DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

CLINICAL REVIEW OF NDA

NDA Number	20,796
Generic (Brand) Name	Comtan (Entacapone)
Sponsor	Orion Corporation (Espoo, Finland)
Indication	Parkinson's Disease
Classification	S
Correspondence Date	24 October 1997
Original Receipt Date	27 October 1997
Sponsor's Resubmission	3 December 1997
Clinical Reviewer	Richard M. Tresley, MD
Review Completed	2 November 1998

CONTENTS

I Introduction

The new molecular entity, entacapone, is a COMT inhibitor that has been proposed as an adjunct to levodopa/dopa decarboxylase inhibitor (DDCI) therapy for Parkinson's Disease (PD): "Entacapone increases the bioavailability of levodopa by decreasing its peripheral elimination by COMT, thereby enhancing the therapeutic effect of levodopa in the treatment of PD."

II Materials Used in Review

Volume	*Submission Date*	*Material*
1, 75	10/27/97 (not filable); resubmission (new volume 1), 12/3/97 (filable)	Summary; Chemistry; Animal Toxicology; Human Pharmacokinetics/Pharmacodynamics; Labeling
1, 75	10/27/97 (not filable); resubmission (new volume 1), 12/3/97 (filable)	Human Pharmacokinetics and Biopharmaceutics
136-43	10/27/97 (not filable); resubmission (new volume 1), 12/3/97 (filable)	Study 33: Clinical and Statistical
122-35	10/27/97 (not filable); resubmission (new volume 1), 12/3/97 (filable)	Study 44: Clinical and Statistical
144-48	10/27/97 (not filable); resubmission (new volume 1), 12/3/97 (filable)	Study 52: Clinical and Statistical
160-61 + Four-Month Safety Update, v 1	10/27/97 (not filable); resubmission (new volume 1), 12/3/97 (filable)	Studies 63 and 65 (study protocols only)
304	10/27/97 (not filable); resubmission (new volume 1), 12/3/97 (filable)	Integrated Summary of Efficacy (ISE)

III Background

A. *Indication*

The package insert ("INDICATIONS AND USAGE") states that "COMTAN (Entacapone) is indicated in the treatment of signs and symptoms of PD as an addition to levodopa/DDCI treatment. Efficacy of COMTAN has been proven in two randomized, well-controlled, multicenter, double-blind clinical studies in patients with mild to severe PD." However, elsewhere in the labeling ("CLINICAL STUDIES") the description of these two studies is more fully amplified as "two separate randomized, well-controlled, double-blind, multicenter studies enrolling 376 patients with mild to severe PD *with wearing-off type of motor fluctuations*" [my emphasis]. The true indication, then, should be for patients with mild to severe PD with wearing-off motor fluctuations. (For the purposes of this NDA, such patients will be called "fluctuators," in contrast to "nonfluctuators," or patients without wearing-off motor fluctuations.)

B. *Administrative History*

(viii) NDA acceptable for filing . . . . . Feb 19, 1998

NDA primary data cutoff date: Oct 31, 1996.

C. *Related INDs and NDAs*

Tasmar (tolcapone), another COMT inhibitor, was approved on Jan 29, 1998.

D. *Proposed Directions for Use*

DRAFT LABELING

E. *Foreign Marketing Experience*

COMTAN has not been approved for marketing in any country. However, "the European Agency for the Evaluation of Medicinal Products has given an approval on May 27, 1998, for entacapone marketing authorization" (letter from Jill Powers, Regulatory Affairs, Target Research Associates [New Jersey], dated 21 Aug 1998).

IV Chemistry

COMTAN, a catechol-0-methyltransferase inhibitor, is a nitrocatechol-structured compound with a molecular mass of 305.28; the chemical name (E)-2-cyano-N,N-diethyl-3-(3,4-dihydroxy-5-nitrophenyl) propamide; an empirical formula, $C_{14}H_{15}N_3O_5$. The structure has been reproduced in the Appendix.

COMTAN is supplied as a 200-mg tablet. Inactive ingredients include microcrystalline cellulose, mannitol, croscarmellose sodium, hydrogenated vegetable oil, polysorbate 80, glycerol 85%, sucrose, magnesium stearate, yellow iron oxide, red iron oxide, and titanium dioxide. The maximum dose (2000 mg/d) recommended by the

sponsor in labeling contains 5.1 mg elemental iron (mostly in the coating), which exceeds allowed limits for drugs (5.0 mg/d; see CFR 73.1200[c]). Dr. Martha Heimann (Chemistry) will cite the iron oxide levels as a deficiency.

V Animal toxicology

A. *General Information*

At doses of 3,10, and 30 mg/kg, entacapone potentiated levodopa/carbidopa locomotor activity in catecholamine-depleted reserpine-treated mice, as well as the turning behavior in brain-lesioned rats at doses of 1, 3, and 10 mg/kg (the rotation count increased maximally from 29 turns/5h to 975 turns/5h). Entacapone (at 12.5 mg/kg) increased L-dopa-induced locomotor activity -- and correspondingly potentiated an L-dopa-induced decrease in motor dysfunction -- in MPTP-treated marmosets. When administered alone, entacapone was inactive in these animal models.

Preclinical pharmacology and toxicology will be dealt with in detail in the review of Dr. Thomas Steele, and therefore only a brief overview will be attempted here.

VI Description of clinical data sources

A. *Study Type and Design/Patient Enumeration*

Tables 1, 2, and "Cumulative Exposure," reproduced in the Appendix of tables (pp 38-40), list Phase 2 and 3 clinical trials by type.

B. *Demographic Profile for the Pivotal Phase 3 Double-Blind, Placebo-Controlled Trials*

Tables 3-10, reproduced in the Appendix (pp 41-2), provides a demographic profile for the pivotal Phase 3 clinical trials.

C. *Extent of Exposure*

Because of conflicting numbers in the NDA and 120-Day Safety Update, the Agency requested that the sponsor resubmit information about the total number of subjects, dose, and duration of exposure. New tables ("Cumulative Exposure" and "Number of Patients"), from the sponsor's 11 September 1998 submission, re-examine patient data through 31 October 1997 (the cutoff date for the 120-Day Safety Update); see the appendix to this review (pp 39-40).

VII Human pharmacokinetics

Entacapone is an orally active, potent, selective, reversible peripheral COMT inhibitor (the

drug does not cross the blood brain barrier). The sponsor contends that, when administered concomitantly with levodopa and an aromatic amino-acid decarboxylase inhibitor, it leads to more stable plasma levels of levodopa by reducing its metabolism to 3-0-methyldopa (3-OMD). Because 3-OMD has been associated, according to the sponsor, with poor response to levodopa, the decrease in 3-OMD may, in turn, result in an improvement in symptomatic response and may allow for a reduction of the daily dose of levodopa.

COMTAN acts almost immediately after the very first dose, reaching maximum inhibitory effect (corresponding to C_{max}) within 1-2 hours and wearing off in 3-4 hours (see Dr. Al-Habet's biopharm review). This time-frame corresponds to statistically significant efficacy as demonstrated in single- (#26) and 4-week multiple-dose studies (#30), employing ON time, UPDRS subscale 3 motor scores, and finger-tapping tests as outcome measures.

[redacted] T_{max} was delayed with increasing dose (likely due to slower dissolution at higher doses, according to sponsor speculation). Coadministration of levodopa/carbidopa did not significantly change the t_{max} of entacapone, nor did food affect its absorption. Entacapone is described as a high-clearance drug with substantial first-pass metabolism. It is rapidly distributed into tissues with low steady-state volumes of [redacted] L (roughly corresponding to the extracellular volume). It is about 98% bound to plasma proteins (mainly albumin), binding to site on albumin that also binds ibuprofen and diazepam in a competitive manner; the clinical significance is unknown. Clearance rate is high [redacted] elimination half-lives are short, about 0.5 h for the beta-phase and 2.4 h for the gamma-phase. Accumulation is insignificant.

It should be emphasized, as pointed out by Dr. Sayed Al-Habet (Biopharm), that the sponsor's single and multiple (4 weeks) dose biopharm studies show no significant differences in ON time among 50 mg, 100 mg, 200 mg, and 400 mg doses (see the Appendix, p 37). Therefore, it is difficult to argue for the use of any dose higher than 50 mg, especially in light of the safety issues raised by other COMT inhibitors and the increase in dyskinesias triggered by higher doses of the medication (see below).

The drug is extensively metabolized in man, mainly in the liver, with only [redacted] of the dose remaining unchanged (based on urinary excretion). Entacapone is an [E]-isomer, and the main metabolic pathways in man are isomerization to the (Z)-isomer (the only active metabolite) and conjugation (glucuronidation) of both isomers (Z and E). The glucuronide conjugates of the two isomers account for over [redacted] of all substances found in human urine, and during a 48 h collection time, recovery of entacapone accounts for only [redacted] of an oral dose, indicating that it is also excreted in the bile and feces. The entire quantity of entacapone was excreted within 8 h in the urine; the amount of unchanged entacapone accounted for only [redacted] of the dose.

Pharmacokinetics do not differ significantly by age; but no formal gender studies were performed by the sponsor, according to Dr. Al-Habet. Hepatic impairment may increase bioavailability by [redacted] allowing reduction in the oral dose by [redacted] Patients on renal replacement therapy (dialysis) demonstrate a slowed rate of elimination; dosing intervals should therefore be increased. Nonetheless, the sponsor recommends decreasing the frequency of dosing in patients with liver impairment only. However, in view of the short half-life of Comtan and no accumulation, the patient with liver disease would receive benefit for no more than very small part of the day, raising the question of whether he should take the drug at all.

Single entacapone doses ≥400 mg may reduce the absorption of carbidopa, resulting in diminished levodopa availability. However, PD patient studies show that doses up to 200 mg do not significantly affect the PK of carbidopa. Entacapone has no kinetic interaction with selegiline, dopamine agonist, anticholinergics, or amantadine.

Orally administered entacapone dose-dependently and reversibly inhibits COMT activity in erythrocytes by a maximum of [redacted] in healthy volunteers after a single dose of 200 and 800

mg, respectively. The percentage inhibition in PD patients is about 40% after a single 200 mg dose coadministered with LDDCI. For age, there was a 35% increase in C_{max} (after single dose) but no difference in AUC.

According to the sponsor, due to the short elimination half-life, true steady state was difficult to obtain even with frequent dosing. In PD patients after a 7-day treatment (200 mg tid or qid), no changes in PK parameters were found. However, the increase in AUC -- after a 4-week period of repeated dosing (4-6 times/day) -- was statistically significant (16%, $p< 0.01$) when compared with the first dose."The drug accumulated, to some extent, as a result of frequent dosing during the day would be eliminated during the night" (v 1, p 2-258).

There are three types of tablets involved: (1) the tablet used in Phase 1 and early Phase 2 studies (manufactured by), (2) the tablet used in late Phase 2 and Phase 3 studies ( ), and (3) the to-be-marketed formulation, which supposedly has not been used in the pivotal or other Phase 3 trials ( ). All batches were bioequivalent with respect to AUC, but not to C_{max}, because, according to the sponsor, "Entacapone can be considered a moderately variable drug in absorption" (see v 1.75, p 8-031). However, according to Dr. Al-Habet's biopharm review: "Bioequivalence studies were not required in this NDA, because there were no major formulation changes during the clinical program" (draft p 34).

The rationale for the 200-mg entacapone dose, based on efficacy data, rests on the results of one single-dose study. It appears to be derived entirely from Phase 2 study #26 (see v 1, pp 356, 393-397; the number of study patients is incorrectly noted as 24), a randomized, double-blind, placebo-controlled, single-dose (separated by one week) trial comparing entacapone 50, 100, 200, and 400 mg with placebo. 25 (only 22 were evaluable) male and female PD patients with wearing-off symptoms were enrolled (Hoehn & Yahr stages 2-4, mean age 63, mean duration of PD 14.1±4.6 years, mean duration of levodopa therapy 11.2±3.4 years, daily levodopa dose ranged from 400-1450 mg, divided 4-11 times per day). The primary outcome measure was ON-time defined as duration of motor response (namely, the time the total motor score remained 10% below baseline) and based on the UPDRS subscale III (motor) score assessed every 30 minutes after levodopa + drug/placebo administration until baseline or 10%-below baseline scores were achieved (the actual total test time is not given in the study report in v 93). Mean ON times for the five treatments were 160 min (placebo), 180 min (50 mg), 183 min (100 mg), 193 mg (200 mg), and 187 min (400 mg). Mean ON time was highest for the 200-mg dose (20.6%), the only statically significant increase, compared to placebo ($CI_{95\%}$ 0.0832,0.9427). Secondary efficacy parameters were:

(1) the latency of onset of clinical response: 43 min (placebo), 52 min (50 mg), 53 min (100 mg), 55 min (200 mg), and 58 min (400 mg); the latter two doses reached statistical significance (respective $CI_{95\%}$ 0.0009,0.3835 and 0.0511, 0.4243);
(2) magnitude of clinical response (lowest motor score): 31.7 (placebo), 32.5 (50 mg), 31.6 (100 mg), 30.2 (200 mg), and 30.8 (400 mg); no statistical difference;
(3) duration, starting time, and magnitude of dyskinesia (maximum dyskinesia score on the UPDRS is 28), assessed every 30 minutes until return to baseline (amount of total test time not given):
   (a) the duration increased from 142 min (placebo) to 158 min (50 mg) to 161 min (100 mg) to 187 min (200) and 172 min (400 mg); the mean increase was highest with

200 mg (31.7%) and statistically significant ($CI_{95\%}$ 0.2336, 1.1062 hr);

(b) the starting time was "significantly delayed" from 46 min (placebo) to 47 min (50 mg) to 55 min (100 mg) to 52 min (200 mg) and 63 min (400 mg); the increase was statistically significant with the 400 mg dose ($CI_{95\%}$ 0.1200,0.4220 hr);

(c) there was no difference between treatments with respect to the maximal intensity of dyskinesia;

(d) tapping test (number of times in 60 s that the patient could alternately tap two levers 25 cm apart): duration of tapping ranged from 77 min (placebo) to 106 min (50 mg) to 93 min (100 mg) to 139 min (200 mg) and 128 min (400 mg); the tapping was fastest with the 200-mg dose (80.5%) and statistically significant with the 200- and 400-mg doses (respectively, $CI_{95\%}$ 0.1746,1.5073 hrs and 0.1367 and 1.4343 hrs);

(e) walking test (timed walking test: beginning with the patient arising from a chair, walking 6 m and returning to a seated position in the chair again): the duration of faster wlking increased from 79 min (placebo) to 82 min (50 mg) to 80 min (100 mg), to 127 min (200 mg) and 90 min (400 mg); the mean increase in walking speed was highest (60.8%) and statistically significant ($CI_{95\%}$ 0.0730,1.8108) with the 200-mg dose.

A second dose-finding study (#28), a multiple-dose crossover study (2 weeks on each dose) failed to detect any difference in efficacy among placebo and 100-mg, 200-mg, and 400-mg entacapone doses with respect to ON-time as determined from home diaries or from ON time calculated from the tapping and walking tests.

VIII Efficacy findings

A. *General Overview of All Studies*

The sponsor presents evidence from two multicenter, double-blind, placebo-controlled Phase 3 trials (#33, #44) to support of COMTAN's effectiveness. There are three additional long-term studies (#52, #63, #65), described as intended mainly to provide safety information; but only one of them (#52) is discussed in any detail, and only interim (6 months of a planned 1-year study) efficacy results are given. Three single-dose and three multiple-dose placebo-controlled studies, each involving a single center, are also partly discussed in the NDA. For the purposes of this review, I have only briefly touched about the single-dose studies, since Parkinson's Disease is a chronic condition requiring life-long medication. Lengthy studies are therefore needed to determine a medication's effectiveness.

Please see the appendix for Tables 1.1 and 1.2 (p 43) in which the sponsor summarizes results of the two randomized double-blind, placebo-controlled studies (numbers 33 and 44), which are submitted in support of the NDA. Both employed "ON-time" as primary outcome measures. However, as will be discussed below, Study 33 assessed, as its primary outcome measure, the change in the absolute amount of ON time compared to baseline -- that is, the actual number of minutes -- in an 18-hour day, whereas Study 44 assessed the proportion of ON-time -- that is, the percentage -- in a 24-hour day. For the theoretical rationale behind the choice of the 200-mg dose, see the Pharmacokinetics section above.

Both Studies 33 and 44 enrolled only *fluctuating* PD patients. Fluctuating PD patients demonstrate an unstable response to L-dopa medications (Sinemet or Madopar) and experience "wearing off," manifested by the shortening of the duration of action of each L-dopa intake.

Fluctuators may thus require larger amounts of L-Dopa and ever-briefer intervals between doses. The wearing-off phenomenon affects about 50% of PD patients after five years of treatment with L-dopa. In contrast, nonfluctuators, or those usually within the five-year period of starting L-dopa, can be placed on a relatively "stable" regimen.

Phase 3 Study 52 (a year-long double-blind, placebo controlled study which, according to the sponsor, was designed primarily to evaluate safety; only 6-month interim results are available) and 2 of the 3 short-term (4-8 weeks), double-blind, placebo-controlled Phase 2 studies (numbers 16, 28, 30) enrolled both *fluctuators* and *nonfluctuators*. Primary and secondary outcome measures failed to attain statistical significance in all of these clinical trials but one (short-term study #30) because, the sponsor contends, nonfluctuators were included.

Among the multiple-dose Phase 2 studies, there were the three above-mentioned blinded, crossover studies of 4-8 weeks in duration (#16, 8 weeks; #28, 4 weeks; #30, 8 weeks). In addition, there are three open-label studies of 4-8 weeks in duration (#12, 8 weeks; #13, 4 weeks; #14, unknown duration) and two open-label interaction studies (safety) with selegiline (#35, 4 weeks; #48, 6 weeks). ON-time was not an outcome measure in any of these studies.

Note that copies of all evaluation forms (both patient and physician derived) that are mentioned below can be found at the end of this review.

Tables 11-31 (pp 44-52) display the efficacy data (primary and secondary), comparatively side by side, for Studies 33 and 44.

Study 33 (see Appendix, pp 53-62, for data tables)

TRIAL DESIGN: This Phase 3, multicenter (16 centers in Denmark, Finland, Norway, and Sweden), randomized, double-blind, placebo-controlled study was conducted Dec 1993-Feb 1995 to evaluate the safety and efficacy of entacapone as an adjunct to levodopa/DDCI treatment (either Sinemet=levodopa/carbidopa or Madopar=levodopa/benserazide) in PD patients with motor fluctuations.

The study consisted of three parts:

(1) 2-4-week run-in, without study medication, to stabilize levodopa treatment;

(2) 6-month (24-week) double-blind period, with active or placebo treatment; during the first 8 weeks, the daily levodopa dose could be adjusted in the event of insufficient efficacy, hallucinations, or disabling dyskinesias; and

(3) 2-week washout period (to evaluate the effect of withdrawal of study medication).

Essentially, then, each patient was treated with either study drug or placebo for 28 weeks.

Patients presented for a screening visit and six study visits (weeks 0, 2, 4, 8, 16, 24, and 26; the last two were "washout period" visits). Efficacy measures for each visit including ON, OFF, and IN BED times from an 18-hour (0600-2400) home diary, as recorded by the patient over three consecutive days prior to the visit (although patients filled in data for 5 days prior to the next clinic visit, the mean of data from only the last 3 diary days was used in the evaluation of this parameter, as specified in the protocol); UPDRS rating; global evaluation (separate assessments by the investigator and patient); evaluation of daily fluctuations in disability; and records of daily levodopa doses (patient and investigator assessment forms are reproduced in the appendix). Treats discontinued entacapone at visit 6 (week 24) and were then scheduled for a post-study visit at week 26 to check for the effects of withdrawal and make any necessary levodopa dose adjustments. Compliance measures were tablet count and 3-OMD plasma concentrations (baseline and weeks 4, 8, 16, 24, and 26).

Two amendments to the original protocol were implemented:

(a) AMENDMENT ONE, DATED 10/29/93: the definition of ON was changed to "functioning as good as possible whether or not the patient has dyskinesias" (in order to parallel the definitions in earlier

studies); an OFF column was added to patient diaries (to avoid confusion with missing data); global evaluations were amended to indicate that the patient would "evaluate his/her condition in the home diary before coming to the clinic. The investigator transcribes the information from the diary to the global evaluation."

(b) AMENDMENT TWO, DATED 10/25/95: primary variable was more fully defined as "ON time during an 18-hour recording period (from 0600 to 2400, mean of three diary days)"; the UPDRS secondary efficacy variable was more fully defined as the "UPDRS sub scores (Part 1, Part 2, Part 3, and the sum of Parts 1-3) will be summed up and the differences between two parallel groups are evaluated. Complications of therapy (Part 4), Hoehn and Yahr (Part 5) and Schwab and England (Part 6) will be evaluated as categorical variables." The amendment also enacted extensive changes to the original statistical plan, well known to FDA statistical reviewer, Dr. J. Choudhury (see below under "Planned Analyses."

INCLUSION/EXCLUSION CRITERIA: Males and females, over 18 years, with idiopathic PD, except for females of childbearing potential; at Hoehn and Yahr stage 1.5-4.0 (defined when ON); levodopa responsive and on a stable regimen of 4-10 doses/day on any levodopa preparation (patients were on either levodopa/carbidopa or levodopa/benseraside in the study), except the CR (controlled release) formulation; with motor fluctuations and ON time, on average, less than 4 hours after each single levodopa dose; use of amantadine, anticholinergics, selegiline, and/or dopamine agonists acceptable; without marked dementia, other significant neurological disease, major psychiatric disorder (as severe depression), or serious medical illness (as cardiac, pulmonary, GI, hepatic); treatment with anti-dopaminergic drugs (as alpha-methyldopa, reserpine, neuroleptics, antiemetics), MAO-AI or nonselective MAOI, rimiterol, isoprenaline, adrenaline, dopamine, dobutamide, apomorphine or nomifensine within one month prior to the study; females of childbearing age.

NOTE: in contrast to Study 33 which did not allow the use of the CR (controlled-release) formulation, patients could be on either the regular or the CR formulation in Study 44 (US/Canadian trial). Furthermore, patients in Study 33 were on either levodopa/carbidopa or levodopa/benserazide, whereas in Study 44, they were only on levodopa/carbidopa.

POPULATION: 171 patients (n_{treat}=85, $n_{placebo}$=86) were enrolled. Tables R3, R4, R9, and R10 display baseline demographic characteristics for the entacapone and placebo groups. There were statistically significant differences at baseline, in favor of the entacapone cohort, with respect to duration of PD and duration of levodopa treatment. However, the two groups were very similar in terms of disease stage (Hoehn and Yahr), UPDRS, and ratings of neurological condition. "All patients had end-of-dose failure" (v 1.136, p 33), but the occurrence of clinically disabling symptoms appeared to be slightly higher in the entacapone group (see Tables R9 and R10). FDA statistician, Dr. J. Choudhury, reviewed the data by my request to determine whether the statistically significant differences at baseline might have affected the study results, and he found no interaction.

Tables R5 and R6 compare the two groups on the basis of general medical condition, and R7 and R8 in terms of medication use. Cardiac disease, angina, and hypertension appear more prevalent among the entacapone patients, as well as use drugs for the treatment of those disease. "Sex hormones and modulators of the genital system" (eg, estrogen/progesterone replacements) were also more common among the treats. More patients in both groups used benserazide than carbidopa as part of their levodopa/DCCI medication, but carbidopa was more commonly in evidence among the entacapone patients. Use of other anti-PD medications/dopamine agonists was roughly similar for the two groups, though the percentage for some agents may have been very slightly higher for placebo patients.

Finally, according to the sponsor, the majority of patients had 4-6 levodopa intakes per day, which in the clinical trial resulted in 4-6 doses of COMTAN per day (one entacapone dose

with each levodopa intake).

WITHDRAWALS: 170 PD patients entered (85 treats, 86 placebo), and 152 completed, the trial: 8/85 treats and 11/86 placebo dropped out because of adverse events, inefficacy, and "other reasons" (left unspecified), as detailed in Table R1. Withdrawals due to adverse events can be found in Table R28.

PROTOCOL DEVIATIONS: 23/85 treats and 24/86 placebo patients were excluded from the per-protocol analyses of primary efficacy parameters. Premature withdrawals and medication noncompliance (see Appendix III, v 1.139, pp 1-12) were the most common reasons. To be included in the per-protocol analysis, patients had to have not more than 1 h of missing data on 2 of the 3 baseline diary days or 2 h cumulatively over all 3 baseline days; not vary the dosing frequency of levodopa more than 1 dose/day within the 3 diary days at baseline; must be OFF $\geq$0.5 h every day; have at least one eligible morning to determine ON period after the first morning dose; have a stable levodopa regimen prior to baseline and during the study; have evaluable ON time data for visits at 8, 16, and 24 weeks (at least 2 eligible diary days for each visit, with missing entries not exceeding 3 hours/18-h recording day); have evaluable data for at least one eligible morning to determine ON period after the first morning dose for visits at 8, 16, and 24 weeks; maintain 80-120% medication compliance (based on tablet count) within 2 consecutive visits prior to visits at weeks 8, 16, and 24; and must continue the trial up to the week 24 visit.

DOSAGE FORM: Comtan was supplied as 200-mg tablets from batch numbers MTS03-T59-04, MTS03-U01-03, MTS03-U02-03, MTS03-U03-03. Matching placebo from batch numbers SCT08-T01-02, SCT03-01-02, SCT08-U01-07, SCT08-U03-03). Each to be administered concurrently with either Sinemet (levodopa/carbidopa) or Madopar (levodopa/benserazide).

OUTCOME MEASURES:

PRIMARY: Increase in the mean daily ON time during an 18-hour waking day (6 am-12 midnight), as determined from values derived from patient diaries for weeks 8, 16, and 24.

"Entacapone is considered to bring significant clinical benefit if
- *it increases the mean daily 'ON' time by at least 1 hour more than placebo*
- *the mean 'ON' period after the first morning dose of levodopa increases at least by 25% more in entacapone-treated patients than in the placebo group" (v 1.138, p 29).*

SECONDARY: The first four are determined from values derived from visits on weeks 8, 16, and 24:

(1) duration of ON time after the first morning dose
(2) decrease in daily "OFF" time (UPDRS, Part 4, question 39) by one category
(3) improvement in the total and individual (Parts 3 and 4) scores of the UPDRS scale
(4) improvement in the "daily fluctuations in disability" scores
(5) global evaluations prepared independently by the patient and the investigator at the end of week 24, as compared to baseline (first visit); an increase "by one class" on the global evaluation scale is to be considered clinically significant
(6) decrease in mean levodopa total daily dose and the mean number of daily doses

(Patient compliance to be determined by:)

(7) decrease in 3-OMD by at least 30%, compared to baseline (this value is used to measure compliance).

STATISTICAL ANALYSES: Calculation of sample size was based on the assumption that the

duration of ON time in COMTAN-treated patients would be at least 25% longer than the placebo group, as determined from an earlier study (Rinne UK et al, "The Effects of OR-611 on the PK and Motor Responses of Levodopa in Patients with PD: a 4-week phase II study," Orion-Farmos Pharmaceuticals, 1993). Assuming a power of 0.80 and 0.05 one-sided significance level, the sample size was calculated to be 140 (divided equally between treated and placebo groups). In view of an unknown dropout rate, 180 patients were to be enrolled from 15-20 centers in the Denmark, Finland, Norway, and Sweden (ideally 12 patients/center, but not less than 6 patients/center).

Planned (as modified by protocol amendment, 10/25/95) and performed statistical methods were identical:

> The aim of this study was to compare the effects of entacapone and placebo both during the six-month double-blind and during the two -week washout period. The primary evaluation was performed with ITT analysis, using the response from weeks 8, 16, and 24 during the stable treatment period. Per protocol analyses were performed additionally.
>
> Analysis of covariance (ANCOVA) for repeated measures was used for continuous variables, with the baseline measurement as covariate. Center was used as a random factor, to generate a global estimate for the treatment effect. Mean differences between treatments were estimated with 95% confidence intervals. For categorical variables, in order to compare proportions of patients, Cochran-Mantel-Haenszel test was used.
>
> A two-way significance level of 5% was considered to be statistically significant [v 136, p x].

The second amendment, dated 10/25/95, eight months after the clinical trial had ended, implemented several noteworthy changes to the original statistical plan. In the initial protocol, the primary outcome measure was change from baseline after 6 months; whereas in the revision, baseline was used as a covariate in the ANCOVA analysis. Second, the protocol originally planned to employ chi-square as the statistical method for analyzing categorical variables; this was later changed to Cochran-Mantel-Haenszel.

In a fax to Dr. J. Choudhury (16 October 1998), the sponsor gave Study 33's unblinding date as 8 December 1995, or about six weeks after the new statistical plan was provided. Reasons for designing a new statistical plan at such a late date, as well as for the delay in its implementation, are as follows (from the 16 October 1998 fax, appended to this review):

> In the meeting at the FDA on August 11, 1995, the statistical analysis plans included in the study protocols of phase III studies 33 and 44 were considered insufficient. More detailed statistical analysis plans were requested, and they were prepared prior to breaking the treatment code for each of the studies. The plans were harmonized with each other, resulting in considerably similar methods of analysis and reporting of the studies. The plans were submitted to the FDA on October 3, 1995.

It should be noted that, with respect to the primary outcome measure, the sponsor has analyzed the data by both methods -- improvement in ON time compared to baseline as well as by ANCOVA (with baseline as covariate) -- and, according to FDA statistician Dr. Choudhury, the results appear statistically significant and robust either way.

The assessments of the first study visit (week 0) were taken as baseline. The change in "ON" time was calculated on the basis of values of the three visits (weeks 8, 16, and 24), during a period of stable levodopa treatments. A home diary recording was employed for evaluation (v 125, p 46). The second protocol amendment further clarified mean ON time and mean duration of benefit (ON period after the first morning levodopa dose) on the basis of an 18-hour waking-day diary. Mean ON time was defined as the mean of ON times for three diary days (the mean could be calculated over two home diary days, if one of the days were not evaluable).

Reasons for premature withdrawal included "failure to stick to the protocol, severe adverse event, or patient's own request to withdraw" (v 1.138, p 49). It should be noted, however, that the sponsor did not designate a statistical method for handling dropouts. The revision enacted by the second amendment proposed an ITT analysis as the primary method, based on data from visits

4, 5, and 6 (the last three visits). It also made provision for dropouts -- ITT LOCF, with the exception that the baseline values would be carried forward for patients who withdrew before visit 4 (in the sponsor's parlance, an ITT-LOCF[BL] analysis: such an analysis would ensure that "all measurements in the efficacy analyses are taken only from the stable levodopa treatment period" [v 1.138, pp 164-5).

The per-protocol patient set was finalized prior to breaking the blind. The results of both ITT and per-protocol analyses were similar, demonstrating the study to be highly significant by both statistical methods. The per-protocol analysis included only patients who were a stable levodopa dose 2-4 weeks prior to visit 1 (baseline), compliance based on tablet count, a valid home diary (with no less than 3 hours of missing data daily for at least 2 of the 3 home rating days), and no major protocol violations. Finally, the sponsor also planned traditional LOCF and observed-cases analyses, but these results were presented only in Appendix V of the statistical report.

Finally, note that Dr. Choudhury has questioned the use of ITT analysis for repeated measures. ITT analysis is more appropriate for time points, whereas the ITT-OC analysis is the traditional method accepted for repeated measures. Dr. Choudhury has therefore re-analyzed the results by the ITT-OC method and nonetheless found them, similarly, to be statistically significant (see his review).

Secondary variables, as mean ON, OFF, and ASLEEP times; the scheduled total daily levodopa dose and number of doses; the four subscores for UPDRS Parts 1, 2, and 3, as well as their total sum, were analyzed by ANCOVA (as above). Those defined by categorical variable -- global evaluations (change from baseline to week 26, or visit 6, by at least one category), the proportion of waking time spent OFF (question 39 of UPDRS Part 4, as measured on a categorical ordinal scale; changes of one category from baseline to week 24 were considered significant); number of patients with decreased severity of fluctuations -- were analyzed by the Cochran-Mantel-Haenszel test.

The washout period incorporated visits 6-7 (weeks 24-26). Patients presumably completed diaries as before. The results of the last visit *on study medication* (week 24) were compared with results from the post-study visit at week 26 (off medication for two weeks) by means of an ITT observed-cases analysis.

COMPLIANCE: According to the sponsor, tablet counts demonstrated that almost 100% of the entacapone tablets were used during the entire study. However, there was intersubject variability: 9 treats and 12 placebo patients were excluded from the per-protocol analysis for noncompliance (see Table 3.4).

RESULTS:

PRIMARY OUTCOME VARIABLE:

By ITT analysis, mean (±SD) daily ON time -- the primary outcome measure determined from home diary recordings for weeks 8, 16, and 24 -- increased from the baseline 9.3±2.2 to 10.7±2.2 hours among entacapone patients and from 9.2±2.5 to 9.2±2.6 hours in the placebo group. This treatment difference of 1.3 hours was statistically significant in favor of entacapone ($p<0.001$; $CI_{95\%}$ 0.8,1.9). According to the sponsor, results were the same when the analysis used duration of PD and duration of levodopa treatment as covariate; FDA statistician, Dr. J. Choudhury, has looked at the results and found no issues of concern. The per-protocol analysis was also statistically significant ($p<0.01$; $CI_{95\%}$ 0.4,2.1) and demonstrated a treatment difference of 1.2 hours in favor of entacapone (ON time increased from 9.1±2.1 to 10.6±2.2 hours in the entacapone group vs 8.9±2.2 to 9.4±2.1 hours in the placebo group).

The home diary recordings were also analyzed from the standpoint of *proportion of daily ON time* (based on an 18-hour daily diary). Though not a protocol-specified primary endpoint for study 33, proportion of daily ON time was the primary outcome measure in study 44, where it was based on a 24-hour daily diary; and, statistically significant results notwithstanding, the two

studies are therefore not really comparable. (This difference between the two studies was clarified in a phone conversation with Ilkka Larma on 9/15/98; the sponsor has, however, not as yet explained whether the same mathematical formula was used in both calculations). According to an ITT analysis, there was an increase from the baseline 62.7% to 72.0% in the entacapone group vs 63.8% to 64.4% in the placebo, yielding a statistically significant treatment difference of 8.3% in favor of entacapone ($p<0.001$; $CI_{95\%}$ 4.5,12.1). Similarly, the per-protocol analysis was statistically significant, demonstrating an increase from 60.6% to 70.9% among entacapone patients vs 61.4% to 64.1% among placebo -- a treatment difference of 7.7% in favor of entacapone ($p<0.01$, $CI_{95\%}$ 2.5,13.0).

Mean ON time after the *first morning dose*, also considered by the sponsor as a primary efficacy variable) and assessed by patient diary, demonstrated an increase -- in the ITT analysis -- from 2.1±0.7 to 2.3±0.7 hours among entacapone patients vs 2.2±0.9 to 2.1±0.9 hours among placebo, yielding a statistically significant treatment difference of 0.24 hours in favor of entacapone ($p<0.05$; $CI_{95\%}$ 0.06,0.43). According to the sponsor, the morning levodopa dose were maintained at constant levels throughout the entire study for 66% of entacapone-treated and 71% of placebo patients, but overall was slightly lowered in the former group while remaining unchanged in the latter. However, statistical results were similar whether the analysis was done with morning levodopa dose, duration of PD, and duration of levodopa treatment as covariate. In the per-protocol analysis, there was an increase from 2.1±0.7 to 2.4±0.8 hours among entacapone patients vs 2.2±0.8 to 2.2±0.9 hours, yielding a treatment difference of 0.3 hours in favor of entacapone ($p<0.05$; $CI_{95\%}$ 0.03,0.53).

The *average duration of benefit* (determined from patient diary information) from a single levodopa dose -- not a protocol-specified endpoint -- was also studied: there was an increase for the ITT population from 2.4+0.7 to 2.8+0.8 hours among entacapone patients vs 2.3+0.8 to 2.2+0.8 hours in the placebo group, which yielded a statistically significant treatment difference of 0.5 hours in favor of entacapone ($p<0.001$). The treatment difference for the per-protocol population was 0.4 hours, also statistically significant in favor of entcapone ($p<0.01$).

Individual center results were provided in the statistical volumes. According to Dr. Choudhury, there was consistency overall; in only two centers did placebo do marginally better than entacapone (see his review, p 13).

Finally, note that the trial achieved clinical -- as well as statistical -- significance by the sponsor's definition:

> "Entacapone is considered to bring significant clinical benefit if
> - it increases the mean daily 'ON' time by at least 1 hour more than placebo
> - the mean 'ON' period after the first morning dose of levodopa increases at least by 25% more in entacapone-treated patients than in the placebo group" (v 1.138, p 29).

For mean ON time, the treatment difference was, in fact, 1.3 hours in favor of entacapone. Furthermore, mean ON time after the first morning dose demonstrated an *increase* of 0.2 hour in the entacapone group and a *decrease* in the placebo group, substantiating the second condition.

SECONDARY OUTCOME VARIABLES:

(a) *Daily OFF time:* In the ITT analysis, OFF time -- as assessed from home diaries over weeks 8, 16, and 24 -- decreased from the baseline 5.5±2.2 to 4.3±2.2 hours in the entacapone group and 5.3±2.4 to 5.2±2.5 hours in the placebo, for a statistically significant treatment difference of 1.2 hours in favor of entacapone ($p<0.001$; $CI_{95\%}$ -1.8,-0.7). The results were similar in the per-protocol analysis: a decrease from 5.8±1.8 to 4.4±2.1 hours in the entacapone group vs 5.6±2.1 to 5.3±2.0 hours in the placebo, yielding a statistically significant treatment difference of 1.1 hours in favor of entacapone ($p<0.01$; $CI_{95\%}$ -1.9, -0.4).

IN BED time, assessed over the 18 hours of the home diary, showed no changes for either the entacapone or placebo patients.

(b) *UPDRS:* Scores were assessed when the patients were ON before noon ("best" ON time). Mean time between intake of the latest levodopa dose and UPDRS scoring when the patient varied between 1.5 and 1.8 hours, with maximal ON time about 5 hours; no differences were appreciated between treats and placebo patients in the time intervals between intake of the latest levodopa dose and the UPDRS assessment.

For **Part 1** (mentation, behavior, and mood), no treatment difference was noted for the ITT population: mean baseline and end-of-study scores generally remained unchanged for treats (1.8±1.4 and 1.8±1.4) and showed a small increase for placebo patients (2.0±1.5 and 2.2±1.7), yielding a difference of 0.25 (p=0.11; $CI_{95\%}$ -0.6,0.06). The per-protocol analysis found a difference of 0.2 between treatments, also not statistically significant (p=0.23; $CI_{95\%}$ -0.06,0.14).

Scores for **Part 2** (ADL) demonstrated statistically significant treatment differences in favor of entacapone for both ITT and per-protocol populations. In the ITT analysis, scores for the entacapone group declined from the baseline 11.2±5.0 to 9.5±5.4 vs 11.2±5.0 to 10.6±4.8, yielding a difference of 1.4 (P<0.01; CI95% -2.2,-0.6). The difference was also statistically significant for the per-protocol population (p<0.05; $CI_{95\%}$ -3.6,-0.14).

Part 3 (motor examination) scores demonstrated a statistically significant treatment difference in favor of entacapone for the ITT population: scores in the entacapone group dropped from the baseline 25.5±13.1 to 22.0±13.7 vs 24.6±12.3 to 22.8±12.3, yielding a difference of 1.9 (p<0.05; CI95% -3.6,-0.14). In the per-protocol analysis, the treatment difference did not attain statistically significance (p=0.12; $CI_{95\%}$ -3.6,0.4).

Total UPDRS score (sum of Parts 1, 2, and 3) realized a statistically significant treatment difference in favor of entacapone for the both ITT and per-protocol populations. In the ITT analysis, the mean baseline score decreased among entacapone patients from the baseline 38.5±16.8 to 34.1±17.7 vs 37.4±15.8 to 36.3±16.6 among the placebo, producing a between-group difference of 3.6 (p<0.01; $CI_{95\%}$ -6.0,-1.13). In the per-protocol analysis, the mean baseline score of 39.5±16.7 in the entacapone group declined to 34.6±17.9 vs 38.2±16.5 to 36.6±17.3 in the placebo group, yielding a between-group difference of 3.3 (p<0.05; $CI_{95\%}$ -6.2,-0.4).

(c) *Global evaluation:* There were no statistically significant differences between groups in patient-assessed global evaluations in either the ITT or the per-protocol analyses. The investigator's evaluations demonstrated improvement in the ITT and corresponding per-protocol analyses (see Table R20).

(d) *Daily fluctuations in disability:* All entacapone, and all but 3 placebo, patients noted daily wearing-off symptoms at baseline, but by the end of the study 9 entacapone, and only 1 placebo, patient reported no further wearing-off episodes. Moreover, the daily wearing-off was less severe among entacapone patients, compared with placebo (P<0.001), at each the last study visits (weeks 8,16, and 24); see Table R18. The occurrence of OFF period freezing was about 30% in both groups, and each group saw a slight tendency in its reduction over the course of the study. Random freezing was reported in about 20% of the patients in both groups at baseline; its frequency and severity tended to decrease slightly among entacapone -- while remaining unchanged among placebo -- patients. There were no real changes in either group in early morning akinesia, peak-dose dyskinesias, early morning dystonia, off-period dystonia, or on-period dystonia.

(e) *Levodopa doses on home diary days:* The mean daily levodopa doses over weeks 8, 16, and 24 (based on **patient diaries**) *decreased* from 701±293 (baseline) to 614±250 mg in the entacapone group, and *increased* from 705±283 to 720±302 mg in the placebo. The difference between the two treatment groups was statistically significant both by ITT (102 mg difference; p<0.001; $CI_{95\%}$ -137,-67) and per-protocol (81 mg; p<0.0001; $CI_{95\%}$ -117,-44) analyses. Mean daily dosing frequency, in the ITT analysis, similarly saw a *decrease* from 6.2±1.8 at baseline to 5.8±1.6 at week 24 in the entacapone group vs an *increase* from 6.1±1.7 to 6.3±1.8 in the placebo group, yielding a statistically significant difference of 0.6 in favor of entacapone (p<0.001;

$CI_{95\%}$ -0.8,-0.3). The per-protocol analysis, also statistically significant, saw a between-group difference of 0.4 in favor of entacapone ($p<0.01$; $CI_{95\%}$ -0.6,-0.1).

The mean daily levodopa doses over weeks 8, 16, and 24 (based on information recorded by **investigators at study visits**) *decreased* from 699±294 (baseline) to 620±252 mg in the entacapone group, and *increased* from 723±306 to 735±330 mg in the placebo. The difference between the two treatment groups was statistically significant both by ITT (92 mg difference; $p<0.001$; $CI_{95\%}$ -128,-56) and per-protocol (69 mg; $p<0.01$; $CI_{95\%}$ -107,-31) analyses. Mean daily dosing frequency, in the ITT analysis, similarly saw a *decrease* from 6.1±1.7 at baseline to 5.8±1.6 at week 24 in the entacapone group vs an *increase* from 6.3±1.7 to 6.3±1.8 in the placebo group, yielding a statistically significant difference in favor of entacapone ($p<0.01$; $CI_{95\%}$ -0.6,-0.2). The per-protocol analysis, also statistically significant, saw a between-group difference in favor of entacapone ($p<0.05$; $CI_{95\%}$ -0.4,-0.02).

Other nonprotocol efficacy measures considered included the UPDRS Part 4 (complications of therapy), comparing the categorical variables (listed in bold type) at week 24 (time of maximum exposure) to baseline. With respect to **dyskinesias**, Tables R12-R14 show a slight trend toward increased duration of dyskinesias among entacapone patients (no difference between baseline and week 24 percentages), but no recognizable trends for either group in the occurrence of disabling dyskinesias or in painful dyskinesias. Both groups demonstrated a declining prevalence (trend) of **early morning dystonia**, and fewer patients in both groups (8/85 entacapone, 3/86 placebo) noting **predictable OFF periods** at baseline reported them at the week 24 visit. There appeared to be no real change from baseline in the percentage of patients reporting **unpredictable OFF periods** (36% entacapone vs 45% placebo); the percentage of patients reporting **sudden OFF periods**, however, appeared to decline slightly in both groups. There was a statistically significant reduction ($p<0.001$) in the **proportion of OFF time** in favor of entacapone-treated patients at the end of week 24 (the change was stable for weeks 8, 16, and 24). **Anorexia, nausea, vomiting** increased in treats (reported in 5 patients at baseline, and 13 and 14 at weeks 4 and 8, then 7 at week 24), but remained unchanged in the placebo groups. Finally, there were no changes in the proportion of patients complaining about **sleep disturbance**, but a slight trend in increased reporting of **symptomatic orthostasis** among entacapone patients, most marked at weeks 4 and 8 (there was no change in the placebo group).

Finally, there were no changes in baseline Hoehn & Yahr staging scores (UPDRS Part 5) in either patient group, but there was a slight improvement in Schwab & England scores (UPDRS Part 6) -- higher percent indicates better function -- among entacapone, not placebo, patients.

WITHDRAWAL EFFECT: Study drug was withdrawn at the last visit at week 24, and levodopa medication was to be "kept constant during the post-study period as far as possible." A post-study visit was scheduled for week 26 (two weeks after study drug discontinuation), at which all exams conducted at the first visit were repeated, any necessary levodopa dose adjustments were to be made, and both placebo and entacapone patients completing the trial were also given the opportunity to enter an open-label, uncontrolled long-term extension (see v 1.136, p 45). Exam results from visits 24 and 26 were compared by an observed-cases analysis (see v 1.136, pp 198-209).

Mean ON time decreased from 10.7±2.4 to 9.1±2.7 hours among entacapone patients, yielding a statistically significant difference in the entacapone group for the ITT ($p<0.001$; $CI_{95\%}$ -2.13,-1.10) and per-protocol ($p<0.001$; $CI_{95\%}$ -2.25,-1.09) analyses; no change, on the other hand, was appreciated in the placebo group (corresponding values: 9.4±2.8 to 9.3±2.9; ITT analysis, p=0.50, per-protocol analysis, p=0.42). **The proportion of ON time** declined from 72±16.3% to 61.6±17.6%, also statistically significant in both the ITT ($p<0.001$; $CI_{95\%}$ -13.9, -7.0) and per-protocol ($p<0.001$; $CI_{95\%}$ -13.9,-6.6) analyses; no differences were appreciated in the placebo group (ITT analysis, p=0.22; per-protocol analysis, p=0.16). **OFF time** increased

from 4.2±2.5 to 5.6±2.6 hours, a statistically significant difference in both ITT ($p<0.001$) and per-protocol ($p<0.001$) analyses; no real change was noted in the placebo group (ITT analysis, $p=0.19$; per-protocol analysis, $p=0.13$). **IN BED time** did not change for either the treats or placebo patients, about 3 hours for each on an 18-hour diary. **ON time after the first levodopa morning dose** declined from 2.3±0.9 to 2.0±0.8 hours, yielding a statistically significant result in the ITT ($p<0.001$; $CI_{95\%}$ -0.45, -0.16) and per-protocol ($p<0.001$; $CI_{95\%}$ -0.40,-0.12) analyses; corresponding times for the placebo group, from 2.1±0.9 to 2.0±0.9 hours, were not significant (ITT analysis, $p=0.10$; per-protocol analysis, $p=0.08$). **Average duration of benefit from a single levodopa dose** decreased from 2.8+0.8 to 2.3+0.8 hours, a statistically significant difference in both the ITT ($p<0.001$) and per-protocol ($p<0.001$) analyses; no change was noted in the placebo group (ITT analysis, $p<0.25$; per-protocol analysis, $p<0.15$).

UPDRS scores showed no change for Part 1 (mentation), but statistically significant increases for Part 2, or ADL (2 points: ITT, $p<0.001$; per-protocol, $p<0.001$); Part 3, or motor exam (3 points: ITT, $p<0.001$; per-protocol, $p<0.001$); and the sum of Parts 1, 2, and 3 (5 points: ITT, $p<0.001$; per-protocol, $p<0.001$). There were no changes in the scores of the placebo group. With respect to proportion of OFF time (Part 4, question 39), there was a large increase (see Table R23), but no changes were noted in the placebo group. There were also no appreciable changes in Part 5 (Hoehn & Yahr staging). However, patients' conditions generally worsened when assessed by Part 6, the Schwab & England scale: at week 24, 39 entacapone patients were in the 90-100% category, compared to 32 in the placebo group. At week 26, the respective numbers were 27 vs 25.

No changes were recognized in either treats or placebo patients in the occurrence, frequency, or severity of wearing-off, nocturnal akinesia, early morning akinesia, OFF-period freezing, peak-dose dyskinesias, early-morning dystonia, OFF- and ON-period dystonia, and unpredictable rapid fluctuations.

Patient- and investigator-assessed global evaluations registered worsening of condition after study drug discontinuation: 63.2% of entacapone and 23.7% of placebo patients reported a decline in their condition, and investigators reported 68.4% of entacapone and 23.7% of placebo patients worsening. The differences between entacapone and placebo groups were statistically significant ($p<0.001$) in ITT and per-protocol analyses of both patient and investigator global evaluations.

Mean daily levodopa dose from home diaries increased from 612±228 (week 24) to 665±256 mg (week 26) in the entacapone group (statistically significant in both ITT and per-protocol analyses; $p<0.001$) , and from 738±326 to 745±321 in the placebo group (not statistically significant). Levodopa dosing frequency also showed a statistically significant increase for the entacapone group: with respect to the ITT analysis, from 5.7±1.5 to 6.0±1.7 doses/day ($p<0.001$; $CI_{95\%}$ 0.13,0.40) and, for the per-protocol analysis, from 5.6±1.5 to 5.8±1.7 doses/day ($p<0.01$). No difference was appreciated in the placebo group. Levodopa dose and dosing frequency, as recorded at study visits, also demonstrated parallel statistically significant results in both ITT and per-protocol analyses.

PHARMACOKINETIC DATA: Entacapone decreased plasma 3-OMD levels by about 55% (a change consistent over time, according to the sponsor), whereas levels in placebo patients [redacted] resulting in a highly significant treatment difference ($p<0.001$). After medication withdrawal, 3-OMD values increased, in entacapone patients, from 3.1±2.3 ug/ml at visit 24 to 7.9±5.3 ug/ml, a statistically significant difference ($p<0.001$; $CI_{95\%}$ 3.82,5.72). Levels were unchanged in the placebo group (10.2±7.7 ug/ml at visit 24 and 10.4±8.2 ug/ml at visit 26).

SUBGROUP ANALYSES: There were no statistically significant response differences for gender or

age (<65 vs ≥65). There were no nonwhites in the study. No conclusions can therefore be reached about the effect of COMTAN on groups other than Caucasian.

Study 44 (see the Appendix, pp 63-72 for data tables)

TRIAL DESIGN: This Phase 3, multicenter (17 centers in the US and 1 in Canada; 18 investigators), randomized, double-blind, placebo-controlled study was conducted 6/2/94-5/29/95 "to evaluate efficacy and safety of a 200-mg dose of entacapone, when compared with placebo, as an adjunct to levodopa/carbidopa treatment of PD with motor fluctuations" (v 125, p 29).

The study consisted of three parts:

(1) 4-week run-in, without study medication, to stabilize levodopa treatment;

(2) 6-month double-blind period, with active or placebo treatment; during the first 8 weeks, the daily leviodopa dose could be adjusted in the event of insufficient efficacy, hallucinations, or disabling dyskinesias; and

(3) 4-week staggered washout period (to evaluate the effect of withdrawal of study medication). Entacapone patients were randomly and in double-blind fashion withdrawn from active medication and transferred to placebo either after week 24 or after week 26.

Essentially, then, each patient was treated with either study drug or placebo for 28 weeks or the 28- to 30-week study duration (the staggered withdrawal accounted for the 2-week difference).

Patients presented for a screening visit and 8 study visits (weeks 0, 2, 4, 8, 16, 24, 26, and 28; the last two were "washout period" visits). At each visit, data for efficacy variables would be collected and include ON, OFF, and ASLEEP times from a 24-hour home diary (recorded by the patient over three consecutive days prior to the visit); UPDRS rating, global evaluation, evaluation of daily fluctuations in disability; and records of daily levodopa doses (patient and investigator assessment forms are reproduced in the appendix). Compliance measures were tablet count and 3-OMD plasma concentrations (baseline and weeks 4, 8, 16, 24, 26, and 28). A blindness control was completed at visit 6 (or at discontinuation).

Four amendments to the original protocol were implemented:

(a) AMENDMENT ONE, DATED 3/18/94: the lower age limit was increased from 18 to 30; the proposed quality of life data would not be collected ("no suitable validated scale available for PD patients"); the home diary would be considered analyzable if not more than 4 hours/day of data were missing and data completed for all 3 consecutive days prior to the study visit; the run-in period was changed to 2-4 weeks, and patients had to be on a stable regimen of levodopa for 4 weeks prior to enrollment; females of childbearing potential could be included if not nursing and used adequate methods of contraception (pregnancy testing would be done at each visit); additional exclusion criteria were treatment with clozapine, domperidone, or ondansetrone within 1 month of study initiation; and carbidopa preparations were allowed in the event of excess dopaminergic adverse events (eg, vomiting).

(b) AMENDMENT TWO, DATED 6/24/94: the upper age limit was set at 90 in Canada.

