Date:

Statistical Review and Evaluation NOV 16 1998

NDA #: 20-796

Applicant: Orion Corporation

Name of the Drug: Comtan® (entacapone) Tablets

Indication: Treatment of signs and symptoms of Parkinson's disease as an addition to levodopa/DDC inhibitor treatment

Documents Reviewed: Volumes 1.1, 1.168 to 1.217 and amendments dated December 30 ,1997; 8-27-1998; 9-10-98; 10-1-98; and 10-27-98

Clinical Reviewer: Richard Tresley, M.D. (HFD-120)

The issues in this review have been discussed with the reviewing medical officer, Dr. Tresley, M.D. (HFD-120).

Various Sections of this review are:

I. Background/Introduction

II. Clinical Studies
   1. Study 2939044
   2. Study 2939033

III. Overall Reviewer's Comments
IV. Overall Conclusion

I. Background/Introduction

The sponsor stated that nine placebo-controlled studies were conducted in the clinical program for entacapone. Two multicenter, parallel-group, double-blind primary phase III studies (2939033 and 2939044) involved 188 Parkinsonian patients treated with entacapone, and another 188 patients treated with placebo, over a period of 24 to 26 weeks. A third phase III controlled study (2939052) was conducted to exclusively provide safety data.

Six phase II studies - three single-dose and three multiple-dose studies - were conducted at single centers to provide supportive evidence of the effectiveness of entacapone as an adjunct to levodopa/DDC inhibitor treatment in Parkinson's disease patients with motor fluctuations.

Summary information of these studies is attached as Table 0.1.1[1].

The two primary Phase III studies have been reviewed here.

II. Clinical Studies

All analyses referred to in this report are the sponsor's analyses, except where specifically mentioned to be done by this reviewer.

In the Oct.1, 1998 submission, the sponsor reconfirmed that the statistical analysis plans, which slightly differed from what was written in the protocol, were finalized before unblinding the studies. However, the sponsor did not provide the date of unblinding (provided later to be October 6, 1995 for Study 44 and December 8, 1995 for Study 33). The date on the Analysis Plan is Sept. 29, 1995. The study period shown for Study 44 is April 1994 - June 1995 and for Study 33, December 1993 - February 1995.

Alternative analyses adjusting for some imbalances in covariates were provided in the NDA.

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[1] In the Table (or Appendix or Figure; no separate numbering systems have been created for these) number i.j.k, i stands for the serial number of the study in the list of studies above (except that 0 indicates overall or "common to all"), j stands for the Section or Group number for the tables in a particular study, and k stands for the Table number in that Section.

1. **Study 2939044 (US and Canada)**

This was a multi-center, placebo-controlled, double-blind study with randomized, parallel-group design, and with staggered withdrawal of study drug.

Entacapone 200 mg in combination with each levodopa/carbidopa dose was compared with placebo in combination with each L-dopa/carbidopa dose. The total study duration for each patient was 30 to 32 weeks. The study included a 2- to 4-week run-in period, a 24-week double-blind treatment period, and a 4-week randomized and double-blind staggered withdrawal period during which entacapone-treated patients were tranferred to placebo either after 24 weeks or 26 weeks of double-blind treatment.

1A. Objective

To study the efficacy and safety of a 200mg dose of entacapone, compared with placebo, as an adjunct to levodopa/carbidopa treatment of Parkinson's disease with motor fluctuations.

1B. Disposition of Patients

Altogether 205 patients (133 males and 72 females) participated, 103 in the entacapone and 102 in the placebo group. Thirteen patients in the entacapone group and 11 patients in the placebo group discontinued the study prematurely. There was no major imbalance between the entacapone and placebo groups in this respect.

The percent of patients continuing in the study over time is presented in the attached Figure 1.2.1, by treatment group. At Week 24, there were 90% patients under placebo and 85% under entacapone.

Numbers of patients who discontinued due to adverse events were 11 from entacapone and 7 from placebo.

1C. Some Baseline Characteristics

The sponsor stated, "About 2/3 of the patients randomized were males in both the treatment groups and about 96% of the patients were Caucasians. Similarly, distributions by sex, age, weight and height for the entacapone and placebo treatment groups were

comparable ..."

There was a statistically significant difference between entacapone (54%) and placebo (40%) treatment groups with respect to "Previous use of CR levodopa (% of patients)" (p-value=.0421). Adjustment of this imbalance did not change the significance of the treatment factor (Oct.1, 1998 submission).

At baseline, in the entacapone group and the placebo group, respectively, the mean age of the patients was 64 and 63; the mean duration of PD was 10.7 and 11.3 years; the wearing off phenomenon had continued for 4.2 and 4.5 years; the mean number of daily levodopa doses (at baseline) was 6.1 and and 6.0; the total daily levodopa dose was 791mg and 752mg. The levodopa treatment had continued for about 9 years in both groups.

Disease severity for the 205 patients in the study (comparable across entacapone and placebo) according to Hoehn and Yahr stages was 1 (n=2), 1.5 (n=4), 2 (n=96), 2.5 (n=41), 3 (n=52), and 4 (n=10).

1D. Efficacy Results (Sponsor's Analyses)

Method 1, which was for continuous variables, of the Statistical Analysis Plan reads:

An analysis of variance (ANOVA) for repeated measures will be applied. The model includes terms of treatment, time, their interaction, center and center*treatment-interaction, and the baseline measurement as a covariate.

If the interaction between time and treatment appears to be statistically significant, pairwise comparisons within time points will be calculated. For pairwise comparisons 95% confidence intervals will be constructed, using Bonferroni adjustment for multiple comparisons.

In a June 27, 1995 submission the sponsor stated, "

Primary Efficacy Variable (The proportion of ON-time while awake during 24 hours) - -

The results, by repeated measures analysis over weeks 8, 16, and 24 (the **stable treatment period**) are following:

Percent of Daily ON time (% of awake time); ITT-LOCF$_{(BL)}$*

Time	Entacapone (N=103)	Placebo (N=102)	Entac.vs Plac. P-value
	Mean	Mean	
Baseline	60.0	60.8	
Mean for weeks 8,16,24	66.8	62.8	.0163

* (BL) indicates that baseline measurement was carried forward for any patient who prematurely discontinued before visit 4. Although the sponsor stated this method to be the primary method in the Statistical Analysis Plan, for traditional repeated measures analysis, OC is used. This reviewer would put primary emphasis on OC results presented below (from December 30, 1997 submission).

By the above (protocol mentioned) primary analysis (adjusting for the baseline % ON time, which had a high correlation with response), there was statistically significant evidence in favor of the efficacy of entacapone. The difference between entacapone and placebo treatments in changes from baseline was 4.8 (6.8-2.0) in percent of Daily ON Time (% of awake time).

Changes from baseline and p-values for entacapone vs placebo comparisons, by week, are in the attached Table 1.3.1. Since these were not intended by Method 1 of the protocol or the Statistical Analysis Plan unless there was statistically significant treatment by visit interaction and there was no statistically significant interaction in this case, these are just for descriptive purposes. Strict multiple comparison adjustments for multiple times would be too conservative because the results over time are highly correlated. However, fortunately for the sponsor, if the Hochberg method of multiple comparison adjustment is applied, all the p-values are significant.

Percent of Daily ON time (% of awake time); ITT-OC

Time	Entacapone (N=103)	Placebo (N=102)	Entac.vs Plac. P-value
	Mean	Mean	
Baseline	60.0	60.8	
Mean for weeks 8,16,24	67.1	63.1	.0147

By this OC analysis also (adjusting for the baseline % ON time, which had a high correlation with response), there was statistically significant evidence in favor of the efficacy of entacapone. The difference between entacapone and placebo treatments in changes from baseline was 4.8 (7.1-2.3) in percent of Daily ON Time (% of awake time), which is the same as in the analysis by $LOCF_{(BL)}$.

Additional analyses provided in Appendix V of the NDA, were not much different, with respect to statistical significance. All these results support the conclusion of the primary analysis of the primary efficacy variable.

The analyses of this primary efficacy variable by the reviewer (data provided by the sponsor on a floppy diskette) for change from baseline by t-test also provided evidence of efficacy in favor of entacapone. However, by none of the some other one-way alternative analyses (say, nonparametric or t-test of % ON Time instead of Change From Baseline of % ON Time) done by the reviewer was any of the p-values significant. Therefore, the sponsor was fortunate to show the efficacy of the drug just by the protocol mentioned analysis of the primary efficacy variable; the result was not strongly robust.

The graph for the cumulative distribution function for the primary efficacy variable is attached as Figure 1.3.2. The separation of the entacapone treatment from the placebo treatment is not as clear as in the next study.

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Individual Center Results

Out of 18 centers, in 9 centers placebo did better than entacapone (submission of Dec. 30, 1997). While the overall

difference between entacapone and placebo treatments in changes from baseline was 4.8% in percent of Daily ON Time (% of awake time), in Center 23 the difference was -8.75% (in Center 15, nearly so). On the opposite end, in Center 29, the difference was as big as 24.5%. The results excluding 12 patients in this center (analyses done by this reviewer) are not statistically significant and difference with placebo also becomes around 3.5% instead of 4.8%.

The sponsor tried to explain these extreme results in various ways, including that of mentioning "by chance" variation due to very few patients. As a sample of other explanations, the following for Center 23 is quoted here: "..., the overall PD severity in most of the patients is milder in this center than in average. Expected treatment effect may less clear or less predictable in such patients. Further, evaluation of ON, OFF and ASLEEP times may have been recorded incorrectly and obviously this has remained undetected during the study."

However, the p-value (0.2367) for the center by treatment interaction was not significant.

There were some GCP violations in Center 12. The sponsor performed a ITT sub-analysis excluding the 12 patients in this center. This exclusion did not change conclusions, although the p-values became larger.

The mean daily ON Time, a **secondary efficacy variable**, increased from baseline by 1.0 and 0.4 hour, respectively, in the entacapone and placebo groups. The 95% confidence interval and the p-value for the difference were, respectively, (-0.04 to 1.19) and .0633. The analysis was based on Method I described earlier (over weeks 8, 16, and 24) in the ITT population. In the September 10, 1998 submission, where center was treated as a fixed factor (for the main results in the NDA text, it was considered "random"), p-values with respect to mean ON time (.0376) and mean OFF time (.0067) were significant.

Withdrawal Effect (From home diary)

The active treatment was withdrawn in a stepwise manner after week 24. The patients treated with entacapone were gradually transferred to placebo treatment either after 24 weeks treatment (on visit 6) or after 26 weeks treatment (on visit 7).

The results of withdrawal effect are presented for observed cases

(OC) of the ITT population (attached Table 1.3.3). The withdrawal of entacapone decreased the proportion of daily ON time by 8% by the end of the first day after entacapone withdrawal. In almost all cases, after entacapone withdrawal, the entacapone results became statistically significantly inferior to placebo results (Vol 1.172, Table 10.1.1). Correspondingly, the actual daily ON time decreased by about 1.5 hours and the OFF time increased. There was no <u>further</u> deterioration or the deterioration was minimal after Day 1 of withdrawal.

Withdrawal deterioration in the placebo-treated patients was none after Week 24 and negligible after Week 26.

