



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

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

**NDA/Serial Number:** 20-717

**Drug Name:** Provigil® (Modafinil)

**Indication(s):** Narcolepsy

**Applicant:** Caphalon

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## **1. EXECUTIVE SUMMARY**

Provigil is marketed in the United States for the treatment of adult patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea/hypopnea syndrome (OSAHS), and shift work sleep disorder (SWSD).

A Pediatric Written Request (PWR) was issued by the FDA on 17 June 2004 to evaluate the use of Provigil therapy in pediatric patients (children and adolescents ages 6 through 16 years) with excessive sleepiness associated with narcolepsy and OSAHS. The original PWR required the conduct of two phase III double-blind, placebo-controlled studies: one in patients with narcolepsy and one in patients with OSAHS. An amendment to the PWR in August 2005 removed the requirement for the study in patients with OSAHS. The current submission included one efficacy study of Provigil in pediatric patients with excessive sleepiness associated with narcolepsy.

### **1.1 Conclusions and Recommendations**

The study failed to demonstrate that there is a linear dose response in the primary efficacy variable of MSLT, which was the designated primary analysis. Although there appeared to have a larger increase in sleep latency in the Provigil treated patients than in the placebo treated patients, direct comparison between Provigil and placebo in MSLT was not planned. The treatment difference in the co-primary efficacy variable of CGI-C failed to reach statistical significance.

### **1.2 Brief Overview of Clinical Studies**

The phase III clinical program included one randomized, placebo-controlled study (study 3027) of 6 weeks in duration to evaluate the efficacy and safety of Provigil (100, 200, and 400 mg/day) in pediatric patients of age 5 to 17 years with excessive sleepiness associated with narcolepsy. The primary efficacy variables were the change from baseline to Week 6 in the mean multiple sleep latency test (MSLT) and Clinical Global Impression of Change (CGI-C) at Week 6. A total of 166 pediatric patients entered study in 46 centers in North America.

### **1.3 Statistical Issues and Findings**

The study designated a linear trend test to demonstrate the dose response of Provigil. Such dose response was not found in the study. The inference of treatment difference in sleep latency measured by MSLT between Provigil treated patients and placebo treated patients could not be drawn since no treatment effect comparisons were prospectively designated. The treatment differences in the co-primary endpoint of CGI-C failed to reach statistical significance.

## **2. INTRODUCTION**

Provigil® (modafinil) Tablets C-IV is a wakefulness-promoting agent for oral administration. Provigil is marketed in the United States for the treatment of adult patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea/hypopnea syndrome (OSAHS), and shift work sleep disorder (SWSD).

A Pediatric Written Request (PWR) was issued by the FDA to evaluate the use of Provigil therapy in pediatric patients (children and adolescents ages 6 through 16 years) with excessive sleepiness associated with narcolepsy. This current submission fulfills the requirements of the PWR and includes one efficacy study in this patient population.

### **2.1 Overview**

The phase III clinical program included one randomized, placebo-controlled study (study 3027) of 6 weeks in duration to evaluate the efficacy and safety of Provigil (100, 200, and 400 mg/day) in pediatric patients of age 5 to 17 years with excessive sleepiness associated with narcolepsy. The primary efficacy variables were the change from baseline to Week 6 in the mean multiple sleep latency test (MSLT) and Clinical Global Impression of Change (CGI-C) at Week 6. A total of 166 pediatric patients entered study in 46 centers in North America.

### **2.2 Data Sources**

All documents reviewed for this MDA are in electronic form. The path to CDER Electronic Document Room for this submission is listed below:

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### **3. STATISTICAL EVALUATION**

#### **3.1 Evaluation of Efficacy**

##### **3.1.1 Description of the Study**

The efficacy of Provigil in pediatric population included one study, Study 3027. The primary objective of the study was to determine the efficacy of Provigil treatment, compared to placebo treatment, in children and adolescents with excessive sleepiness associated with narcolepsy.

The study was a randomized, multicenter, double-blind, placebo-controlled, parallel-group study. Following the baseline visit, patients were randomized in equal numbers to receive Provigil 100, 200, or 400 mg/day or matching placebo in a 6 weeks double-blind treatment period. Patients who completed at least 3 weeks of double-blind treatment and who did not discontinue due to adverse events were eligible to enroll in an open-label extension study.

A total of 166 pediatric patients were randomized in 46 study sites in North America.