(c) AMENDMENT THREE, DATED 7/1/94: fluctuators were defined as having "clear motor ON-OFF fluctuations, along with experiencing daily OFF time that amounted to at least 3 hours during each of the three 24-hour home diary days at baseline" (to avoid enrolling non-fluctuators); patients treated with standard levodopa only prior to the run-in period must have a run-in period of at least 2 weeks without any changes in regimen, but those on CR preparations must have a run-in period of at least 4 weeks, off CR and without any changes in regimen for at least 2 weeks before randomization; if the patient take booster doses of levodopa on all three days of the baseline diary assessment, the baseline diary must be repeated; the maximum daily dose of entacapone was set at 2,000 mg, administered 10 times/day; the primary efficacy measure was restated as,

Entacapone is considered to be of clinical [sic] significant benefit, if it increases the mean "ON" time by about 10% of daily awake time more than placebo. The estimated mean awake time per day is 15 hours. 10% increased in mean awake time is approximately equivalent to 1.5 hours. Eg, in a placebo-treated patients [sic], the mean "ON' time is 6 h, thus the proportion of daily "ON" time is 6h/15h=0.4 (the patients are "ON" 40% of the awake day). 10% increase in the "ON" time of awake hours is 1.5 h. Thus, to be considered to have clinically significant benefit for the patients, entacapone should increase the mean "ON" time to 7.5 hours per day. This means that the proportion will be 7.5h/15h=0.5 (which means that the ON time is 50% of the awake day) [v 125, pp 189-90].

(d) AMENDMENT 4, DATED 8/11/94 (IMPLEMENTED FOR THE CANADIAN STUDY): visits 4 and 5 were to have the same evaluations as visit 3; for visits 7 and 8, the patient was requested to return to the clinic every two weeks and complete a home diary for the 2 days immediately after the visit; patients with pheochromocytoma were excluded.

INCLUSION/EXCLUSION CRITERIA: Males and females, over 18 years, with idiopathic PD, except for females of childbearing potential; at Hoehn and Yahr stage 1.5-4.0 (defined when OFF); levodopa responsive (based on patient records) and on a stable regimen of 4-10 doses/day on any levodopa preparation; with motor fluctuations; use of amantadine, anticholinergics, selegiline, and dopamine agonists acceptable; without marked dementia, other significant neurological disease, major psychiatric disorder (as severe depression), or serious medical illness (as cardiac, pulmonary, GI, hepatic); treatment with anti-dopaminergic drugs (as alpha-methyldopa, reserpine, neuroleptics, antiemetics), MAO-AI or nonselective MAOI, rimiterol, isoprenaline, adrenaline, dopamine, dobutamide, apomorphine or nomifensine within one month prior to the study.

NOTE: in contrast to Study 44 (US/Canadian study) which did not allow the use of the CR (controlled-release) formulation, patients were on either formulation in Study 33. Furthermore, in Study 44, patients were only on levodopa/carbidopa, as opposed to Study 33, in which patients were on either levodopa/carbidopa or levodopa/benserazide.

POPULATION: 205 patients (133 males, 72 females), divided into 103 treats and 102 placebo. The mean age was 64±8 years (mean±SD). Mean duration of PD for the treats was 10.7±4.9 years and 11.3±6.4 for the placebo; disease severity for the 205 patients, by Hoehn and Yahr stages, showed 1 (n=2), 1.5 (n=4), 2)n=96), 2.5 (n=41), 3 (n=52), and 4 (n=10), and patients were distributed comparably in both treatment groups. Wearing-off had continued for 4.2±3 years for the treats and 4.5±4.3 years for the placebo. Duration of levodopa treatment was about 9 years for both groups: total daily levodopa dose was 791±375 mg for the treats, 752±435 for placebo, and the mean number of daily doses at baseline was 6.1 for the treats, 6.0 for placebo. 54% of the treats and 40% of the placebo patients had been treated with CR levodopa prior to the study. According to the sponsor, the majority of patients had 4-6 levodopa intakes per day, which in the clinical trial resulted in 4-6 doses of COMTAN per day with each levodopa intake.

There was a statistically significant difference between treats (54%) and placebo (40%) with respect to percentages of patients who had prior use of long-acting levodopa/carbidopa (p=0.0421). However, this difference does not appear to be clinically significant for the trial, in view of the similarity between the two groups for disease severity, duration of disease, duration of wearing-off phenomenon, and mean number of daily levodopa doses at baseline and total daily levodopa dose.

WITHDRAWALS: 13 patients discontinued prematurely, 13 treats and 11 placebo. See tables R1 and R14 for reasons.

PROTOCOL DEVIATIONS: There were four types of protocol deviations, as described in table R2. It should be noted that the both ITT and per-protocol analyses led to similar conclusions.

DOSAGE FORM: Entacapone 200-mg tablets; batches MTS03-T68-02 and MTS03-U01-03. Placebo 200-mg tablet; batch SCT08-U01-07.

OUTCOME MEASURES:

PRIMARY: Increase in the proportion of daily ON time over a 24-hour day.

"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" (v 125, p 46). NOTE: This statement was changed, in protocol amendment three (dated 7/1/94) to read: "Entacapone is considered to be of clinical [sic] significant benefit, if it increases the mean 'ON' time by about 10% of daily awake time more than placebo. The estimated mean awake time per day is 15 hours. 10% increased in mean awake time is approximately equivalent to 1.5 hours" (see above).

SECONDARY: The first three are to be determined from values derived from visits on weeks 8, 16, and 24:

(1) decrease in daily "OFF" time (UPDRS, Part 4, question 39) by one category
(2) improvement in the total and individual (Parts 3 and 4) scores of the UPDRS scale
(3) improvement in the "daily fluctuations in disability" scores
(4) global evaluations, prepared independently by patients and investigators, at the end of week 24 and during the washout period (visits 26 and 28), as compared to baseline (first visit) -- omitted by amendment dated 3/18/94 (see above)
(5) decrease in mean levodopa total daily dose and the mean number of daily doses

Mentioned in the protocol but not included in the study report:

(6) decrease in 3-OMD by at least 30%, compared to baseline (this value is used to measure compliance)
(7) extra of booster doses of levodopa needed during the 4-week double-blind staggered washout period.

STATISTICAL ANALYSES: Calculation of sample size was based on the assumption that the mean proportion of ON time while awake in COMTAN-treated patients would be at least 10% (about 1.5 hours) longer than the placebo group and determined from an earlier study (Nutt J et al, "Effects of an Inhibitor of Catechol-O-methyltransferase on the PKL and PD of Levodopa," *Neurology* 43 suppl [1993]:A332). Assuming a power of 0.95 and 0.05 two-sided significance level, the sample size was calculated to be 140 (divided equally between treated and placebo groups). In view of an unknown dropout rate, 200 patients were to be enrolled from 16-20 centers in the US and Canada (12 patients/center).

Planned (as modified by protocol amendment, 10/25/95) and performed statistical methods were identical:

> The primary evaluation was performed with ITT analysis, using the response from weeks 8, 16, and 24. In addition, per protocol analyses were performed.
>
> Continuous variables were analyzed with the analysis of covariance (ANCOVA) for repeated measures, by using the baseline as a covariate. Center was used as a random factor to generate a global estimate for the treatment effect. Mean differences between treatments were estimated with 95% confidence intervals.
>
> In order to compare proportions of patients, Cochran-Mantel-Haenszel test was to be used for categorical variables.

A two-way significance level of 5% was considered statistically significant [v 122, p ix].

As with Study 33, similar changes were made to the statistical plan of Study 44 as originally presented in the initial protocol. In the initial protocol, the primary outcome measure was change from baseline after 6 months; whereas in the planned analysis, according to the final study report, an ANCOVA analysis was to be performed, employing baseline as covariate. In addition, the protocol originally planned to employ chi-square as the statistical method for analyzing categorical variables; this was later changed to Cochran-Mantel-Haenszel. No information about any change in statistical design was provided in the NDA. Only when Dr. Choudhury confronted with sponsor was documentation offered. The new detailed statistical plan (faxed to Dr. Choudhury on 16 October 1998) is dated 29 September 1995, *four months after* the clinical trial was completed. The unblinding date for Study 44 was 6 October 1995, *seven days later.* In its 16 October 1998 fax, the sponsor offers the following explanation for the changes in the statistical plan and the later date in which they were implemented:

> In the meeting at the FDA on August 11, 1995, the statistical analysis plans included in the study protocols of phase III studies 33 and 44 were considered insufficient. More detailed statistical analysis plans were requested, and they were prepared prior to breaking the treatment code for each of the studies. The plans were harmonized with each other, resulting in considerably similar methods of analysis and reporting of the studies. The plans were submitted to the FDA on October 3, 1995.

With respect to the primary outcome measure, the sponsor has analyzed the data by both methods -- proportion of ON time compared to baseline as well as by ANCOVA (with baseline as covariate) -- and, according to Dr. Choudhury, the results appear statistically significant either way.

The assessments of the first study visit (week 0) were taken as baseline. The change in proportion of "ON" time, based on a 24-hour day, was calculated from the values of the three visits at weeks 8, 16, and 24, during a period of stable levodopa treatments. A home diary recording was employed for evaluation. With respect to the ITT population, baseline values were carried forward for all dropouts before visit 4, but for all dropouts after visit 4, LOCF obtained; the results are presented below derive from this method. However, the sponsor also analyzed the data by the traditional LOCF method and found similar results.

The proportion of ON time was defined as the sum of ON times over 3 days divided by awake time (or "3*24 hours minus the sum of ASLEEP times over three days) and analyzed by ANCOVA. If any of the home-diary days were not evaluable (missing data), calculations were made over data from the remaining two days.

Finally, note -- as also for study 33 discussed above -- that Dr. Choudhury has considered the use of ITT analysis for repeated measures. ITT analysis is more appropriate for time points, whereas the ITT-OC analysis is the traditional method accepted for repeated measures. Dr. Choudhury has therefore re-analyzed the results by the ITT-OC method and nonetheless found them, similarly, to be statistically significant (see his review).

Secondary variables that were defined as continuous variables -- such as mean ON, OFF, and ASLEEP times; the scheduled total daily levodopa dose and number of doses; the four subscores for UPDRS Parts 1, 2, and 3, as well as their total sum -- were analyzed by ANCOVA. Those defined as categorical variables – global evaluations (change from baseline to week 26, or visit 6, by at least one category), the proportion of waking time spent OFF (question 39 of UPDRS Part 4, as measured on a categorical ordinal scale; changes of one category from baseline to week 24 were considered significant); number of patients with decreased severity of fluctuations – were analyzed by the Cochran-Mantel-Haenszel test.

The number of dose failures recorded in the home diaries were summed over the three diary days preceding each clinic visit, and the results were presented in frequency tables for original

values and for changes from baseline. A similar assessment was performed for the number of booster doses taken. Finally, a blindness evaluation was conducted on visit 6 or at premature discontinuation and the results tabulated against the treatment received by the patients, then assessed descriptively.

The washout period incorporated visits 6-8 (weeks 24-28). Unlike Study 33, it was staggered: half the patients had their medication withdrawn at week 24 and their final evaluation (off medication) at week 26; the other half were discontinued at week 26 and received their final evaluation (off medication) at week 28. Patients completed 3-day home diaries immediately prior to visit 6 and a 2-day home diary during the first two days after visit 6. Changes in the home-diary variables were analyzed by comparing the group withdrawing at visit 6 with the placebo treatment, by using the mean over the three days prior to visit 6 and the mean over two days after visit 7. Changes in the UPDRS scores, from visits 6 to 7 and 8, were compared among the placebo and the two entacapone groups. Clinical parameters were statistically evaluated by ANCOVA, estimating treatment differences with 95% CI, and using baseline visit 1 as covariate; analyses were done for both ITT and per-protocol populations.

COMPLIANCE: Compliance was determined by tablet count at each clinic visit and by decreases in 3-OMD (drawn on visits 1, 3, 4, 5, 6, 7, and 8; a decrease of at least 30%, compared to baseline, signalled compliance). According to the sponsor (see Tables 3.5.1, 3.6.1, and 3.7.1), the mean treatment compliance approximated 100% throughout the study: 23 treats and 29 placebo violated compliance criteria with respect to taking fewer or more tablets at one time or another up to week 24 of the study. As to plasma 3-OMD levels, the mean concentration remained unchanged in the placebo group but declined at least 30% during weeks 8, 16, and 24 for between 76 and 86% of the treats. Withdrawal of treatment led to increases in 3-OMD levels in treats.

RESULTS:

PRIMARY OUTCOME VARIABLE:

The proportion of daily ON time was about 60% in both treats and placebo at baseline. In the ITT population, the proportion of ON time increased by 6.7% over baseline in the entacapone, and 2.0% in the placebo, group, yielding a difference between treatments of 4.5% which was statistically significant ($p<0.05$). COMTAN's benefit was most apparent at the end of the day: the difference between treatments was 1.1% in the morning hours (6 am-12 noon), 3.9% for the afternoon (12 noon-6 pm), and 7.1% ($p<0.05$) for the evening (6 pm-12 midnight). In contrast, results of the per-protocol analysis were not statistically significant; but it should be noted that sample sizes were smaller (ITT populations: entacapone, $n_{treat}=103$ and $n_{placebo}=102$; placebo, $n_{treat}=65$ and $n_{placebo}=65$). The proportion of ON time increases were 8.9% for the entacapone group and 2.8% for the placebo, yielding a difference of 6.1% which failed to attain statistical significance ($p>0.05$; $CI_{95\%}$ -0.27,10.14). (It should be noted that the text incorrectly presents the data as 2.9% for placebo, and the difference between groups as 4.9%; see v 122, p 46; my data was taken from Table R16).

A third analysis was performed, in accordance with the third protocol amendment, to determine COMTAN's benefit in patients defined as true fluctuators. Any patient who was OFF for at least 3 hours during each of the three 24-hour home-diary days at baseline was classified as a fluctuator. For these patients, the proportion of daily ON time at baseline was about 56% in both treatment groups ($n_{treat}=88$, $n_{placebo}=83$). COMTAN-treated fluctuators saw an increase in proportion of ON time of 8.3%, as compared to 2.6% in the placebo group, yielding a difference of 5.7% in this subpopulation which was statistically significant ($p<0.01$).

The sponsor also presented daily ON time diary data in terms of absolute time increases; mean awake time for both groups was about 15 hours. COMTAN-treated patients saw an increase from baseline of 1.0 h in daily ON time, as compared to 0.4 h in the placebo group, a differences

of 0.58 h which was not statistically significant (p=0.0633; $CI_{95\%}$=-0.04,1.19). Increases in absolute time for the per-protocol population also failed to achieve statistical significance (COMTAN=1.3 h, placebo=0.5 h, difference=0.8 h [p=0.1652; $CI_{95\%}$=-0.29,1.55). For the subpopulation of true fluctuators, however, increases in absolute ON time were significant for COMTAN-treated patients: 1.2 h for COMTAN vs 0.4 h for placebo, difference=0.75 h (p<0.05, $CI_{95\%}$=0.11,1.39).

An analysis of individual center results, according to data the sponsor provided Dr. Choudhury (see his review, pp 6-7), showed that placebo beat entacapone in 9 of 18 centers. Although the overall difference in treatments (as change from baseline) translated into an increase of 4.8% in percent of daily ON time *(percent awake time)*, center 23 saw a difference of -8.75%; the difference for center 15 was similar. On the other hand, center 29 had a difference as large as 24.5%. The p-value for center by treatment interaction was consequently not significant (p=0.2367). Reasons supplied by the sponsor to explain these extreme results included chance variaitions in disease severity (in center 23, PD patients were "milder" than average and therefore treatment effects may be less clear) and the possibility of undetected inaccuracies in recording ON, OFF, and ASLEEP times (Choudhury, p 7). Both explanations would tend to weaken further the studies results.

Finally, note should be made that, although the trial attained statistical significance with regard to the primary outcome measure as set forth in the protocol, it did not satisfy the protocol's definition of clinical significance, namely, a 10% difference between treatments which would translate into an approximate increase of 1.5 hours in ON time. The estimated difference between treatments was 0.58 hours (p=0.0633; $CI_{95\%}$ -0.04,1.19). Compared to study 33 (which employed absolute ON time -- as a fraction of the waking day -- as its primary outcome measure), the treatment difference was small (4.8% vs 8.3%).

The Agency's statistician, Dr. Japo Choudhury has described the results of study 44 as statistically significant but non-robust (p 6):

> 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 Chnage From Baseline of %ON time) done by the reviewer were 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.

SECONDARY OUTCOME VARIABLES:

(a) *Daily OFF time*: For the ITT analysis, daily OFF time was decreased by 1.2 h from baseline in the entcapone group, as compared to 0.3 h for placebo, resulting in a difference of 0.9 h for weeks 8, 16, and 24 between the two treatments which was statistically significant (p<0.01; $CI_{95\%}$ -1.52,-0.28). The per-protocol difference was also statistically significant (mean OFF time for the treats, 1.6 h; for placebo, 0.4 h; difference, 0.99 h [p<0.05; $CI_{95\%}$ -1.90,-0.08]), as was the analysis for the subpopulation of true fluctuators (mean OFF time for the treats, 1.5 h; for placebo, 0.4 h; difference, 1.11 h [p<0.01; $CI_{95\%}$ -1.81,-0.42]).

(b) *UPDRS*: No significant difference was found between the two treatments in either the ITT or per-protocol analyses for Parts I (mentation, behavior, mood), II (ADL), and III (motor) or for the sum of the scores for the three subscales, though all demonstrated a trend in favor of entacapone treatment.

(c) *Global evaluation*: The difference between the entacapone and placebo groups with regard to patient reports of clinical improvement or worsening was clinically significant, in favor of the entacapone group, at the end of the study (week 24; p<0.05), as well as over weeks 8, 16, and 24 (p<0.05). The investigators' evaluations showed demonstrated a statistically significant improvement at week 24 (p<0.05), but not over weeks 8, 16, and 24.

(d) *Daily fluctuations in disability*: There was a trend in favor of entacapone with respect to a decrease in the frequency and severity of daily wearing-off periods; in nocturnal, but not early morning, akinesia; and in the daily frequency, but not the severity, of OFF-period freezing. Peak-dose dyskinesias increased in entacapone-treated patients, though there were no changes in daily frequencies. Early morning dystonia and OFF-period dystonia were less severe in the entacapone treats, but no changes in the occurrence or daily frequencies were observed. The occurrence and daily frequencies of ON-period dystonias increased in the entacapone treats. No changes were seen in he daily frequency or disability of unpredictable rapid fluctuations. Finally, the mean daily frequency of random freezing periods decreased in the entacapone treats and increased in the placebo patients.

(e) *Levodopa doses on home diary days*: The mean daily levodopa doses over weeks 8, 16, and 24 decreased by 93 mg in entacapone treats and increased by 19 mg in placebo patients, and the estimated difference in the daily levodopa dose between the two treatment groups was 112 mg over that period (reported as 106 mg; v 122, p 8-074), which was statistically significant both by ITT ($P<0.001$) and per-protocol ($p<0.01$) analyses. Dosing frequency on average remained unchanged from baseline in both groups throughout the 24 weeks (on average 6 doses per day). The proportion of patients taking booster doses of levodopa in both groups remained unchanged throughout the 24-week study, and there was also no significant difference between the groups with respect to levodopa dose failures, thought there was a trend in favor of entacapone treats.

Other nonprotocol efficacy measures considered included the UPDRS Part 4 (complications of therapy), comparing the categorical variables (listed in bold type) at week 24 (time of maximum exposure) to baseline. As for **duration of dyskinesias**, the number of nondyskinetic patients did not significantly changes in either the treated or placebo group. However, for those patients with dyskinesias at baseline, the duration of dyskinesias increased in both the ITT and per-protocol entacapone treated populations from week 2 onward; there were no such changes in the placebo group. Furthermore, with respect to **disability of dyskinesias**, the proportion of patients with mildly disabling dyskinesias decreased, while the proportion of those with more completely disabling dyskinesias increased. There were no marked changes in the frequency of **painful dyskinesias**, and no marked differences between treats and placebo with regard to the proportion of patients experiencing **early morning dystonia**, though a slight increase was observed in the ITT and per-protocol entacapone-treated population who did not experience early-morning dystonia. There were no changes in the proportion of patients who experienced **predictable OFF periods**, but the percentage of patients reporting **unpredictable OFF periods** decreased in the entacapone group (both the ITT and per-protocol population). There was essentially no difference between treats and placebo with respect to reports of **sudden OFF periods**. A trend in favor of entacapone-treated patients was observed for the **reduction in OFF time**; the difference was statistically significant, however, when changes from baseline were considered for each of weeks 8, 16, and 24 ($p<0.05$) for both the ITT and per-protocol populations. **Anorexia, nausea, vomiting** increased in both the treated and placebo groups; at week 24 of the study, 14% in both groups complained of these symptoms. Finally, there were no changes in the proportion of patients complaining about **symptomatic orthostasis** or **sleep disturbance** at baseline.

WITHDRAWAL EFFECT: The active treatment was withdrawn in a stepwise manner after week 24, with half the entacapone patients transferred to placebo after 24 weeks of treatment (visit 6) and receiving their final evaluation at week 26 (visit 7), and the other half withdrawn after 26 weeks of treatment (visit 7) and receiving their final evaluation at week 28 (visit 8). The sponsor then compared data from the final visit with those from the penultimate visit. Results are presented by the sponsor as analyzed by the ITT-OC method.

Note that, according to the sponsor, "the blindness evaluation 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" (quoted by Dr. Choudhury, p 8; text not available in the volumes given to me). I have discussed the matter with Dr. Choudhury, who considers the results less valuable owing to the broken blind; one cannot, however, speculate otherwise at this point about what the results might have been like were the blind not broken. Recall that the withdrawal period was also unblinded for study 33.

By the end of the first discontinuation day, daily ON time was decreased by 8-10%, or about 1.5 hours in actual time, and daily OFF time increased proportionally the following day, in both ITT and per-protocol populations. Both changes occurred maximally on the first two days of withdrawal: no further deterioration was observed from week 24 to 26, and were statistically significant. No statistically significant change in ASLEEP time was recorded.

It should be noted that patients withdrawn at week 24 were not allowed to make any (compensatory) changes in their levodopa dose during the two days immediately after withdrawal, and booster doses were also not recommended. For patients withdrawn at week 26, however, the levodopa dose had increased from 758±415 mg to 815±490 mg ($p<0.01$) by the end of the second day, and the dosing frequency increased as well from 6.2±2.0 to 6.5±2.6. For treats withdrawn at week 24, the mean levodopa dose was increased by about 10% (from 640±275 mg at week 24 to about 711±378 mg at week 26; $p<0.01$) within two weeks after discontinuation; the increase was from 744±401 mg to 801±430 ($p<0.05$) Levodopa doses remained unchanged in the placebo group during the washout period. Furthermore, with respect to the entacapone group that withdrew at week 26 (there was no comparable data for the earlier withdrawal group), booster (or unscheduled) levodopa doses were totaled for weeks 25 and 26 (prior to withdrawal) and for weeks 27 and 28 (after withdrawal). The cumulative levodopa dosage taken as booster doses increased from 480±903 mg to 1468±801 mg.

The UPDRS scores also deteriorated, by week 28 after entacapone withdrawal (either 2 or 4 weeks post-discontinuation), for Parts II (ADL), III (motor), and the sum of Parts I, II, and III. The change for total score (Parts I, II, III) attained statistical significance at weeks 26 ($p<0.01$) and 28 ($p<0.01$) for week 24 withdrawals, and for week 28 ($p<0.05$) for week 26 withdrawals. The change in Part III scores was statistically significant only for week 24 withdrawals at weeks 26 ($p<0.01$) and 28 ($p<0.001$). Part I (mentation) remained unchanged.

Patient and investigator global evaluations also reflected a deterioration during the withdrawal period, and the results of their surveys were statistically significant for both withdrawal groups (week 24 and week 26). No significant change was observed for daily fluctuations of disability.

Minimal increases were noted in the disability of dyskinesias, early morning dyskinesias, unpredictable OFF periods and sudden OFF periods (but not in the number of predictable OFF periods), and sleep disturbances. No changes were seen in; anorexia, nausea, vomiting; and symptomatic orthostasis. While patients exhibited no changes in the Hoehn & Yahr scale, patient-assessed Schwab & England ADL numbers demonstrated deterioration in the degree of independence.

Blindness Evaluation: Most treats and placebo patients guessed their allocation correctly, apparently basing their judgment on the improvement or lack of improvement of symptoms (159 patients, 79%), the presence or absence of adverse events (18, 9%), or other reasons (24 patients). According to the sponsor, urine color "was, therefore, not a to be a decisive element" (v 122, p 69).

Subgroup Analyses: There were no statistically significant response differences for gender or age (<65 vs ≥65). Racial representation was sparse (4 nonwhites in each of the groups), and no conclusions can therefore be reached about the effect of COMTAN on groups other than Caucasian.

SUMMARY

The sponsor has displayed results of the pooled populations from Studies 33 and 44. Despite differences in outcome measures between the two trials, the sponsor has also pooled the data with respect to proportion of daily ON time, the parameter for which both studies were positive. See Tables 24-30 for the data. Statistical significance is attained for the combined population with respect to proprotion of daily ON time.

It should be noted that Study 44 allowed only the use of *immediate-release* levodopa/dopa-decarboxylase inhibitor formulations, whereas Study 33 permitted *both immediate- and controlled-release* levodopa/dopa-decarboxylase preparations. Furthermore, patients in Study 33 could be treated with either levodopa/carbidopa or levodopa/benserazide, while those in Study 44 (US/Canadian study) were treated only with levodopa/carbidopa. That both studies attained statistical significance led the sponsor to conclude that entacapone was effective with all levodopa/dopa-decarboxylase inhibitor preparations. Whether entacapone shows better effect with one or another of the preparations has not been assessed.

Study 52

TRIAL DESIGN: This Phase 3, multicenter (20 centers, 37 investigators), randomized, double-blind, placebo-controlled study was conducted entirely in Finland to "study the safety and efficacy of the long-term use of entacapone as an adjunct to levodopa/dopa decarboxylase inhibitor treatment in fluctuating and nonfluctuating patients with PD" (v 144, p x). "Safety data is the basis for the whole program to register entacapone and the aim is to collect safety data from a maximally large patient population" (v 147, p 261).

Study duration was set at one year, but a 6-month interim analysis was called for in the protocol to assess both the safety and efficacy of entacapone. Efficacy data included in the present NDA encompasses the initial 6-month double-blind period; dates for this period -- from enrollment up through the 6-month interim analysis -- are May 1995-June 1996. The Four-Month Safety Update compiles safety information for the remaining 6 months of the study (to be examined in detail by Dr. Michael Sevka, medical officer in charge of safety for the NDA).

Although biostatisticians would break the treatment code for the interim analysis, study team members (investigators and nursing staff) as well as patients were to continue blinded until the end of the study.

Table 9.4 illustrates the trial plan. A 2-4 week run-in screening period preceded the double-blind portion of the trial. Five visits were scheduled during the 6-month study period, one at baseline before treatment, then at week 2, month 3, and month 6. Subjects could continue on in the study for up to 1 year. Subjects took one 200-mg dose of entacapone, or placebo, with every scheduled levodopa dose, up to 10 times per day.

Efficacy measures, considered secondary variables (the safety assessments -- labs, adverse events, drug interactions, and hemodynamics -- were considered primary; see v 147, p 258), consisted of UPDRS evaluations when the patient was "on," global evaluations of the patient's disease (completed by both the investigator and the patient), duration of ON time, the dosing interval between the first two morning doses of levodopa/DCCI, total daily levodopa dose, and the number of daily doses. Compliance measures were tablet count and 3-OMD plasma concentrations (see the trial plan).

Three amendments to the original protocol were implemented:

(a) AMENDMENT ONE, DATED 6/25/95: excludable concomitant medication, study medication are

clarified, as above.
(b) AMENDMENT TWO, DATED 8/30/95: added a new investigator and center.
(c) AMENDMENT THREE, DATED 8/30/96:
(i) clarified scheduling of efficacy assessments which would be done at visits 4 (at 6 months) and 6 (study end);
(ii) identified the primary efficacy parameters, (UPDRS motor score, subscale 3) and secondary parameters (sum of the scores of UPDRS Parts 1-3, as well as individual scores for Part 1, 2, 4, 5, and 6; global evaluations; total levodopa dose and the number of doses on visits 4 and 6; duration of benefit of a single levodopa dose and the time interval between the first 2 daily doses; and 3-OMD concentrations), all evaluated at visits 4 (month 6) and 6 (study end) and compared to baseline;
(iii) set guidelines for the preparation of the 6-month interim report and the maintenance of the blind for the treatment staff and patients; and
(iv) set forth the statistical methodology to be employed (see below).

INCLUSION/EXCLUSION CRITERIA: Males and females, aged 30-80, with idiopathic PD "needing an enhancement and/or smoothening of levodopa effects" (v 147, p 261), except for females of childbearing potential; at Hoehn and Yahr stage 1.5-4.0 (defined when ON); levodopa responsive and on a stable regimen of 2-10 doses/day on any levodopa preparation [NOTE: both the immediate-release and CR preparations were allowed, as well as both levodopa/carbidopa and levodopa/benserazide]; use of amantadine, anticholinergics, selegiline, and/or dopamine agonists acceptable; without marked dementia, other significant neurological disease, major psychiatric disorder (as severe depression), or serious medical illness (as cardiac, pulmonary, GI, hepatic); treatment with anti-dopaminergic drugs (as alpha-methyldopa, reserpine, neuroleptics, antiemetics), MAO-AI or nonselective MAOI, rimiterol, isoprenaline, adrenaline, dopamine, dobutamide, apomorphine or nomifensine within one month prior to the study; females of childbearing age.

POPULATION: 326 patients (217 males, 109 females) participated in the study, 218 randomized to entacapone and 108 to placebo. "Due to the primary aim of the study in gathering larger patient population for safety data base, no sample size calculations were performed for the efficacy variables" (v 144, p x).

WITHDRAWALS AND PROTOCOL DEVIATIONS: 20/218 (9%) entacapone and 14/108 (13%) placebo patients discontinued the study. Adverse events were the main reason (18, or 18%, of entacapone and 11, or 10%, placebo patients): in the entacapone group, diarrhea (3), abdominal pain (4), dyskinesia (4), confusion and paranoia (1), syncope (1), postural hypotension (1), nausea and insomnia (1), cold and clammy skin (1), and sepsis and subsequent death (1); and in the placebo group, abdominal pain (1), lack of effect (2), malignancy leading to death (2), suicide (1 who had malignancy), stroke (2; one leading to death), amnesia (1), vomiting and confusion (1), nausea (1), headache (1), and tremor (1). Other reasons included protocol violations (1 entacapone) and noncompliance (2 entacapone, 1 placebo). Dr. Michael Sevka (responsible for the safety portion of the NDA) will review the adverse event profile in detail.

DOSAGE FORM: Comtan was supplied as 200-mg tablets; batches MTS03-V01-03, MTS03-V03-03, VH002, VK004, XA001, XA002, XB00401. Placebo: batches SCT08-U03-03, SCT08-UC2-03, VK001, XA001.

OUTCOME MEASURES:

PRIMARY: Improvement in the UPDRS motor score (subscale III), compared to placebo.

SECONDARY: (1) Improvement in the sum of the scores for UPDRS Parts I, II, and III, compared to placebo.
(2) Improvement in UPDRS subscores for Parts I. II, IV, V, and IV, compared to placebo.
(3) Improvement in the patient and investigator global evaluations, compared to placebo.
(4) Decrease in the total daily levodopa dose, compared to placebo.
(5) Prolongation in the duration of benefit of the first morning levodopa dose, compared to placebo.
(6) Prolongation of the dosing interval, compared to placebo.

PLANNED ANALYSES: Both ITT and per-protocol analyses were to be performed for efficacy parameters. ANCOVA for repeated measures, with treatment, time, their interaction, center and center*treatment interaction, and baseline measurements as covariate, was the method chosen to analyze (1) the sum of UPDRS subscores for Parts I, II, and III and individual scores; (2) the average duration of benefit of a single levodopa dose; (3) the time interval between the two first daily doses; (4) change in the total daily levodopa dose; and (5) change in the number of levodopa doses per day. Patient and investigator global evaluations were to be analyzed by chi-square. For dichotomized response variables, relative risks were to be tested and 95% confidence intervals calculated by Cochran-Mantel-Haenszel test. A two-way significance level of 5% was to be considered statistically significant.

PERFORMED ANALYSES: Efficacy evaluations were performed with both the ITT and per-protocol populations, using the response at 6 months to estimate the treatment difference. ANCOVA for repeated measures was employed to study continuous variables; the baseline was used as a covariate. Center was used as a random factor to generate a global estimate for the treatment effect. Mean differences between treatments were estimated with 95% confidence intervals. For categorical variables, the Cochran-Mantel-Haenszel test was used to compare proportions of patients. A two-tailed significance level of 5% was considered to be statistically significant.

COMPLIANCE: Compliance was determined by tablet count at each clinic visit and by decreases in 3-OMD (drawn on visits 1, 3, 4, 5, and 6; a decrease of at least 30%, compared to baseline, signalled compliance). According to the sponsor, the mean treatment compliance 96-98% throughout the study: 4 treats and 1 placebo violated compliance criteria with respect to taking fewer or more tablets at one time or another between months 3 and 6. There was missing data for 14 placebo patients who discontinued the study prior to month 6.

As to plasma 3-OMD levels, the mean concentration declined in treats from 4.9±3.6 ug/ml at baseline (n=210) to 2.7±1.9 ug/ml at month 3 (n=208). On average, there was no evident change in the placebo group for that period (5.1±4.5 ug/ml at baseline [n=104] and 5.0±3.9 ug/ml at month 3 [n=101]); however, in about 6% of placebo patients, a decrease of more than 30% from baseline was observed. The between-group difference was statistically significant , in favor of entacapone.($p<0.001$; $CI_{95\%}$ -1.6,-1.0).

RESULTS: The Table of Efficacy Variables shows that there was no statistically significant difference, for the ITT population (results were similar for the per-protocol population) between the entacapone and placebo groups with respect to the primary outcome measure, the UPDRS motor score while ON. The mean score on the UPDRS Part III declined slightly in both treatment groups (see Table R29); UPDRS evaluations were performed from 2.5-2.8 hours after the last levodopa dose.

With respect to secondary parameters, no differences were found between treats and

placebo for scores on the UPDRS Parts I (mentation, behavior, mood), II (activities of daily living), and the sum of Parts I, II and III; see Tables R30 and R31. As for complications of therapy, or Part IV, the proportion of patients not dyskinetic at baseline declined slightly in the entacapone group (from 59.2 to 56.0%) and increased correspondingly in the placebo (from 60 to 66%). However, the number of patients in whom the *duration of dyskinesias* exceeded 50% of the day increased in the entacapone group (from 1.8 to 7.3%), but saw little change in the placebo (from 0.9 to 1.9%); see Table R32). As to the category of *disability of dyskinesias* (Table R33), the proportion of entacapone patients experiencing severely disabling dyskinesias increased (from 0.9 to 5.4%), whereas a decline was seen in placebo (from 4.2 to 0%) at the end of 6 months. Severely *painful dyskinesias* were experienced by slightly more placebo (from 0 to 4.2%) than entacapone (from 0 to 1.8%) patients at the end of 6 months (Table R34), but a corresponding decrease in the presence of *early morning dystonia* was noted in both groups at the end of 6 months (entacapone, from 14.2 to 11.5%; placebo, from 14.8% to 13.9%). The presence of *predictable OFF periods* decreased in both groups at the end of 6 months (entacapone, from 22.9 to 16.1%; placebo, from 23.1% to 18.5%); little change in either group was evident for *sudden OFF periods*. A decrease in the *proportion of OFF time* was observed in both groups at the end of 6 months (see Table R35), but the differences were not statistically significant. *Anorexia, nausea, and vomiting* increased in the entacapone group from 7.3 to 11.0% after 6 months, but declined in the placebo from 6.5 to 4.6%; these are known side effects of other COMT inhibitor drug (Tasmar), as well. *Sleep disturbances* decreased in both groups at 6 months (entacapone, from 34.9 to 31.2%; placebo, from 44.4% to 33.3%), as did complaints of *symptomatic orthostasis* (see Table 9.16.1).

There were no significant changes in Hoehn & Yahr staging after 6 months in either treatment group. Schwab & England ADL scores of activities of daily living, however, showed improvement (see Table R36) -- albeit not statistically significant -- among more entacapone than placebo patients. Grading is categorized as <80% (meaning the patient is no completely independent), 80% (meaning that the patient is conscious of his difficulty and slowness), and >80% (meaning that the patient may exhibit some slowness already).

Global evaluations (see Table R38), completed by patients and divided into grades of "very poorly, poorly, rather poorly," "not well, nor poorly," and "rather well, well, and very well," show an increase in the negative and a decline in the positive categories. Those patients taking fewer doses per day (2-4) appeared in better condition than those taking more (5-10). Nonetheless, no statistically significant differences between groups were apparent in either the ITT or per-protocol analyses.

As for *duration of benefit from the first morning levodopa dose* , no statistically significant difference between treats or placebo patients were demonstrated either by ITT or per-protocol analysis. However, the dosing interval between the first two daily levodopa doses demonstrated a statistically significant prolongation at month 6: for the entacapone group, from 4.6 to 4.8 hours; for the placebo, from 4.3 to 4.4 hours (between-group difference by ITT analysis, $p<0.01$; results similar for the per-protocol analysis). Similarly, with respect to *daily levodopa dose*. By month 6, total daily levodopa dose decreased among entacapone patients by 38 mg and among placebo patients by 11 mg, yielding a between group difference that was statistically significant (ITT Analysis [see Table R40]: $p<0.01$; $CI_{95\%}$ -68.12,-19.75). But the dosing frequency of levodopa did not change significantly for either treatment group: for entacapone patients, the mean number of levodopa doses per day was 4.2 at baseline and 4.1 at month 6; for placebo, 4.3 and 4.3, respectively (see Table R42). Neither the ITT nor the per-protocol analyses demonstrated statistical significance.

Finally, there was a statistically significant decrease in 3-OMD levels for the entacapone population, compared to placebo: for entacapone patients, from 4.9 ± 3.6 at baseline to 2.7 ± 1.9 at month 6; and for placebo, from 5.1 ± 4.5 to 5.0 ± 3.9 ($p<0.001$ in favor of entacapone; $CI_{95\%}$ -1.6, -1.0).

SUBGROUP ANALYSES: No subgroup analyses were performed for any of the efficacy parameters.

CONCLUSION: From the efficacy standpoint, study 52 is a failed clinical trial. According to the sponsor's analysis, the failure was due entirely to the mixed population -- both fluctuating and nonfluctuating PD patients were enrolled, in contrast to studies 33 and 44 which included only fluctuators: "There were no restrictions in the inclusion criteria in respect to the severity of the disease nor to the drug treatments. Therefore, patients with or without motor fluctuations, with or without other complications of the treatment (eg, dyskinesias) were accepted and any commercially available forms of levodopa preparations and their combinations with other registered anti-PD drugs were allowed. . . .This resulted in a heterogenous population in regard to disease severity, duration, and treatment that can confound estimation of effectiveness" [v 144, pp 89, 98].

Other NDA Studies

PHASE 2 MULTIPLE DOSE CONTROLLED TRIALS:

Three Phase 2 double-blinded, placebo-controlled, multiple-dose crossover trials (16, 28, and 30) were conducted, varying in duration from 6 to 8 weeks.

STUDY 28

Study 28, conducted to determine the optimal COMTAN dose, was a multicenter, randomized, double-blind, placebo-controlled cross-over study, and consisted of a 7-day run-in phase, 4 consecutive 14-day double-blind treatment periods, and a 7- to 14-day follow-up period at the end. Entacapone -- or placebo) -- was administered at doses of 100, 220, or 400 mg) concomitantly with every scheduled levodopa/carbidopa dose. Inclusion criteria were mainly idiopathic PD, age >30, 4-6 daily L-dopa intakes, and symptom fluctuations in motor performance. Primary efficacy variables were (1) ON time by tapping and walking tests; (2) magnitude of critical response by tapping and walking tests; (3) sum of daily scores of tremor and dyskinesia; (4) maximum change in global scores (9-point scale); (5) proportion of daily ON time using an 18-hour home diary; (6) UPDRS subscores and sum of UPDRS scores for Parts 1-3; and (7) the energy rating scale (5-point scale from much more energy than normal [5] to much less energy than normal [1]). The home diaries were completed on 2 consecutive days prior to each clinic visit; to determine ON time after a standard L-dopa dose, with/without different entacapone dose levels, the symptoms were assessed every 15-30 minutes up to 6 hours after dosing and assessed by tapping and walking tests. Patients were ON if the tapping speed exceeded baseline values by 15% or the walking time decreased by 20% the baseline values. UPDRS scoring was performed at 90 minutes after drug administration.

The trial enrolled 25 patients, 21 of whom completed the study; mean age was 63.5 years (range: 43-77), mean disease duration 10.6 years (range 3-23), and mean duration of levodopa treatment 8.4 years (range 3-15 years). The daily levodopa dose was between 300 and 1550 mg, and the single morning dose of levodopa (the test dose) was between 50-250 mg. Concomitant adjunctive medications included selegiline (16 patients), bromocriptine (6), pergolide (6), benzhexol hydrochloride (4), amantadine (2), additional carbidopa (1).

Table 10 shows that the proportion of daily ON time failed to reach statistical significance for any of the entacapone doses (76% or 11.5 hours for placebo, 78% or 11.5 hours for 100 mg, 80% or 12.2 hours for 200 mg, and 81% or 12.3 hours for 400 mg). There was, however, a statistically significant decrease in levodopa dose. UPDRS subscores and the energy scale also failed to demonstrate statistically significant differences between entacapone and placebo.

Failure to show statistically significant improvement in the clinical parameters was

explained by the sponsor as "probably because a proportion of the patients did not fluctuate" (v 1, p 396).

STUDY 30

Study 30 was a multicenter (2 centers) randomized, double-blind, placebo-controlled crossover study with two 4-week periods without a washout interval at crossover. In such a trial design lacking a washout period, there is the very real possibility of enrichment bias in treats administered entacapone who are then immediately placed on placebo; nonetheless, the drug's half-life is very short and would be out of the body in less than 24 hours.

26 PD patients with wearing-off fluctuations were enrolled, 23 of whom completed the trial; their mean age was 62 (range: 46-75); mean duration of PD 13.3 years (Hoehn & Yahr stage 2-4), and mean duration of levodopa therapy 10.5 years. Daily levodopa dose varied from 300-1550 mg, divided in 4-10 doses per day. The single standard morning dose varies between 50 and 250 mg.

The primary outcome measure was "duration of motor response (ON time) evaluated by the levodopa test" (v 304, p 8) -- that is, the motor part of the UPDRS (subscale 3) after a levodopa dose. Secondary variables included (1) parameters studied during the levodopa test: magnitude of peak effect (lowest total motor scored and maximal change from baseline), starting time (latency to onset), of motor response, duration and magnitude (maximum score) of dyskinesias (2) ON time, levodopa dose, time of sleep and dyskinesias from home diary information, (3) total score of UPDRS subscale 3 (motor), (4) daily fluctuations in disability, predictable fluctuations (end-of-dose failure and dyskinesias) and unpredictable fluctuations, and subjective patient evaluations of the duration of action of a levodopa dose. Patient diaries recorded daily levodopa dosage, ON time, SLEEP time, and occurrence of dyskinesias. On clinic days, frequent scoring was conducted using the UPDRS Part 3 and repeated measurement of dyskinesias every 30 minutes until they returned to baseline or were maximally below 10% of baseline value (for up to 6 hours after dosing) or until OFF. Home diaries were completed by the patient on 3 consecutive days preceding each study day; recorded were levodopa dosing, ON time, SLEEP time, and occurrence of dyskinesias. Statistical analyses were based on the results from 23 patients (2 treats and 1 placebo dropped out prematurely; see v 75, p 8-345).

Table 10.3 shows that the trial achieved statistical significance, in favor of entacapone, with respect to prolongation of mean daily ON time (2.5 hours), mean ON time after a single levodopa dose, and motor response as determined by the UPDRS Part 3 subscale. A statistically significant decrease in mean daily levodopa dose was also attained. However, no difference was appreciated between treats and placebo with respect to time of onset of the motor response and maximal change in the UPDRS motor score (see Table 10.4).

Prolongation of ON time correlated with an increase in levodopa's AUC by 35% following a single levodopa dose. Note, too, that the mean duration of dyskinesias was prolonged by 39 minutes with entacapone, as compared to placebo.

STUDY 16

Study 16 was "prematurely stopped after studying 10 patients owing to lack of suitable patients [only 10 of the planned 20 patients actually enrolled]. The protocol required that the patients should be in the OFF stage in the morning before levodopa tests. The results could not be used properly for a variety of reasons, including incomplete data, changed levodopa dose in 5 of 10 patients, and lack of OFF stage in two patients" (v 75, p 8-351).

PHASE 2 MULTIPLE DOSE UNCONTROLLED TRIALS:

Three open-label studies of 4-8 weeks in duration (#12, 8 weeks; #13, 4 weeks; #14, unknown duration), and two interaction studies (safety) with selegiline (#35, 4 weeks; #48, 6

weeks) will be briefly reviewed. Daily ON-time was not an outcome measure in any of these studies. Little information was provided about the specifics of these studies in the NDA.

These studies explored the pharmacokinetics of levodopa dose with and without entacapone in an attempt to correlate levodopa kinetics with clinical efficacy (maximal clinical response based upon the UPDRS subscale 3 motor score). The sponsor interprets the results (see Table 11.2): "Adding entacapone to levodopa treatment significantly increases the AUC of levodopa, the clinical result being the prolongation of ON time. The maximum plasma levodopa concentration (C_{max}) does not change with entacapone, correlating with a mainly unchanged maximum magnitude of improvement in the motor score of the UPDRS. The t_{max} tends to be prolonged in most of the studies without concomitant prolongation in the latency to clinical efect" (v 75, p 8-359). Little comment can be made since the data in Table 11.2 is limited.

Additional Studies On-going or Completed Since the NDA Submission Date

(1) Study 52 (see above for description): still outstanding is the one-year efficacy report.

(2) Study 63 (German trial): original and amended protocols, but no study report, have been included in the NDA package (v 160). Trial design and emphasis (to acquire long-term safety data), involved population, and entacapone dosing regimen were similar to study 52 (see above), save for duration which is 24 weeks in study 63 (and one year in 52). According to the Four-Month Safety Update (see Tables 4.3-4.4; v 1, pp 33), 301 PD patients have been enrolled ($n_{entacapone}$=197, $n_{placebo}$=104). Primary outcome measures were safety variables; secondary were efficacy variables:
   (a) UPDRS evaluation when the patient is ON, including individual subscores for Parts I, II, and III; sum of scores for Parts I, II, and III; and scores for Parts IV, V, and IV
   (b) patient global assessment
   (c) ON time (based on patient diaries completed on 3 consecutive days prior to study visit)
   (d) total daily levodopa dose and number of daily levodopa doses.

(3) Study 65 (UK-Irish trial): original and amended protocols, but no study report, have been included in the NDA package (v 161). About 400 patients were expected to be enrolled, divided as treats:placebo::2:1. Trial design, duration (24 weeks plus a 2-week "withdrawal period" off all medication; in study 44, there was a staggered withdrawal period), and entacapone dosing regimen were similar to study 44 (see above); however, the planned study population was different, involving both fluctuating and nonfluctuating PD patients. Primary efficacy variables included:
   (a) **primary:** proportion of daily ON time while awake (the total number of ON hours over three consecutive diary days, divided by the total number of awake hours; study 44, in contrast, employed proportion of ON time over a 24-hour day)
   (b) **secondary:**
      (i) UPDRS evaluation when the patient is ON, including individual subscores for Parts I, II, and III; sum of scores for Parts I, II, and III; and scores for Parts IV, V, and IV
      (ii) patient global assessment
      (iii) mean ON, OFF, and ASLEEP times (over 3 consecutive diary days)
      (iv) total daily levodopa dose and number of daily levodopa doses
      (v) number of booster levodopa doses needed during home diary days and the number of dose failures.

(vi) withdrawal effect.

IX Dosing Recommendations

Based on the submitted labeling the "recommended dose of COMTAN (entacapone) is one 200 mg tablet administered concomitantly with each levodopa/DDCI dose up to 10 times daily (10 x 200 mg, 2000 mg). . . . COMTAN has no antiparkinsonian effect of its own, and must always be administered in association with a[n] levodopa/DDCI. COMTAN can be used with both immediate-release and sustained-release levodopa/DDCI preparations."

Because there is very limited exposure with total daily doses above 1600 mg (see the exposure table below), the maximum total daily dose should not exceed 1600 mg.

X Conclusion

The available efficacy data from studies 33 and 44 supports approval of Comtan as an adjunctive agent to levodopa for the treatment of fluctuating patients with Parkinson's Disease.

The safety review, done by Dr. Michael Sevka (Neuropharm Safety group), is pending.

XI Recommendations

1. The labeling should clearly state that Comtan is indicated for mild to severe PD with wearing-off symptoms.

2. The sponsor should submit 1-year efficacy data for study 52.

3. The sponsor should submit 6-month efficacy data for study 63.

4. The sponsor should submit 6-month efficacy data for study 65.

5. The sponsor's multiple (4 weeks) dose biopharm studies show no significant differences in ON time among 50 mg, 100 mg, 200 mg, and 400 mg doses. In light of thecurrent TASMAR scenario, justification for any doses higher than 50 mg should be provided.

6. The maximum dose (2000 mg/d) recommended by the sponsor in labeling contains 5.1 mg elemental iron (mostly in the coating), which exceeds allowed limits for drugs (5.0 mg/d; see CFR 73.1200[c]). Dr. Martha Heimann (Chemistry) will cite the iron oxide levels as a deficiency.

7. Biopharm studies in patients with renal and hepatic impairment were done on single-dose Comtan alone, without concomitant levodopa/carbidopa. The sponsor should provide justification of the reliability of these studies for projecting possible adverse effects with long-term therapy on both Comtan and L-DOPA.

8. The sponsor recommends decreasing the frequency of dosing in patients with liver impairment. Given the short half-life of Comtan and no accumulation, the patient should receive benefit for only a very small part of the day. Consequently, the sponsor needs to provide a rationale justifying administration of Comtan to patients with liver disease.

9. All drug-interaction studies (except for selegiline) were also done with single-dose Comtan alone, without concomitant L-DOPA/carbidopa. These studies may not adequately characterize the associated risks when Comtan is taken with other drugs.

10. There is a problem of bioavailabilty with the actual compound (only 30-40% absorbed). The to-be-marketed form has a new coating, different from the one found on the tablet used in Phase 3 studies. Since the to-be-marketed drug has not been tested in clinical studies, it is not known whether the efficacy achieved in the two pivotal trials could be reproduced with the to-be-marketed tablet, or if there are new safety concerns owing to the new coating.

11. There is very limited experience with doses greater than 1600 mg/d. Therefore, the maximum dose should be 1600 mg -- and not 2000 mg -- per day.

/S/

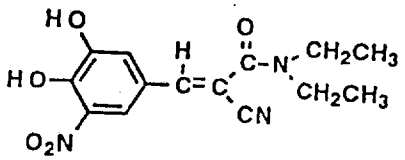
Richard M. Tresley MD
Medical Reviewer

NDA 20,796 div file/Katz R/Wheelous T/Tresley R/2 November 1998

APPEARS THIS WAY
ON ORIGINAL

XII Tables

(Each section of this review has its own tables, reproduced from the NDA, and these tables are consecutively displayed in order of their textual reference.)



