

Placebo Response Assessed by Site and Remote Blinded Centralized Raters in a GAD Trial

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ABSTRACT

Introduction: High placebo response in anxiety studies contributes to a 50% study failure rate. Remote centralized raters offer a solution that may address several causes of failed clinical trials. We compared the rate of placebo response assessed by site vs. central raters in the same group of subjects.

Methods: This double-blind, placebo-controlled, multi-center study examined the efficacy and safety of two doses of an experimental compound to treat Generalized Anxiety Disorder. The primary outcome measure was the Hamilton Anxiety Scale (HAM-A). Site raters assessed subjects 6 times over an 8 week period. Remote centralized raters independently rated the same subjects on the HAM-A at baseline and week 6. 119 site raters were trained and qualified by a leading rater training company at the investigator meeting. 22 remote centralized raters were trained and calibrated by MedAvante, and maintained high interrater reliability throughout the study with quarterly group calibrations and regular observations by trainers.

Results: Site raters admitted 122 subjects to the placebo arm of the study. At baseline, remote centralized raters scored 59 (48%) of these admitted subjects at or above the HAM-A entry criterion and rated 63 (52%) of the admitted subjects below the entry criterion. At baseline, site raters' mean HAM-A score was 24.0 (SD= 3.3; N=122), compared to 19.8 (SD=6.0; N=122) for remote centralized raters. In addition, site raters' mean scores were higher than remote raters' on all of the individual HAM-A items at baseline. At endpoint, however, site raters' scores were similar to remote raters' (14.6 vs. 14.0). Exploratory analyses found the mean placebo change by site raters was -9.3. This was significantly higher than the -5.9 point mean placebo change as measured by the remote raters.

Discussion: Blinded remote raters showed a 36% reduction in placebo response compared to site raters. This may be due to the blinded remote ratings being independent from the study enrollment process. A decrease in placebo response may reduce the risk of study failure in clinical trials. There was no active comparator, and neither method detected a significant difference between drug and placebo.

Disclosures: Williams, JBW, Detke, M and Giller, E are employed by MedAvante. Kobak, K is a consultant for MedAvante. Dunn, J was formerly employed by Sepracor. Curry, L and Wilson, P are employed by Sepracor.

INTRODUCTION

The placebo response rate in anxiety disorder studies is growing, leading to an increasing concern regarding the rate of failed trials (Khan, 2005).

Possible reasons for placebo response rate include:

- Variability in administration of primary outcome measure across sites and raters
- Poor interrater reliability (ICC) of scale administration
- Regression to the mean where measurement error lowers the correlation between similar scores
- Possible biases stemming from enrollment pressure, therapeutic alliances, and expectation of improvement

This was a double-blind randomized multi-center study of the efficacy and safety of an experimental compound to treat Generalized Anxiety Disorder (GAD), using site and remote centralized raters. There was no active comparator, and neither method detected a significant difference between drug and placebo.

Two rating methods were compared to assess the rate of placebo response: site rater administration versus remote centralized rater administration of the primary outcome measure.

METHODS

Subject selection by Site Raters:

- 122 subjects were admitted to the placebo arm of the study, determined to have GAD by site raters using the MINI
- **Severity inclusion criteria:** Screen and baseline HAM-A total score of ≥ 20 AND a score of ≥ 2 on HAM-A items 1 (anxious mood) and 2 (tension)

Study Design:

- No active comparator
- Primary outcome measure: HAM-A (site-rater administered)
- Two rating methods examined: site raters versus remote centralized raters

RATERS:

Site Raters:

- 119 site raters at 45 sites were trained and qualified by a leading rater training company based on lecture and scoring of a patient video at an Investigator Meeting
- Assessed subjects 6 times over 8 weeks face-to-face

Remote Centralized Raters:

- 22 remote centralized raters were trained and calibrated by MedAvante
- Assessed subjects at baseline (after site rater's assessment) and week 6 (counterbalanced administration with site raters)
- Blind to protocol requirements, visit number, and prior knowledge of subject
- All assessments done by telephone

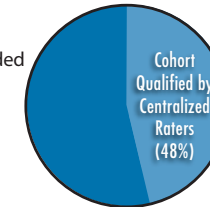
RESULTS

1. Subject Selection (using baseline HAM-A scores)

Site raters admitted 122 subjects to the placebo arm of the study.

Remote centralized raters would have admitted only 59 (48%) and excluded 63 (52%) of the subjects in the placebo arm.