However,the sponsor stated, "The study protocol was not adhered to in respect of the blindness evaluation on weeks 26 and 28. Thus, a valid blindness evaluation was available only at the end of the actual treatment period (visit 6, week 24) for all the 205 patients."

For the patients withdrawn at Week 26, the levodopa dose had increased by the second day following withdrawal: the mean levodopa dose increased from 758 to 815 mg and the mean dosing frequency increased from 6.2 to 6.5.

The sponsor reported that within two weeks after entacacpone withdrawal at Week 24, the mean levodopa dose was increased from 655mg at Week 24 to about 722mg at Week 26. In the placebo-treated patients group, the mean levodopa dosage remained unchanged.

1E. **<u>Reviewer's Comments and Conclusions on Study 293044</u>**

With respect to the protocol mentioned primary efficacy variable, the proportion of ON-time while awake during 24 hours, there was statistical evidence in favor of the efficacy of entacapone. However, the consistency of results across centers or alternative analyses was unsatisfactory as detailed above. Overall, this study provided non-robust statistical evidence (not that strong).

The numerical results also do not quite satisfy what the protocol stated, "Entacapone is considered to be of significant clinical benefit if

- it increases the mean proportion of daily "ON" time (total "ON" time/total hours awake during a 24 hour daily recording, mean of three days) at least by approximately 10% more than

placebo. This 10% change in proportion of "ON" time is approximately equivalent to an increase of **1.5** hours in "ON" time."

For example, as stated in the report, "The estimated difference between the two treatment groups was **0.58** hours (p=0.0633, $CI_{95\%}$ -0.04; 1.19), which marginally failed to attain the limit of statistical significance (p<0.05)." The difference that resulted is nowhere near what was considered to be of clinical significance. This difference was neither statistically significant. It should be noted that this "ON" time is the primary efficacy variable for the Nordic study (next Section), although the definitions are slightly different in the two studies.

Also, although the result was statistically significant with respect to Percent of Daily ON Time (% of awake time), the difference between entacapone and placebo treatments in changes from baseline was only 4.8% compared with 8.3% in the Nordic study (next one). [The percentages were calculated slightly differently in the two studies.]

The mean daily levodopa doses (on home-diary days) over weeks 8, 16, and 24 decreased by 93mg in patients treated with entacapone and increased by 19mg in patients treated with placebo. The dosing frequency (about 6) remained unchanged from baseline for both treatment groups. Therefore, the benefit in the entacapone treatment group was not because of more use of levodopa in the entacapone group.

With respect to Withdrawal effect, the sponsor stated, "The study protocol was not adhered to in respect of the blindness evaluation on weeks 26 and 28." As it is, there was a clear effect of withdrawal from entacacpone at the end of first day of withdrawal. There was no further deterioration or the deterioration was minimal after Day 1 of withdrawal.

2. **Study 2939033** [redacted]

This was a multi-center, placebo-controlled, double-blind study with randomized, parallel-group design.

Entacapone 200 mg in combination with each levodopa/carbidopa dose was compared with placebo in combination with each levodopa/DDC inhibitor (either carbidopa or benserazide). The

total study duration for each patient was 30 weeks. The patients were on study medication for 24 weeks. There was a 2-week follow-up period to evaluate the effects of withdrawal of study medication.

2A. Objective

To study the efficacy and safety of a 200mg dose of entacapone, compared with placebo, as an adjunct to levodopa/DDC inhibitor treatment of Parkinson's disease with motor fluctuations.

2B. Disposition of Patients

Altogether 171 patients (94 males and 77 females) participated, 85 in the entacapone and 86 in the placebo group. Eight patients in the entacapone group and 11 patients in the placebo group discontinued the study prematurely.

The percent of patients continuing in the study over time is presented in the attached Figure 2.2.1, by treatment group.

Numbers of patients who discontinued due to adverse events were 6 from entacapone and 5 from placebo.

2C. Some Baseline Characteristics

The percent of male was 55% in each treatment group. The mean age (years), weight (kg), and height (cm) were, respectively, 62.6, 69.1, and 171.2 in the entacapone group and 62.8, 71.1, and 170.0 in the placebo group.

The sponsor stated, "The duration of PD and of levodopa treatment was about 1 year longer in the placebo- than in the entacapone treatment group. Although these differences between the groups are statistically significant, they are relatively small, in absolute terms and are not considered to be significant, either clinically or in respect of the findings of the study. The possible effect of this difference was taken into account in the analysis of results concerning primary efficacy variables..."

In both treatment groups there were more patients using levodopa/benserazide than levodopa/carbidopa. Still, there was a statistically significant difference between entacapone and placebo treatment groups in this respect.

	Benzerazide	Carbidopa	
Entacapone	52	33	
Placebo	67	19	P-value= .0174

Adjustment of this imbalance did not change the significance of the treatment factor (October 1, 1998 submission).

In the entacapone and placebo group, respectively, the duration of fluctuations was 4.2 and 4.7 years, the mean total daily levodopa dose was 699mg and 723mg.

Disease severity for the 171 patients in the study according to Hoehn and Yahr stages was 1.5 (n=16), 2 (n=80), 2.5 (n=38), 3 (n=33), and 4 (n=4).

2D. Efficacy Results (Sponsor's Analyses)

Method 1 of the Statistical Analysis Plan, which was for continuous variables, was the same as given earlier for Study 44 under Section 1D.

Primary Efficacy Variable (Mean Daily ON-time during 18 hours from 0600 to 2400 hours)

The results, by repeated measures analysis over weeks 8, 16, and 24 are following:

ON time (hours) from home diary, ITT-LOCF$_{(BL)}$*

Time	Entacapone (N=85) Mean±SD	Placebo (N=86) Mean±SD	Entac.vs Plac. P-value
Baseline	9.3±2.2	9.2±2.5	
Mean for weeks 8,16,24	10.7±2.2	9.4±2.6	.0002

* (BL) indicates that baseline measurement was carried forward for any patient who prematurely discontinued before visit 4.

Although the sponsor stated this method to be the primary method in the Statistical Analysis Plan, for traditional repeated measures analysis, OC is used. This reviewer would put primary emphasis on OC p-values presented below.

By the above (protocol mentioned) primary analysis, there was statistically highly significant evidence in favor of the efficacy of entacapone. The difference between entacapone and placebo treatments in changes from baseline was 1.2 hours (general expectation seemed to be 1.5 hours) in ON time.

Changes from baseline and p-values for entacapone vs placebo comparisons by week are in the attached Table 2.3.1. Since these were not intended by Method 1 of the protocol or statistical analysis plan unless there was statistically significant treatment by visit interaction and there was no significant interaction in this case, these are just for descriptive purposes. However, even by strict multiple comparison adjustments, all these p-values were significant.

ON time(hours) from home diary; ITT-OC

Time	Entacapone (N=103)	Placebo (N=102)	Entac.vs Plac. P-value
	Mean	Mean	
Baseline	9.3	9.2	
Mean for weeks 8,16,24	10.8	9.5	.0004

By this OC analysis also there was statistically highly significant evidence in favor of the efficacy of entacapone. The difference between entacapone and placebo treatments in changes from baseline was 1.2 hours (general expectation seemed to be 1.5 hours) in ON time, which is the same as in the analysis by $LOCF_{(BL)}$.

Additional analyses provided in Appendix V of the NDA, were not much different, with respect to statistical significance. All these results support the conclusion of the primary analysis of the primary efficacy variable.

The graph for the cumulative distribution function for the primary efficacy variable is attached as Figure 2.3.2. The separation of entacapone treatment from placebo treatment or from baseline status is clear.

Individual Center Results

Out of 16 centers, in 2 centers placebo did marginally better than entacapone. The overall consistency of results across centers was satisfactory in this study.

Mean ON Time After First Morning Dose of Levodopa (also primary)
ITT-LOCF$_{(BL)}$*

Time	Entacapone (N=85) Mean	Placebo (N=86) Mean	Entac.vs Plac. P-value
Baseline	2.1	2.2	
Mean for weeks 8,16,24	2.3	2.1	.0138

* (BL) indicates that baseline measurement was carried forward for any patient who prematurely discontinued before visit 4. The p-value by the OC analysis was .0128.

By the above (protocol mentioned) primary analysis, there was statistically significant evidence in favor of the efficacy of entacapone. The difference (in favor of entacapone) between entacapone and placebo treatments in changes from baseline was 0.3 hours in ON time after the first morning dose of levodopa.

Changes from baseline and p-values for entacapone vs placebo comparisons, by week, are in the attached Table 2.4.1. Since these were not intended by Method 1 of the protocol or Statistical Analysis Plan unless there was treatment by visit interaction and there was no significant interaction in this case, these are just for descriptive purposes. By strict multiple comparison adjustments, only the p-value for Week 8 was significant (again, please remember that these were not intended by the protocol or by the primary analysis plan).

Overall, the results for this second primary efficacy variable is not as strong as those for the first primary efiicacy variable.

With respect to the Percent of Daily ON time, a **secondary efficacy varaible**, the difference (with the superiority of entacapone) of 8.3% between the entacapone and placebo groups was statistically significant, with $p<0.001$ and 95% confidence interval, 4.5% to 12.2%.

Withdrawal Effect (From home diary)

The results from the last visit on study medication (entacapone/placebo) on Week 24 were compared by using the ITT-OC method with the results from the post-study visit on Week 26, scheduled to occur in both groups two weeks after stopping the study medication.

The mean ON time in hours decreased from 10.7 to 9.1 for entacapone and 9.4 to 9.3 for placebo. The difference in the entacapone group was highly significant, $p=.001$.

The mean ON time in hours after the first morning dose of levodopa decreased from 2.3 to 2.0 for entacapone and 2.1 to 2.0 for placebo. The difference in the entacapone group was highly significant, $p<.001$.

The duration of benefit in hours from a single dose of levodopa as reported by the patients was 2.8 at the last study visit and 2.3 at the post-study visit in the entacapone group. The difference was statistically significant in the ITT analysis. No changes occurred in the placebo group.

A statistically significant increase (53) in mean daily levodopa dose (mg) from 612 at the last visit to 665 at the post study visit occurred in the entacapone group. The corresponding figures for the placebo group were 738 and 745.

The average daily dosing frequency increased statistically significantly from 5.7 to 6.0, in the entacapone group. There was no difference ~~in the placebo group~~ between the last study visit and the post-study visit.

2E. Reviewer's Comments and Conclusions on Study 293033

Study 2939033 provided acceptable statistical evidence in favor of the efficacy of entacapone.

The mean daily levodopa doses (on home-diary days) over weeks 8, 16, and 24 decreased by 87mg in patients treated with entacapone

and increased by 15mg in patients treated with placebo. The difference of 0.6 between entacapone (less) and placebo in the mean daily dosing frequency (around 6) reached statistical significance. Therefore, the benefit in the entacapone treatment group was not because of more use of levodopa in the entacapone group.

III. Overall Reviewer's Comments

[redacted] Study 2939033 provided strong statistical evidence and U.S./Canada Study 2939044 provided non-robust and weaker statistical evidence, in favor of the efficacy of entacapone, although the Nordic study was smaller in size.

