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Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

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1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The data from the three pivotal studies 309, 310, and 311 demonstrate the efficacy of Modafinil in children and adolescents with ADHD.

1.2 Brief Overview of Clinical Studies

Studies 309 and 311 were identically designed flexible-dosage studies with 9-week double-blind treatment periods. Study 310 had a fixed-dosage design with a 7-week double-blind treatment period followed by a 2-week randomized-withdrawal period. In these studies, the primary measure of efficacy was the teacher/physician-completed ADHD Rating Scale, Fourth Edition (ADHD-RS-IV) (School Version). The studies were all done concurrently in the United States between Nov 2003 and June 2004. Patients who completed at least 4 weeks of the double-blind treatment period and did not withdraw due to an adverse event were eligible to enroll in a 1 year open label extension study. This may partially explain the relatively low completion rates (see Table 1).

Table 1 Characteristics of Key Efficacy Studies

STUDY #	RANDOMIZED N	RANDOMIZATION/ DOSING	DURATION	PRIMARY EFFICACY	AGES	COMPLETE N (%)
309	133 Modafinil 67 Placebo	2:1 Mod/Pla flexible dose: 170 to 425 mg/day	9 weeks DB treatment	ADHD-RS-IV (School Version)	6-16	100 (75) 41 (61)
310	126 Modafinil 64 Placebo	2:1 Mod/Pla fixed dose: 340 mg if weight < 30 kg 425 mg if weight ≥ 30 kg	7 weeks DB treatment then 2 week withdrawal period	ADHD-RS-IV (School Version)	6-17	7 weeks: 80 (63) 40 (63)
311	164 Modafinil 84 Placebo	2:1 Mod/Pla flexible dose: 170 to 425 mg/day	9 weeks DB treatment	ADHD-RS-IV (School Version)	6-17	97 (59) 33 (39)

1.3 Statistical Issues and Findings

With double blind treatment periods of 9 weeks (or 7 in one case) these studies were longer than the 4 weeks seen in some studies of stimulants for ADHD. There were a considerable number of early withdrawals in these studies which resulted in missing data at the endpoint; the placebo group had a much larger dropout rate (most due to lack of efficacy) in Studies 309 and 311. The primary LOCF analysis of the ITT population was positive in all three studies ($p<0.001$) as was the analysis of the Observed Cases. A mixed model for repeated measures analysis approach was investigated as a sensitivity analysis. This approach also found statistically significant treatment

group differences in the primary endpoint at the end of week 9 (or 7). Given the agreement of the ITT-LOCF, Observed Case, and mixed model analyses, the dropouts do not seem to have biased the conclusion of efficacy. However, since there is a high proportion of dropouts the LOCF analysis doesn't permit us to say with certainty that there is a significant group difference at the planned end of the study, week 9. This is because carrying forward ratings from earlier times for those who dropped out means that the comparison no longer only involves week 9 ratings. Therefore, it is confounded with the treatment group differences at earlier weeks. The observed case analysis does not overcome this problem because it omits randomized patients. Although it seems unlikely given the strength of the LOCF and observed case results, if the unobserved week 9 treatment group difference for dropouts was different than the treatment group difference observed for completers then the true overall week 9 difference might not be statistically significant.

The sponsor does not appear to have provided any rationale for the high dropout rate or the difference in dropout rates between the identically designed studies 309 and 311. This reviewer noted a nominally significant difference between study 309 and 311 in the mean baseline ADHD-RS-IV Total scores (309: 38.3; 311: 35.6 p=0.001). This difference could be associated with the overenrollment in study 311 (311: N=244 309: N=194). The lower baseline scores in study 311 indicate that the patients were less severely affected at baseline on average and therefore potentially more inclined to drop out.

Although the timepoint for the primary analysis was the end of week 9 it was also planned to test the change in ADHDRS school version from baseline to weeks 1, 2, 3, 5, and 7 as secondary analyses. In study 309 the earliest timepoint at which the treatment group difference in changes in ADHD-RS-IV total scores was nominally significant was the end of week 3. In studies 310 and 311 the treatment group difference was nominally significant as early as the end of the first week. However, the analyses of the ADHD-RS-IV (school) at earlier timepoints were not the only secondary analyses. Numerous other secondary analyses were also planned including the TOVA omission errors, TOVA commission errors, and TOVA reaction time. These TOVA endpoints were listed earlier in the list of secondary variables than the ADHDRS (school) at weeks 1, 2, 3, 5, and 7. Although there was a list there was no plan to avoid the increase in type I error associated with reporting all the secondary analyses. Since the group comparison of the TOVA commission errors was not significant at the last post-baseline visit in any of the studies and there was no formal plan for adjusting for the multiplicity of secondary endpoints, from a statistical perspective, no claim should be allowed on the first week that modafinil separated from placebo on the change in ADHDRS (school version).

One question of interest is whether efficacy was demonstrated in both children and adolescents. Ages ranged between 6 and 17 across the three pivotal studies and the mean age was 10. About 67% of patients were under age 12. Nevertheless, nominally significant p-values for the treatment group comparison of the change in ADHD-RS-IV total score (school version) were seen in both age subgroups in studies 309 and 310. There were 61, 58, and 90 patients age 12 or older in studies 309, 310, and 311, respectively. In study 311 the treatment comparison was nominally significant only in the age < 12 subgroup but overall there is no compelling evidence of a difference in efficacy between the age subgroups.

One of the secondary objectives of study 310 was to assess withdrawal from the drug and to this end the last 2 weeks of the study were a randomized withdrawal phase. At the end of week 7 the withdrawal period began. Patient's initially randomized to the Modafinil/Placebo sequence received placebo from this time until the end of week 9. The other patients' double blind treatment was unchanged for the final two weeks. All three groups worsened to some extent over the two week withdrawal period. The Modafinil/Placebo group's mean change from week 7 to week 9 was numerically worse than the Modafinil/Modafinil group's mean by 4.3 points suggesting some rebound, but the difference was not statistically significant. Note that about 1/3 of the modafinil patients had dropped out of the study before the start of the withdrawal period and thus did not have an assessment at the end of the withdrawal period. Therefore, this comparison may be underpowered and no definitive conclusions on the existence or absence of a withdrawal effect can be made on the basis of this study.

In study 311 about 38% more patients were randomized than originally planned (248 vs. 180). However, the LOCF analysis of the first 180 patients screened and randomized still produced a statistically significant result favoring modafinil ($p<0.0001$). Therefore, the over-enrollment doesn't seem to be a serious issue.

2 INTRODUCTION

2.1 Overview

PROVIGIL (modafinil) Tablets C-IV (CEP-1538) are a novel wakefulness-promoting agent indicated for excessive daytime sleepiness in patients with narcolepsy, obstructive sleep apnea/hypopnea syndrome (OSAHS), and shift work sleep disorder (SWSD). Modafinil is currently being evaluated for the treatment of children and adolescents with attention-deficit/hyperactivity disorder (ADHD).

Three Phase 3, placebo-controlled studies (C1538d/**309**/AD/US, C1538d/**310**/AD/US, and C1538d/**311**/AD/US; hereafter referred to as studies 309, 310, and 311) and the on-going long-term open-label study (C1538d/**312**/AD/US) were undertaken and are presented in this submission as the primary basis to demonstrate the efficacy and safety of modafinil tablets for use in the treatment of children and adolescents with ADHD. A total of 638 patients were enrolled in the 3 Phase 3 placebo-controlled studies. Two of these studies 309 and 311, were identically designed flexible-dosage studies with a 9-week double-blind treatment period. Study 310 had a weight-based fixed-dosage design with a 7-week double-blind treatment period followed by a 2-week randomized-withdrawal period. Following the placebo-controlled studies, patients were given the option to enroll into a 1-year open-label study (study 312) to assess longer term safety and efficacy of modafinil.

2.2 Data Sources

The datasets for this application are located at the following address:
\\Cdsesub1\n20717\S_019\2004-12-20\crt\datasets

There are folders named for each of the pivotal studies 309, 310, and 311.
The data for the primary endpoint is found in the D_ADHDS.xpt file in the respective study folder.

3 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study 309

The first patient was enrolled on 8 November 2003 and the last patient completed the study on 27 May 2004.

3.1.1.1 Objective

The primary objective of this study was to evaluate the efficacy of modafinil treatment, as compared to a placebo, in alleviating the symptoms of ADHD in children and adolescents as assessed by the change from baseline to the last postbaseline visit (week 9 or early termination) in the total score from the teacher/physician-completed ADHD Rating Scale, Fourth Edition (ADHD-RS-IV) (School Version).

3.1.1.2 Study Design

This was a multicenter, 9-week, randomized, double-blind, placebo-controlled, flexible-dosage, parallel-group study to compare the efficacy and safety of modafinil treatment to placebo treatment in children and adolescents with ADHD. Patients were randomized in a 2:1 ratio to receive either modafinil or placebo tablets. The study consisted of a 1- to 4-week screening/washout period, followed by 9 weeks of double-blind treatment. Visits included screening, washout (if needed), baseline, and weeks 1, 2, 3, 5, 7, and 9 (or early termination).

Study drug was titrated individually for each patient on the basis of tolerability and efficacy. At the end of each week of treatment, a patient may have remained at the current dosage or the dosage may have been increased (up to 425 mg/day). If a patient was unable to tolerate the study drug, the dosage may have been decreased (minimum dosage of 170 mg/day). At the completion of the study, patients were eligible to enroll into a 1-year open-label extension study. In addition, patients who completed at least 4 weeks of double-blind treatment and did not withdraw due to an adverse event were also eligible to enroll into the open-label extension study.

3.1.1.3 Efficacy Assessments

Primary

The primary efficacy variable was the change from baseline to the last postbaseline visit (week 9 or early termination) in the total score of the teacher/physician-completed ADHD Rating Scale-

IV (ADHD-RS-IV) (School Version). The ADHD-RS-IV (School Version) (Barkley 1990) was developed to evaluate the occurrence of ADHD symptoms in children and has been shown to be sensitive to drug effects in children. The ADHD-RS-IV assesses the frequency of each of 18 individual criteria symptoms of ADHD in the DSM-IV on a 4-point Likert scale (0=never or rarely, 1=sometimes, 2=often, or 3=very often). The ADHD-RS-IV (School Version) was completed by the investigator by interviewing the patient's weekday teacher. At the assessment, the rater asked the teacher to make a determination of symptomatic frequency that best described the child's school behavior (in accordance with DSM-IV guidelines) since the last clinic visit.

Secondary

Secondary efficacy variables were:

- the change from baseline to each time point for the following:
  - TOVA response time and errors of omissions and commissions at weeks 3, 7, and 9, and last postbaseline visit
  - teacher/physician-completed ADHD-RS-IV (School Version) total scores at weeks 1, 2, 3, 5, 7, and 9; subscale scores for inattention and hyperactivity-impulsivity at weeks 1, 2, 3, 5, 7, and 9, and last postbaseline visit
  - parent/physician-completed ADHD-RS-IV (Home Version) total and subscale (inattention and hyperactivity-impulsivity) scores at weeks 1, 2, 3, 5, 7, and 9, and last postbaseline visit
- CGI-C ratings (for improvement of ADHD symptoms) at weeks 1, 2, 3, 5, 7, and 9, and last postbaseline visit.

The Test of Variables of Attention (TOVA) is a computerized continuous performance test (CPT) that objectively measures a child's or adolescent's inattention and hyperactivity/impulsivity. It was completed by the child or adolescent in approximately 22 to 25 minutes via a computer with the TOVA electronic microswitch. (A practice test lasting approximately 2 - 5 minutes was performed at the baseline visit.) The following secondary efficacy variables were obtained from the TOVA: omission errors, commission errors, and response time (RT).

