

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-609**

**STATISTICAL REVIEW(S)**



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Pharmacoepidemiology and Statistical Science  
Office of Biostatistics

### Memorandum of Statistical Review

**NDA:** 21609 (Response to Not Approvable Letter)

**Name of drug:** Enjuvia™ (synthetic conjugated estrogens, B)

**Applicant:** Barr Research, Inc.

**Indication:** Treatment for Moderate-to-Severe Vasomotor Symptoms

**Project manager:** George Lyght

**Clinical reviewer:** Bruce Patsner, M.D.

**Dates:** Received 6/30/04; User Fee 12/30/04

**Reviewer:** Moh-Jee Ng, M.S.

**Biometrics Team Leader:** Mike Welch, Ph.D.

#### Summary

The sponsor provided new efficacy analyses in response to the not approvable letter dated April 22, 2003. These new results, based on a non-parametric analysis, show that subjects who received Enjuvia™ 0.3 mg tablets has statistically significant reductions in frequency and severity of moderate-to-severe vasomotor symptoms (MSVS) as compared to placebo at weeks 4 and 12.

#### Background

NDA 21443 was originally submitted March 22, 2002 with three studies supporting dose strengths 0.3 mg, 0.625 mg and 1.25 mg, respectively. The sponsor's intent was to show that positive study results for the 0.3 mg and 0.625 doses could also support approval of a "bracketed" dose of 0.45 mg. However, the 0.3 mg dose study failed to show efficacy for the MSVS endpoints at week 4. (See statistical review dated December 11, 2002.) After receiving additional safety information, the Division issued an approval letter May 10, 2004, for the two higher doses only.

The not approvable letter of April 22, 2003 for the 0.3 mg dose under NDA 21609 stated that the sponsor needed to demonstrate efficacy of the 0.3 dose and that the Agency would consider approval for a 0.45 mg dose in that case.

## Statistical Analyses

The Division met with the sponsor on May 21, 2003 to discuss the "not approvable" issues. The sponsor presented new analyses for additional endpoints to demonstrate statistical significance with respect to frequency and severity in the Intent-to-Treat (ITT) population. These new endpoints included percent change in frequency; change in frequency for severe hot flushes only; and change in a severity index, the latter being defined as a cumulative daily sum of severity scores. (See sponsor's meeting briefing package dated May 9, 2003.)

The Division recommends that the severity index be based on the sum of moderate-to-severe hot flush scores divided by the number of moderate-to-severe hot flushes. A secondary endpoint definition includes mild hot flushes (sum of all hot flush scores divided by the total number of all hot flushes). In any event, the sponsor's analyses presented in the May 9, 2003 package are considered exploratory although they did bring to fore the need for critical re-examination of endpoint definition, especially in the context of detecting low-dose effectiveness.

In the original NDA submission, the sponsor's efficacy analysis, using Division-recommended endpoints, was based on analysis of covariance (ANCOVA) with baseline, treatment, center, and treatment-by-center interaction. Although the protocol indicated that a non-parametric procedure would be applied if the ANCOVA model did not fit the data well, the sponsor's analysis did not include a non-parametric analysis, even though the sponsor's data showed significant departures from the normality assumption.

In the complete response package dated June 29, 2004, the sponsor re-analyzed all primary efficacy results using a rank-based procedure. This method essentially applies an ANCOVA procedure to the ranked observations. The results show that Enjuvia<sup>TM</sup> 0.3 mg is statistically different than placebo in change from baseline for frequency and severity of moderate-to-severe hot flushes at week 4. (See Sponsor's Tables 1, 2, and 5.)

However, the use of ANCOVA applied directly to the rank-based observations is not recommended by this reviewer; a preferred method is the stratified Wilcoxon test. This reviewer performed new analyses based on this method, and the results are shown in Tables 1 and 2 to this review. In this approach the tests for statistical significance are based on the Wilcoxon test. The descriptive statistics (means, mean changes, standard errors, etc.) however are based on the parametric ANCOVA. The significance levels and the descriptive statistics are consistent with the sponsor's results; these results show that the changes from baseline in the frequency and severity endpoints at weeks 4 and 12 are statistically different between the Enjuvia<sup>TM</sup> and placebo groups.

