

CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)



DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIostatISTICS

Statistical Review and Evaluation CLINICAL STUDIES

NDA: 21-397
Name of drug: Neurontin (gabapentin)
Applicant: Pfizer
Indication: _____
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| | | |
|---------|---|----|
| 1 | Executive Summary of Statistical Findings | 3 |
| 1.1 | Conclusions and Recommendations | 3 |
| 1.2 | Overview of Clinical Program and Studies Reviewed | 3 |
| 1.3 | Principal Findings | 4 |
| 2 | Statistical Review and Evaluation of Evidence | 4 |
| 2.1 | Introduction and Background | 4 |
| 2.2 | Data Analyzed and Sources | 4 |
| 2.3 | Statistical Evaluation of Evidence on Efficacy / Safety | 5 |
| 2.3.1 | <i>Sponsor's Results and Conclusions</i> | 5 |
| 2.3.1.1 | <i>Primary efficacy: Study 945-211</i> | 5 |
| 2.3.1.2 | <i>Primary efficacy: Study 945-295</i> | 6 |
| 2.3.1.3 | <i>Secondary analyses</i> | 6 |
| 2.3.2 | <i>Detailed Review of Individual Studies</i> | 11 |
| 2.3.2.1 | <i>Study 945-211</i> | 11 |
| 2.3.2.2 | <i>Study 945-295</i> | 13 |
| 2.3.3 | <i>Statistical Reviewer's Findings</i> | 15 |
| 2.4 | Findings in Special/Subgroup Populations | 15 |
| 2.4.1.1 | <i>Race</i> | 16 |
| 2.4.1.2 | <i>Gender</i> | 16 |
| 2.4.1.3 | <i>Age Group</i> | 18 |
| 2.5 | Statistical and Technical Issues | 19 |
| 2.6 | Statistical Evaluation of Collective Evidence | 19 |
| 2.7 | Conclusions and Recommendations | 19 |
| 2.8 | Appendix | 20 |

1 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 CONCLUSIONS AND RECOMMENDATIONS

The data support the applicant's claim that gabapentin is efficacious in pain relief in post-herpetic neuralgia. Pain reduction relative to placebo is seen early in the clinical trials, during the titration phase, and sustained and improved through the end of the trials at either seven or eight weeks. Analyses of secondary variables, which are mostly alternate ways of measuring pain and pain reduction at the conclusion of the trials, support the primary findings.

The clinical program includes two adequate and well-controlled studies supporting efficacy, at some dose. There is, strictly speaking, no dose replication in the clinical program among post-herpetic patients. Because of the titration scheme, there is dose overlap between the studies, although the overlap is not as clean nor as clear as the design alone implies. There is also information available on dose-response. Conclusions can be drawn on a crude level by examining group average clinical endpoints (pain scores and percent responding) versus the corresponding assigned maintenance dose; and on a less crude basis by modeling daily pain scores as a function of administered daily gabapentin dose. The former approach shows effects in the gabapentin groups that are different from placebo but vary little among the gabapentin dose groups. (The variation is greater between the two placebo groups in the primary endpoint.) The second approach, discussed in detail in the clinical biopharmaceutics review, yields a dose-response curve that implies an increase in pain reduction with increasing dose. That increase is very small over the maintenance dose range of these studies. The implication is that gabapentin reaches full efficacy with titration up to 1800 mg/day.

1.2 OVERVIEW OF CLINICAL PROGRAM AND STUDIES REVIEWED

Neurontin (gabapentin) is an anticonvulsant approved in the United States in 1993 for use in adult patients with epilepsy. The applicant has submitted this NDA in support of a claim of pain relief in patients with post-herpetic neuralgia.

The current NDA includes clinical efficacy studies 945-210, -211, -224, -295 and -306. Studies 945-211 and 945-295 were both on patients with post-herpetic neuralgia. Study 945-211 was 8 weeks long, and included a total of 229 patients: 116 randomized to placebo and 113 randomized to gabapentin, titrated up to 3600 mg/day. Study 945-295 was 7 weeks long, and included a total of 334 patients: 111 patients randomized to placebo, 108 randomized to gabapentin, titrated up to 1800 mg/day, and 111 randomized to gabapentin, titrated up to 2400 mg/day.

The applicant originally asked for an indication _____ . To this end, the submission includes two studies on patients with painful diabetic peripheral neuropathy (210, 224) as well as one on patients with neuropathic pain (306). Since the Agency does not recognize _____ as an indication, and since one of the two diabetic studies was unsuccessful, during the review period the applicant changed the labeled indication to specify only post-herpetic neuralgia.