3.1.1.4 Statistical Methods

The full analysis set, defined as all randomized patients that received at least one dose of study drug and had at least one post-baseline efficacy assessment, was to be used for all efficacy analyses. Summaries were to be presented by treatment group. The null hypothesis to be tested was that the mean change from baseline to endpoint (week 9 or last postbaseline visit) in the total score from the ADHD-RS-IV (School Version) was equal between modafinil and placebo treatment groups. This hypothesis was to be tested by means of an analysis of covariance (ANCOVA) model with treatment and center as factors and the corresponding baseline value as a covariate. This test and all other tests were to be 2-tailed, at a significance level of 0.05.

Sample Size Considerations

From Cephalon's Phase 2 study in children with ADHD (study C1538a/213/AD/US), the standard deviation of the change from baseline to week 4 (or the final visit of double-blind period) in the teacher/physician-completed ADHD-RS-IV (School Version) total score was 10.69 in a subset of patients similar to that proposed for this study who took either modafinil (49 patients) at a dose of 300 mg in the morning or placebo (48 patients). Assuming the same variability in this study, approximately 100 patients in the modafinil treatment group and 50 patients in the placebo group will be required to detect a between-group difference of 6.03 units in the mean change from baseline for the teacher/physician-completed ADHD-RS-IV (School Version) total score with at least 90% power, using a 2-tailed t-test at the 0.05 level of significance. After accounting for the possibility of dropouts, a total sample size of 180 patients will be required in this study.

Analysis Populations

The set of randomized patients includes all patients who were randomized to a treatment group, regardless of whether or not a patient received any study drug. The safety analysis set includes all patients who received 1 or more doses of study drug. The full analysis set includes those in the safety analysis set who have at least 1 postbaseline primary efficacy assessment.

Primary Analysis Method

The full analysis set will be used for all efficacy analyses. Summaries will be presented by treatment group. The null hypothesis to be tested is that the mean change from baseline to endpoint (week 9 or last postbaseline visit) in the total score from the ADHD-RS-IV (School Version) is equal between modafinil and placebo treatment groups. This hypothesis will be tested by means of an analysis of covariance (ANCOVA) model with treatment and center as factors and the corresponding baseline value as a covariate. All tests will be 2-tailed, at a significance level of 0.05.

The assumption of no treatment-by-center interaction will be evaluated by a separate ANCOVA model with treatment, center, treatment-by-center interaction, and baseline in the model. If there is evidence of treatment-by-center interaction (p-value≤0.10), further exploratory analyses based on individual centers will be performed. Centers with inconsistent treatment effects will be identified and further investigated.

The assumption of no treatment-by-covariate interaction will be evaluated by a separate ANCOVA model with treatment, center, baseline, and treatment-by-baseline interaction in the model. If there is evidence of treatment-by-covariate interaction (p-value≤0.10), the above primary efficacy analysis to determine the treatment differences will be replaced by an analysis of variance model without the baseline value as a covariate. Because ANCOVA procedures are usually robust against the normal distribution assumption for large samples, no plans are deemed necessary to check this assumption.

Actual values and changes from baseline to endpoint in the total score from the teacher/physician-completed ADHD-RS-IV (School Version) will be summarized by treatment group using descriptive statistics.

Secondary Analysis Methods

With the exception of CGI-C ratings, the secondary and additional efficacy variables will be analyzed at each time point using the same model as the primary efficacy analysis. The CGI-C ratings on the CGI-C scale will be compared between the treatment groups at each time point using the Cochran-Mantel-Haenszel test adjusted for centers.

3.1.1.5 Disposition of Patients

A total of 200 patients at 18 centers were randomized into the study. Two patients randomized to the modafinil treatment group did not receive study drug. Three additional patients randomized to the modafinil treatment group and 1 patient randomized to the placebo treatment group were not evaluable for efficacy. Of the 200 randomized patients, 141 (71%) completed at least 9 weeks of double-blind treatment, and 59 (30%) patients were withdrawn from the study (33 and 26 patients from the modafinil and placebo treatment groups, respectively). Overall, 170 (85%) patients entered the open-label extension study. Of the 59 patients who withdrew from the study, 10 (6 and 4 patients from the modafinil and placebo treatment groups, respectively) withdrew due to adverse events. The most frequent reason for withdrawal was lack of efficacy (34 [17%] patients, 15 [11%] and 19 [28%] patients from the modafinil and placebo treatment groups, respectively).

Table 2 Study 309: Patient Disposition

	Number (%) of patients		
Patient disposition	**Modafinil**	**Placebo**	**Total**
Screened	NA	NA	295
Randomized	133 (100)	67 (100)	200 (100)
Randomized, not treated	2 (2)	0	2 (1)
Safety analysis set	131 (98)	67 (100)	198 (99)
Full analysis set[a]	128 (96)	66 (99)	194 (97)
Completed	100 (75)	41 (61)	141 (71)
Discontinued study	33 (25)	26 (39)	59 (30)
Death	0	0	0
Adverse event	6 (5)	4 (6)	10 (5)
Lack of efficacy	15 (11)	19 (28)	34 (17)
Consent withdrawn	5 (4)	1 (1)	6 (3)
Protocol violation	0	0	0
Lost to follow-up	5 (4)	0	5 (3)
Noncompliance	0	0	0
Other	2 (2)	2 (3)	4 (2)
Enrolled into open-label study	113 (85)	57 (85)	170 (85)

SOURCE: Summary 15.1, Listing 2.

[a]Three patients in the modafinil safety analysis set and 1 patient in the placebo safety analysis set were not evaluable for efficacy.

NA=not applicable.

Copied from table 6 on page 51 of sponsor's study report.

3.1.1.6 Patient Demographics

Of the 198 patients who received study drug, 144 (73%) were boys and 54 (27%) were girls. The majority (142 [72%]) of the patients were white. The mean age of the patients was 9.9 years (range 6 to 16 years), and the mean weight was 40.1 kg (range 18.6 to 87.1 kg). No statistically significant differences were observed between the treatment groups with regard to demographic characteristics.

Table 3 Study 309: Baseline Demographic Characteristics

Demographic variable	Modafinil (N=131)	Placebo (N=67)	Overall (N=198)
Age, years			
n	131	67	198
Mean	9.9	9.9	9.9
SD	2.64	2.90	2.72
Median	9.0	10.0	9.0
Min, max	6.0, 16.0	6.0, 16.0	6.0, 16.0
Sex, n (%)			
Male	95 (73)	49 (73)	144 (73)
Female	36 (27)	18 (27)	54 (27)
Race, n (%)			
White	95 (73)	47 (70)	142 (72)
Black	24 (18)	12 (18)	36 (18)
Asian	0	1 (1)	1 (<1)
American Indian or Alaskan Native	2 (2)	0	2 (1)
Pacific Islander	1 (<1)	1 (1)	2 (1)
Other	9 (7)	6 (9)	15 (8)
Weight, kg			
n	131	67	198
Mean	39.7	40.9	40.1
SD	15.88	16.50	16.06
Median	36.3	36.7	36.3
Min, max	18.6, 87.1	20.0, 85.3	18.6, 87.1
Height, cm			
n	131	67	198
Mean	141.1	143.3	141.8
SD	16.72	18.52	17.33
Median	136.7	140.5	137.2
Min, max	114.3, 186.2	118.1, 184.2	114.3, 186.2

Copied from Table 8 on page 54 of sponsor's study report c1538d-309-ad-us.pdf

Baseline ADHD Severity

All patients had ADHD at baseline, and the majority (70%) had the combined subtype. CGI-S scores at baseline indicated that approximately 82% of patients were moderately to markedly ill and approximately 17% were severely ill.

3.1.1.7 Sponsor's Results

The primary efficacy variable was the change from baseline to the last postbaseline visit (week 9 or early termination) in the total score from the ADHD-RS-IV (School Version). The change from baseline was analyzed using an ANCOVA model with treatment and center as factors, and the corresponding baseline value as a covariate. For patients in the modafinil treatment group, a statistically significant ($p<0.0001$) improvement from baseline to the last postbaseline visit was observed for the ADHD-RS-IV (School Version) total score when compared to patients in the placebo treatment group. The mean decrease (unadjusted) was 17.5 points for the modafinil treatment group and 9.7 points for the placebo treatment group, with a difference between groups of 7.8 points.

Table 4 Study 309: Mean Change From Baseline to Week 9 in ADHD-RS (school)

Time point Statistic	Modafinil (N=128)	Placebo (N=66)
Baseline		
n	128	66
Mean	38.6	37.8
SD	8.81	9.02
Median	39.0	39.0
Min, max	12.0, 53.0	10.0, 53.0
Final visit		
n	128	66
Mean	21.1	28.0
SD	13.57	12.70
Median	20.0	26.5
Min, max	0.0, 52.0	2.0, 50.0
Change from baseline to final visit		
n	128	66
Mean	-17.5	-9.7
SD	13.11	10.28
Median	1.16	1.27
Min, max	-46.0, 16.0	-32.0, 14.0
p-value[a]	<0.0001**	NA

SOURCE: Summary 15.9, Listing 11.

NOTE: The final visit is the last postbaseline visit.

**p<0.01.

[a]The p-value for the treatment comparison of modafinil to placebo is from an analysis of covariance (ANCOVA) model with treatment and center as factors, and the baseline value as a covariate.
Min=minimum; max=maximum; NA=not applicable.
Copied from table 14 on page 62 of sponsor's study report.

Secondary Endpoints

The change from baseline to the last postbaseline visit (week 9 or early termination) in the

ADHD score from the TOVA indicated a statistically significant difference (p=0.0006) between the modafinil and placebo treatment groups in favor of modafinil.

Reviewer's Comment: *The ADHD subpart of the TOVA was not listed as a secondary endpoint in the protocol or protocol amendments - Omission errors, Commission errors, and Reaction time were the only subparts of the TOVA mentioned.*

The CGI-C is a clinician-rated assessment of change over time in the patient's ADHD during the study, as compared to the CGI-S which measures the severity at baseline. The CGI-C ratings were analyzed at each visit and the last postbaseline visit, using the CMH test adjusted for center. Nominally significant improvement (much improved or very much improved) in ADHD symptoms was seen for patients in the modafinil treatment group when compared with patients in the placebo treatment group at each visit beginning at week 1 (p=0.0004) through week 9 (p<0.0001) and at the last postbaseline visit (p<0.0001). CGI-C ratings at the last postbaseline visit are presented in Table 5.

Table 5 Study 309: CGI-C ratings at Week 9 (or LOCF)

	Number (%) of patients	
CGI-C Category	**Modafinil (N=128)**	**Placebo (N=65[a])**
Very much improved	19 (15)	0
Much improved	47 (37)	12 (18)
Minimally improved	25 (20)	15 (23)
No change	32 (25)	33 (51)
Minimally worse	3 (2)	4 (6)
Much worse	2 (2)	1 (2)
Very much worse	0	0
p-value[b]	<0.0001**	NA

copied from table 19 on page 70 of sponsor's study report c1538d-309-ad-us.pdf

3.1.1.8 Reviewer's Results

This was a flexible dose study with doses starting at 85 mg and being titrated up to an optimum dose (in terms of tolerability) between 170 and 425 mg. Stable dose was defined as the dose that the patient took for the longest amount of time. The average stable dose for the Modafinil group was 367 mg and the median was 425 (only 40% were dosed below 425 mg). Ages ranged between 6 and 16; the mean age was 9.9 and the median age was 9.0.

This reviewer verified the primary ANCOVA analysis result that the modafinil group was significantly better (p<0.001) than the placebo group in terms of the change in ADHD-RS (school) total score at the end of week 9 (or last post-baseline observation for dropouts). As 25% of the modafinil group and 39% of the placebo group failed to complete the study it is important to assess the impact the dropouts might have had on the results and conclusions. One way to do this is to check for consistency of the results for the ITT and Completers populations.

As seen in Table 6 it turns out that the analysis of the completers population, those patients who had an ADHDRS (school) measurement at the end of week 9, supports the ITT-LOCF analysis result.