The benefit in the entacapone treatment group was not because of more use of levodopa in the entacapone group.

Cumulative distribution functions for Proportion of daily ON-time on 24-hour home diary in Study 2939044 and for Mean ON time (hours) on 18-hour home diary in Study 2939033 are attached as Figures 1.3.2 and 2.3.2, respectively. Separation of the curve of the cumulative distribution for entacapone mean over weeks 8, 16, and 24 from the remaining three curves (entacapone at baseline and placebo at baseline and placebo mean over weeks 8, 16, and 24) is clear in the second and less clear in the first (clear in the range 40 to less than 80 for the value of percent of daily ON-time) study.

Dropout Cohorts

Whether among the observed cases or among the dropouts, entacapone group performed, at least, numerically better than the placebo group with respect to the primary efficacy variables (Table 3 for each study in the submission of December 30, 1997; not attached here). Therefore, there is not a big concern about bias due to dropouts.

Consistency Across Sites

In the Nordic Study 2939033, the results were consistent across centers (submission of Dec. 30, 1997). In the U.S./Canada Study 2939044, the results were inconsistent across centers as detailed in Section 1.D, "Efficacy Results," for that study, although the p-value (0.2367) for the center by treatment interaction was not

significant.

Subgroup Analyses

Subgroup analyses (ANCOVA on Endpoint) were performed after pooling data from the two studies 33 and 44 (change from baseline to Endpoint in proportion of ON Time during 18-hour day 06:00 to 24:00 in both studies), as presented in the attached Table 0.4.1. None of the interaction p-values were significant and the entacapone was superior to placebo in both subgroups with respect to age, gender, and weight (stated in Vol. 1.168, pp 67-68; results in Vol. 1.169, pp 216-228).

The effect of different races could not be analyzed since all patients in Study 33 and more than 95% patients in Study 44 were white.

In the pooled results provided, there were no statistically significant treatment by levodopa dose, treatment by baseline Hoehn & Yahr stage, or treatment by dopamine agonist use interaction. However, there was some trend of treatment by selegiline use interaction, though statistically non-significant; results in the group of patients with selegiline use were relatively weaker.

Treatment by Study Interaction

In the various subgroup analyses done by pooling the data from the two studies -44 and -33, there were nearly significant treatment by study interaction p-values. We already know that results in the Nordic Study -33 were strong and those in the U.S./Canada Study -44 were only marginally acceptable.

Effect of Withdrawal

The entacapone withdrawal in Study 33 was conducted in an open manner while a placebo-controlled, blind (however, the sponsor stated that blinding during the withdrawal periods was not maintained properly) staggered withdrawal of entacapone was performed in Study 44.

In Study 44, the withdrawal of entacapone decreased the percent of daily ON time by an amount about 8(%) by the end of the first day after entacapone withdrawal. In almost all cases, after entacapone withdrawal, the entacapone results became

statistically significantly inferior to placebo results (Vol. 1.172, Table 10.1.1). Correspondingly, the actual daily ON time decreased by about 1.5 hours and the OFF time increased. There was no further deterioration or the deterioration was minimal after Day 1 of withdrawal.

There were no obvious withdrawal changes in the placebo-treated patients.

"Withdrawal Effects" for study 33 can be seen under Section 2D.

IV. Overall Conclusion

Overall, [redacted] Study 2939033 provided strong statistical evidence and U.S./Canada Study 2939044 provided non-robust statistical evidence, in favor of the efficacy of entacapone.

/S/ 11-4-98

Japobrata Choudhury, Ph.D.
Mathematical Statistician

Concur: Dr. Jin /S/

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This review consists of 17 pages of text and 10 pages of Tables, Figures, etc.

Table 0.1.1

Table 1. Controlled clinical studies

Study no.	Study title	Study design	No. of patients/ study duration
Phase III Multiple-dose			
2939033	A [redacted] phase III multicenter study on the efficacy and safety of entacapone, a catechol *O*-methyltransferase inhibitor, in patients with Parkinson's disease with motor fluctuations.	Double-blind, parallel-group, randomized, multicenter (16 centers)	171 24 weeks
2939044	A phase III multicenter study to evaluate the efficacy and safety of entacapone, compared to placebo, in the treatment of Parkinson's disease with motor fluctuations.	Double-blind, parallel-group, randomized, multicenter (16 centers)	205 24 to 26 weeks
2939052	A Finnish long-term Phase III multicenter safety study on entacapone in patients with Parkinson's disease.	Double-blind, parallel-group, randomized, multicenter (20 centers)	326 6 months* (12 months)
Phase II Multiple-dose			
293930	Clinical effect of entacapone, a catechol-*O*-methyltransferase inhibitor. On the disability of levodopa-treated parkinsonian patients. A double-blind, cross-over, phase II study.	Double-blind, repeated-dose, placebo-controlled, randomized, cross-over, multicenter (2 centers)	25 4 weeks
293928	Dose-finding study with repeated doses of entacapone in patients with advanced Parkinson's disease.	Double-blind, single-dose, placebo-controlled, randomized, cross-over, multicenter (3 centers)	25 3 x 2 weeks
293916	Treatment with a catechol-*O*-methyltransferase inhibitor, entacapone, as an adjunct to levodopa: a Phase II study in patients with advance Parkinson's disease.	Double-blind, placebo-controlled, randomized, cross-over, multicenter (2 centers)	10 4 weeks
Phase II Single-dose			
293917	The effect of a novel catechol-*O*-methyltransferase inhibitor, entacapone, on the pharmacokinetics and pharmacodynamic responses of levodopa.	Double-blind, single-dose, placebo-controlled, randomized, cross-over, single-center	12 Three 1-day periods
293926	The effect of entacapone, a catechol-*O*-methyltransferase inhibitor, on the motor response and pharmacokinetics of levodopa in Parkinson's disease. A phase II, single-dose dose-finding study.	Double-blind, single-dose, placebo-controlled, randomized, cross-over, single-center	22 Five 1-day periods
293929	Comparison of the effect of entacapone used as an adjunct to levodopa/carbidopa and levodopa/benserazide on the motor response and pharmacokinetics of levodopa in Parkinson's disease.	Single-blind, single-dose, placebo-controlled, randomized, cross-over, single-center	17 Two single doses on 2 study days

* A 6-month study report available

Table 0.4.1

~~Table 8.1.~~ **Summary of the entacapone effects on subsets of the combined population of studies -33 and -44**

Variable		Mean change from baseline in the proportion of ON time		Treatment effect between entacapone and placebo	Interaction between treatment and variable
		Entacapone	Placebo	p value	p value
Age					
< 65	(n=194)	7.0	0.6	0.0001	0.5714
≥ 65	(n=182)	7.6	0.7		
Sex					
Men	(n=227)	6.2	-0.1	0.0002	0.8957
Women	(n=149)	8.9	1.8		
Weight					
<70	(n=183)	8.2	0.9	0.0001	0.9313
≥70	(n=193)	6.5	0.4		
H&Y					
≤ 2	(n=198)	5.9	0.8	0.0001	0.2939
> 2	(n=178)	8.8	0.5		
Selegiline					
Yes	(n=178)	6.8	2.6	0.0002	0.1649
No	(n=198)	7.6	0.7		
Dopamine agonist					
Yes	(n=190)	7.6	0.7	0.0001	0.8311
No	(n=186)	6.9	0.6		
Levodopa daily dose (mg)					
< 500	(n=104)	7.9	2.0		
500 to < 1000	(n=203)	7.2	0.5	0.0008	0.9007
≥ 1000	(n=69)	6.2	-0.3		

Reference: Post-text Tables 34 to 39

Study 2939044 Figure 1.2.1

~~Table 2.~~ Number (%) of Patients continuing in the Study over Time

Treatment duration (weeks)	Entacapone N (%)	Placebo N (%)	Total N (%)
< 1	103 (100)	102 (100)	205 (100)
1	101 (98)	102 (100)	204 (99.5)
4	99 (96)	99 (97)	198 (97)
8	96 (93)	98 (96)	194 (95)
12	93 (90)	97 (95)	190 (93)
16	92 (89)	92 (90)	184 (90)
20	91 (88)	92 (90)	183 (89)
24	88 (85)	92 (90)	180 (88)

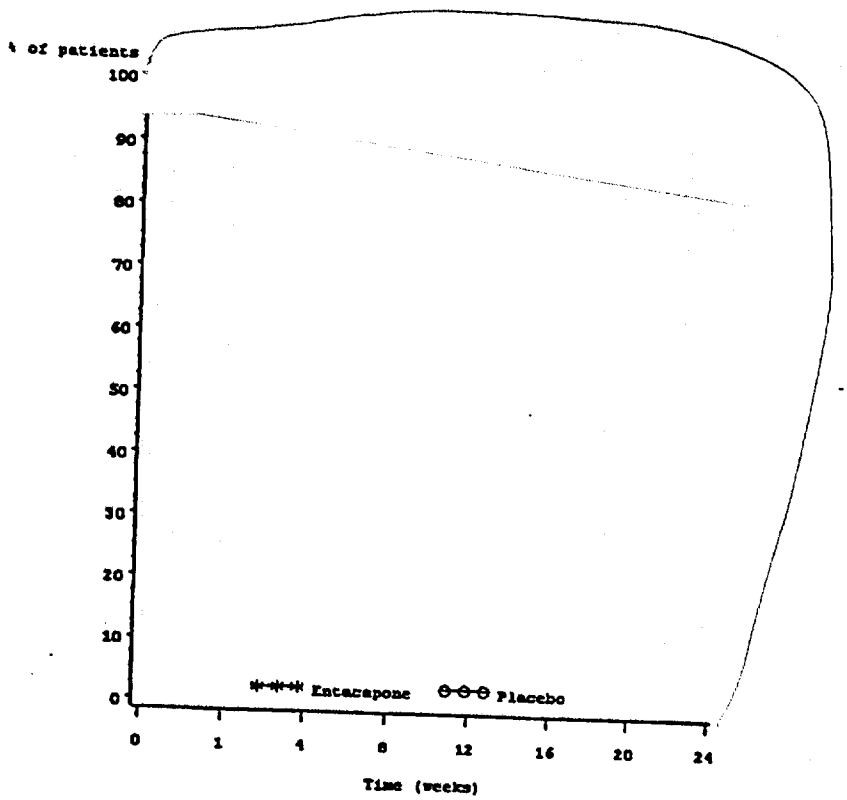


Table 1.3.1.