The primary endpoint in both trials 945-211 and 945-295 was patient-reported daily diary pain on an 11-point scale, averaged over the last seven days on the trial and compared to the baseline 7-day average diary score. Gabapentin patients in study 945-211 had a mean decrease from baseline of 2.1 compared to 0.5 in the placebo group ($p < 0.001$). The comparison between groups was based an ANCOVA model including fixed terms of treatment, center, treatment-by-center along with baseline pain score as covariates. Study 945-295 found mean changes from baseline were -1.0 for placebo, -2.1 for gabapentin 1800 mg, and -2.3 for gabapentin 2400 mg. The comparison between groups was based on an ANCOVA model using treatment, center and baseline pain score as covariates. Under this model, differences between placebo and 1800 mg gabapentin, and between placebo and 2400 mg gabapentin, were highly statistically significant ($p = 0.001$ in both cases), while the difference between the two gabapentin groups was not ($p = 0.62$)

No differential effect of gender was found. Small samples precluded the analysis of race. Gabapentin appears to have greater effect in patients ≥ 75 years of age .

For a discussion of dose-response, see section 1.1 above.

1.3 PRINCIPAL FINDINGS

The applicant's results, above in section 1.2, were borne out by my review. Further analysis of the data found that, despite a 20% drop-out rate, there was little effect of missing data upon the conclusions

2 STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

2.1 INTRODUCTION AND BACKGROUND

Neurontin (gabapentin) is an anticonvulsant approved in the United States in 1993 for use in adult patients with epilepsy. The applicant has submitted this NDA in support of a claim of _____

2.2 DATA ANALYZED AND SOURCES

The current NDA includes clinical efficacy studies 945-210, -211, -224, -295 and -306. Studies 945-211 and 945-295, on post-herpetic neuralgia, are described in detail below and

their efficacy findings examined. The applicant originally asked for an indication of . To this end, the submission includes two studies on patients with painful diabetic peripheral neuropathy (210, 224) as well as one on patients with neuropathic pain (306). Since the Agency does not recognize as an indication, and since one of the two diabetic studies was unsuccessful, during the review period the applicant changed the labeled indication to specify only post-herpetic neuralgia. Hence studies 945-210, 945-224, and 945-306 are not reviewed here (although the applicant examined the subset of 40 patients in 945-306 who had PHN and cites the results as supportive evidence of efficacy).

2.3 STATISTICAL EVALUATION OF EVIDENCE ON EFFICACY / SAFETY

2.3.1 SPONSOR'S RESULTS AND CONCLUSIONS

2.3.1.1 Primary efficacy: Study 945-211

A statistically significant improvement in average pain rating favoring the gabapentin patients was found among the efficacy evaluable as well as the intent-to-treat populations.

In the intent-to-treat population, the gabapentin patients had a mean decrease from baseline of 2.1 (on the 11-point rating scale), compared to 0.5 in the placebo group ($p < 0.001$). The comparison between groups was based an ANCOVA model including fixed terms of treatment, center, treatment-by-center along with baseline value as covariates using ranked data.

In the efficacy evaluable population, the gabapentin patients had a mean decrease from baseline of 2.7 (on the 11-point rating scale), compared to 0.5 in the placebo group ($p = 0.001$). The comparison between groups was based an ANCOVA model including fixed terms of treatment, center, interaction terms of treatment-by-center and treatment-by-duration of zoster along with baseline value and duration of zoster as covariates. There was a minor deviation from the analysis plan: In the final model, the p-value for zoster duration was $p = 0.0035$ and for the interaction of treatment and zoster duration was $p = 0.047$. The analysis plan, however, stated

...The null hypothesis of no treatment-by-factor interaction will be tested at the 0.10 level to evaluate the consistency of difference between treatment means across levels of the factor. When the alpha level of factor-by-treatment interaction is ≤ 0.10 , the factor will be considered significant. Then, the final analysis model for testing between treatment groups will include the main effect term of the factor and the treatment-by-factor term....

According to this plan, at least the interaction and possibly the main effect of zoster duration should not have been in the model for testing treatment differences in the efficacy evaluable population. Since the intent-to-treat population is of primary interest in review, this deviation from protocol was not pursued further.

2.3.1.2 Primary efficacy: Study 945-295

The primary efficacy measure showed statistically significant improvements in endpoint pain scores for both the 1800 and 2400 gabapentin dose groups compared to placebo in the intent-to-treat population.

Prior to analysis the data were converted to percentage change from baseline in order to normalize the distribution. The applicant analyzed these transformed data using ANCOVA with treatment, geographic cluster and mean baseline pain score as covariates. The (pre-specified) criterion for including terms in the model differed from Study 211, in that terms were included only if the corresponding p-value was less than or equal to 0.05, not 0.10.

The applicant reports that least squares treatment mean percentage changes, adjusted for baseline and cluster, were -16% for placebo, -35% for gabapentin 1800 mg, and -34% for gabapentin 2400 mg. Each dose of gabapentin was compared with placebo, using Dunnett's procedure to control for multiplicity. The difference between placebo and gabapentin 1800 was 19% with a 95% CI of 11% to 27% ($p < 0.01$). The difference between placebo and gabapentin 2400 was 19% with a 95% CI of 11% to 27% ($p < 0.01$).

