

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-711

STATISTICAL REVIEW(S)

Statistical Secondary Review

NDA# 20-711

Drug name: Wellbutrin/Zyban (Bupropion Hydrochloride) SR

Applicant: Glaxo Wellcome Inc.

Indication: Smoking cessation

Documents reviewed: Medical review by Chang Qing Li, MD, MSHA, DrPH

Reviewer: Z. Jonathan Ma, Ph.D., HFD-720

Date of Review: 29 April 1997

Project manager: Bonnie McNeal

The original NDA submission contains three controlled clinical trials: Study 401, Study 402 and Study 403 to investigate the safety and efficacy of Wellbutrin SR. I have finished a joint review for these studies with the medical officer Dr. Celia Winchell recommending an approval in November, 1996. Now, the sponsor submitted the results from a new trial: Study 405, which finished late, and would like to use some of the results in their labeling. Dr. Chang Qing Li has done a medical review and addressed most of the statistical issues.

This statistical secondary review focuses on the efficacy issues addressed in the medical officer's review for Study 405, titled: A Multicenter Evaluation of Wellbutrin (Bupropion Hydrochloride) Sustained Release, Habitrol (Nicotine Transdermal System), and Combination Wellbutrin SR/Habitrol Treatment Versus Placebo as Aids to Smoking Cessation.

Design Summary

This was a multicenter, double-blind, randomized, parallel-group trial. The objective was to investigate the safety and efficacy of Wellbutrin SR 300 mg/day and its combination with Habitrol 21 mg/day patch in a factorial design.

Out of 1,182 screened subjects, 893 of them were randomized into four treatment groups: PBO (160), WB SR (244), HAB (244), and WB SR/HAB (245). The sponsor used intent-to-treat analysis for the efficacy evaluation, which is appropriate.

Subjects baseline data looked quite similar across the four treatment groups with respect to demographic variables such as age, sex, race, education etc, and other variables such as smoking patterns, baseline cotinine level, and depression history, etc. It is, therefore, unlikely that these baseline characteristics would contribute to the difference in the outcomes.

Efficacy Summary

The primary efficacy endpoint was the 4-week (Day 22 through Day 49) continuous quit rate, which was 23.1% for PBO, 49.2% for WB SR, 36.1% for HAB and 57.6% for WB SR/HAB. Pairwise comparisons showed that the treatment groups are all statistically significantly different from the PBO group, and WB SR/HAB and WB SR groups are statistically significantly different from HAB group. The p-values for these comparisons are quite small

($p < 0.01$ or $p < 0.001$). Therefore, the results may be considered significant despite the multiple tests.

The 4-week quit rate was also analyzed by gender, age, race and history of depression. WB SR group had a higher quit rate in the older patients (67% for age > 60 vs. 48% for age < 60). Otherwise, all subgroups did not show much difference in the 4-week quit rate.

Craving and Withdrawal Symptoms

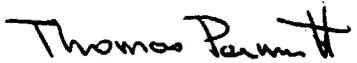
The change in craving scores for WB SR 300 mg/day tended to be smaller than the PBO, but did not reach statistical significance for this difference, again indicating that efficacy of WB SR may not be entirely explained by the reduction of craving (which is a similar result to the one in Study 403). The analyses of the withdrawal symptom scores, however, showed a different story from the one in Study 403 where almost no symptom scores were in favor of the WB treatment groups. In this study, statistically significant differences ($p < 0.05$) in favor of the treatment groups (WB SR, HAB, or WB SR/HAB) over the PBO group were seen in six out of the eight symptom scores and in the composite score. Especially, four of symptom scores and the composite score reached the significance in most of the weeks from Week 2 through Week 10, as shown on page 19 of the medical officer's review.

Conclusions

Study 405 showed that WB SR 300 mg/day it alone or in combination with Habitrol patch may provide an aid for smoking cessation. It seems that WB SR may not significantly reduce craving for smokers, but may effectively reduce most of the withdrawal symptoms.

The statistical issues in this medical review are appropriately addressed.

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Statistical reviews were done in conjunction with the medical reviews. Please look under the medical review tab to locate these reviews.