(E)-2-cyano-*N,N*-diethyl-3-(3,4-dihydroxy-5-nitrophenyl) propamide[4]

Molecular formula $C_{14}H_{15}N_3O_5$[5]

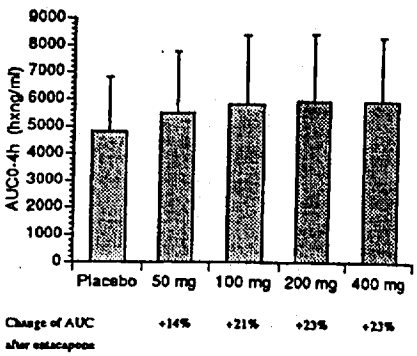


Figure 12.9 Change in area under the curve (AUC) values (mean +SD) of levodopa following single oral doses of entacapone in PD patients treated with levodopa/DDC inhibitor

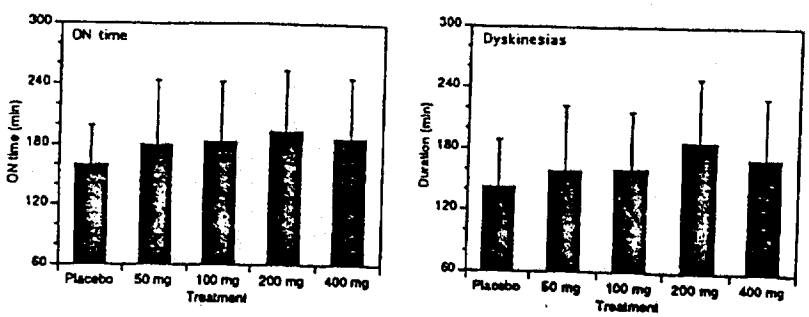


Figure 12.10. The mean (+SD) duration of motor response (ON-time, mins) and dyskinesias (mins) after single increasing doses of entacapone

Table 1. **Listing of Phase II trials according to type of studies**

Study number	Number of patients		Duration of medication
	Entacapone	Placebo	
1. Controlled studies, multiple dose			
293916	10	10	4 weeks + 4 weeks
293927	12	12	10 days
293928	23	25	2 weeks on each dose
293930	25	25	4 weeks + 4 weeks
2. Controlled studies, single dose			
293908	12	12	one dose
293917	12	12	one dose
293926	22	22	one dose
293929	17	17	one dose
3. Open-label studies			
293912	16	16	8 weeks
293913	12	12	4 weeks
293914	10	10	1 week
4. Interaction studies with selegiline			
2939035	13	13	2 weeks + 2 weeks
2939048	10	16	2 weeks + 2 weeks + 2 weeks

Table 2. **Listing of Phase III trials according to type of studies**

Study number	Number of patients		Duration of medication
	Entacapone	Placebo	
1. Controlled studies			
2939044 Efficacy	103	102	24/26 weeks
2939033 Efficacy	85	86	24 weeks
2939052 Safety	218	108	52 weeks
2. Uncontrolled studies			
2939054 (cont. of study -44)	169	-	up to 3 years
2939034 (cont. of study -33)	132	-	up to 3 years
2939061	24	-	up to 3 years

Table 3.1 **Summary of overall exposure in entacapone efficacy studies (E= entacapone, P= placebo, PK/CL= pharmacokinetics and clinical effects)**

Study No.	Study Type	Number of Patients		Treatment Duration	Comment
		E	P		
Phase III					
Primary Efficacy Studies					
-33	Controlled, parallel-group	85	86	24 weeks	
-44	Controlled, parallel-group	103	102	24 weeks	Staggered washout
Other Supportive Efficacy Studies					
-34	Uncontrolled, long-term	132	-	3 years	1-year data
-54	Uncontrolled, long-term	169	-	3 years	1-year data
Phase II					
Supportive Efficacy Studies					
-30	Controlled, crossover	25	25	4 weeks	
Other Supportive Efficacy Studies					
Controlled studies					
-16	Crossover, multiple dose	10	10	4 weeks	10 patients total
-28	Crossover, multiple dose	24	22	2 weeks x 3	24 patients total
-17	Crossover, single-dose	12	12	1 day	12 patients total
-26	Crossover, single-dose	22	22	1 day	22 patients total
-29	Crossover, single-dose	17	17	1 day	17 patients total, Sinemet® and Madopar® preparations
Uncontrolled Studies					
-12	Multiple-dose, PK/CL	16	-	8 weeks	i.v. and oral levodopa
-13	Multiple-dose, PK/CL	12	-	4 weeks	
-14	Multiple-dose, PK/CL	10	-	1 week	
-27	Multiple-dose, PK/CL	12	- -	2 x 10 days	2 levodopa formulations
-35	Multiple-dose,interaction	13	-	2 x 14 days	double-blind regarding selegiline
-48	Multiple-dose, interaction	16	-	14 days	

Cumulative exposure to entacapone according to time and mean dose levels in phase I and II studies and phase III double-blind and open long-term extension studies at the time of the cut-off of the 120-day Safety Update

Dose: tablets/day	< 2		2-3		4-5		6-7		8-9		10			
mg/day	< 400		400-600		800-1000		1200-1400		1600-1800		2000		Total*	
Time (weeks)	NDA	Overall	NDA	Overall	NDA	Overall	NDA	Overall	NDA	Overall	NDA	Overall	NDA	Overall
< 1	374	389	235	310	391	540	192	279	61	83	14	32	1267	1633
≥ 1	8	8	148	223	343	491	191	278	61	83	13	31	764	1114
≥ 4	0	0	114	184	311	451	178	256	59	79	13	18	675	988
≥ 8	0	0	99	166	266	401	137	211	52	70	9	14	563	862
≥ 12	0	0	98	164	257	389	117	185	51	67	9	14	532	819
≥ 24	0	0	95	151	233	349	107	167	48	62	7	11	490	740
≥ 36	0	0	52	145	179	306	97	151	43	52	6	8	377	662
≥ 48	0	0	39	137	140	284	84	133	38	47	6	8	307	609
≥ 52	0	0	35	118	122	249	79	120	34	46	6	6	276	539
≥ 60	0	0	4	92	78	200	59	110	25	39	3	5	169	446
≥ 72	0	0	3	84	57	168	40	93	19	34	3	4	122	383
≥ 84	0	0	2	77	22	154	20	86	10	32	1	4	55	353
≥ 96	0	0	1	74	7	140	9	80	1	31	0	4	18	329
≥ 108	0	0	0	8	0	84	0	61	0	24	0	4	0	181
≥ 120	0	0	0	7	0	72	0	49	0	23	0	4	0	155
≥ 132	0	0	0	5	0	54	0	40	0	16	0	3	0	118
≥ 144	0	0	0	3	0	42	0	28	0	14	0	3	0	90
≥ 156	0	0	0	2	0	22	0	17	0	8	0	2	0	51
≥168	0	0	0	0	0	6	0	7	0	1	0	0	0	14
≥ 180	0	0	0	0	0	3	0	4	0	0	0	0	0	7
n	374	389	235	310	391	540	192	279	61	83	14	32	1267	1633**
%	30 %	24 %	19 %	19 %	31 %	33 %	15 %	17 %	5 %	5 %	1 %	2 %	100 %	100 %
% > 1 wk	1 %	1 %	19 %	20 %	45 %	46 %	25 %	23 %	8 %	8 %	2 %	1 %	100 %	68 %

* Exposure times of double-blind and open long-term extension phase III studies combined, see ISS 5.2.5

** includes altogether 85 patients who participated into more than one study, i.e. if the patient participated into single dose study with a 400 mg dose, he/she is included in that box, if he/she then later participated in another 4 weeks with 1000 mg daily dose he/she is recounted in that box.

Reference: ISS Table 5.11, Post-text Table 4h and data based on phase III data base.

Number of patients in the NDA using Benserazide, Carbidopa and CR preparations

The following table presents the breakdown of the total # patients in the NDA who received Benserazide (Madopar) and Carbidopa with standard and CR levodopa preparations concomitantly with entacapone.

Study class	Levodopa + Benserazide N (%)			Levodopa + Carbidopa N (%)			Both*** N (%)
	STD[a]	CR[b]	Both[c]	STD[a]	CR[b]	Both[c]	
Phase III controlled studies							
2939044 (N=103)	-	-	-	103 (100)	-	-	-
2939033 (N=85)	33 (39)	-	-	52 (61)	-	-	-
2939052 (N=218)	48 (22)	25 (11)	11 (5)	26 (12)	49 (22)	42 (19)	17 (8)
Total (N=406)	81 (20)	25 (6)	11 (3)	181 (45)	49 (12)	42 (10)	17 (4)
Phase III uncontrolled studies							
2939054 (N=169)	-	-	-	121 (72)	-	48 (28)	-
2939061 (N=24)	-	-	-	15 (62)	2 (8)	7 (29)	-
2939034 (N=132)*	94 (71)	-	-	37 (28)	-	-	1 (1)
Total (N=325)	94 (29)	-	-	173 (53)	2 (1)	55 (17)	1 (0)
Phase II multiple dose studies in patients							
293912 (N=16)	-	-	-	16 (100)	-	-	-
292913 (N=12)	10 (83)			2 (17)	-	-	-
293914 (N=10)	10 (100)	-	-	-	-	-	-
293916 (N=10)	-	-	-	10 (100)	-	-	-
293927 (N=12)**	-	-	-	-	12 (100)	-	-
293928 (N=25)	-	-	-	25 (100)	-	-	-
293930 (N=26)	20 (77)	-	-	6 (23)	-	-	-
2939035 (N=13)	13 (100)	-	-	-	-	-	-
2939048 (N=16)	13 (81)	-	-	3 (19)	-	-	-
2939055 (N=15)	6 (40)	-	-	9 (60)	-	-	-
Total (N=155)	72 (46)	-	-	71 (46)	12 (8)	-	-
Phase II single dose studies in patients							
293908 (N=12)	-	-	-	12 (100)	-	-	-
293917 (N=12)	-	-	-	12 (100)	-	-	-
293926 (N=22)	16 (73)	-	-	6 (27)	-	-	-
293929 (N=17)	9 (53)	-	-	8 (47)	-	-	-
293915B (N=4)	-	-	-	4 (100)	-	-	-
293918 (N=16)	-	-	-	16 (100)	-	-	-
2939031 (N=6)	-	-	-	6 (100)	-	-	-
2939037 (N=18)	-	-	-	18 (100)	-	-	-
Total (N=107)	25 (23)	-	-	82 (77)	-	-	-

a) Standard preparation, [b] CR preparation, [c] Both standard and CR preparations

* In study 2939034 all patients are classified to standard levodopa users.

** Cross-over study, in which patients received both standard and CR preparations in subsequent periods

***Received benserazide/levodopa and carbidopa/levodopa combinations.

Table 3. Demographic data of the patients enrolled in studies 2939033 and 2939044, Intent-to-Treat Analysis

Parameter	Study -33		Study -44		Studies -33 and -44	
	Entacapone (N=85)	Placebo (N=86)	Entacapone (N=103)	Placebo (N= 102)	Entacapone (N=188)	Placebo (N=188)
[illegible]						
	62.6 ± 7.6	62.8 ± 8.7	63.9 ± 8.0	62.7 ± 9.7	63.3 ± 7.8	62.7 ± 9.2
	44 - 81	42 - 78	30 - 79	36 - 79	64 (30 - 81)	64 (36 - 79)
(N,%)	50 (58.8)	46 (53.5)	49 (47.6)	49 (48.0)	99 (52.7)	95 (50.5)
≥65 years (N,%)	35 (41.2)	40 (46.5)	54 (52.4)	53 (52.0)	89 (47.3)	93 (49.5)
ace (N,%)						
White	85 (100)	86 (100)	99 (96.1)	98 (96.1)	184 (97.9)	184 (97.9)
Nonwhite	0	0	4 (3.9)	4 (3.9)	4 (2.1)	4 (2.1)
ex (N,%)						
Male	47 (55.3)	47 (54.7)	69 (67.0)	64 (62.7)	116 (61.7)	111 (59.0)
Female	38 (44.7)	39 (45.3)	34 (33.0)	38 (37.3)	72 (38.3)	77 (41.0)
Duration of PD (yrs)						
Mean ± SD	10.2 ± 4.8	11.3 ± 4.8	10.7 ± 4.9	11.3 ± 6.4	10.5 ± 4.8	11.3 ± 5.7
Range	3 - 29	3 - 35	2 - 27	1 - 36	9 (2 - 29)	10 (1 - 36)
Levodopa (yrs)						
Mean ± SD	7.9 ± 4.2	9.0 ± 4.1	9.0 ±4.7	8.9 ± 6.0	8.5 ± 4.5	8.9 ± 5.2
Range	2 - 25	1 - 22	1 - 25	1 - 33	7 (1 - 25)	8 (1 - 33)
H & Y class (N,%)						
1	0	0	1 (1.0)	1 (1.0)	1 (0.5)	1 (0.5)
1.5	9 (10.6)	7 (8.1)	3 (2.9)	1 (1.0)	12 (6.4)	8 (4.3)
2	38 (44.7)	42 (48.8)	46 (44.7)	50 (49.0)	84 (44.7)	92 (48.9)
2.5	18 (21.2)	20 (23.3)	22 (21.4)	19 (18.6)	40 (21.3)	39 (20.7)
3	17 (20.0)	16 (18.6)	27 (26.2)	25 (24.5)	44 (23.4)	41 (21.8)
4	3 (3.5)	1 (1.2)	4 (3.9)	6 (5.9)	7 (3.7)	7 (3.7)
Other PD drugs (N,%)						
Dopamine agonist	42 (49.4)	39 (45.3)	54 (52.4)	55 (53.9)	96 (51.1)	94 (50.0)
Selegiline	39 (45.9)	37 (43.0)	55 (53.4)	47 (46.1)	94 (50.0)	84 (44.7)
Anticholinergic	9 (10.6)	9 (10.5)	11 (10.7)	18 (17.6)	20 (10.6)	27 (14.4)
Amantadine	2 (2.4)	3 (3.5)	17 (16.5)	16 (15.7)	19 (10.1)	19 (10.1)
Other	1 (1.2)	1 (1.2)	3 (2.9)	2 (2.0)	4 (2.1)	3 (1.6)

Table 4. Concomitant antiparkinsonian medication in studies 2939033 and 2939044

Concomitant antiparkinsonian medication	2939033				2939044				2939033+2939044			
	Entacapone (N=85)		Placebo (N=86)		Entacapone (N = 103)		Placebo (N =102)		Entacapone (N = 188)		Placebo (N=188)	
	N	%	N	%	N	%	N	%	N	%	N	%
nly	20	23.5	23	26.7	11	10.7	21	20.6	31	16.5	44	23.4
	39	45.9	37	43.0	55	53.4	47	46.1	94	50.0	84	44.7
Dopamine agonists	42	49.4	39	45.3	54	52.4	55	53.9	96	51.1	94	50.0
- Bromocriptine	34	40.0	28	32.6	15	14.6	19	18.6	49	26.1	47	25.0
- Pergolide	5	5.9	5	5.8	39	37.9	37	36.3	44	23.4	42	22.3
- Lisuride	3	3.5	6	7.0	0	0	0	0	3	1.6	6	3.2
Anticholinergics	9	10.6	9	10.5	11	10.7	18	17.6	20	10.6	27	14.4
- Trihexylphenidyl	5	5.9	5	5.8	8	7.8	12	11.8	13	6.9	17	9.0
- Ethopropazine	0	0	0	0	1	1.0	2	2.0	1	0.5	2	1.1
- Benzatropine	0	0	1	1.2	3	2.9	3	2.9	3	1.6	4	2.1
- Procyclidine	0	0	0	0	0	0	1	1.0	0	0	1	0.5
- Orfenadrine	4	4.7	2	2.3	0	0	0	0	4	2.1	2	1.1
- Biperiden	0	0	1	1.2	0	0	0	0	0	0	1	0.5
Amantadine	2	2.4	3	3.5	17	16.5	16	15.7	19	10.1	19	10.1
Other	1	1.2	1	1.2	3	2.9	2	2.0	4	2.1	3	1.6

Table 5. Demographic data of the patients enrolled in studies 2939033 and 2939044, tabulated by age

Parameter	2939033 and 2939044 combined			
	Entacapone		Placebo	
	< 65 Years (N = 99)	≥ 65 Years (N = 89)	< 65 Years (N = 95)	≥ 65 Years (N = 93)
Race (N,%)				
Caucasian	95 (96.0)	89 (100)	94 (98.9)	90 (96.8)
Non-Caucasian	4 (4.0)	0	1 (1.1)	3 (3.2)
Sex (N,%)				
Male	60 (60.6)	56 (62.9)	60 (63.2)	51 (54.8)
Female	39 (39.4)	33 (37.1)	35 (36.8)	42 (45.2)
Duration of Parkinson's disease (years)				
Mean ± SD	10.4 ± 4.6	10.6 ± 5.1	11.2 ± 5.3	11.4 ± 6.1
Range	3 - 27	2 - 29	1 - 33	3 - 36
Duration of levodopa treatment (years)				
Mean ± SD	8.3 ± 4.3	8.7 ± 4.7	8.8 ± 5.2	9.1 ± 5.2
Range	1 - 25	1 - 25	1 - 33	1 - 26
Hoehn & Yahr classification (N,%)				
1	0	1 (1.1)	1 (1.1)	0
1.5	11 (11.1)	1 (1.1)	8 (8.4)	0
2	46 (46.5)	38 (42.7)	54 (56.8)	38 (40.9)
2.5	25 (25.3)	15 (16.9)	17 (17.9)	22 (23.7)
3	16 (16.2)	28 (31.5)	12 (12.6)	29 (31.2)
4	1 (1.0)	6 (6.7)	3 (3.2)	4 (4.3)
Other antiparkinsonian medication (N,%)				
Dopamine agonist	52 (52.5)	44 (49.4)	55 (57.9)	39 (41.9)
Selegiline	59 (59.6)	35 (39.3)	45 (47.4)	39 (41.9)
Anticholinergic	14 (14.1)	6 (6.7)	14 (14.7)	13 (14.0)
Amantadine	7 (7.1)	12 (13.5)	14 (14.7)	14 (15.0)
Other	2 (2.0)	2 (2.2)	2 (2.1)	5 (5.4)
				1 (1.1)

Table 6. Demographic data of the patients enrolled in 2939033 and 2939044, tabulated by sex

Parameter	2939033 and 2939044 combined			
	Entacapone		Placebo	
	Male (N = 116)	Female (N = 72)	Male (N = 111)	Female (N = 77)
Age (years)				
Mean ± SD	63.3 ± 7.6	63.3 ± 8.2	61.6 ± 9.5	64.3 ± 8.7
Range	44 - 79	30 - 81	36 - 79	39 - 79
< 65 years of age (N,%)	60 (51.7)	39 (54.2)	60 (54.1)	35 (45.5)
≥ 65 years of age (N,%)	56 (48.3)	33 (45.8)	51 (45.9)	42 (54.5)
Race (N,%)				
Caucasian	113 (97.4)	71 (98.6)	109 (98.2)	75 (97.4)
Non-Caucasian	3 (2.6)	1 (1.4)	2 (1.8)	2 (2.6)
Duration of Parkinson's disease (years)				
Mean ± SD	10.6 ± 4.9	10.3 ± 4.7	11.4 ± 6.2	11.0 ± 4.9
Range	3 - 29	2 - 24	1 - 36	2 - 25
Duration of levodopa treatment (years)				
Mean ± SD	8.7 ± 4.7	8.1 ± 4.1	8.8 ± 5.5	9.1 ± 4.7
Range	1 - 25	2 - 20	1 - 33	1 - 22
Hoehn & Yahr classification (N,%)				
1	1 (0.9)	0	0	1 (1.3)
1.5	6 (5.2)	6 (8.3)	5 (4.5)	3 (3.9)
2	57 (49.1)	27 (37.5)	54 (48.6)	38 (49.4)
2.5	26 (22.4)	14 (19.4)	24 (21.6)	15 (19.5)
3	23 (19.8)	21 (29.2)	25 (22.5)	16 (20.8)
4	3 (2.6)	4 (5.6)	3 (2.7)	4 (5.2)
Other antiparkinsonian medication (N,%)				
Dopamine agonist	61 (52.6)	35 (48.6)	56 (50.5)	38 (49.4)
Selegiline	65 (56.0)	29 (40.3)	57 (51.4)	27 (35.1)
Anticholinergic	16 (13.8)	4 (5.6)	16 (14.4)	11 (14.3)
Amantadine	12 (10.3)	7 (9.7)	10 (9.0)	9 (11.7)
Other	2 (1.7)	2 (2.8)	1 (0.9)	2 (2.6)

Table 6.2 Subgroups used in pooled data of the studies -33 and -44

Explanatory variable	Subgroups
Age	<65 years / ≥65 years
Sex	Male / Female
Weight	<70 kg / ≥70 kg
Hoehn and Yahr staging at baseline	≤2 / >2
Daily levodopa dose (mg) from 18-hour Home diary at endpoint	<500 / ≥500 and <1000 / ≥1000
Use of dopamine agonists	Use / no use
Use of selegiline (MAO-B inhibitor)	Use / no use

Table 7. Demographic data of the patients enrolled in studies 2939033 and 2939044, tabulated by Hoehn & Yahr classification

Parameter	2939033 and 2939044 combined			
	Entacapone		Placebo	
	Hoehn & Yahr ≤ 2 (N = 97)	Hoehn & Yahr > 2 (N = 91)	Hoehn & Yahr ≤ 2 (N = 101)	Hoehn & Yahr > 2 (N = 87)
Age (years)				
Mean ± SD	62.1 ± 7.7	64.6 ± 7.8	61.3 ± 8.8	64.4 ± 9.5
Range	44.0 - 78.0	30.0 - 81.0	39.0 - 78.0	36.0 - 87.0
< 65 years of age (N,%)	57 (58.8)	42 (46.2)	63 (62.4)	32 (36.8)
≥ 65 years of age (N,%)	40 (41.2)	49 (53.8)	38 (37.6)	55 (63.2)
Race (N,%)				
Caucasian	96 (99.0)	88 (96.7)	98 (97.0)	86 (98.9)
Non-Caucasian	1 (1.0)	3 (3.3)	3 (3.0)	1 (1.1)
Sex (N,%)				
Male	64 (66.0)	52 (57.1)	59 (58.4)	52 (59.8)
Female	33 (34.0)	39 (42.9)	42 (41.6)	35 (40.2)
Duration of Parkinson's disease (years)				
Mean ± SD	9.5 ± 4.5	11.6 ± 5.0	10.6 ± 5.0	12.1 ± 6.3
Range	2 - 27	4 - 29	2 - 33	1 - 36
Duration of levodopa treatment (years)				
Mean ± SD	7.5 ± 4.3	9.5 ± 4.5	8.4 ± 5.0	9.6 ± 5.3
Range	1 - 25	1 - 25	1 - 33	1 - 26
Other antiparkinsonian medication (N,%)				
Dopamine agonist	46 (47.4)	50 (54.9)	45 (44.6)	49 (56.3)
Selegiline	53 (54.6)	41 (45.1)	49 (48.5)	35 (40.2)
Anticholinergic	13 (13.4)	7 (7.7)	14 (13.9)	13 (14.9)
Amantadine	10 (10.3)	9 (9.9)	11 (10.9)	8 (9.2)
Other	3 (3.1)	1 (1.1)	1 (1.0)	2 (2.3)

Table 8. Demographic data of the patients enrolled in studies 2939033 and 2939044, tabulated by the use of selegiline

Parameter	2939033 and 2939044 combined			
	Entacapone		Placebo	
	Selegiline (n = 94)	No Selegiline (n = 94)	Selegiline (n = 84)	No Selegiline (n = 104)
Age (years)				
Mean ± SD	62.3 ± 7.1	64.3 ± 8.5	62.2 8.7	63.1 ± 9.7
Range	48.0 - 79.0	30.0 - 81.0	42.0 - 79.0	36.0 - 79.0
< 65 years of age (N,%)	59 (62.8)	40 (42.6)	45 (53.6)	50 (48.1)
≥ 65 years of age (N,%)	35 (37.2)	54 (57.4)	39 (46.4)	54 (51.9)
Race (N,%)				
Caucasian	92 (97.9)	92 (97.9)	84 (100)	100 (96.2)
Non-Caucasian	2 (2.2)	2 (2.1)	0	4 (3.8)
Sex (N,%)				
Male	65(69.1)	51(54.3)	57(67.9)	54(51.9)
Female	29(30.9)	43(45.7)	27(32.1)	50(48.1)
Duration of Parkinson's disease (years)				
Mean ± SD	10.4 ± 4.6	10.6 ± 5.1	11.1 ± 5.5	11.4 ± 5.9
Range	2 - 27	3 - 29	1 - 33	2 - 36
Duration of levodopa treatment (years)				
Mean ± SD	8.4 ± 4.4	8.6 ± 4.5	8.7 ± 5.2	9.1 ± 5.2
Range	1 - 25	2 - 25	1 - 33	1 - 26
Hoehn & Yahr classification (N,%)				
1	1 (1.1)	0	1 (1.2)	0
1.5	9 (9.6)	3 (3.2)	3 (3.6)	5 (4.8)
2	43 (45.7)	41 (43.6)	45 (53.6)	47 (45.2)
2.5	23 (24.5)	17 (18.1)	18 (21.4)	21 (20.2)
3	16 (17.0)	28 (29.8)	15 (17.9)	26 (25.0)
4	2 (2.1)	5 (5.3)	2 (2.4)	5 (4.8)

Table 9. Demographic data of the patients enrolled in studies 2939033 and 2939044, tabulated by the use of dopamine agonists

Parameter	2939033 and 2939044 combined			
	Entacapone		Placebo	
	Dopamine agonist (n = 96)	No Dopamine agonist (n =92)	Dopamine agonist (n = 94)	No Dopamine agonist (n = 94)
Age (years)				
Mean ± SD	63.4 ± 6.8	63.2 ± 8.8	61.4 ± 9.6	64.1 ± 8.8
Range	48.0 - 78.0	30.0 - 81.0	36.0 - 79.0	42.0 - 79.0
< 65 years of age (N,%)	52 (54.2)	47 (51.1)	55 (58.5)	40 (42.6)
≥ 65 years of age (N,%)	44 (45.8)	45 (48.9)	39 (41.5)	54 (57.4)
Race (N,%)				
Caucasian	94 (97.9)	90 (97.8)	94 (100)	90 (95.7)
Non-Caucasian	2 (2.1)	2 (2.2)	0	4 (4.3)
Sex (N,%)				
Male	61(63.5)	55(59.8)	56(59.6)	55(58.6)
Female	35(36.5)	37(40.2)	38(40.4)	39(41.5)
Duration of Parkinson's disease (years)				
Mean ± SD	11.6 ± 4.9	9.4 ± 4.5	12.6 ± 5.2	9.9 ± 5.9
Range	3 - 29	2 - 27	3 - 36	1 - 35
Duration of levodopa treatment (years)				
Mean ± SD	9.6 ± 4.6	7.3 ± 4.1	10.2 ± 5.0	7.7 ± 5.1
Range	1 - 25	2 - 25	1 - 26	1 - 33
Hoehn & Yahr classification (N,%)				
1	1 (1.1)	0	0	1 (1.1)
1.5	3 (3.1)	9 (9.8)	4 (4.3)	4 (4.3)
2	42 (43.8)	42 (45.7)	41 (43.6)	51 (54.3)
2.5	24 (25.0)	16 (17.4)	17 (18.1)	22 (23.4)
3	22 (22.9)	22 (23.9)	29 (30.9)	12 (12.8)
4	4 (4.2)	3 (3.3)	3 (3.2)	4 (4.3)

Table 10. Demographic data of the patients enrolled in studies 2939033 and 2939044, tabulated by weight

Parameter	2939033 and 2939044 combined			
	Entacapone		Placebo	
	< 70 kg (N = 85)	≥70 kg (N = 102)	< 70 kg (N = 97)	≥ 70 kg (N = 91)
Age (years)				
Mean ± SD	62.6 ± 8.5	63.9 ± 7.3	64.6 ± 9.1	60.7 ± 9.0
Range	30 - 77	48 - 81	39 - 79	36 - 77
< 65 years of age (N,%)	47 (55.3)	51 (50.0)	39 (40.2)	56 (61.5)
≥ 65 years of age (N,%)	38 (44.7)	51 (50.0)	58 (59.8)	35 (38.5)
Race (N,%)				
Caucasian	83 (97.6)	100 (98.0)	95 (97.9)	89 (97.8)
Non-Caucasian	2 (2.4)	2 (2.0)	2 (2.1)	2 (2.2)
Sex (N,%)				
Male	27 (31.8)	88 (86.3)	36 (37.1)	75 (82.4)
Female	58 (68.2)	14 (13.7)	61 (62.9)	16 (17.6)
Duration of Parkinson's disease (years)				
Mean ± SD	10.3 ± 4.5	10.7 ± 5.1	11.7 ± 5.7	10.8 ± 5.7
Range	3 - 24	2 - 29	2 - 36	1 - 35
Duration of levodopa treatment (years)				
Mean ± SD	8.4 ± 4.2	8.6 ± 4.7	9.6 ± 5.0	8.2 ± 5.3
Range	1 - 20	1 - 25	1 - 26	1 - 33
Hoehn & Yahr classification (N,%)				
1	0 (0.0)	1 (1.0)	1 (1.0)	0 (0.0)
1.5	7 (8.2)	5 (4.9)	1 (1.0)	7 (7.7)
2	31 (36.5)	53 (52.0)	49 (50.5)	43 (47.3)
2.5	16 (18.8)	23 (22.5)	21 (21.6)	18 (19.8)
3	26 (30.6)	18 (17.6)	19 (19.6)	22 (24.2)
4	5 (5.9)	2 (2.0)	6 (6.2)	1 (1.1)

Table 1.1 Phase III double-blind, placebo-controlled efficacy studies

	Study 2939033 (Nordic study)	Study 2939044 (US-Canadian study)
• Number of centers	• 16	• 18
• Countries	• Denmark, Finland, Norway, and Sweden	• US and Canada
• Objectives	• Efficacy and safety	• Efficacy and safety
• Efficacy Variables: Primary	1) Daily ON time (from home diary) 2) ON time after the first morning dose of levodopa (from home diary)	1) Proportion of daily ON time (from home diary)
Secondary	1) Daily OFF time (from home diary) 2) Global score 3) UPDRS, total and subscores 4) Daily fluctuations in disability scores 5) Average duration of benefit from a single dose of levodopa as evaluated by the patient 6) Total daily levodopa dose (mg) and number of daily levodopa doses 7) Plasma concentrations of 3-OMD 8) Withdrawal effect	1) Daily ON and OFF times (from home diary) 2) Global score 3) UPDRS; total and subscores 4) Daily fluctuations in disability scores 5) Daily levodopa dose 6) Plasma concentrations of 3-OMD 7) Withdrawal effect
• Times of assessment (weeks)	• 0 (baseline), 2, 4, 8, 16, 24, and 26	• 0 (baseline), 2, 4, 8, 16, 24, 26 , and 28
• Patients randomized (n);	• total - active -placebo; 171 - 85 - 86	• total - active -placebo; 205 - 103 - 102
• Discontinued patients(n);	• total - active -placebo; 19 - 8- 11	• total - active -placebo; 24 - 13 - 11

For further details see Attachment D; Synopsis 293933 and Synopsis 293944
E = entacapone, P = placebo

Table 1.2 Efficacy of entacapone: summary of the mean changes from baseline and statistical comparison to placebo in the phase III double-blind, placebo-controlled primary efficacy studies

Variable	Study 2939033			Seesaw 2939044		
	Entacapone	Placebo	Sig	Entacapone	Placebo	Sig
Home diary variables [a]						
ON-time % ITT	+ 9.3	+ 0.6	***	+ 6.7 [b]	+ 2.0	*
% ITT (3h OFF at BL) [c]	nd	nd		+ 8.3	+ 2.6	**
% PP	+ 10.3	+ 2.7	**	+ 8.9	+ 2.9	0.06
ON-time h ITT	+ 1.5 [b]	+ 0.1	***	+ 1.0	+ 0.4	0.06
PP	+ 1.6	+ 0.5	**	+ 1.3	+ 0.5	0.17
OFF-time h ITT	- 1.3	- 0.0	***	- 1.2	- 0.3	**
PP	- 1.5	- 0.3	**	- 1.6	- 0.4	*
Morning levodopa effect h ITT	+ 0.2 [b]	+ 0.0	*	nd	nd	nd
Single dose levodopa benefit h ITT	+ 0.4	-0.1	***	nd	nd	nd
UPDRS at wk 24 ITT						
Total score	- 4.8	- 1.1	**	- 0.6	+ 2.8	*
Motor score	- 3.3	- 0.7	*	- 0.9	+ 1.2	*
ADL-score	- 1.8	- 0.4	*	0.0	+1.1	*
Global score by patient at wk 24						
Improved	39 %	22 %	0.07	31 %	20 %	*
Unchanged	38 %	49 %		38 %	38 %	
Worsened	24 %	28 %		31 %	42 %	
Global score by investigator at wk 24						
Improved	56 %	28 %	**	34 %	21 %	*
Unchanged	29 %	49 %		36 %	40 %	
Worsened	14 %	23 %		30 %	39 %	
Levodopa dose (home diary) [a]						
Total daily dose, change, mg ITT	- 87	+ 14	***	- 93	+ 9	***
Dosing frequency / day ITT	-0.4	+0.1	***	-0.0	+0.2	ns
Proportion of OFF at week 24 (UPDRS question 39) Decreased	39%	12%		24%	17%	
No change	55%	74%	***	61%	63%	
Increased	6	14%		15%	21%	ns

a) For the home diary variables the mean over weeks 8, 16, and 24 is presented
b) Primary efficacy variable
c) Only patients with 3 hours OFF at baseline were included in the analysis, s, nd = not done, *p< 0.05, **p< 0.01, ***p< 0.001

Table 11. * Proportion of daily ON time, daily ON, OFF, ASLEEP and IN BED times for baseline, mean of weeks 8, 16, and 24, and for the endpoint in studies 2939033 and 2939044; Intent-to-Treat analysis, Mean ± SD

Variable	Treatments						Difference between treatments			
	Entacapone (N = 85 in 2939033 and N = 103 in 2939044)			Placebo (N= 86 in 2939033 N = 102 in 2939044)			Mean of weeks 8, 16 and 24 A)		Endpoint B)	
	Baseline	Mean of weeks 8, 16 and 24	Endpoint	Baseline	Mean of weeks 8, 16 and 24	Endpoint	p value	CI 95%	p value	CI 95%
2939033										
* Proportion of daily ON time (%)	62.7 ± 14.6	72.0 ± 14.4	72.1 ± 16.5	63.8 ± 15.8	64.4 ± 16.9	63.9 ± 18.5	0.0003	4.5, 12.2	0.0011	4.2, 13.6
* Daily ON time* (h)	9.3 ± 2.2	10.7 ± 2.2	10.8 ± 2.5	9.2 ± 2.5	9.4 ± 2.6	9.3 ± 2.7	0.0002	0.8, 1.9	0.0004	0.8, 2.2
* Daily OFF time (h)	5.5 ± 2.2	4.2 ± 2.2	4.2 ± 2.6	5.3 ± 2.4	5.2 ± 2.5	5.4 ± 2.8	0.0004	-1.8, -0.7	0.0011	-2.0, -0.6
* IN BED time (h)	3.2 ± 1.6	3.1 ± 1.3	3.0 ± 1.3	3.5 ± 1.7	3.4 ± 1.8	3.3 ± 2.0	0.4563	-0.5, 0.2	0.4034	-0.6, 0.2
2939044										
* Proportion of daily ON time (%)*	60.0 ± 15.2	66.8 ± 14.5	65.2 ± 16.6	60.8 ± 14.0	62.8 ± 16.8	61.8 ± 18.5	0.0163	0.9, 8.0	0.0457	0.1, 8.5
* Daily ON time (h)	10.2 ± 2.5	11.2 ± 2.3	11.0 ± 2.8	10.3 ± 2.5	10.7 ± 2.8	10.5 ± 3.1	0.0633	-0.0, 1.2	0.0651	-0.1, 1.4
* Daily OFF time (h)	6.8 ± 2.8	5.6 ± 2.6	5.9 ± 2.9	6.6 ± 2.4	6.4 ± 3.0	6.5 ± 3.3	0.0070	-1.5, -0.3	0.0310	-1.6, -0.1
* ASLEEP time (h)	7.0 ± 1.7	7.2 ± 1.6	7.1 ± 1.7	7.1 ± 1.5	7.0 ± 1.5	7.0 ± 1.7	0.1074	-0.1, 0.6	0.4601	-0.2, 0.5

18 hour home diary in study 2939033; 24 hour home diary in study 2939044, * Primary efficacy variable
A) Statistical method A, Repeated measures analysis of covariance, ITT-LOCF(BL) B) Statistical method B, Analysis of covariance

Table 14. UPDRS Part IV (Motor fluctuations, Dyskinesias and other complications) at endpoint when compared with baseline in studies * 2939033 and 2939044; Intent-to-Treat Analysis

Change from baseline to endpoint		2939033					2939044				
		Entacapone		Placebo		Difference A) (p value)	Entacapone		Placebo		Difference A) (p value)
		N	(%)	N	(%)		N	(%)	N	(%)	
Motor fluctuations											
* Predictable OFF	Improved	7	8.5	1	1.2	0.0253	5	5.0	7	7.0	0.1796
	No change	75	91.5	85	98.8		86	85.1	88	88.0	
	Worsened	0	0	0	0		10	9.9	5	5.0	
* Unpredictable OFF	Improved	7	8.5	8	9.3	0.8229	25	24.8	18	18.0	0.0886
	No change	71	86.6	72	83.7		67	66.3	66	66.0	
	Worsened	4	4.9	6	7.0		9	8.9	16	16.0	
* Sudden OFF	Improved	8	9.8	9	10.5	0.6201	16	15.8	13	13.0	0.6879
	No change	73	89.0	73	84.9		72	71.3	74	74.0	
	Worsened	1	1.2	4	4.7		13	12.9	13	13.0	
* Proportion OFF	Improved	34	41.5	12	14.0	0.0001	26	25.7	16	16.0	0.0534
	No change	43	52.4	61	70.9		61	60.4	63	63.0	
	Worsened	5	6.1	13	15.1		14	13.9	21	21.0	
Dyskinesias											
* Duration	Improved	9	11.0	7	8.1	0.9759	16	15.8	20	20.0	0.1188
	No change	60	73.2	68	79.1		58	57.4	63	63.0	
	Worsened	13	15.9	11	12.8		27	26.7	17	17.0	
* Disabling	Improved	11	13.4	10	11.6	0.2854	17	17.0	17	17.0	0.9030
	No change	56	68.3	69	80.2		66	66.0	67	67.0	
	Worsened	15	18.3	7	8.1		17	17.0	16	16.0	
Dyskinesias											
* Painful	Improved	12	14.6	9	10.5	0.8050	6	6.0	11	11.0	0.3429
	No change	65	79.3	74	86.0		82	82.0	78	78.0	
	Worsened	5	6.1	3	3.5		12	12.0	11	11.0	
* Early morning dystonia	Improved	9	11.0	11	12.8	0.5747	14	13.9	9	9.0	0.4376
	No change	71	86.6	74	86.0		78	77.2	82	82.0	
	Worsened	2	2.4	1	1.2		9	8.9	9	9.0	
Other Complications											
* Anorexia, nausea, vomiting	Improved	2	2.4	3	3.5	0.3946	3	3.0	4	4.0	0.4507
	No change	75	91.5	80	93.0		86	85.1	87	87.0	
	Worsened	5	6.1	3	3.5		12	11.9	9	9.0	
* Sleep disturbances	Improved	8	9.8	10	11.6	0.3683	13	12.9	13	13.0	0.7767
	No change	67	81.7	72	83.7		75	74.3	76	76.0	
	Worsened	7	8.5	4	4.7		13	12.9	11	11.0	
* Symptomatic orthostatism	Improved	3	3.7	5	5.8	0.2000	9	8.9	12	12.0	0.9987
	No change	74	90.2	79	91.9		84	83.2	77	77.0	
	Worsened	5	6.1	2	2.3		8	7.9	11	11.0	

A) Statistical method D, Cochran-Mantel-Haenszel test

Table 13. UPDRS and Parts I, II and III, and total (Parts I, II and III) at baseline, mean of weeks 8, 16, and 24 with changes and at endpoint for studies 2939033 and 2939044; Intent-to-Treat Analysis

Study 2939033		UPDRS Treatments Entacapone N	Entacapone mean ± SD	Placebo N	Placebo mean ± SD	Difference between treatments p value	Difference between treatments CI 95%
Part I							
Baseline		85	1.8±1.4	86	2.0±1.5		
Week 24	Mean A)	82	1.8±1.4	86	2.2±1.7	0.1063	-0.6, 0.1
	Change	82	-0.0±0.8	86	0.2±1.1		
Endpoint	Mean B)	74	1.9±1.4	77	2.2±1.6	0.1059	-0.6, 0.1
	Change	74	-0.0±0.8	77	0.2±1.2		
Part II							
Baseline		85	11.2±5.0	85	11.0±4.5		
Week 24	Mean A)	82	9.5±5.4	85	10.6±4.8	0.0026	-2.2, -0.6
	Change	82	-1.8±2.7	85	-0.4±2.4		
Endpoint	Mean B)	74	1.9±1.4	77	2.2±1.6	0.0016	-2.5, -0.7
	Change	74	-0.0±0.8	77	0.2±1.2		
Part III							
Baseline		85	25.5±13.1	86	24.6±12.3		
Weeks 8-24	Mean A)	82	22.0±13.7	86	22.8±12.3	0.0364	-3.6, -0.1
	Change	82	-3.7±5.4	86	-1.7±5.1		
Endpoint	Mean B)	85	22.2±13.7	86	23.8±12.7	0.0136	-4.5, -0.6
	Change	85	-3.4±6.0	86	-0.7±6.4		
Total							
Baseline		85	38.5±16.8	85	37.4±15.8		
Week 24	Mean A)	82	34.1±17.7	85	36.3±16.6	0.0070	-6.00, -1.13
	Change	82	-4.8±7.4	85	-1.1±7.3		
Endpoint	Mean B)	74	34.3±18.3	76	36.4±17.2	0.0071	-7.63, -1.43
	Change	74	-5.3±7.7	76	-0.9±8.3		

A) Statistical method A, Repeated measures analysis of covariance, ITT-LOCF(BL)
B) Statistical method B, Analysis of covariance

Table 13. UPDRS and Parts I, II and III, and total (Parts I, II and III) at baseline, mean of weeks 8, 16, 24 with changes and at endpoint for studies 2939033 and 2939044; Intent-to-Treat Analysis

Study		UPDRS Treatments Entacapone N	Entacapone mean ± SD	Placebo N	Placebo mean ± SD	Difference between treatments p value	Difference between treatments CI 95%
Part I							
Baseline		103	1.3±1.2	102	1.5±1.7		
Week 8-24	Mean A)	103	1.5±1.2	102	1.8±1.8	0.5119	-0.4, 0.2
	Change	103	0.2±0.9	102	0.3±0.9		
Endpoint	Mean B)	101	1.5±1.3	100	2.0±2.1	0.3159	-0.5, 0.2
	Change	101	0.3±1.2	100	0.4±1.2		
Part II							
Baseline		103	11.9±6.2	102	11.7±6.7		
Week 8-24	Mean A)	103	11.5±6.4	102	12.1±6.8	0.0849	-1.6, 0.1
	Change	103	-0.3±3.0	102	0.4±3.0		
Endpoint	Mean B)	101	11.9±6.8	100	13.0±7.2	0.0309	-2.3, -0.1
	Change	101	0.0±3.3	100	1.3±4.1		
Part III							
Baseline		103	22.0±11.7	100	22.6±12.0		
Weeks 8-24	Mean A)	103	21.1±11.2	100	22.9±11.9	0.1415	-3.1, 0.5
	Change	103	-0.9±6.8	100	0.3±6.8		
Endpoint	Mean B)	101	21.0±12.2	98	23.3±13.2	0.1156	-4.4, 0.5
	Change	101	-1.0±8.2	98	0.9±7.2		
Total							
Baseline		103	35.1±15.9	100	35.6±17.2		
Week 8-24	Mean A)	102	34.1±16.1	100	36.6±17.7	0.0724	-4.26, 0.21
	Change	103	-1.0±8.2	100	1.0±8.0		
Endpoint	Mean B)	101	34.3±17.2	98	38.1±19.4	0.0384	-6.28, -0.19
	Change	101	-0.7±9.6	98	2.6±9.2		

A) Statistical method A, Repeated measures analysis of covariance, ITT-LOCF(BL)
B) Statistical method B, Analysis of covariance

Table 16. Patient's and Physician's Global evaluation scores at endpoint when compared to baseline in studies 2939033 and 2939044; Intent-to-Treat Analysis

Patient's evaluation

Change from baseline to endpoint	Number (%) of patients in each category Entacapone		Placebo		Difference between treatments A)
2939033	n = 85		n = 85		
	n	(%)	n	(%)	p value
Improved	33	38.8	19	22.4	0.0372
No change	31	36.5	38	44.7	
Worsened	21	24.7	28	32.9	
2939044	N=101		N=100		
	N	(%)	N	(%)	
Improved	33	32.7	20	20.0	0.0610
No change	34	33.7	38	38.0	
Worsened	34	33.7	42	42.0	

A) Statistical method D, Cochran-Mantel-Haenszel test
Reference: Attachment B, Statistical table 1.2

Physician's evaluation

Change from baseline to endpoint	Number (%) of patients in each category Entacapone		Placebo		Difference between treatments B)
2939033	n = 85		n = 86		
	n	(%)	n	(%)	p value
Improved	49	57.6	24	27.9	0.0006
No change	23	27.1	40	46.5	
Worsened	13	15.3	22	25.6	
2939044	N = 101		N = 100		
	N	(%)	N	(%)	
Improved	37	36.6	20	20.0	0.0353
No change	30	29.7	39	39.0	
Worsened	34	33.7	41	41.0	

B) Statistical method D, Cochran-Mantel-Haenszel test

Table 31. UPDRS Parts II, III, and total (Parts I, II, and III) at baseline and at 1 year in studies 2939034 and 2939054; Intent-to-Treat Analysis

	UPDRS ADL (Part II)	UPDRS Motor score (Part III)	UPDRS TOTAL (Parts I, II, and III)
2939034			
- Baseline (N = 132)	11.0 ± 5.1	26.7 ± 12.5	39.6 ± 16.6
- At 1 year (N = 96)	10.4 ± 5.1	28.0 ± 12.6	40.3 ± 16.3
- Difference between baseline and 1 year (N = 95)	-0.4 ± 3.1	-0.2 ± 6.7	-0.6 ± 8.2
2939054			
- Baseline (N = 167)	13.0 ± 7.0	23.3 ± 12.8	38.1 ± 18.5
- At 1 year (N = 103)	13.1 ± 7.0	22.0 ± 13.6	37.6 ± 19.3
- Difference between baseline and 1 year (N = 103)	0.4 ± 4.1	-2.1 ± 10.6	-1.6 ± 13.3

Table 12. Proportion of daily ON time at baseline and at weeks 8, 16, and 24 in studies 2939033 and 2939044; Intent-to-Treat Analysis

	Proportion of daily on time (%)					
	Entacapone		Placebo		Difference between treatments[A]	
	N	mean ± SD	N	mean ± SD	p value	CI 95%
[illegible]	85	62.7 ± 14.6	86	63.8 ± 15.8	-	-
• Week 8*	83	72.0 ± 14.8	81	65.6 ± 17.5	0.0026	3.1, 12.2
• Week 16*	79	72.2 ± 15.8	77	65.9 ± 18.2	0.0023	3.3, 12.5
• Week 24*	77	72.0 ± 16.3	75	64.7 ± 18.4	0.0008	4.4, 13.7
• Change between baseline and Week 24	77	10.0 ± 15.1	75	0.3 ± 15.4	-	-
2939044						
• Baseline	103	60.0 ± 15.2	102	60.8 ± 14.0	-	-
• Week 8*	96	68.3 ± 15.1	98	64.6 ± 17.8	0.0396	0.3, 9.1
• Week 16*	92	67.8 ± 17.6	95	63.4 ± 18.2	0.0229	0.8, 9.8
• Week 24*	90	65.4 ± 17.1	92	62.2 ± 18.5	0.0483	0.0, 9.1
• Change between baseline and Week 24	90	5.3 ± 16.5	92	0.8 ± 12.3	-	-

A) Statistical method A, Repeated measures analysis of covariance, ITT-OC
*Statistical significance levels are: 0.0167 (5%), 0.0033 (1%) and 0.0003 (0.1%)

Table 15. Duration of dyskinesias (% of patients) in studies 2939033 and 2939044; ITT-LOCF(BL)

Study -33 Treatment group	Visit	Percent of patients with dyskinesias			
		None	1-25% of the day	26-50 % of the day	51-100 % of the day
Entacapone (N=85)	Baseline	32.9	42.4	18.8	5.9
	Week 2	29.4	38.8	20.0	11.8
	Week 24	30.6	41.2	18.8	9.4
Placebo (N=86)	Baseline	36.0	38.4	18.6	7.0
	Week 2	34.9	34.9	24.4	5.9
	Week 24	33.7	39.5	17.4	9.3

Study -44 Treatment	Time	Percent of patients with dyskinesias			
		None	1-25 % of the day	26-50 % of the day	>50 % of the day
[illegible]one	Baseline	27	52	9	12
	Week 2	26	35	22	17
	Week 24	28	37	21	14
[illegible]bo (N=102)	Baseline	31	39	22	8
	Week 2	32	43	19	6
	Week 24	33	39	14	14

APPEARS THIS WAY
ON ORIGINAL

Table 17. Daily levodopa dose and the number of daily doses from home diary at baseline and at weeks 8, 16 and 24 in studies 2939033 and 2939044; Intent-to-Treat Analysis

	Entacapone			Placebo		
	n	Daily dose of levodopa (mg) (Mean ± SD)	Number of doses (Mean ± SD)	n	Daily dose of levodopa (mg) (Mean ± SD)	Number of doses (Mean ± SD)
2939033						
Baseline	85	701.3 ± 293.4	6.2 ± 1.8	86	705.3 ± 283.0	6.1 ± 1.7
Week 8	83	599.4 ± 244.3	5.6 ± 1.6	81	717.0 ± 297.5	6.2 ± 1.8
Week 16	79	598.7 ± 237.7	5.6 ± 1.5	78	729.0 ± 307.3	6.3 ± 1.8
Week 24	77	612.4 ± 228.5	5.7 ± 1.5	75	738.2 ± 326.2	6.3 ± 2.0
Mean Weeks 8, 16, 24	83	604.8 ± 245.2	5.7 ± 1.5	81	726.3 ± 304.7	6.3 ± 1.8
2939044						
Baseline	103	803.5 ± 387.5	6.2 ± 2.0	102	757.7 ± 434.6	6.0 ± 1.9
Week 8	96	710.0 ± 322.0	6.2 ± 2.0	98	779.2 ± 465.5	6.1 ± 2.1
Week 16	92	709.9 ± 341.7	6.2 ± 2.0	95	782.5 ± 455.1	6.1 ± 2.1
Week 24	90	710.7 ± 342.7	6.2 ± 2.0	92	797.4 ± 458.8	6.0 ± 1.9
Mean Weeks 8, 16, 24	96	711.8 ± 330.0	6.2 ± 1.9	98	788.0 ± 456.8	6.2 ± 2.0

24-hour home diary in 2939044; 18-hour home diary in 2939033.
Only observed cases at visit included in the analysis

Table 18. Average scheduled daily levodopa dose and the number of daily doses at baseline and at weeks 8, 16 and 24 in studies 2939033 and 2939044; Intent-to-Treat Analysis

	Entacapone			Placebo		
	n	Daily dose of levodopa (mg) (Mean ± SD)	Number of doses (Mean ± SD)	n	Daily dose of levodopa (mg) (Mean ± SD)	Number of doses (Mean ± SD)
2939033						
Baseline	85	698.5 ± 294.2	6.1 ± 1.7	86	723.3 ± 305.7	6.3 ± 1.7
Week 8	83	610.2 ± 247.7	5.7 ± 1.6	81	734.6 ± 334.2	6.3 ± 1.9
Week 16	80	605.0 ± 234.0	5.7 ± 1.7	78	752.6 ± 339.3	6.4 ± 1.9
Week 24	77	618.5 ± 235.1	5.7 ± 1.5	77	752.6 ± 342.8	6.4 ± 2.0
Mean Weeks 8, 16, 24	83	614.7 ± 248.7	5.8 ± 1.6	81	742.8 ± 333.6	6.4 ± 1.8
2939044						
Baseline	103	791.0 ± 374.7	6.1 ± 1.9	102	752.1 ± 434.7	6.0 ± 1.9
Week 8	100	702.3 ± 316.7	6.1 ± 1.8	98	767.1 ± 461.1	5.9 ± 1.9
Week 16	95	704.5 ± 336.7	6.1 ± 1.8	97	771.0 ± 449.7	5.9 ± 1.8
Week 24	91	691.8 ± 347.4	6.1 ± 2.0	92	782.6 ± 447.9	5.9 ± 1.7
Mean Weeks 8, 16, 24	100	699.1 ± 320.3	6.1 ± 1.9	98	775.9 ± 451.1	6.0 ± 1.8

Only observed cases at visit included in the analysis

Table 19. Daily dose of entacapone at weeks 2, 4, 8, 16 and 24 in studies 2939033 and 2939044; Intent-to-Treat Analysis

	N	Average daily dose of entacapone (mg)
2939033		
Week 2	85	1186±332
Week 4	84	1160±325
Week 8	83	1137±317
Week 16	80	1138±313
Week 24	77	1145±305
2939044		
Week 2	103	1212±371
Week 4	101	1216±371
Week 8	100	1216±368
Week 16	95	1194±363
Week 24	91	1204±383

Only observed cases at visit included in the analysis

BEST POSSIBLE COPY

Table 3.2. Overall extent of exposure to entacapone and placebo in the phase III controlled efficacy studies -33 and -44

Treatment duration (weeks)	Entacapone			Placebo		
	2939033 (n=85)	2939044 (n=103)	Total (n=188)	2939033 (n=86)	2939044 (n=102)	Total (n=188)
< 1	85	103	188	86	102	188
≥ 1	85	101	186	86	102	188
≥ 4	84	99	183	84	99	183
≥ 8	82	96	178	81	98	179
≥ 12	81	93	173	78	97	175
≥ 16	77	92	168	77	92	169
≥ 20	77	91	168	76	92	168
≥ 24 a)	75	88	163	71	92	163
≥ 26	6	35	41	2	91	93

Patients attending visits as scheduled a) Primary study end-point

Table 3.3 Overall extent of exposure (by daily dose and number of tablets) to entacapone in phase III studies -33 and -44

Treatment duration (weeks)	Number of patients by daily dose of entacapone				
	400 - 600 mg (2 - 3 tablets)	800 - 1000 mg (4 - 5 tablets)	1200 - 1400 mg (6 - 7 tablets)	1600 - 1800 mg (8 - 9 tablets)	2000 mg (10 tablets)
< 1	3	90	62	24	9
≥ 1	3	88	61	24	9
≥ 4	3	87	61	23	9
≥ 8	3	86	60	22	8
≥ 12	3	84	56	22	8
≥ 16	3	84	53	22	7
≥ 20	3	84	53	22	7
≥ 24	3	78	53	22	7

Patients attending visits as scheduled

Table 7.17 Changes in the efficacy variables two weeks after withdrawal in study -33

Variable	Entacapone (n=77)		Placebo (n=76)		Significance
	Week 24 Mean ± SD	Change Mean ± SD	Week 24 Mean ± SD	Change Mean ± SD	
Home diary parameters:					
Daily ON time (h)	10.7 ± 2.4	-1.6 ± 2.4	9.4 ± 2.8	-0.2 ± 1.8	p<0.001
Proportion of ON time (%)	72.0 ± 16.3	-10.2 ± 14.9	64.7 ± 18.4	-1.9 ± 11.4	p<0.001
aily OFF time (h)	4.2 ± 2.5	1.4 ± 2.1	5.2 ± 2.8	0.3 ± 1.6	p<0.001
N time after the first orning dose of levodopa (h)	2.3 ± 0.9	-0.3 ± 0.6	2.1 ± 0.9	-0.1 ± 0.6	p=0.07
Levodopa dose (mg)	612 ± 229	51 ± 105	738 ± 326	2 ± 33	p<0.01
UPDRS					
ADL (Part II)	9.1 ± 5.2	1.8 ± 2.4	10.3 ± 4.8	0.3 ± 1.7	p<0.001
Motor (Part III)	23.3 ± 14.0	3.1 ± 6.1	23.9 ± 13.2	0.0 ± 5.6	p<0.01
Total (Parts I, II, and III)	34.3 ± 18.3	4.9 ± 7.0	36.4 ± 17.2	0.1 ± 6.0	p<0.001
Global by patient (%)					
worsened	-	63%	-	24%	p<0.001
no change	-	29%	-	57%	
improved	-	8%	-	20%	
Global by investigator (%)					
worsened	-	68%	-	24%	p<0.001
no change	-	21%	-	62%	
improved	-	11%	-	14%	

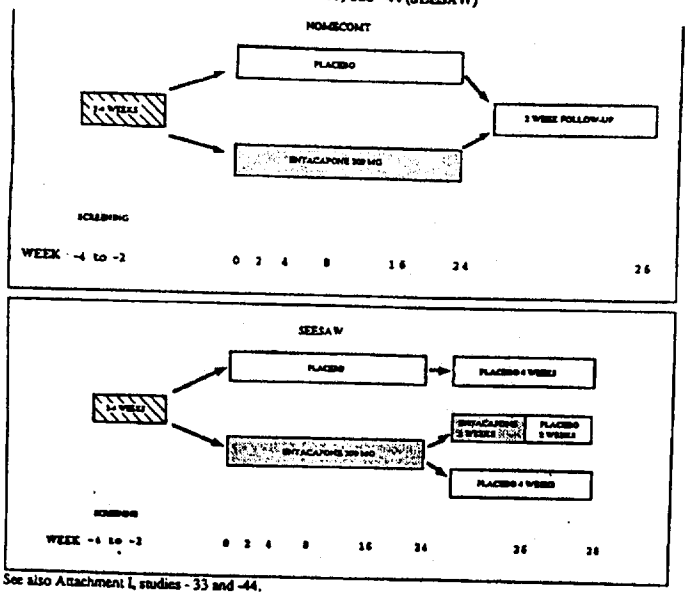
Reference: Study Report 2939033. *Post-text Tables 21, 22 and 23*

Table 7.18 Changes in the efficacy variables two weeks after withdrawal in study -44

Variable	Entacapone		Placebo		Significance
	Week 24 Mean ± SD (n=44) 1)	Change Mean ± SD	Week 24 Mean ± SD (n=92)	Change Mean ± SD	
Home diary parameters:					
Daily ON time (h)	11.1 ± 2.6	-1.3 ± 2.9	10.5 ± 3.1	-0.2 ± 1.7	p<0.001
Proportion of ON time (%)	66.3 ± 15.0	-15.2 ± 9.6	62.2 ± 18.5	-1.3 ± 9.6	p<0.01
Daily OFF time (h)	5.7 ± 2.7	1.3 ± 2.5	6.4 ± 3.3	0.2 ± 1.9	p<0.01
Levodopa dose (mg)	655 ± 283	86 ± 178	797 ± 459	-1 ± 90	p<0.05
	At withdrawal (n=91)		At withdrawal (n=92)		
UPDRS					
ADL (Part II)	11.7 ± 6.3	0.9 ± 3.3	12.7 ± 7.3	0.0 ± 2.4	p<0.05
Motor	20.5 ± 11.2	3.0 ± 8.0	23.2 ± 13.4	0.1 ± 6.6	p<0.05
Total	33.7 ± 15.7	4.2 ± 9.2	37.7 ± 19.7	0.0 ± 7.8	p<0.01
Global by patient (%)					
worsened	-	67%	-	35%	p<0.001
no change	-	26%	-	42%	
improved	-	7%	-	23%	
Global by investigator (%)					
worsened	-	75%	-	30%	p<0.001
no change	-	19%	-	46%	
improved	-	6%	-	24%	

ence: Study Report 2939044, *Post-text Tables 21, 22 and 23*
ithdrawal home-diary was collected only for patients withdrawn at week 24

Figure 5.1 Designs of studies - 33 (NOMECOMT) and - 44 (SEESAW)



See also Attachment I, studies - 33 and -44.