Table 6 Study 309: Comparison of ITT-LOCF and Observed Case Results for ADHD-RS-IV (school) (Reviewer's Results)

		PROVIGIL		PLACEBO			
Population	Study	N	LS Mean Change	N	LS Mean Change	LS Mean Difference	P-value*
ITT-LOCF	309	128	-17.5	66	-9.7	7.7	<0.001
OC	309	100	-19.9	41	-11.6	8.3	0.001

* based on ANCOVA model adjusted for baseline ADHDRS Total, site, treatment

Within each treatment group patients that stayed in the study until the end tended to do better than those who dropped out early. However, the difference between treatment group means was similar for the completers population and the ITT population (using LOCF for dropouts).

This reviewer also investigated a mixed model for repeated measures analysis as a sensitivity analysis. If we assume that missing data is missing at random, which means that the probability of a missing score does not depend on the unobserved score, then a mixed model for repeated measures may be appropriate. In this approach all the observed post-baseline data for each patient is modeled rather than just the final measurement and there is no imputation of missing data or observations carried forward. The validity of this analysis depends on whether or not the missing at random assumption holds and correct specification of the form of the model.

The mixed model investigated here included fixed effects for treatment group, week, week by treatment group interaction, and the baseline ADHD-RS-IV score as a covariate. In addition, it was assumed that observations from the same patient were correlated but no structure was prescribed for the pairwise correlations (corresponding to each possible pair of measurement times). For example, if a patient completed the study then they should have one ADHD-RS-IV measurement for each of the 6 visits (week 1, 3, 5, 7, and 9). We assume that the week 9 ADHD-RS-IV score is correlated with each of the week 1, 3, 5, and 7 scores and likewise for each other possible pair of measurement times. It is sometimes assumed that ratings made closer together in time are more strongly correlated (e.g., the patient's week 7 and 9 ADHD-RS-IV scores are more strongly correlated than the week 1 and week 9 scores). However, this may not be the case and it is not necessary to make this assumption. At the price of adding a few extra parameters we can avoid the need to make any assumptions about how the correlation depends on the time between ratings. So, this reviewer chose this unstructured correlation approach for the mixed model. A comparison of the treatment group mean ADHD-RS changes at the end of week 9 based on this mixed model yielded an estimated difference of 7.2 points ($p<0.001$). Therefore, the mixed model analysis also supports the primary LOCF analysis.

Figure 1 shows the change from baseline in the ADHD-RS-IV (school) total score over time. Scores were not always taken at the protocol specified times. For constructing the figure the time at which a score was taken was classified according to the closest protocol specified visit week. The treatment group difference did not reach nominal significance until after week 3.

Figure 1 Study 309: Change from Baseline in ADHD-RS-IV (school) by Week

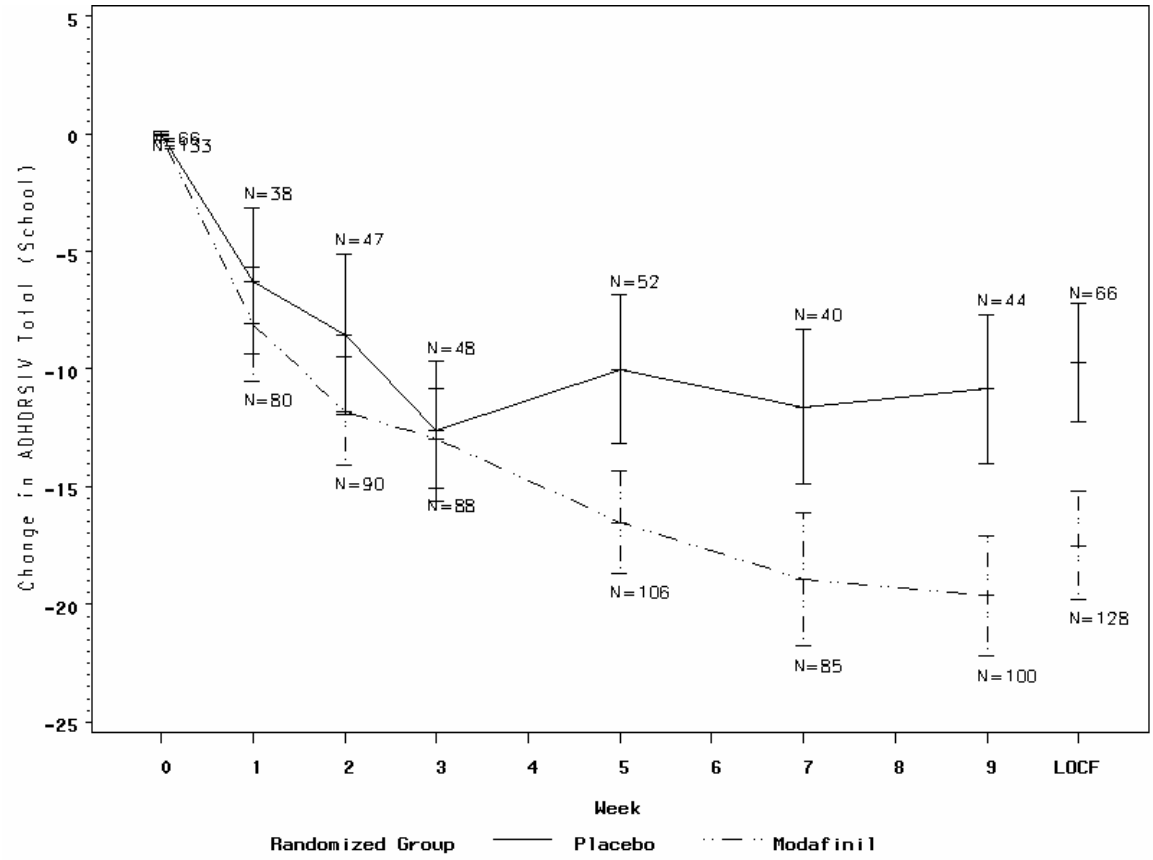


Table 7 shows the mean changes from baseline to week 9 in the ADHD-RS-IV (school) by termination reason. The most common reason given for early withdrawal was lack of efficacy. This was more frequent in the placebo group than the modafinil group(28% vs. 11%). The treatment group difference was smaller in the group of patients that withdrew early but still favored modafinil numerically. On the whole, given the concurrence of the LOCF, OC, and mixed model analyses it seems unlikely that the dropouts biased the results.

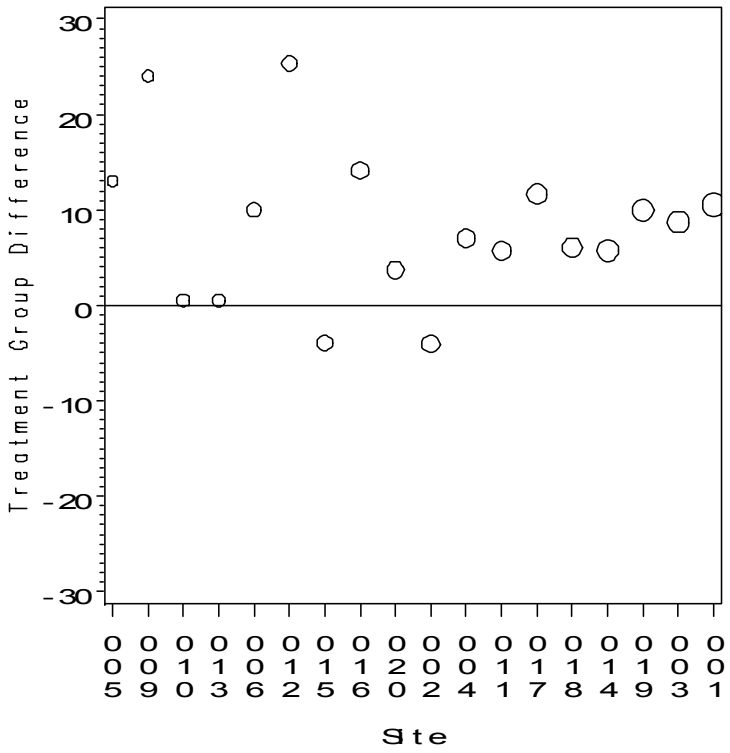
Table 7 Study 309: Mean ADHDRS Change from Baseline (LOCF) by Termination Reason

			MODAFINIL			PLACEBO	
COMPLETE	REASON	N	BASELINE	CHANGE MEAN (SD)	N	BASELINE	CHANGE MEAN (SD)
NO	ADVERSE EVENT	4	39.8 (8.9)	-8.3 (8.7)	4	36.5 (8.7)	-6.8 (12.2)
NO	CONSENT WITHDRAWN	4	43.6 (5.6)	-6.8 (10.5)	0		
NO	LACK OF EFFICACY	15	40.0 (10.9)	-9.1 (11.6)	19	39.7 (11.9)	-5.5 (8.8)
NO	LOST TO FOLLOW-UP	3	37.0 (11.1)	-2.3 (5.5)	.		.
NO	OTHER	2	31.5 (9.2)	-21.5 (3.5)	2	31.5 (12.0)	-17.5 (12.0)
NO	ALL	28	39.5 (9.7)	-8.8 (10.5)	25	38.8 (11.1)	-6.7 (9.7)
YES		100	38.7 (8.6)	-19.9 (12.8)	41	37.3 (7.4)	-11.6 (10.3)

Treatment Group Differences within Individual Sites

The following figure displays the differences in treatment group mean changes from baseline to week 9 (or LOCF) in ADHD-RS (school) total score by site. The size of the plotting symbol indicates the relative number of patients in the site. The treatment effect was relatively consistent across sites as evidenced by the fact that the placebo mean change was numerically better than the modafinil mean change in only 2 centers. There were no centers with treatment effects farther from the average than expected due to random variation.

Figure 2 Study 309: Differences in Treatment Group Mean Changes in ADHD-RS (school) by Site



3.1.1.9 Conclusions for Study 309

In summary, modafinil was significantly better than placebo in terms of efficacy for the treatment of children and adolescents with ADHD in study 309.

3.1.2 Study 310

3.1.2.1 Study Design

This was a multicenter, 9-week, randomized, double-blind, placebo-controlled, parallel-group study to compare the efficacy and safety of modafinil treatment (340 or 425 mg/day) to a placebo treatment in children with ADHD. The study consisted of a 1- to 4-week screening/washout period, followed by 9 weeks of treatment with the study drug. For the first 7 weeks, patients weighing less than 30 kg were to be randomized to receive 340 mg/day of modafinil or a placebo. Patients weighing at least 30 kg were to be randomized to receive 425 mg/day of modafinil or a placebo. Study drug was to be titrated during the first 7 to 9 days of the treatment period. Patients were to remain at their dose for the remainder of the 7-week, double-blind treatment period.

The final 2 weeks (weeks 8 and 9) was a blinded withdrawal period, when modafinil-treated patients were randomized to receive either modafinil or placebo and placebo-treated patients continued taking the placebo for a 2-week period. Patients were to receive either 4 or 5 tablets per day (on the basis of body weight) of modafinil or placebo during the withdrawal period. In order to maintain the blind throughout the study patients were randomized to 1 of 3 treatment sequences in a 1:1:1 ratio (modafinil/modafinil, modafinil/placebo, or placebo/placebo) within each weight stratum. Visits were to include screening, washout (if needed), baseline, and weeks 1, 2, 3, 5, 7, and 9 (or early termination).

3.1.2.2 Statistical Methods

The full analysis set consisting of all patients that received study drug and had at least one post-baseline primary efficacy assessment was to be used for all efficacy analyses. Summaries were to be presented by treatment group. The null hypothesis to be tested was that the mean change from baseline to endpoint (week 7 or last double-blind treatment period visit) in the total score from the ADHD-RS-IV (School Version) was equal between modafinil and placebo. This hypothesis was to be tested by means of an analysis of covariance (ANCOVA) model with treatment, weight stratum, and treatment-by-stratum interaction as factors, and the corresponding baseline value as a covariate. All tests were to be 2-tailed, at a significance level of 0.05.

