



DO ELIGIBILITY CRITERIA MATTER? VIEW FROM A 3RD BLIND EYE

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Introduction

Concern over high failure rates in CNS studies fuels a search for better solutions. Computer-administered assessments offer opportunities to collect data consistently across global study sites and may provide a useful standard for exploring hypotheses regarding the performance of studies and clinical trial sites.

Methods

Computer-administered YMRS assessments (YMRS_{Comp}) were added to a double-blind protocol investigating low (MS+ZLo) and higher doses of ziprasidone (MS+ZHi) vs. placebo (MS+PBO) as an adjunct to mood stabilizer (MS = lithium or valproate) treatment for manic and mixed episodes. The primary outcome variable in this protocol was change from baseline to endpoint YMRS score based on the site-based rater's (SBR) YMRS scores. The analysis plan called for comparison SBR versus computer ratings overall and a comparison of subgroups defined by computer determination of key eligibility criteria. (E.g., at screen and baseline subjects meets DSM IV criteria for a manic or mixed episode, YMRS ≤ 18 and YMRS change from Screen to baseline < 25%) The diagnosis of acute mania or mixed episode was considered valid if ≤ 3 items on the YMRS_{Comp} were of clinically significant severity (defined as a score of ≤ 5 on items 5, 6, 8, and 9 or score ≤ 3 on other YMRS items.) The analysis plan called for one way ANOVA to compare the three treatment groups for both SBR assessments and computer assessments overall and for comparisons of subgroups defined by the computer assessment of key eligibility criteria.

Results

Of 505 enrolled subjects with ≤ 1 post-randomization assessment, <37% met the protocol eligibility requirements based on the computer assessments. No statistically significant differences were found between MS+ZLo or MS+ZHi and MS+PBO based on YMRS_{SBR} or YMRS_{Comp}. A numerically larger change from baseline to day 21 (LOCF) was seen among subjects with a valid diagnosis (MS+ZLo vs MS+PBO = -3.2, MS+ZHi vs MS+PBO = -1.6) compared to those without a valid diagnosis. (MS+ZLo vs MS+PBO = +0.3, MS+ZHi vs MS+PBO = +1.7)

Conclusions

The failure to demonstrate efficacy of adjunctive ziprasidone for acute mania is surprising given its proven efficacy as monotherapy. Several issues may contribute to the lack of observed efficacy. The computer assessment data suggests the study was impacted by enrollment of a large number of subjects that, based on computer assessments, did not meet the protocol eligibility requirements. Less than 32% of the enrolled sample met the protocol specified entry criteria. The results show numerically greater separation for MS+ZLo subjects meeting each eligibility requirement than those considered ineligible by the computer assessments. (Figures 1, 2)

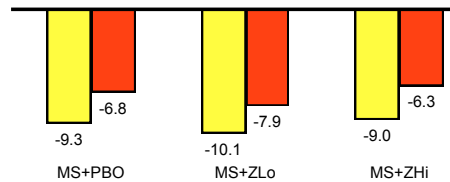
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*Gary S Sachs, Daniel DeBonis, Suzanne Edman, Claudia F Baldassano, Bryce Kasuba, Louisa Sylvia, and Eben Goodman are employees or contractors of CRS. Douglas Vanderburg is an employee of Pfizer.

Results (con't.)

■ SBR ■ Computer ■ Computer Change (LOCF)

Figure 1: Change from Baseline-LOCF, all subjects (n=505)



Impact of eligibility criteria based on computer assessments:

Figure 2: Comparison of LOCF SBR-administered YMRS change scores for all subjects.

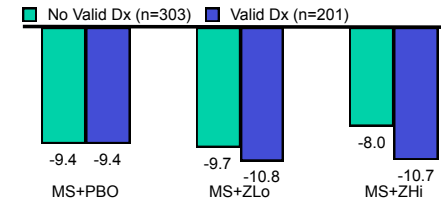
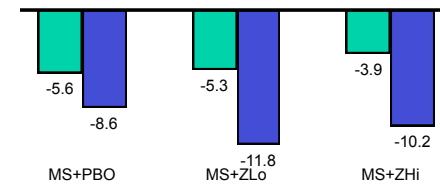


Figure 3: Comparison of LOCF computer-administered YMRS change scores for all subjects.



Baseline-LOCF change scores based on computer baseline total score cutoff:

Figure 4: Computer BL ≥ 18 (n=442)

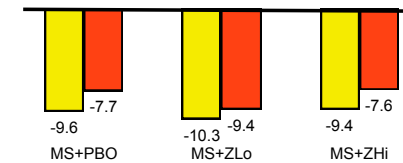


Figure 5: Computer BL < 18 (n=63)

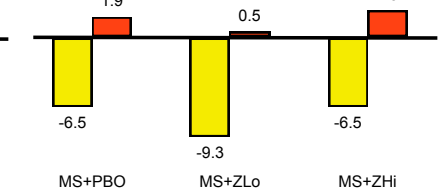


Figure 6: Meets DSM criteria for Acute manic or mixed episodes and YMRS ≥ 18 at Screen and Baseline (n=200)

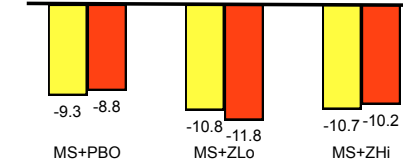


Figure 7: Does not meet DSM criteria for Acute manic or mixed episodes and/or YMRS < 18 at Screen or Baseline (n=304)

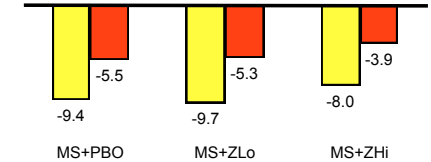


Figure 8: Valid Diagnosis and Better Quality Ratings