Figure 5.2 Time schedule of efficacy-related assessments in study -33

STUDY VISITS	Screening visit	1a)	2	3	4	5	6	Post study visit
STUDY WEEKS	-4 to -2	0	2	4	8	16	24	26
Recording of medication	X	X	X	X	X	X	X	X
Diary review		X	X	X	X	X	X	X
UPDRS (Parts I-VI)	X	X					X	X
UPDRS (Parts III and IV)			X	X	X	X		
Daily fluctuations in disability	X	X	X	X	X	X	X	X
Global evaluation		X	X	X	X	X	X	X
3-OMD concentration		X		X	X	X	X	X

a) baseline evaluation

Figure 5.3 Time schedule of efficacy-related assessments in study -44

STUDY VISITS	Screening visit	1a)	2	3	4	5	6	7	8
STUDY WEEKS	-4 to -2	0	2	4	8	16	24	26	28
Recording of medication	X	X	X	X	X	X	X	X	X
Diary review		X	X	X	X	X	X	X	X
UPDRS (Parts I-VI)	X	X	X	X	X	X	X	X	X
Daily fluctuations in disability	X	X	X	X	X	X	X	X	X
Global evaluation		X	X	X	X	X	X	X	X
3-OMD concentration		X		X	X	X	X	X	X

a) baseline evaluation

Table 5.1 Inclusion criteria in primary studies -33 and -44

Study 2939033	Study 2939044
• Idiopathic PD	• Idiopathic PD
• H & Y 1.5-4.0 in ON state	• H & Y 1.5-4.0 in OFF state
• Levodopa responsive	• Levodopa responsive
• Motor fluctuations	• Motor fluctuations
• Stable levodopa treatment, 4 - 10 doses/day	• Stable levodopa treatment, 4 - 10 doses/day
• Standard levodopa/carbidopa or levodopa/benserazide preparations	• Standard levodopa/carbidopa preparations
• Other antiparkinsonian drugs	• Other antiparkinsonian drugs
• Average ON time after a single levodopa dose less than 1 hours	• ≥ 3 hours OFF time (Amendment 3)

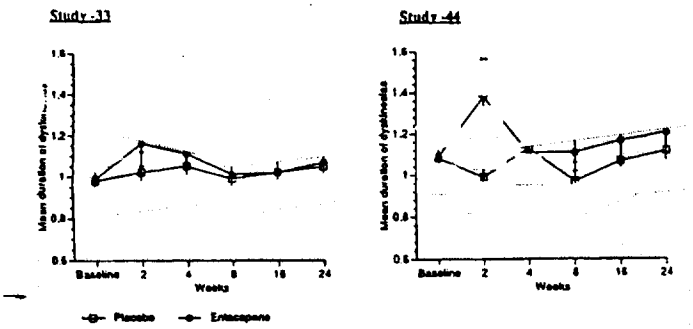
Table 7.2 Disposition of patients in studies -33 and -44

	Study -33		Study -44		Combined studies	
Patient disposition	Entacapone n (%)	Placebo n (%)	Entacapone n (%)	Placebo n (%)	Entacapone n (%)	Placebo n (%)
Enrolled	85	86	103	102	188	188
Discontinued	8 (9.4)	11 (12.8)	13 (12.6)	11 (10.8)	21 (11.1)	22 (11.7)
adverse event	6 (7.0)	5 (5.8)	11 (10.8)	7 (6.9)	17 (9.0)	12 (6.4)
other reasons	2 (2.4)	6 (7.0)	2 (1.9)	4 (3.9)	3 (1.6)	10 (5.3)
Completed	77 (90.5)	75 (87.2)	90 (87.4)	91 (89.2)	167 (88.8)	166 (88.3)
Evaluated for efficacy	85 (100)	86 (100)	103 (100)	102 (100)	188 (100)	188 (100)

Reference: Study reports -33 and -44

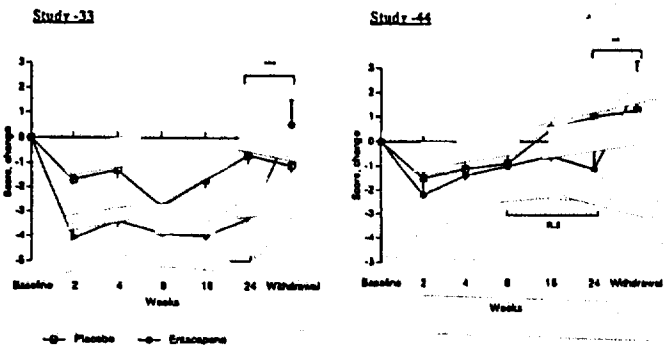
Table 6.1 Differences between the LOCF(BL) and endpoint populations

	LOCF(BL)	Endpoint
Patients with only baseline measurement	included	not included
Patients, who completed the study, but had missing scheduled measurements	no imputation	the last prior observation available is carried forward
Patients, who prematurely discontinued	baseline is carried forward	the last prior observation available is carried forward



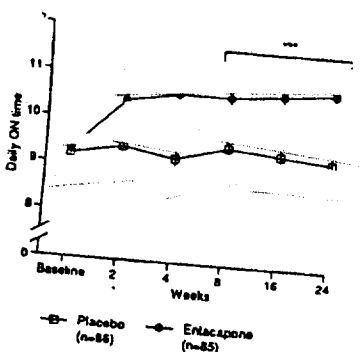
ITT analysis, mean ± SEM
Reference: Study Reports 2939033 and 2939044

Figure 7.4 The duration of dyskinesias (UPDRS Part IV) in studies -33 and -44



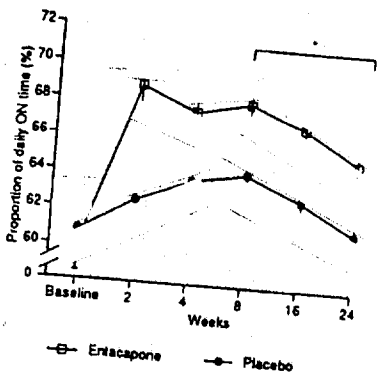
ITT-analysis, Mean ± SEM
*p<0.05, **p<0.01, ***0.001

Figure 7.5 Changes from baseline in the UPDRS motor scores in studies -44 and -33 (observed cases)



-analysis, Mean ± SEM
ference between the groups ***p<0.001

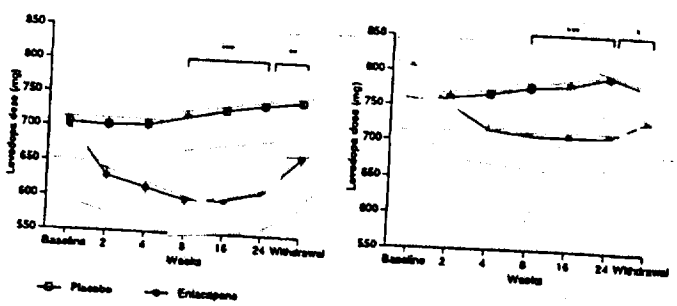
are 7.1 Daily ON time in hours during the 18-hour diary day in study -33



Mean ± SEM, * p<0.05

Figure 7.2 Proportion of daily ON time during the 24-hour diary day in study -44

Study -33
Study -44



ITT analysis, Mean ± SEM
***p< 0.001 compared with placebo

Figure 7.3 Daily levodopa dose from home diaries in studies -33 and -44 (observed cases)

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

Table 7.3 Daily ON time in hours during the 18-hour diary day in study -33

Visit	Entacapone (N=85)	Placebo (N=86)	Difference (CI 95%)	Significance
Baseline	9.3 ± 2.2	9.2 ± 2.5		
Mean for weeks 8, 16, and 24	10.7 ± 2.2	9.4 ± 2.6	1.3 (0.8, 1.9)	p<0.001
- change from baseline	1.5 ± 1.9	0.1 ± 2.0		
Endpoint	10.8 ± 2.5	9.3 ± 2.7	1.5 (0.8, 2.2)	p<0.001
- change from baseline	1.5 ± 2.4	0.0 ± 2.3		

Mean ± SD

Table 7.4 ON time in hours after the first morning dose of levodopa in study -33

Visit	Entacapone (N=85)	Placebo (N=86)	Difference (CI 95%)	Significance
Baseline	2.1 ± 0.7	2.2 ± 0.9		
Mean for weeks 8, 16, and 24	2.3 ± 0.7	2.1 ± 0.9	0.2 (0.1, 0.4)	p<0.05
- change from baseline	0.2 ± 0.6	0.0 ± 0.5		
Endpoint	2.2 ± 0.8	2.1 ± 0.9	0.2 (0.0, 0.5)	p<0.05
- change from baseline	0.2 ± 0.7	-0.1 ± 0.7		

Mean ± SD

Table 7.5 Proportion of daily ON time during the 24-hour diary day in study -44

Visit	Entacapone (n=103)	Placebo (n=102)	Difference (CI 95%)	Significance
Baseline	60.0 ± 15.2	60.8 ± 14.0		
Mean for weeks 8, 16, and 24	66.8 ± 14.5	62.8 ± 16.8	4.5 (0.9, 8.0)	p<0.05
- change from baseline	6.7 ± 14.0	2.0 ± 11.1		
Endpoint	65.2 ± 16.6	61.8 ± 18.5	4.3 (0.1, 8.5)	p<0.05
- change from baseline	5.1 ± 16.3	0.5 ± 12.8		

Mean ± SD

Table 7.6 Proportion of daily ON time during the 18-hour diary day in study -33

Visit	Entacapone (n=85)	Placebo (n=86)	Difference (CI 95%)	Significance
Baseline	62.7 ± 14.6	63.8 ± 15.8		
Mean for weeks 8, 16, and 24	72.0 ± 14.4	64.4 ± 16.9	8.3(4.5, 12.2)	p<0.001
- change from baseline	9.3 ± 12.4	0.6 ± 13.0		
Endpoint	72.1 ± 16.5	63.9 ± 18.5	8.9(4.2, 13.6)	p<0.01
- change from baseline	9.4 ± 15.1	0.2 ± 15.5		

Mean ± SD

Table 7.7 Daily ON time in hours during the 24-hour diary day in study - 44

Visit	Entacapone (n=103)	Placebo (n=102)	Difference (CI 95%)	Significance
Baseline	10.2 ± 2.5	10.3 ± 2.5		
Mean for weeks 8, 16, and 24	11.2 ± 2.3	10.7 ± 2.8	0.6 (-0.0, 1.2)	p=0.06
- change from baseline	1.0 ± 2.3	0.4 ± 1.8		
Endpoint	11.0 ± 2.8	10.5 ± 3.1	0.7 (-0.1, 1.4)	p=0.07
- change from baseline	0.8 ± 2.9	0.1 ± 2.1		

Mean ± SD

Table 7.8 OFF time in hours during the 18-hour diary day in study -33

Visit	Entacapone (n=85)	Placebo (n=86)	Difference (CI 95%)	Significance
Baseline	5.5 ± 2.2	5.3 ± 2.4		
Mean for weeks 8, 16, and 24	4.2 ± 2.2	5.2 ± 2.5	-1.2 (-1.8, -0.7)	p<0.001
- change from baseline	-1.3 ± 1.8	0.0 ± 1.9		
Endpoint	4.2 ± 2.6	5.4 ± 2.8	-1.3 (-2.0, -0.6)	p<0.01
- change from baseline	-1.3 ± 2.2	0.1 ± 2.3		

Mean ± SD

Table 7.9 OFF time in hours during the 24-hour diary day in study -44

Visit	Entacapone (n=103)	Placebo (n=102)	Difference (CI 95%)	Significance
Baseline	6.8 ± 2.8	6.6 ± 2.4		
Mean for weeks 8, 16, and 24	5.6 ± 2.6	6.4 ± 3.0	-0.9 (-1.5, -0.3)	p<0.01
- change from baseline	-1.2 ± 2.4	-0.3 ± 2.0		
Endpoint	5.9 ± 2.9	6.5 ± 3.3	-0.8 (-1.6, -0.1)	p<0.05
- change from baseline	-0.9 ± 2.7	0.0 ± 2.4		

Table 7.12 Distribution of patients by at least one category change[a] in global score as evaluated by patient and investigator in study -33

Measurement	Patients evaluation			Investigators evaluation		
	Entacapone (n=103)	Placebo (n=102)	Sig.	Entacapone (n=103)	Placebo (n=102)	Sig.
Weeks 8-24[b]						
Worsened (%)	10.6	8.1	p=0.30	2.4	5.8	p<0.001
Unchanged (%)	65.9	79.1		56.5	79.1	
Improved (%)	23.5	12.8		41.2	15.1	
Endpoint						
Worsened (%)	24.7	32.9	p<0.05	15.3	25.6	p<0.001
Unchanged (%)	36.5	44.7		27.1	46.5	
Improved (%)	38.8	22.4		57.6	27.9	

a) change= change (improvement or worsening) by at least one category from baseline b) Improvement or worsening from baseline by at least one category in patients' condition on each of weeks 8, 16, and 24.
Reference: Study Report 2939033, *Post-text Table 16*

Table 7.13 Distribution of patients by at least one category change[a] in global score as evaluated by patient and investigator in study -44

Measurement	Patients evaluation			Investigators evaluation		
	Entacapone (n=103)	Placebo (n=102)	Sig.	Entacapone (n=103)	Placebo (n=102)	Sig.
Weeks 8-24[b]						
Worsened (%)	11.7	18.6	p<0.05	12.6	14.7	p=0.12
Unchanged (%)	70.9	74.5		68.0	75.5	
Improved (%)	17.5	6.9		19.4	9.8	
Endpoint						
Worsened (%)	33.7	42.0	p=0.06	33.7	41.0	p<0.05
Unchanged (%)	33.7	38.0		29.7	39.0	
Improved (%)	32.7	20.0		36.6	20.0	

a) change= change (improvement or worsening) by at least one category from baseline
b) Improvement or worsening from baseline by at least one category in patients' condition on each of weeks 8, 16, and 24.
Reference: *Post-text Table 16*

Table 7.14 Daily levodopa dose and dosing frequency from 18-hour home diaries in study -33

	Baseline		Change from baseline over weeks 8,16, and 24		
Variable	Entacapone (n = 85)	Placebo (n = 86)	Entacapone (n = 85)	Placebo (n = 86)	Significance
Dose (mg)	701 ± 293	705 ± 283	-87.1 ± 127	14.4 ± 92	p<0.001
Dosing frequency (doses/day)	6.2 ± 1.8	6.1 ± 1.7	-0.4 ± 0.8	+0.1 ± 0.7	p<0.001

Mean ± SD
Reference: Study Report 2939033, *Post-text Table 17*, Attachment B, Statistical Table 5.2

Table 7.15 Daily levodopa dose and dosing frequency from home diaries in study -44

	Baseline		Change from baseline over weeks 8,16, and 24		
Variable	Entacapone (n = 103)	Placebo (n = 102)	Entacapone (n = 103)	Placebo (n = 102)	Significance
Dose (mg)	803 ± 387	758 ± 435	-93.4 ±184.0	9.4 ± 107.6	p<0.001
Dosing frequency (doses/day)	6.2 ± 2.0	6.0 ± 1.9	-0.0 ± 0.6	0.2 ± 0.8	p=0.24

Mean ± SD
Reference: Study report 2939044, *Post-text Table 17*, Attachment B, Statistical Table 5.2

Table 7.10 **UPDRS scores at baseline and after 24 weeks treatment with changes from baseline by week 24 and by endpoint in study -33**

Variable/visit		Entacapone (n=85)	Placebo (n=86)	Significance
UPDRS I	Baseline	1.8 ± 1.4	2.0 ± 1.5	
	Week 24	1.8 ± 1.4	2.2 ± 1.7	
	Change by week 24	-0.0 ± 0.8	0.2 ± 1.1	p=0.11
	Change by endpoint	-0.0 ± 0.8	0.2 ± 1.2	p=0.11
UPDRS II	Baseline	11.2 ± 5.0	11.0 ± 4.5	
	Week 24	9.5 ± 5.4	10.6 ± 4.8	
	Change by week 24	-1.8 ± 2.7	-0.4 ± 2.4	p<0.01
	Change by endpoint	-0.0 ± 0.8	0.2 ± 2	p<0.01
UPDRS III	Baseline	25.5 ± 3.1	24.6 ± 12.3	
	Week 24	22.5 ± 13.8	23.8 ± 12.7	
	Change by week 24	-3.3 ± 6.0	-0.7 ± 6.3	p<0.05
	Change by endpoint	-3.4 ± 6.0	-0.7 ± 6.4	p<0.05
Total (I-III)	Baseline	38.5 ± 16.8	37.4 ± 15.8	
	Week 24	34.1 ± 17.7	36.3 ± 16.6	
	Change by week 24	-4.8 ± 7.4	-1.1 ± 7.3	p<0.01
	Change by endpoint	-5.3 ± 7.7	-0.9 ± 8.3	p<0.01

Mean ± SD
Reference: Study Report 2939033, *Post-text Table 13*

Table 7.11 **UPDRS scores at baseline, during treatment over weeks 8, 16, and 24, and the changes from baseline as a mean over weeks 8,16, and 24 and at endpoint in study -44**

Variable/visit		Entacapone (n=103)	Placebo (n=102)	Significance
UPDRS I	Baseline	1.3 ± 1.2	1.5 ± 1.7	
	Weeks 8-24	1.5 ± 1.2	1.8 ± 1.8	
	Change by weeks 8-24	0.2 ± 0.9	0.3 ± 0.9	p=0.51
	Change by endpoint	0.3 ± 1.2	0.4 ± 1.2	p=0.32
UPDRS II	Baseline	11.9 ± 6.2	11.7 ± 6.7	
	Weeks 8-24	11.5 ± 6.4	12.1 ± 6.8	
	Change by weeks 8-24	-0.3 ± 3.0	0.4 ± 3.0	p=0.08
	Change by endpoint	0.0 ± 3.3	1.1 ± 4.0	p<0.05
UPDRS III	Baseline	22.0 ± 11.7	22.6 ± 12.0	
	Weeks 8-24	21.1 ± 11.2	22.9 ± 11.9	
	Change by weeks 8-24	- 0.9 ± 6.8	0.3 ± 6.8	p=0.14
	Change by endpoint	-1.0 ± 8.2	0.9 ± 7.2	p=0.12
Total (I-III)	Baseline	35.1 ± 15.9	35.6 ± 17.2	
	Weeks 8-24	34.1 ± 16.1	36.6 ± 17.7	
	Change by weeks 8-24	-1.0 ± 8.2	-1.0 ± 8.0	p=0.07
	Change by endpoint	-0.7 ± 9.6	2.6 ± 9.2	p<0.05

Mean ± SD
Reference: Study Report 2939044, *Post-text Table 13*

SCHEDULE OF ASSESSMENTS

STUDY 33

JDY ,ITS	Screening	1	2	3	4	5	6	Post study
STUDY WEEKS	-2 to -4	0	2	4	8	16	24	26
STUDY DISIGN								
Individual levodopa medication	X---------->							
Entacapone/placebo medication		X---------->					X	
SCREENING								
Informed consent	X							
Inclusion/exclusion	X							
EFFICACY MEASURES								
Recording of medication	X	X	X	X	X	X	X	X
UPDRS, parts I-VI	X	X					X	X
UPDRS, parts III and IV			X	X	X	X		
Daily fluctuations in disability	X	X	X	X	X	X	X	X
Diary review		X	X	X	X	X	X	X
Global evaluation		X	X	X	X	X	X	X
SAFETY MEASURES								
Hematology/biochemistry	X	X		X	X	X	X	X
Plasma 3-OMD		X		X	X	X	X	X
Tablet count			X	X	X	X	X	
Blood pressure, heart rate, ECG	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X

Summary efficacy:	Summary of efficacy results in study 2939033.				
	Efficacy variables from home diaries				
	Entacapone		Placebo		
	Baseline	mean over weeks 8, 16, and 24	Baseline	mean over weeks 8, 16, and 24	Difference between treatments over weeks 8, 16 and 24 (ANOVA) p [CI95%]
Daily ON time (h)	9.3 ± 2.2	10.7 ± 2.2	9.2 ± 2.5	9.4 ± 2.6	p<0.001 [0.8; 1.9]
Proportion of daily ON time (%)	62.7 ± 14.6	72.0 ± 14.4	63.8 ± 15.8	64.4 ± 16.9	p<0.001 [4.5; 12.2]
Daily OFF time (h)	5.5 ± 2.2	4.2 ± 2.2	5.3 ± 2.4	5.2 ± 2.5	p<0.001 [-1.8; -0.6]
ON time (h) after the first morning dose of levodopa	2.1 ± 0.7	2.3 ± 0.7	2.2 ± 0.9	2.1 ± 0.9	p<0.05 [0.1; 0.4]
Duration of benefit (h) of a single dose of levodopa	2.4 ± 0.7	2.8 ± 0.8	2.3 ± 0.8	2.2 ± 0.8	p<0.001 [0.2; 0.7]
	Efficacy variables from home diaries at withdrawal				
	Entacapone		Placebo		
Scheduled L-dopa dosing:	Visit week 24	Withdrawal	Visit week 24	Withdrawal	Difference between treatments after withdrawal (ANOVA) p [CI95%]
Daily ON time (h)	10.7 ± 2.4	9.1 ± 2.7	9.4 ± 2.8	9.3 ± 2.9	p<0.001 [-2.2; -0.7]
Proportion of ON time (%)	72.0 ± 16.3	61.6 ± 17.6	64.7 ± 18.4	62.7 ± 18.1	p<0.01 [-13.0; -3.8]
Daily OFF time (h)	4.2 ± 2.5	5.6 ± 2.6	5.2 ± 2.8	5.5 ± 2.7	p<0.01 [0.5; 1.8]
ON time (h) after the first morning dose of levodopa	2.3 ± 0.9	2.0 ± 0.8	2.1 ± 0.9	2.0 ± 0.9	NS [-0.4; 0.02]
Duration of benefit (h) of a single dose of levodopa	2.8 ± 0.8	2.3 ± 0.8	2.2 ± 0.8	2.2 ± 0.8	p<0.001 [-0.7; -0.3]

ON time was defined as the period during which the patient was benefiting from the levodopa medication
OFF time was defined as the period during which the patient was not benefiting from the levodopa medication

Table R 1. Fate of patients in the study.

	Entacapone	Placebo
Subjects entered	85	86
Subjects excluded	0	0
Withdrawn, adverse events	6	5
Withdrawn, inefficacy	0	3*
Withdrawn, other reasons	2	3
Completed	77	75
Evaluated for efficacy (intention-to-treat analysis)	85	86
Evaluated for safety	85	86

* The patients 3304, 3305 and 4609 were withdrawn due to inefficacy. This information is marked on the CRFs as remarks.

Table R 28. Patients on entacapone withdrawn due to AEs.

Pat. no.	Reason for discontinuation (duration of treatment, days; entacapone dose, mg)
4105	SAE: Feeling of intoxication; levodopa dosage was reduced from 2000 mg to 1350 mg (2 days, 2000 mg).
3401	SAE: Nausea, pain in lower extremities, abnormal laboratory values. Levodopa dosage was reduced from 1000 mg to 800 mg (28 days; 1800 mg).
1302	SAE: Suspected pericarditis. Diagnosis of prolapse of the mitral valve and dilatation of aorta was set after examination in the cardiological department (111 days, 1000 mg).
1209	SAE: Diarrhoea; levodopa was reduced during the study from 175 mg to125 mg (31 days; 1000 mg).
1406	Diarrhoea, patient wanted to change to Sinemet CR; Sinemet (daily dose 900 mg) was changed to CR (daily dose1000 mg) (84 days, 1200 mg).
1310	Severe diarrhoea that was not affected by patient's antiparkinsonian medication. (2) (63 days, 1400 mg).
4105	SAE: Feeling of intoxication; levodopa dosage was reduced from 2000 mg to 1350 mg (2 days, 2000 mg).
3401	SAE: Nausea, pain in lower extremities, abnormal laboratory values. Levodopa dosage was reduced from 1000 mg to 800 mg (28 days; 1800 mg).
1302	SAE: Suspected pericarditis. Diagnosis of prolapse of the mitral valve and dilatation of aorta was set after examination in the cardiological department (111 days, 1000 mg).
1209	SAE: Diarrhoea; levodopa was reduced during the study from 175 mg to125 mg (31 days; 1000 mg).
1406	Diarrhoea, patient wanted to change to Sinemet CR; Sinemet (daily dose 900 mg) was changed to CR (daily dose1000 mg) (84 days, 1200 mg).
1310	Severe diarrhoea that was not affected by patient's antiparkinsonian medication. (2) (63 days, 1400 mg).

Table R 3. Demographic features at baseline (mean ± SD).

ɔopulation	Entacapone	Placebo	Significance
...mber of patients	85	86	-
Male gender (%)	55	55	NS
Age (years)	62.6 ± 7.6	62.8 ± 8.7	NS
Weight (kg)	69.1 ± 12.5	71.1 ± 14.7	NS
Height (cm)	171.2 ± 9.0	170.0 ± 9.2	NS

PP-population	Entacapone	Placebo	Significance
Number of patients	62	56	-
Male gender (%)	52	55	NS
Age (years)	62.2 ± 7.4	64.4± 8.3	NS
Weight (kg)	67.9 ± 11.6	71.5 ± 14.4	NS
Height (cm)	169.8 ± 8.9	170.2 ± 9.0	NS

Table R 4. History of Parkinson's disease (mean ± SD).

ITT-population	Entacapone n = 85	Placebo n = 86	Significance
Age at onset of PD (years)	52.9 ± 8.0	52.0 ± 9.3	NS
Duration of PD (years)	10.2 ± 4.8	11.3 ± 4.8	p< 0.05
Duration of levodopa treatment (years)	7.9 ± 4.2	9.0 ± 4.1	p< 0.05
Duration of fluctuations (years)	4.2 ± 3.4	4.7 ± 3.5	NS

ɔpulation	Entacapone n = 62	Placebo n = 56	Significance
Age at onset of PD (years)	53.3 ± 8.0	53.6 ± 8.9	NS
Duration of PD (years)	9.4 ± 3.8	11.3 ± 3.9	p< 0.01
Duration of levodopa treatment (years)	7.3 ± 3.3	9.0 ± 3.6	p< 0.01
Duration of fluctuations (years)	3.8 ± 3.0	4.5 ± 3.0	NS

Table R 5. Other concurrent drug therapy at baseline, ITT-population.

Drug therapy group[1]	Entacapone n = 85 %	Placebo n = 86 %
Psycholeptics*	22.4	20.9
Cardiac therapy	12.9	3.5
Analgesics	10.6	7.0
Diuretics	10.6	9.3
Psychoanaleptics**	10.6	8.1
Sex hormones and modulators of the genital system	8.2	3.5
Antihypertensives	7.1	4.7
Beta blocking agents	7.1	4.7
Anti-inflammatory and antirheumatic products	7.1	4.7
Laxatives	5.9	2.3
Anti-asthmatics	0	7.0

[1] Drug therapy group as given in the ATC-classification by WHO
*tipsychotics, anxiolytics, hypnotics and sedatives
**idepressants and psychostimulants and their combination with psycholeptics.

Table R 6. Other concurrent diseases at baseline, ITT-population.

Diseases	Entacapone n = 85 %	Placebo n = 86 %
rtension	11.8	10.5
ral symptoms	7.1	3.5
Insomnia	7.1	3.5
Cardiac disease	7.1	3.5
Spondylarthrosis/pain	5.9	4.7
Neurosis/anxiety	5.9	7.0
Angina pectoris	4.7	2.3
Prostatic hypertrophy	2.4	0
Urinary tract infection/polyposis	2.4	3.5
Constipation	2.4	0
Oesophagitis/gastritis	2.4	3.5
Depression	2.4	1.2
Hypothyreosis	2.4	1.2

Table R 7. Levodopa medication (mean ± SD).

	Entacapone n = 85	Placebo n = 86	Significance
Total levodopa dosage, mg/day	699 ± 294	723 ± 306	NS
Number of levodopa doses/day	6.1 ± 1.7	6.3 ± 1.7	NS
Levodopa + carbidopa/benserazide	33/52	19/67	p< 0.05

Table R 8. Antiparkinsonian medication at baseline, ITT-population.

Therapy group	Entacapone n = 85		Placebo n = 86	
	%	Daily dose (mg) mean±SD	%	Daily dose (mg) mean±SD
Selegiline	44.7	8.9±2.2	43.0	9.3±1.7
Dopamine agonists				
Pergolide	5.9	1.5±1.4	5.8	2.4±2.0
Bromocriptine	40.0	13.4±7.1	32.5	19.5±11.6
Lisuride	3.5	1.1±0.8	7.0	1.9±0.9
Amantadine	2.4	200.0±0.0	3.5	200.0±0.0
Anticholinergic agents				
Orfenadrine	4.7	200.0±100.0	2.3	125.0±35.4
Trihexyphenidyl	4.7	3.8±1.5	5.9	6.0±2.4
Biperidene	0	0	1.2	4.0±0
Benzatropine	0	0	1.2	4.0±0

Table R 9. Clinical disability- UPDRS and Hoehn and Yahr (mean±SD), at baseline, for the ITT-population.

UPDRS subscore	Entacapone n = 85	Placebo n = 86
Mentation, behavior, mood	1.8 ± 1.4	2.0 ± 1.5
Activities in daily living	11.2 ± 5.0	11.0 ± 4.5
Motor examination (Part III)	25.5 ± 13.1	24.6 ± 12.3
of Parts I, II, and III	38.5 ± 16.8	37.4 ± 15.8
Hoehn & Yahr	%	%
1.5	11	8
2.0	45	49
2.5	21	23

APPEARS THIS WAY ON ORIGINAL

BEST POSSIBLE COPY

Table R 10. Clinical disability-Daily fluctuations in disability, ITT-population.

Symptom	Entacapone n = 85 %	Placebo n = 86 %
Daily wearing-off	100.0	96.5
Off period freezing	32.9	26.7
Unpredictable rapid fluctuations	15.3	19.8
Random freezing	21.2	16.3
Noctural akinesia	61.2	51.2
Early morning akinesia	57.6	58.1
Peak-dose dyskinesias	61.2	58.1
Early morning dystonia	31.8	22.1
Daily off period dystonia	29.4	25.6
Daily on period dystonia	14.1	4.7

Table R 11. UPDRS scores in ITT analyses.

	Baseline		On treatment		Significance
	Entacapone	Placebo	Entacapone	Placebo	
UPDRS I	1.8±1.4	2.0±1.5	1.8±1.4	2.2±1.7	NS
UPDRS II	11.2±5.0	11.0±4.5	9.5±5.4	10.6±4.8	p<0.01
UPDRS III	25.5±13.1	24.6±12.3	22.0±13.7	22.8±12.3	p<0.05
Total UPDRS (I-III)	38.5±16.8	37.4±15.8	34.1±17.7	36.3±16.6	p<0.01

Table R 12. Duration of dyskinesias (% of the patients, ITT analysis).

		None	1-25% of the day	26-50 % of the day	51-100 % of the day
apone .. - 85	Baseline	32.9	42.4	18.8	5.9
	Week 2	29.4	38.8	20.0	11.8
	Week 24	30.6	41.2	18.8	9.4
Placebo n = 86	Baseline	36.0	38.4	18.6	7.0
	Week 2	34.9	34.9	24.4	5.9
	Week 24	33.7	39.5	17.4	9.3

Table R 13. Occurrence of disabling dyskinesias (% of the patients, ITT analysis).

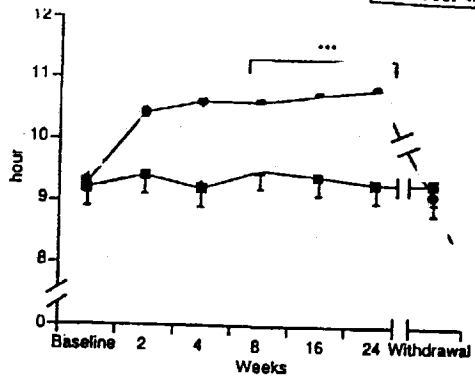
		None	Mild	Moderate-severe
Entacapone n = 85	Baseline	52.9	25.9	21.2
	Week 2	49.4	28.2	22.3
	Week 24	51.8	25.9	22.4
Placebo n = 86	Baseline	50.0	25.6	24.4
	Week 2	50.0	27.9	22.1
	Week 24	53.5	23.3	23.2

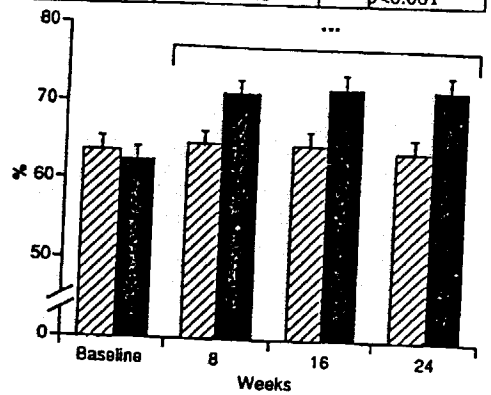
Table R 14. Painful dyskinesias (% of patients, ITT analysis).

		None	Slight-moderate	Severe-marked
Entacapone n = 85	Baseline	76.5	21.2	2.4
	Week 2	78.8	17.7	3.5
	Week 24	81.2	15.3	3.6
Placebo 86	Baseline	79.1	18.6	2.4
	Week 2	83.7	14.0	2.4
	Week 24	87.2	10.5	2.4

ON time from home diary (hours, mean ± SD), ITT-analysis

	Entacapone n=85	Placebo n=86	Significance
Baseline	9.3±2.2	9.2±2.5	NS
Mean for weeks 8, 16 and 24	10.7±2.2	9.4±2.6	p<0.001



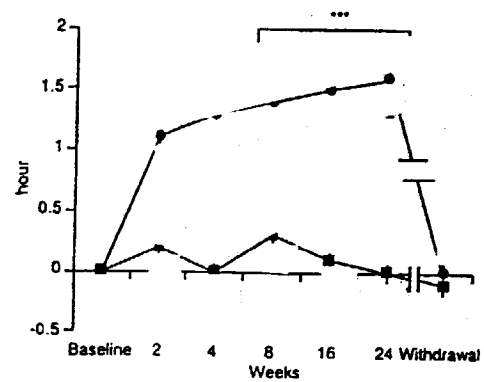


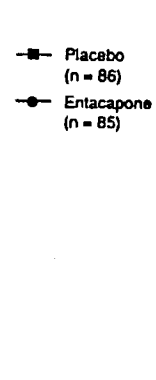
ITT-analysis, Mean±SEM
Difference between the groups ***p<0.001

Figure 4. Mean ON time/day$_{18h}$ from home diaries.

ITT-analysis, Mean±SEM
Difference between the groups ***p<0.001

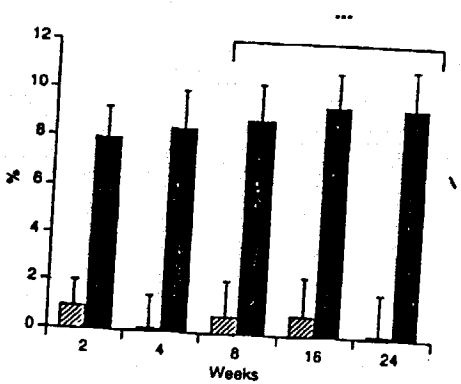
Proportion of ON time (%).

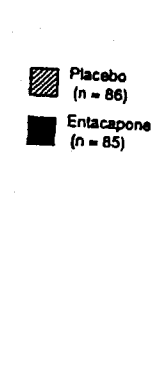




ITT-analysis, Mean±SEM
Difference in means between the groups ***p<0.001

Figure 6. ON time/day$_{18h}$ from HD as changes from baseline.





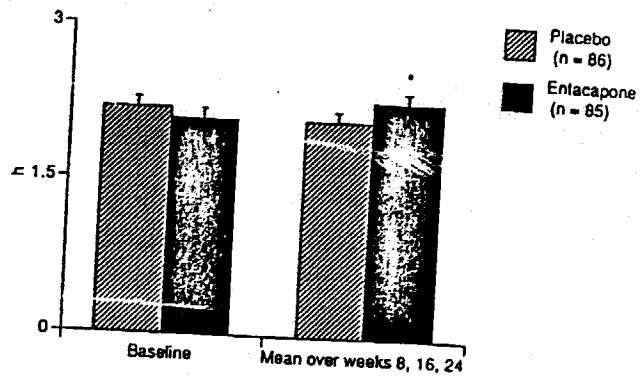
ITT-analysis, Mean±SEM
Difference between the groups *** p<0.001

Figure 7. Changes in proportion of ON time (%).

Table R 21. Mean daily levodopa dose and dosing frequency in the ITT analyses.

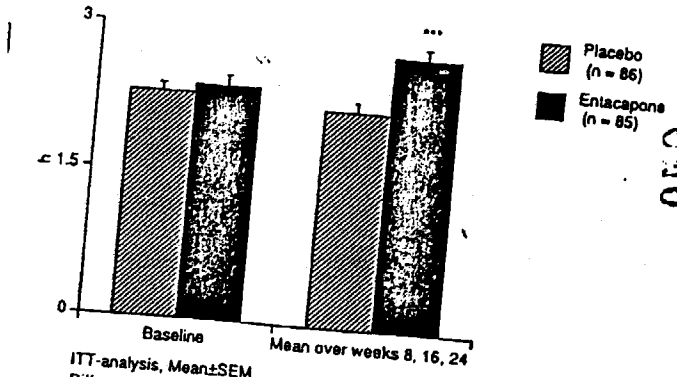
	Baseline		On treatment		Differ.*	Signif.
	Entacapone n = 85	Placebo n = 86	Entacapone n = 85	Placebo n = 86		
Daily levodopa dose (mg) (home diaries)	701±293	705±283	614±250	720±302	102±16	p<0.001
Levodopa dosing frequency (home diaries)	6.2±1.8	6.1±1.7	5.8±1.6	6.3±1.8	0.6±0.1	p<0.001
Daily levodopa dose (mg) (visit recording)	699±294	723±306	620±252	735±330	92±17	p<0.001
Levodopa dosing frequency (visit recording)	6.1±1.7	6.3±1.7	5.8±1.6	6.3±1.8	0.4±0.1	p<0.01

* Difference between means at three last visits using baseline as a covariate.



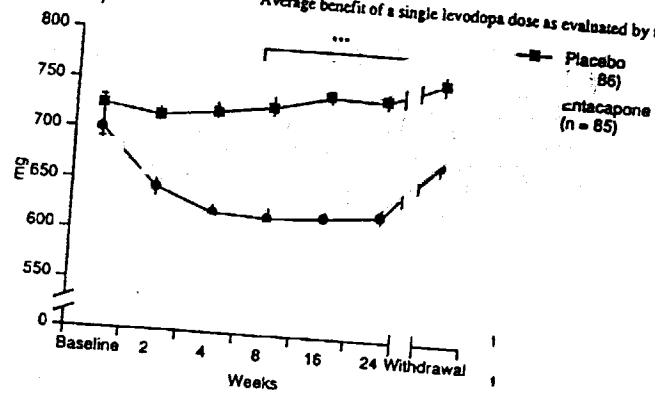
ITT-analysis, Mean±SEM
Differences between the groups *p<0.05

Figure 10. ON time accounted from the morning levodopa response from home diaries.



ITT-analysis, Mean±SEM
Differences between the groups ***p<0.001

Figure 11. Average benefit of a single levodopa dose as evaluated by the patient.

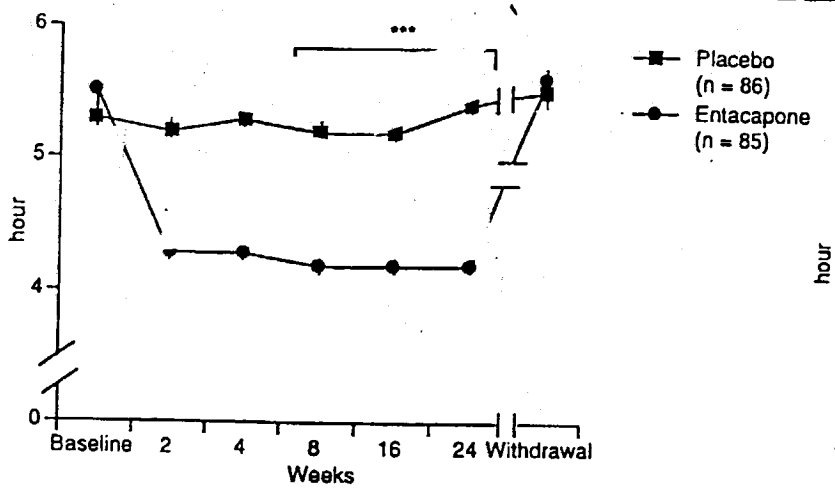


ITT-analysis, Mean±SEM
Difference between the groups ***p<0.001

Figure 15. Total daily levodopa dose.

OFF time from home diary (hours), ITT analysis

	Entacapone n = 85	Placebo n = 86	Significance
Baseline	5.5±2.2	5.3±2.4	
Mean over weeks 8, 16 and 24	4.2±2.2	5.2±2.5	p<0.001

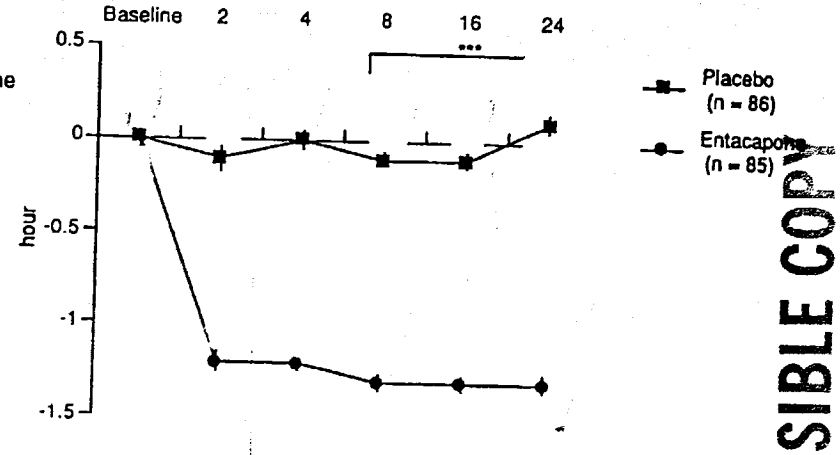


ITT-analysis, Mean±SEM
Difference in means between the groups ***p<0.001

Figure 8. Mean OFF time/day$_{18h}$ from home diaries.

Table R 18. Severity of daily wearing-off (% of patients).

		Slight	Moderate	Severe to very severe
Entacapone n = 85	Baseline	12.9	51.8	35.3
	Week 24	32.1	48.8	9.5
Placebo n = 84	Baseline	9.5	53.6	35.7
	Week 24	10.7	51.2	35.7



ITT-analysis, Mean±SEM
Difference in means between the groups ***p<0.001

Figure 9. OFF time/day$_{18h}$ from HD as changes from baseline.

Table R 15. Predictable OFF periods (% of the patients, ITT analysis).

		Yes	No
Entacapone n = 85	Baseline	98.8	1.2
	Week 24	90.6	9.4
Placebo n = 86	Baseline	97.7	2.3
	Week 24	96.5	3.5

Table R 16. Proportion of OFF time (% of patients, ITT-analysis).

		None	1-25%	26-50%	>50%
Entacapone n = 85	Baseline	1.2	50.6	30.6	17.7
	Week 24	7.1	67.1	22.4	3.5
Placebo n = 86	Baseline	2.3	45.3	34.9	17.4
	Week 24	7.0	40.7	26.7	25.6

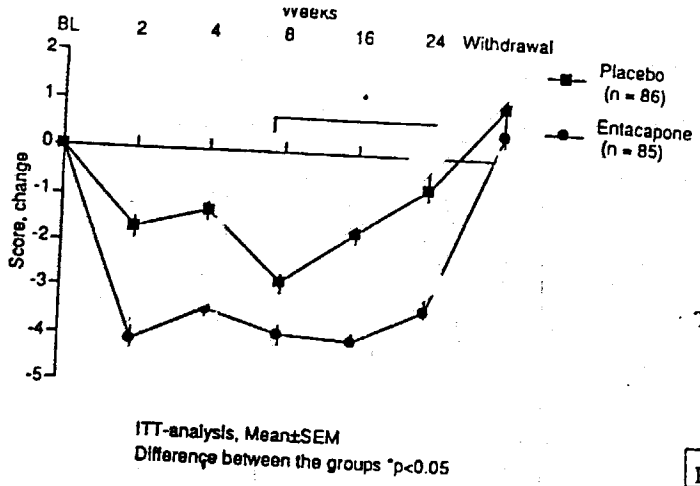


Figure 12. Change in UPRDS motor score from baseline.

Table R 19. Severity of nocturnal akinesia, % of patients (ITT analysis).

		Slight	Moderate	Severe to very severe
Entacapone n = 56	At baseline	10.7	55.3	26.8
	Week 24	38.0	25.5	10.9
Placebo n = 55	At baseline	16.4	34.5	29.1
	Week 24	10.9	32.7	34.5

Table R 20. Global evaluation by the patient and by the investigator.

Global evaluation, change from baseline(% of patients); ITT-analysis							
	Entacapone n = 85			Placebo n = 86			Signif.
	worsened	same	improved	worsened	same	improved	
Patient	23.5	37.6	38.8	28.2	49.4	22.4	ns
Investigator	14.1	29.4	56.5	23.3	48.8	27.9	p<0.01

Table R 22. UPDRS evaluation at week 24 and poststudy, ITT analysis.

	Week 24		Post study	
	Entacapone n = 85	Placebo n = 86	Entacapone n = 76	Placebo n = 76
UPDRS I	1.9±1.4	2.2±1.6	1.9±1.6	2.1±1.6
UPDRS II	9.1±5.2	10.3±4.8	11.0±5.5	10.5±4.7
UPDRS III	23.3±14.0	23.9±13.2	26.6±13.8	23.8±13.0
Total UPDRS (I-III)	34.3±18.3	36.4±17.2	3>.6±18.5	36.2±16.7

Table R 17. UPDRS part VI frequencies (%) by category, ITT-analysis.

	Entacapone n = 85			Placebo n = 86		
	< 80%	80%	> 80%	< 80%	80%	>80%
Baseline	22.4	45.9	31.7	23.2	40.7	36.1
Week 24	15.4	36.5	48.3	24.4	37.2	38.4

ON time (hours) after withdrawal, ITT analysis

Entacapone n = 77	Week 24	10.7 ± 2.4
	Post-study	9.1± 2.7
Placebo n = 76	Week 24	9.4 ± 2.8
	Post-study	9.3 ± 2.9

Table R 23. Proportion of OFF time (% of patients, ITT analysis).

		None	1-25%	26-50%	>50%
Entacapone n = 77	Week 24	7.8	66.2	23.4	2.6
	Post-study	6.5	35.1	33.8	24.7
Placebo n = 76	Week 24	7.8	42.9	26.0	23.4
	Post-study	2.6	46.1	28.9	22.3

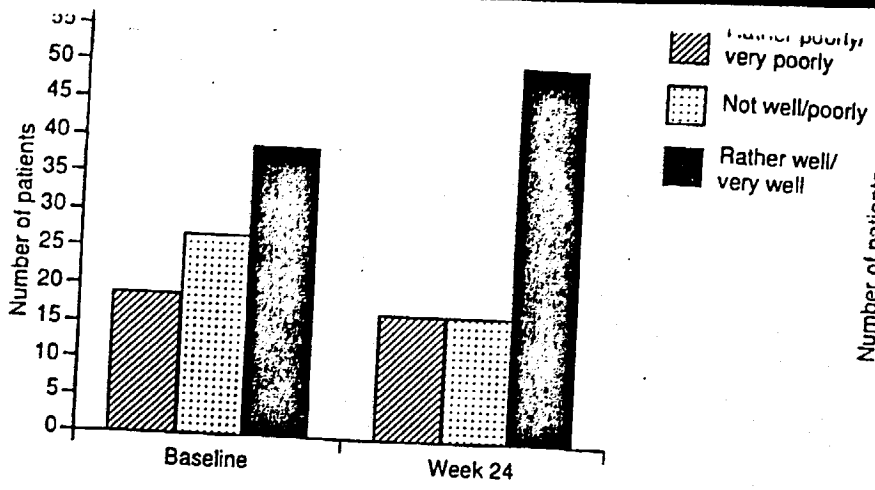


Figure 13. Global evaluation of disability by the patient in the entacapone group.

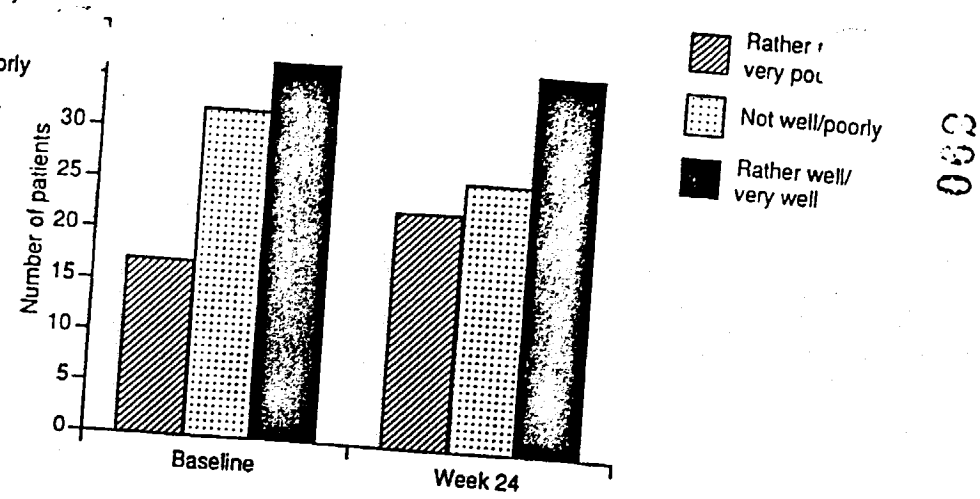


Figure 14. Global evaluation of disability by the patient in the placebo group.