STUDY 2939044

Table 4.2.1 Changes from baseline in proportion of daily ON time (%) on 24-hour home diary - ITT-LOCF(BL)

	Statistic	Week 2	Week 4	Week 8	Week 16	Week 24	Mean over weeks 8, 16 and 24
Entacapone	MEAN	8.8	7.5	8.1	6.9	4.9	6.7
	SD	14.1	14.2	14.3	16.9	15.8	14.0
	SEM	1.4	1.4	1.4	1.7	1.6	1.4
	MIN						
	MAX						
	N	103.0	103.0	103.0	103.0	102.0	103.0
Placebo	MEAN	1.7	2.9	3.4	2.1	0.6	2.0
	SD	10.6	10.8	13.3	13.9	12.6	11.1
	SEM	1.1	1.1	1.3	1.4	1.2	1.1
	MIN						
	MAX						
	N	102.0	102.0	102.0	102.0	102.0	102.0

Analysis of variance separately for weeks 2, 4, 8, 16 and 24

Week	Source	DF (nomin)	DF (denomin)	F-value	p-value
Week 2	Treatment	1	17	16.68	0.0008
Week 4	Treatment	1	17	6.79	0.0185
Week 8	Treatment	1	17	6.20	0.0234
Week 16	Treatment	1	17	4.87	0.0414
Week 24	Treatment	1	17	4.76	0.0435

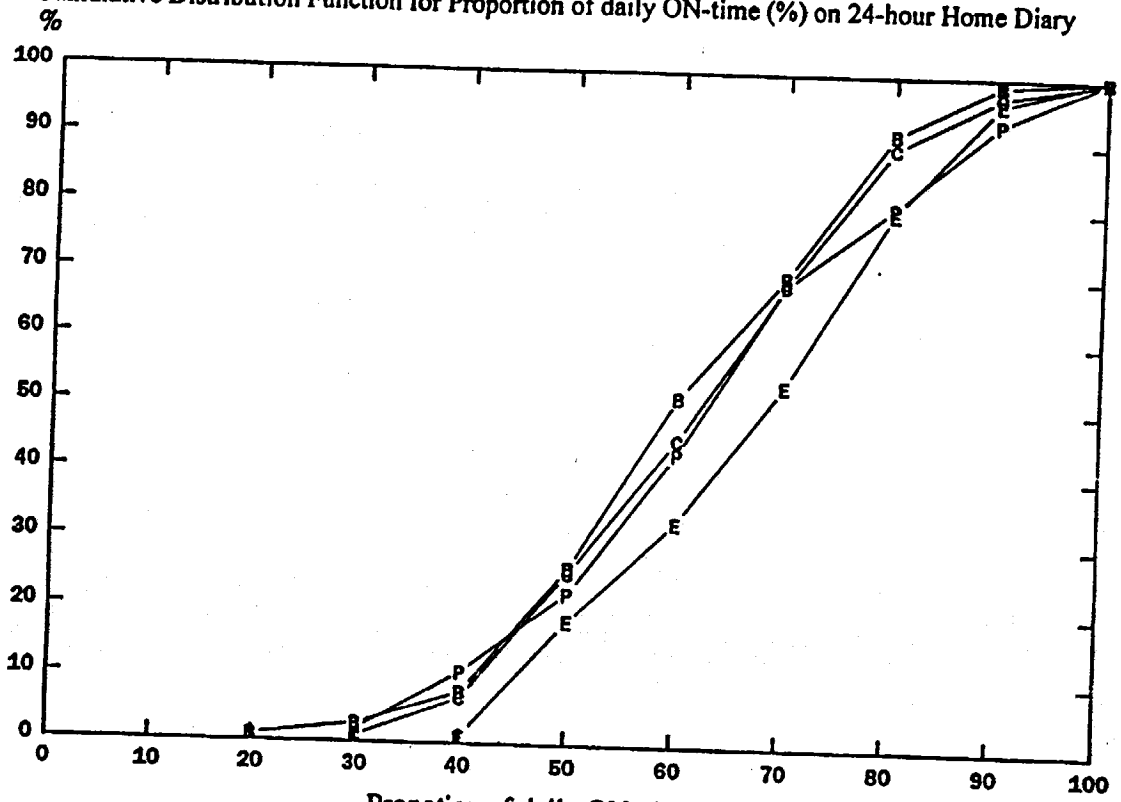
Estimation of treatment differences

Week	Comparison	Difference	Stand. error	DF	95% CI lower	95% CI upper	p-value
Week 2	Entacapone - P	7.13	1.75	17	3.45	10.82	0.0008
Week 4	Entacapone - P	4.58	1.76	17	0.87	8.30	0.0185
Week 8	Entacapone - P	4.75	1.91	17	0.73	8.77	0.0234
Week 16	Entacapone - P	4.79	2.17	17	0.21	9.37	0.0414
Week 24	Entacapone - P	4.36	2.00	17	0.14	8.57	0.0435

Statistical significance levels: 0.01 (5%), 0.002 (1%) and 0.0002 (0.1%)

Figure 1.3.2

~~Table 5.~~ Cumulative Distribution Function for Proportion of daily ON-time (%) on 24-hour Home Diary



B Entacapone (baseline)

E Entacapone (mean over weeks 8,16 and 24)

C Placebo (baseline)

P Placebo (mean over weeks 8,16 and 24)

Study BAB 44

Table 1.3.3.

~~Table R 35~~. Proportion of daily ON time, daily ON time, and daily OFF time during the withdrawal period (mean ± SD); ITT(OC)

	Entacapone (n = 90)				Placebo (n = 92)	
	At week 24 (Only patients withdrawn at week 24 included ; n = 44)		At week 26 Only patients withdrawn at week 26 included; n = 46)		At week 24	At week 26
Proportion of ON time of the awake time (%)						
On drug [1]	66 ± 15.0		64 ± 19.1		62 ± 18.5	62 ± 19.2 [2]
Withdrawal D1	58 ± 19.0	**	56 ± 20.5	***	63 ± 20.3	60 ± 20.2
Withdrawal D2	60 ± 18.3	*	54 ± 24.2	***	62 ± 19.2	61 ± 19.5
Daily ON time (hours)						
On drug [1]	11.1 ± 2.6		10.8 ± 3.2		10.5 ± 3.1	10.6 ± 3.4 [2]
Withdrawal D1	9.7 ± 3.2	**	9.2 ± 3.7	**	10.5 ± 3.4	10.2 ± 3.4
Withdrawal D2	10.0 ± 3.2	*	8.9 ± 4.2	***	10.6 ± 3.4	10.5 ± 3.4
Daily OFF time (hours)						
On drug [1]	5.7 ± 2.7		6.0 ± 3.3		6.4 ± 3.3	6.4 ± 3.1 [2]
Withdrawal D1	7.3 ± 3.6	**	7.3 ± 3.5	**	6.4 ± 3.5	6.7 ± 3.4
Withdrawal D2	6.7 ± 3.4	*	7.6 ± 4.3	***	6.4 ± 3.1	6.7 ± 3.3

[1] Last value on entacapone treatment for patients treated with entacapone [2] Value from week 24, second day after visit (D2)

*** p< 0.001, **p < 0.01, * p< 0.05 the change after the last evaluation on study drug compared with the change on placebo treatment at the same time point. The baseline (visit 1) value was used as covariate in the statistical model.

D1: First day after entacapone withdrawal, D2: Second day after entacapone withdrawal

Study 2939033 Figure 2.2.1

~~Table 2.~~ Number (%) of Patients continuing in the Study over Time

Treatment duration (weeks)	Entacapone N (%)	Placebo N (%)	Total N (%)
< 1	85 (100)	86 (100)	171 (100)
1	85 (100)	86 (100)	171 (100)
4	84 (99)	84 (98)	168 (98)
8	82 (96)	81 (94)	163 (95)
12	81 (95)	78 (91)	159 (93)
16	77 (91)	77 (90)	154 (90)
20	77 (91)	76 (88)	153 (89)
24	75 (88)	71 (83)	146 (85)

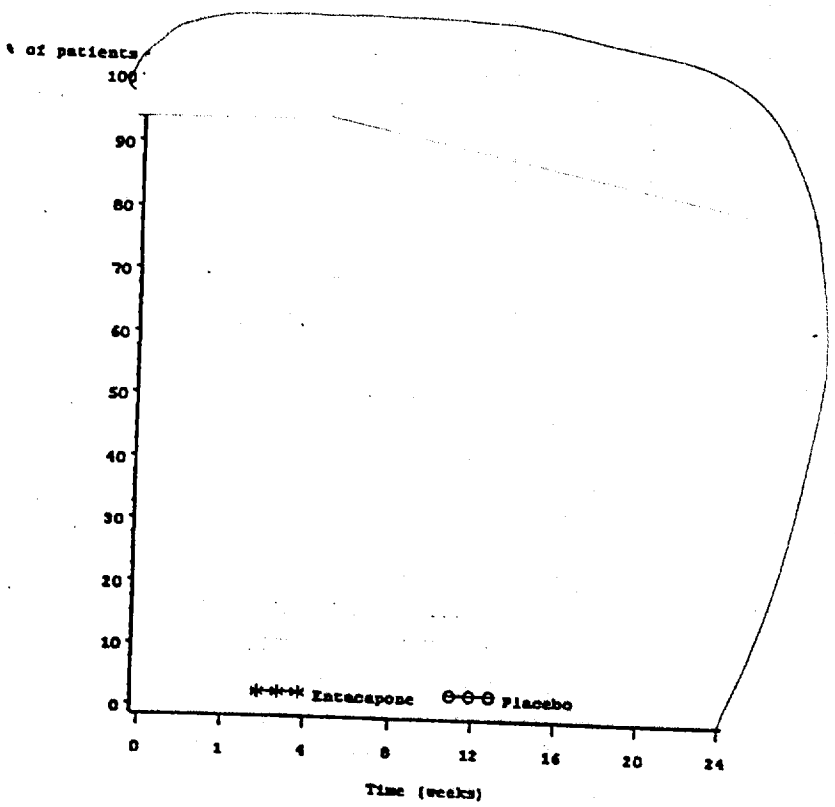


Table 2.3.1

STUDY 2939033

Table 4.2.1 Changes from baseline in ON-time (hours) on 18-hour Home diary - ITT-LOCF(BL)

	Statistic	Week 2	Week 4	Week 8	Week 16	Week 24	Mean over weeks 8, 16 and 24
Entacapone	MEAN	1.1	1.3	1.4	1.5	1.6	1.5
	SD	2.2	2.2	2.1	2.0	2.4	1.9
	SEM	0.2	0.2	0.2	0.2	0.3	0.2
	MIN						
	MAX						
	N	85.0	85.0	85.0	85.0	85.0	85.0
Placebo	MEAN	0.2	0.0	0.3	0.1	0.0	0.1
	SD	1.7	2.1	2.2	2.2	2.3	2.0
	SEM	0.2	0.2	0.2	0.2	0.3	0.2
	MIN						
	MAX						
	N	86.0	86.0	86.0	85.0	85.0	86.0

Analysis of variance separately for weeks 2, 4, 8, 16 and 24

Week	Source	DF (nomin)	DF (denomin)	F-value	p-value
Week 2	Treatment	1	15	9.38	0.0079
Week 4	Treatment	1	15	15.80	0.0012
Week 8	Treatment	1	15	10.76	0.0051
Week 16	Treatment	1	15	16.91	0.0009
Week 24	Treatment	1	15	14.25	0.0018