2.3.1.3 Secondary analyses

Responder Analysis

Response to treatment was defined as a 50% or greater reduction in mean pain score between baseline and the end of treatment. Patients withdrawing from the study due to lack of efficacy were classified as non-responders irrespective of pain score. The response rate was significantly higher in all three gabapentin groups compared to the corresponding placebo groups (see table below). It is also of interest to note that the response rates are approximately the same in all gabapentin groups (between 29% and 34%).

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(from ise.pdf, 2001-12-20; Pfizer research report no. 720-30136 issued 13 Dec 2001, p35)

Results of Analysis of Responder Status

| Study/Treatment Group | Number Assessed | Number (%) of Responders | p-Value* |
|------------------------|-----------------|--------------------------|----------|
| Study 945-211 | | | |
| Placebo | 116 | 14 (12) | 0.002 |
| Gabapentin 3600 mg/day | 109 | 32 (29) | |
| Study 945-295 | | | |
| Placebo | 111 | 16 (14) | 0.001 |
| Gabapentin 1800 mg/day | 115 | 37 (32) | |
| Gabapentin 2400 mg/day | 108 | 37 (34) | |

*based on a Cochran-Mantel-Haenszel test, adjusting for center.

Week-to-week differences

Weekly mean pain scores were analyzed by the applicant separately at each week in each study and are given in the table below. A significant treatment effect was found by Week 1 in Studies 945-211 and -295, and was maintained for the duration of both studies.

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(pp. 285-286, ise.pdf)

Study 945-211: Weekly Mean Pain Scores

| Treatment Group | N | Least Square Means* | SE | Difference |
|-----------------|-----|---------------------------|-----|------------|
| Week 1 | | | | |
| Placebo | 115 | 6.3 | 0.1 | |
| Gabapentin | 109 | 5.6 | 0.1 | -0.6 |
| Week 2 | | | | |
| Placebo | 111 | 6.2 | 0.1 | |
| Gabapentin | 105 | 5.0 | 0.1 | -1.2 |
| Week 3 | | | | |
| Placebo | 109 | 6.0 | 0.2 | |
| Gabapentin | 98 | 4.4 | 0.2 | -1.7 |
| Week 4 | | | | |
| Placebo | 106 | 6.0 | 0.2 | |
| Gabapentin | 97 | 4.3 | 0.2 | -1.8 |
| Week 5 | | | | |
| Placebo | 103 | 6.0 | 0.2 | |
| Gabapentin | 95 | 4.3 | 0.2 | -1.6 |
| Week 6 | | | | |
| Placebo | 100 | 5.9 | 0.2 | |
| Gabapentin | 92 | 4.1 | 0.2 | -1.8 |
| Week 7 | | | | |
| Placebo | 95 | 6.0 | 0.2 | |
| Gabapentin | 89 | 4.1 | 0.2 | -1.9 |
| Week 8 | | | | |
| Placebo | 93 | 5.8 | 0.2 | |
| Gabapentin | 87 | 4.0 | 0.2 | -1.8 |

*from ANCOVA using baseline score and center as covariates

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| Study 945-295: Weekly Mean Pain Scores | | | |
|---|----------------|-------------------------------|-------------------------------|
| | Placebo | Gabapentin 1800 mg | Gabapentin 2400 mg |
| Baseline, N | 111 | 115 | 108 |
| Mean (SD) | 6.4 (1.6) | 6.5 (1.7) | 6.5 (1.6) |
| Week 1, N | 109 | 113 | 106 |
| Mean (SD) | 5.9 (2.0) | 5.1 (2.2) | 5.0 (1.8) |
| Week 2, N | 107 | 103 | 98 |
| Mean (SD) | 5.8 (2.0) | 4.7 (2.3) | 4.7 (2.1) |
| Week 3, N | 103 | 99 | 95 |
| Mean (SD) | 5.5 (2.2) | 4.4 (2.4) | 4.4 (2.1) |
| Week 4, N | 99 | 95 | 92 |
| Mean (SD) | 5.6 (2.1) | 4.4 (2.3) | 4.5 (2.2) |
| Week 5, N | 96 | 94 | 88 |
| Mean (SD) | 5.3 (2.3) | 4.4 (2.4) | 4.5 (2.0) |
| Week 6, N | 95 | 94 | 88 |
| Mean (SD) | 5.3 (2.3) | 4.3 (2.5) | 4.3 (2.0) |
| Week 7, N | 91 | 92 | 85 |
| Mean (SD) | 5.3 (2.4) | 4.1 (2.5) | 4.2 (2.0) |
| End of study (LOCF) | | | |
| N | 111 | 115 | 108 |
| Mean (SD) | 5.3 (2.3) | 4.3 (2.5) | 4.2 (2.1) |

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Sleep Interference

Gabapentin at doses of 1800 mg/day (Study 945-295), 2400 mg/day (Study 945-295), and 3600 mg/day (Study 945-211) was effective in reducing sleep interference due to PHN as measured by endpoint mean sleep interference scores. Differences between placebo and gabapentin were on the order of one point on an 11-point scale. The effect on sleep interference was seen at Week 1 and was maintained to the end of each study

VAS and PPI

In contrast to the endpoint mean pain score, which is the average of the last 7 daily diary scores, the endpoint VAS asks the patients to provide a rating of their pain over the last week in the study. Results of this SF-MPQ VAS pain analysis supported the primary endpoint mean pain score analysis. Differences from the corresponding placebo groups were 18 for 3600 mg, 8 for 2400 and 7 for 1800.