Secondary variables were the same as those in study 309 (see section 3.1.1.3 page 8) except that the length of the double blind treatment period was only 7 weeks instead of 9. All secondary variables other than the CGI-C ratings were analyzed with ANCOVA models including the same effects as the primary analysis model. The CGI-C ratings were to be analyzed using a Cochran-Mantel-Haenszel test adjusted for weight strata.

Assuming the standard deviation of the change from baseline in the teacher/physician-completed ADHD-RS-IV (School Version) total score is 10.69, which is based on the results of a phase II study, approximately 100 patients in the modafinil treatment group and 50 patients in the placebo group would be required to detect a between-group difference of 6.03 units in the mean change from baseline for the teacher/physician-completed ADHD-RS-IV (School Version) total score (the observed difference at week 4 or final visit of double-blind period in C1538a/213/AD/US) with at least 90% power using a 2-tailed t-test at the 0.05 level of significance. Accounting for the possibility of dropouts, the sponsor anticipated that a total sample size of 180 patients would be required.

3.1.2.3 Patient Disposition

A total of 190 patients at 17 centers entered the study and were randomized. Of these, 189 patients received at least 1 dose of study drug (safety analysis set), 183 patients had at least 1 post-baseline efficacy assessment (full analysis set), and 120 (63%) patients completed at least 7 weeks of double-blind treatment. In addition, 120 patients entered, and 115 (61%) patients completed the randomized withdrawal period. Seventy (37%) patients were withdrawn from the study during the double-blind treatment period (see Table 8). The most frequent reasons for

withdrawal in modafinil-treated patients during the double-blind treatment period were lack of efficacy (18 [14%]), adverse event (11 [9%]), and consent withdrawn (7 [6%]). In the placebo treatment group, the most frequent reasons for withdrawal were lack of efficacy (17 [27%]) and consent withdrawn (6 [9%]). Eleven (6%) patients, all receiving modafinil, withdrew from the double-blind treatment period of the study due to adverse events.

Table 8 Study 310: Patient Disposition

	Number (%) of patients				
Patient disposition	**Modafinil 340 mg/day (N=44)**	**Modafinil 425 mg/day (N=82)**	**All Modafinil (N=126)**	**Placebo (N=64)**	**Overall (N=190)**
Screened	NA	NA	NA	NA	316
Randomized	44[a]	82[b]	126	64	190
Completed double-blind treatment period	26 (59)	54 (66)	80 (63)	40 (63)	120 (63)
Withdrawn during double-blind treatment period	18 (41)	28 (34)	46 (37)	24 (38)	70 (37)
Adverse event	5 (11)	6 (7)	11 (9)	0	11 (6)
Lack of efficacy	8 (18)[c]	10 (12)	18 (14)	17 (27)	35 (18)
Consent withdrawn	1 (2)	6 (7)	7 (6)	6 (9)	13 (7)
Protocol violation	1 (2)	0	1 (<1)	1 (2)	2 (1)
Lost to follow-up	1 (2)	0	1 (<1)	0	1 (<1)
Noncompliance to study medication	1 (2)	0	1 (<1)	0	1 (<1)
Noncompliance to study procedures	0	1 (1)	1 (<1)	0	1 (<1)
Other	1 (2)	5 (6)	6 (5)	0	6 (3)
Completed randomized withdrawal period	26 (59)	53 (65)	79 (63)	36 (56)	115 (61)
Withdrawn during randomized withdrawal period	0	1 (1)	1 (<1)	4 (6)	5 (3)
Lack of efficacy	0	1 (1)	1 (<1)	3 (5)	4 (2)
Consent withdrawn	0	0	0	1 (2)	1 (<1)
Full analysis set	41 (93)	79 (96)	120 (95)	63 (98)	183 (96)
Safety analysis set	44 (100)	81 (99)	125 (>99)	64 (100)	189 (>99)
Withdrawal analysis set	26 (59)	54 (66)	80 (63)	40 (63)	120 (63)
Enrolled into open-label extension study	27 (61)	57 (70)	84 (67)	49 (77)	133 (70)

SOURCE: Summary 15.1, Listing 2, Listing 3, Listing 21, and Listing 22.

NA=not applicable; CRF=case report form.

[a]Patient 023615 was properly assigned the 425 mg/day dosage of modafinil, but according to treatment records only took 340 mg of modafinil on days 13 through 60. [b]Patient 027609 who was assigned to, and received, 425 mg of modafinil on days 9 through 63, should have been
assigned to receive 340 mg of modafinil (based on body weight).

[c]According to the termination page of the CRF, lack of efficacy was the reason for withdrawal for 8 patients receiving

Patient disposition	Number (%) of patients				
	Modafinil 340 mg/day (N=44)	Modafinil 425 mg/day (N=82)	All Modafinil (N=126)	Placebo (N=64)	Overall (N=190)

340 mg of modafinil; however, according to the adverse event page of the CRF, 1 of these patients was withdrawn due to adverse event.
Copied from table 6 of sponsor's study report 310.pdf

3.1.2.4 Patient Demographics

Of the 189 patients receiving study drug, 71% were boys and 29% girls. The mean age was 10.0 years (range 6.0 to 17.0 years). The majority of patients (121 [64%]) weighed at least 30 kg. The mean age for patients receiving 340 mg of modafinil was 7.5 years (range 6.0 to 11.0 years) compared to 11.6 years (range 7.0 to 17.0 years) for patients receiving 425 mg of modafinil because dosage was based on body weight and, therefore, correlated with age. The mean age in the placebo group was 9.7 years (range 6.0 to 17.0 years). Thirty-eight percent of patients in the placebo group weighed less than 30 kg. Mean weight in the placebo group (39.9 kg) was comparable to the mean weight for all modafinil patients (40.5 kg). The majority of patients were white (80%) or black (11%). No statistically significant differences were observed between the modafinil and placebo treatment groups with regard to demographic characteristics.

Table 9 Study 310: Baseline Demographic Characteristics

Demographic variable	Modafinil 340 mg/day (N=44)	Modafinil 425 mg/day (N=81)	All modafinil (N=125)	Placebo (N=64)	Overall (N=189)
Age, years					
Mean	7.5	11.6	10.1	9.7	10.0
SD	1.41	2.56	2.98	3.07	3.01
Min, max	6.0, 11.0	7.0, 17.0	6.0, 17.0	6.0, 17.0	6.0, 17.0
Sex, n (%)					
Male	30 (68)	63 (78)	93 (74)	42 (66)	135 (71)
Female	14 (32)	18 (22)	32 (26)	22 (34)	54 (29)
Race, n (%)					
White	33 (75)	67 (83)	100 (80)	51 (80)	151 (80)
Black	5 (11)	10 (12)	15 (12)	6 (9)	21 (11)
American Indian or Alaskan Native	0	1 (1)	1 (<1)	1 (2)	2 (1)
Other	6 (14)	3 (4)	9 (7)	6 (9)	15 (8)
Weight, kg					
Mean	25.2	48.8	40.5	39.9	40.3
SD	2.92	15.26	16.76	18.43	17.29
Min, max	19.6, 29.9	30.5, 98.4	19.6, 98.4	20.1, 91.2	19.6, 98.4
n (%) <30 kg	43 (98)	1 (1)[a]	44 (35)	24 (38)	68 (36)

Demographic variable	Modafinil 340 mg/day (N=44)	Modafinil 425 mg/day (N=81)	All modafinil (N=125)	Placebo (N=64)	Overall (N=189)
n (%) ≥ 30 kg	1 (2)[b]	80 (99)	81 (65)	40 (63)	121 (64)
Height, cm					
Mean	124.5	151.6	142.0	141.0	141.7
SD	5.80	14.56	17.80	17.22	17.56
Min, max	112.0, 137.2	123.2, 185.0	112.0, 185.0	113.0, 172.7	112.0, 185.0

SOURCE: Summary 15.2, Listing 5.

[a]Patient 027609 weighed 66 pounds at screening, was assigned to the 425 mg treatment group using a conversion factor of 2.2 performed at the study center. [b]Patient 023615 who weighed 45.8 kg at screening was assigned to receive 425 mg/day of modafinil; however, this
patient took 340 mg/day of modafinil during the double-blind treatment period.

Copied from table 8 on page 56 of sponsor's study report 310.pdf

The majority (91%) of patients were moderately ill (117 [62%]) or markedly ill (55 [29%)] according to the CGI-S rating at baseline. Most patients had the combined (126 [67%]) or inattentive (51 [27%]) ADHD subtypes.

Table 10 Study 310: Baseline ADHD Severity

Characteristic	Number (%) of patients[a]				
	Modafinil 340 mg/day (N=44)	Modafinil 425 mg/day (N=81)	All modafinil (N=125)	Placebo (N=64)	Overall (N=189)
CGI.S					
Normal	0	0	0	0	0
Borderline ill	0	0	0	0	0
Slightly ill	0	0	0	0	0
Moderately ill	29 (66)	50 (62)	79 (63)	38 (59)	117 (62)
Markedly ill	7 (16)	25 (31)	32 (26)	23 (36)	55 (29)
Severely ill	8 (18)	6 (7)	14 (11)	3 (5)	17 (9)
Among the most extremely ill	0	0	0	0	0
Current ADHD subtype					
Inattentive	11 (25)	24 (30)	35 (28)	16 (25)	51 (27)
Hyperactive/impulsive	4 (9)	1 (1)	5 (4)	5 (8)	10 (5)
Combined	29 (66)	55 (68)	84 (67)	42 (66)	126 (67)
Total number of symptoms					
Inattention					
n	41	78	119	63	-
Mean	21.4	22.2	21.9	21.0	ND
SD	3.90	3.91	3.91	4.25	ND
Median	22.0	23.0	23.0	22.0	ND
Min, max	10.0, 27.0	10.0, 27.0	10.0, 27.0	7.0, 27.0	ND
Hyperactive/impulsive					
n	41	78	119	63	-
Mean	17.5	15.1	15.9	15.7	ND
SD	7.94	7.56	7.75	7.12	ND
Median	20.0	16.0	17.0	16.0	ND

Characteristic	Number (%) of patients[a]				
	Modafinil 340 mg/day (N=44)	Modafinil 425 mg/day (N=81)	All modafinil (N=125)	Placebo (N=64)	Overall (N=189)
Min, max	0, 27.0	0, 27.0	0, 27.0	0, 27.0	ND
Combined					
n	41	78	119	63	-
Mean	38.9	37.3	37.8	36.6	ND
SD	9.39	8.68	8.93	9.24	ND
Median	41.0	37.0	39.0	38.0	ND
Min, max	18.0, 54.0	18.0, 53.0	18.0, 54.0	16.0, 54.0	ND

SOURCE: Summary 15.3 and Summary 15.10, and Listing 11 and Listing 14.

a Except as otherwise indicated, percentages are based on safety analysis set; values may not have been obtained for all children.

ADHD=attention-deficit hyperactivity disorder; ND=not determined.

Copied from table 9 on page 57 of sponsor's study report.

3.1.2.5 Sponsor's Results

The primary efficacy variable was the change from baseline to the last double-blind treatment period visit (week 7 or early termination) in the teacher/physician-completed ADHD-RS-IV (School Version) total score (Table 11). The change from baseline was analyzed using an ANCOVA model with treatment, stratum, and treatment-by-stratum interaction as factors, and the corresponding baseline value as a covariate. A statistically significant improvement in total score on the ADHD-RS-IV (School Version) was observed in patients taking modafinil when compared with the placebo group ($p<0.0001$). The mean change was -17.2 points for the modafinil treatment group and -8.2 points for the placebo treatment group, with a difference between groups of 9.0 points. The magnitude of the improvement was numerically greater in patients treated with 340 mg of modafinil (-18.1) compared to patients treated with 425 mg of modafinil (-16.8).