##### **3.1.2 Efficacy Variables and Statistical Analysis Methods**

The primary efficacy variables were the change from baseline to the last post-baseline observation in mean sleep latency from the MSLT and the proportion of patients with at least minimal improvement on the CGI-C ratings at the last post-baseline observation.

The mean of MSLT was calculated from the 4 20-minute naps performed at 0900, 1100, 1300, and 1500. The sleep latency value was assigned to 20 minutes if a patient did not fall asleep during the 20-minute MSLT session. CGI-I was an assessment of change in the patient's severity of disease during the course of the study by the investigator. It used a 7-category scoring from 1 (very much improved) to 7 (very much worse).

The primary variable of MSLT was to be analyzed using an analysis of covariance (ANCOVA) with treatment as a factor, and the corresponding baseline value as a covariate. The statistical hypothesis to be tested for MSLT was a test for linear trend among the placebo and Provigil treatment groups. Specifically the null hypothesis of

$$H_0: \mu_{pbo} = \mu_{100} = \mu_{200} = \mu_{400}$$

was to be tested against the alternative hypothesis of

$$H_a: \mu_{pbo} \leq \mu_{100} \leq \mu_{200} \leq \mu_{400} \text{ (with at least 1 inequality)}$$

using a contrast with coefficients of  $-0.59$ ,  $-0.25$ ,  $0.08$ , and  $0.76$  corresponding to treatment with placebo, and 100, 200, and 400 mg/day of Provigil, respectively.

The primary efficacy variable of the proportion of patients with at least minimal improvement in the CGI-C rating was to be tested using a chi-square test. The primary comparison between the combined Provigil treatment group and the placebo treatment group was to be performed by combining the data from the Provigil treatment groups and comparing to the placebo group. In addition, individual Provigil treatment group comparisons versus the placebo treatment group were to be performed by sub setting the data for the respective treatment group and comparing it to the placebo treatment group.

Secondary efficacy variables include the following:

- The percentage of patients with at least minimal improvement in the CGI-C rating (for severity of excessive sleepiness) at weeks 3 and 6;
- The change from baseline for the total score from the PDSS at weeks 3 and 6, and at the last postbaseline observation;
- The change from baseline to week 6, for the mean sleep latency from the MSLT (from the 4 naps performed at 0900, 1100, 1300, and 1500).

Secondary efficacy variables were to be tested similarly to the primary efficacy variables.

### **3.1.3 Study Subjects**

A total of 166 patients were randomized at 46 centers in the US and Canada. Of the 166 patients randomized, 160 patients received at least 1 dose of study drug and had at least 1 postbaseline MSLT or CGI-C assessment.

A total of 22 (13%) patients withdrew from the study, 17 (14%) from Provigil group and 5 (12%) from placebo group. The reasons for withdrawal were mostly consent withdrawn or noted as "other", which included various reasons. One study site (site ID 079) entered 9 subjects. All but one discontinued prematurely.

### **3.1.4 Patients Demographic and Baseline Characteristics**

The average age of the patients enrolled in the study was 12.5 years (range 5 to 17 years), with an average weight of 63.4 kg (range 18.8 to 156.5 kg). Slightly more than half (57%) of the patients were boys. Approximately half (51%) of the patients were white, and the remaining patients were mostly black. Thirty percent (30%) of the patients enrolled were less than 12 years of age and 70% were at least 12 years of age.

Patient demographic characteristics were generally similar across the treatment groups except the following: the 100-mg/day Provigil treatment group had a greater percentage of older children (74%  $\geq$ 12 years) and fewer black children (31%) than the 400-mg/day (65% and 40%, respectively) or 200-mg/day (66% and 49%, respectively) treatment groups.

Four patients who did not meet the inclusion criterion for age were granted protocol exceptions to enroll in the study: one 5 years old patient was randomized into Provigil 100 mg, and three 17 year old patients were randomized, one in each, into Provigil 400 mg, Provigil 200 mg, and placebo.

All patients enrolled in this study had narcolepsy. At baseline, there were no statistically significant differences between treatment groups with regard to severity of illness. Overall, CGI-S scores indicated that at least 95% of patients in each treatment group were at least moderately ill. Provigil 400-mg/day treatment group had the highest percentage of patients (58%) considered markedly, severely, or extremely ill.