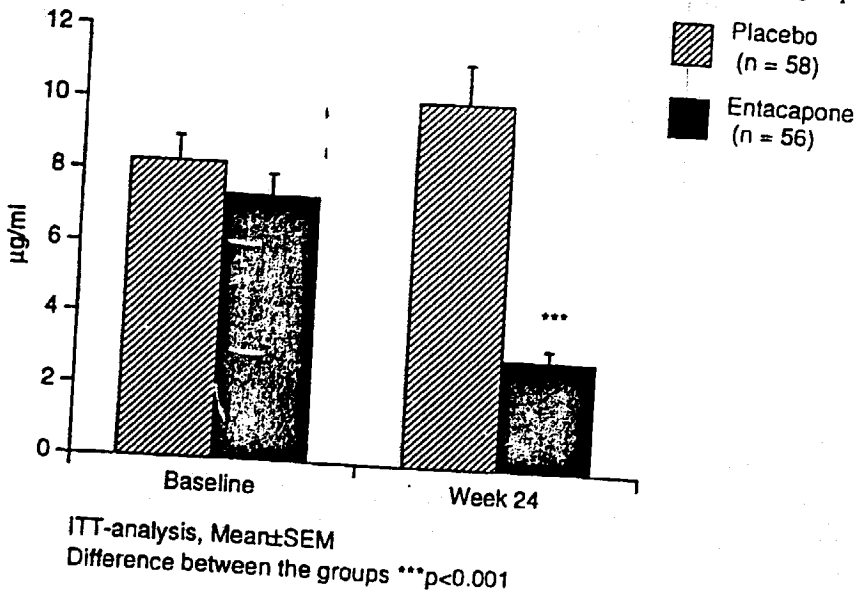


Figure 16. Plasma 3-OMD concentrations during the study.

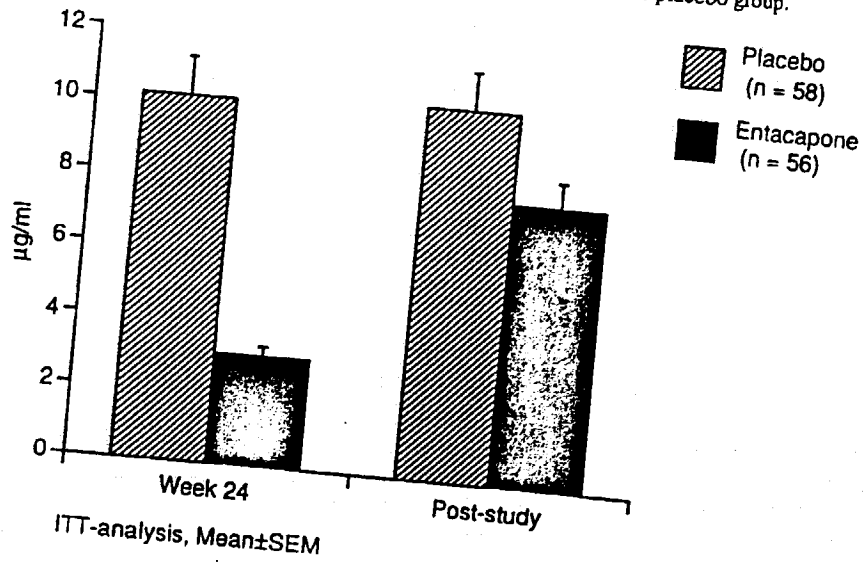


Figure 17. Plasma 3-OMD concentrations at withdrawal.

STUDY 44

Table R 1. Patients randomized

Event	Entacapone	Placebo
Patients initially randomized	103	102
Prematurely discontinued, due to adverse events	11	7
Prematurely discontinued, due to inefficacy	0	0
Prematurely discontinued, due to other reasons	2	4
Patients having completed study	90	91
Patients evaluated for efficacy	103	102
Patients evaluated for safety	103	102

Table R 2. Protocol deviations

Type of deviation	Number of patients
Patients who did not satisfy the entry criteria	1. One patient on entacapone was allocated to take three doses of levodopa per day at baseline. Minimum dose required was four.
Patients who deviated from protocol in any other important way	1. 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. 2. There were protocol deviations with regard to the observance of visit windows in all the study centers. The patients were, however, treated with the study medication on a continuous basis and these deviations were considered not significantly to impinge on the interpretation of either the efficacy or safety results. 3. There were some deviations in the source documentation in center 12; the documentation did not satisfy the GCP requirements. All patients from this center (12 patients), therefore, were excluded from the PP analysis. ITT analysis was conducted for all the patients. In addition, a subanalysis without site number 12 (12 patients) was conducted.

APPEARS THIS WAY
ON ORIGINAL

	SCREENING	VISITS 1-8							
WEEK	-4	1 0	2 2	3 4	4 8	5 16	6 24	7 26	8 28
STUDY DESIGN									
- Individual L-dopa medication		X ######							
- Entacapone or placebo		X----------				##########X			
- Staggered washout							X---------		X
SCREENING									
- Informed consent	X								
- Inclusion/exclusion criteria	X								
- Patients were randomized in the study		X							
EFFICACY MEASURES									
- Doses of medications		X	X	X	X	X	X	X	X
- Home Diary	X	X	X	X	X	X	X	X	X
- UPDRS		X	X	X	X	X	X	X	X
- Daily fluctuations in disability	X	X	X	X	X	X	X	X	X
- Global evaluation	X	X	X	X	X	X	X	X	X
SAFETY MEASURES									
Hematology/biochemistry	X	X		X	X	X	X	X	X*
BP, HR, ECG (12-lead)	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X
Plasma 3-OMD		X		X	X	X	X	X	X
Tablet count			X	X	X	X	X	X	X
OTHER MEASURES									
Blindness control							X	X	X**

Constant dose of levodopa

* Optional, was performed only for patients with any abnormal changes on the previous visit. Additional visits were included, if clinically indicated.

** Blindness control was also conducted if the patient prematurely discontinued the study medication.

Summary - efficacy:

	Primary efficacy variable from home diary (mean±SD)						
Variable	Entacapone			Placebo			Significance
	Baseline	mean over weeks 8, 16, and 24	mean change from baseline	Baseline	mean over weeks 8, 16, and 24	mean change from baseline	Difference between treatments over weeks 8, 16, and 24 p [CI_{95} %]
Proportion of daily ON time (%)	60.0±15.2	66.8±14.5	6.7±14.0	60.8±14.0	62.8±16.8	2.0±11.1	<0.05 [0.93; 7.97]

	Secondary efficacy variables from home diary (mean±SD)						
Variable	Entacapone			Placebo			Significance
	Baseline	mean over weeks 8, 16, and 24	mean change from baseline	Baseline	mean over weeks 8, 16, and 24	mean change from baseline	Difference between treatments over weeks 8, 16, and 24 p [CI_{95} %]
Daily ON time (h)	10.2±2.5	11.2±2.3	1.0±2.3	10.3±2.5	10.7±2.8	0.4±1.8	NS [-0.04; 1.19]
Daily OFF time (h)	6.8±2.8	5.6±2.6	-1.2±2.4	6.6±2.4	6.4±3.0	-0.3±2.0	p<0.01 [-1.52; -0.28]
ASLEEP time (h)	7.0±1.7	7.2±1.6	-	7.1±1.5	7.0±1.5	-	NS [-0.07; 0.63]
Daily levodopa dose (mg)	803±388	710±321	-93±202	758±435	777±452	19±165	p<0.001 [-151.74; -61.20]
Number of levodopa doses (doses/day)	6.2±2.0	6.2±1.9	-	6.0±1.9	6.2±2.1	-	NS [-0.38; 0.01]

	UPDRS evaluation (mean±SD)						
Variable	Entacapone			Placebo			Significance
	Baseline	mean over weeks 8, 16, and 24	mean change from baseline	Baseline	mean over weeks 8, 16, and 24	mean change from baseline	Difference between treatments over weeks 8, 16, and 24; p [CI_{95} %]
Total score (parts I, II, and III)	35.1±15.9	34.1±16.1	-1.0±8.2	35.6±17.2	36.6±17.7	1.0±8.0	NS [-4.26; 0.21]
Mentation, behavior, and mood (part I)	1.3±1.2	1.5±1.2	-	1.5±1.7	1.8±1.8	-	NS [-0.35; 0.18]
ADL (part II)	11.9±6.2	11.5±6.4	-	11.7±6.7	12.1±6.8	-	NS [-1.63; 0.12]
Motor part (part IV)	22.0±11.7	21.1±11.2	-0.9±6.8	22.6±12.0	22.9±11.9	0.3±6.8	NS [-3.09; 0.48]

Time	Entacapone (n = 90)		Placebo (n = 91)
	Patients withdrawn at week 24 (n = 43)	Patients withdrawn at week 26 (n = 47)	
	UPDRS motor score (mean±SD)		UPDRS motor score (mean±SD)
Week 24	20.3 ± 11.2	19.9 ± 12.0	23.2 ± 13.4
Week 26	24.6 ± 12.1 (p<0.01)	20.7 ± 11.2	23.4 ± 13.4
Week 28	25.0 ± 13.7 (p<0.001)	22.4 ± 11.7 (NS)	22.7 ± 12.8
	UPDRS total score (mean±SD)		UPDRS total score (mean±SD)
Week 24	34.2 ± 14.7	32.0 ± 17.4	37.7 ± 19.7
Week 26	39.6 ± 16.5 (p<0.01)	33.3 ± 16.7	37.9 ± 19.6
Week 28	40.1 ± 18.7 (p<0.01)	36.3 ± 17.2 (p<0.05)	37.3 ± 18.9

Significance vs. placebo at the same time-point, baseline (visit 1) value was used as covariate in the statistical model

At least one category change in global score by patient self-assessment (% of patients)

	Entacapone patients withdrawn at week 24 (n=44)			Placebo (n=92)			
Change from week 24	Worsened	No change	Improved	Worsened	No change	Improved	Significance
Week 26	63.6	25.0	11.4	35.2	41.8	23.1	p<0.01
Week 28	69.8	18.6	11.6	34.8	32.6	32.6	p<0.001
	Entacapone patients withdrawn at week 26 (n=46)			Placebo (n=92)			
Change from week 26	Worsened	No change	Improved	Worsened	No change	Improved	Significance
Week 28	71.1	26.7	2.2	27.5	38.5	34.1	p<0.001

Global evaluation by the patient (% of patients)

Time	Entacapone			Placebo			Significance
	Worsened	No change	Improved	Worsened	No change	Improved	Difference between treatments; p
Week 24	31	38	31	42	38	20	<0.05
Weeks 8-24*	12	71	17	19	75	7	<0.05

* At least one category change in global score on each of weeks 8, 16, and 24.

Global evaluation by the investigator (% of patients)

Time	Entacapone			Placebo			Significance
	Worsened	No change	Improved	Worsened	No change	Improved	Difference between treatments; p
Week 24	30	36	34	39	40	21	<0.05
Weeks 8-24*	13	68	19	15	75	10	NS

* At least one category change in global score on each of weeks 8, 16, and 24.

Scheduled levodopa dosing (mean ± SD)

Time	Entacapone			Placebo			Significance
	Baseline	mean over weeks 8, 16, and 24	mean change from baseline	Baseline	mean over weeks 8, 16, and 24	mean change from baseline	Difference between treatments over weeks 8, 16, and 24; p [$CI_{95\ \%}$]
Scheduled levodopa dose (mg/day)	791 ± 375	698 ± 316	-93 ± 184	752 ± 435	761 ± 444	9.4 ± 108	p<0.001 [-140.45;-57.43]
Dosing frequency (doses/day)	6.1 ± 1.9	6.0 ± 1.9	-	6.0 ± 1.9	6.0 ± 1.8	-	NS [-0.26; 0.07]

Effects after entacapone withdrawal (mean ± SD)

Time	Entacapone		Placebo	
	Withdrawal at week 24	Withdrawal at week 26	At week 24	At week 26
	Proportion of ON time (%)		Proportion of ON time (%)	
On drug 1)	66 ± 15.0	64 ± 19.1	62 ± 18.5	62 ± 19.2
First day after withdrawal	58 ± 19.0 (p<0.01) 2)	56 ± 20.5 (p<0.001) 2)	63 ± 20.3	60 ± 20.2
Second day after withdrawal	60 ± 18.3 (p<0.05)	54 ± 24.2 (p<0.001)	62 ± 19.2	61 ± 19.5
	Daily ON time (h)		Daily ON time (h)	
On drug 1)	11.1 ± 2.6	10.8 ± 3.2	10.5 ± 3.1	10.6 ± 3.4
Withdrawal D1	9.7 ± 3.2 (p<0.01)	9.2 ± 3.7 (p<0.01)	10.5 ± 3.4	10.2 ± 3.4
Withdrawal D2	10.0 ± 3.2 (p<0.05)	8.9 ± 4.2 (p<0.001)	10.6 ± 3.4	10.5 ± 3.4
	Daily OFF time (h)		Daily OFF time (h)	
On drug 1)	5.7 ± 2.7	6.0 ± 3.3	6.4 ± 3.3	6.4 ± 3.1
Withdrawal D1	7.3 ± 3.6 (p<0.01)	7.3 ± 3.5 (p<0.01)	6.4 ± 3.5	6.7 ± 3.4
Withdrawal D2	6.7 ± 3.4 (p<0.05)	7.6 ± 4.3 (p<0.001)	6.4 ± 3.1	6.7 ± 3.3

1) Last value with entacapone treatment for patients treated with entacapone
2) Significance vs. placebo at the same time-point, baseline (visit 1) value was used as covariate in the statistical model
D1: First day after entacapone withdrawal
D2: Second day after entacapone withdrawal

Table R 3. Demographic features at baseline

Parameter	Entacapone	Placebo	Significance
Number of patients	103	102	-
Sex M/F (%)	67 / 33	63 / 37	NS
Age (years)	63.9 ± 8.0	62.7 ± 9.7	NS
Weight (kg)	74.2 ± 14.2	70.6 ± 14.6	NS
Height (cm)	170.2 ± 9.4	168.9 ± 10.1	NS

- Not applicable
NS Not statistically significant

Table R 4. Demographic features at baseline

Parameter	Entacapone	Placebo	Significance
Number of patients	65	65	-
Sex M/F (%)	60 / 40	62 / 39	NS
Age (years)	64.4 ± 8.3	61.2 ± 10.2	p<0.05
Weight (kg)	73.2 ± 13.9	70.9 ± 14.5	NS
Height (cm)	169.3 ± 9.7	169.2 ± 10.3	NS

- Not applicable
NS Not statistically significant

Table R 5. History of Parkinson's disease (mean ± SD)

Parameter	Entacapone (n = 103)	Placebo (n = 102)	Significance
Age at onset of PD (years)	53.7 ± 10.0	52.0 ± 11.2	NS
Duration of PD (years)	10.7 ± 4.9	11,3 ± 6.4	NS
Duration of levodopa treatment at baseline (years)	9.0 ± 4.7	8.9 ± 6.0	NS
Duration of fluctuations (years)	4.2 ± 3.0	4.5 ± 4.3	NS
Previous use of CR levodopa (% of patients)	54	40	p<0.05

NS Not statistically significant

Table R 6. History of Parkinson's disease (mean ± SD)

	Entacapone (n = 65)	Placebo (n = 65)	Significance
Age at onset of PD (years)	54.0 ± 10.1	50.5 ± 11.0	p<0.05
Duration of PD (years)	10.9 ± 4.7	11.2 ± 6.4	NS
Duration of fluctuations (years)	4.5 ± 2.8	4.6 ± 4.6	NS
Duration of levodopa treatment at baseline (years)	9.1 ± 4.4	8.6 ± 5.9	NS
Previous use of CR levodopa (% of patients)	54	37	NS

NS Not statistically significant

Table R 7. Levodopa dose at baseline (mean ±SD)

Parameter	Entacapone (n=103)	Placebo (n=102)	Significance
Total levodopa dose (mg/day)	791 ± 375	752 ± 435	NS
Number of levodopa doses per day	6.1 ± 1.9	6.0 ± 1.9	NS

NS Not statistically significant

Table R 8. Levodopa dose at baseline (mean ±SD)

Parameter	Entacapone (n=65)	Placebo (n=65)	Significance
Total levodopa dose (mg/day)	809 ± 397	773 ± 498	NS
Number of levodopa doses per day	6.2 ± 1.9	5.8 ± 1.7	NS

Table R 9. Antiparkinsonian medication at baseline for the ITT population.

Therapy group	Entacapone (n=103) %	Daily dose (mg) mean ± SD	Placebo (n=102) %	Daily dose (mg) mean ± SD
Amantadine	17	200.0 ± 61.2	16	212.5 ± 61.9
Dopamine agonists	50	-	53	-
Pergolide	36	1.7 ± 1.0	35	2.2 ± 1.9
Bromocriptine	15	21.0 ± 12.5	19	18.1 ± 11.4
Anticholinergic agents	12	-	18	-
Trihexyphenidyl	8	3.5 ± 1.5	12	4.3 ± 3.1
Benzatropine	3	0.8 ± 0.3	3	3.4 ± 2.9
Procyclidine	1	NA	1	5.0 ± 0
Ethopropazine	1	300.0	2	5.0
Selegiline	53	8.2 ± 2.5	45	8.2 ± 2.5

- Not applicable
NA Not available

Table R 10. Proportion of patients with concurrent diseases at baseline

Disease	Entacapone (n=103) %	Placebo (n=102) %
Insomnia	28.2	27.5
Constipation	21.4	22.5
Osteoarthrosis	20.4	13.7
Pain in joints	16.5	14.7
Hypertension	15.5	17.6
Anxiety	13.6	8.8
Depressive disorders	11.7	9.8
Hypothyroidism	9.7	5.9
Urinary problems	7.8	5.9
Neurotic depression	7.8	7.8
Prostate hyperplasia	5.8	4.9
Orthostatic hypotension	5.8	5.9
Dizziness and giddiness	2.9	8.8
Miscellaneous reports (entacapone 236 reports, placebo 228 reports)	-	-

Table R 11. Concomitant drug therapy at baseline for the ITT population.

Drug therapy group [1]	Entacapone (n=103) %	Placebo (n=102) %
Vitamins	56.3	43.1
Psychoanaleptics (antidepressants and psychostimulants, and their combination with psycholeptics)	36.9	29.4
Analgesics	32.0	38.2
Antacids and medication for peptic ulcers and flatulence	21.4	16.7
Psycholeptics (antipsychotics, anxiolytics, hypnotics, and sedatives)	21.4	17.6
Laxatives	20.4	12.7
Antihistamines for systemic use	14.6	3.9
Sex hormones and modulators of the genital system	12.6	16.7
Anti-inflammatory and antirheumatic products	13.6	14.7
Mineral supplements	10.7	3.9
Antihypertensives	10.7	6.9

[1] Drug therapy group according to the ATC classification by WHO

Table R 12. Clinical disability - UPDRS and Hoehn & Yahr for the ITT population

UPDRS subscore	Entacapone (n=103) (mean ± SD)	Placebo (n=102) (mean ± SD)
Mentation, behavior, mood (part I)	1.3 ± 1.2	1.5 ± 1.7
Activities in daily living (part II)	11.9 ± 6.2	11.7 ± 6.7
Motor examination (part III)	22.0 ± 11.7	22.6 ± 12.0
Sum of parts I, II, and III	35.1 ± 15.9	35.6 ± 17.2
Hoehn & Yahr	%	%
1	1.0	1.0
1.5	2.9	1.0
2	44.7	49.0
2.5	21.4	18.6
3	26.2	24.5
4	3.9	5.9

Table R 13. Clinical disability - Daily fluctuations in disability for the ITT population

Symptom	Entacapone (n=103) %	Placebo (n=102) %
Daily wearing-off	99.0	98.0
Nocturnal akinesia	47.6	51.0
Early morning akinesia	59.2	53.9
OFF-period freezing	45.6	52.0
Peak-dose dyskinesias	67.0	59.8
Early morning dystonia	25.2	34.3
Daily OFF period dystonia	23.3	24.5
Daily ON period dystonia	13.6	15.7
Unpredictable rapid fluctuations	21.4	29.4
Random freezing	19.4	16.7
Other symptoms	2.7	6.1

Table R 14. Reasons for premature discontinuation

Reason for discontinuation	Entacapone (n=103) n	%	Symptom	Placebo (n=102) n	%	Symptom
Dyskinesia	2	(1.9)	Dyskinesias	2	(2.0)	Dyskinesias
	1	(1.0)	Vivid dreams, facial dyskinesias, GI symptoms, sleepiness			
Dyskinesia total	3	(2.9)		2	(2.0)	
Gastrointestinal symptoms	1	(1.0)	GI symptoms	0	(0)	
	1	(1.0)	Abdominal pain and diaphoresis (SAE)			
Gastrointestinal symptoms total	2	(1.9)		0	(0)	
Other adverse event	1	(1.0)	Paranoid psychosis	1	(1.0)	Rigidity and tremor
	2	(1.9)	Increased severity of symptoms of PD	1	(1.0)	Weakness, confusion, increased tremor
	1	(1.0)	Chest tightness	1	(1.0)	Recurrence of depression
	1	(1.0)	Hypotension, light-headedness, dizziness	1	(1.0)	Confusion
	1	(1.0)	Palpitations and feeling of 'pins and needles' in extremities (SAE)	1	(1.0)	Constipation, sleeplessness, dry skin, dizziness, headache
Other adverse events total	6	(5.8)		5	(4.9)	
Adverse events total	11	(10.7)		7	(6.7)	
Other reasons	1	(1.0)	Non-compliance	1	(1.0)	Non-compliance
	1	(1.0)	Patient withdrew consent due to irritability, insomnia, mood swings, and anxiety	1	(1.0)	Patient withdrew consent
				1	(1.0)	Patient withdrew consent
				1	(1.0)	Exacerbation of PD symptoms
Other reasons total	2	(1.9)		4	(3.9)	
Total	13	(12.7)		11	(10.8)	

Table R 15. Proportion of daily ON time (% of awake time); ITT-LOCF(BL)

Time	Entacapone (n=103)	Placebo (n=102)	Significance
Baseline	60.0 ± 15.2	60.8 ± 14.0	
Mean for weeks 8, 16, and 24	66.8 ± 14.5	62.8 ± 16.8	p<0.05

Table R 16. Proportion of daily ON time (% of awake time); PP population

Time	Entacapone (n = 65)	Placebo (n = 65)	Significance
Baseline	58.1 ± 15.0	60.6 ± 12.7	
Mean for weeks 8, 16, and 24	67.0 ± 14.8	63.4 ± 16.6	NS

NS Not statistically significant

Table R 17. Proportion of daily ON time (% of awake time); ITT-LOCF(BL)-subanalysis

Time	Entacapone (n = 88)	Placebo (n = 83)	Significance
Baseline	56.4 ± 13.3	56.5 ± 11.4	
Mean for weeks 8, 16, and 24	64.7 ± 14.2	59.1 ± 15.5	p<0.01

Table R 18. Daily ON time (hours, mean ± SD); ITT-LOCF(BL)

Time	Entacapone (n = 103)	Placebo (n = 102)	Significance
Baseline	10.2 ± 2.5	10.3 ± 2.5	
Mean for weeks 8, 16, and 24	11.2 ± 2.3	10.7 ± 2.8	NS

Table R 19. Daily ON time (hours, mean ± SD); ITT-LOCF$_{(BL)}$ subanalysis

Time	Entacapone (n = 88)	Placebo (n = 83)	Significance
Baseline	9.7 ± 2.4	9.7 ± 2.2	
Mean for weeks 8, 16, and 24	10.9 ± 2.3	10.1 ± 2.7	p<0.05

Table R 20. Daily OFF time (hours, mean ± SD); ITT-LOCF$_{(BL)}$

Time	Entacapone (n = 103)	Placebo (n = 102)	Significance
Baseline	6.8 ± 2.8	6.6 ± 2.4	
Mean for weeks 8, 16, and 24	5.6 ± 2.6	6.4 ± 3.0	p<0.01

Table R 21. Daily OFF time (hours, mean ± SD); ITT-LOCF$_{(BL)}$ subanalysis

Time	Entacapone (n = 88)	Placebo (n = 83)	Significance
Baseline	7.5 ± 2.4	7.4 ± 2.0	
Mean for weeks 8, 16, and 24	6.0 ± 2.6	7.0 ± 2.8	p<0.01

Table R 22. Daily ASLEEP time (hours, mean ± SD); ITT-LOCF$_{(BL)}$

Time	Entacapone (n = 103)	Placebo (n = 102)	Significance
Baseline	7.0 ± 1.7	7.1 ± 1.5	
Mean for weeks 8, 16, and 24	7.2 ± 1.6	7.0 ± 1.5	NS

NS Not statistically significant

Table R 23. Total score of UPDRS (mean ± SD); ITT-LOCF$_{(BL)}$

Time	Entacapone (n = 103)	Placebo (n = 102)	Significance
Baseline	35.1 ± 15.9	35.6 ± 17.2	
Mean for weeks 8, 16, and 24	34.1 ± 16.1	36.6 ± 17.7	NS
Week 24	34.5 ± 17.1	38.4 ± 19.4	NS

NS Not statistically significant

Table R 24. Duration of dyskinesias (% of patients); ITT-LOCF$_{(BL)}$

Treatment	Time	None	1-25 % of day	26-50 % of day	>50 % of day
Entacapone	baseline	27	52	9	12
(n=103)	week 2	26	35	22	17
	week 24	28	37	21	14
Placebo	baseline	31	39	22	8
(n=102)	week 2	32	43	19	6
	week 24	33	39	14	14

Table R 25. Disability of dyskinesias (% of patients); ITT-LOCF$_{(BL)}$

Treatment	Time	Not disabling	Mildly disabling	Moderately -completely disabling
Entacapone	baseline	57	22	22
(n=103)	week 24	57	17	26
Placebo	baseline	54	24	23
(n=103)	week 24	59	16	25

Table R 26. Unpredictable OFF periods (% of patients); ITT-LOCF$_{(BL)}$

Time	Entacapone (n = 103)		Placebo (n = 102)	
	No	Yes	No	Yes
Baseline	31	69	46	54
Week 24	48	52	47	53

Table R 27. Proportion of OFF time (% of patients); ITT analysis

Treatment	Time	None	1-25 %	26-50 %	>50 %
Entacapone	baseline	0	43	50	8
(n=103)	week 24	1	53	35	11
Placebo	baseline	1	41	50	8
(n=102)	week 24	1	40	49	10

Table R 28. One category change at least in the proportion of OFF time (% of patients); ITT analysis

Time	Entacapone (n=103)			Placebo (n=102)			Signi-ficance
	OFF time increased	No change in OFF time	OFF time decreased	OFF time increased	No change in OFF time	OFF time decreased	
Week 24	14.6	61.2	24.3	20.6	62.7	16.7	NS
Weeks 8 -24*	2.9	83.5	13.6	7.8	86.3	5.9	p<0.05

* Increase or decrease from baseline in the proportion of the OFF time by at least one category on each of weeks, 8, 16, and 24.

NS Not statistically significant.

Table R 29. One category change at least in global score as evaluated by patient (%); ITT-LOCF(BL)

Time	Entacapone (n=103)			Placebo (n=102)			Signifi-cance
	Worsened	No change	Improved	Worsened	No change	Improved	
Week 24	31.1	37.9	31.1	42.2	38.2	19.6	p<0.05
Weeks 8-24*	11.7	70.9	17.5	18.6	74.5	6.9	p<0.05

* Improvement or worsening from baseline by at least one category in patients' condition on each of weeks, 8, 16 and 24.

Table R 30. One category change at least in global score as evaluated by investigator (%); ITT-LOCF(BL)

Time	Entacapone (n=103)			Placebo (n=102)			Signifi-cance
	Worsened	No change	Improved	Worsened	No change	Improved	
Week 24	30.1	35.9	34.0	39.2	40.2	20.6	p<0.05
Weeks 8-24*	12.6	68.0	19.4	14.7	75.5	9.8	NS

* Improvement or worsening from baseline by at least one category in patients' condition on each of weeks, 8, 16 and 24.

NS Not statistically significant.

Table R 31. Mean daily levodopa dose (mg, mean ± SD); ITT-LOCF(BL)

Time	Entacapone (n =103)	Placebo (n =102)	Significance
Baseline	803 ± 388	758 ± 435	
Mean for weeks 8, 16, and 24*	710 ± 321	777 ± 452	p<0.001

Table R 32. Booster doses (% of patients); ITT-LOCF(BL)

Time	Entacapone (n =103)	Placebo (n =102)
Baseline	24.3	15.7
Week 24	22.8	24.5

Table R 33. Levodopa dose failures (% of patients); ITT-LOCF(BL)

Time	Entacapone (n =103)	Placebo (n =102)
Baseline	28.2	29.4
Week 24	15.8	18.6

Table R 34. Mean scheduled daily levodopa dose (mg, mean ± SD); ITT-LOCF(BL)

Time	Entacapone (n =103)	Placebo (n =102)	Significance
Baseline	791 ± 375	752 ± 435	
Mean for weeks 8, 16, and 24	698 ± 316	762 ± 444	p<0.001

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

Table R 36. Levodopa dosing on home-diary days (mg, 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
Daily dose (mg)						
On drug 1)	655 ± 283		758 ± 415		796 ± 454	781 ± 431 2)
Withdrawal D1	653 ± 274	NS	795 ± 423	NS	778 ± 426	809 ± 468
Withdrawal D2	653 ± 276	NS	815 ± 490	**	781 ± 431	795 ± 442
Dosing frequency (doses per day)						
On drug 1)	6.2 ± 2.1		6.2 ± 2.0		6.0 ± 1.9	6.0 ± 1.8 2)
Withdrawal D1	6.1 ± 2.1	NS	6.5 ± 2.4	*	6.0 ± 1.8	6.1 ± 2.0
Withdrawal D2	6.1 ± 2.1	NS	6.5 ± 2.6	**	6.0 ± 1.8	6.0 ± 1.8

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

Table R 37. UPDRS total score (mean ± SD); $ITT_{(OC)}$

Time	Entacapone (n = 90)		Placebo (n = 91)
	Patients withdrawn at week 24 (n = 43)	Patients withdrawn at week 26 (n = 47)	
Week 24	34.2 ± 14.7	32.0 ± 17.4	37.7 ± 19.7
Week 26	39.6 ± 16.5 **	33.3 ± 16.7	37.9 ± 19.6
Week 28	40.1 ± 18.7 **	36.3 ± 17.2 *	37.3 ± 18.9

** 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.

Table R 38. UPDRS part III (mean ± SD); $ITT_{(OC)}$

Time	Entacapone (n = 90)		Placebo (n = 91)
	Patients withdrawn at week 24 (n = 43)	Patients withdrawn at week 26 (n = 47)	
Week 24	20.3 ± 11.2	19.9 ± 12.0	23.2 ± 13.4
Week 26	24.6 ± 12.1 **	20.7 ± 11.2	23.4 ± 13.4
Week 28	25.0 ± 13.7 ***	22.4 ± 11.7 NS	22.7 ± 12.8

*** 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 compared to the week 24 withdrawal subgroup.

Table R 39. Duration of dyskinesias; Entacapone-treated patients (n=91)

Time	Proportion of day							
	None		1-25 %		26-50 %		>50 %	
Week 24 n (%)	27	(29.7)	31	(34.1)	20	(22.0)	13	(14.3)
Week 28* n (%)	26	(28.6)	33	(36.3)	20	(22.0)	11	(12.1)

* After treatment withdrawal

Table R 40. Disability of dyskinesias; Entacapone-treated patients (n=91)

Time	Disability							
	Not		Slight		Moderate		Severe to very severe	
Week 24 n (%)	55	(60.4)	14	(15.4)	16	(17.6)	6	(6.6)
Week 28* n (%)	52	(57.1)	18	(19.8)	12	(13.2)	8	(8.8)

* After treatment withdrawal

Table R 41. Disability of dyskinesias; Entacapone-treated patients (n=91)

Time	Painful					
	No		Slightly		Moderately to severely	
Week 24 n (%)	74	(81.3)	8	(8.8)	9	(9.9)
Week 28* n (%)	70	(76.9)	7	(7.7)	13	(14.3)

* After treatment withdrawal

Table R 42. Incidence of early morning dystonia; Entacapone-treated patients (n=91).

Time	Early morning dystonia			
	No		Yes	
Week 24 n (%)	67	(73.6)	24	(26.4)
Week 28* n (%)	56	(61.5)	34	(37.4)

* After treatment withdrawal

Table R 43. Incidence of unpredictable OFF periods, and of sudden OFF periods; Entacapone-treated patients (n=91).

Time		Unpredictable OFF periods				Sudden OFF periods			
		No		Yes		No		Yes	
Week 24	n (%)	44	(48.4)	47	(51.6)	59	(64.8)	32	(35.2)
Week 28*	n (%)	39	(42.9)	51	(56.0)	44	(48.4)	46	(50.5)

* After treatment withdrawal

Table R 44. One category change at least in the proportion of OFF time (% of patients); ITT-LOCF(BL)

Change from week 24	Entacapone patients withdrawn at week 24 (n=44)			Placebo (n=92)			Signifi-cance
	Worsened	No change	Improved	Worsened	No change	Improved	
Week 26 (%)	50.0	40.9	9.1	19.8	63.7	16.5	p<0.01
Week 28 (%)	50.0	36.4	13.6	20.7	64.1	15.2	p<0.01
Change from week 26	Entacapone patients withdrawn at week 26 (n=46)			Placebo (n=92)			
	Worsened	No change	Improved	Worsened	No change	Improved	
Week 28 (%)	53.3	42.2	4.4	14.3	73.6	12.1	p<0.001

Table R 45. Incidence of sleep disturbances; Entacapone-treated patients (n=91).

Time		Sleep disturbances			
		No		Yes	
Week 24	n (%)	53	(58.2)	38	(41.8)
Week 28*	n (%)	47	(51.6)	43	(47.3)

* After treatment withdrawal

Table R 46. Schwab and England ADL by patient

Time		Entacapone (n=91) Degree of independence			Placebo (n=92) Degree of independence		
		<80 %	80 %	>80 %	<80 %	80 %	>80 %
Week 24	(n)	15	45	31	28	38	26
Week 28*	(n)	31	39	20	29	34	29

* after treatment withdrawal

Table R 47. Schwab and England ADL by investigator

Time		Entacapone (n=91) Degree of independence			Placebo (n=92) Degree of independence		
		<80 %	80 %	>80 %	<80 %	80 %	>80 %
Week 24	(n)	15	47	29	26	37	29
Week 28*	(n)	29	41	20	26	41	25

* after treatment withdrawal

Table R 48. One category change at least in global score by patient self-assessment (% of patients); ITT-LOCF(BL)

Change from week 24	Entacapone patients withdrawn at week 24 (n=44)			Placebo (n=92)			Signifi-cance
	Worsened	No change	Improved	Worsened	No change	Improved	
Week 26 (%)	63.6	25.0	11.4	35.2	41.8	23.1	p<0.01
Week 28 (%)	69.8	18.6	11.6	32.6	32.6	34.8	p<0.001
Change from week 26	Entacapone patients withdrawn at week 26 (n=46)			Placebo (n=92)			
	Worsened	No change	Improved	Worsened	No change	Improved	
Week 28 (%)	71.1	26.7	2.2	27.5	38.5	34.1	p<0.001

Table R 49. One category change at least in global score by investigator assessment (% of patients); ITT-LOCF(BL)

Change from week 24	Entacapone patients withdrawn at week 24 (n=44)			Placebo (n=92)			Signifi-cance
	Worsened	No change	Improved	Worsened	No change	Improved	
Week 26 (%)	75.0	18.2	6.8	29.7	46.2	24.2	p<0.001
Week 28 (%)	60.5	34.9	4.7	31.5	35.9	32.6	p<0.001
Change from week 26	Entacapone patients withdrawn at week 26 (n=46)			Placebo (n=92)			
	Worsened	No change	Improved	Worsened	No change	Improved	
Week 28 (%)	75.6	20.0	4.4	31.9	35.2	33.0	p<0.001

Table R 50. Blindness evaluation

Actual treatment	Patient's guess n (%)						
	Entacapone		Placebo		Cannot say		Total
Entacapone (n=103) 1)	63	(61.2)	21	(20.4)	18	(17.5)	102
Placebo (n= 102) 2)	22	(21.6)	67	(65.7)	10	(9.8)	99

1) One missing observation

2) Three missing observations

Table 20. Proportion of daily ON time, daily ON, OFF and ASLEEP times at baseline, before withdrawal (at week 24 or 26) and immediately (the 2 days immediately after stopping the treatment either at week 24 or 26) after withdrawal in study 2939044; Intent-to-Treat analysis

At week 24	Entacapone (n = 44)†)			Placebo (n =92)			Difference between treatments A)	
	Baseline	Before withdrawal	After withdrawal	Baseline	Before withdrawal	After withdrawal	p value	CI 95%
• Proportion of daily ON time (%)	62.0 ± 15.0	66.3 ± 15.0	58.4 ± 17.3	60.8 ± 14.0	62.2 ± 18.5	62.2 ± 18.7	0.0018	3.0, 13.1
• Daily ON time (h)	10.4 ± 2.4	11.1 ± 2.6	9.8 ± 3.0	10.3 ± 2.5	10.5 ± 3.1	10.6 ± 3.2	0.0028	0.5, 2.3
• Daily OFF time (h)	6.5 ± 2.8	5.7 ± 2.7	7.0 ± 3.2	6.6 ± 2.4	6.4 ± 3.3	6.4 ± 3.2	0.0021	-2.3, -0.5
• ASLEEP time (h)	7.0 ± 1.5	7.1 ± 1.7	7.2 ± 1.9	7.1 ± 1.5	7.0 ± 1.7	7.0 ± 2.1	0.9458	-0.6, 0.5
At week 26	Entacapone (n = 46)*)			Placebo (n =92)			Difference between treatments A)	
	Baseline	Before withdrawal	After withdrawal	Baseline	Before withdrawal	After withdrawal	p value	CI 95%
• Proportion of daily ON time (%)	58.0 ± 15.4	64.4 ± 19.1	54.9 ± 20.6	60.8 ± 14.0	62.2 ± 18.5	60.7 ± 18.0	0.0015	3.1, 13.0
• Daily ON time (h)	9.9 ± 2.7	10.9 ± 3.2	9.0 ± 3.6	10.3 ± 2.5	10.5 ± 3.1	10.3 ± 3.1	0.0004	0.7, 2.5
• Daily OFF time (h)	7.2 ± 2.7	6.0 ± 3.3	7.4 ± 3.7	6.6 ± 2.4	6.4 ± 3.3	6.7 ± 3.1	0.0091	-2.1, -0.3
• ASLEEP time (h)	6.9 ± 1.9	7.0 ± 1.6	7.5 ± 2.1	7.1 ± 1.5	7.0 ± 1.7	7.0 ± 1.8	0.1348	-1.0, 0.1

A) Statistical method A, Repeated measures analysis of covariance, ITT-OC
†) Only patients withdrawn at week 24 included
*) Only patients withdrawn at week 26 included

Table 21. Proportion of daily ON time, daily ON, daily OFF, ASLEEP and IN BED times at baseline, before withdrawal (week 24) and two weeks after withdrawal in studies 2939033 and 2939044; Intent-to-Treat analysis

	Treatments						Difference between treatments A)	
	Entacapone (n = 77 in 2939033, n = 44 in 2939044)			Placebo (n = 76 in 2939033, n = 92 in 2939044)				
	Baseline	Before withdrawal	2 weeks after withdrawal	Baseline	Before withdrawal	2 weeks after withdrawal	p value	CI 95%
2939033								
• Proportion of daily ON time (%)	62.7 ± 14.6	72.0 ± 16.3	61.6 ± 17.6	63.8 ± 15.8	64.7 ± 18.4	62.7 ± 18.1	0.0015	-12.7, -3.8
• Daily ON time (h)	9.3 ± 2.2	10.7 ± 2.4	9.1 ± 2.7	9.2 ± 2.5	9.4 ± 2.8	9.3 ± 2.9	0.0007	-2.2, -0.7
• Daily OFF time (h)	5.5 ± 2.2	4.2 ± 2.5	5.6 ± 2.6	5.3 ± 2.4	5.2 ± 2.8	5.5 ± 2.7	0.0024	0.5, 1.8
• IN BED time (h)	3.2 ± 1.6	3.1 ± 1.3	3.2 ± 1.5	3.5 ± 1.7	3.3 ± 2.0	3.2 ± 1.8	0.0320	0.0, 0.6
2939044†)								
• Proportion of daily ON time (%)	62.0 ± 15.5	66.3 ± 15.0	59.1 ± 17.0	60.8 ± 14.0	62.2 ± 18.5	60.7 ± 18.0	0.0008	-13.5, -3.5
• Daily ON time (h)	10.4 ± 2.4	11.1 ± 2.6	10.0 ± 2.8	10.3 ± 2.5	10.5 ± 3.1	10.3 ±3.1	0.0011	-2.4, -0.6
• Daily OFF time (h)	6.5 ± 2.8	5.7 ± 2.7	6.9 ± 3.0	6.6 ± 2.4	6.4 ± 3.3	6.7 ± 3.1	0.0034	0.4, 2.2
• ASLEEP time (h)	7.0 ± 1.5	7.1 ± 1.7	7.1 ± 1.7	7.1 ± 1.5	7.0 ± 1.7	7.0 ± 1.8	0.5587	-0.4, 0.7

A) Statistical method A, Repeated measures analysis of covariance, ITT-OC
18-hour home diary in 2939033; 24-hour home diary in 2939044
†) Only patients withdrawn at week 24 included

Table 22. UPDRS Part I, II, III and total (sum of Parts I, II, and III) at baseline, before withdrawal and two weeks after withdrawal in studies 2939033 and 2939044; Intent-to-Treat analysis

	Treatments						Difference between treatments A)	
	Entacapone			Placebo				
	Baseline	Before withdrawal B)	2 weeks after withdrawal	Baseline	Before withdrawal C)	2 weeks after withdrawal	p value	CI 95%
2939033	N=85	N=74	N=76	N=86	N=77	N=76		
UPDRS Part I	1.8±1.4	1.9±1.4	1.9±1.6	2.0±1.5	2.2±1.6	2.1±1.6	0.3248	-0.5, 0.2
UPDRS Part II	11.2±5.0	9.1±5.2	11.0±5.5	11.0±4.5	10.3±4.8	10.5±4.7	0.0004	-2.3, -0.8
UPDRS Part III	25.5±13.1	23.3±14.0	26.6±13.8	24.6±12.3	23.9±13.2	23.8±13.0	0.0033	-5.5, -1.3
UPDRS sum of Parts I, II and III	38.5±16.8	34.3±18.3	39.6±18.5	37.4±15.8	36.4±17.2	36.2±16.7	0.0003	-7.4, -2.8
2939044	N=103	N=91	N=90	N=102	N=92	N=91		
UPDRS Part I	1.3±1.2	1.5±1.3	1.6±1.6	1.5±1.7	2.0±2.1	1.8±1.8	0.1518	-0.7, 0.1
UPDRS Part II	11.9±6.2	11.7±6.3	12.6±6.8	11.7±6.7	12.7±7.3	12.8±7.2	0.0346	-1.8, -0.1
UPDRS Part III	22.0±11.7	20.5±11.2	23.5±11.9	22.6±12.0	23.2±13.4	23.4±13.4	0.0114	-5.0, -0.6
UPDRS sum of Parts I, II and III	35.1±17.2	33.7±15.7	37.9±16.9	35.6±17.2	37.7±19.7	37.9±19.6	0.0016	-6.6, -1.6

A) Statistical method A, Repeated measures analysis of covariance, ITT-OC B) Last rating on study drug C) Rating at week 24

Table 24. Proportion of daily ON time by age at baseline and endpoint; Intent-to-Treat Analysis, 18-hour data (06:00 - 24:00) in studies 2939033 and 2939044 combined

	Proportion of daily on time							
	< 65 Years (N = 194)				≥ 65 Years (N = 182)			
	Entacapone (N = 99)	Placebo (N = 95)	Difference between treatments[A]	CI 95%	Entacapone (N = 89)	Placebo (N = 93)	Difference between treatments[A]	CI 95%
Baseline	62.7±13.5	64.2±15.2			61.7±16.2	61.6±14.5		
Endpoint	69.7±14.4	65.1±17.2	5.7	0.9, 10.6 [b]	69.2±18.5	62.5±19.3	7.3	2.3, 12.4 [b]
Change from baseline	7.0±14.3	0.6±13.1			7.6±17.9	0.7±14.7		

	Difference between treatments	CI 95%	p value
Overall treatment effect between Entacapone and Placebo	6.5	3.5, 9.5	0.0001
Interaction between Treatment and Age			0.5714

A) Statistical method E, Analysis of covariance for subgroups
b) Bonferroni adjusted confidence intervals

Table 25. Proportion of daily ON time by sex at baseline and endpoint; Intent-to-Treat Analysis, 18-hour data (06:00 - 24:00) in studies 2939033 and 2939044 combined

	Proportion of daily on time							
	Male (N = 227)				Female (N = 149)			
	Entacapone (N = 116)	Placebo (N = 111)	Difference between treatments[A]	CI 95%	Entacapone (N = 72)	Placebo (N = 77)	Difference between treatments[A]	CI 95%
Baseline	63.9±14.7	63.9±14.7			59.5±14.7	61.6±15.0		
Endpoint	70.2±17.4	64.0±18.2	6.3	0.7, 11.8 [b]	68.4±14.7	63.5±18.4	6.7	2.2, 11.2 [b]
Change from baseline	6.2±16.4	-0.1±14.2			8.9±15.6	1.8±13.4		

	Difference between treatments	CI 95%	p value
Overall treatment effect between Entacapone and Placebo	6.5	3.4, 9.6	0.0002
Interaction between Treatment and Gender			0.8957

A) Statistical method E, Analysis of covariance for subgroups
b) Bonferroni adjusted confidence intervals

Table 26. Proportion of daily ON time by weight at endpoint; Intent-to-Treat Analysis, 18-hour data (06:00 - 24:00) in studies 2939033 and 2939044 combined

	Proportion of daily on time							
	Weight < 70 kg (N = 183)				Weight ≥ 70 kg (N = 193)			
	Entacapone (N = 86)	Placebo (N = 97)	Difference between treatments[A]	CI 95%	Entacapone (N = 102)	Placebo (N = 91)	Difference between treatments[A]	CI 95%
Baseline	60.1±13.5	61.6±15.1			64.0±15.7	64.4±14.6		
Endpoint	68.3±15.2	63.0±18.7	6.6	1.6, 11.6 [b]	70.4±17.4	64.7±17.9	6.3	1.5, 11.2 [b]
Change from baseline	8.2±15.7	0.9±14.0			6.5±16.5	0.4±13.8		

	Difference (CI 95%)	p value
Overall treatment effect between Entacapone and Placebo	6.5 (3.4, 9.5)	0.0001
Interaction between Treatment and Weight		0.9313

A) Statistical method E, Analysis of covariance for subgroups
b) Bonferroni adjusted confidence intervals

APPEARS THIS WAY
ON ORIGINAL

Table 27. Proportion of daily ON time by Hoehn & Yahr classification at baseline and endpoint; Intent-to-Treat Analysis, 18-hour data (06:00 - 24:00) in (studies 2939033 and 2939044 combined

	Proportion of daily on time							
	Hoehn & Yahr ≤ 2 (N = 198)				Hoehn & Yahr > 2 (N = 178)			
	Entacapone (N = 97)	Placebo (N = 101)	Difference between treatments[A]	CI 95%	Entacapone (N = 91)	Placebo (N = 87)	Difference between treatments[A]	CI 95%
Baseline	64.2±14.1	64.3±15.2			60.0±15.3	61.3±14.3		
Endpoint	70.0±15.8	65.1±18.3	5.0	0.3, 9.8[b]	68.9±17.2	62.2±18.1	8.2	3.0, 13.3[b]
Change from baseline	5.9±14.6	0.8±15.5			8.8±17.5	0.5±11.8		

	Difference between treatments	CI 95%	p value
Overall treatment effect between Entacapone and Placebo	6.6	(3.6, 9.6)	0.0001
Interaction between Treatment and Hoehn & Yahr			0.2939

A) Statistical method E, Analysis of covariance for subgroups
b) Bonferroni adjusted confidence intervals

Table 28. Proportion of daily ON time by the use of selegiline at baseline and endpoint; Intent-to-Treat Analysis, 18-hour data (06:00 - 24:00) in studies 2939033 and 2939044 combined

	Proportion of daily on time							
	Selegiline (N = 178)				No Selegiline (N = 198)			
	Entacapone (N = 94)	Placebo (N = 84)	Difference between treatments[A]	CI 95%	Entacapone (N = 94)	Placebo (N = 104)	Difference between treatments[A]	CI 95%
Baseline	63.1±14.5	64.2±13.2			61.3±15.2	61.9±16.0		
Endpoint	69.9±16.6	66.7±16.6	4.2	-0.9, 9.3[b]	69.1±16.3	61.5±19.2	8.3	3.6, 13.1[b]
Change from baseline	6.8±16.3	2.6±12.3			7.8±15.9	-0.9±14.9		

	Difference between treatments	CI 95%	p value
Overall treatment effect between Entacapone and Placebo	6.3	3.2, 9.3	0.0002
Interaction between Treatment and Selegiline			0.1649

A) Statistical method E, Analysis of covariance for subgroups
b) Bonferroni adjusted confidence intervals

Table 29. Proportion of daily ON time by the use of dopamine agonists at baseline and endpoint; Intent-to-Treat Analysis, 18-hour data (06:00 - 24:00) in studies 2939033 and 2939044 combined

	Proportion of daily on time							
	Dopamine agonist (N = 190)				No Dopamine agonist (N = 186)			
	Entacapone (N = 96)	Placebo (N = 94)	Difference between treatments[A]	CI 95%	Entacapone (N = 89)	Placebo (N = 93)	Difference between treatments[A]	CI 95%
Baseline	63.0±14.9	64.0±14.1			61.4±14.8	61.9±15.6		
Endpoint	70.5±16.5	64.9±15.8	6.8	1.8, 11.7[b]	68.4±16.4	62.8±20.4	6.1	1.2, 11.1[b]
Change from baseline	7.6±17.1	0.7±12.6			6.9±15.1	0.6±15.1		

	Difference between treatments	CI 95%	p value
Overall treatment effect between Entacapone and Placebo	6.4	3.4, 9.5	0.0001
Interaction between Treatment and Donamine Agonists			0.8311

A) Statistical method E, Analysis of covariance for subgroups
b) Bonferroni adjusted confidence intervals

Table 30. Proportion of daily ON time by mean daily dose of levodopa (mg) from home diary at endpoint; Intent-to-Treat Analysis, 18 hour data (06:00 - 24:00) in studies 2939033 and 2939044 combined

	Proportion of daily on time								
	Entacapone (N = 188)				Placebo (N = 188)				Difference between treatments[A]
Daily levodopa dose (mg)	N	Baseline	Endpoint	Change from baseline	N	Baseline	Endpoint	Change from baseline	Difference (CI 95%)
< 500	55	61.1±16.2	68.9±15.9	7.9±17.3	49	63.4±14.4	66.2±19.7	2.0±14.8	5.3 (-2.1, 12.6)[b]
≥ 500 to < 1000	109	63.1±14.4	70.3±15.6	7.2±14.6	94	62.5±16.2	63.0±18.8	0.5±13.7	6.8 (1.8, 11.9)[b]
≥ 1000	24	60.7±13.8	66.8±21.1	6.2±20.0	45	63.5±12.4	63.2±15.6	-0.3±13.6	6.9 (-2.4, 16.1)[b]

	Difference (CI 95%)	p value
Overall treatment effect between Entacapone and Placebo	6.3 (2.9, 9.8)	0.0008
Interaction between Treatment and Levodopa dose		0.9007

A) Statistical method E, Analysis of covariance for subgroups
b) Bonferroni adjusted confidence intervals

6-month report[1)]

MONTH		0	0,5	3	6	9	12	12,5
Visit window (days)			±7	±14	±14	±14	±14	±7
VISIT	SCREENING	1	2	3	4	5	6	POST STUDY
STUDY DESIGN								
• Individual levodopa medication	X#####	X-----				#######		----->
• Entacapone/placebo medication		X-----					X	
SCREENING								
• Inclusion/exclusion	X							
• Informed consent	X							
• Randomization		X						
• Physical examination	X							X
SAFETY MEASURES								
• Recording of medication	X	X	X	X	X	X	X	X
• Hematology/biochemistry	X	X	X	X	X	X	X	X
• BP, HR, ECG	X	X	X	X	X	X	X	X
• Adverse events		X	X	X	X	X	X	X
EFFICACY MEASURES								
• UPDRS		X	X	X	X	X	X	X
• Global evaluation		X	X	X	X	X	X	X
• Duration of benefit of a single levodopa dose		X	X	X	X	X	X	X
• Dosing interval		X	X	X	X	X	X	X
OTHER								
• Recording of medications								
• Plasma 3-OMD		X		X	X	X	X	
• Tablet count				X	X	X	X	

- 1) For this report, data up to month 6 (visit 4) was included. The 3-OMD concentrations were obtained from baseline (visit 1) and at month 3 (visit 3).
- Screening visit was scheduled 2 to 4 weeks before visit 1.
- ###: stable treatment period (levodopa dosing frequency and amount of levodopa per dose should not have been changed).