Table 11 Study 310: Mean Change in ADHD-RS (school) at week 9 (or LOCF)

Time point Statistic	Modafinil 340 mg/day (N=41)	Modafinil 425 mg/day (N=79)	All modafinil (N=120)	Placebo (N=63)
Baseline				
n	41	78	119	63
Mean	38.9	37.3	37.8	36.6
SD	9.39	8.68	8.93	9.24
Median	41.0	37.0	39.0	38.0
Min, max	18.0, 54.0	18.0, 53.0	18.0, 54.0	16.0, 54.0
Final visit				
n	41	79	120	63
Mean	20.8	20.6	20.7	28.4
SD	13.89	12.68	13.05	12.71
Median	19.0	20.0	19.5	28.0
Min, max	1.0, 49.0	0, 50.0	0, 50.0	0, 50.0

Time point Statistic	Modafinil 340 mg/day (N=41)	Modafinil 425 mg/day (N=79)	All modafinil (N=120)	Placebo (N=63)
Change from baseline to final visit				
n	41	78	119	63
Mean	-18.1	-16.8	-17.2	-8.2
SD	15.42	11.20	12.76	10.27
Median	-19.0	-16.0	-17.0	-8.0
Min, max	-50.0, 5.0	-44.0, 6.0	-50, 6.0	-32.0, 13.0
p.value[a]	NA	NA	<0.0001**	NA

SOURCE: Summary 15.9, Listing 11.
NA=not applicable.
*p < 0.05; **p < 0.01.
[a] The p-value for the overall treatment comparison is from an ANCOVA model, with treatment, stratum, and treatment-by-stratum interaction as factors, and the corresponding baseline value as a covariate.
Copied from table 13 on page 64 of sponsor's study report.

Secondary Endpoints
The change from baseline to the final double-blind visit in ADHD score on the TOVA was statistically significant in the comparison of modafinil treated patients and placebo treated patients (p=0.0462). The changes from baseline to the final double-blind treatment visit were not statistically significant for response time, errors of omission, errors of commission, RT variability, and D prime TOVA scores.

At the last postbaseline visit of the double-blind treatment period, the number of patients who were improved on the CGI-C was nominally significant (p=0.0037) for patients in the modafinil treatment group when compared with patients in the placebo treatment group. The percentage of patients who were improved was nominally significant starting at week 1 (p=0.0002) and continuing through last visit of the double-blind period (week 7; p=0.0013).

3.1.2.6 Reviewer's Results

Patients randomized to Modafinil received 340 mg if they weighed less than 30 kg or 425 mg otherwise. The sponsor's ANCOVA model planned for the primary analysis included effects for weight stratum, treatment, treatment by stratum interaction and baseline ADHD-RS-IV score. This model is useful for testing for a difference between modafinil and placebo within each of the two weight classes and determining whether the differences between modafinil and placebo depend on the baseline weight class. Note that it does not allow an assessment of a dose by weight interaction since no patients < 30 kg received the 425 dose and none >= 30 kg received the 340 dose. In addition, it does not permit a test of the difference in modafinil and placebo groups irrespective of the weight class, i.e., a global test. Therefore, it creates a multiplicity problem. The sponsor did not propose any multiplicity adjustment for doing the 2 comparisons. However, modafinil was significantly better than placebo in both weight subgroups (p<0.001). It turns out that the multiplicity is not really an issue since the two p-values are smaller than 0.025 or any other reasonable multiplicity-adjusted critical significance level. Removing the effects for the interaction between weight stratum and treatment group from the model permits conducting

the global treatment comparison. This was also statistically significant in favor of modafinil (p<0.0001).

Table 12 shows the results of the primary ITT-LOCF analysis and the analysis of the Observed Cases. The mean changes were smaller (larger in absolute value) for both groups in the Observed cases than in the ITT population overall. This suggests that completers' last scores were better than dropouts' last scores. However, since the treatment group differences and the p-values were similar for the ITT-LOCF and the Observed Cases analyses the dropouts do not seem to have had much impact on the analysis conclusions.

Table 12 Study 310: Comparison of ITT-LOCF and Observed Case Results for ADHD-RS-IV (school)

		PROVIGIL		PLACEBO			
Population	Study	N	LS Mean Change	N	LS Mean Change	LS Mean Difference	P-value*
ITT-LOCF	310	119	-17.2	63	-8.2	9.0	<0.001
OC	310	79	-20.2	36	-11.6	8.6	0.001

* based on ANCOVA model adjusted for baseline ADHDRS Total, site, treatment

The most frequent reason given for early termination from the study was lack of efficacy. Table 13 shows the mean changes in ADHD-RS (school) total score by termination reason. Although, as one would expect, patients that terminated early due to lack of efficacy did worse than completers those in the modafinil group still fared better than those in the placebo group. Among those who terminated early those in the modafinil group averaged 7.7 points better than those in the placebo group. This is slightly less than the group difference among the completers. Overall there is no compelling evidence that the dropouts biased the treatment comparison at the end of week 7.

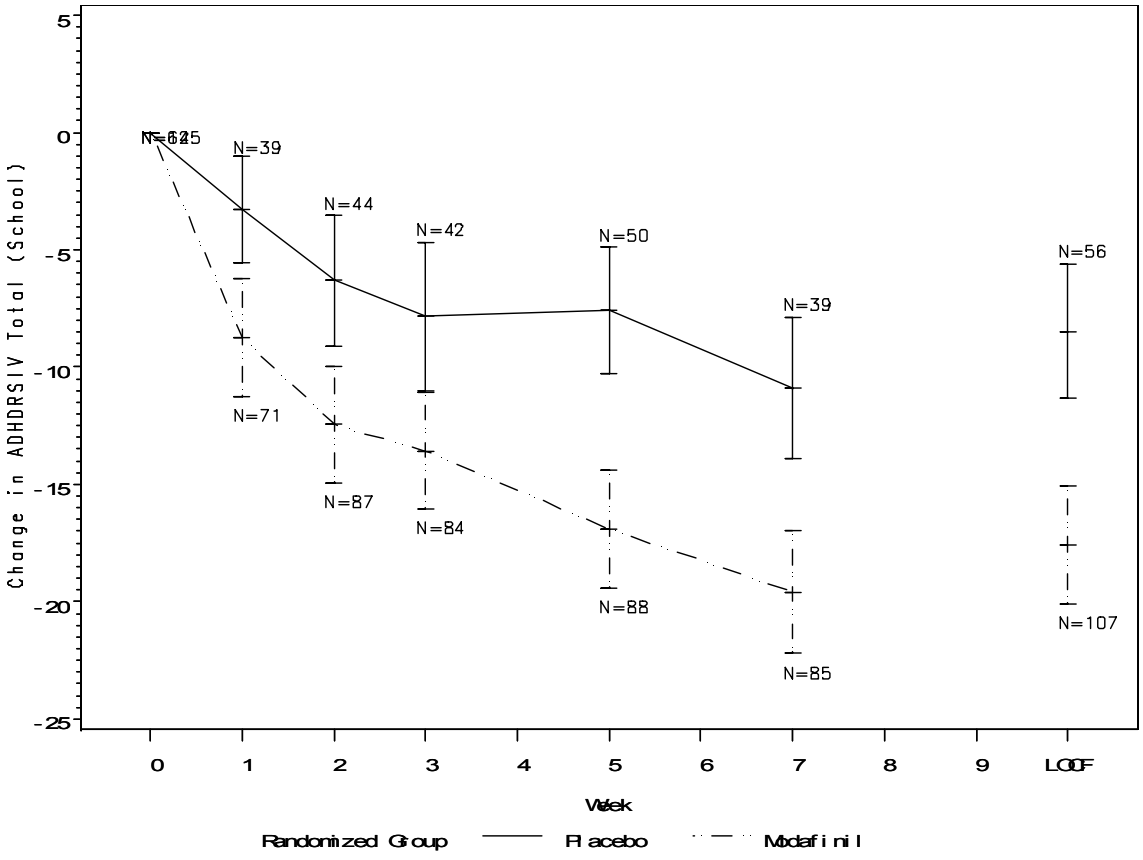
Table 13 Study 310: Mean Changes in ADHD-RS (school) by Early Termination Reason

			MODAFINIL			PLACEBO	
COMPLETE	REASON	N	BASELINE	CHANGE	N	BASELINE	CHANGE
			MEAN (SD)	MEAN (SD)		MEAN (SD)	MEAN (SD)
NO	ADVERSE EVENT	9	34.3 (9.9)	-9.2 (11.9)	.	.	.
NO	CONSENT WITHDRAWN	5	32.9 (8.8)	-20.4 (13.5)	6	40.9 (7.3)	-10.5 (10.0)
NO	LACK OF EFFICACY	17	40.7 (9.3)	-9.1 (14.1)	20	38.6 (7.4)	-0.5 (8.5)
NO	LOST TO FOLLOW-UP	1	50.0 (.)	-39.0 (.)	.	.	.
NO	NON-COMPLIANCE TO STUDY PROCEDURES	1	33.0 (.)	-6.0 (.)	.	.	.
NO	OTHER	6	32.3 (10.5)	-9.8 (9.4)	.	.	.

			MODAFINIL			PLACEBO	
COMPLETE	REASON	N	BASELINE	CHANGE	N	BASELINE	CHANGE
			MEAN (SD)	MEAN (SD)		MEAN (SD)	MEAN (SD)
NO	PROTOCOL VIOLATION	1	27.0 (.)	-10.0 (.)	1	41.0 (.)	-23.0 (.)
NO	ALL	40	36.8 (9.8)	-11.3 (13.2)	27	39.2 (7.2)	-3.6 (10.2)
YES		79	38.3 (8.6)	-20.2 (11.5)	36	34.9 (10.3)	-11.6 (9.0)

Figure 3 shows the change from baseline in the ADHD-RS-IV (school) total score over time. Scores were not always taken at the protocol specified times. For constructing the figure the time at which a score was taken was classified according to the closest protocol specified visit week. The treatment group difference reached nominal significance by the end of week 1. However, since there was no pre-specified plan for adjusting for the multiplicity of secondary analyses no claim related to the time of onset is permissible from a statistical perspective.

Figure 3 Study 310: Change from Baseline in ADHD-RS-IV (school) over Time



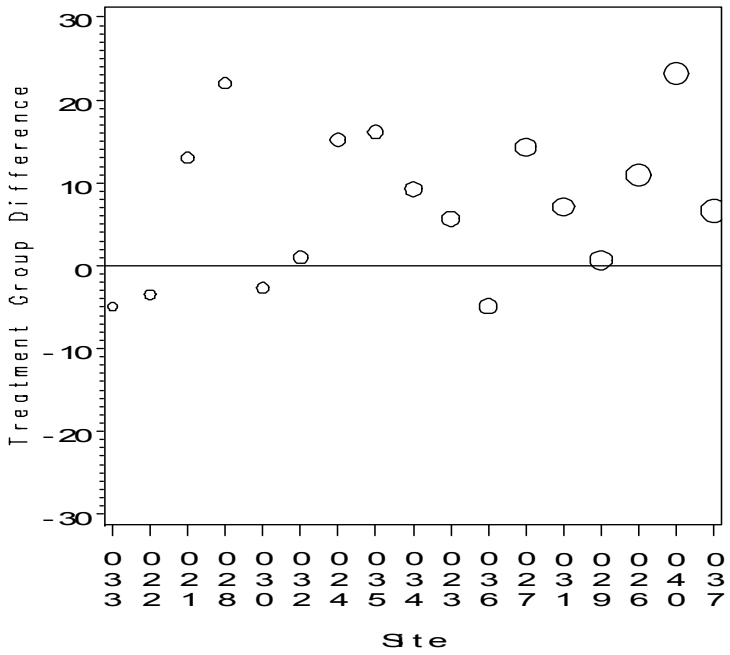
The mixed model for repeated measures approach provides another reasonable sensitivity analysis to compare with the LOCF method. The mixed model investigated here included fixed effects for treatment group, week, week by treatment group interaction, and the baseline ADHD-RS-IV score as a covariate. In addition, it was assumed that observations from the same patient were correlated but no structure was prescribed for the pairwise correlations (corresponding to each possible pair of measurement times, e.g., the week 7 and week 9 ratings). A comparison of the treatment group mean ADHD-RS changes at the end of week 7 based on this mixed model yields an estimated difference of 8.5 points ($p<0.001$). Therefore, the mixed model analysis also supports the primary LOCF analysis.

