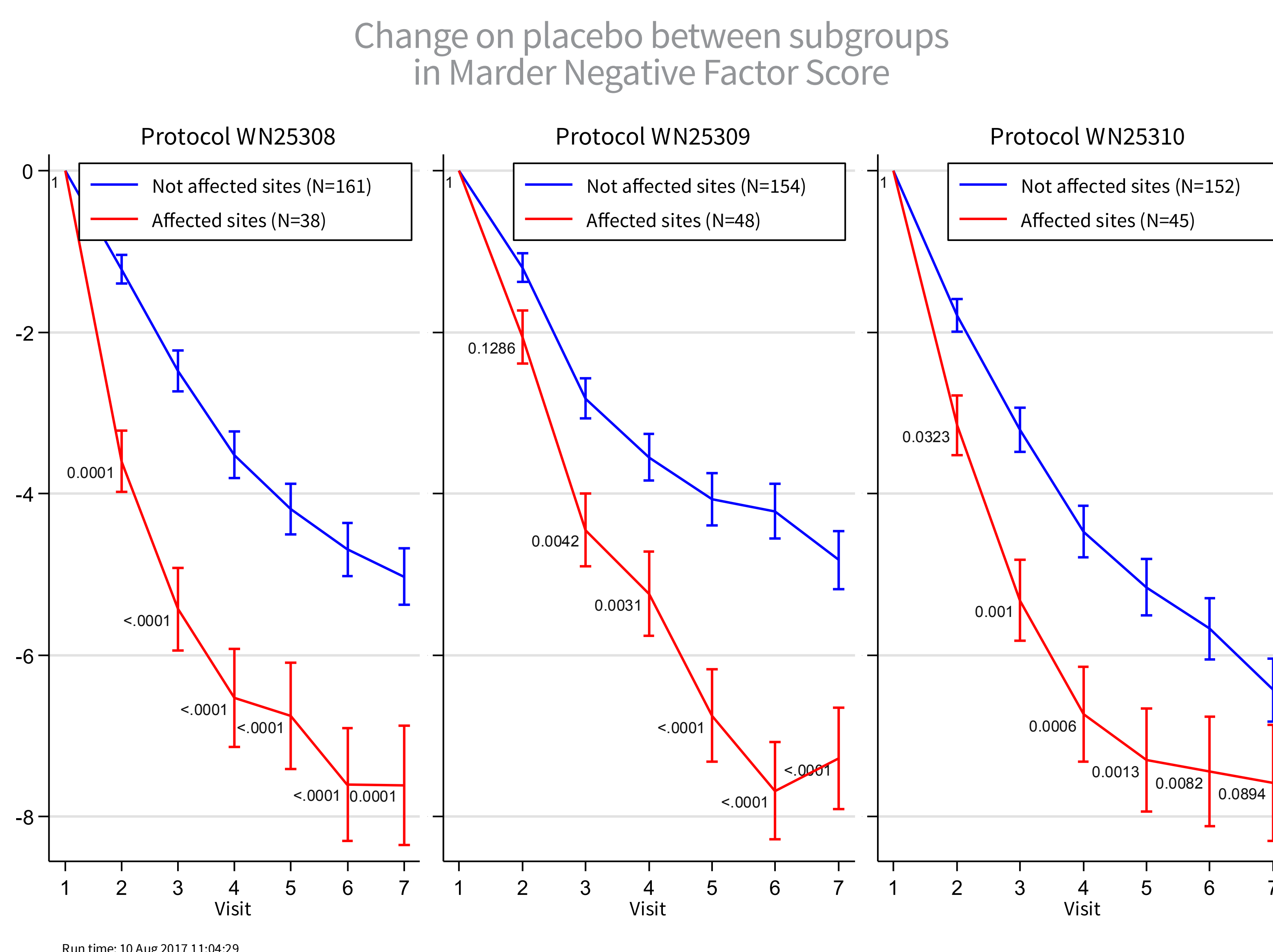
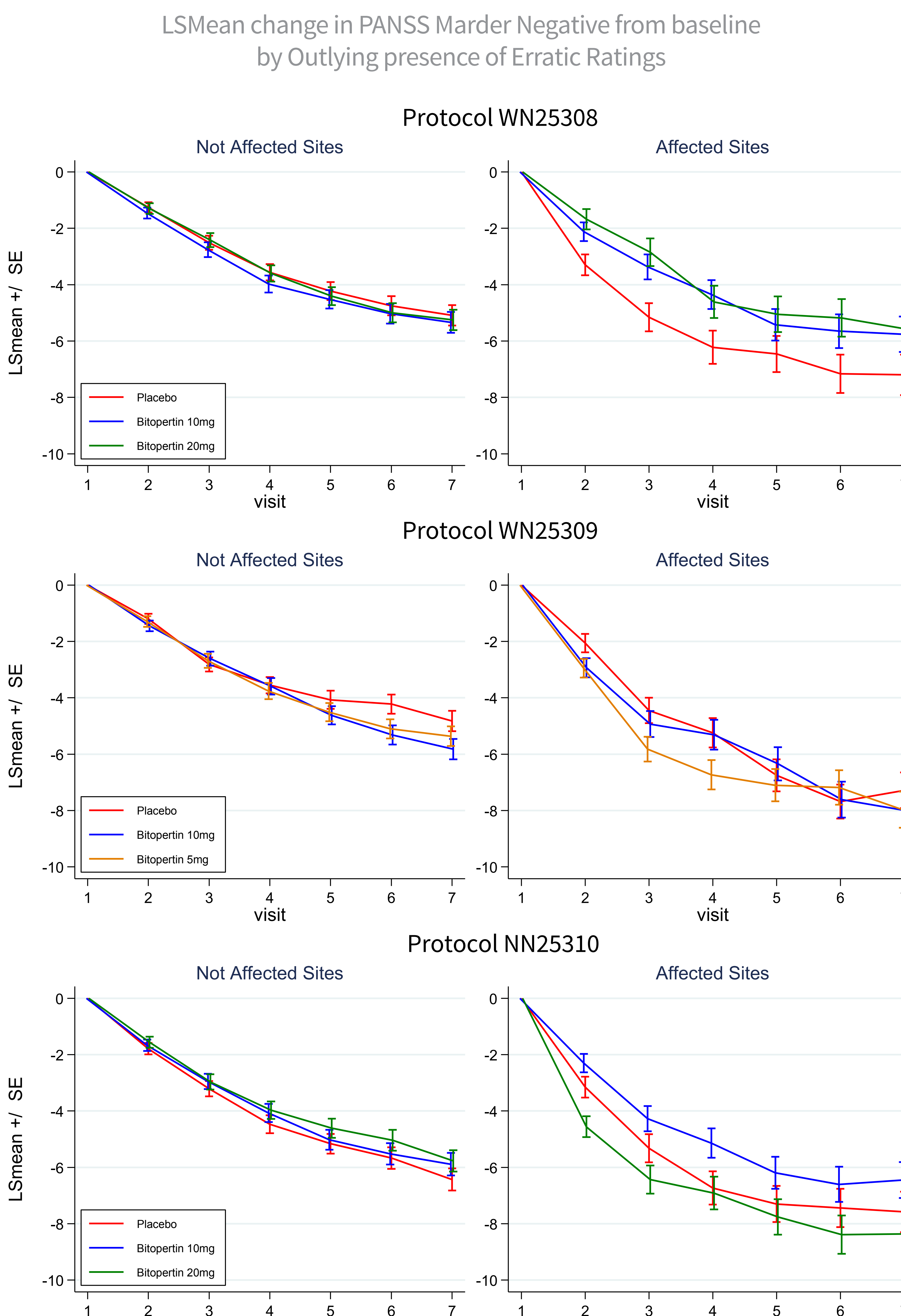


Figure 2: LS Mean change from baseline in Marder Negative Factor score by Treatment and presence of Erratic Ratings subgroup



REFERENCES

- Kott, Alan; Umbricht, Daniel; Wang, Xingmei; Daniel, David (2017): Erratic Changes in the PANSS are Associated with Greater Placebo Response in a Schizophrenia Negative Symptom Trial - A Post hoc Analysis. Poster presentation at the 2017 International Society for CNS Clinical Trials and Methodology (ISCTM) 13th Annual Scientific Meeting, 21-23 February 2017 - The Fairmont, Washington DC, USA.