PPI provides a rating of overall pain intensity at the time the questionnaire is administered. Gabapentin at 3600 mg/day in Study 945-211 was superior to placebo in improving endpoint PPI scores. No other doses of gabapentin showed notable difference in endpoint PPI scores

SF-MPQ Scores

Gabapentin at doses of 1800 mg/day (Study 945-295), 2400 mg/day (Study 945-295), and 3600 mg/day (Study 945-211) improved SF-MPQ sensory scores

Gabapentin at a dose of 3600 mg/day improved patients' SF-MPQ affective scores in Study 945-211. Differences between placebo and gabapentin 1800 and 2400 mg/day were not significant in Study 945-295.

Gabapentin at doses of 1800 mg/day (Study 945-295), 2400 mg/day (Study 945-295), and 3600 mg/day (Study 945-211) consistently improved patients' SF-MPQ total score.

Global Impressions of Change

The PGIC (Table 21) and CGIC (Table 22) mean scores for patients receiving gabapentin at doses of 1800 mg/day (Study 945-295), 2400 mg/day (Study 945-295), and 3600 mg/day (Study 945-211) were better than those of the placebo group.

Patient Global Impression of Change

| Patient Status | Study 945-211 | | | Study 945-295 | | |
|----------------|--------------------|-------------------------------------|---------|--------------------|--------------------------------------|-------------------------------------|
| | Placebo N = 103 | Gabapentin 3600 mg/day N = 94 | | Placebo N = 105 | Gabapentin 1800 mg/day N = 107 | Gabapentin 2400 mg/day N = 98 |
| | N | (%) | n (%) | n (%) | n (%) | n (%) |
| Improved | 23 | (22) | 66 (70) | 47 (45) | 66 (62) | 63 (64) |
| No Change | 69 | (67) | 25 (27) | 45 (43) | 34 (32) | 27 (28) |
| Worse | 11 | (11) | 3(3) | 13 (13) | 7 (7) | 8 (8) |

Clinician Global Impression of Change

| Patient Status | Study 945-211 | | | Study 945-295 | | |
|----------------|--------------------|-------------------------------------|---------|--------------------|---|--------------------------------------|
| | Placebo N = 103 | Gabapentin 3600 mg/day N = 94 | | Placebo N = 107 | Gabapentin 1800 mg/day N = 108 | Gabapentin 2400 mg/day N = 103 |
| | n (%) | n (%) | n (%) | n (%) | n (%) | |
| Improved | 22 (21) | 62 (66) | 50 (47) | 64 (59) | 71 (69) | |
| No Change | 71 (69) | 29 (31) | 46 (43) | 37 (34) | 25 (24) | |
| Worse | 10 (10) | 3 (2) | 11 (10) | 7 (6) | 7 (7) | |

Quality of Life/Mood

Gabapentin treatment improved QOL measurements in both studies, especially in the domains of bodily pain, mental health, and vitality. Gabapentin treatment improved mood in Study 945-211. (POMS was not measured in study 945-295.)

2.3.2 DETAILED REVIEW OF INDIVIDUAL STUDIES

2.3.2.1 Study 945-211

Study 945-211 is an 8-week, randomized, double-blind, placebo-controlled, multicenter (17 sites), parallel-group trial in the U.S. The applicant randomized a total of 229 patients with PHN, 116 in the placebo group and 113 in the gabapentin 3600 mg/day group. The study consisted of a one-week baseline phase, an 8-week double-blind treatment phase, which includes a four-week titration period, and a two-week follow-up phase for patients who did not choose to enter a subsequent open-label study. Patients in the gabapentin treatment group were begun at 300 mg and titrated up to 900 mg by the end of the first week of

titration, to 1800 mg by the end of the second week, to 2400 by the end of the third week, and finally to 3600 at the end of the four-week titration period. If a patient experienced an intolerable adverse event during the titration period, the patient's dosage could have been decreased one dosage level and then kept constant for the duration of the study.

In study 945-211, efficacy analysis was performed on both the intent-to-treat and the evaluable population, the latter defined as

the subset of subjects who complied with the protocol-directed concurrent pain medication regimen, were at least 80% compliant with treatment medication during the stable dosing phase, completed at least 4 out of 7 days of diaries from the week prior to baseline as well as the last week of stable dosing phase, and were not determined to be significant protocol violators. [protocol, p. 224 of Vol.77]

The evaluable population consisted of 51 patients in the placebo group and 45 patients in the gabapentin group (out of the original 116 and 113 randomized, respectively). The analysis of the intent-to-treat population was used as a confirmatory analysis. [Vol. 77, p.036]

Four centers were pooled for the efficacy evaluable analysis and two centers for the intent-to-treat analysis.