LOCF analyses of the Change from Baseline in ADHD-RS Total Score to some earlier timepoints (week 3, week 5) were also nominally significant and thus support the significance of the primary analysis at the end of 7 weeks.

Treatment Group Differences within Individual Sites

The following figure displays the differences in treatment group mean changes from baseline to week 7 (or LOCF) in ADHD-RS (school) Total score by site. The size of the plotting symbol indicates the relative number of patients in the site. The treatment effect was relatively consistent across sites as evidenced by the fact that the placebo mean change was better than the modafinil mean change in only a few centers. The results were also robust to the exclusion of individual sites.

Figure 4 Study 310: Differences in Treatment Group Mean Changes in ADHD-RS (school) by Site



Withdrawal Period

At the end of week 7 the withdrawal period began. Patient's initially randomized to the Modafinil/Placebo sequence received placebo from this time until the end of week 9. The other patient's double blind treatment was unchanged for the final two weeks. All three groups worsened to some extent over the two week withdrawal period. The Modafinil/Placebo group mean change from week 7 to week 9 was numerically worse than the Modafinil/Modafinil group mean by 4.3 points but the difference was not statistically significant. Note that about 1/3 of the modafinil patients had dropped out of the study before the start of the withdrawal period and thus did not have an assessment at the end of the withdrawal period. Therefore, this comparison may be underpowered.

Table 14 Study 310: ADHDRS-IV (School) Change From Week 7 to Week 9 (Withdrawal Period)

Subscale Timepoint Statistic	Modafinil- after-modafinil (N=43)	Placebo- after-modafinil (N=37)	Placebo– after-placebo (N=40)
Total score			
Last double-blind visit			
n	43	37	40
Mean	19.7	16.6	24.8
SD	12.13	12.59	12.83
Median	18.0	14.0	22.0
Min, max	1.0, 43.0	0, 49.0	0, 50.0
Last withdrawal visit			
n	38	36	33
Mean	20.9	22.0	24.3
SD	12.55	14.61	14.12
Median	20.5	20.5	24.0
Min, max	2.0, 46.0	0, 53.0	0, 49.0
Change from last double-blind visit to last withdrawal visit			
n	38	36	33
Mean	0.8	5.1	0
SD	8.57	11.17	7.20
Median	0	2.5	0
Min, max	-19.0, 43.0	-17.0, 32.0	-21.0, 24.0

copied from sponsor's table 17 on page 71 of study report c1538d-310-ad-us.pdf

3.1.2.7 Conclusions for Study 310

In summary, modafinil was significantly better than placebo in terms of efficacy for the treatment of children and adolescents with ADHD in study 310.

3.1.3 Study 311

This study was conducted between 11 November 2003 and 11 June 2004.

3.1.3.1 Study Design

The design of this study was identical to that of study 309. Like study 309 this study was a multicenter, 9-week, randomized, double-blind, placebo-controlled, flexible-dosage, parallel-group study to compare the efficacy and safety of modafinil treatment to placebo treatment in children and adolescents with ADHD. Patients were randomized in a 2:1 ratio to receive either modafinil or placebo tablets. The study consisted of a 1- to 4-week screening/washout period, followed by 9 weeks of double-blind treatment. Visits included screening, washout (if needed), baseline, and weeks 1, 2, 3, 5, 7, and 9 (or early termination).

3.1.3.2 Statistical Methods

The primary efficacy variable was the change from baseline to the last postbaseline visit (week 9 or early termination) in the total score of the teacher/physician-completed ADHD Rating Scale-IV (ADHD-RS-IV) (School Version). The full analysis set, defined as all randomized patients that received at least one dose of study drug and had at least one post-baseline efficacy assessment, was to be used for all efficacy analyses. The null hypothesis to be tested was that the mean change from baseline to endpoint (week 9 or last postbaseline visit) in the total score from the ADHD-RS-IV (School Version) was equal between modafinil and placebo treatment groups. This hypothesis was to be tested by means of an analysis of covariance (ANCOVA) model with treatment and center as factors and the corresponding baseline value as a covariate. Secondary efficacy variables were the same as those in study 309. All tests were to be 2-tailed, at a significance level of 0.05.

On the basis of a phase 2 study it was thought that approximately 100 patients in the modafinil treatment group and 50 patients in the placebo group would be required to detect a between-group difference of 6.03 units in the mean change from baseline for the teacher/physician-completed ADHD-RS-IV (School Version) total score (the observed difference at week 4 or final visit of double-blind period in C1538a/213/AD/US) with at least 90% power using a 2-tailed t-test at the 0.05 level of significance. After taking possible dropouts into account a total sample size of 180 patients was planned for this study.

3.1.3.3 Patient Disposition

A total of 248 patients at 24 centers were randomized into the study. The excess over the planned sample size of 180 was attributed to aggressive screening efforts. Two patients randomized to the placebo group did not receive study drug. One additional patient randomized to the placebo group and 1 patient randomized to the modafinil group were not evaluable for efficacy. Of the 248 randomized patients, 130 (52%) completed at least 9 weeks of double-blind treatment, and 118 (48%) patients were withdrawn from the study (67 and 51 patients from the modafinil and placebo treatment groups, respectively). Overall, 205 (83%) patients entered the open-label extension study. Of the 118 patients who withdrew from the study, 7 (4 and 3 patients from the modafinil and placebo treatment groups, respectively) withdrew due to adverse events. The most frequent reason for withdrawal was lack of efficacy (71 patients [29%]; 34 (21%) and 37 (44%) patients from the modafinil and placebo treatment groups, respectively). Of the 21 patients withdrawn from the study due to other reasons, 8 of the 16 in the modafinil treatment group and all 5 patients in the placebo treatment group were withdrawn because of a change in the teacher performing the rating scale.

Table 15 Study 311: Patient Disposition

	Number (%) of patients		
Patient disposition	**Modafinil**	**Placebo**	**Total**
Screened	NA	NA	372

Randomized	164 (100)	84 (100)	248 (100)
Randomized, not treated	0	2 (2)	2 (<1)
Safety analysis set	164 (100)	82 (98)	246 (>99)
Full analysis set[a]	163 (>99)	81 (96)	244 (98)
Completed	97 (59)	33 (39)	130 (52)
Discontinued study	67 (41)	51 (61)	118 (48)
Death	0	0	0
Adverse event	4 (2)	3 (4)	7 (3)
Lack of efficacy	34 (21)	37 (44)	71 (29)
Consent withdrawn	5 (3)	4 (5)	9 (4)
Protocol violation	0	0	0
Lost to follow-up	6 (4)	1 (1)	7 (3)
Noncompliance to study medication	1 (<1)	0	1 (<1)
Noncompliance to study procedures	1 (<1)	1 (1)	2 (<1)
Other	16 (10)[b]	5 (6)	21 (8)
Enrolled into open-label protocol	133 (81)	72 (86)	205 (83)

SOURCE: Summary 15.1, Listing 2.

[a]One patient in the safety analysis set for each treatment group was not evaluable for efficacy. [b]According to the termination page of the case report form (CRF), .other. was the reason for withdrawal for
16 patients in the modafinil treatment group, however, according to the adverse event page of the CRF, 1 of these patients was withdrawn due to adverse events.
NA=not applicable.
copied from table 6 on page 50 of sponsor's study report 311.pdf

3.1.3.4 Patient Demographics

Of the 246 patients who received study drug, 174 (71%) were boys and 72 (29%) were girls. The majority (190 [77%]) of the patients were white. The mean age of the patients was 10.3 years (range 6 to 17 years), and the mean weight was 42.9 kg (range 18.6 to 85.4 kg). No statistically significant differences were observed between the treatment groups with regard to demographic characteristics.

Table 16 Study 311: Baseline Demographic Characteristics

Demographic variable	Modafinil (N=164)	Placebo (N=82)	Overall (N=246)
Age, years			
n	164	82	246
Mean	10.4	10.1	10.3
SD	2.88	2.86	2.87
Median	10.0	10.0	10.0
Min, max	6.0, 17.0	6.0, 17.0	6.0, 17.0
Sex, n (%)			
Male	113 (69)	61 (74)	174 (71)
Female	51 (31)	21 (26)	72 (29)
Race, n (%)			
White	127 (77)	63 (77)	190 (77)
Black	17 (10)	8 (10)	25 (10)
Asian	3 (2)	1 (1)	4 (2)
American Indian or Alaskan Native	2 (1)	0	2 (<1)

Demographic variable	Modafinil (N=164)	Placebo (N=82)	Overall (N=246)
Other	15 (9)	10 (12)	25 (10)
Weight, kg			
n	164	82	246
Mean	43.6	41.4	42.9
SD	16.34	15.96	16.21
Median	41.0	36.7	39.4
Min, max	20.2, 85.4	18.6, 82.1	18.6, 85.4
Height, cm			
n	164	82	246
Mean	145.1	142.3	144.2
SD	17.61	16.92	17.40
Median	146.7	142.1	144.8
Min, max	115.5, 195.6	110.2, 179.1	110.2, 195.6

Copied from table 8 on page 53 of sponsor's study report 311.pdf.

Baseline ADHD Characteristics

All patients had ADHD at baseline, and the majority (59%) had the combined subtype. CG I-S scores at baseline indicated that 85% of patients were moderately to markedly ill and 15% were severely ill.

Table 17 Study 311: Baseline ADHD Severity

	Number (%) of patients		
Characteristic	**Modafinil (N=164)**	**Placebo (N=82)**	**Overall (N=246)**
CGI-S rating			
Normal	0	0	0
Borderline ill	0	0	0
Slightly ill	0	0	0
Moderately ill	72 (44)	43 (52)	115 (47)
Markedly ill	66 (40)	27 (33)	93 (38)
Severely ill	25 (15)	12 (15)	37 (15)
Among the most extremely ill patients	1 (<1)	0	1 (<1)
Not assessed	0	0	0
Current ADHD subtype			
Inattentive	61 (37)	33 (40)	94 (38)
Hyperactive/impulsive	6 (4)	1 (1)	7 (3)
Combined	97 (59)	48 (59)	145 (59)

Copied from table 9 on page 54 of sponsor's study report 311.pdf

3.1.3.5 Sponsor's Results

The primary efficacy variable was the change from baseline to the last postbaseline visit (week 9 or early termination) in the total score from the ADHD-RS-IV (School Version). The change from baseline was analyzed using an ANCOVA model with treatment and center as factors, and the corresponding baseline value as a covariate. For patients in the modafinil treatment group, a statistically significant ($p<0.0001$) improvement from baseline to the last postbaseline visit was

observed for the ADHD RS-IV (School Version) total score when compared to patients in the placebo treatment group. The mean decrease was 15.0 points for the modafinil treatment group and 7.3 points for the placebo treatment group, a difference between groups of 7.7 points.