### 3.1.5 Efficacy Analyses and Results

The primary statistical analysis for the mean change in MSLT is a linear dose trend test. The data suggest that the dose response may not be linear. The p-value of the trend test is 0.0604. The least square estimates, which are almost identical to the raw means, showed that Provigil 200 mg had the largest increase in the mean MSLT, followed by Provigil 100 mg and 400 mg (Table 1).

In the analysis of CGI-C, the proportion of patients with at least minimum improvement was 80.67% in the combined Provigil group and 65.85% in the placebo group. The comparison between the combined Provigil group and the placebo group yielded a p-value of 0.0523 from the chi-square test. The global test across all treatment groups yielded a p-value of 0.1333. The Provigil 100 mg had the largest proportion of patients with improvement (85.37%), followed by Provigil 200 mg (82.93%), and 400 mg (72.97%) (Table 1).

**Table 1 Efficacy Results from Analysis of MSLT and CGI-C (Reviewer's Analysis)**

|                        | Placebo     | Provigil 100 mg | Provigil 200 mg | Provigil 400 mg | p-value |
|------------------------|-------------|-----------------|-----------------|-----------------|---------|
| <b>MSLT, mean (SD)</b> |             |                 |                 |                 |         |
| N                      | 40          | 40              | 40              | 36              |         |
| Baseline               | 6.74 (4.47) | 7.76 (4.79)     | 5.43 (3.91)     | 6.56 (4.72)     |         |
| Week 6                 | 7.34 (5.31) | 11.53 (5.65)    | 10.26 (6.22)    | 9.57 (6.71)     |         |
| Change                 | 0.60 (3.86) | 3.76 (4.01)     | 4.83 (4.34)     | 3.01 (5.11)     |         |
| LS mean (SE)           | 0.61 (0.69) | 3.85 (0.69)     | 4.74 (0.69)     | 3.00 (0.72)     | 0.0604  |
| <b>CGI-C, n (%)</b>    |             |                 |                 |                 |         |
| N                      | 41          | 41              | 41              | 37              |         |
| Improved (1-3)         | 27 (65.85)  | 35 (85.37%)     | 34 (82.93%)     | 27 (72.97%)     | 0.1333  |

The direct comparison between Provigil treated patients and placebo-treated patients in MSLT was not planned in the study. The reviewer performed 3 different tests in order to examine the effect of each dose of Provigil.

First, the contrast comparison of equal weight (1/3 for each dose group and 1 for placebo) was used and a p-value of <.0001 was obtained. Second, Dunnett's adjustment for all dose groups versus placebo was used, and the p-values for Provigil 100 mg, 200 mg, and 400 mg vs. placebo

are 0.005, <0.001 and 0.046, respectively. Finally, the reviewer performed pairwise test comparing each dose group of Provigil and placebo. The resulting p-values are 0.0003 for Provigil 100 mg vs. placebo, 0.0001 for Provigil 200 mg vs. placebo, and 0.0239 for Provigil 400 mg vs. placebo. Therefore, Provigil 100 mg and 200 mg would be considered effective doses if a Hochberg procedure, a Bonferroni adjustment, or a stepdown procedure from the highest dose group was specified. The Provigil 400 mg would not be considered effective if Bonferroni method was specified, but would be considered effective by using the Hochberg procedure or a stepdown procedure from the highest dose group versus placebo.

Similarly, pairwise comparisons in CGI-C are performed using chi-square test. The p-values are 0.0397 for Provigil 100 mg vs. placebo, 0.0766 for Provigil 200 mg vs. placebo, and 0.4963 for Provigil 400 mg vs. placebo.

It appeared that Provigil 100 mg and 200 mg might be effective in MSLT. An additional study with better statistical analysis plan and larger sample size might be able to give definitive answer for the efficacy of Provigil.

In conclusion, the effective doses of Provigil can not be definitively determined based on MSLT, and the treatment difference in CGI-C failed to reach the statistical significance. The study failed to demonstrate the efficacy by showing significant treatment difference for both primary efficacy variables as required.

### **3.2 Evaluation of Safety**

Refer to Clinical Review by Dr. Elizabeth McNeil for evaluation of safety.



## 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

### 4.1 Gender, Race and Age

Efficacy analyses by gender and age group were performed by the reviewer. A smaller percentage of patients who improved by CGI-C was observed among the female patients than in the male patients in all Provigil groups, noticeably Provigil 400 mg in which such percentage fell below the corresponding one in the placebo group. The following table presents the results.