Table. **Efficacy variables (mean±SD), ITT-LOCF**

Variable	Entacapone (n=218)		Placebo (n=108)		Difference between treatments (ANOVA)
	baseline	month 6	baseline	month 6	p [CI95%]
UPDRS: Motor score(part III)	23.1±11.3	20.8±12.4	21.9±10.5	20.0±11.4	NS
Mentation, behavior, and mood (part I)	1.2±1.3	1.3±1.6	1.3±1.4	1.2±1.4	NS
ADL (part II)	9.5±5.6	8.9±6.2	8.9±4.6	8.6±4.9	NS
Total score (parts I, II, and III)	33.9±16.1	31.0±18.3	32.1±14.0	29.8±15.6	NS
Levodopa dosing: Dose (mg/day)	605±298	567±272	662±362	651±362	p<0.01 [-68.13;-19.75]
Dosing frequency (doses/day)	4.2±1.4	4.1±1.3	4.3±1.5	4.3±1.5	NS
Benefit of morning levodopa	3.7±1.6	4.0±1.5	3.7±1.0	3.8±1.3	NS
Morning levodopa dosing interval	4.6±2.0	4.8±1.8	4.4±1.7	4.4±1.8	p<0.01 [0.08;0.51]
Global evaluation - worsened (%)	-	28	-	26	NS
- no change (%)	-	48	-	57	
- improved (%)	-	24	-	18	
3-OMD (µg/ml)	4.9±3.6	2.7±1.9	5.1±4.5	5.0±3.9	p<0.001 [-1.6;-1.0]

STUDY 52

BEST COPY AVAILABLE

070

Table R1. Patients randomized.

Patient group	Entacapone (n)	Placebo (n)
Total number of patients entered	218	108
Discontinued due to adverse events	17	11
Discontinued due to lack of efficacy	0	2
Discontinued due to other reasons	3	1
Completed	198	94
Evaluated for safety	218	108
Evaluated for efficacy (ITT)	218	108
- Patients using 2-4 daily levodopa doses	147	72
- Patients using 5-10 daily levodopa doses	71	36
Evaluated for efficacy (PP)	187	89
- Patients using 2-4 daily levodopa doses	131	62
- Patients using 5-10 daily levodopa doses	56	27

Table. Background information of ITT population

Parameter	Entacapone	Placebo	Significance
No. of patients	218	108	-
Age (yrs)	61.6± 9.2	62.8± 9.4	NS
Sex F/M (%)	67/33	70/38	NS
Age at onset of PD (yrs)	55.7±10.2	57.4±10.1	NS
Duration of PD (yrs)	6.3 ± 4.7	5.7± 4.2	NS
Modified H&Y	2.2±0.7	2.1±0.6	-
Schwab & England ADL	83.2±11.2	83.9±10.0	-
Levodopa dose (mg)	605±298	662±362	NS
CR preparations (%)	66	76	-

Table R3. Protocol deviations.

Type of deviation	Number of patients and description of deviation
Patients who did not satisfy the entry criteria	- two patients were treated with apomorphine occasionally during the study - one patient had periciazine as concomitant medication, the patient was dropped out - three patients did not meet the criteria for stable levodopa treatment for 2 weeks prior to randomization - one patient enrolled was of fertile age and without contraception (patient's own wish, consent in writing)
Other important deviations	- one patient took only half of the entacapone tablet with each levodopa dose during the study after being 5 days without study treatment due to diarrhea - there were 11 patients temporarily without study medication for some periods between the study visits (6 patients for 1-14 days and 5 patients for 15-30 days) - eight patients took 1-2 doses and one patient 4 doses less study treatment than scheduled for different periods during the study - thirteen patients did not meet the compliance criteria - visit windows were exceeded by some patients for a variety of reasons; this was not considered to represent a major protocol violation - written informed consent was not obtained until study visit 1 from 22 patients - in some centers a couple of 3-OMD samples were handled at room temperature at the beginning of the study

Table R2. Reasons for discontinuations.

Reason for discontinuation	Entacapone (n=218) n	(%)	Symptom	Placebo (n=108) n	(%)	Symptom
Dyskinesias	4	1.8	Dyskinesias	0	0	
Gastrointestinal symptoms	3	1.4	Abdominal pain	1	0.9	Abdominal pain
	4	1.8	Diarrhea			
Subtotal	7	3.2		1	0.9	
Other AEs	1	0.5	Confusion and paranoia (SAE)	1	0.9	Stomach carcinoma, died (SAE)
	1	0.5	Syncope (SAE)	1	0.9	Amnesia
	1	0.5	Nausea, insomnia	1	0.9	Nausea
	1	0.5	Postural hypotension (SAE)	1	0.9	Leukemia, died (SAE) (suicide)
	1	0.5	Sepsis, died (SAE)			
	1	0.5	Skin cold clammy	1	0.9	Esophageal carcinoma, died (SAE)
				1	0.9	Brain infarction, died (SAE)
				1	0.9	Hemiparesis (SAE)
				1	0.9	Tremor
				1	0.9	Nausea, headache
				1	0.9	Vomiting, confusion (SAE)
Subtotal	6	2.8		10	8.3	
Other reasons	1	0.5	Protocol violation	2	1.9	Lack of efficacy
	2	0.9	Non-compliance	1	0.9	Non-compliance
Subtotal	3	1.4		3	2.8	
Total no of discontinuations	20	9		14	13	

Table R6. History of Parkinson's disease by stratification (mean±SD); ITT population

Parameter	Entacapone		Placebo		Signific.
Stratification (no. of daily doses)	2 - 4	5 - 10	2 - 4	5 - 10	-
Number of patients	147	71	72	36	-
Age at baseline(years)	62.0±9 .1	60.9±9.4	63.8±9.1	60.6±9.8	NS
Age at onset of PD (years)	57.6±9.3	51.6±10.9	59.5±9.6	52.9±10.1	NS
Duration of PD (years)	4.7±3.8	9.5±4.7	4.7±3.7	8.1±4.7	NS
Duration of levodopa treatment (years)	4.4±3.5	8.7±4.5	4.2±3.6	7.3±4.0	NS

Table R7. Levodopa dosing at baseline (mean±SD); ITT population.

Parameter	Entacapone	Placebo	Significance
Daily levodopa dose (mg)	605±298	662±362	NS
Number of daily doses	4.2±1.4	4.3± 1.5	NS

Table R8. Levodopa doses at baseline by stratification and treatment group (%); ITT population.

Parameter	Stratification								
	2 to 4 levodopa doses (entacapone n=147) (placebo n=72)			5 to 10 levodopa doses (entacapone n=71) (placebo n=36)					
No. of doses	2	3	4	5	6	7	8	9	10
Entacapone (%)	6.1	53.1	40.8	43.7	33.8	12.7	7.0	2.8	0
Placebo (%)	6.9	38.9	54.2	38.9	33.3	19.4	2.8	2.8	2.8

Table R9. DDC inhibitor used at baseline; ITT population.

Treatment	Entacapone		Placebo		Signific.
	n	%	n	%	
Carbidopa	117	54	66	61	-
Benserazide	84	38	32	30	-
Carbidopa and benserazide	17	8	10	9	-
Total	218	100	108	100	NS

Table R10. Levodopa preparations at baseline; ITT population.

Type of levodopa preparation	Entacapone		Placebo	
	n	%	n	%
Standard preparations	72	33	26	24
CR preparations	74	34	42	39
Combination of standard and CR	62	28	37	34
Other CR combinations	7	3	3	3
Other combinations	3	1	0	0
Total	218	100	108	100

Table R11. Concomitant antiparkinsonian medication at baseline; ITT population.

Therapy group	Entacapone (n=218)			Placebo (n=108)		
	n	%	daily dose (mg) mean ± SD	n	%	daily dose (mg) mean ± SD
Selegiline	180	83	9.0 ± 2.0	91	84	9.1 ± 1.9
opamine agonists	114	52		52	48	
Pergolide	43	20	1.1 ± 0.9	17	16	1.3 ± 1.0
Bromocriptine	71	33	10.4 ± 5.3	35	32	10.2 ± 5.4
Amantadine	9	4.1	122 ± 51	1	0.9	200
Apomorphine	1	0.5	NA	1	0.9	NA
Anticholinergic agents	16	7.3		11	10	
Trihexyphenidyl	4	1.8	4.8 ± 3.6	0	0	-
Benzatropine	2	0.9	1.5 ± 0.7	0	0	-
Procyclidine	1	0.5	15.0	0	0	-
Biperidine	5	2.3	4.0 ± 2.0	4	3.7	5.5 ± 1.0
Orfenadine	4	1.8	93.8 ± 42.7	7	6.5	85.7 ± 24.4

Table R12. Concurrent diseases at baseline; ITT population.

Disease	Entacapone (n=218)		Placebo (n=108)	
	n	%	n	%
Coronary heart disease	24	11.0	4	14.8
Arterial hypertension	23	10.6	9	8.3
Hyperplasia of prostate	11	5.0	1	0.9
Asthma (bronchial asthma)	9	4.1	4	3.7
Disease of spinal column	9	4.1	1	0.9
Diabetes mellitus	8	3.7	7	6.5
Glaucoma	8	3.7	3	2.8
Cardiac arrhythmia	8	3.7	3	2.8
Hypothyreosis	6	2.8	3	2.8
Arthrosis/ arthritis	6	2.8	4	3.7
Sleep disturbances (insomnia)	5	2.3	4	3.7
Cardiac insufficiency	5	2.3	4	1.9
Miscellaneous	88	-	42	-

Table R13. Concomitant drug therapy at baseline; ITT population.

Drug therapy group	Entacapone (n=218)		Placebo (n=108)	
	n	%	n	%
Psycholeptics (antipsychotics, anxiolytics, hypnotics, and sedatives)	58	26.6	28	25.9
Psychoanaleptics (antidepressants and psychostimulants and their combination with psycholeptics)	34	15.6	11	10.2
Anti-inflammatory drugs	28	12.8	10	9.3
Diuretics	18	8.3	5	4.6
ertensives	16	7.3	5	4.6
s	14	6.4	3	2.8
ics	13	6.0	6	5.6

Table R14. Clinical disability (mean ± SD); ITT population.

UPDRS sub scores	Entacapone (n=218)	Placebo (n=108)
Mentation, behavior, mood, (Part I)	1.2 ± 1.3	1.3 ± 1.4
Activities in daily living (Part II)	9.5 ± 5.6	8.9 ± 4.6
Motor examination (Part III)	23.1 ± 11.3	21.9 ± 10.5
Sum of Parts I, II, and III	33.9 ± 16.1	32.1 ± 14.0
Modified Hoehn and Yahr	%	%
1	7.8	10.2
1.5	11.9	11.1
2	36.2	41.7
2.5	25.2	22.2
3	15.1	12.0
4	3.2	2.8
5	0.5	0
Modified Hoehn and Yahr (mean±SD)	2.2±0.7	2.1±0.6
Schwab and England ADL (mean±SD)	83.2±11.2	83±10.0

Table R29. Motor examination (mean±SD) of UPDRS Part III; ITT-LOCF.

Stratification	Time	Entacapone	Placebo	Significance
2-4 doses	baseline	22.5±10.0	21.7± 9.5	-
	month 6	19.5±10.8	19.5± 8.8	NS
5-10 doses	baseline	24.4±13.5	22.2±12.3	-
	month 6	23.5±14.9	21.1±15.4	NS
All patients	baseline	23.1±11.3	21.9±10.5	-
	month 6	20.8±12.4	20.0±11.4	NS

Table R30. Activities of daily living (mean±SD), (UPDRS Part II) ; ITT-LOCF.

Stratification	Time	Entacapone	Placebo	Significance
2-4 doses	baseline	8.1±4.1	8.0± 3.6	-
	month 6	7.4±5.0	7.6 ± 3.9	NS
5-10 doses	baseline	12.4 ± 7.0	10.7 ± 5.7	-
	month 6	11.9 ± 7.3	10.6 ± 6.1	NS
All patients	baseline	9.5 ± 5.6	8.9 ± 4.6	-
	month 6	8.9 ± 6.2	8.6 ± 4.9	NS

Table R31. UPDRS, Sum of Parts I, II and III, (mean±SD); ITT-LOCF.

Stratification	Time	Entacapone	Placebo	Significance
2-4 doses	baseline	31.7±13.4	30.9±12.1	-
	month 6	28.0±15.5	28.1±11.9	NS
5-10 doses	baseline	38.4±19.9	34.4±17.2	-
	month 6	37.2±22.0	33.3±20.8	NS
All patients	baseline	33.9±16.1	32.1±14.0	-
	month 6	31.0±18.3	29.8±15.6	NS

Table R32. Duration of dyskinesias as % of day (UPDRS Part IV) (% of the patients); ITT-LOCF.

Treatment	Time	None (%)	1-25 % (%)	26-50 % (%)	>50 % (%)
Entacapone (n=218)	baseline	59.2	30.7	8.3	1.8
	month 6	56.0	30.3	6.4	7.3
Placebo (n=108)	baseline	60.2	29.6	9.3	0.9
	month 6	65.7	25.9	6.5	1.9

Table R33. Disability of dyskinesias (% of the patients with dyskinesia) ; ITT-LOCF.

Treatment	Time	Not disabling	Mildly disabling	Moderately disabling	Severely disabling
Entacapone (n=110)	baseline	43.6	32.7	22.7	0.9
	6 months	41.8	32.7	20.0	5.4
Placebo (n=48)	baseline	45.8	33.3	16.7	4.2
	6 months	50.0	25.0	25.0	0

Table R34. Painful dyskinesias (% of the patients with dyskinesias).

Treatment	Time	Not painful	Slighdy painful	Moderately painful	Severely painful
Entacapone (n=110)	baseline	80.0	14.5	5.5	0
	6 months	76.4	14.5	7.3	1.8
Placebo (n=48)	baseline	83.3	10.4	6.3	0
	6 months	81.3	12.5	2.1	4.2

Table R35. Proportion of OFF time (% of patients); ITT-LOCF.

Treatment	Time	None	1-25 %	26-50 %	>50 %
Entacapone	baseline	42.7	43.6	11.5	2.3
(n=218)	month 6	48.2	42.7	6.4	2.8
Placebo	baseline	42.6	48.1	8.3	0.9
(n=108)	month 6	45.4	47.2	3.7	3.7

Table R37. Schwab and England ADL by stratification (% of patients), ITT LOCF.

ADL score	Stratification 2-4 doses				Stratification 5-10 doses			
	Entacapone		Placebo		Entacapone		Placebo	
	baseline	month 6	baseline	month 6	baseline	month 6	baseline	month 6
>80%	64.4	72.8	58.4	65.3	35.2	39.4	55.6	44.4
80%	27.4	15.0	33.3	25.0	39.4	32.4	27.8	25.0
<80%	8.3	12.3	8.4	9.7	25.3	28.1	16.7	30.6

Table R38. Global evaluation by categories (% of patients); ITT-LOCF.

Treatment	Time	Very poorly, poorly, rather poorly	Not well, nor poorly	Rather well, well, very well
Entacapone	baseline	11.9	19.3	68.8
	month 6	14.3	19.3	66.5
Placebo	baseline	6.5	20.4	73.1
	month 6	13.0	18.5	68.5

Table R39. Global evaluation (% of patients); ITT-LOCF

Stratification	Entacapone			Placebo		
	Worsened	No change	Improved	Worsened	No change	Improved
2-4 doses	23.8	51.7	24.5	25.0	55.6	19.4
5-10 doses	36.6	39.4	23.9	27.8	58.3	13.9
All patients	28.0	47.7	24.3	25.9	56.5	17.6

Table R41. Patients (%) changing their scheduled daily levodopa doses from baseline to month 6; ITT-LOCF.

Stratification	Entacapone			Placebo		
	Decrease	No change	Increase	Decrease	No change	Increase
2-4 doses	18.4	66.7	15.0	12.5	79.2	8.3
5-10 doses	46.5	50.7	2.8	27.8	55.6	16.7
All patients	27.5	61.5	11.0	17.6	71.3	11.1

Table R42. Mean dosing frequency (mean±SD) of levodopa; ITT-LOCF.

Stratification	Time	Entacapone (n=218)	Placebo (n=108)	Significance
2-4 doses	baseline	3.3±0.6	3.5±0.6	NS
	month 6	3.4±0.6	3.5±0.7	NS
5-10 doses	baseline	5.9±1.1	6.1±1.2	NS
	month 6	5.5±1.2	5.9±1.3	NS
All patients	baseline	4.2±1.4	4.3±1.5	NS
	month 6	4.1±1.3	4.3±1.5	NS

Table R36. Schwab and England ADL (% 0f patients), ITT-LOCF.

Treatment	Time	<80 %	80 %	>80 %
Entacapone	baseline	13.8	31.3	54.6
	month 6	17.4	20.6	61.9
Placebo	baseline	11.1	31.5	57.4
	month 6	16.7	25.0	58.3

Table 10.5 Controlled phase II studies: multiple-dose study - 28

Assessment Methodology	Results
Clinical effects: …ration of ON time [1]) was …ined at hospital after a …rd levodopa dose: frequent …g with tapping and walking …s were used. In addition, global evaluation of PD symptoms, and scoring of tremor and dyskinesias were performed frequently. All these ratings were conducted up to 6 h after the test dose. • Duration of daily ON and OFF times were determined during 2 consecutive days preceding each study visit using a home diary. *Biochemistry:* Plasma concentrations of levodopa, 3-OMD, and entacapone, and the COMT enzyme activity in red blood cells were determined. *Safety:* AEs, vital signs, and lab safety parameters were followed.	*Clinical effects:* Levodopa test at hospital: • No statistically significant differences in the duration of ON time were observed between different doses of entacapone and placebo probably because the Parkinson's disease fluctuations were mild in many patients. Home Diary: • The proportion of daily ON time slightly but not statistically significantly increased with different doses of entacapone (placebo 76%; 100 mg 78%; 200 mg 80%; 400 mg 81 %) • Daily ON time increased dose-dependently by 0 to 7% compared with placebo • Daily OFF time decreased dose-dependently by 11 to 20% compared with placebo • At the same time, daily levodopa dosage decreased significantly ($p<0.05$, compared with placebo period) with each dose level: 100 mg -3%; 200 mg -15%; 400 mg - 17%. *Biochemical effects :* Entacapone • increased dose-dependently the AUC_{0-6h} of levodopa: +17% ($p<0.05$, 100 mg), +27% ($p<0.001$, 200 mg), +37% ($p<0.001$, 400 mg) • increased dose-dependently the $t_{1/2el}$ of levodopa: +23% ($p<0.05$, 100 mg), +26% ($p<0.001$, 200 mg), +48% ($p<0.001$, 400 mg) • decreased dose-dependently the AUC of 3-OMD: -39% (100 mg), -54% (200 mg), -66% (400 mg) ($p<0.001$ for each dose, compared with placebo) • inhibited COMT activity at 90 min: by 24% (100 mg), by 32% (200 mg), by 33% (400 mg), ($p<0.001$ for each dose, compared with placebo) A positive correlation between entacapone dose and its plasma levels at 90 min ($p<0.05$). *Safety:* No dose-related adverse events.

1) The criteria for ON: A) The tapping speed exceeded the baseline value (mean of three testings prior to drug intake in the morning) by at least 15% B) The walking time was at least 20% less than the baseline value (mean of three testings prior to drug intake in the morning).

Table 10.6 Changes in the daily ON and OFF times during the 12-hour diary day in study -28

	Placebo	Entacapone 100 mg	Entacapone 200 mg	Entacapone 400 mg
• Proportion of ON time during the 12-hour diary day	76%	78%	80%	81%
• ON time (hours)	11.5	11.5	12.2	12.3
• Change in ON time compared to placebo; hours (%)	-	+ 0.0 (0%)	+0.8 (7%)	+0.7 (6%)
…portion of OFF time during …2-hour diary day	24%	22%	20%	19%
…time (hours)	3.7	3.3	3.0	2.8
…ge in OFF time compared …o placebo; hours (%)	-	- 0.39 (-11%)	- 0.67 (-18%)	-0.73 (-20%)
• Levodopa (mg/day)	626 ± 295	608 ± 349*	530 ± 273*	518 ± 232*

* $p<0.05$

Table 10.7 Effect of entacapone on levodopa pharmacokinetics in study -28

Variable	Placebo	Entacapone 100 mg	Entacapone 200 mg	Entacapone 400 mg
C_{max} (h)	1688 ± 752	1459 ± 661 NS	1426 ± 585 NS	1434 ± 534 NS
t_{max} (h)	0.71 ± 0.32	0.83 ± 0.64 NS	1.12 ± 0.67 NS	1.00 ± 0.50 NS
AUC_{0-4h} (nghml-1)	2630 ± 1040	2900 ± 1375 NS	3073 ± 1255**	3250 ± 1332***
AUC_{0-6h} (nghml-1)	2868 ± 1093	3361 ± 1590*	3655 ± 1589***	3937 ± 1678***
$t_{1/2}$ (h)	1.344 ± 0.216	1.654 ± 0.380*	1.691 ± 0.274***	1.984 ± 0.490***

Mean ± SD, number of patients =18-19, *$p<0.05$, **$p<0.01$, ***$p<0.001$

Table 10.4 ON time during levodopa test, ON time from home diary and the motor score of UPDRS during entacapone and placebo phases in study -30

Parameter	Entacapone	Placebo	p value	CI 95%
ON time in levodopa test (min)	174 ± 52	140 ± 55	0.0012	15.6,54.4
ON time from home diary (h)	11.5 ± 3.0	9.2 ± 3.2	0.0049	0.7,3.5
UPDRS motor score	41.4 ± 6.3	42.8 ± 5.6	0.0248	-2.5,-0.2

Mean ± SD
Patients with both treatment periods are included (N=23). The p value refers to difference between entacapone and placebo treatments.

Table 10.2 Multiple-dose, placebo-controlled, double-blind, crossover studies with simultaneous measurement of levodopa pharmacokinetics and clinical disability in PD patients with end-of-dose response fluctuations.

Study	• Treatment periods • DDC inhibitor	Number of patients	Age range (years)	Mean disease duration (years)	Entacapone doses (mg)	Methods
2939 30	• Two 4-week periods • carbidopa, benserazide	26	46-75	13.3	200	UPDRS Part III, dyskinesia score, plasma levodopa, home diary
2939 28	• Four 2-week periods • carbidopa	25	43-77	10.6	100, 200, 400	Tapping and walking tests, tremor and dyskinesia score, global evaluation, plasma levodopa, and home diary
2939 16	• Two 4-week periods • carbidopa	10	42-66	11.7	200	Tapping and walking tests, tremor and dyskinesia score, global evaluation, plasma levodopa, and home diary

Table 10.3 Controlled phase II studies: multiple-dose dose study - 30

Assessment Methodology	Results
Clinical effects: • Duration of ON time [1]) was determined after a single, standard levodopa dose at hospital: scoring with modified motor part of the UPDRS supplemented with an assessment of dyskinesias was conducted frequently up to 6 h after dosing. • Duration of daily ON time was determined during three consecutive days preceding each study visit using a home diary. *Biochemistry:* Plasma consecrations of levodopa, 3-OMD, HVA, DOPAC, entacapone, and the Z-isomer were determined. *Safety:* AEs, vital signs, and lab safety parameters were followed.	*Clinical effects:* Testing at hospital: • The duration of motor response prolonged by 34 min (24%) with entacapone compared with placebo ($p<0.01$, difference between treatments). • The duration of dyskinesias after a standard levodopa dose increased from 119 to 145 min with entacapone and decreased to 106 min with placebo ($p<0.01$, difference between treatments). Home Diary: • The mean daily ON time increased by 2.5h (+27%) with entacapone and by 0.35 h (+4%) with placebo; difference between treatments is 2.1 h ($p<0.01$) • The mean daily levodopa dose was decreased from 860 mg to 720 mg ($p<0.01$). *Biochemical effects* • AUC_{0-4h} of levodopa increased by 35% ($p<0.001$) • $t_{1/2el}$ of levodopa increased by 30% ($p<0.001$) • No changes in C_{max} and t_{max} of levodopa • AUC of 3-OMD decreased by 64% ($p<0.001$) *Safety:* • Urine discoloration, nausea, abdominal pain, and dyskinesias were the most frequent AEs

1) Duration of the ON time was defined as the time during which the score was at least 10% below the baseline score (the mean of the first two scores in the morning, i.e., 30 min and just before the test dose of levodopa).

Table 11.2 The duration and magnitude of response, the latency to response and the pharmacokinetic parameters of levodopa after a single standard dose of levodopa without (control) and with entacapone 200 mg

Study	Parameter	Control (mean)	Entacapone (mean)	Increase vs. control (%)	p value
- 12[a])	Levodopa AUC (n=16)	3887	5314	+37	$p<0.001$
	Motor ON time, min (n=15)	92	120	+30	ns
- 13	Levodopa AUC (n=12)	4427	5720	+29	$p<0.05$
	Motor ON time, hours (n=12)	2.3	3.2	+39	$p<0.05$
- 14	Levodopa AUC (n=10)	3704	4998	+35	$p<0.001$
	Motor ON time (n=10)	nd	nd	nd	nd
- 27	Levodopa AUC (n=6)	4392	5836	+33	$p<0.001$
	Motor ON time, min (n=12)	210	260	+24	$p<0.05$
- 35	Levodopa AUC (n=12)	5982	9106	+52	$p<0.001$
	Motor ON time, hours (n=11)	3.1	2.9	-6	ns

a)Two separate 200 mg doses of entacapone, data from the first levodopa test (acute dosing)
AUC of levodopa is presented as h · ng/mL b) for ratio of means, nd= not determined
- Tapping-test was used in study -12 to determine ON-time. The ON time results in other studies are based on the motor score of the UPDRS (Part III).
Study Reports -12, -13, -14, -27, -35

2939 033

Subject No. ____

Subject Initials ____ (First Last)

Visit: POST STUDY

REVIEW OF THE HOME DIARY

TOTAL SCORES FROM THE HOME DIARIES FIVE DAYS PRECEDING THE VISIT TO THE CLINIC

MORNING LEVODOPA TEST

day / month	levodopa preparation	mg	time the dose was taken	time the benefit started	time the benefit ended
Day -5			hour min	hour min	hour min
Day -4			hour min	hour min	hour min

Comments: _____

DAILY "ON" TIME (EVALUATION BETWEEN 6.00 - 24.00)

day / month	total daily dose of levodopa (mg)	number of doses/day	TOTAL ON	TOTAL OFF	TOTAL IN BED
Day -3			hour min	hour min	hour min
Day -2			hour min	hour min	hour min
Day -1			hour min	hour min	hour min

Comments: _____

Please, attach the home diary after this page.

Date: ____ (D M Y)

Investigator's Signature _____

2939 033

Subject No. ⌊_|_|_|_⌋

Subject Initials ⌊_|_|_|_⌋ First Last

Visit: POST STUDY

GLOBAL EVALUATION

GENERAL EVALUATION

Please evaluate the patient's condition DURING THE WEEK PRECEDING THIS VISIT on the following 7-point scale.

The patient has coped with his/her Parkinson's disease

Investigator's evaluation	Patient's evaluation (copied from the home diary)		
☐	☐	+ 3	very well
☐	☐	+ 2	well
☐	☐	+ 1	rather well
☐	☐	0	not well, not poorly
☐	☐	- 1	rather poorly
☐	☐	- 2	poorly
☐	☐	- 3	very poorly

DURATION OF BENEFIT OF A SINGLE LEVODOPA DOSE

How long does the patient have benefit from a single levodopa dose on average?
(Record with 15 minutes accuracy e.g. 1 h 15 min)

⌊_|_|_|_⌋ hour min

Date: ⌊_|_|_|_|_|_⌋ D M Y

Investigator's Signature

2939 033		
Subject No.	Subject Initials First Last	Visit 1

* DAILY FLUCTUATIONS IN DISABILITY (past week)

Symptom		Yes	No	(If yes) Frequency /day	(If yes) Severity 0 = none 1 = slight 2 = moderate 3 = severe 4 = very severe
Predictable fluctuations (dose related)	**I - End of dose failure**				
	1 Daily wearing-off	☐	☐	☐☐	☐
	2 Nocturnal akinesia	☐	☐	☐☐	☐
	3 Early morning akinesia	☐	☐		☐
	4 "Off" period freezing	☐	☐	☐☐	☐
	II - Dyskinesia				
	1 Peak-dose dyskinesias	☐	☐	☐☐	☐
	2 Early morning dystonia	☐	☐		☐
	3 Daily "off" period dystonia	☐	☐	☐☐	☐
	4 Daily "on" period dystonia	☐	☐	☐☐	☐
Unpredictable fluctuations	1 Unpredictable rapid fluctuations (complex "on" - "off")	☐	☐	☐☐	☐
	2 Random freezing	☐	☐	☐☐	☐
Other, specify		☐	☐	☐☐	☐

Date: ☐☐☐☐☐☐ (D M Y)

Investigator's Signature

2939 033		
Subject No.	Subject Initials First Last	Visit SCRE

Last levodopa medication taken at (hour min) ____ o'clock

Time of the assessment ____ o'clock

Note! The rating will be done when the patient is best "on", - before noon.

* UNIFIED PARKINSON'S DISEASE RATING SCALE (UPDRS)

I: MENTATION, BEHAVIOR AND MOOD

Rate items 1-4 by interview. Please sign the score in the appropriate box.

1. **Intellectual impairment:**
   - 0 = None
   - 1 = Mild; consistent forgetfulness with partial recollection of events and no other difficulties
   - 2 = Moderate memory loss, with disorientation and moderate difficulty handling complex problems; mild but definite impairment of function at home, with need of occasional prompting
   - 3 = Severe memory loss with disorientation for time and often to place, severe impairment in handling problems
   - 4 = Severe memory loss with orientation preserved to person only; unable to make judgments or solve problems; requires much help with personal care; cannot be left alone at all

   ☐

2. **Thought disorder (due to dementia or drug intoxication):**
   - 0 = None
   - 1 = Vivid dreams
   - 2 = "Benign" hallucinations with insight retained
   - 3 = Occasional to frequent hallucinations or delusions; without insight; could interfere with daily activities
   - 4 = Persistent hallucinations, delusions, or florid psychosis: not able to care for self

   ☐

3. **Depression:**
   - 0 = Not present
   - 1 = Periods of sadness or guilt greater than normal but never sustained for days or weeks
   - 2 = Sustained depression (1 week or more)
   - 3 = Sustained depression with vegetative symptoms (insomnia, anorexia, weight loss, loss of interest)
   - 4 = Sustained depression with vegetative symptoms and suicidal thoughts or intent

   ☐

4. **Motivation / Initiative:**
   - 0 = Normal
   - 1 = Less assertive than usual; more passive
   - 2 = Loss of initiative or disinterest in elective (nonroutine) activities
   - 3 = Loss of initiative or disinterest in day-to-day (routine) activities
   - 4 = Withdrawn; complete loss of motivation

   ☐

2939 033		
Subject No. ⌊⌊⌊⌊⌋	Subject Initials ⌊⌊⌊⌊⌋ First Last	Visit SCRE

UNIFIED PARKINSON'S DISEASE RATING SCALE (UPDRS)

II: ACTIVITIES IN DAILY LIVING

Rate items 5-17 by interview. Please sign the score in the appropriate box.

5. **Speech:** ⌊⌋
   - 0 = Normal
   - 1 = Mildly affected; no difficulty being understood
   - 2 = Moderately affected; sometimes asked to repeat statements
   - 3 = Severely affected; frequently asked to repeat statements
   - 4 = Unintelligible most of the time

6. **Salivation:** ⌊⌋
   - 0 = Normal
   - 1 = Slight but definite excess of saliva in mouth; may have night-time drooling
   - 2 = Moderately excessive saliva; may have minimal drooling
   - 3 = Marked excess of saliva; some drooling
   - 4 = Marked drooling; requires constant use of tissue or handkerchief

7. **Swallowing:** ⌊⌋
   - 0 = Normal
   - 1 = Rare choking
   - 2 = Occasional choking
   - 3 = Requires soft food
   - 4 = Requires nasogastric tube or gastrotomy feeding

8. **Handwriting:** ⌊⌋
   - 0 = Normal
   - 1 = Slightly slow or small
   - 2 = Moderately slow or small; all words are legible
   - 3 = Severely affected; not all words are legible
   - 4 = The majority of words are not legible

9. **Cutting food and handling utensils:** ⌊⌋
   - 0 = Normal
   - 1 = Somewhat slow and clumsy, but no help needed
   - 2 = Can cut most foods, although clumsy and slow; some help needed
   - 3 = Food must be cut by someone, but can still feed slowly
   - 4 = Needs to be fed

10. **Dressing:** ⌊⌋
    - 0 = Normal
    - 1 = Somewhat slow, but no help needed
    - 2 = Occasional assistance needed with buttoning, getting arms into sleeves
    - 3 = Considerable help required, but can do some things alone
    - 4 = Helpless

11. **Hygiene:** ⌊⌋
    - 0 = Normal
    - 1 = Somewhat slow, but no help needed
    - 2 = Needs help to shower or bathe, very slow in hygienic care
    - 3 = Requires assistance for washing, brushing teeth, combing hair, going to bathroom
    - 4 = Needs Foley catheter or other mechanical aids

(continued)

2939 033		
Subject No.	Subject Initials First Last	Visit SCRE

UNIFIED PARKINSON'S DISEASE RATING SCALE (UPDRS)

II: ACTIVITIES IN DAILY LIVING (continued)

12. Turning in bed and adjusting bedclothes: ☐
    - 0 = Normal
    - 1 = Somewhat slow and clumsy, but no help needed
    - 2 = Can turn alone or adjust sheets, but with great difficulty
    - 3 = Can initiate attempt, but cannot turn or adjust sheets alone
    - 4 = Helpless

13. Falling (unrelated to freezing): ☐
    - 0 = None
    - 1 = Rare falling
    - 2 = Occasionally falls, less than once daily
    - 3 = Falls an average of once daily
    - 4 = Falls more than once daily

14. Freezing when walking: ☐
    - 0 = None
    - 1 = Rare freezing when walking; may have start hesitation
    - 2 = Occasional freezing when walking
    - 3 = Frequent freezing; occasionally falls because of freezing
    - 4 = Frequently falls because of freezing

15. Walking: ☐
    - 0 = Normal
    - 1 = Mild difficulty; may not swing arms or may tend to drag leg
    - 2 = Moderate difficulty, but requires little or no assistance
    - 3 = Severe disturbance of walking; requires assistance
    - 4 = Cannot walk at all, even with assistance

16. Tremor: ☐
    - 0 = Absent
    - 1 = Slight and infrequently present
    - 2 = Moderate; bothersome to patient
    - 3 = Severe; interferes with many activities
    - 4 = Marked; inteferes with most activities

17. Sensory complaints related to parkinsonism: ☐
    - 0 = None
    - 1 = Occasionally has numbness, tingling, or mild aching
    - 2 = Frequently has numbness, tingling, or aching; not distressing
    - 3 = Frequent painful sensations
    - 4 = Excruciating pain

ORION-FARMOS PHARMACEUTICALS Entacapone 16 (137)

2939 033		
Subject No. ⌊⌊⌊⌊	Subject Initials ⌊⌊⌊⌊ First Last	Visit SCRE

UNIFIED PARKINSON'S DISEASE RATING SCALE (UPDRS)

III: MOTOR EXAMINATION

18. Speech: ⌊⌋
    - 0 = Normal
    - 1 = Slight loss of expression, diction and/or volume
    - 2 = Monotone, slurred but understandable; moderately impaired
    - 3 = Marked impairment, difficult to understand
    - 4 = Unintelligible

19. Facial expression: ⌊⌋
    - 0 = Normal
    - 1 = Minimal hypomimia; could be normal "poker face"
    - 2 = Slight but definitely abnormal diminution of facial expression
    - 3 = Moderate hypomimia; lips are parted some of the time
    - 4 = Masked or fixed facies, with severe or complete loss of facial expression; lips parted 1/4 inch or more

20. Tremor at rest:
    - 0 = Absent
    - 1 = Slight and infrequently present
    - 2 = Mild in amplitude and persistent, or moderate in amplitude but only intermittently present
    - 3 = Moderate in amplitude and present most of the time
    - 4 = Marked in amplitude and present most of the time

    ⌊⌋ face, lips, chin
    ⌊⌋ right hand
    ⌊⌋ left hand
    ⌊⌋ right foot
    ⌊⌋ left foot

21. Action or postural tremor of hands:
    - 0 = Absent
    - 1 = Slight; present with action
    - 2 = Moderate in amplitude; present with action
    - 3 = Moderate in amplitude; present with posture-holding as well as with action
    - 4 = Marked in amplitude; interferes with feeding

    ⌊⌋ right
    ⌊⌋ left

22. Rigidity (judged on passive movement of major joints with patient relaxed in sitting position; "cogwheeling" to be ignored):
    - 0 = Absent
    - 1 = Slight or detectable only when activated by mirror or other movements
    - 2 = Mild to moderate
    - 3 = Marked, but full range of motion easily achieved
    - 4 = Severe; range of motion achieved with difficulty

    ⌊⌋ neck
    ⌊⌋ right upper extremity
    ⌊⌋ left upper extremity
    ⌊⌋ right lower extremity
    ⌊⌋ left lower extremity

23. Finger taps (patient taps thumb with index finger in rapid succession with widest amplitude possible, each hand separately):
    - 0 = Normal
    - 1 = Mild slowing and/or reduction in amplitude
    - 2 = Moderately impaired; definite and early fatiguing; may have occasional arrests in movement
    - 3 = Severely impaired; frequent hesitation in initiating movements or arrests in ongoing movement
    - 4 = Can barely perform the task

    ⌊⌋ right
    ⌊⌋ left

(continued)

2939 033		
Subject No.	Subject Initials First Last	Visit SCRE

UNIFIED PARKINSON'S DISEASE RATING SCALE (UPDRS)

III: MOTOR EXAMINATION (continued)

24. Hand movements (patient opens and closes hands in rapid succession with widest amplitude possible, each hand separately):
    - 0 = Normal
    - 1 = Mild slowing and/or reduction in amplitude
    - 2 = Moderately impaired; definite and early fatiguing; may have occasional arrests in movement
    - 3 = Severely impaired; frequent hesitation in initiating movements or arrests in ongoing movement
    - 4 = Can barely perform the task

    ☐ right ☐ left

25. Rapid alternating movements of hand (pronation-supination movements of hands, vertically or horizontally, with as large an amplitude as possible both hands simultaneously):
    - 0 = Normal
    - 1 = Mild slowing and/or reduction in amplitude
    - 2 = Moderately impaired; definite and early fatiguing; may have occasional arrests in movement
    - 3 = Severely impaired; frequent hesitation in initiating movements or arrests in ongoing movement
    - 4 = Can barely perform the task

    ☐ right ☐ left

26. Leg agility (patient taps heel on ground in rapid succession, picking up entire leg; amplitude should be about 3 inches):
    - 0 = Normal
    - 1 = Mild slowing and/or reduction in amplitude
    - 2 = Moderately impaired; definite and early fatiguing; may have occasional arrests in movement
    - 3 = Severely impaired; frequent hesitation in initiating movements or arrests in ongoing movement
    - 4 = Can barely perform the task

    ☐ right ☐ left

27. Arising from chair (patient attempts to arise from a straight-backed wood or metal chair, with arms folded across chest):
    - 0 = Normal
    - 1 = Slow, or may need more than one attempt
    - 2 = Pushes self up from arms of seat
    - 3 = Tends to fall back and may have to try more than one time but can get up without help
    - 4 = Unable to arise without help

    ☐

28. Posture:
    - 0 = Normal erect
    - 1 = Not quite erect, slightly stooped posture; could be normal for older person
    - 2 = Moderately stooped posture, definitely abnormal; can be slightly leaning to one side
    - 3 = Severely stooped posture with kyphosis; can be moderately leaning to one side
    - 4 = Marked flexion, with extreme abnormality of posture

    ☐

29. Gait:
    - 0 = Normal
    - 1 = Walks slowly; may shuffle with short steps, but not festination or propulsion
    - 2 = Walks with difficulty but requires little or no assistance; may have some festination, short steps, or propulsion
    - 3 = Severe disturbance of gait; requires assistance
    - 4 = Cannot walk at all, even with assistance

    ☐

(continued)

2939 033		
Subject No.	Subject Initials First Last	Visit SCRE

UNIFIED PARKINSON'S DISEASE RATING SCALE (UPDRS)

III: MOTOR EXAMINATION (continued)

30. Postural stability (response to sudden posterior displacement produced by pull on shoulders while patient is erect, with eyes open and feet slightly apart; patient is prepaired):
    0 = Normal
    1 = Retropulsion, but recovers unaided
    2 = Absence of postural response; would fall if not caught by examiner
    3 = Very unstable; tends to lose balance spontaneously
    4 = Unable to stand without assistance

31. Body bradykinesia and hypokinesia (combining slowness, hesitancy, decreased arm swing, small amplitude and poverty of movement in general):
    0 = None
    1 = Minimal slowness, giving movement a deliberate character; could be normal for some persons; possibly reduced amplitude
    2 = Mild degree of slowness and poverty of movement that is definitely abnormal; alternatively, some reduced amplitude
    3 = Moderate slowness; poverty or small amplitude of movement
    4 = Marked slowness; poverty or small amplitude of movement

IV: COMPLICATIONS OF THERAPY (in the past week)

Please sign the score to the appropriate box

A. Dyskinesias

32. Duration: What proportion of the waking day are dyskinesias present? (historical information):
    0 = None
    1 = 1-25 % of day
    2 = 26-50 % of day
    3 = 51-75 % of day
    4 = 76-100 % of day

33. Disability: How disabling are the dyskinesias? (historical information; may be modified by office examination):
    0 = Not disabling
    1 = Mildly disabling
    2 = Moderately disabling
    3 = Severely disabling
    4 = Completely disabling

34. Painful dyskinesis: How painful are the dyskinesias?
    0 = No painful dyskinesias
    1 = Slightly
    2 = Moderately
    3 = Severely
    4 = Markedly

35. Presence of early morning dystonia (historical information):
    0 = No
    1 = Yes

(continued)

2939 033		
Subject No. ⌊⌋⌊⌋⌊⌋⌊⌋	Subject Initials ⌊⌋⌊⌋⌊⌋⌊⌋ First Last	Visit SCRE

UNIFIED PARKINSON'S DISEASE RATING SCALE (UPDRS)

IV: COMPLICATIONS OF THERAPY (in the past week) (continued)

B. Clinical Fluctuations

36. Are any "off" periods predictable as to timing after a dose of medication? ⌊⌋
    0 = No
    1 = Yes

37. Are any "off" periods unpredictable as to timing after a dose of medication? ⌊⌋
    0 = No
    1 = Yes

38. Do any "off" periods come on suddenly (e.g., within a few seconds)? ⌊⌋
    0 = No
    1 = Yes

39. What proportion of the waking day is the patient "off", on average? ⌊⌋
    0 = None
    1 = 1-25 % of day
    2 = 26-50 % of day
    3 = 51-75 % of day
    4 = 76-100 % of day

C. Other Complications

40. Does the patient have anorexia, nausea, or vomiting? ⌊⌋
    0 = No
    1 = Yes

41. Does the patient have any sleep disturbances (e.g., insomnia or hypersomnolence)? ⌊⌋
    0 = No
    1 = Yes

42. Does the patient have symptomatic orthostasis? ⌊⌋
    0 = No
    1 = Yes

2939 033		
Subject No. ⌊⌋⌊⌋⌊⌋⌊⌋	Subject Initials ⌊⌋⌊⌋⌊⌋⌊⌋ First Last	Visit SCRE

UNIFIED PARKINSON'S DISEASE RATING SCALE (UPDRS)

V: MODIFIED HOEHN AND YAHR STAGING

Stage 0 = No signs of disease
Stage 1 = Unilateral disease
Stage 1.5 = Unilateral plus axial involvement
Stage 2 = Bilateral disease without impairment of balance
Stage 2.5 = Mild bilateral disease with recovery on pull test
Stage 3 = Mild to moderate bilateral disease; some postural instabilty; physically independent
Stage 4 = Severe disability; still able to walk or stand unassisted
Stage 5 = Wheelchair-bound or bedridden unless aided

Stage ⌊⌋.⌊⌋

VI: SCHWAB AND ENGLAND ACTIVITIES OF DAILY LIVING SCALE

100 % = Completely independent; able to do all chores without slowness, difficulty, or impairment; essentially normal; unaware of any difficulty
90 % = Completely independent; able to do all chores with some degree of slowness, difficulty and impairment; may take twice as long as normal; beginning to be aware of difficulty
80 % = Completely independent in most chores; takes twice as long as normal; conscious of difficulty and slowness
70 % = Not completely independent; more difficulty with some chores; takes three to four times as long as normal in some; must spend a large part of the day with chores
60 % = Some dependency; can do most chores, but exceedingly slowly and with considerable effort and errors; some chores impossible
50 % = More dependent; needs help with half the chores, slower, etc.; difficulty with everything
40 % = Very dependent; can assist with all chores but does few alone
30 % = With effort, now and then does a few chores alone or begins alone; much help needed
20 % = Does nothing alone; can be a slight help with some chores; severe invalid
10 % = Totally dependent and helpless; complete invalid
0 % = Vegetative functions such as swallowing, bladder and bowel funtions are not functioning; bedridden

Percentage given by:
Patient

⌊⌋⌊⌋⌊⌋ %

Physician

⌊⌋⌊⌋⌊⌋ %

Date: ⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋
D M Y

Investigator's Signature

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

REVIEW AND EVALUATION OF CLINICAL DATA

NDA Number	20,796
Generic (Brand) Name	Comtan (Entacapone)
Sponsor	Orion Corporation (Espoo, Finland)
Indication	Parkinson's Disease
Material Submitted	Response to approvable letter
Correspondence Date	7 Dec 1999
Receipt Date	8 Dec 1997
Review Completed	20 Jul 1999

[All Tables referenced in the text -- flow diagram of the trial design, statistical results from ITT-LOCF, ITT-OC, and per-protocol analyses -- can be found at the end of this document.]

INTRODUCTION: An approvable letter, dated 31 Dec 1998, was sent to the sponsor for its NDA to support the new molecular entity Comtan as an adjunctive agent to treat Parkinson's disease (PD). The company forwarded a response on 19 Apr 1999.

This review examines the request for efficacy information; Dr. Kun He (Biostatistics) will verify the statistical material provided by the sponsor. Review of the safety data has been assigned to Dr. Michael Sevka.

With respect to efficacy, the 31 Dec 1999 approvable letter signed by Dr. Robert Temple indicated that only study 33 (Scandinavian) demonstrated "clear clinically meaningful effect." While study 44 (US) was deemed supportive, having met its prospectively identified endpoint, its results were not considered as robust since "half of the clinics showed numerical superiority for the placebo group and the favorable outcome is importantly driven by a single clinic with 12 patients. The mean percent ON effect, moreover, translates to well less than one added hour of ON time per day compared to placebo, less than a value prospectively considered clinically meaningful at the start of the study and less than what was considered meaningful in study 33."

Additionally problematic was the lack of success of the large study 52, and Dr. Temple found the sponsor's explanation -- namely, the inclusion of both fluctuators and nonfluctuators -- unconvincing since Tasmar was found to be acceptable in both groups. He suggested that dose-finding may have been "deficient in this case," since "studies identifying 200 mg as the optimal dose were small , with little capacity to distinguish regimens." Furthermore, the "pooled analyses of results by levodopa total dose (and therefore by entacapone total dose) show no difference over the range of <500 to >1000 mg."

In view of the absence of support provided by study 52, Dr. Temple felt that additional data from studies 63 and 65 were needed. In a face-to-face meeting with the sponsor on 11 Feb 1999, subsequently reaffirmed in a 23 Feb 1999 internal Division meeting (the results of which were conveyed to the sponsor), the request was limited to results from study 63 (Celomen). This review examines study 63.

TRIAL DESIGN: This Phase 3, multicenter (32 centers throughout Germany and Austria, 32 investigators), randomized, double-blind, placebo-controlled study was conducted entirely in Finland to "study the safety and efficacy of the long-term use of entacapone as an adjunct to levodopa/dopa decarboxylase inhibitor [DDCI] treatment compared with placebo in patients with PD. . . A long-term, double-blind, placebo-controlled study was considered necessary for a safety evaluation of entacapone. . ." (v 2, p 14, 27). "The efficacy was to be evaluated in a wide range of

patients with PD" (v 2, p 26).

Total study duration for each patient varied from 6.5 to 7 months. Patients took either 200 mg entacapone or placebo with each dose of levodopa/DDCI, up to 10 doses per day; about two-thirds were randomized to receive study drug and one-third to placebo. Table 3.7 illustrates the trial plan. A 2-4 week run-in screening period, during which levodopa doses were stabilized, preceded the 6-month double-blind portion of the trial. Six visits in all were scheduled: at baseline (screening period), week 2 (visit 2), week 6 (visit 3), month 4 (visit 4), month 6 (visit 5), and a post-study visit (withdrawal period) 2 weeks after completion of the double-blind portion.

Efficacy measures, considered secondary variables (the safety assessments -- labs, adverse events, drug interactions, and hemodynamics -- were considered primary; see v 147, p 258), consisted of UPDRS evaluations when the patient was "on," global evaluations of the patient's disease (completed by both the investigator and the patient), duration of ON time, the dosing interval between the first two morning doses of levodopa/DCCI, total daily levodopa dose, and the number of daily doses. Compliance measures were tablet count.

Three amendments to the original protocol were implemented:

(a) AMENDMENT ONE, DATED 6/28/96: the recruitment time was extended, reporting of unexpected AEs was clarified, added new study monitors and CRO.

(b) AMENDMENT TWO, DATED 1/9/97: added a new study monitor, extended the recruitment time, patient race information was to be collected, and original EKGs to be stored in the patient's hospital files.

(c) AMENDMENT THREE, DATED 12/12/97 (after completion of the clinical phase, but before opening of the treatment code on 12/19/97):
   (i) set the main comparison for efficacy parameters at week 24 between treatment groups
   (ii) defined fluctuators as "patients with ≥0.5 h daily OFF time to be determined from 3 home-diary days at baseline, and ≥4.5 h OFF time over the 3 home-diary days at baseline"
   NOTE: pivotal study 44, in contrast, limited the definition of fluctuators to patients having "clear ON-OFF fluctuations, along with experiencing daily OFF time that amounted to at least 3 hours during each of the three 24-hour home-diary days at baseline." Pivotal study 33 defined fluctuators as "patients with an average ON time after each single levodopa dose of less than 4 hours," "who use 4-10 daily doses of levodopa" (see the study's inclusion criteria).
   (iii) home-diary parameters were to be analyzed for fluctuators and patients with 5-10 daily levodopa intakes
   (iv) other efficacy parameters (UPDRS, global assessment, scheduled total daily levodopa dose, dosing frequency and withdrawal effect) were to be analyzed for the total population, the two stratification groups, and fluctuating patients
   (v) the data processing and statistical methods sections were revised "according to the methods used in the other phase III studies of entacapone"
   (vi) the method of analysis of the withdrawal period was added to the statistical section
   (vii) all randomized patients, with at least one measurement on study treatment, were to be included in the ITT analysis.

INCLUSION/EXCLUSION CRITERIA: Males and females, aged 30-80, with idiopathic PD "needing an enhancement and/or smoothening of levodopa effects" (v 147, p 261), except for females of childbearing potential; at Hoehn and Yahr stage 1.5-4.0 (defined when ON); levodopa responsive and on a stable regimen of 2-10 doses/day on any levodopa preparation [NOTE: both the immediate-release and CR preparations were allowed, as well as both levodopa/carbidopa and levodopa/benserazide]; use of amantadine, anticholinergics, selegiline, and/or dopamine agonists acceptable; without marked dementia, other significant neurological disease, major psychiatric

disorder (as severe depression), or serious medical illness (as cardiac, pulmonary, GI, hepatic); treatment with anti-dopaminergic drugs (as alpha-methyldopa, reserpine, neuroleptics, antiemetics), MAO-AI or nonselective MAOI, rimiterol, isoprenaline, adrenaline, dopamine, dobutamide, apomorphine or nomifensine within one month prior to the study; females of childbearing age.

POPULATION: 326 patients (217 males, 109 females) participated in the study, 218 randomized to entacapone and 108 to placebo. "Because of the safety nature of this study, no sample size calculations were performed and no main efficacy parameter was chosen" (v 2, p 035). Tables R4-R14 display baseline characteristics (treats vs placebo) for the total study population and three stratification groups, namely, fluctuators and patients with 2-4 and 5-10 daily levodopa doses. In general, treatment groups were very similar, except for a preponderance of males in the entacapone -- compared to the placebo -- group (statistically significant, $p<0.05$).

WITHDRAWALS AND PROTOCOL DEVIATIONS: 48/197 (24.4%) entacapone and 15/104 (14.4%) placebo patients discontinued the study. There were no deaths. Adverse events were the main reason for discontinuation, as shown in Table R2. The most significant protocol deviations are given in Table R3.

DOSAGE FORM: Comtan was supplied as 200-mg tablets, in the 200-54 pharmaceutical formulation; batches VH001, VH002, VK001, VK004, XA001, XA002, XB00401, XB00402. Placebo: batches SCT08-U03-03, SCT08-U02-03, VK001, XA001.

OUTCOME MEASURES: No outcome measure was distinguished as primary. Efficacy was examined in three ways:

(1) Differences between treats and placebo were evaluated for the total population, for stratification groups (patients on 2-4 and 5-10 daily levodopa doses), and fluctuators (defined as patients with ≥4.5 hours cumulative OFF time over 3 baseline home diary days and at least 0.5 hours OFF time one each day). The following parameters were employed:

(a) change in UPDRS (Parts I, II, III, and total scores [I +II + III], IV, V, and VI) during the ON phase, as compared to placebo. The UPDRS was evaluated on all five clinic visits.
(b) change in OFF time, as compared to placebo, recorded in home diaries.
(c) change in investigator global evaluations, compared to placebo. During the week prior to the study visit, patients assessed their own condition on a 7-point scale (very well; well; rather well; not well, not poorly; rather poorly; and very poorly), and this scale was then recorded patient responses on the CRFs.
(d) change in the total daily levodopa dose (total mg per day), compared to placebo.
(e) change in the daily dosing frequency (number of intakes per day), compared to placebo.