Table 18 Study 311: Mean Change From Baseline to week 9 (or LOCF) in ADHD-RS (school)

Time point Statistic	Modafinil (N=163)	Placebo (N=81)
Baseline		
n	163	81
Mean	35.7	35.3
SD	9.25	8.75
Median	36.0	35.0
Min, max	6.0, 53.0	14.0, 54.0
Final visit		
n	163	81
Mean	20.7	28.0
SD	13.86	12.69
Median	19.0	26.0
Min, max	0.0, 53.0	3.0, 54.0
Change from baseline to final visit		
n	163	81
Mean	-15.0	-7.3
SD	11.78	9.66
Median	-15.0	-6.0
Min, max	-43.0, 17.0	-31.0, 13.0
p-value[a]	<0.0001**	NA

SOURCE: Summary 15.9, Listing 11.

NOTE: The final visit is the last postbaseline visit.

[a]The p-value for the treatment comparison of modafinil to placebo is from an analysis of covariance (ANCOVA) model with treatment and center as factors, and the baseline value as a covariate.

**p<0.01.

Min=minimum; max=maximum; NA=not applicable.

Copied from table 14 on page 60 of sponsor's study report 311.pdf

Secondary Endpoints

The change from baseline to the last postbaseline visit (week 9 or early termination) in the ADHD score from the TOVA indicated improvement and a statistically significant difference (p=0.0121) between the modafinil and placebo treatment groups in favor of modafinil. There were no statistically significant differences between the 2 treatment groups in the change from baseline to the last postbaseline visit for errors of omission, errors of commission, or response time.

The CGI-C ratings were analyzed at weeks 1, 2, 3, 5, 7, and 9 and at the last postbaseline visit, using the CMH test adjusted for centers. Statistically significant improvement (much improved or very much improved) in ADHD symptoms was seen for patients in the modafinil treatment

group when compared with patients in the placebo treatment group at week 2 (p=0.0022), week 3 (p=0.0044), week 7 (p=0.0071), and week 9 (p=0.0348) and at the last postbaseline visit (p<0.0001).

The CGI-C ratings were also divided into categories of very much improved or much improved; minimally improved; and no change, minimally worse, much worse, or very much worse. On the basis of these categories, nominally significant improvement in ADHD symptoms was seen for patients in the modafinil treatment group when compared with patients in the placebo treatment group at each visit from week 2 (p=0.0034) through week 9 (p=0.0367) and at the last postbaseline visit (p<0.0001).

3.1.3.6 Reviewer's Results

This was a flexible dose study with doses starting at 85 mg and being titrated up to an optimum dose (in terms of tolerability) between 170 and 425 mg. Stable dose was defined as the dose that the patient took for the longest amount of time. The average stable dose for the Modafinil group was 369 mg and the median was 425 (only 40% were dosed below 425 mg). Ages ranged between 6 and 17; the mean age was 10.3 and the median age was 10.0.

This reviewer verified the sponsor's primary analysis. Table 19 shows the results of the primary ITT-LOCF analysis and the analysis of the Observed Cases. The mean changes were smaller (larger in absolute value) for both groups in the Observed cases than in the ITT population overall. This suggests that completers' last scores were better than dropouts' last scores. However, since the treatment group differences were similar and the p-values were < 0.05 for the ITT-LOCF and the Observed Cases analyses the dropouts do not seem to have had much impact on the analysis conclusions.

Table 19 Study 311: Comparison of ITT-LOCF and Observed Case Results for Change in ADHD-RS-IV (school)

		PROVIGIL		PLACEBO			
Population	Study	N	LS Mean Change	N	LS Mean Change	LS Mean Difference	P-value*
ITT-LOCF	311	163	-15.0	81	-7.3	7.7	<0.001
OC	311	97	-18.2	33	-10.7	7.5	0.032

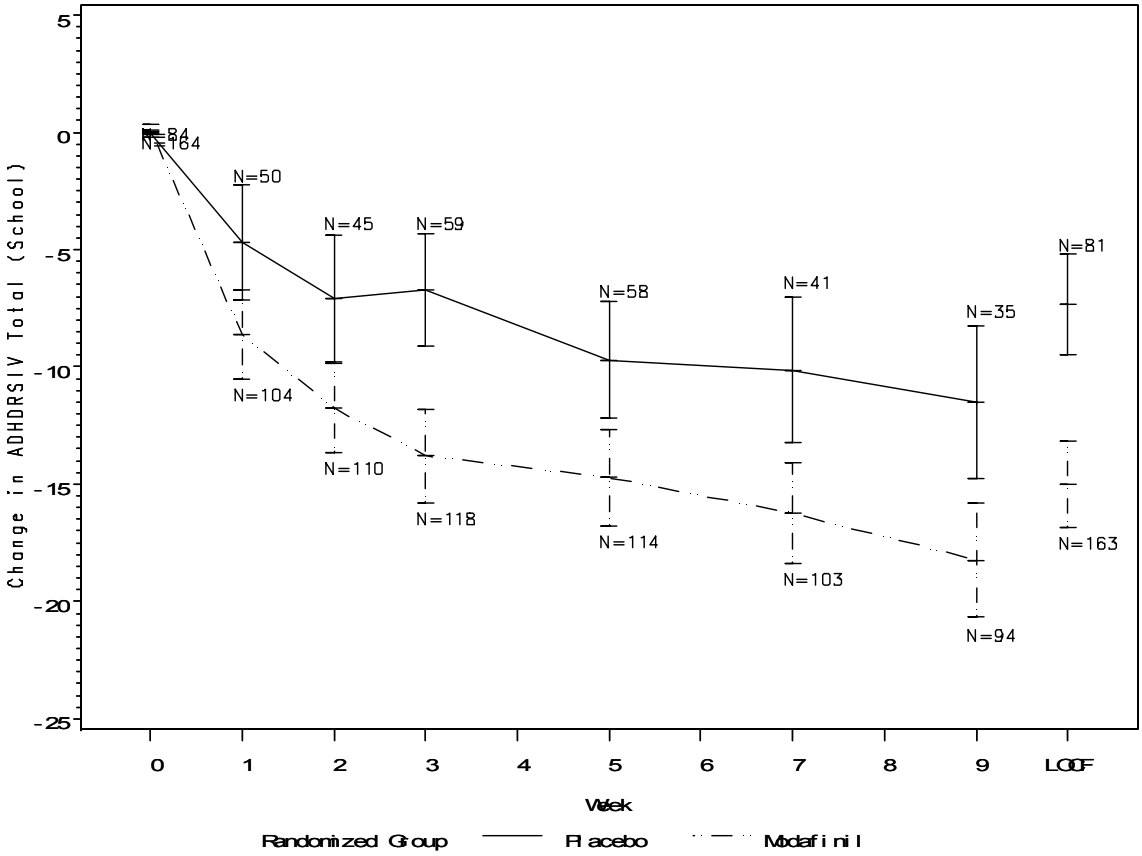
* based on ANCOVA model adjusted for baseline ADHDRS Total, site, treatment

The mixed model for repeated measures approach provides another reasonable sensitivity analysis to compare with the LOCF method. The mixed model investigated here included fixed effects for treatment group, week, week by treatment group interaction, and the baseline ADHD-RS-IV score as a covariate. In addition, it was assumed that observations from the same patient were correlated but no structure was prescribed for the pairwise correlations (corresponding to

each pair of measurement times, e.g., the week 7 and week 9 ratings). A comparison of the treatment group mean ADHD-RS changes at the end of week 9 based on this mixed model yields an estimated difference of 6 points (p=0.002). Therefore, this mixed model analysis also supports the primary LOCF analysis.

Figure 5 shows the change from baseline in the ADHD-RS-IV (school) total score over time. Scores were not always taken at the protocol specified times. For constructing the figure the time at which a score was taken was classified according to the closest protocol specified visit week. The treatment group difference reached nominal significance by the end of week 1. However, since there was no pre-specified plan for adjusting for the multiplicity of secondary analyses no claim related to the time of onset is permissible from a statistical perspective.

Figure 5 Study 311: Change from Baseline in ADHD-RS-IV (school) over time



The most common reason given for early termination was lack of efficacy. Table 20 shows the mean changes in ADHD-RS (school) total score by termination reason. Although, as one would expect, patients that terminated early due to lack of efficacy did worse than completers those in the modafinil group still fared better than those in the placebo group. Overall, among those who terminated early those in the modafinil group averaged 5.3 points better than those in the placebo group. This is a couple of points less than the group difference among the completers. Overall,

there is no compelling evidence that the dropouts biased the treatment comparison at the end of week 9.

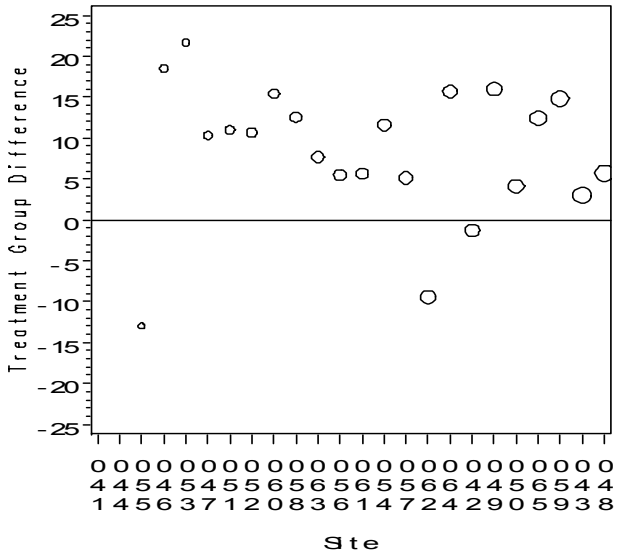
Table 20 Study 311: Mean Change in ADHD-RS (school) by Early Termination Reason

			MODAFINIL			PLACEBO	
COMPLETE	REASON	N	BASELINE	CHANGE	N	BASELINE	CHANGE
			Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)
NO	ADVERSE EVENT	4	38.3 (11.6)	-18.0 (13.8)	3	37.0 (7.2)	-0.3 (6.7)
NO	CONSENT WITHDRAWN	5	33.2 (6.3)	-14.2 (4.4)	3	35.0 (13.7)	-0.3 (2.5)
NO	LACK OF EFFICACY	34	37.8 (9.6)	-9.1 (9.6)	37	35.0 (8.4)	-4.6 (8.6)
NO	LOST TO FOLLOW-UP	6	33.0 (7.8)	-17.3 (6.8)	0		
NO	NON-COMPLIANCE TO STUDY MEDICATION	1	36.0 (.)	1.0 (.)	0		
NO	NON-COMPLIANCE TO STUDY PROCEDURES	1	27.0 (.)	-20.0 (.)	1	42.0 (.)	-16.0 (.)
NO	OTHER	15	34.9 (8.4)	-6.9 (10.4)	4	43.4 (8.9)	-13.3 (11.0)
NO	ALL	66	36.1 (9.0)	-10.3 (10.0)	48	36.3 (8.9)	-5.0 (8.8)
YES		97	35.5 (9.4)	-18.2 (11.9)	33	34.2 (9.0)	-10.7 (9.9)

Treatment Group Differences within Individual Sites

The following figure displays the differences in treatment group mean changes from baseline to week 9 (or LOCF) in ADHD-RS (school) Total score by site. The size of the plotting symbol indicates the relative number of patients in the site. The treatment effect was relatively consistent across sites as evidenced by the fact that the placebo mean change was better than the modafinil mean change in only a few centers. The results were also robust to the exclusion of individual sites.

Figure 6 Study 311: Differences in Treatment Group Mean Changes in ADHD-RS (school) by Site



3.1.3.7 Conclusions for Study 311

In summary, modafinil was significantly better than placebo in terms of efficacy for the treatment of children and adolescents with ADHD in study 311.

3.2 Evaluation of Safety

Please see the clinical review(s) for the evaluation of safety.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

This section summarizes the results of this reviewer's exploratory subgroup analyses.

4.1 Gender, Race and Age

4.1.1 Gender

Because studies 309 and 311 were identically designed flexible dose studies they are combined here to provide a more accurate estimate of the treatment effect within each gender.