**Table 2 Primary Efficacy Results by Gender and Age Group (Reviewer's Analysis)**

|                        | Placebo     | Provigil 100 mg | Provigil 200 mg | Provigil 400 mg | p-value |
|------------------------|-------------|-----------------|-----------------|-----------------|---------|
| <b>MSLT, mean (SD)</b> |             |                 |                 |                 |         |
| <b>Gender</b>          |             |                 |                 |                 |         |
| Male                   |             |                 |                 |                 |         |
| N                      | 25          | 22              | 20              | 20              |         |
| Baseline               | 6.97 (4.57) | 6.98 (4.65)     | 5.66 (3.70)     | 8.03 (5.10)     |         |
| Change                 | 0.65 (4.23) | 3.11 (3.65)     | 5.38 (4.63)     | 2.55 (5.96)     | 0.0175  |
| Female                 |             |                 |                 |                 |         |
| N                      | 15          | 18              | 20              | 16              |         |
| Baseline               | 6.35 (4.41) | 8.73 (4.91)     | 5.21 (4.19)     | 4.73 (3.53)     |         |
| Change                 | 0.53 (3.30) | 4.55 (4.38)     | 4.28 (4.38)     | 3.58 (3.92)     | 0.0237  |
| <b>Age, years</b>      |             |                 |                 |                 |         |
| < 12                   |             |                 |                 |                 |         |
| N                      | 21          | 18              | 19              | 18              |         |
| Baseline               | 7.98 (4.89) | 9.60 (4.51)     | 6.29 (3.90)     | 6.04 (4.37)     |         |
| Change                 | 0.19 (2.91) | 3.80 (3.37)     | 4.47 (4.01)     | 2.83 (4.79)     | 0.0041  |
| > 12                   |             |                 |                 |                 |         |
| N                      | 19          | 22              | 21              | 18              |         |
| Baseline               | 5.37 (3.59) | 6.27 (4.57)     | 4.65 (3.84)     | 7.08 (5.11)     |         |
| Change                 | 1.06 (4.75) | 3.73 (4.55)     | 5.15 (4.70)     | 3.19 (5.55)     | 0.0813  |
| <b>CGI-C, n (%)</b>    |             |                 |                 |                 |         |
| <b>Gender</b>          |             |                 |                 |                 |         |
| Male                   |             |                 |                 |                 |         |
| N                      | 26          | 22              | 21              | 20              |         |
| Improved (1-3)         | 17 (65.38%) | 20 (90.91%)     | 19 (90.48%)     | 16 (80.00%)     | 0.0836  |
| Female                 |             |                 |                 |                 |         |
| N                      | 15          | 19              | 20              | 17              |         |
| Improved (1-3)         | 10 (66.67%) | 15 (78.95%)     | 15 (75.00%)     | 11 (64.71%)     | 0.7573  |
| <b>Age, years</b>      |             |                 |                 |                 |         |
| ≤ 12                   |             |                 |                 |                 |         |
| N                      | 21          | 18              | 19              | 19              |         |
| Improved (1-3)         | 15 (71.43%) | 17 (94.44%)     | 15 (78.95%)     | 15 (78.95%)     | 0.3411  |
| > 12                   |             |                 |                 |                 |         |
| N                      | 20          | 23              | 22              | 18              |         |
| Improved (1-3)         | 12 (60.00%) | 18 (78.26%)     | 19 (86.38%)     | 12 (66.67%)     | 0.2227  |

### 4.2 Other Special/Subgroup Populations

No other special / subgroup population analyses were performed.

## **5. SUMMARY AND CONCLUSIONS**

### **5.1 Statistical Issues and Collective Evidence**

The study designated a linear trend test to demonstrate the dose response of Provigil. Such dose response was not found in the study. The inference of treatment difference in sleep latency measured by MSLT between Provigil treated patients and placebo treated patients could not be drawn since no treatment comparisons were planned. The treatment differences in the co-primary endpoint of CGI-C failed to reach statistical significance.

### **5.2 Conclusions and Recommendations**

The study failed to demonstrate that there is a linear dose response in the primary efficacy variable of MSLT, which was the designated primary analysis. The treatment difference in the co-primary efficacy variable of CGI-C failed to reach statistical significance. Although there appeared to have a larger increase in sleep latency in the Provigil treated patients than in the placebo treated patients, the significance of such difference can not be conclusively determined since no treatment comparisons were prospectively specified.

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