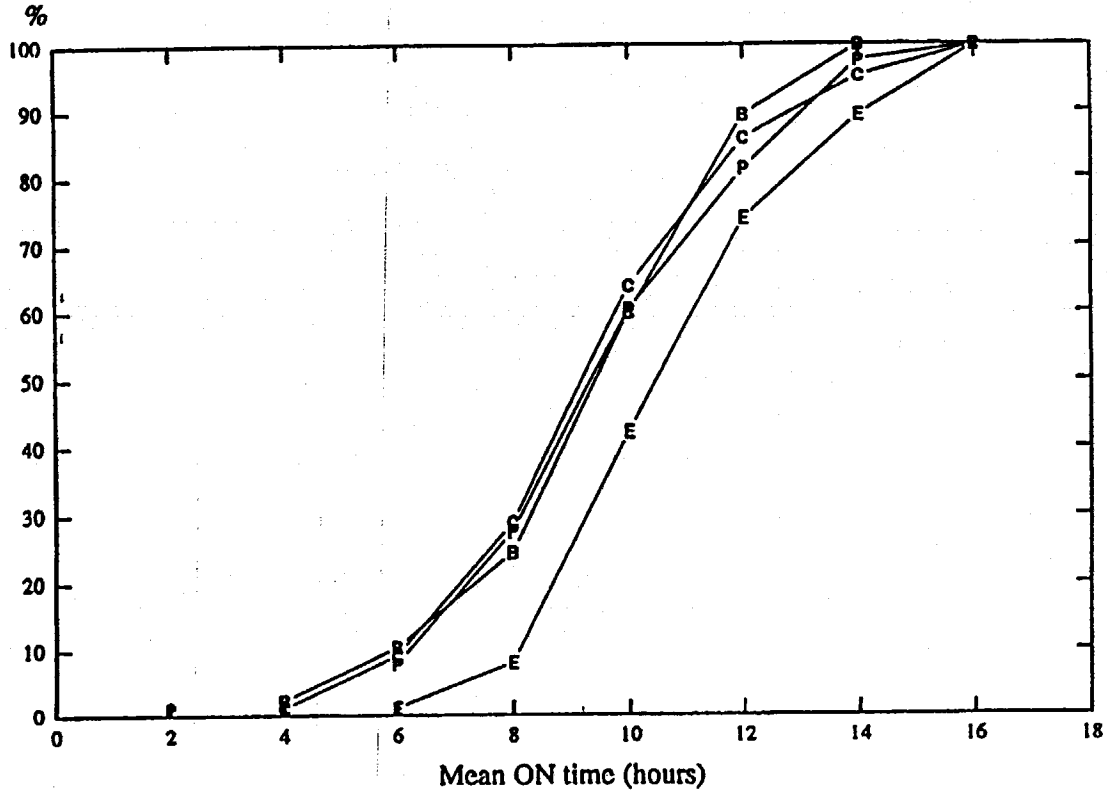
Estimation of treatment differences

Week	Comparison	Difference	Stand. error	DF	95% CI lower	95% CI upper	p-value
Week 2	Entacapone - P	0.92	0.30	15	0.28	1.56	0.0079
Week 4	Entacapone - P	1.31	0.33	15	0.61	2.02	0.0012
Week 8	Entacapone - P	1.20	0.37	15	0.42	1.98	0.0051
Week 16	Entacapone - P	1.36	0.33	15	0.65	2.06	0.0009
Week 24	Entacapone - P	1.55	0.41	15	0.68	2.43	0.0018

Statistical significance levels: 0.01 (5%), 0.002 (1%) and 0.0002 (0.1%)

Figure 2.3.2

~~Table 5.~~ Cumulative Distribution Function for Mean ON Time (hours) on 18-hour Home Diary



Study 33

B Entacapone (baseline)

E Entacapone (mean over weeks 8,16 and 24)

C Placebo (baseline)

P Placebo (mean over weeks 8,16 and 24)

Table 2.4.1.

STUDY 2939033

~~Table 4.9.1~~ Changes from baseline in ON time (hours) after the first morning dose of levodopa on 18-hour Home diary - ITT-LOCF(BL)

	Statistic	Week 2	Week 4	Week 8	Week 16	Week 24	Mean over weeks 8, 16 and 24
Entacapone	MEAN	0.2	0.3	0.3	0.2	0.2	0.2
	SD	0.7	0.7	0.7	0.8	0.7	0.6
	SEM	0.1	0.1	0.1	0.1	0.1	0.1
	MIN						
	MAX						
	N	82.0	81.0	82.0	83.0	83.0	83.0
Placebo	MEAN	0.1	0.1	-0.1	-0.0	-0.1	-0.0
	SD	0.7	0.9	0.6	0.6	0.7	0.5
	SEM	0.1	0.1	0.1	0.1	0.1	0.1
	MIN						
	MAX						
	N	82.0	81.0	82.0	79.0	80.0	82.0

Analysis of variance separately for weeks 2, 4, 8, 16 and 24

Week	Source	DF (nomin)	DF (denomin)	F-value	p-value
Week 2	Treatment	1	15	2.35	0.1464
Week 4	Treatment	1	15	1.97	0.1805
Week 8	Treatment	1	15	13.86	0.0020
Week 16	Treatment	1	15	3.75	0.0720
Week 24	Treatment	1	15	4.68	0.0471

Estimation of treatment differences

Week	Comparison	Difference	Stand. error	DF	95% CI lower	95% CI upper	p-value
Week 2	Entacapone - P	0.17	0.11	15	-0.07	0.40	0.1464
Week 4	Entacapone - P	0.17	0.12	15	-0.09	0.44	0.1805
Week 8	Entacapone - P	0.36	0.10	15	0.15	0.56	0.0020
Week 16	Entacapone - P	0.21	0.11	15	-0.02	0.45	0.0720
Week 24	Entacapone - P	0.24	0.11	15	0.00	0.47	0.0471

Statistical significance levels: 0.01 (5%), 0.002 (1%) and 0.0002 (0.1%)

COMPLETED SEP 17 1999

Statistical Review and Evaluation

SEP 15 1999

NDA NO: 20-796

DRUG NAME: Comtan (entacapone) Tablets

SPONSOR: Orion Corporation

INDICATION: Treatment of signs and symptoms of Parkinson's disease as an addition to levodopa/dopadecarboxylace inhibitor (either carbidopa or benserazide) treatment

DOSES STUDIED: One 200 mg tablet entacapone or placebo

STUDY: 2939 063

Clinical Reviewer: Richard Tresley, M.D. (HFD-120)

The results on three efficacy variables UPDRS II, UPDRS III, and daily ON- time, based on ANCOVA using LOCF for mean change, the Wilcoxon rank sum test using LOCF for mean change, visitwise ANCOVA using LOCF and OC for mean change, and ANCOVA for repeated measures, indicate that patients in entacapone group had a statistically significant greater mean change, in both UPDRS II and UPDRS III, from baseline to endpoint, compared to patients in placebo group. However, there is no statistically significant difference between two treatment groups in daily ON-time.

This review is arranged as follows. The BACKGROUD will be introduced in the first section. After that, the STUDY SPECIFICATIONS will be discussed. SPONSOR'S RESULTS AND CONCLUSION will be presented in Section 3, and REVIEWER'S ANALYSES AND CONCLUSION will be presented in the final section.

1. BACKGROUND

Entacapone is a catechol-O-methyltransferase inhibitor, synthesized and developed by Orion Pharma. The action of entacapone is mainly peripheral. Both animal experiments and human studies in healthy volunteers and patients with Parkinson's disease, as claimed by Orion, have shown that entacapone increases the bioavailability of levodopa and inhibits the formation of 3-O-methyldopa, the main metabolite of levodopa, when both drugs are given at the same time. The clinical studies in patients with Parkinson's disease, as claimed by Orion, have demonstrated that it is of clinical benefit in combination with levodopa/DDC inhibitor, particularly in patients with motor fluctuations by prolonging the ON- phase and shortening the OFF- phase during a day.

Two previous studies, the US-Canadian Study 2939-044 and the Nordic Study 2939-033, were submitted to FDA. Those two studies were both randomized, double-blind, multicenter studies with two parallel treatment groups, entacapone and placebo. In both studies, the duration of the double-blind treatment period was 24 weeks. The primary efficacy variables were the proportion of ON-time (%) from the home diary in Study 2939-044, and the mean ON- time (hours) from the home diary in Study 2939-033, respectively. According to the previous reviews, Study 2939-033 was statistically significant, and Study 2939-044 was not robust because it was not statistically significant after removing Center 23.

The current study was originally planned to be merely a safety study. No protocol specifications in defining the primary efficacy variable and statistical analysis were discussed between the sponsor and FDA. The sponsor analyzed all data collected for this study.

After the meeting with the medical division on June 14, 1999, it is decided to analyze UPDRS II, UPDRS III and ON- time. The main purpose of the current review is to verify the sponsor's results on the three variables.

2. STUDY SPECIFICATIONS

2.1 Objective

The primary objective was to study safety and efficacy of the long-term use of entacapone as an adjunct to levodopa/dopadecarboxylace (DDC) inhibitor treatment compared with placebo in patients with Parkinson's disease.

2.2 Efficacy Measures

The efficacy characteristics are measured by: (1) UPDRS (Parts I, II, III, total (I+II+III), IV, V and VI), (2) ON-, OFF-, and ASLEEP- times from home diary, (3) Global evaluation, and (4) Total daily levodopa dose and levodopa daily dosing.

UPDRS was to be performed when the patient was in ON- phase. It included the evaluation of various parkinsonian symptoms and signs, and disease-related or treatment-related complications as follows:

- Part I: mentation, behavior, and mood
- Part II: activities of daily living
- Part III: motor examination
- Part IV: complications of therapy
- Part V: Modified Hoehn and Yahr staging
- Part VI: Schwab and England activities of daily living

Home diary was recorded by patients on three consecutive days prior to each study visit for 24 hours each day on every 30 minutes whether the patient is ON-, OFF- or ASLEEP.

- ON-: the time when the patient was mobile (or capable of moving with relative ease and independence).
- OFF-: the time when the patient was immobile (or incapable of moving with relative ease and independence).
- ASLEEP: the time when the patient was sleeping.

Global evaluation was performed by asking the patient to assess his/her own condition during the week preceding the study visit. A seven-point scale was used in the evaluation. The investigator interpreted the scale to the patient and recorded the answer to the CRFs.

The total daily levodopa dose (mg) and dosing frequency (i.e., the number of daily doses) between two consecutive visits were recorded on the CRFs.

2.3 Study Design

This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group design. The study consists of the following three periods:

- a 2- to 4-week screening period without study treatment to control the response of the stable levodopa/DDC inhibitor dose regimen
- a 6-month double-blind period on the study treatment to evaluate the safety and efficacy of entacapone
- a 1- to 3-week post-study period without study treatment

The patients were taking investigational drugs, either entacapone or placebo, for about 6 months.

2.4 Patient Population

The study included male/female with idiopathic Parkinson's disease (ICD 9 code 3320A) within the age range of 30 to 80. Most of the patients were fluctuating (86%) according to the criteria, ≥ 4.5 hours OFF- time over 3 home diary days and at least 0.5 hours on each home diary day. The criteria for fluctuations were set afterwards when all patients had already passed the clinical phase so no a priori criteria to classify the patients as non-fluctuating or fluctuating were applied. This is different than the previous two Studies 2939-044 and 2939-033 in which only fluctuating patients were recruited.