The primary efficacy endpoint is the change from baseline to the final week in the average daily pain rating score, reported by the patient. This rating score is based on an 11-point numeric scale ranging from 0 ("no pain") to 10 ("worst possible pain"). Patients describe their pain during the past 24 hours by choosing the appropriate number between 0 and 10. Self-assessment is supposed to be performed daily and recorded in a pain diary. At baseline and at the end of the stable dosing phase of treatment, the average pain rating was calculated by averaging the daily pain rating over the prior week. The applicant states that last-observation-carried-forward (LOCF) was used: "Any missing post-baseline value was replaced with the last available post-baseline observation regardless of its assessment time" [Vol. 77, p. 043]. Average pain scores were calculated as follows in the presence of missing data, according to the sponsor's study report:

For the efficacy evaluable analysis, if four or more ratings were available, the average score was used. If the average score was based on less than four ratings, it was considered missing. For the intent-to-treat analysis, any average scores for the given week were used, regardless of the number of ratings included.

The last available score after baseline was carried forward for missing values in the intent-to-treat analysis. This was also done in the efficacy evaluable analysis for dropouts due to PHN pain.

According to the data dictionary in the electronic submission ("define.pdf"), the average pain rating score at endpoint was calculated as follows:

The mean is based on the last 7 available scores up to and including the last day on study med. If less than 7 scores were available then the mean is based on all available scores.

The protocol specified only that a LOCF approach would be used for all subjects missing

the last week of stable dosing diaries.

In practice, it seemed as though the number of observations used to calculate endpoint values varied for patients who dropped out early. It is not clear why the calculations were not done according to the definition; however, the impact seems minimal.

The analysis planned in the protocol is as follows:

The average pain rating change from baseline will be summarized by treatment group and evaluated for within treatment changes using the paired t-test. Between treatment comparison will be accomplished using a linear regression model with treatment and site as experimental factors and baseline average pain rating, gender, and race will be candidate covariates. The treatment interaction with each factor and covariate will be evaluated and included in the model if $p \leq 0.10$ Normality of the residuals from the linear regression model will be evaluated to determine the appropriateness of using parametric models for inference. If the residuals are not normally distributed, the Wilcoxon signed rank test will be used for within treatment comparisons while Friedman's randomized block model for ranked data will be used for between treatment comparison.

The final analysis plan was more detailed and included days since last zoster eruption and selected concomitant pain medications as candidate covariates.

Secondary efficacy variables include the weekly mean pain scores; Short Form – McGill Pain Questionnaire (SF-MPQ, a set of scores of pain descriptors and intensity, including the Visual Analog Scale (VAS) and the Present Pain Intensity (PPI)), the endpoint and weekly mean sleep interference scores from the daily sleep diary (and the change in these scores from baseline) and the Clinical and Patient Global Impression of Change (CGIC and PGIC). Quality of life was assessed using the SF-36 Quality of Life questionnaire and the Profile of Mood States (POMS). Descriptive statistics and the corresponding 95% confidence intervals were to be calculated.

For results of these analyses, see results section, above.

2.3.2.2 Study 945-295

Study 945-295 is a 7-week, randomized, double-blind, placebo-controlled, multicenter (45 sites), parallel-group trial in the U.K. and Ireland. The applicant randomized 334 patients with painful post-herpetic neuropathy, with 115 receiving gabapentin 1800 mg, 108 receiving gabapentin 2400 and 111 receiving placebo. The study consisted of a one-week baseline phase and a 7-week double-blind treatment phase, which includes a three-week titration period. Patients in the gabapentin treatment groups were begun at 300 mg and titrated up to 1200 mg by the end of the first week of titration and to 1800 mg by the end of the second week. During the third week they were either maintained at 1800 mg or increased to 2400, depending on their assigned dose group.

The study was analyzed on an intent-to-treat basis. None of the 334 randomized patients were excluded from the primary analysis.

The primary efficacy parameter is the mean weekly pain score from the daily pain diary. According to the protocol (p. 8) and study report, the final weekly mean pain score was defined as the mean pain score from the last 7 days preceding Visit 6 (at week 7) or the last 7 days on study medication for patients who did not complete the study. According to the protocol (p.13) and the data dictionary define.pdf, "the mean daily endpoint pain score is based on the last 7 available up to and including the day of last dose. This could include pre-treatment scores if <7 scores were available."

The analysis planned in the protocol is as follows:

The primary analysis will compare the final weekly mean pain score between treatment groups of the studied population using analysis of covariance (ANCOVA) with treatment (fixed effect and cluster (fixed effect) in the model and the screening mean pain score as covariate.