(2) Additionally, *fluctuators* and *patients with 5-10 daily levodopa doses* were also evaluated by home-diary parameters:

(a) change in the proportion of daily ON, OFF, and ASLEEP time. ON (when the patient was mobile or capable of moving with relative ease and independence), OFF when the patient was immobile or incapable of moving with relative ease and independence), and ASLEEP times were recorded by patients in home diary every 30 minutes over a 24-hour day on 3 consecutive days prior to each study visit.

(b) change in home-diary daily levodopa dose.
(c) change in home-diary dosing frequency (number of daily intakes).

(3) Finally, changes after medication withdrawal were assessed from week 24 to the post-study visit and compared between treatment groups for
(a) UPDRS (Parts I, II, III, and total scores [I +II + III])
(b) global assessment
(c) total levodopa daily dose
(d) dosing frequency (number of intakes per day).

Both Drs. Robert Temple and Russell Katz decided during the 14 June 1999 HFD-120 divisional meeting to use UPDRS (subscales II and III) and ON time (repeated measures analysis, as employed in the analysis of previous Comtan trials) to assess efficacy of study 63. Neither of the parameters would be regarded as primary.

PLANNED AND PERFORMED ANALYSES: All randomized patients who had taken at least one dose of study drug were included in the safety analysis. Safety will be examined by Dr. Michael Sevka.

Both ITT and per-protocol analyses were to be performed for efficacy parameters, using the response at 6 months to estimate the treatment difference. ANCOVA for repeated measures was employed to study continuous variables (UPDRS Parts I, II, III, and total scores [I +II + III]; proportion of daily ON, OFF, and ASLEEP time; total daily levodopa dose; dosing frequency; and the withdrawal effect on UPDRS, total daily levodopa dose, and dosing frequency). Baseline, treatment, center, and treatment by center interaction were used as a covariates; center and treatment by center interaction were used as random factors. Center was used as a random factor to generate a global estimate for the treatment effect. Terms for a stratification variable (2-4 and 5-10 levodopa doses) and for treatment -by-stratification interaction were included. Mean differences between treatments were estimated with 95% confidence intervals.

For categorical variables (UPDRS IV item 39 [proportion of waking time spent OFF]. V, and VI; global evaluation; and the withdrawal effect on the global evaluation), the Cochran-Mantel-Haenszel test was used to compare proportions of patients. A two-tailed significance level of 5% was considered to be statistically significant.

With respect to ITT analyses, 2 types of populations were identified:
--ITT-LOCF = patients who prematurely discontinued had their last measurement on study drug carried forward; however, the baseline value was not carried forward. Patients were not included in the analysis if only a baseline measurement -- and no study drug measurement -- were available. Occasional missing values were replaced by the last available measurement prior to the missing one. In such cases, baseline values were also carried forward.
--ITT-OC = observed cases, without imputations. For discontinued patients, measurements after study drug withdrawal were excluded.

The per-protocol population included all patients who completed the study up to the 6-month visit (visit 5), had a full data set for the variable to be analyzed at baseline and at month 6, exhibited sufficient compliance based on drug accountability (compliance at visit 6 between 70-130% of the scheduled treatment), had stable levodopa treatment for at least 2 weeks prior to baseline and between visits 4 and 5, were randomized into the proper stratification group, and had no major protocol deviations.

COMPLIANCE: Compliance was determined by tablet count at each clinic visit. Patients were deemed compliant if 100±30% of "the intended use of the investigational drugs" were taken. "The mean compliance rate of the study was more than 95% during the study and 96-100% at endpoint,

without significant differences between treatment groups" (v 2, p 125).
RESULTS: Note that the sponsor provides data for three of the four groups mentioned above, the total population, patients on 5-10 daily levodopa doses, and fluctuators; results for patients on 2-4 daily levodopa doses are not displayed.

(a) UPDRS: Scores were assessed when the patients were ON before noon ("best" ON time). In the pivotal studies 33 and 44, mean time between intake of the latest levodopa dose and UPDRS scoring when the patient varied between 1.5 and 1.8 hours, with maximal ON time about 5 hours (no differences were appreciated between treats and placebo patients in the time intervals between intake of the latest levodopa dose and the UPDRS assessment). Testing appears to have been similar for study 63 (see Appendix 6.7.1, v 9, pp 1-49).

No difference was found between treats and placebo for **Part I (mentation, behavior, mood)** for the ITT-LOCF, ITT-OC (see Table R35), and per-protocol (v 6, pp 177-81) analyses for all groups considered (total population, fluctuators, and patients on 5-10 daily levodopa doses).

For **Parts II (ADL)** and **III (motor)**, as well as for the **total score (Parts I + II + III)**, however, show that results for all three groups (total population, fluctuators, and patients on 5-10 daily levodopa doses) met the nominal p-value ($p<0.05$) for the ITT-LOCF and ITT-OC (Tables R36-38) and per-protocol (v 6, pp 199) analyses.

UPDRS Part IV (complications of therapy) consists of categorical variables (the sponsor presents only ITT-LOCF and ITT-OC anlyses). The proportion of patients with or without complications at baseline and at month 6 are presented by the sponsor as percentages of the total patient population (see Tables R39-47). The proportion of patients not *dyskinetic* at baseline did not change in the entacapone group (about 57%) but increased slightly in the placebo (from 64 to 66%) for the ITT-LOCF cohort; for the ITT-OC cohort, both remained unchanged (57% for treats, 63% for placebo). *Duration of dyskinesias* was calculated by converting the percent proportions to numerical categories (none=0, 1-25% of day=1, 26-50% of day=2, 51-75% of day=3, 76-100% of day=4). There was essentially no change from baseline to month 6. As to *disability of dyskinesias* (Tables R41-42), the proportion of entacapone and placebo patients experiencing disabling dyskinesias increased in both the ITT-LOCF (from 59% to 63% for treats vs 58% to 66% for placebo) and ITT-OC (from 59% to 63% for treats vs 58% to 68% for placebo), and patients with mildly disabling dyskinesias showed the largest increase. Severely *painful dyskinesias* (Table R34) declined among placebo patients (from 33 to 25%) but remained unchanged for treats (30%); nonetheless, both treats and placebo experienced a decrease in the presence of *early morning dystonia* at the end of 6 months (entacapone, from 40 to 35%; placebo, from 39% to 38%). The presence of *predictable OFF periods* decreased for both treats and placebo in the ITT-LOCF cohort at the end of 6 months, but the entacapone group saw a slight increase -- and placebos a slight decrease -- in the ITT-OC cohort. As for unpredictable *OFF periods*, there was decline for treats and placebo in both cohorts (ITT-LOCF: 57% to 47% for treats vs 63% to 49% for placebo; ITT-OC: 57% to 44% for treats vs 63% to 47% for placebo. Decreases in *sudden OFF periods* were observed for both treats and placebo and were comparable for the ITT-LOCF and ITT-OC cohorts (from 35% to 30% for treats vs 37% to 34% for placebo) and the *proportion of OFF time* (ITT-LOCF: from 57% to 47% for treats vs 63% to 49% for placebo; ITT-OC: from 57% to 47% for treats vs 63% to 49% for placebo) was observed in both groups at the end of 6 months (see Table R35), but the differences were not statistically significant. With respect to proportion *of OFF time* (proportion of OFF time was calculated by converting the percent proportions to numerical categories: none=0, 1-25% of day=1, 26-50% of day=2, 51-75% of day=3, 76-100% of day=4), an increase was observed in both groups at the end of 6 months in the number of patients reporting no OFF time, from 6.3 to 9.4% for treats and 6.7 to 8.7% for placebo for the ITT-LOCF cohort (see Figure 8; results were comparable for the ITT-OC cohort). However, there was also an increase in the proportion of patients in the ITT-LOCF cohort with OFF time >50% (from 6.3 to 7.3% for treats and 9.6 to 12.5% for placebo); whereas treats in the

ITT-OC cohort saw a modest improvement (from 6.3 to 5.4% for treats vs 9.6 to 14.6% for placebo). *Anorexia, nausea, and vomiting* increased in the entacapone group from 5 to 12% after 6 months (higher in the 5-10 daily levodopa dose group [6 to 14%] than in the 2-4 dose group [5-8%], but declined in the placebo from 11 to 6% (results were comparable for both the ITT-LOCF and ITT-OC cohorts). *Sleep disturbances* decreased in both groups at 6 months (entacapone, from 44 to 37%; placebo, from 48% to 44%), while complaints of *symptomatic orthostasis* increased minimally among treats but declined for placebo (entacapone, from 19 to 20%, and placebo, from 23% to 19%; results were comparable for both the ITT-LOCF and ITT-OC cohorts).

Results for **UPDRS Part V (Hoehn & Yahr staging)** show 18% treats vs 22% placebo whose disease stage worsened after 6 months (baseline staging was comparable for both groups; see Table R48); the difference failed to reach statistical significance, according to the sponsor (v 2, p 97). **UPDRS Part VI (Schwab & England ADL scores of activities of daily living)**, showed 15% of treats and 23% of placebo patients reporting worsening of their condition during the 6-month period, compared to 20% treats and 18% placebo with improvement (results for both the ITT-LOCF and ITT-OC cohorts were comparable; see Table R49), albeit not a statistically significant difference. Grading is defined as <80% (meaning the patient is no completely independent), 80% (meaning that the patient is conscious of his difficulty and slowness), and >80% (meaning that the patient may exhibit some slowness already).

(b) *Home diary recordings (proportion of ON time, ON time, OFF time, ASLEEP time)*: For the ITT-LOCF cohort, **proportion of daily ON time** (see Table R50; figure 10), based on an *24-hour* daily diary (as with study 44; study 33 used absolute ON time based on an 18-hour day) increased 6.4% among entacapone patients vs 2.8% among placebo in the 5-10 daily levodopa dose group, 7.9 vs 5.7% for all fluctuating patients, and 6.5 vs 3.5% for fluctuating patients on 5-10 daily levodopa doses; all results were statistically nonsignificant. However, results were -- or trended towards -- statistically significance for the ITT-OC cohort: 9% for entacapone patients vs 2.2% for placebo in the 5-10 daily levodopa dose group ($p<0.05$), 9.9 vs 5.8% for all fluctuating patients ($p=0.073$), and 9.1 vs 3.6% for fluctuating patients on 5-10 daily levodopa dose ($p<0.05$). Per-protocol analyses of changes in proportion of ON time were statistically nonsignificant for the three groups (v 6, pp 200-4).

A similar pattern was demonstrated for absolute **daily ON time**: for the ITT-LOCF cohort, increasing 1.1 hr after 6 months for treats vs 0.5 for placebo in the 5-10 dose group, 1.3 hr vs 0.9 in the all fluctuators group, and 1.1 hr vs 0.5 in the fluctuators on 5-10 doses group; all statistically nonsignificant increases. For the ITT-OC cohort, increases amounted to 1.7 hr after 6 months for treats vs 0.3 for placebo in the 5-10 dose group ($p<0.05$), 1.7 hr vs 0.9 in the all fluctuators group ($p=0.106$), and 1.7 hr vs 0.5 in the fluctuators on 5-10 doses group ($p<0.05$). Per-protocol analyses of changes in absolute ON time were statistically nonsignificant for the three groups (v 6, pp 205-9).

In the ITT-LOCF analysis, **daily OFF time** decreased (see Table R52; figure 12) 1.1 hr after 6 months for treats vs 0.5 for placebo in the 5-10 dose group (statistically nonsignificant), 1.3 hr vs 0.9 in the all fluctuators group (statistically nonsignificant), and 1.2 hr vs 0.6 in the fluctuators on 5-10 doses group ($p=0.07$ but fails to meet the nominal p-value) . For the ITT-OC cohort, decreases amounted to 1.4 hr after 6 months for treats vs 0.7 for placebo in the 5-10 dose group ($p=0.068$ but fails to meet the nominal p-value), 1.6 hr vs 0.9 in the all fluctuators group ($p=0.077$ but fails to meet the nominal p-value), and 1.5 hr vs 0.6 in fluctuators on 5-10 doses ($p<0.05$). Per-protocol analyses of changes in OFF time were statistically nonsignificant for the three groups (v 6, pp 210-14).

ASLEEP time showed no changes for either the entacapone or placebo patients in all of the analyses performed (ITT-LOCF, ITT-OC, and per-protocol).

(c) Global Evaluations: (see Tables R53-54): These were completed by patients and

divided into grades of "worsening by ≥2 categories," "worsening 1 category," and "no change" show an increase in the negative and a decline in the positive categories. In the ITT-LOCF cohort, 38.2% of treats and 33.7% of placebo in the entire population reported an improvement of at least one category by month 6. For fluctuating patients, the percentages were 36.5% vs 35.2%, and in fluctuators on 5-10 daily levodopa doses, 36.5% vs 35.2%, respectively. In the ITT-OC cohort, 42.4% of treats and 38.2% of placebo in the entire population reported an improvement of at least one category by month 6. For fluctuating patients, the percentages were 39.3% vs 39.4%, and in fluctuators on 5-10 daily levodopa doses, 41.1% vs 31.6%, respectively. Results for the per-protocol analyses (v 6, pp 218-27) were comparable.

Correspondingly, the proportion of the total population in the ITT-LOCF analysis who reported getting worse amounted to 25.7% of treats and 26.9% of placebo in the entire population reported an improvement of at least one category by month 6. For fluctuating patients, the percentages were 25.1% vs 27.3%, and in fluctuators on 5-10 daily levodopa doses, 26.4% vs 33.3%, respectively. Results for the ITT-OC and per-protocol analyses were comparable.

No changes in the ITT-LOCF, ITT-OC, or per-protocol (v 6, pp 218-27) analyses achieved statistical significance.

(d) Levodopa dosing: Over the 6-month period, for the ITT-LOCF analysis, **mean daily levodopa doses** (based on patient diaries) *decreased* 35 mg for the entire entacapone population vs a 4 mg increase among placebo, 47 mg for the 5-10 daily levodopa group vs a 4 mg increase among placebo, and 38 mg for fluctuators vs a 7 mg decrease among placebo. Results for the ITT-OC and per-protocol analyses were comparable. No analysis achieved statistical significance (see Table R55 for ITT-LOCF and ITT-OC results and v 6, pp 228-35, for per-protocol results).

Mean daily dosing frequency, in the ITT-LOCF analysis (see Table R57), remained unchanged for the entire entacapone population but increased slightly (from 5.6 to 5.8) for the corresponding placebo population; the difference reached statistical significance ($p<0.01$). Similarly, for fluctuators (treats, unchanged at 5.6; placebo, increase from 6.5 to 6.7; $p<0.01$) and patients on 5-10 levodopa doses per day (treats, decrease from 5.6 to 5.7; placebo, increase from 6.5 to 6.7; $p<0.01$). In the ITT-OC analysis, mean daily dosing frequency decreased (from 5.5 to 5.4) for the entire entacapone population but increased slightly (from 5.6 to 5.7) for the corresponding placebo population; the difference reached statistical significance ($p<0.05$). For fluctuators, dosing frequency remained unchanged in both treats and placebo patients; for patients on 5-10 levodopa doses per day, dosing frequency for treats remained unchanged, but placebo patients saw an increase from 6.5 to 6.6; $p<0.05$). Results of the per-protocol analyses of between-treatment differences were, similarly, statistically significant for the total population, fluctuators, and patients on 5-10 daily levodopa doses ($p<0.05$; v 6, pp 236-45).

With respect to ITT-LOCF and ITT-OC cohorts, data for **mean daily levodopa dose on home diary days** are displayed in Table R59 and results are comparable. However, results for **mean daily dosing frequency on home diary days** (Tables R59) did not meet the nominal p-value.

WITHDRAWAL EFFECT: Study drug was withdrawn (washout period) at the last visit, at which time levodopa medication was to be "kept constant during the post-study period as far as possible." A post-study visit was scheduled two weeks after study drug discontinuation, at which all exams conducted at the first visit were repeated and any necessary levodopa dose adjustments were to be made. Exam results from the last on-drug and post-study off-drug visits were compared by an observed-cases analysis.

(a) UPDRS scores : Part I scores showed an increase (=worsening) for **Part I (mentation)** for all treats (from 1.4 to 1.7) and a decrease for all placebo patients (from 1.5 to

1.4); this change was statistically significant (pp<0.05) in the ITT-OC analysis (see Tables R62-64) and, similarly, for patients with 5-10 daily doses and fluctuators. Results of per-protocol analyses were comparable (v 6, pp 255-6). In contrast, neither pivotal study (33 or 44) demonstrated any change in Part I scores.

A statistically significant change was also observed for **Part II (ADL)** for the total population group: an increase from 11 to 12.7 for treats but no change for placebo (12.5; p<0.01). Similar statistically significant differences were observed for fluctuators and patients on 5-10 daily levodopa doses. Results were comparable for the per-protocol analyses (v 6, pp 257-60).

Part 3 (motor) demonstrated an increase for the entacapone population (21.6-25.5) and a decrease for placebo (24.5 to 24.4), a statistically significant difference (p<0.01). Similar statistically significant differences were observed for fluctuators and patients on 5-10 daily levodopa doses. Results were comparable for the per-protocol analyses (v 6, pp 261-4).

Total scores (Parts I + II + III) demonstrated statistical significance for all three groups, total population, fluctuators, and patients on 5-10 levodopa doses per day. Results were comparable for the per-protocol analyses (v 6, pp 265-8).

(b) Global evaluations: For the total population, nearly twice as many placebo patients (18%) reported improvement in at least 1 category during the 2-week withdrawal period as treats (9%). Furthermore, almost twice as many treats (56%) reported worsening as placebo (30%). A greater proportion of treats (52%) as placebo (34%) remained unchanged. This between-group difference was statistically significant (p<0.001). Comparable between-group differences (p<0.001) were also observed for fluctuators and patients on 5-10 daily levodopa doses (see Table R65-66). Results were similar for the per-protocol analyses (v 6, pp 269-78).

(c) Levodopa dosing: Mean daily levodopa dose increases were statistically significant in favor of entacapone (p<0.05) for all three groups, total population, fluctuators, and patients on 5-10 daily levodopa intakes (see Table R67). However, levodopa dosing frequencies remained essentially unchanged for the three groups (see Table R68). Results were comparable in the per-protocol analyses for for the total population and fluctuators (v 6, pp 269-84).

SUMMARY: With respect to the three parameters which Drs. Temple and Katz have agreed to consider as crucial, study 63 meets the nominal p-value for UPDRS subscales II (ADL) and III (motor), but not for ON time.

CONCLUSION: Dr. Kun He is currently examining the accuracy of the statistical package. Dr. Michael Sevka will review safety data. The final conclusion await their results.

/S/

Richard M. Tresley MD
Medical Reviewer

NDA 20,796 div file/Katz R/Wheelous T/Tresley R/20 July 1999

APPEARS THIS WAY
ON ORIGINAL

3.7 Study procedures and schedule of events

Procedures on each study visit are given in the assessment schedule below:

MONTH *Visit window (days)* VISIT	SCREENING*	0 1	0.5 ±7 2	1.5 ±7 3	3 ±14 4	6 ±14 5	6.5 ±7 POST STUDY
STUDY DESIGN							
• Individual levodopa medication		X#####X-	----------	----------	----------	######	------>
• Entacapone/placebo medication		X-	----------	----------	----------	-X	
SCREENING							
• Inclusion/exclusion	X						
• Informed consent	X						
• Randomization		X					
• Physical examination	X						X
SAFETY MEASURES							
• Hematology/clin.chemistry	X	X	X	X	X	X	X
• BP, HR, ECG	X	X	X	X	X	X	X
• Adverse events		X	X	X	X	X	X
EFFICACY MEASURES							
• UPDRS		X	X	X	X	X	X
• Home diary (ON, OFF, ASLEEP time)		X	X	X	X	X	
• Global evaluation		X	X	X	X	X	X
OTHER							
• Recording of medications	X	X	X	X	X	X	X
• Tablet count				X	X	X	

*; screening visit was scheduled 2 to 4 weeks before visit 1
###; stable treatment period (levodopa dosing frequency and the amount of levodopa per dose should not have been changed)

Table R1. Patient disposition

Patient group	Entacapone		Placebo	
	n	%	n	%
Patients randomized and entered	197	100	104	100
- patients with 2-4 doses of levodopa	66	33.5	35	33.7
- patients with 5-10 doses of levodopa	131	66.5	69	66.3
Discontinued	48	24.4	15	14.4
Completed	149	75.6	89	85.6
Evaluated for safety	197	100	104	100
Fluctuating patients (≥4.5 h OFF time over 3 home diary days, and at least 0.5 hours on each day)	172	87.3	88	84.6

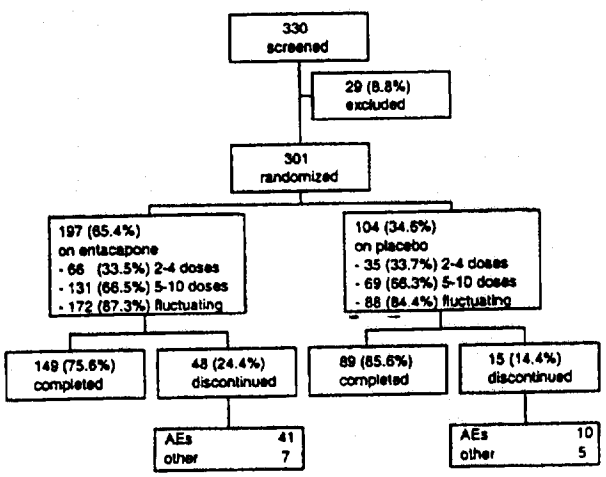


Figure 1. Flow-chart of patient disposition

Table R2. Discontinuations

Patient group/ reason for discontinuation	Entacapone (n=197) n	%	Placebo (n=104) n	%
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

Table R3. Most significant protocol violations and deviations during the study

Type of violation / deviation	Entacapone (n=197) n	%	Placebo (n=104) n	%
Withdrawal criteria developed during the study				
- forbidden medication	7	3.2	4	3.7
- no stable levodopa period prior to study entry	2	0.9	2	1.9
- fertile woman	4	1.8	1	0.9
- written informed consent obtained not until visit 1	8	3.7	3	2.8
- non-compliance between visits 4 and 5	6	2.8	6	5.6
- no stable levodopa period between visits 4 and 5	7	3.2	4	3.7
Missing safety recordings	missing* / total**	% of total	missing* / total**	% of total
- ECG not recorded (no. of recordings)	44/1379	3.2	22/728	3.0
- Blood pressure or heart rate not measured (no. of recordings)	20/1379	1.5	3/728	0.4
- laboratory samples missing (no. of recordings)	49/1379	3.6	27/728	3.7
Missing efficacy recordings				
- UPDRS I, II, III (no. of recordings)	18/1032	1.7	11/580	1.9
- UPDRS IV, V, VI (no. of recordings)	3/1032	0.2	8/580	1.4
- home diary (no. of recordings)	8/837	1.0	24/477	5.0
- global assessment (no. of recordings)	2/1032	0.2	3/580	0.5
Visit window deviation (no. of visits)	93/1379	6.7	50/728	6.9

* Discontinued patients are included until their last scheduled study visit

** Due to discontinuations the total no. of expected recordings for UPDRS I-VI recordings and global assessment is 1032 (1182 - 150) in the entacapone group, and 580 (624 - 44) in the placebo group; for home diary these figures are 837 (985 – 148) and 477 (520 – 43)

Table R4. Demographic features at baseline for total population and fluctuating patients

Parameter	Total population (n=301)		Fluctuating patients (n=260)		Significance
	Entacapone	Placebo	Entacapone	Placebo	total/fluctuating
Number of patients	197	104	172	88	-
Sex					
- Male, n (%)	119 (60.4 %)	54 (51.9 %)	104 (60.5 %)	46 (52.3 %)	
- Female, n (%)	78 (39.6 %)	50 (48.1 %)	68 (39.5 %)	42 (47.7 %)	NS / NS
Age, mean ± SD (years)	60.7 ± 9.6	61.1 ± 9.9	60.1± 9.6	61.0 ± 10.1	NS / NS
Race	all Caucasians	all Caucasians	all Caucasians	all Caucasians	-
Weight, mean ± SD (kg)	72.8 ± 12.5	71.4 ± 12.8	72.2 ±12.2	71.1 ±13.0	NS / NS
Height, mean ± SD (cm)	171.1 ± 8.6	169.3 ± 8.1	171.1 ±8.7	169.6 ±8.4	NS / NS

Table R5. History of Parkinson's disease, mean ± SD (range); total population and fluctuating patients

Parameter	Total population (n = 301)		Fluctuating patients (n = 260)		Significance
	Entacapone (n = 197)	Placebo (n = 104)	Entacapone (n = 172)	Placebo (n = 88)	total / fluctuating
Age at onset of PD (years)	53.0 ± 10.3	52.2 ± 10.2	52.3 ± 10.4	51.9 ± 10.2	NS /NS
Duration of PD (years)	8.3 ± 4.5	9.5 ± 4.9	8.4 ± 4.6	9.7 ± 4.8	p<0.05 / p<0.05
Duration of levodopa treatment (years)	7.6 ± 4.5	8.2 ± 4.7	7.6 ± 4.6	8.5 ± 4.6	NS /NS

Table R6. History of Parkinson's disease by stratification (mean ± SD); total population

Parameter	Entacapone (n=197)		Placebo (n=104)		Significance
	2 – 4 doses (n = 66)	5 – 10 doses (n = 131)	2 – 4 doses (n= 35)	5 – 10 doses (n = 69)	2-4 / 5-10
Age at baseline(years)	62.2 ± 9.6	60.0 ± 9.5	62.7 ± 10.8	60.3 ± 9.5	NS / NS
Age at onset of PD (years)	56.5 ± 9.6	51.2 ± 10.2	55.4 ± 10.6	50.6 ± 9.6	NS / NS
Duration of PD (years)	6.3 ± 3.8	9.4 ± 4.5	7.9 ± 4.6	10.3 ± 4.8	NS / NS
Duration of levodopa treatment (years)	5.3 ± 3.6	8.7 ± 4.5	6.5 ± 4.7	9.0 ± 4.5	NS / NS

Table R7. Levodopa dosing at baseline (mean ± SD); total population and fluctuating patients

Parameter	Total population (n = 301)		Fluctuating patients (n = 260)		Significance
	Entacapone (n = 197)	Placebo (n = 104)	Entacapone (n = 172)	Placebo (n = 88)	total / fluctuating
Daily levodopa dose (mg)	570 ± 273	572 ± 329	588 ± 270	593 ± 342	NS / NS
Number of daily doses	5.5 ± 1.9	5.6 ± 1.9	5.6 ± 1.9	5.7 ±1.9	NS / NS

Table R8. The frequency of levodopa doses at baseline by stratification and treatment group (%); total population

Parameter	Stratification								
	2 – 4 daily levodopa doses (entacapone n=66) (placebo n=35)			5 - 10 daily levodopa doses (entacapone n=131) (placebo n=69)					
No. of doses	2	3	4	5	6	7	8	9	10
Entacapone (%)	2.5	13.2	18.3	17.3	26.9	7.1	7.1	2.5	5.1
Placebo (%)	0	10.6	23.1	23.1	16.3	8.7	9.6	3.8	4.8

Table R9. DDC inhibitor used at baseline; total population and fluctuating patients

DDC inhibitor	Total population (n = 301)				Fluctuating patients (n = 260)			
	Entacapone (n=197)		Placebo (n=104)		Entacapone (n=172)		Placebo (n=88)	
	n	%	n	%	n	%	n	%
Carbidopa	78	39.6	41	39.4	70	40.7	33	37.5
Benserazide	92	46.7	49	47.1	76	44.2	44	50.0
Carbidopa and Benserazide	27	13.7	14	13.5	26	15.1	11	12.5

Table R10. Levodopa preparations at baseline; total population

Levodopa preparation	Total population (n = 301)				Fluctuating patients (n = 260)			
	Entacapone (n=197)		Placebo (n=104)		Entacapone (n=172)		Placebo (n=88)	
	n	%	n	%	n	%	n	%
Standard	91	46.2	45	43.3	74	43.0	37	42.0
Standard + CR	92	46.7	53	51.0	85	49.4	45	51.1
CR	14	7.1	6	5.8	13	7.6	6	6.8

Table R11. Concomitant antiparkinsonian medication at baseline; total population

Therapy group	Entacapone (n=197)			Placebo (n=104)		
	n	%	Total daily dose (mg) (mean ± SD)	n	%	Total daily dose (mg) (mean ± SD)
Selegiline	102	51.8	7.4 ± 2.6	58	55.8	7.6 ± 2.2
Dopamine agonists	146	74.1	-	86	82.7	-
Pergolide	87	44.2	2.5 ± 2.3	58	55.8	2.1 ± 1.5
Bromocriptine	30	15.2	18.2 ± 11.9	16	15.4	17.5 ± 6.1
Lisuride	26	13.2	0.6 ± 0.2	9	8.7	0.5 ± 0.2
Dihydroergocryptine mesylate	3	1.5	31.7 ± 24.7	3	2.9	63.3 ± 49.3
Amantadine	63	32.0	260 ± 99	37	35.6	276 ± 86
Amantadine derivatives	8	4.1	24.4 ± 8.6	6	5.8	15.0 ± 13.4
Anticholinergic agents	37	18.8	-	20	19.2	-
Biperidine	15	7.6	5.1 ± 2.6	10	9.6	4.2 ± 1.5
Bornaprine	5	2.5	6.6 ± 2.6	5	4.8	8.0 ± 3.7
Metixene	11	5.6	12.3 ± 4.5	3	2.9	8.3 ± 5.8
Trihexyphenidyl	6	3.0	3.5 ± 1.9	2	1.9	3.0 ± 1.4
Other Pridinol	1	0.5	10.0	0	0	0
Patients with any antiparkinsonian treatment	183	92.9	-	98	94.2	-

Table R12. Concomitant antiparkinsonian medication at baseline; fluctuating patients

Therapy group	Entacapone (n=172)			Placebo (n=88)		
	n	%	Total daily dose (mg) (mean ± SD)	n	%	Total daily dose (mg) (mean ± SD)
Selegiline	91	52.9	7.4 ± 2.6	47	53.4	7.4 ± 2.3
Dopamine agonists	132	76.7	-	73	83.0	-
Pergolide	77	44.8	2.5 ± 2.4	52	59.1	2.3 ± 1.6
Bromocriptine	28	16.3	19.0 ± 11.9	12	13.6	17.7 ± 6.8
Lisuride	24	14.0	0.6 ± 0.2	6	6.8	0.6 ± 0.2
Dihydroergocryptine mesylate	3	1.7	31.7 ± 24.7	3	3.4	63.3 ± 49.3
Amantadine	58	33.7	253 ± 92	29	33.0	280 ± 86
Amantadine derivatives	8	4.7	24.4 ± 8.6	5	5.7	10.0 ± 6.1
Anticholinergic agents	32	18.6	-	16	18.2	-
Biperidine	12	7.0	5.3 ± 2.9	9	10.2	4.2 ± 1.6
Bornaprine	5	2.9	6.6 ± 2.6	3	3.4	7.3 ± 4.2
Metixene	9	5.2	11.7 ± 4.8	2	2.3	10.0 ± 7.1
Trihexyphenidyl	6	3.5	3.5 ± 1.9	2	2.3	3.0 ± 1.4
Other Pridinol	1	0.6	10.0	0	0	0
Patients with any antiparkinsonian treatment	163	94.8	-	82	93.2	-

Table R13. Concurrent diseases at baseline; total population

Disease	Entacapone (n=197)		Placebo (n=104)	
	n	%	n	%
Diseases of spinal column	35	17.8	15	14.4
Arterial hypertension	30	15.2	14	13.5
Lipid disorders	23	11.7	9	8.7
Cardiac arrhythmia	18	9.1	5	4.8
Arterial hypotension	17	8.6	7	6.7
Arthrosis / arthritis	17	8.6	6	5.8
Depression	14	7.1	8	7.7
Coronary heart disease	14	7.1	5	4.8
Hyperplasia of prostate	13	6.6	7	6.7
Sleep disturbances	12	6.1	6	5.8
Osteoporosis	12	6.1	2	1.9
Hyperthyreosis	10	5.1	1	1.0
Obstipation	9	4.6	6	5.8
Diabetes mellitus	8	4.1	4	3.8
Hypothyreosis	7	3.6	4	3.8
Cardiac insufficiency	7	3.6	3	2.9
Gastric/duodenal disorders	7	3.6	8	7.7

Table R14. Concomitant drug therapy (>5% incidence) at baseline; total population

Drug therapy group	Entacapone (n=197)		Placebo (n=104)	
	n	%	n	%
Cardiac therapy	36	18.3	22	21.2
Mineral supplements	31	15.7	10	9.6
Psychoanaleptics (antidepressants and psychostimulants and their combination with psycholeptics)	30	15.2	13	12.5
Psycholeptics (antipsychotics, anxiolytics, hypnotics, and sedatives)	26	13.2	14	13.5
Beta blocking agents	23	11.7	10	9.6
Thyroid therapy	20	10.2	9	8.7
Antispasmodic and anticholinergic agents and propulsives	11	5.6	11	10.6
Antigout preparations	11	5.6	11	10.6
Patients with any drug therapy	144	73.1	75	72.1

Table R15. Clinical disability (mean ± SD); total population and fluctuating patients

UPDRS subscores	Total population (n = 301)		Fluctuating patients (n = 260)		Significance
	Entacapone (n = 197)	Placebo (n = 104)	Entacapone (n = 172)	Placebo (n = 88)	Total / Fluctuating
Mentation, behavior and mood (Part I)	1.7 ± 1.5	1.6 ± 1.5	1.7 ± 1.5	1.6 ± 1.4	NS / NS
Activities in daily living (Part II)	12.3 ± 6.1	12.0 ± 5.8	12.5 ± 6.1	12.4 ± 5.7	NS / NS
Motor examination (Part III)	24.6 ± 12.9	24.1 ± 12.1	24.1 ± 12.6	24.0 ± 12.2	NS / NS
Total (Parts I+II+III)	38.6 ± 18.2	37.7 ± 16.8	38.3 ± 17.9	37.9 ± 16.5	NS / NS
Modified Hoehn and Yahr stage	%	%	%	%	
1	4.1	1.0	2.9	1.1	
1.5	11.2	5.8	11.6	5.7	
2	23.9	33.7	22.1	30.7	
2.5	29.9	20.2	30.2	20.5	-
3	23.4	32.7	25.0	34.1	
4	7.6	6.7	8.1	8.0	
5	0	0	0	0	
≤ 2.0 (%)	39.1	40.3	36.6	37.5	-
≥ 2.5 (%)	60.9	59.6	63.4	62.5	-
Schwab and England ADL					
> 80 %	31.5	26.0	29.0	23.8	-
= 80 %	34.5	36.5	35.5	37.5	-
< 80 %	34.0	37.5	35.5	38.6	-

-, not performed

Table R16. Treatment compliance (%, mean ± SD) based on tablet count between months 4 and 6; total population

Stratification	Entacapone	Placebo
2-4 doses	100.3 ± 4.3	99.8 ± 9.2
5-10 doses	96.4 ± 8.9	97.0 ±9.3
All patients	97.8 ± 7.8	98.0 ±9.3

Table R34. Disposition (number) of patients in efficacy analyses (ITT-LOCF, ITT-OC, PP) for each parameter

Patient population /Visit	UPDRS I-III			Home diary			Global evaluation		
	ITT-LOCF E/P	ITT-OC E/P	PP E/P	ITT-LOCF E/P	ITT-OC E/P	PP E/P	ITT-LOCF E/P	ITT-OC E/P	PP E/P
Total population									
Baseline	191/104	191/104	129/75	NA	NA	NA	191/104	191/104	132/76
Visit 2	191/104	188/102	127/75	NA	NA	NA	191/104	190/104	131/76
Visit 3	191/104	174/96	129/75	NA	NA	NA	191/104	175/101	132/76
Visit 4	191/104	158/87	129/75	NA	NA	NA	191/104	162/89	132/76
Visit 5	191/104	147/88	129/75	NA	NA	NA	191/104	151/89	132/76
Post-study	NA	148/88	127/71	NA	NA	NA	NA	151/88	131/72
5-10 doses									
Baseline	124/68	124/68	80/45	120/67	120/67	77/43	125/69	125/69	81/46
Visit 2	124/68	122/68	78/45	120/67	119/66	76/43	125/69	124/69	80/46
Visit 3	124/68	112/63	80/43	120/67	105/63	76/43	125/69	113/67	81/46
Visit 4	124/68	99/55	79/45	120/67	97/53	77/41	125/69	102/57	81/46
Visit 5	124/68	93/56	80/45	120/67	92/54	77/43	125/69	95/57	81/46
Post-study	NA	95/57	79/42	NA	NA	NA	NA	95/57	80/43
Fluctuating									
Baseline	167/88	167/88	114/63	165/87	165/87	110/62	167/88	167/88	117/64
Visit 2	167/88	164/86	112/63	165/87	163/86	108/62	167/88	166/88	116/64
Visit 3	167/88	152/80	114/61	165/87	146/82	107/62	167/88	153/85	117/64
Visit 4	167/88	138/74	113/63	165/87	135/74	109/60	167/88	141/76	117/64
Visit 5	167/88	131/75	114/63	165/87	129/74	110/62	167/88	135/76	117/64
Post-study	NA	133/76	113/60	NA	NA	NA	NA	135/76	116/61

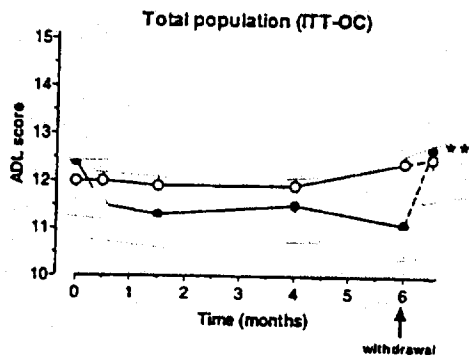
E, entacapone; P, placebo; NA, not applicable

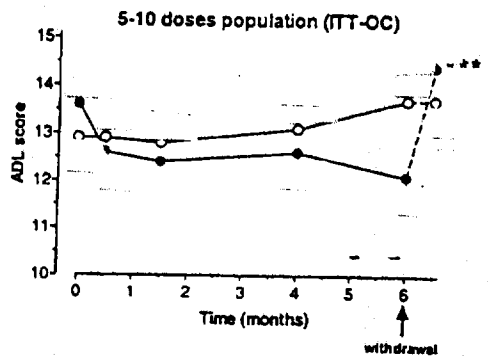
Table R35. Mentation, behavior and mood (UPDRS Part I) (mean ± SD), ITT-LOCF and ITT-OC

Analysis/ Patient population		Entacapone n	Entacapone mean ± SD	Placebo n	Placebo mean ± SD	Significance
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	NS
	- change	191	-0.0 ± 1.2	104	-0.1 ± 1.4	
5-10 doses	- baseline	125	1.8 ± 1.5	69	1.6 ± 1.5	
	- month 6	125	1.8 ± 1.6	69	1.5 ± 1.2	NS
	- change	125	-0.1 ± 1.3	69	-0.1 ± 1.5	
Fluctuating	- baseline	167	1.7 ± 1.5	88	1.6 ± 1.4	
	- month 6	167	1.6 ± 1.6	88	1.6 ± 1.3	NS
	- change	167	-0.1 ± 1.2	88	-0.0 ± 1.3	
ITT-OC						
All patients	- baseline	191	1.7 ± 1.5	104	1.6 ± 1.5	
	- month 6	149	1.4 ± 1.5	89	1.5 ± 1.4	NS
	- change	149	-0.2 ± 1.2	89	-0.1 ± 1.4	
5-10 doses	- baseline	125	1.8 ± 1.5	69	1.6 ± 1.5	
	- month 6	95	1.6 ± 1.5	57	1.5 ± 1.2	NS
	- change	95	-0.2 ± 1.3	57	-0.2 ± 1.5	
Fluctuating	- baseline	167	1.7 ± 1.5	88	1.6 ± 1.4	
	- month 6	133	1.5 ± 1.5	76	1.5 ± 1.4	NS
	- change	133	-0.1 ± 1.2	76	-0.1 ± 1.3	

Table R36. Activities of daily living (UPDRS Part II) (mean ± SD); ITT-LOCF and ITT-OC

Analysis/ Patient population		Entacapone n	Entacapone mean ± SD	Placebo n	Placebo mean ± SD	Significance [95% CI]
ITT-LOCF						
All patients	- baseline	191	12.4 ± 6.1	104	12.0 ± 5.8	p<0.05
	- month 6	191	11.5 ± 6.4	104	12.5 ± 6.5	[-2.46; -0.29]
	- change	191	-0.9 ± 3.4	104	0.5 ± 4.0	
5-10 doses	- baseline	125	13.6 ± 6.2	69	12.9 ± 6.1	p<0.05
	- month 6	125	12.6 ± 6.5	69	13.4 ± 6.8	[-2.58;-0.13]
	- change	125	-1.0 ± 3.7	69	0.6 ± 4.2	
Fluctuating	- baseline	167	12.6 ± 6.1	88	12.4 ± 5.7	p<0.05
	- month 6	167	11.6 ± 6.4	88	12.8 ± 6.2	[-2.46; -0.10]
	- change	167	-1.0 ± 3.5	88	0.4 ± 4.1	
ITT-OC						
All patients	- baseline	191	12.4 ± 6.1	104	12.0 ± 5.8	p<0.05
	- month 6	148	11.1 ± 6.3	89	12.4 ± 6.5	[-2.54; -0.16]
	- change	148	-1.0 ± 3.4	89	0.3 ± 4.0	
5-10 doses	- baseline	125	13.6 ± 6.2	69	12.9 ± 6.1	p<0.05
	- month 6	94	12.1 ± 6.7	57	13.7 ± 6.9	[-2.83; -0.10]
	- change	94	-1.1 ± 3.7	57	0.2 ± 4.2	
Fluctuating	- baseline	167	12.6 ± 6.1	88	12.4 ± 5.7	p=0.054
	- month 6	132	11.2 ± 6.3	76	12.5 ± 6.2	[-2.46; 0.02]
	- change	132	-1.1 ± 3.5	76	0.2 ± 4.1	





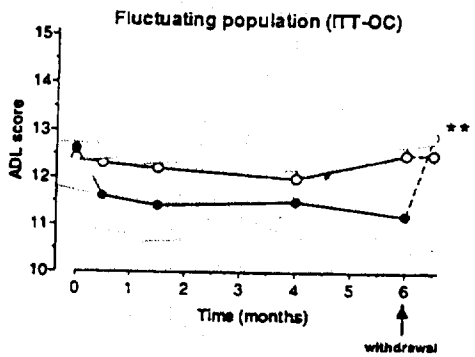


Figure 2. Changes in UPDRS Part II score (activities of daily living) for the total population, for the patients with 5-10 doses of levodopa, and for the fluctuating patients (ITT-OC analysis)(mean ± SEM). * p<0.05; ** p<0.01; *** p<0.001

Table R37. Motor examination (UPDRS Part III) (mean ± SD); ITT-LOCF and ITT-OC

Analysis/ Patient population		Entacapone n	Entacapone mean ± SD	Placebo n	Placebo mean ± SD	Significance [95% CI]
ITT-LOCF						
All patients	- baseline	190	24.9±12.9	102	24.1±12.1	p<0.05
	- month 6	190	22.4±12.4	102	24.2±12.7	[-3.98; -0.09]
	- change	190	-2.5±8.0	102	0.1±8.1	
5-10 doses	- baseline	124	25.0±13.5	68	23.3±12.1	p<0.01
	- month 6	124	22.6±13.2	68	24.5±13.2	[-5.47;-0.94]
	- change	124	-2.4±8.7	68	1.2±8.3	
Fluctuating	- baseline	166	24.4±12.6	86	24.0±12.2	p<0.05
	- month 6	166	21.7±11.9	86	23.9±12.0	[-4.42; -0.18]
	- change	166	-2.8±8.0	86	-0.1±8.1	
ITT-OC						
All patients	- baseline	190	24.9±12.9	102	24.1±12.1	p<0.05
	- month 6	148	21.7±12.1	88	24.3±12.9	[-4.95; -0.71]
	- change	148	-3.2±8.0	88	0.1±8.4	
5-10 doses	- baseline	124	25.0±13.5	68	23.3±12.1	p<0.01
	- month 6	94	21.5±12.8	56	25.0±13.7	[-7.09; -1.96]
	- change	94	-3.2±8.7	56	1.2±8.9	
Fluctuating	- baseline	166	24.4±12.6	86	24.0±12.2	p<0.05
	- month 6	132	21.2±11.9	75	23.9±12.0	[-5.13; -0.46]
	- change	132	-3.3±8.1	75	-0.1±8.4	

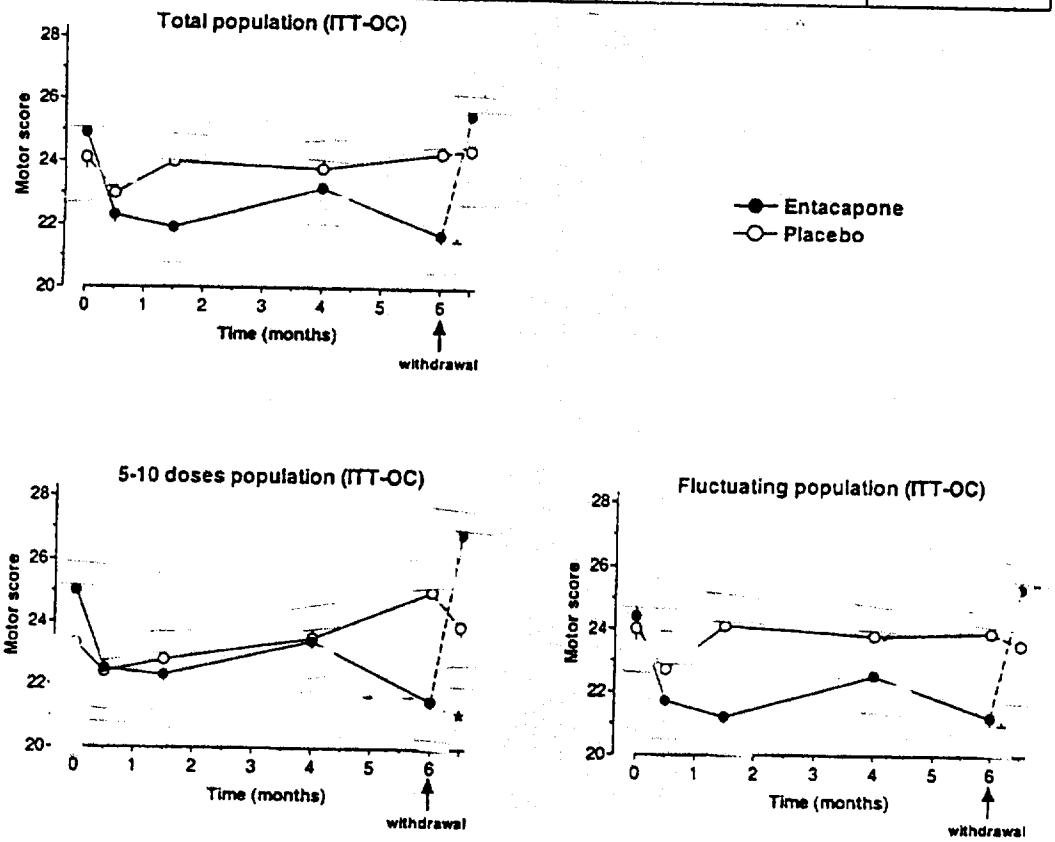
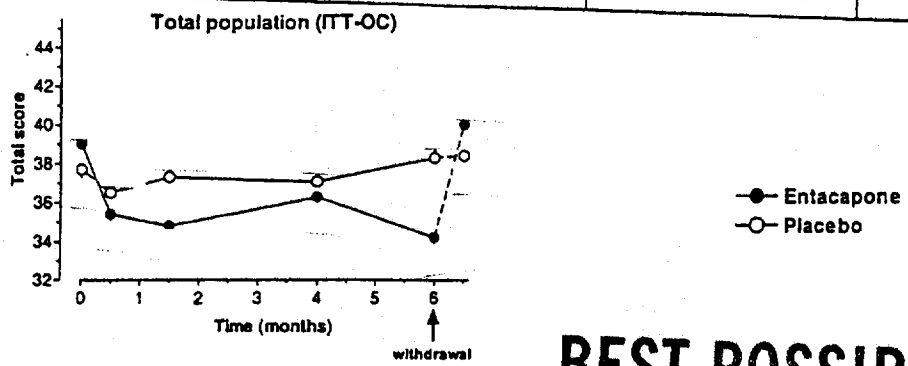


Figure 3. Changes in UPDRS Part III score (motor examination) for the total population, for the patients with 5-10 doses of levodopa, and for the fluctuating patients (ITT-OC analysis)(mean ± SEM). * p<0.05; ** p<0.01; *** p<0.001

Table R38. Total UPDRS, Sum of Parts I, II and III (mean ± SD); ITT-LOCF and ITT-OC

Analysis/ Patient population		Entacapone n	Entacapone mean ± SD	Placebo n	Placebo mean ± SD	Significance [95% CI]
ITT-LOCF						
All patients	- baseline	190	39.0 ± 18.3	102	37.7 ± 16.8	p<0.05
	- month 6	190	35.6 ± 18.3	102	38.3 ± 17.9	[-6.37; -0.73]
	- change	190	-3.4 ± 10.2	102	0.6 ±10.3	
5-10 doses	- baseline	124	40.4 ± 19.2	68	37.8 ± 17.1	p<0.01
	- month 6	124	37.1 ± 19.3	68	39.5 ± 18.7	[-7.98; -1.50]
	- change	124	-3.4 ± 11.2	68	1.7 ± 10.5	
Fluctuating	- baseline	166	38.7 ± 17.9	86	37.9 ± 16.5	p<0.05
	- month 6	166	35.0 ± 17.8	86	38.3 ± 16.9	[-6.59; -0.67]
	- change	166	-3.7 ± 10.3	86	0.4 ± 10.5	
ITT-OC						
All patients	- baseline	190	39.0 ±18.3	102	37.7 ± 16.8	p<0.01
	- month 6	147	34.2 ± 17.8	88	38.3 ± 18.1	[-7.47; -1.28]
	- change	147	-4.2 ± 10.0	88	0.4 ± 10.5	
5-10 doses	- baseline	124	40.4 ± 19.2	68	37.8 ± 17.1	p<0.01
	- month 6	93	35.2 ± 18.9	56	40.3 ± 19.2	[-9.56; -2.32]
	- change	93	-4.3 ± 11.0	56	1.3 ± 11.0	
Fluctuating	- baseline	166	38.7 ± 17.9	86	37.9 ± 16.5	p<0.05
	- month 6	131	33.9 ± 17.6	75	38.0 ± 16.8	[-7.35; -0.91]
	- change	131	-4.3 ± 10.3	75	0.0 ±10.6	



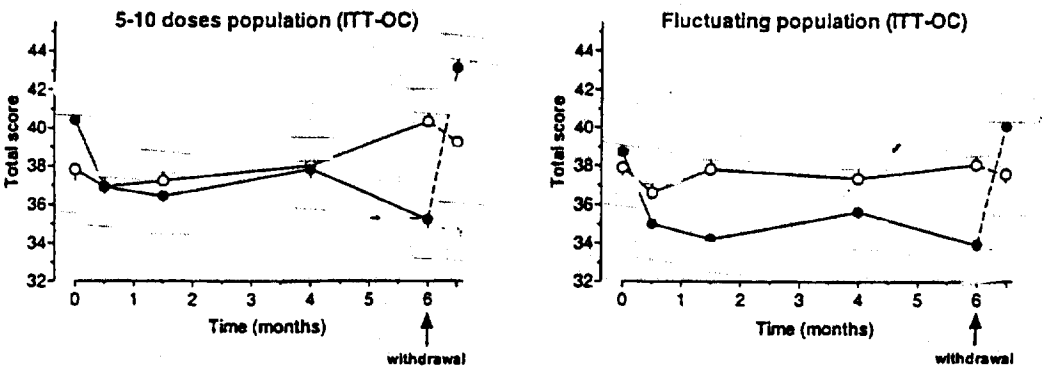


Figure 4. Changes in total UPDRS score (sum of Parts I, II, III) for the total population, for the patients with 5-10 doses of levodopa, and for the fluctuating patients (ITT-OC analysis)(mean ± SEM). * p<0.05; ** p<0.01; *** p<0.001

Table R39. Duration of dyskinesias as % of day (UPDRS Part IV) (% of the patients); ITT-LOCF

Treatment / Patient population	Time	n	None %	1-25% %	26-50% %	>50% %	Dyskinetic total %
Entacapone							
All patients	- baseline	191	43.5	32.5	16.8	7.3	56.5
	- month 6	191	42.9	30.4	17.8	8.9	57.1
5-10 doses	- baseline	125	27.2	37.6	24.0	11.2	72.8
	- month 6	125	28.0	36.0	24.0	12.0	72.0
Fluctuating	- baseline	167	37.7	35.9	18.6	7.8	62.3
	- month 6	167	38.3	32.3	19.2	10.2	61.7
Placebo							
All patients	- baseline	104	36.5	41.3	14.4	7.7	63.5
	- month 6	104	33.7	42.3	19.2	4.8	66.3
5-10 doses	- baseline	69	26.1	44.9	18.8	10.1	73.9
	- month 6	69	23.2	44.9	24.6	7.2	76.8
Fluctuating	- baseline	88	31.8	45.5	15.9	6.8	68.2
	- month 6	88	28.4	47.7	19.3	4.5	71.6

Table R40. Duration of dyskinesias as % of day (UPDRS Part IV) (% of the patients); ITT-OC

Treatment / Patient population	Time	n	None %	1-25% %	26-50% %	>50% %	Dyskinetic total %
Entacapone							
All patients	- baseline	191	43.5	32.5	16.8	7.3	56.5
	- month 6	149	43.0	30.9	19.5	6.7	57.0
5-10 doses	baseline	125	27.2	37.6	24.0	11.2	72.8
	- month 6	95	28.4	35.8	26.3	9.5	71.6
Fluctuating	- baseline	167	37.7	35.9	18.6	7.8	62.3
	- month 6	133	39.1	32.3	21.1	7.5	60.9
Placebo							
- All patients	- baseline	104	36.5	41.3	14.4	7.7	63.5
	- month 6	89	37.1	40.4	19.1	3.4	62.9
5-10 doses	-baseline	69	26.1	44.9	18.8	10.1	73.9
	- month 6	57	26.3	43.9	24.6	5.3	73.7
Fluctuating	- baseline	88	31.8	45.5	15.9	6.8	68.2
	- month 6	76	31.6	46.1	18.4	3.9	68.4

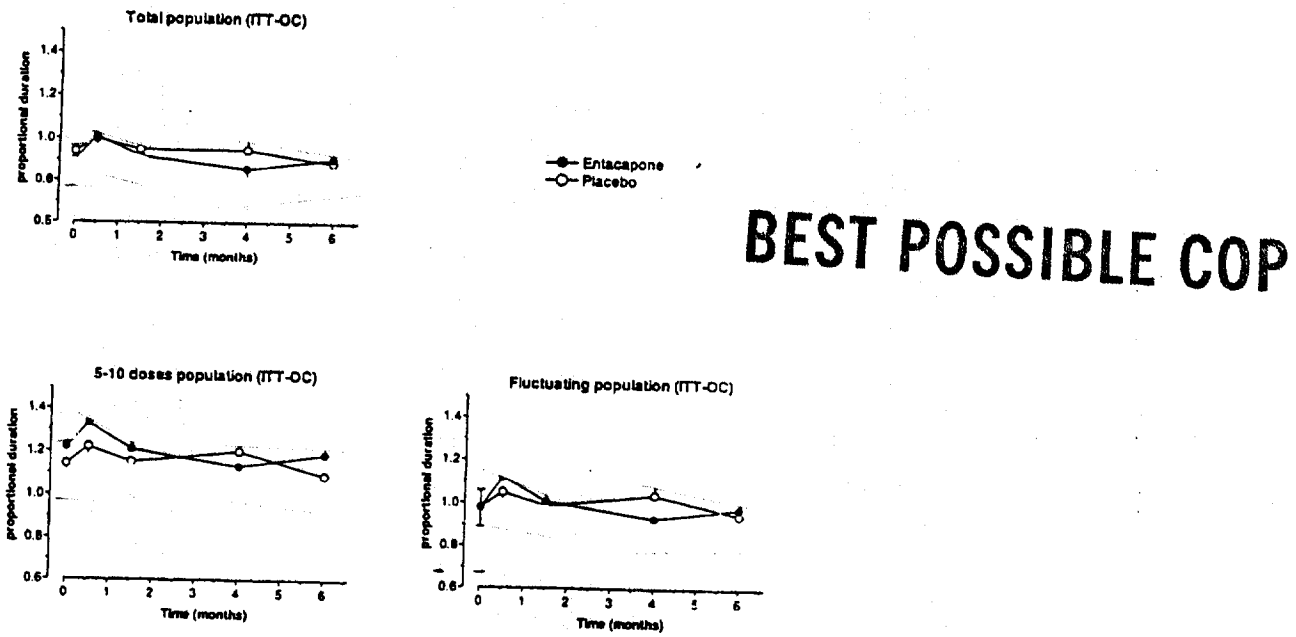


Figure 5. Proportional duration of dyskinesias for the total population, for the patients with 5-10 doses of levodopa and for the fluctuating patients. (ITT-OC analysis) (mean ± SEM)

Table R41. Disability of dyskinesias (% of the patients with dyskinesia), ITT-LOCF

Treatment / Patient population	Time	n	Not disabling %	Mildly disabling %	Moderately disabling %	Severely disabling %	Completely disabling %
Entacapone							
All patients	- baseline	123	41.5	25.2	21.1	9.8	2.4
	- month 6	123	37.4	31.7	22.0	5.7	3.3
5-10 doses	- baseline	100	37.0	28.0	20.0	12.0	3.0
	- month 6	100	34.0	33.0	24.0	6.0	3.0
Fluctuating	- baseline	116	39.7	25.9	21.6	10.3	2.6
	- month 6	116	37.9	31.0	21.6	6.0	3.4
Placebo							
All patients	- baseline	76	42.1	19.7	31.6	6.6	-
	- month 6	76	34.2	35.5	18.4	11.8	-
5-10 doses	- baseline	59	44.1	18.6	30.5	6.8	-
	- month 6	59	32.2	40.7	15.3	11.9	-
Fluctuating	- baseline	70	40.0	20.0	32.9	7.1	-
	- month 6	70	35.7	35.7	15.7	12.9	-

Table R42. Disability of dyskinesias (% of the patients with dyskinesia , ITT-OC

Treatment / Patient population	Time	n	Not disabling %	Mildly disabling %	Moderately disabling %	Severely disabling %	Completely disabling %
Entacapone							
All patients	- baseline	123	41.5	25.2	21.1	9.8	2.4
	- month 6	98	36.7	35.7	20.4	5.1	2.0
5-10 doses	- baseline	100	37.0	28.0	20.0	12.0	3.0
	- month 6	77	31.2	37.7	23.4	5.2	2.6
Fluctuating	- baseline	116	39.7	25.9	21.6	10.3	2.6
	- month 6	93	37.6	35.5	19.4	5.4	2.2
Placebo							
All patients	- baseline	76	42.1	19.7	31.6	6.6	-
	- month 6	63	31.7	33.3	22.2	12.7	-
5-10 doses	- baseline	59	44.1	18.6	30.5	6.8	-
	- month 6	48	29.2	39.6	18.8	12.5	-
Fluctuating	- baseline	70	40.4	20.0	32.9	7.1	-
	- month 6	59	33.9	33.9	18.6	13.6	-

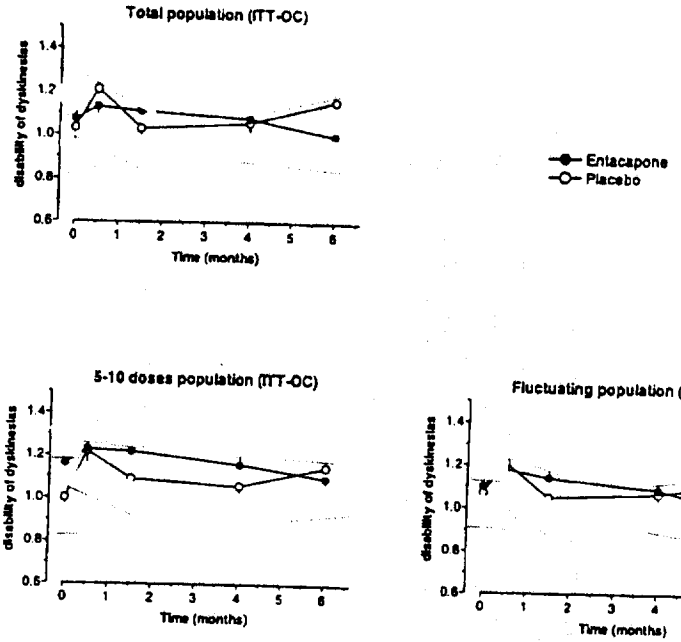


Figure 5. Disability of dyskinesias for the total population, for the patients with 5-10 doses of levodopa and for the fluctuating patients (ITT-OC analysis) (mean ± SEM).