2.5 Statistical Analyses

Both intent-to-treat (ITT) and per protocol analyses were conducted for efficacy variables. For ITT analyses, efficacy variables were analyzed using the last observation carried forward (LOCF) and

observed cases (OC).

For continuous variables, analysis of covariance (ANCOVA) was used. The model included terms for treatment, center (random) and treatment-by-center (random) interaction, and the baseline measurement as a covariate. In addition, the model included terms for a stratification variable (2 to 4 or 5 to 10 doses of levodopa) and for treatment-by-stratification interaction.

For categorical variables, the Cochran-Mantel-Haenszel test was used. The response variable was change from baseline to month 6.

3. SPONSOR'S RESULTS AND CONCLUSION

3.1 Demographic

Table 3.1.1 presents the demographic configuration of the study. As Table 3.1 shows, the treatment groups are very much homogeneous with respect to the demographic configuration. The results show that there were no statistically significant differences between the two treatment groups, with respect to all variables.

Table 3.1.1 Demographic and Baseline Configuration

Parameter	Entacapone	Placebo	Significance
Number of patients	197	104	-
Sex			NS
- Male, n (%)	119 (60.4%)	54 (51.9%)	
- Female, n (%)	78 (39.6%)	50 (48.1%)	
Age, mean ± SD (years)	60.7 ± 9.6	61.1 ± 9.9	NS
Race	all Caucasians	all Caucasians	

3.2 Patient Disposition

As Table 3.2.1 shows, the percentage of the completed patients in the entacapone group is lower than that in placebo group. The numerical results show that the percentage of the patients who dropped the study because of the other adverse events is higher in the entacapone group than that in placebo group.

Table 3.2.1 Patients Disposition

Patient group Reason for discontinuation	Entacapone (n=197)		Placebo (n=104)	
	n	%	n	%
Randomized	197		104	
Completed	149	75.6	89	85.6

Discontinued (total)	48	24.4	15	14.4
- deaths	0	0	0	0
- other adverse events	41	20.8	10	9.6
- lack of efficacy	1	0.5	2	1.9
- non-compliance	1	0.5	0	0
- consent withdrawn	1	0.5	1	1.0
- protocol violation	2	1.0	1	1.0
- lost to follow-up	1	0.5	1	1.0
- other	1	0.5	0	0

3.3 Efficacy Results

The sponsor analyzed all data collected for the current study. The analyses on daily ON- time, proportion of daily ON- time, daily OFF- time, main daily levodopa dose on home diary, and mean daily dosing frequency of levodopa on home diary are performed on all fluctuating patients.

Among all variables the sponsor analyzed, there are statistically significant differences on UPDRS II, UPDRS III, Sum of UPDRS I, II, and III, mean daily dosing frequency of levodopa, and mean daily levodopa dose on home diary. The details are presented in the following tables.

Table 3.3.1 UPDRS I: Mentation, Behavior and Mood

Analysis/ Patient population		Entacapone n	Entacapone mean ± SD	Placebo n	Placebo mean ± SD	Diff	P-value
ITT-LOCF							
All patients	-baseline	191	1.7 ± 1.5	104	1.6 ± 1.5		
	-month 6	191	1.6 ± 1.6	104	1.5 ± 1.3		
	-change	191	-0.0 ± 1.2	104	-0.1 ± 1.4	0.1	.7813

Table 3.3.2 UPDRS II: Activities of Daily Living

Analysis/ Patient population		Entacapone n	Entacapone mean ± SD	Placebo n	Placebo mean ± SD	Diff	P-value
ITT-LOCF							
All patients	-baseline	191	12.4 ± 6.1	104	12.0 ± 5.8		
	-month 6	191	11.5 ± 6.4	104	12.5 ± 6.5		
	-change	191	-0.9 ± 3.4	104	0.5 ± 4.0	-1.4	.0147

Table 3.3.3 UPDRS III: Motor Examination

Analysis/ Patient population		Entacapone n	Entacapone mean ± SD	Placebo n	Placebo mean ± SD	Diff	P-value
ITT-LOCF							
All patients	-baseline	190	24.9 ± 12.9	102	24.1 ± 12.1		
	-month 6	190	22.4 ± 12.4	102	24.2 ± 12.7		
	-change	190	-2.5 ± 8.0	102	0.1 ± 8.1	-2.6	.0414

Table 3.3.4 UPDRS Total: Sum of I, II and III

Analysis/ Patient population		Entacapone n	Entacapone mean ± SD	Placebo n	Placebo mean ± SD	Diff	P-value
ITT-LOCF							
All patients	-baseline	190	39.0 ± 18.3	102	37.7 ± 16.8		
	-month 6	190	35.6 ± 18.3	102	38.3 ± 17.9		
	-change	190	-3.4 ± 10.2	102	0.6 ± 10.3	-4.0	.0155

Table 3.3.5 Home Diary: Daily ON- Time (hours)

Analysis/ Patient population		Entacapone n	Entacapone mean ± SD	Placebo n	Placebo mean ± SD	Diff	P-value
ITT-LOCF							
All fluctuating	-baseline	165	10.0 ± 2.6	87	9.7 ± 2.8		
	-month 6	165	11.2 ± 3.0	87	10.6 ± 3.0		
	-change	165	1.3 ± 2.8	87	0.9 ± 3.1	0.4	.2860

Table 3.3.6 Home Diary: Proportion of Daily ON- Time (% of awake time)

Analysis/ Patient population		Entacapone n	Entacapone mean ± SD	Placebo n	Placebo mean ± SD	Diff	P-value
ITT-LOCF							
All fluctuating	-baseline	165	61.7 ± 15.8	87	59.1 ± 16.6		
	-month 6	165	69.6 ± 18.5	87	64.8 ± 18.7		
	-change	165	7.9 ± 17.2	87	5.7 ± 19.3	2.2	.2105

Table 3.3.7 Home Diary: Daily OFF- Time (hours)

Analysis/ Patient population		Entacapone n	Entacapone mean ± SD	Placebo n	Placebo mean ± SD	Diff	P-value
ITT-LOCF							
All fluctuating	-baseline	165	6.2 ± 2.7	87	6.7 ± 3.0		
	-month 6	165	4.9 ± 3.0	87	5.8 ± 3.3		
	-change	165	-1.3 ± 2.7	87	-0.9 ± 3.3	-0.4	.1684

Table 3.3.8 Global Evaluation (% of patients) at Month 6 Compared to Baseline

Analysis/Patient population	Entacapone Worsened	Entacapone No change	Entacapone Improved	Placebo Worsened	Placebo No change	Placebo Improved	P-value
ITT-LOCF							
All patients	25.7	36.1	38.2	26.9	39.4	33.7	.5426

Table 3.3.9 Mean Scheduled Daily Levodopa Dose (mg)

Analysis/ Patient population		Entacapone n	Entacapone mean ± SD	Placebo n	Placebo mean ± SD	Diff	P-value
ITT-LOCF							
All patients	-baseline	191	566 ± 274	104	572 ± 329		
	-month 6	191	531 ± 261	104	575 ± 282		
	-change	191	-35 ± 102	104	4 ± 224	-39	.1146

Table 3.3.10 Mean Daily Dosing Frequency of Levodopa

Analysis/ Patient population		Entacapone n	Entacapone mean ± SD	Placebo n	Placebo mean ± SD	Diff	P-value
ITT-LOCF							
All patients	-baseline	191	5.4 ± 1.9	104	5.6 ± 1.9		
	-month 6	191	5.4 ± 1.8	104	5.8 ± 2.0		
	-change	191	-0.0 ± 0.6	104	0.2 ± 0.7	-0.2	.0048

Table 3.3.11 Mean Daily Levodopa Dose (mg/day) on Home Diary

Analysis/ Patient population		Entacapone n	Entacapone mean ± SD	Placebo n	Placebo mean ± SD	Diff	P-value
ITT-LOCF							
Fluctuating	-baseline	118	594 ± 276	52	567 ± 293		
	-month 6	118	541 ± 242	52	590 ± 321	-49	.0190

Table 3.3.12 Mean Daily Dosing Frequency of Levodopa on Home Diary

Analysis/ Patient population		Entacapone n	Entacapone mean ± SD	Placebo n	Placebo mean ± SD	Diff	P-value
ITT-LOCF							
Fluctuating	-baseline	158	5.3 ± 2.2	83	5.6 ± 2.1		
	-month 6	158	5.7 ± 1.9	83	6.1 ± 2.3	-0.4	.1458

3.4 Subgroup Analyses

There were several subgroup analyses, including fluctuating patients, patients with 2-4 or 5-10 daily doses of levodopa, fluctuating patients with 5-10 daily doses of levodopa.

In Section 4.4, the analyses on age and gender, by this reviewer, will be presented.

3.5 Sponsor's Summary and Conclusion

Entacapone treatment has a consistent beneficial clinical effect on parkinsonian symptoms, as

evaluated objectively by UPDRS scoring and subjectively by ON- and OFF- time measures from home diaries. Entacapone decreased the total UPDRS score by average 4.2 points compared with an increase by 0.4 points in the patients treated with placebo ($p<0.01$; ITT-OC analysis). The fluctuating patients treated with entacapone changed their OFF- time category to milder one significantly more often ($p<0.05$) compared with the placebo treated patients. In the global evaluation more patients improved with entacapone compared with placebo but the difference was not statistically significant.

Entacapone treatment increased both the proportion of ON- time and the absolute daily ON- time almost significantly in the fluctuating patient population. In the entacapone group the ON- time increased by average 1.7 hours compared with an increase by average 0.9 hours in the placebo group (fluctuating group). Conversely, the daily OFF- time was decreased by entacapone by average 1.6 hours compared with a decrease of 0.9 hours in the placebo group. Mean daily levodopa dose decreased by about 40 mg after entacapone treatment but the change was not statistically significant. The levodopa dosing frequency slightly decreased on entacapone treatment compared with placebo.

The beneficial effect of entacapone was thus consistent both in different assessments and different patient populations. Though the differences compared with placebo were not in some comparisons nominally statistically significant there was always a positive trend. As this study was originally planned to be a safety study, no a priori sample size calculations for efficacy parameters were performed. Consequently, the lack of power is probably the main reason for failure to demonstrate statistically significancies in every comparison.

It is concluded that clinical benefit is obtained using entacapone in combination with levodopa. The data from this study provides supportive evidence for the effectiveness of entacapone, particularly in the patients with fluctuating symptoms and frequent daily levodopa doses.

4. REVIEWER'S ANALYSES AND CONCLUSION

Because there are no protocol specifications in defining the primary efficacy variable, and the primary analysis, according to the meeting with the medical division, the variables UPDRS II, UPDRS III, and daily ON- time will be analyzed.

The ANCOVA and the Wilcoxon rank sum test, using LOCF mean change from baseline to endpoint performed on both UPDRS II and UPDRS III, demonstrate statistically significant differences between entacapone and placebo groups. The ANCOVA, the Wilcoxon rank sum test, and ANCOVA for repeated measures performed on daily ON- time, using LOCF mean change from baseline to endpoint, are not statistically significant.