Centers will be managed by pooling centers into geographic clusters. A center will be considered a cluster if at least 20 patients are randomized in that center. Otherwise, a cluster is an aggregation of centers which are located in the same geographic area....

In case of heterogeneity of variances or major deviation from normality in the analysis of residuals, data transformations will be used to normalize residuals or homogenize variances. Both results of original raw data and transformed data will be displayed and discussed. In case of failure of data transformations, a non-parametrics ANCOVA will be applied.

Supplemental analyses of weekly mean pain score will be:
Analysis of mean pain score for each week separately
Change of weekly mean pain score from baseline at endpoint and at each week separately.

These supplemental analyses will include the same model as the main model.

In addition, age, duration of pain and use of tricyclic antidepressants will be investigated for their effect on the conclusions

The percentage of patients achieving a 50% reduction in mean pain scores will be analyzed.

Secondary efficacy parameters include the SF-MPQ, the endpoint and weekly mean sleep interference scores from the daily sleep diary and the Clinical and Patient Global Impression of Change (CGIC and PGIC). Quality of life was assessed using the SF-36 Quality of Life questionnaire.

Continuous secondary efficacy variables were analyzed in the same way as the primary efficacy variable, using the respective values at randomization as a covariate in ANCOVA. The proportion of responders was compared between each of the two gabapentin-treatment groups and the placebo group using the Cochran-Mantel-Haenszel (CMH) procedure, adjusting for site cluster. Global impression of change scores were analyzed using a modified ridit transformation with the CMH procedure, adjusting for site cluster.

For the results of these analyses, see results section, above.

2.3.3 STATISTICAL REVIEWER'S FINDINGS

The applicant's results were borne out by my review and analysis.

I carried out additional analysis on the raw, untransformed change scores in Study 945-295. The mean changes from baseline were -1.0 (sd=2.1) for placebo, -2.1 (sd=2.0) for gabapentin 1800 mg, and -2.3 (sd=2.0) for gabapentin 2400 mg. I performed an ANCOVA on the raw, untransformed change scores, using treatment, geographic cluster and mean baseline pain score as covariates. Under this model, differences between placebo and 1800 mg gabapentin, and between placebo and 2400 mg gabapentin, were highly statistically significant ($p = 0.001$ in both cases), while the difference between the two gabapentin groups was not ($p = 0.62$). (These p-values are not adjusted for multiplicity.)

2.4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Approximately half of the patients were female, and half were over 75 years of age. Study 945-295 did not collect data on race; approximately 90% of the patients in study 945-211 were white.

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Demographic Characteristics
 (Studies 945-211 and 945-295, combined)

| Population Characteristic | Number (%) of Patients ^a | |
|----------------------------|-------------------------------------|---------|
| Gender | | |
| Men | 256 | (45.8) |
| Women | 303 | (54.2) |
| Total | 559 | (100.0) |
| Age Group (years) | | |
| 18-64 | 109 | (19.5) |
| 65-74 | 171 | (30.6) |
| ≥75 | 279 | (49.9) |
| Total | 559 | (100.0) |
| Race | | |
| White | 204 | (36.5) |
| Black | 13 | (2.3) |
| Hispanic/Other | 8 | (1.4) |
| Not specified ^b | 334 | (59.7) |
| Total | 559 | (100.0) |

^a Number of patients with both baseline and endpoint mean pain scores in Study 945-211, and baseline mean pain scores in Study 945-295.

^b Study 945-295 did not collect race.

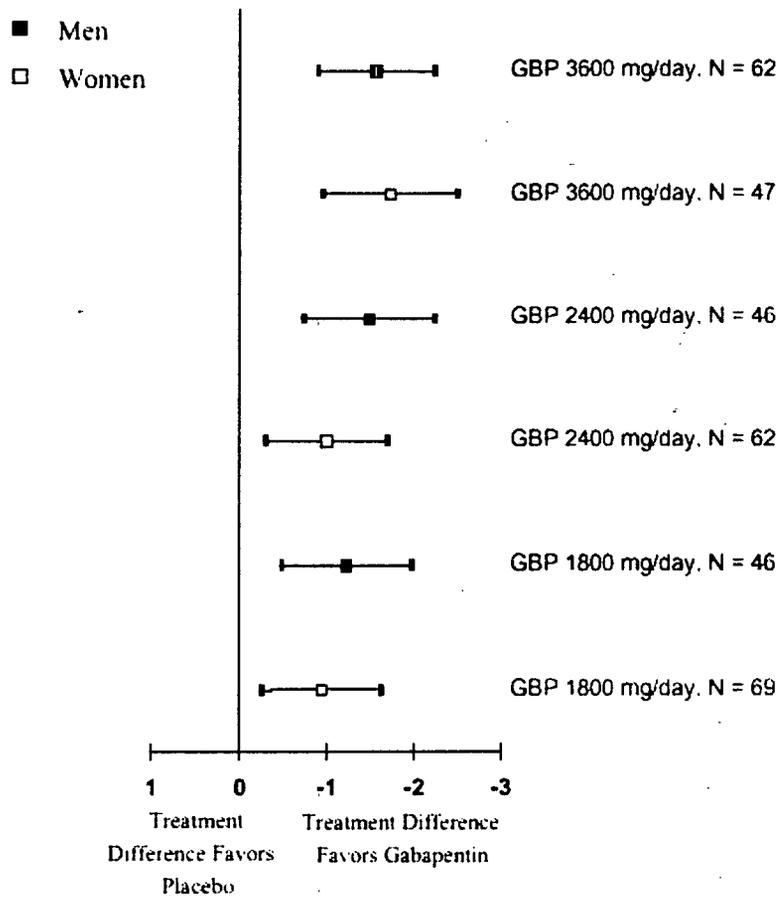
The applicant reported primary efficacy results broken down by race, gender and age for the combined sample from studies 945-211 and 945-295.