## Conclusion

Subjects assigned Enjuvia<sup>TM</sup> 0.3 mg tablets showed statistically significant reductions at weeks 4 and 12 in both frequency and severity of moderate-to-severe vasomotor symptoms.

**Table 1**  
**Study GA326**  
**Mean Change from Baseline in Frequency of MSVS per week**  
**in the ITT<sup>a</sup> using LOCF<sup>b</sup> Analysis**

| <b>Week</b>                    | <b>Placebo<br/>N=70</b> | <b>Enjuvia 0.3 mg<br/>N=66</b> |
|--------------------------------|-------------------------|--------------------------------|
| <b>Baseline [1]</b>            |                         |                                |
| Mean (SD)                      | 96.4 (58.2)             | 104.3 (57.7)                   |
| <b>Week 4*</b>                 |                         |                                |
| Mean (SD)                      | 57.8 (47.5)             | 47.0 (52.9)                    |
| Mean change from baseline (SE) | - 39.2 ( 5.8)           | - 52.9 ( 6.0)                  |
| P-values [2]                   |                         | 0.0164                         |
| <b>Week 8</b>                  |                         |                                |
| Mean (SD)                      | 49.5 (47.9)             | 34.8 (50.8)                    |
| Mean change from baseline (SE) | - 47.9 ( 5.8)           | - 64.8 ( 6.1)                  |
| <b>Week 12*</b>                |                         |                                |
| Mean (SD)                      | 47.5 (49.8)             | 30.7 (47.7)                    |
| Mean change from baseline (SE) | - 50.5 ( 5.7)           | - 69.7 ( 6.0)                  |
| P-values [2]                   |                         | 0.0075                         |

Sources: SAS dataset

<sup>a</sup>ITT=Intent-to-Treat, <sup>b</sup>LOCF=Last Observation Carried Forward.

Mean change is ANCOVA adjusted mean change. SD=Standard Deviation, SE= Standard Error

\* : Primary endpoint

[1]: The number of MSVS at baseline was the weekly average number of MSVS using the last 14 days of diary data that were recorded prior to randomization

[2]: P-values based on Wilcoxon rank sum test (Van Elteren test)

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**Table 2**  
**Study GA326**  
**Mean Change from Baseline in Severity [1] of MSVS per week**  
**in the ITT<sup>a</sup> using LOCF<sup>b</sup> Analysis**

| <b>Week</b>                    | <b>Placebo<br/>N=70</b> | <b>Enjuvia 0.3 mg<br/>N=66</b> |
|--------------------------------|-------------------------|--------------------------------|
| <b>Baseline [2]</b>            |                         |                                |
| Mean (SD)                      | 2.5 (0.3)               | 2.5 (0.3)                      |
| <b>Week 4*</b>                 |                         |                                |
| Mean (SD)                      | 2.2 (0.8)               | 2.1 (0.8)                      |
| Mean change from baseline (SE) | - 0.3 (0.1)             | - 0.5 (0.1)                    |
| P-values [3]                   |                         | 0.0218                         |
| <b>Week 8</b>                  |                         |                                |
| Mean (SD)                      | 2.0 (0.9)               | 1.7 (1.1)                      |
| Mean change from baseline (SE) | - 0.5 (0.1)             | - 0.8 (0.1)                    |
| <b>Week 12*</b>                |                         |                                |
| Mean (SD)                      | 1.9 (1.1)               | 1.5 (1.2)                      |
| Mean change from baseline (SE) | - 0.6 (0.1)             | - 1.0 (0.1)                    |
| P-values [3]                   |                         | 0.0239                         |

Sources: SAS dataset

<sup>a</sup>ITT=Intent-to-Treat, <sup>b</sup>LOCF=Last Observation Carried Forward.

Mean change is ANCOVA adjusted mean change. SD=Standard Deviation, SE= Standard Error

\* : Primary endpoint, statistically significance at 0.05 level is marked gray

[1] Severity =  $(2*nr\_mod + 3*nr\_sev) / (nr\_mod + nr\_sev)$

where nr\_mod and nr\_sev were the numbers of moderate and severe hot flushes

[2]: The number of MSVS at baseline was the weekly average number of MSVS using the last

14 days of diary data that were recorded prior to randomization

[3]: P-values based on Wilcoxon rank sum test (Van Elteren test)

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/s/

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Mike Welch

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BIOMETRICS

Submitted to DFS for primary reviewer. Concur with review.