4.1 UPDRS II

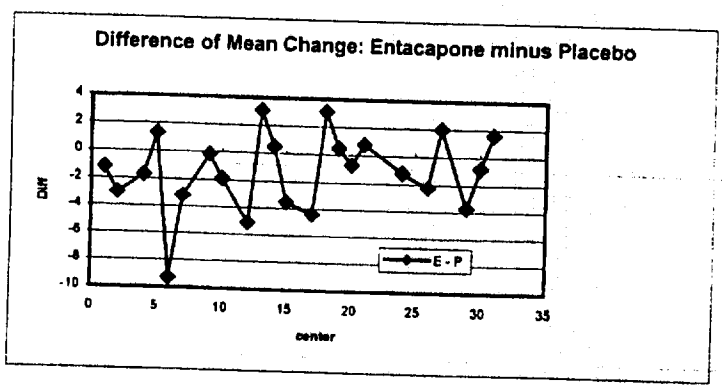
The ANCOVA using LOCF for change shows a statistically significant difference between two treatment groups. The Wilcoxon rank sum test using LOCF for change is also statistically significant. Visitwise LOCF and OC analyses, except visit 4, are statistically significant.

4.1.1 LOCF Analyses for Change

After duplicating the sponsor's ANCOVA results whose model includes terms treatment, center (random) and treatment-by-center (random) interaction, and the baseline measurement as a covariate, we will consider the ANCOVA with terms baseline, treatment, and center (fixed). 8 centers (08, 11, 14, 16, 22, 23, 25 and 32) whose sizes ≤ 4, among 30 centers in the study, are combined together. The ANCOVA gives p-value .0010 for treatment.

Figure 4.1.1 gives the difference of mean change between entacapone and placebo for each center. A negative value indicates that entacopone is better than placebo.

Figure 4.1.1 UPDRS II Difference of Mean Change for Center



From the graph, and the analysis after adding treatment-by-center to the model, Center 6 with 4 patients in entacapone group and 2 patients in placebo group is the main reason for the interaction. Among 30 centers excluding 7 with only 1 patient in an arm, there are 16 centers where the entacapone show numerical superiority over the placebo, and 7 centers don't.

Because Center 6 has the largest treatment effect, there is concern whether the overall significant difference is caused by this center. After removing Center 6, ANCOVA gives p-value .0135 for the treatment, and the Wilcoxon rank sum test gives p-value .0067.

Table 4.1.1, as a complementary to Figure 4.1.1, gives the each center's data. The unequal variance T-test for each center is mostly not significant, possibly due to small sample size.

Table 4.1.1 UPDRS II for Centers

Center	n	Baseline mean ±SD	Change mean ±SD	Diff E - P	P-value	Center	n	Baseline mean ± SD	Change mean ± SD	Diff E - P	P-value
1	E 9	7.9 ± 3.8	-0.7 ± 2.7	**-1.2**	.3195	17	E 7	16.9 ± 7.9	-2.4 ± 4.0	**-4.4**	.0694
	P 4	7.3 ± 4.3	0.5 ± 1.3				P 4	17.3 ± 6.7	2.0 ± 2.9		
2	E 9	11.7 ± 4.4	0.3 ± 2.7	**-3.0**	.3143	18	E 3	13.0 ± 12.5	-3.0 ± 5.2	3.1	.9254
	P 4	7.0 ± 3.7	3.3 ± 4.7				P 3	10.7 ± 4.1	-3.3 ± 2.1		
4	E 9	15.8 ± 5.9	-0.3 ± 3.4	**-1.7**	.4368	19	E 4	7.3 ± 7.4	-1.0 ± 2.6	0.5	.8808
	P 5	14.4 ± 10.7	1.4 ± 3.8				P 2	14.0 ± 8.5	-1.5 ± 3.5		
5	E 9	9.2 ± 3.4	0.9 ± 2.7	1.3	.2018	20	E 7	11.0 ± 7.3	-1.0 ± 3.5	**-0.7**	.7462
	P 4	8.8 ± 2.3	-0.4 ± 0.5				P 3	15.3 ± 5.8	-0.3 ± 2.5		
6	E 4	11.5 ± 5.1	-2.8 ± 3.3	**-9.3**	.0973	21	E 11	8.9 ± 4.5	-1.4 ± 1.9	**-0.8**	.5758
	P 2	14.5 ± 3.5	6.5 ± 3.5				P 6	11.3 ± 6.9	-2.2 ± 3.1		
7	E 11	9.8 ± 3.1	-2.0 ± 2.7	**-3.2**	**.0045**	22	E 3	5.7 ± 2.3	2.7 ± 2.1		
	P 5	8.8 ± 4.4	1.2 ± 1.1				P 1	10.0 ± .	0.0 ± .		
8	E 2	10.0 ± 4.2	-2.0 ± 1.4			23	E 1	14.0 ± .	-4.0 ± .		
	P 1	12.0 ± .	5.0 ± .				P	.			
9	E 5	12.4 ± 7.7	-3.2 ± 3.1	**-1.5**	.3629	24	E 6	15.0 ± 3.2	-1.5 ± 3.4	**-1.2**	.5843
	P 3	9.0 ± 1.7	-1.7 ± 1.2				P 3	13.3 ± 8.5	-0.3 ± 2.5		
10	E 5	18.2 ± 7.7	-5.6 ± 2.8	**-1.9**	.6734	25	E 1	10.0 ± .	-7.0 ± .		
	P 3	16.3 ± 3.8	-3.7 ± 6.7				P 1	10.0 ± .	0.0 ± .		
11	E 1	8.0 ± .	-2.0 ± .			26	E 6	10.8 ± 6.2	-0.8 ± 1.3	**-2.2**	.4737
	P 1	4.0 ± .	-1.0 ± .				P 2	15.5 ± 3.5	-3.0 ± 2.8		
12	E 5	10.0 ± 1.9	-0.8 ± 2.6	**-5.1**	.1437	27	E 9	9.6 ± 4.3	0.8 ± 3.7	2.0	.4078
	P 4	16.3 ± 2.5	4.3 ± 5.1				P 5	9.4 ± 2.5	-1.2 ± 4.2		
13	E 5	13.2 ± 2.9	-0.4 ± 1.1	3.1	.4308	29	E 6	15.5 ± 4.2	-4.7 ± 3.8	**-3.7**	.3612
	P 2	13.0 ± 5.7	-3.5 ± 3.5				P 3	16.7 ± 4.2	-1.0 ± 5.3		
14	E 2	8.5 ± 0.7	0.0 ± 1.4	0.5	.8128	30	E 4	9.3 ± 4.6	-1.5 ± 2.4	**-0.8**	.6789
	P 2	11.0 ± 1.4	-0.5 ± 2.1				P 3	9.7 ± 8.0	-0.7 ± 2.5		
15	E 28	14.6 ± 6.2	0.4 ± 4.3	**-3.5**	**.0142**	31	E 16	16.6 ± 6.1	0.3 ± 1.7	1.6	**.0295**
	P 17	10.8 ± 5.8	3.9 ± 4.5				P 9	15.4 ± 6.2	-1.3 ± 1.7		
16	E 1	10.0 ± .	0.0 ± .			32	E 2	21.0 ± 9.9	-4.0 ± 4.2		
	P						P 1	13.0 ± .	-1.0 ± .		

4.1.2 Visitwise LOCF Analyses for Change

Similar procedures as the last section are employed. The ANCOVA model with terms baseline, treatment, and center is used. Center 6 is excluded from the analyses in eliminating the interaction. The p-values are presented in Table 4.1.2.

Table 4.1.2 Visitwise LOCF Analyses

P-value -	Treatment
Visit 2	**.0088**
Visit 3	**.0184**
Visit 4	.0618
Visit 5	**.0038**

4.1.3 Visitwise OC Analyses for Change

For OC analyses, the ANCOVA model used includes terms baseline and treatment only. In case of sparse data due to dropout, the term center is not included in the model.

Table 4.1.3. Visitwise OC Analyses

P-value	Treatment
Visit 2	.0042
Visit 3	.0069
Visit 4	.2254
Visit 5	.0065

4.2 UPDRS III

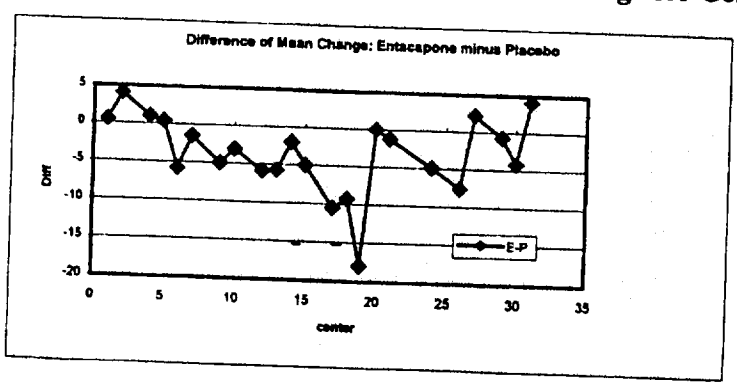
The ANCOVA using LOCF for change shows a statistically significant difference between two treatment groups. The Wilcoxon rank sum test using LOCF for change is also statistically significant. Visitwise LOCF and OC analyses, except visit 4, are statistically significant.

4.2.1 LOCF Analyses for Change

After duplicating the sponsor's ANCOVA results whose model includes terms treatment, center (random) and treatment-by-center (random) interaction, and the baseline measurement as a covariate, same analysis as those in section 4.1.1. is performed, the ANCOVA gives p-value .0063 for treatment.

Figure 4.2.1 gives the difference of mean change between entacapone and placebo for each center. A negative value indicates that the entacapone is better than the placebo.

Figure 4.2.1 UPDRS III Difference of Mean Change for Center



From the graph, Center 19 with 4 patients in entacapone group and 2 patients in placebo group has the largest mean change, but the analysis on the interaction, after adding treatment-by-center to the ANCOVA model, isn't significant. Among 30 centers excluding 7 with only 1 patient in an arm, there are 16 centers where the entacapone show numerical superiority over the placebo, and 7 centers don't.

Because Center 19 has the largest treatment effect, there is concern whether the overall significant difference is caused by this center. After removing Center 19, ANCOVA gives p-value .0166 for the treatment, and the Wilcoxon rank sum test gives p-value .0348.

Table 4.2.1, as a complementary to Figure 4.2.1, gives each center's data. The unequal variance T-test for each center is mostly not significant, possibly due to small sample size.