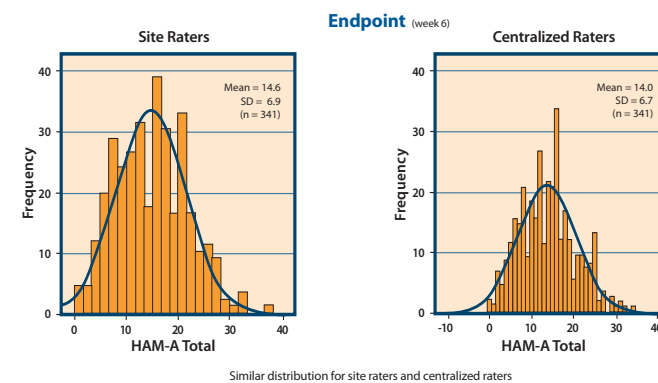
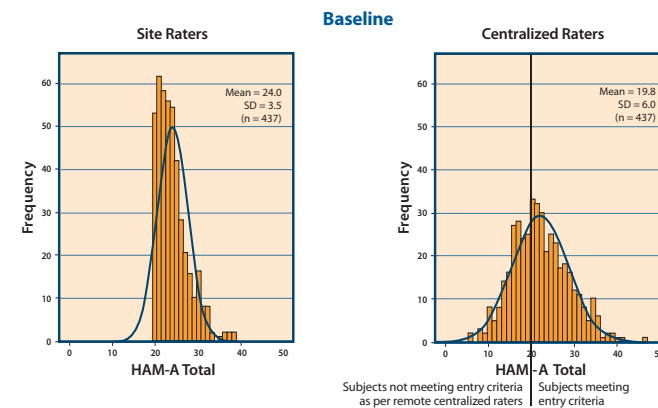
Site Rater Qualified Subjects
(n = 122)



2. HAM-A Frequency Distribution for Subjects Selected by Site Ratings

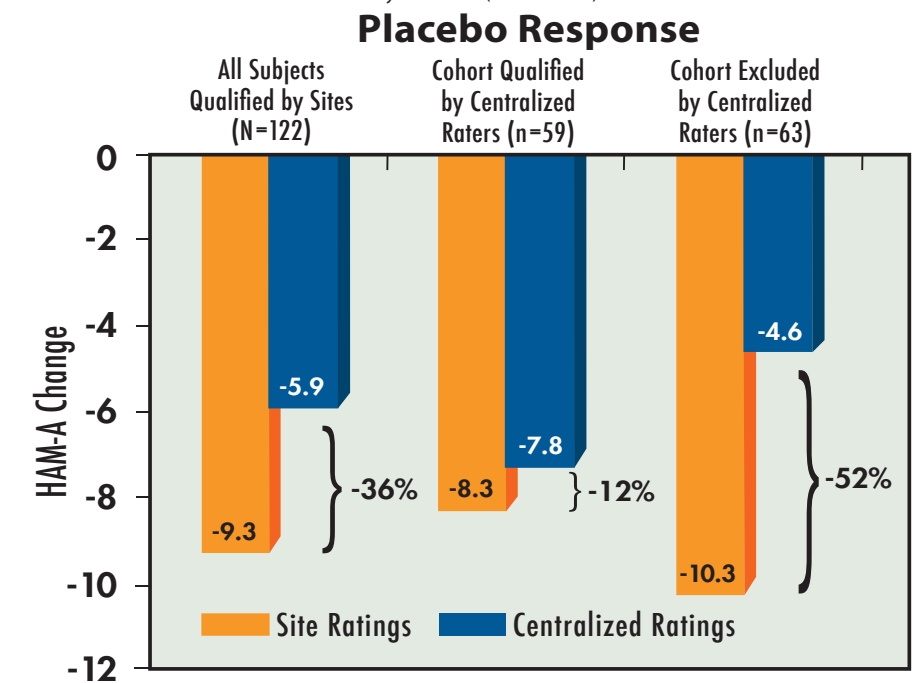
At baseline, site raters' scores were truncated at the inclusion score of 20, as expected. Remote centralized raters' baseline scores were normally distributed, even though site raters scored all subjects as having a HAM-A ≥ 20 .

At endpoint, site raters' and remote centralized raters' scores were similarly distributed.



3. Mean Change from Baseline to Endpoint in HAM-A Total Score for Subjects on Placebo

- Exploratory analyses found placebo response in the placebo group admitted by site raters to be -9.3. Placebo response was -5.9, 36% lower for these same subjects when assessed by remote centralized raters.
- In subjects excluded by the remote centralized raters placebo response measured by remote centralized raters was less than half that measured by site raters (-4.6 vs. -10.3).



CONCLUSION

Placebo Response

- When evaluating All Subjects, enrollment determined by the sites, placebo response was 36% lower in the change scores (Endpoint-Baseline) calculated from the blinded centralized ratings than in the change scores calculated from the site ratings. This reduction in placebo response traces primarily to the cohort of subjects who would have been excluded by the centralized raters as too mildly anxious. In this cohort alone, of more mildly anxious subjects, placebo response was 52% lower in the change scores calculated from the blinded centralized ratings vs. site ratings.

Risk of Study Failure

- Findings suggest that remote centralized raters may reduce a primary risk of study failure in clinical trials by decreasing placebo response as a result of their blinded baseline scoring.

References

Khan A, Kolts RL, Rapaport MH, Krishnan KR, Brodhead AE, Browns WA. Magnitude of placebo response and drug-placebo differences a cross psychiatric disorders. Psychol Med. 2005;35(5):743-9

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