About 70 percent of the patients were male. Since the differences in treatment group mean changes within each gender were similar, as seen in the following table, there is no evidence that the treatment effect depends on gender. The data from the fixed dose study, 310, also supports this conclusion.

Table 21 LOCF Mean Changes in ADHD-RS (School) by Gender in Studies 309 and 311 Combined

GENDER	VARIABLE	MODAFINIL	PLACEBO
Male	N	204.	109.
	Baseline: Mean (SD)	38.4 (8.7)	37.2 (9.1)
	LOCF Change: Mean (SD)	-16.0 (12.7)	-8.6 (10.2)
Female	N	87.	38.
	Baseline: Mean (SD)	34.0 (9.5)	34.7 (8.5)
	LOCF Change: Mean (SD)	-16.3 (11.7)	-7.8 (9.4)
All	N	291.	147.
	Baseline: Mean (SD)	37.1 (9.0)	36.6 (9.0)
	LOCF Change: Mean (SD)	-16.1 (12.5)	-8.4 (10.1)

Table 22 LOCF Mean Changes in ADHD-RS (School) by Gender in Study 310

GENDER	VARIABLE	MODAFINIL	PLACEBO
Male	N	89.	41.
	Baseline: Mean (SD)	39.6 (7.8)	39.3 (8.6)
	LOCF Change: Mean (SD)	-17.9 (12.9)	-9.0 (10.9)
Female	N	30.	22.
	Baseline: Mean (SD)	32.3 (10.2)	32.0 (8.7)
	LOCF Change: Mean (SD)	-15.3 (12.5)	-6.7 (9.0)
All	N	119.	63.
	Baseline: Mean (SD)	37.8 (8.6)	36.8 (8.9)
	LOCF Change: Mean (SD)	-17.2 (13.0)	-8.2 (10.5)

4.1.2 Race

Seventy six (76) percent of patients were white. Black was the second most frequently occurring race, accounting for 13% of patients. Other races represented to a lesser degree included Asians, Native Americans, and Native Alaskans. Although the treatment effect was in the wrong direction for the combined other race category in study 310 this could be attributable to baseline differences within this small subgroup or random fluctuation given the small sample size. Furthermore, the treatment effect for the other category was comparable to that for whites and blacks in studies 309 and 311. Thus, overall there is no evidence that the treatment effect depends on race.

Table 23 LOCF Mean Changes in ADHD-RS (school) from baseline to week 9 by Race: (Studies 309 and 310 combined)

RACE	VARIABLE	MODAFINIL	PLACEBO
White	N	220.	108.
	Baseline: Mean (SD)	36.9 (9.6)	35.9 (9.0)
	LOCF Change: Mean (SD)	-15.7 (12.4)	-8.7 (10.2)
Black	N	39.	20.
	Baseline: Mean (SD)	39.0 (7.9)	37.6 (9.6)
	LOCF Change: Mean (SD)	-16.4 (14.2)	-8.4 (9.5)
Other	N	32.	19.
	Baseline: Mean (SD)	36.4 (7.3)	38.9 (8.4)
	LOCF Change: Mean (SD)	-18.6 (10.5)	-7.1 (9.8)
All	N	291.	147.
	Baseline: Mean (SD)	37.1 (9.2)	36.5 (9.0)

RACE	VARIABLE	MODAFINIL	PLACEBO
	LOCF Change: Mean (SD)	-16.1 (12.5)	-8.5 (10.1)

Table 24 Study 310: LOCF Mean Changes in ADHD-RS (school) from baseline to week 9 by Race

RACE	VARIABLE	MODAFINIL	PLACEBO
White	N	94.	50.
	Baseline: Mean (SD)	38.1 (8.6)	35.9 (9.4)
	LOCF Change: Mean (SD)	-18.6 (12.3)	-7.2 (9.4)
Black	N	15.	6.
	Baseline: Mean (SD)	37.1 (9.1)	39.7 (8.5)
	LOCF Change: Mean (SD)	-16.5 (12.2)	-12.7 (11.6)
Other	N	10.	7.
	Baseline: Mean (SD)	35.0 (12.8)	41.0 (8.1)
	LOCF Change: Mean (SD)	-5.5 (13.0)	-11.6 (14.7)
All	N	119.	63.
	Baseline: Mean (SD)	-17.2 (12.3)	-8.2 (10.2)

4.1.3 Age Group

In the three studies age ranged between 6 and 17. The mean and median age was 10. Adolescents (defined here as age >=12) accounted for about 1/3 of all patients in the three studies. In each study the treatment group differences were nominally significant in both age subgroups except for the age >=12 subgroup in study 311. In Study 311 there was less difference between the treatment groups in the Age >= 12 subgroup than in the Age < 12 subgroup. However, in studies 309 and 310 the treatment effects within the two age subgroups were similar and in fact the difference was numerically larger in the AGE >= 12 subgroup. Thus, overall there was no consistent and compelling evidence that the treatment effect varied with the age group.

Table 25 Mean Change from Baseline in ADHD-RS (school) at Week 9 (or LOCF) by Age Group

STUDY	AGE GROUP	VARIABLE	MODAFINIL	PLACEBO
309	Age < 12	N	92.	41.
		Baseline ADHDRS: Mean (SD)	40.4 (8.2)	40.8 (7.8)
		Change: Mean (SD)	-18.3 (12.2)	-11.2 (9.5)
	Age >= 12	N	36.	25.
		Baseline ADHDRS: Mean (SD)	35.0 (9.3)	32.9 (8.8)
		Change: Mean (SD)	-15.3 (15.1)	-7.3 (11.3)
	All	N	128.	66.
		Baseline ADHDRS: Mean (SD)	38.9 (8.6)	37.8 (8.4)
		Change: Mean (SD)	-17.5 (13.2)	-9.7 (10.5)
311	Age < 12	N	99.	55.
		Baseline ADHDRS: Mean (SD)	38.7 (7.9)	36.5 (9.0)
		Change: Mean (SD)	-16.4 (11.5)	-6.1 (9.6)
	Age >= 12	N	64.	26.
		Baseline ADHDRS: Mean (SD)	31.2 (9.3)	33.1 (8.5)
		Change: Mean (SD)	-12.9 (12.0)	-9.8 (9.4)
	All	N	163.	81.
		Baseline ADHDRS: Mean (SD)	35.8 (8.6)	35.4 (9.0)
		Change: Mean (SD)	-15.0 (11.8)	-7.3 (9.7)
309 & 311	Age < 12	N	191.	96.
		Baseline ADHDRS: Mean (SD)	39.5 (8.1)	38.3 (8.7)
		Change: Mean (SD)	-17.3 (11.9)	-8.3 (9.8)
	Age >= 12	N	100.	51.
		Baseline ADHDRS: Mean (SD)	32.6 (9.5)	33.0 (8.5)
		Change: Mean (SD)	-13.8 (13.2)	-8.6 (10.4)

STUDY	AGE GROUP	VARIABLE	MODAFINIL	PLACEBO
	All	N	291.	147.
		Baseline ADHDRS: Mean (SD)	37.1 (8.7)	36.5 (8.7)
		Change: Mean (SD)	-16.1 (12.4)	-8.4 (10.1)

Table 26 Study 310 Mean Change from Baseline in ADHD-RS (school) at Week 7 (or LOCF) by Age Group

AGE GROUP	VARIABLE	MODAFINIL	PLACEBO
Age < 12	N	81.	43.
	Baseline ADHDRS: Mean (SD)	39.3 (8.8)	39.0 (8.0)
	Change: Mean (SD)	-17.0 (13.8)	-8.4 (10.3)
Age >= 12	N	38.	20.
	Baseline ADHDRS: Mean (SD)	34.4 (8.7)	32.0 (10.2)
	Change: Mean (SD)	-17.6 (10.2)	-7.7 (10.4)
All	N	119.	63.
	Baseline ADHDRS: Mean (SD)	37.7 (8.9)	36.8 (9.0)
	Change: Mean (SD)	-17.2 (12.9)	-8.2 (10.6)

4.2 Other Special/Subgroup Populations

The next section contains this reviewer's exploratory analyses of ADHD diagnosis subtype subgroups.

4.2.1 ADHD diagnosis subtype

At baseline 30 % of ADHD diagnoses were classified as inattentive, 4% were classified as hyperactive, and 66% were classified as the mixed type (hyperactive and inattentive).
For the sake of larger sample size and improved subgroup estimates the identically designed studies, 309 and 311, were combined in Table 27 below. In both study 309 and study 311 a nominally significant difference between the treatment groups in the mean change in ADHD-RS-IV Total score was seen in both the inattentive and mixed ADHD subtypes. Nominally significant results were also observed on the ADHD-RS-IV Hyperactive subscale and the ADHD-RS-IV Inattentive subscale. There were too few patients to draw any conclusions for the only hyperactive subgroup.

Table 27 Mean Changes in ADHD-RS (school) Total by ADHD diagnosis subtype

SUBGROUP	VARIABLE	MODAFINIL	PLACEBO
INATTENTIVE	N	87.	51.
	Baseline ADHDRS: Mean (SD)	32.6 (9.4)	32.9 (9.4)
	Change: Mean (SD)	-15.9 (11.1)	-6.8 (8.3)
HYPERACTIVE	N	15.	2.
	Baseline ADHDRS: Mean (SD)	40.5 (9.6)	33.5 (10.6)
	Change: Mean (SD)	-18.3 (11.9)	-16.5 (21.9)
MIXED	N	188.	93.
	Baseline ADHDRS: Mean (SD)	39.1 (8.2)	38.7 (8.1)
	Change: Mean (SD)	-16.0 (13.1)	-9.4 (10.3)
ALL	N	290.	146.
	Baseline ADHDRS: Mean (SD)	37.2 (8.7)	36.6 (8.6)
	Change: Mean (SD)	-16.1 (12.5)	-8.6 (9.8)

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The identically designed studies 309 and 311 permitted a flexible dose between 170 mg/day and 425 mg/day. Stable dose was defined as the dose that the patient took for the longest amount of time. The average stable dose for the Modafinil group was 367 mg in study 309 and 369 mg in study 311. About 60% of Modafinil group patients in each study had a stable dose of 425 mg. In both studies the Modafinil group was statistically significantly better than the placebo group in terms of the primary endpoint, change in ADHD-RS-IV (school) total score from baseline to week 9 (or LOCF).

Study 310 employed a fixed dose of 340 mg for patients weighing less than 30 kg and 425 mg for patients weighing 30 kg or more. Overall, the treatment group difference was statistically significant in favor of Modafinil and the treatment group difference was similar in both weight subgroups. Note that this design does not permit an evaluation of dose response since the dose is confounded with weight.

Despite there being a considerable number of early withdrawals in the three studies there is no convincing evidence that this introduced a bias in the primary analysis results. For example, as seen in Table 28, the Observed Case analyses, which include only patients that had an ADHD-RS-IV measurement at the end of week 9, resulted in the same conclusions as the ITT-LOCF analyses. The estimates of the treatment group difference were also reasonably similar for the ITT-LOCF and OC analyses.

Table 28 Comparison of ITT and Observed Case analyses of Change from Baseline in ADHDRS Total (School)

		PROVIGIL		PLACEBO			
Population	Study	N	LS Mean Change	N	LS Mean Change	LS Mean Difference	P-value*
ITT-LOCF	309	128	-17.5	66	-9.7	7.7	<0.001
	310	119	-17.2	63	-8.2	9.0	<0.001
	311	163	-15.0	81	-7.3	7.7	<0.001
OC	309	100	-19.9	41	-11.6	8.3	0.001
	310	79	-20.2	36	-11.6	8.6	0.001
	311	97	-18.2	33	-10.7	7.5	0.032

* based on ANCOVA model adjusted for baseline ADHDRS Total, site, treatment

5.2 Conclusions and Recommendations

The data from the three pivotal studies 309, 310, and 311 demonstrate the efficacy of Modafinil in children and adolescents with ADHD.

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/s/

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