Table 4.2.1 UPDRS III for Centers

Center	n	Baseline mean ± SD	Change mean ± SD	Diff E - P	P-value	Center	n	Baseline mean ± SD	Change mean ± SD	Diff E - P	P-value
1	E 9	12.9 ± 7.4	-1.0 ± 2.9	0.5	.8271	17	E 7	39.3 ± 12.9	-7.7 ± 8.6	-10.5	.0447
	P 4	17.3 ± 9.4	-1.5 ± 3.9				P 4	38.3 ± 10.9	2.8 ± 6.0		
2	E 9	25.6 ± 7.5	1.8 ± 10.9	4.1	.3818	18	E 3	31.3 ± 15.5	-9.3 ± 13.7	-9.3	.3850
	P 4	25.8 ± 5.7	-2.3 ± 5.0				P 3	27.3 ± 14.0	0.0 ± 8.7		
4	E 9	29.1 ± 11.7	-3.8 ± 11.7	1.0	.8635	19	E 4	12.3 ± 6.9	-1.0 ± 5.2	-18.0	.5001
	P 5	31.2 ± 18.2	-4.8 ± 9.6				P 2	18.0 ± 2.8	17.0 ± 25.5		
5	E 9	18.2 ± 6.9	2.4 ± 10.2	0.4	.9946	20	E 7	19.0 ± 10.4	-0.3 ± 7.4	0.0	.9890
	P 5	20.0 ± 7.2	2.4 ± 12.0				P 3	27.7 ± 1.5	-0.3 ± 3.2		
6	E 4	17.5 ± 16.5	-6.8 ± 12.9	-5.8	.6539	21	E 11	17.2 ± 6.5	-0.5 ± 6.2	-1.2	.6002
	P 2	20.0 ± 2.8	-1.0 ± 12.7				P 6	14.5 ± 7.8	0.7 ± 3.1		
7	E 11	22.8 ± 6.5	-2.9 ± 2.5	-1.5	.2981	22	E 3	12.3 ± 1.5	-3.0 ± 1.6		
	P 5	22.4 ± 9.9	-1.4 ± 2.5				P 1	27.0 ± .	-5.0 ± .		
8	E 2	24.5 ± 12.0	-2.0 ± 1.4			23	E 1	7.0 ± .	-1.0 ± .		
	P 1	23.0 ± .	20.0 ± .				P				
9	E 5	29.8 ± 13.9	-11.0 ± 6.6	-5.0	.1866	24	E 6	22.3 ± 14.5	-4.2 ± 9.7	-4.9	.4158
	P 3	24.3 ± 3.2	-6.0 ± 2.6				P 3	24.0 ± 11.5	0.7 ± 6.7		
10	E 5	34.2 ± 20.6	-9.8 ± 12.8	-3.1	.3756	25	E 1	4.0 ± .	-2.0 ± .		
	P 3	18.0 ± 2.6	-3.7 ± 4.7				P 1	28.0 ± .	-3.0 ± .		
11	E 1	13.0 ± .	1.0 ± .			26	E 5	26.0 ± 10.4	-2.6 ± 8.4	-7.6	.1887
	P 1	9.0 ± .	-4.0 ± .				P 2	22.0 ± 4.2	5.0 ± 4.2		
12	E 5	21.8 ± 8.4	-2.4 ± 4.8	-5.9	.1410	27	E 9	18.8 ± 9.3	-0.4 ± 5.1	2.2	.4832
	P 4	27.0 ± 6.8	3.5 ± 5.5				P 4	14.3 ± 9.9	-2.6 ± 5.1		
13	E 5	33.0 ± 11.2	-2.2 ± 5.7	-5.7	.8936	29	E 6	33.5 ± 7.0	-9.0 ± 8.5	-0.7	.9072
	P 2	30.0 ± 2.8	-3.5 ± 10.6				P 3	40.3 ± 15.0	-8.3 ± 7.2		
14	E 2	10.0 ± 1.4	-5.5 ± 5.7	-2.0	.3921	30	E 4	25.5 ± 14.2	-9.5 ± 7.2	-4.2	.4348
	P 2	30.0 ± 2.8	-3.5 ± 9.2				P 3	15.7 ± 10.5	-5.3 ± 5.8		
15	E 28	26.2 ± 13.3	0.1 ± 8.3	-5.0	.0360	31	E 16	37.9 ± 10.8	-1.3 ± 3.6	4.1	.1375
	P 17	20.0 ± 9.9	5.1 ± 7.1				P 8	41.3 ± 12.9	-5.4 ± 6.6		
16	E 1	27.0 ± .	-3.0 ± .			32	E 2	33.0 ± 19.8	-3.5 ± 2.1		
	P						P 1	32.0 ± .	0.0 ± .		

4.2.2 Visitwise LOCF Analyses for Change

Similar procedures as those in section 4.1.2 are employed. The p-values are presented in Table 4.2.2.

Table 4.2.2 Visitwise LOCF Analyses

P-value	Treatment
Visit 2	.0458
Visit 3	.0028
Visit 4	.1705
Visit 5	.0063

4.2.3 Visitwise OC Analyses for Change

For OC analyses, the ANCOVA model used includes terms baseline and treatment only. In case of sparse data due to dropout, the term center is not included in the model.

Table 4.2.3. Visitwise OC Analyses

P-value	Treatment
Visit 2	.0486
Visit 3	.0023
Visit 4	.1473
Visit 5	.0023

4.3 Daily ON- Time

The ANCOVA and the Wilcoxon rank sum test, using LOCF for change, show no statistically significant difference between two treatment groups. Visitwise LOCF and OC analyses, except visit 4 and visit 5 for OC, are not statistically significant.

The ANCOVA for repeated measures is also performed, and is not statistically significant.

4.3.1 LOCF Analyses for Change

The same procedure as those in section 4.1.1. is used. The ANCOVA gives p-value .2253 for treatment. The Wilcoxon rank sum test gives p-value is .2220.

Table 4.3.1 LOCF Analyses for Change

		Mean ± SD	Change	Diff	P-value
E	183	10.3 ± 2.9	1.2 ± 2.7	**0.5**	.2253
P	101	10.5 ± 3.2	0.7 ± 3.0		

In addition, the term treatment-by-center is added to the model to check the interaction, and is not statistically significant.

In the previous two studies, the primary efficacy variables are ON- time, and percentage of ON-time, and the primary analysis is the ANCOVA for repeated measures. That model includes terms baseline, treatment, time, treatment-by-time interaction, center (random), and center-by-treatment interaction. The same analysis is performed for the current study, and provides p-value .1979 for the treatment.

4.3.2 Visitwise LOCF Analyses for Change

The ANCOVA model with terms baseline, treatment, and center is used. The p-values for treatment are presented in Table 4.3.2. There are no statistically significant differences between two treatment groups for any visit.

Table 4.3.2 Visitwise LOCF Analyses

Visit		Mean ± SD	Change	Diff	P-value
1	E	10.3 ± 2.9			
	P	10.5 ± 3.2			
2	E	11.0 ± 3.1	0.6 ± 2.3	**0.1**	.8652
	P	11.0 ± 3.2	0.5 ± 2.8		
3	E	11.2 ± 3.0	0.9 ± 2.4	**0.5**	.1658
	P	10.9 ± 3.2	0.4 ± 2.7		
4	E	11.4 ± 2.9	1.0 ± 2.7	**0.5**	.1784
	P	11.0 ± 3.0	0.5 ± 3.2		
5	E	11.5 ± 3.0	1.2 ± 2.7	**0.5**	.2253
	P	11.2 ± 3.2	0.7 ± 3.0		

4.3.3 Visitwise OC Analyses for Change

For OC analyses, the ANCOVA model used includes terms baseline and treatment only. In case of sparse data due to dropout, the term center is not included in the model.

Table 4.3.3 Visitwise OC Analyses

Visit	n	Mean ± SD	Change	Diff	P-value
2 E	183	10.3 ± 2.9			
P	101	10.5 ± 3.2			
2 E	180	10.9 ± 3.1	0.6 ± 2.3	**0.1**	.8394
P	100	11.0 ± 3.2	0.5 ± 2.8		
3 E	162	11.4 ± 2.9	1.0 ± 2.3	**0.6**	.0539
P	96	10.9 ± 3.3	0.4 ± 2.8		
4 E	148	11.7 ± 2.7	1.2 ± 2.6	**0.8**	**.0148**
P	85	10.8 ± 2.9	0.4 ± 3.3		
5 E	140	11.9 ± 2.9	1.5 ± 2.6	**0.7**	**.0375**
P	85	11.1 ± 3.2	0.8 ± 3.1		

4.4 Subgroup Analyses

Because all patients were Caucasian, only age and sex will be analyzed. According to the previous two studies, age groups are divided by <65 and ≥ 65. The ANCOVA model with terms baseline and treatment is used. The interaction treatment-by-age, and treatment-by-sex are checked.

Table 4.4.1 LOCF Analyses on UPDRS II

	Strata	n	Baseline	Change	Diff	P-value
Age	< 65	E 125	11.8 ± 5.9	-1.2 ± 3.6	**-1.1**	.1528
		P 58	10.5 ± 6.0	-0.1 ± 3.7		
	≥ 65	E 66	13.5 ± 6.3	-0.4 ± 2.8	**-1.7**	**.0099**
		P 46	13.9 ± 5.1	1.3 ± 4.2		
Gender	Female	E 74	12.2 ± 6.2	-0.4 ± 3.6	**-0.8**	.1902
		P 50	12.6 ± 6.0	0.4 ± 4.0		
	Male	E 117	12.5 ± 6.0	-1.2 ± 3.2	**-1.8**	**.0030**
		P 54	11.4 ± 5.6	0.6 ± 4.0		

The results from all subgroups indicate positive trends. It is possible that the sample sizes are not big enough to show statistically significant differences for some subgroups.

Table 4.4.2 LOCF Analyses on UPDRS III

	Strata	n	Baseline	Change	Diff	P-value
Age	< 65	E 125	23.2 ± 12.3	-3.0 ± 8.5	-3.0	.0763
		P 57	20.2 ± 10.5	0.0 ± 8.5		
	≥ 65	E 65	28.1 ± 13.4	-1.5 ± 6.8	-1.7	.1451
		P 45	29.2 ± 12.2	0.2 ± 7.7		
Gender	Female	E 74	23.9 ± 12.8	-1.9 ± 9.3	-3.1	.0538
		P 49	23.6 ± 12.0	1.2 ± 8.4		
	Male	E 116	25.5 ± 13.0	-2.9 ± 7.1	-2.0	.1221
		P 53	24.7 ± 12.2	-0.9 ± 7.7		

The results from all subgroups indicate positive trends. It is possible that the sample sizes are not big enough to show statistically significant differences.

Table 4.4.3 LOCF Analyses on ON- Time

	Strata	n	Baseline	Change	Diff	P-value
Age	< 65	E 122	10.4 ± 2.8	1.2 ± 2.7	0.6	.4829
		P 58	11.0 ± 3.2	0.6 ± 3.2		
	≥ 65	E 61	10.3 ± 3.0	1.2 ± 2.5	0.3	.2880
		P 43	9.8 ± 3.1	0.9 ± 2.8		
Gender	Female	E 67	10.0 ± 2.7	0.9 ± 2.5	-0.1	.8808
		P 47	9.5 ± 3.0	1.0 ± 2.5		
	Male	E 116	10.5 ± 2.9	1.4 ± 2.7	0.9	.3267
		P 54	11.3 ± 3.1	0.5 ± 3.5		

The results show positive trends except the subgroup of female.

4.5 Conclusion

Based on the sponsor's results, this study provides nominal statistically significant evidence that entacapone-treated patients had a greater mean change of UPDRS II and UPDRS III from baseline to endpoint than those placebo-treated patients did. Although entacapone helps to improve the daily ON- time, the evidence is not statistically significant.

/S/

Kun He, Ph.D.
Statistical Reviewer

This review consists of 17 pages and contains 26 tables and 2 figures.

Concur:

/S/

Kun Jin, Ph.D.
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