2.4.1.1 Race

Small samples preclude meaningful analysis by race. There were only 14 non-white patients in the gabapentin 3600 mg dose group.

2.4.1.2 Gender

Gabapentin efficacy was similar in men and women (see figure below, from ise.pdf, p. 39). An ANCOVA model that included gender, treatment group, protocol, baseline pain, and treatment group-by-gender interaction indicated no interaction between gender and treatment group ($p = 0.98$), supporting the finding that treatment effects in men and women were similar.



Endpoint Mean Pain Score by Dose and Gender

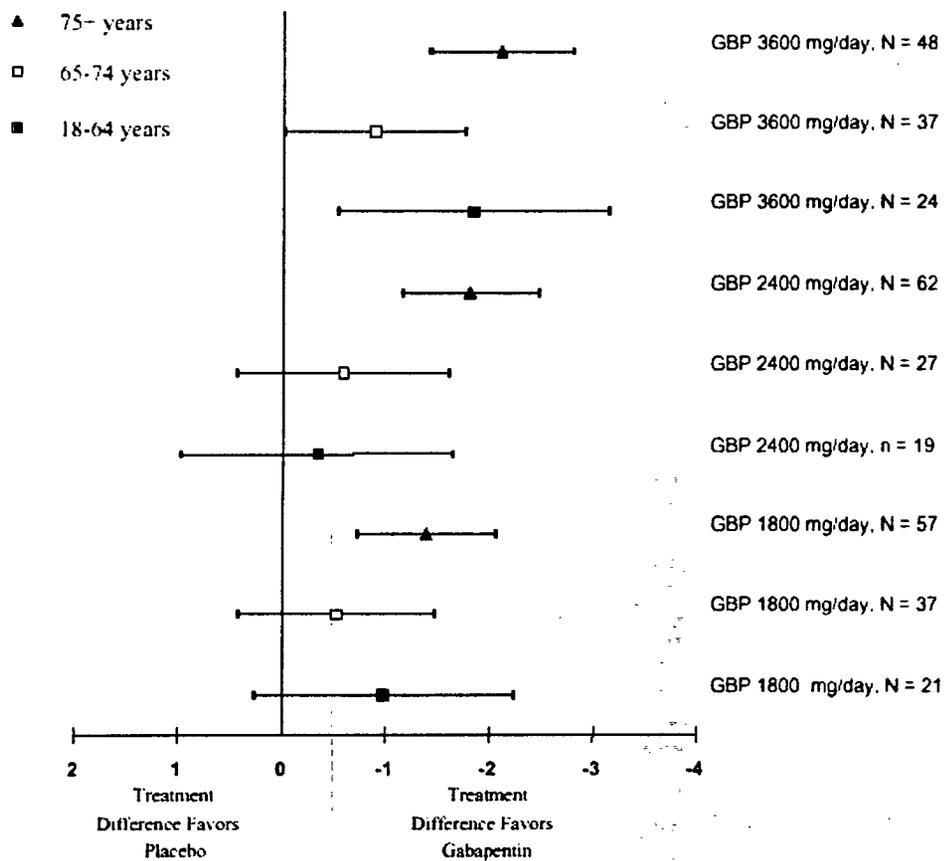
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2.4.1.3 Age Group

Gabapentin appears to have greater effect in patients ≥ 75 years of age (see figure, below). An ANCOVA model that included age category, treatment group, protocol, baseline pain, and treatment group-by-age category interaction indicated a statistically significant interaction between age category and treatment group ($p < 0.01$), supporting the finding that there was a larger treatment effect in patients ≥ 75 years. The applicant concludes (ise.pdf, pp.40-41)

This larger treatment effect in patients ≥ 75 years is consistent with the age-dependent changes observed in gabapentin pharmacokinetics.

Since gabapentin is almost exclusively eliminated by renal excretion, the larger treatment effect observed in patients ≥ 75 years is likely a consequence of increased gabapentin exposure for a given dose that results from an age-related decrease in renal function. However, other factors cannot be excluded.



Endpoint Pain Mean Score by Dose and Age Category

2.5 STATISTICAL AND TECHNICAL ISSUES

20% and 19% of the intent-to-treat population in studies 211 and 295, respectively, discontinued before the final week of the study and therefore had a pain score carried forward for analysis. To investigate the effect of such dropping out, I performed a "worst-case" sensitivity analysis. Details are given in the Appendix. The results of this analysis found a significant improvement in the gabapentin 1800 and 3600 mg groups, and a near significant improvement in the 2400 group, relative to placebo ($p=0.05$, 0.0002 , and $p=0.07$, respectively). That there is still statistically significant or near significant separation argues for the lack of sensitivity of the efficacy finding to the LOCF procedure in these studies.

When I recalculated responder rates counting all dropouts as treatment failures regardless of reason for discontinuation, the results were essentially the same: in study 945-211, 13 (11%) of the placebo group versus 30 (27%) of the gabapentin 3600mg group were responders, and in study 945-295, 16 (14%) of the placebo, 31 (27%) of the gabapentin 1800 mg and 31 (29%) of the gabapentin 2400 mg groups were responders.

2.6 STATISTICAL EVALUATION OF COLLECTIVE EVIDENCE

The applicant's findings were borne out by my review and analysis. For further discussion, see conclusions, below.

A point to note is that, strictly speaking, there is no dose replication across these two studies, that is, the final doses of gabapentin differ between the two. The patients of 945-211 who finish the study at 1800 or 2400 mg do so because they cannot tolerate the full 3600 dose, and therefore are not comparable to the patients in 945-295 who are randomized to one of those doses. During the first three weeks of dosing, while patients are being titrated up to their full assigned dose, the studies are comparable, at least by design. However, an analysis, by the clinical reviewer, of time actually spent on intermediate doses in 945-211 revealed that the median times were on the order of a couple of days, rather than a week. The maintenance dose is therefore reached much sooner than the design would indicate. For more details, see Dr. Hertz's review.

2.7 CONCLUSIONS AND RECOMMENDATIONS

The data support the applicant's claim that gabapentin is efficacious in pain relief in post-herpetic neuralgia. Pain reduction relative to placebo is seen early in the clinical trials, during the titration phase, and sustained and improved through the end of the trials at either seven or eight weeks. Analyses of secondary variables, which are mostly alternate ways of measuring pain and pain reduction at the conclusion of the trials, support the primary

findings.

The clinical program includes two adequate and well-controlled studies supporting efficacy, at some dose. There is, strictly speaking, no dose replication in the clinical program among post-herpetic patients. Because of the titration scheme, there is dose overlap between the studies, although the overlap is not as clean nor as clear as the design alone implies. There is also information available on dose-response. Conclusions can be drawn on a crude level by examining group average clinical endpoints (pain scores and percent responding) versus the corresponding assigned maintenance dose; and on a less crude basis by modeling daily pain scores as a function of administered daily gabapentin dose. The former approach shows effects in the gabapentin groups that are different from placebo but vary little among the gabapentin dose groups. (The variation is greater between the two placebo groups in the primary endpoint.) The second approach, discussed in detail in the clinical biopharmaceutics review, yields a dose-response curve that implies an increase in pain reduction with increasing dose. That increase is very small over the maintenance dose range of these studies. The implication is that gabapentin reaches full efficacy with titration up to 1800 mg/day.

2.8 APPENDIX

20% and 19% of the intent-to-treat population in studies 211 and 295, respectively, discontinued before the final week of the study and therefore had a pain score carried forward for analysis. To investigate the effect of such dropping out, I performed a "worst-case" sensitivity analysis: all dropouts, regardless of reason for discontinuation, were given a final pain change score equal to the worst change observed in the entire patient population for the particular trial. (Patients who completed the study kept their endpoint pain score as observed.) The worst change at endpoint observed in study 211 was in a patient whose pain increased by 3.7 points, and in study 295 the worst change was an increase of 3.5. The mean changes from baseline in the resulting, modified data are shown in the table below. Differences between gabapentin and placebo were tested in the resulting data. An ANCOVA was carried out using treatment, study site or geographic cluster, and mean baseline pain score as covariates to test for significance of the differences between gabapentin and placebo.

"Worst-case" change from baseline

| | Study 945-211 | | Study 945-295 | | |
|-----------|---------------|---------------------------|---------------|---------------------------|---------------------------|
| | Placebo | Gabapentin 3600 mg/day | Placebo | Gabapentin 1800 mg/day | Gabapentin 2400 mg/day |
| Mean (SD) | 0.2 (2.2) | -1.1 (3.1) | -0.4 (2.6) | -1.1 (3.0) | -1.1 (3.1) |

The results of this analysis found a significant improvement in the gabapentin 1800 and 3600 mg groups, and a near significant improvement in the 2400 group, relative to placebo ($p=0.05$, 0.0002 , and $p=0.07$, respectively). That there is still statistically significant or near significant separation argues for the lack of sensitivity, of the efficacy finding, to the LOCF procedure in these studies.

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