Table R43. Painful dyskinesias (% of the patients with dyskinesia), ITT-LOCF

Treatment / Patient population	Time	n	Not painful %	Slightly painful %	Moderately painful %	Severely painful %	Markedly painful %
Entacapone							
All patients	- baseline	123	70.7	13.0	7.3	8.9	-
	- month 6	123	69.9	17.1	9.8	2.4	0.8
5-10 doses	- baseline	100	70.0	11.0	9.0	10.0	-
	- month 6	100	69.0	17.0	10.0	3.0	1.0
Fluctuating	- baseline	116	69.0	13.8	7.8	9.5	-
	- month 6	116	69.8	18.1	8.6	2.6	0.9
Placebo							
All patients	- baseline	76	67.1	17.1	9.2	5.3	1.3
	- month 6	76	75.0	14.5	6.6	3.9	-
5-10 doses	- baseline	59	66.1	18.6	6.8	6.8	1.7
	- month 6	59	74.6	13.6	8.5	3.4	-
Fluctuating	- baseline	70	65.7	17.1	10.0	5.7	1.4
	- month 6	70	75.7	14.3	5.7	4.3	-

Table R44. Painful dyskinesias (% of the patients with dyskinesia), ITT-OC

Treatment / Patient population	Time	n	Not painful %	Slightly painful %	Moderately painful %	Severely painful %	Markedly painful %
Entacapone							
All patients	- baseline	123	70.7	13.0	7.3	8.9	-
	- month 6	98	71.4	14.3	11.2	3.1	-
5-10 doses	- baseline	100	70.0	11.0	9.0	10.0	-
	- month 6	77	71.4	13.0	11.7	3.9	-
Fluctuating	- baseline	116	69.0	13.8	7.8	9.5	-
	- month 6	93	72.0	15.1	9.7	3.2	-
Placebo							
All patients	- baseline	76	67.1	17.1	9.2	5.3	1.3
	- month 6	63	73.0	14.3	7.9	4.8	-
5-10 doses	- baseline	59	66.1	18.6	6.8	6.8	1.7
	- month 6	48	70.8	14.6	10.4	4.2	-
Fluctuating	- baseline	70	65.7	17.1	10.0	5.7	1.4
	- month 6	59	74.6	13.6	6.8	5.1	-

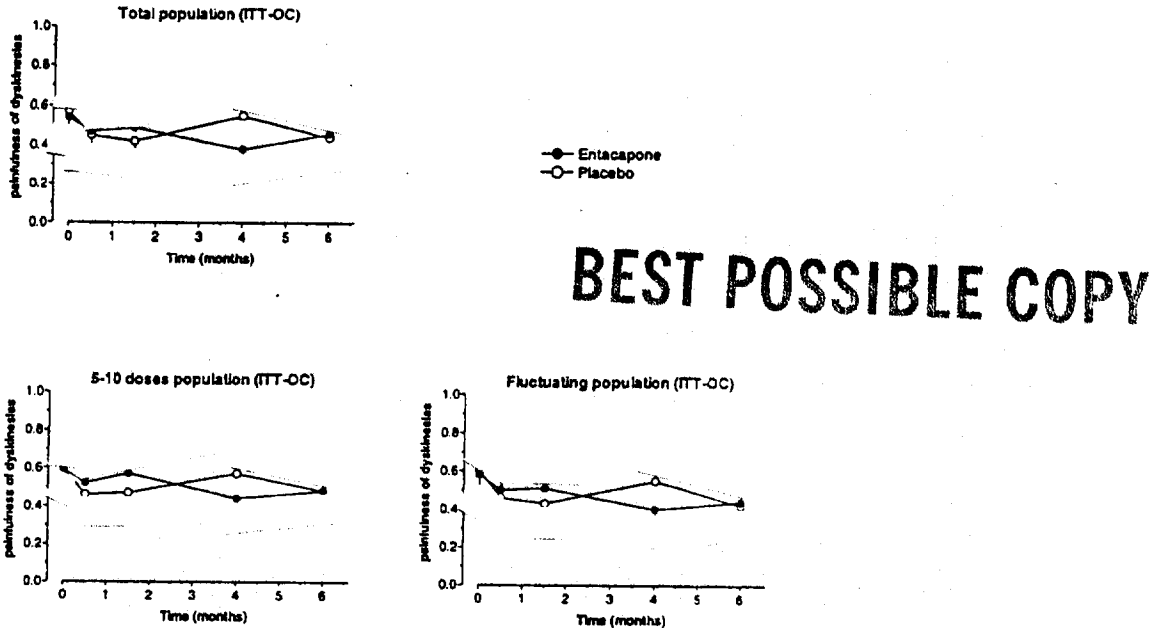


Figure 7. Painfulness of dyskinesias for the total population, for the patients with 5-10 doses of levodopa and for the fluctuating patients (ITT-OC analysis) (mean ± SEM).

Table R45. OFF-periods (% of the patients), ITT-LOCF

Treatment / Patient population	Time	n	Predictable %	Unpredictable %	Sudden %	No OFF time %	OFF time >50% %
Entacapone							
All patients	- baseline	191	66.5	56.5	34.6	6.3	6.3
	- month 6	191	65.4	46.6	29.8	9.4	7.3
5-10 doses	- baseline	125	68.0	57.6	39.2	5.6	6.4
	- month 6	125	69.6	51.2	36.0	8.8	9.6
Fluctuating	- baseline	167	71.9	58.1	35.9	3.6	7.2
	- month 6	167	71.3	46.7	29.9	6.0	8.4
Placebo							
All patients	- baseline	104	66.3	62.5	36.5	6.7	9.6
	- month 6	104	65.4	49.0	33.7	8.7	12.5
5-10 doses	- baseline	69	73.9	73.9	44.9	4.3	10.1
	- month 6	69	71.0	55.1	43.5	7.2	14.5
Fluctuating	- baseline	88	70.5	64.8	39.8	3.4	11.4
	- month 6	88	71.6	50.0	36.4	2.3	14.8

Table R46. OFF-periods (% of the patients), ITT-OC

Treatment / Patient population	Time	n	Predictable %	Unpredictable %	Sudden %	No OFF time %	OFF time >50% %
Entacapone							
All patients	- baseline	191	66.5	56.5	34.6	6.3	6.3
	- month 6	148-149	68.5	44.3	28.9	10.1	5.4
5-10 doses	- baseline	125	68.0	57.6	39.2	5.6	6.4
	- month 6	94-95	71.6	51.6	34.7	9.6	7.4
Fluctuating	- baseline	167	71.9	58.1	35.9	3.6	7.2
	- month 6	132-133	72.9	45.9	29.3	6.8	6.1
Placebo							
All patients	- baseline	104	66.3	62.5	36.5	6.7	9.6
	- month 6	89	64.0	47.2	29.2	9.0	14.6
5-10 doses	- baseline	69	73.9	73.9	44.9	4.3	10.1
	- month 6	57	71.9	52.6	38.6	7.0	17.5
Fluctuating	- baseline	88	70.5	64.8	39.8	3.4	11.4
	- month 6	76	71.1	48.7	31.6	2.6	17.1

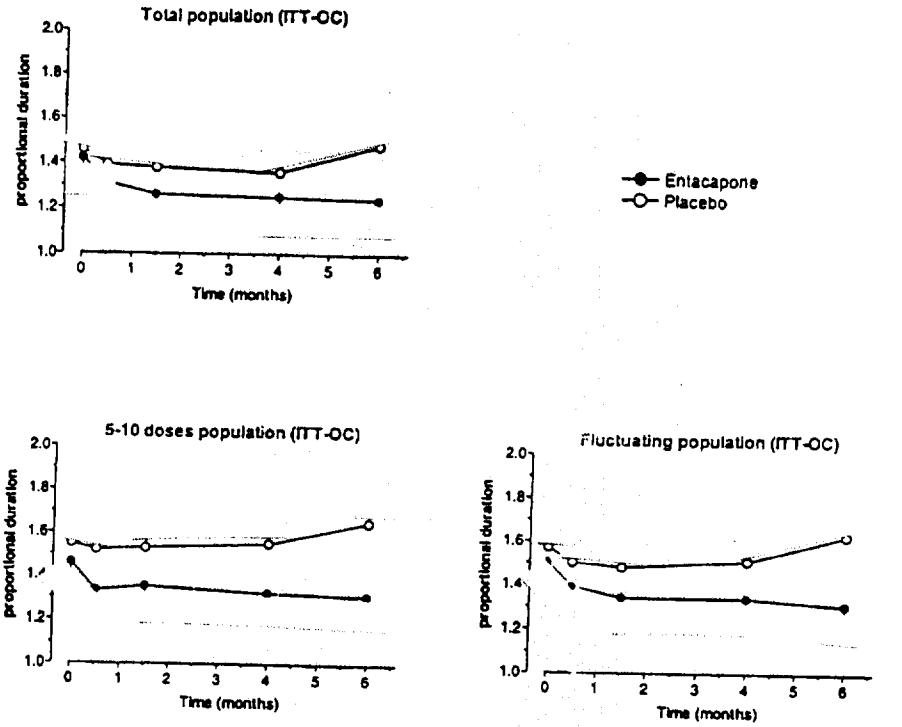


Figure 8. Proportional duration of OFF time of day for the total population, for the patients with 5-10 doses of levodopa and for the fluctuating patients (ITT-OC analysis) (mean ± SEM).

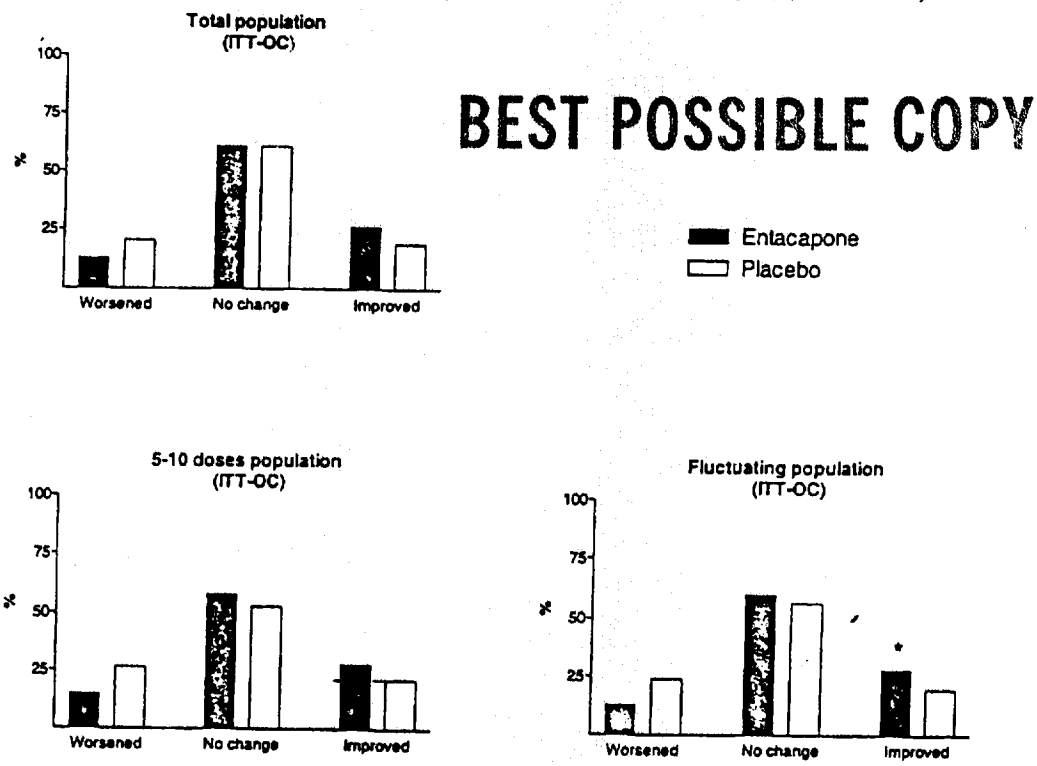


Figure 9. Categorical changes in OFF time for the total population, for the patients with 5-10 doses of levodopa, and for the fluctuating patients (ITT-OC analysis). * $p<0.05$

Table R47. Summary of the UPDRS part IV results; changes from baseline at month 6, ITT-OC

Parameter	Patient population	Entacapone	Placebo
Proportion of dyskinetic patients	- all patients	±	±
	- 5-10 doses	↓	±
	- fluctuating	↓	±
Proportion of patients with dyskinesia >50% of the day	- all patients	±	↓
	- 5-10 doses	↓	↓
	- fluctuating	±	↓
Proportion of patients with disabling dyskinesia	- all patients	↑	↑↑↑
	- 5-10 doses	↑↑	↑↑↑
	- fluctuating	↑	↑↑
Proportion of patients with painful dyskinesia	- all patients	±	↓↓
	- 5-10 doses	↓	↓
	- fluctuating	↓	↓↓
Proportion of patients with early morning dystonia	- all patients	↓↓	↓
	- 5-10 doses	↓	↓
	- fluctuating	↓↓	↓
Proportion of patients with predictable OFF periods	- all patients	↑	↓
	- 5-10 doses	↑	↓
	- fluctuating	±	±
Proportion of patients with unpredictable OFF periods	- all patients	↓↓↓	↓↓↓
	- 5-10 doses	↓↓	↓↓↓
	- fluctuating	↓↓↓	↓↓↓
Proportion of patients with sudden OFF periods	- all patients	↓↓	↓↓
	- 5-10 doses	↓	↓↓
	- fluctuating	↓↓	↓↓
Proportion of patients with no daily OFF time	- all patients	↑	↑
	- 5-10 doses	↑	↑
	- fluctuating	↑	±
Proportion of patients with OFF time >50% of the day	- all patients	±	↑
	- 5-10 doses	±	↑↑
	- fluctuating	↓	↑↑
Proportion of patients with anorexia, nausea, vomiting	- all patients	↑	↓
	- 5-10 doses	↑	↓↓
	- fluctuating	↑	↓↓
Proportion of patients with sleep disturbances	- all patients	↓↓	↓↓
	- 5-10 doses	↓	↓↓
	- fluctuating	↓↓	↓↓
Proportion of patients with symptomatic orthostasis	- all patients	↑	↓↓
	- 5-10 doses	±	↓
	- fluctuating	↑	↓↓

±, no change (±1%); ↑, increase (1-5%); ↓, decrease (1-5%); ↑↑, increase (5-10%); ↓↓, decrease (5-10%) ↑↑↑, increase (>10%); ↓↓↓, decrease (>10%)

Table R48. Modified Hoehn & Yahr staging, proportion of patients (%); ITT-LOCF and ITT-OC

Analysis/ Treatment	Time	n	H&Y 0 – 2 %	H&Y 2.5 – 5 %
ITT-LOCF				
Entacapone	- baseline	191	38.2	61.8
	- month 6	191	40.8	59.2
Placebo	- baseline	104	40.4	59.6
	- month 6	104	34.6	65.4
ITT-OC				
Entacapone	- baseline	191	38.2	61.8
	-month 6	149	39.6	60.4
Placebo	- baseline	104	40.4	59.6
	- month 6	89	36.0	64.0

Table R49. Schwab and England ADL (% of patients), all patients; ITT-LOCF and ITT-OC

Analysis / Treatment	Time	n	<80% %	80% %	>80% %
ITT-LOCF					
Entacapone	- baseline	191	34.0	35.6	30.4
	- month 6	191	34.6	30.4	35.1
Placebo	- baseline	104	37.5	36.5	26.0
	- month 6	104	40.4	33.7	26.0
ITT-OC					
Entacapone	- baseline	191	34.0	35.6	30.4
	- month 6	149	34.2	29.5	36.2
Placebo	- baseline	104	37.5	36.5	26.0
	- month 6	89	37.1	34.8	28.1

Table R50 Proportion of daily ON time (% of awake time) (ITT-LOCF, ITT-OC)

Analysis/ Patient population	Time	Entacapone n	Entacapone mean ± SD	Placebo n	Placebo mean ± SD	Significance [95% CI]
ITT-LOCF						
5-10 doses	- baseline	120	63.2 ± 16.8	67	63.2 ± 17.8	
	- month 6	120	69.5 ± 18.8	67	66.0 ±19.4	NS
	- change	120	6.4 ± 14.6	67	2.8 ± 14.9	
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	NS
	- change	165	7.9 ± 17.2	87	5.7 ± 19.3	
Fluctuating	- baseline	114	62.0 ± 15.7	60	59.8 ± 15.1	
with 5-10 doses	- month 6	114	68.5 ± 18.3	60	63.2 ± 18.3	NS
	- change	114	6.5 ± 14.9	60	3.5 ± 15.2	
ITT-OC						
5-10 doses	- baseline	120	63.2 ± 16.8	67	63.2 ± 17.8	
	- month 6	92	72.2 ± 17.2	54	65.5 ± 19.6	p<0.05
	- change	92	9.0 ± 12.4	54	2.2 ± 14.7	[0.00; 9.25]
All fluctuating	- baseline	165	61.7 ± 15.8	87	59.1 ± 16.6	
	- month 6	129	71.6 ± 17.5	74	64.9 ± 19.3	NS (p=0.073)
	- change	129	9.9 ± 16.4	74	5.8 ± 19.6	[-0.48; 9.83]
Fluctuating	- baseline	114	62.0 ± 15.7	60	59.8 ± 15.1	
with 5-10 doses	- month 6	88	71.1 ± 16.8	50	63.4 ± 18.7	p<0.05
	- change	88	9.1 ± 12.5	50	3.6 ± 15.2	[0.36; 12.08]

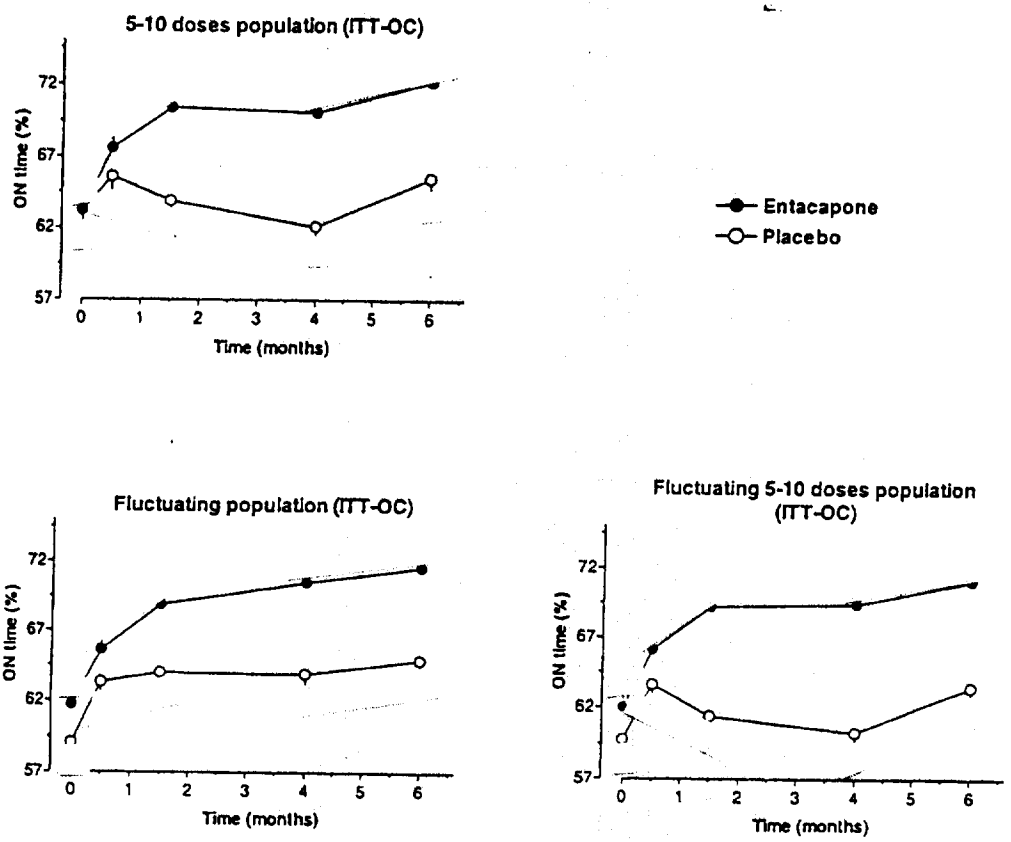
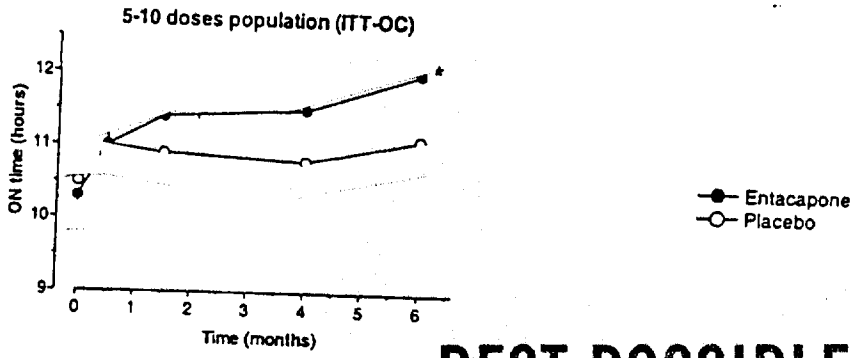


Figure 10. Proportion of ON time (%) for the patients with 5-10 doses of levodopa, for the fluctuating patients, and for the fluctuating patients with 5-10 doses of levodopa (ITT-OC analysis)(mean ± SEM). * $p<0.05$

Table R51. Daily ON time (hours, mean ± SD); ITT-LOCF and ITT-OC

Analysis/ Patient population		Entacapone n	Entacapone mean ± SD	Placebo n	Placebo mean ± SD	Significance [95% CI]
ITT-LOCF						
5-10 doses	- baseline	120	10.3 ± 2.7	67	10.5 ± 2.8	
	- month 6	120	11.4 ± 3.1	67	11.1 ± 3.1	NS
	- change	120	1.1 ± 2.5	67	0.5 ± 2.5	
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	NS
	- change	165	1.3 ± 2.8	87	0.9 ± 3.1	
Fluctuating with 5-10 doses	- baseline	114	10.2 ± 2.6	60	10.1 ± 2.5	
	- month 6	114	11.2 ± 3.1	60	10.6 ± 2.9	NS
	- change	114	1.1 ± 2.6	60	0.5 ± 2.5	
ITT-OC						
5-10 doses	- baseline	120	10.3 ± 2.7	67	10.5 ± 2.8	
	- month 6	92	12.0 ± 2.7	54	10.8 ± 3.0	p<0.05 [0.14; 1.70]
	- change	92	1.7 ± 2.2	54	0.3 ± 2.5	
All fluctuating	- baseline	165	10.0 ± 2.6	87	9.7 ± 2.8	
	- month 6	129	11.7 ± 2.8	74	10.7 ± 3.1	NS (p=0.106) [-0.16; 1.52]
	- change	129	1.7 ± 2.6	74	0.9 ± 3.3	
Fluctuating with 5-10 doses	- baseline	114	10.2 ± 2.6	60	10.1 ± 2.5	
	- month 6	88	11.8 ± 2.7	50	10.6 ± 3.0	p<0.05 [0.13;2.03]
	- change	88	1.7 ± 2.2	50	0.5 ± 2.6	



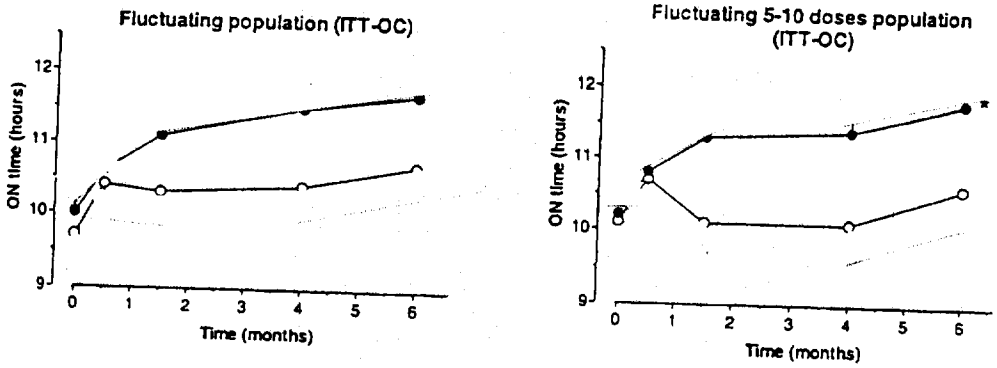
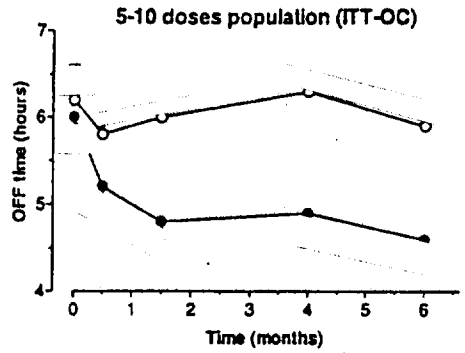
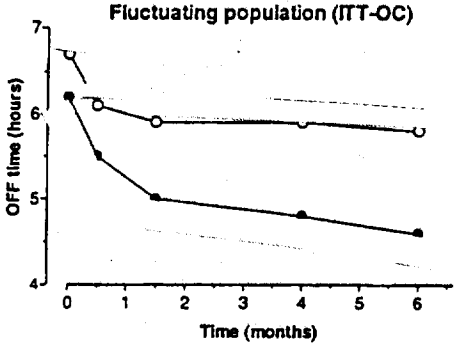


Figure 11. ON time (h) for the patients with 5-10 doses of levodopa, for the fluctuating patients, and for the fluctuating patients with 5-10 doses of levodopa (ITT-OC analysis)(mean ± SEM). * $p<0.05$

Table R52. Daily OFF time (hours, mean ± SD); ITT-LOCF and ITT-OC

Analysis/ Patient population		Entacapone n	Entacapone mean ± SD	Placebo n	Placebo mean ± SD	Significance [95% CI]
ITT-LOCF						
5-10 doses	- baseline	120	6.0 ± 2.9	67	6.2 ± 3.2	
	- month 6	120	4.9 ± 3.2	67	5.7 ± 3.4	NS
	- change	120	-1.1 ± 2.4	67	-0.5 ± 2.6	
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	NS
	- change	165	-1.3 ± 2.7	87	-0.9 ± 3.3	
Fluctuating	- baseline	114	6.3 ± 2.7	60	6.8 ± 2.8	NS (p=0.070)
with 5-10 doses	- month 6	114	5.1 ± 3.1	60	6.2 ± 3.3	[-1.68; 0.07]
	- change	114	-1.2 ± 2.5	60	- 0.6 ± 2.7	
ITT-OC						
5-10 doses	- baseline	120	6.0 ± 2.9	67	6.2 ± 3.2	NS (p=0.068)
	- month 6	92	4.6 ± 3.0	54	5.9 ± 3.5	[-1.66; 0.07]
	- change	92	-1.4 ± 2.1	54	-0.7 ± 2.6	
All fluctuating	- baseline	165	6.2 ± 2.7	87	6.7 ± 3.0	NS (p=0.077)
	- month 6	129	4.6 ± 2.9	74	5.8 ± 3.4	[-1.62; 0.09]
	- change	129	-1.6 ± 2.5	74	-0.9 ± 3.4	
Fluctuating	- baseline	114	6.3 ± 2.7	60	6.8 ± 2.8	p<0.05
with 5-10 doses	- month 6	88	4.8 ± 3.0	50	6.2 ± 3.3	[-2.06; -0.12]
	- change	88	-1.5 ± 2.1	50	-0.6 ± 2.7	





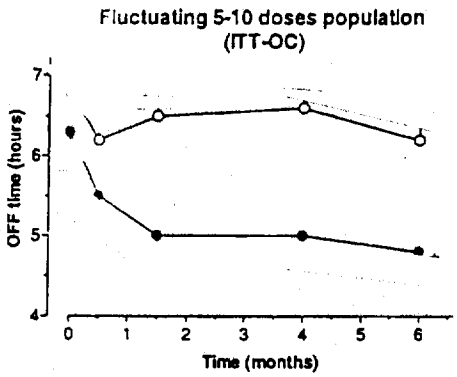


Figure 12. OFF time (h) for the patients with 5-10 doses of levodopa, for the fluctuating patients, and for the fluctuating patients with 5-10 doses of levodopa (ITT-OC analysis)(mean ± SEM)

Table R53. Global evaluation (% of patients) at month 6 compared to baseline; ITT-LOCF and ITT-OC

Analysis/ Patient population	Entacapone			Placebo		
	Worsened %	No change %	Improved %	Worsened %	No change %	Improved %
ITT-LOCF						
All patients	25.7	36.1	38.2	26.9	39.4	33.7
5-10 doses	26.4	35.2	38.4	33.3	40.6	26.1
Fluctuating	25.1	38.3	36.5	27.3	37.5	35.2
ITT-OC						
All patients	22.5	35.1	42.4	24.7	37.1	38.2
5-10 doses	24.2	34.7	41.1	31.6	36.8	31.6
Fluctuating	23.0	37.8	39.3	25.0	35.5	39.5

Table R54. Global evaluation of patients as changes (% of patients) in categories from baseline to 6 months; ITT-LOCF and ITT-OC

Treatment / Patient population	n	Worsening ≥2 categ. %		Worsening 1 categ. %		No change %		Improvement 1 categ. %		Improvement ≥2 categ. %	
	LOCF/ OC	LOCF	OC	LOCF	OC	LOCF	OC	LOCF	OC	LOCF	OC
Entacapone											
All patients	191/151	9.4	7.9	16.2	14.6	36.1	35.1	22.5	25.2	15.7	17.2
5-10 doses	125/95	9.6	9.5	16.8	14.7	35.2	34.7	20.0	21.1	18.4	20.0
Fluctuating	167/135	9.6	8.1	15.6	14.8	38.3	37.8	20.4	22.2	16.2	17.0
Placebo											
All patients	104/89	10.6	9.0	16.3	15.7	39.4	37.0	29.8	33.7	3.8	4.5
5-10 doses	69/57	14.5	12.3	18.8	19.3	40.6	36.8	23.2	28.1	2.9	3.5

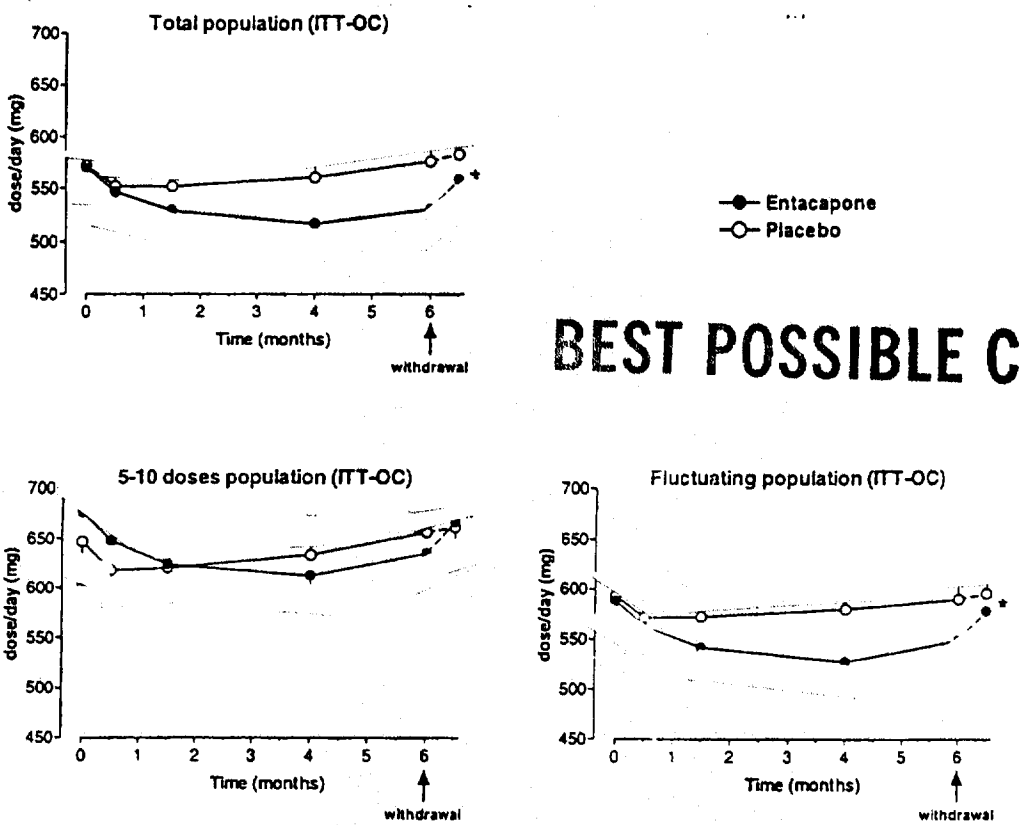


Figure 13. Changes in daily scheduled levodopa dose for the total population, for the patients with 5-10 doses of levodopa and for the fluctuating patients. (ITT-OC analysis)(mean ± SEM). * p<0.05

Table R55. Mean scheduled daily levodopa dose (mg, mean ± SD); ITT-LOCF and ITT-OC

Analysis/ Patient population	Time	Entacapone		Placebo		Significance
		n	mg/day	n	mg/day	
ITT-LOCF						
All patients	- baseline	191	566 ± 274	104	572 ± 329	
	- month 6	191	531 ± 261	104	575 ± 282	NS
	- change	191	-35 ± 102	104	4 ± 224	
5-10 doses	- baseline	125	676 ± 260	69	647 ± 365	
	- month 6	125	629 ± 260	69	641 ± 304	NS
	- change	125	-47 ± 109	69	-7 ±2 70	
Fluctuating	- baseline	167	584 ± 271	88	593 ± 342	
	- month 6	167	546 ± 261	88	598 ± 291	NS
	- change	167	-38 ± 107	88	4 ± 242	
ITT-OC						
All patients	- baseline	197	570 ± 273	104	572 ± 329	
	- month 6	152	530 ± 257	89	576 ± 287	NS
	- change	152	-40±108	89	4±242	
- 5-10 doses	- baseline	131	676 ± 257	69	647 ± 365	
	- month 6	95	635 ± 258	57	656 ± 309	NS
	- change	95	-41 ± 116	57	9 ± 296	
Fluctuating	- baseline	172	588 ± 269	88	593 ± 342	
	- month 6	134	549 ± 259	76	590 ± 301	NS
	- change	134	-39 ± 112	76	-3 ± 260	

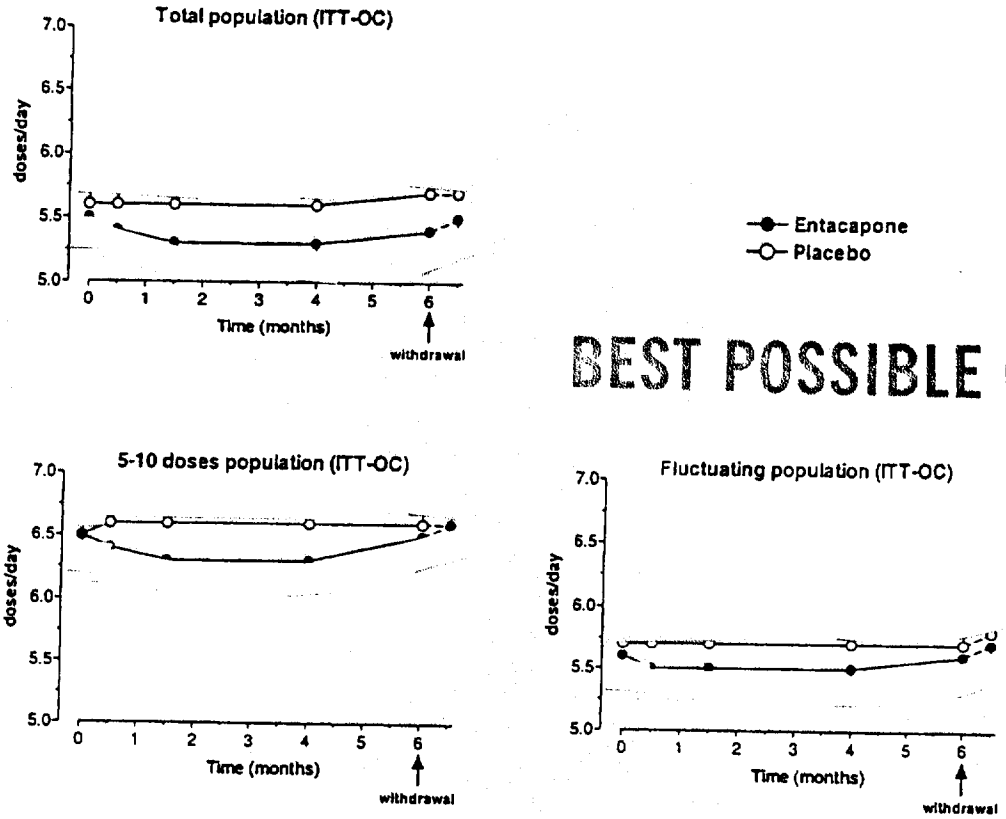


Figure 14. Changes in daily levodopa dosing frequency for the total population, for the patients with 5-10 doses of levodopa and for the fluctuating patients. (ITT-OC analysis)(mean ± SEM). * $p<0.05$

Table R57. Mean daily dosing frequency (mean ± SD) of levodopa; ITT-LOCF

Analysis/ Patient population	Time	Entacapone n	Entacapone doses/day	Placebo n	Placebo doses/day	Significance [95% CI]
ITT-LOCF						
All patients	- baseline	191	5.4 ± 1.9	104	5.6 ± 1.9	p<0.01
	- month 6	191	5.4 ± 1.8	104	5.8 ± 2.0	[-0.43; -0.08]
	- change	191	-0.0 ± 0.6	104	0.2 ± 0.7	
5-10 doses	- baseline	125	6.5 ± 1.5	69	6.5 ± 1.6	p<0.01
	- month 6	125	6.4 ± 1.5	69	6.7 ± 1.8	[-0.48; -0.08]
	- change	125	-0.1 ± 0.7	69	0.2 ± 0.8	
Fluctuating	- baseline	167	5.6 ± 1.9	88	5.7 ± 1.9	p<0.05
	- month 6	167	5.6 ± 1.8	88	5.9 ± 2.0	[-0.41; -0.02]
	- change	167	-0.0 ± 0.6	88	0.2 ± 0.7	
ITT-OC						
All patients	- baseline	197	5.5 ± 1.9	104	5.6 ± 1.9	p<0.05
	- month 6	152	5.4 ± 1.9	89	5.7 ± 2.0	[-0.45; -0.06]
	- change	152	-0.0 ± 0.7	89	0.1 ± 0.7	
5-10 doses	- baseline	131	6.5 ± 1.5	69	6.5 ± 1.6	p<0.05
	- month 6	95	6.5 ± 1.5	57	6.6 ± 1.7	[-0.51; -0.04]
	- change	95	0.0 ± 0.8	57	0.1 ± 0.8	
Fluctuating	- baseline	172	5.6 ± 1.9	88	5.7 ± 1.9	
	- month 6	134	5.6 ± 1.9	76	5.7 ± 2.0	NS
	- change	134	-0.0 ± 0.7	76	0.1 ± 0.7	

Table R59. Mean daily levodopa dose (mg/day) on home diary; ITT-LOCF and ITT-OC

Analysis/ Patient population	Time	Entacapone n	Entacapone mean ± SD	Placebo n	Placebo mean ± SD	Significance [95% CI]
ITT-LOCF						
5-10 doses	- baseline	88	674±260	43	593±301	p<0.05[-132.21;
	- month 6	88	611±237	43	610±336	-16.14]
Fluctuating	- baseline	118	594±276	52	567±293	p<0.05[-117.86;
	- month 6	118	541±242	52	590±321	-11.83]
ITT-OC						
5-10 doses	- baseline	88	674±260	43	593±301	p<0.05[-161.36;
	- month 6	69	598±230	33	650±343	-15.45]
Fluctuating	- baseline	118	594±276	52	567±293	p<0.05[-
	- month 6	93	535±230	42	603±334	135.88±-9.13]

Table R60. Mean daily dosing frequency (mean ± SD) of levodopa on home diary; ITT-LOCF

Analysis/ Patient population	Time	Entacapone n	Entacapone doses/day	Placebo n	Placebo doses/day	Significance [95% CI]
ITT-LOCF						
5-10 doses	- baseline	116	6.2±2.0	66	6.2±1.9	NS
	- month 6	116	6.5±1.6	66	6.8±2.0	
Fluctuating	- baseline	158	5.3±2.2	83	5.6±2.1	NS
	- month 6	158	5.7±1.9	83	6.1±2.3	
ITT-OC						
5-10 doses	- baseline	116	6.2±2.0	66	6.2±1.9	NS
	- month 6	86	6.6±1.6	50	6.9±2.0	
Fluctuating	- baseline	158	5.3±2.2	83	5.6±2.1	NS
	- month 6	121	5.7±1.9	68	6.0±2.3	

Table R62. Activities of daily living during withdrawal (UPDRS Part II), (mean ± SD), ITT-OC

Analysis/ Patient population		Entacapone n	Entacapone mean ± SD	Placebo n	Placebo mean ± SD	Significance [95% CI]
All patients	- month 6	147	11.0 ± 6.3	88	12.5 ± 6.5	p<0.01
	- post-study	147	12.7 ± 6.7	88	12.5 ± 6.2	[0.46; 2.29]
5-10 doses	- month 6	94	12.1 ± 6.7	57	13.7 ± 6.9	p<0.001
	- post-study	94	14.4 ± 7.1	57	13.7 ± 6.6	[1.19; 3.37]
Fluctuating	- month 6	132	11.2 ± 6.3	76	12.5 ± 6.2	p<0.01
	- post-study	132	12.9 ± 6.8	76	12.5 ± 5.9	[0.38; 2.46]

Table R63. Motor score during withdrawal (UPDRS Part III), (mean ± SD), ITT-OC

Analysis/ patient population		Entacapone n	Entacapone mean ± SD	Placebo n	Placebo mean ± SD	Significance [95% CI]
All patients	- month 6	147	21.6 ± 12.1	86	24.5 ± 12.9	p<0.01
	- post-study	147	25.5 ± 13.9	86	24.4 ± 12.6	[0.88; 5.30]
5-10 doses	- month 6	94	21.5 ± 12.8	55	25.0 ± 13.8	p<0.001
	- post-study	94	26.8 ± 15.0	55	23.9 ± 12.8	[3.65; 8.96]
Fluctuating	- month 6	132	21.2 ± 11.9	75	23.6 ± 12.1	p<0.05
	- post-study	132	25.3 ± 14.0	75	23.5 ± 12.0	[0.48; 5.49]

Table R64. UPDRS, Sum of Parts I, II and III, (mean ± SD), ITT-OC

Analysis/ Patient population		Entacapone n	Entacapone mean ± SD	Placebo n	Placebo mean ± SD	Significance [95% CI]
All patients	- month 6	146	34.1 ± 17.7	86	38.5 ± 18.0	p<0.01
	- post-study	146	40.4 ± 20.4	86	38.4 ± 17.7	[1.92; 7.73]
5-10 doses	- month 6	93	35.2 ± 18.9	55	40.2 ± 19.4	p<0.0001
	- post-study	93	43.1 ± 21.9	55	39.2 ± 18.2	[5.45; 12.43
Fluctuating	- month 6	131	33.9 ± 17.6	75	37.6 ± 17.0	p<0.01
	- post-study	131	40.4 ± 20.5	75	37.5 ± 16.6	[1.49; 8.10]

Table R65. Global evaluation (% of patients) during withdrawal, ITT-OC

Analysis/ Patient population	Entacapone			Placebo		
	Worsened %	No change %	Improved %	Worsened %	No change %	Improved %
All patients	56.3	34.4	9.3	29.5	52.3	18.2
5-10 doses	61.1	28.4	10.5	26.3	50.9	22.8
Fluctuating	59.3	31.1	9.6	32.9	47.4	19.7

Table R66. Global evaluation of patients as changes (% of patients) in categories from month 6 to post study visit, ITT-OC

Treatment / Patient population	n	Worsening ≥2 categ. %	Worsening 1 categ. %	No change %	Improvement 1 categ. %	Improvement ≥2 categ. %
Entacapone						
All patients	151	25.8	30.5	34.4	7.9	1.3
5-10 doses	95	29.5	31.6	28.4	9.5	1.1
Fluctuating	135	26.7	32.6	31.1	8.1	1.5
Placebo						
All patients	88	9.1	20.5	50.9	14.8	3.4
5-10 doses	57	7.0	19.3	52.3	19.3	3.5
Fluctuating	76	10.5	22.4	47.4	17.1	2.6

Table R67. Mean scheduled daily levodopa dose during withdrawal (mg, mean ± SD), ITT-OC

Analysis / Patient population	Time	Entacapone n	Entacapone mg/day	Placebo n	Placebo mg/day	Significance [95% CI]
All patients	- month 6	151	531 ± 258	88	578 ± 288	p<0.05
	- post-study	151	558 ± 265	88	583 ± 294	[3.35; 39.51]
5-10 doses	- month 6	95	635 ± 258	57	656 ± 309	p<0.05
	- post-study	95	667 ± 263	57	661 ± 316	[4.60; 47.94]
Fluctuating	- month 6	135	550 ± 258	76	590 ± 301	p<0.05
	- post-study	135	578 ± 264	76	596 ± 307	[0.53; 41.45]

Table R68. Mean dosing frequency during withdrawal (mean ± SD) of levodopa, ITT-OC

Analysis / Patient population	Time	Entacapone n	Entacapone doses/day	Placebo n	Placebo doses/day	Significance
All patients	- month 6	151	5.4 ± 1.9	88	5.7 ± 2.0	NS
	- post-study	151	5.5 ± 2.0	88	5.7 ± 2.0	
5-10 doses	- month 6	95	6.5 ± 1.5	57	6.6 ± 1.7	NS
	- post-study	95	6.6 ± 1.7	57	6.6 ± 1.7	
Fluctuating	- month 6	135	5.6 ± 1.9	76	5.7 ± 2.0	NS
	- post-study	135	5.7 ± 2.0	76	5.8 ± 2.0	

STUDY 2939063
Statistical table 2.1.3 UPDRS part I - Mentation, behavior, and mood for all patients PP-analysis (cont.)

Analysis of variance on month 6

Source	DF (nomin)	DF (denomin)	F-value	p-value
Baseline	1	150	127.94	0.0000
Stratif	1	150	0.65	0.4229
Treatment	1	23	0.23	0.6343
Stratif * Treatment	1	150	0.75	0.3893

Estimation of treatment differences

Comparison	Difference	Standard error	DF	95% CI lower	95% CI upper	p-value
Entacapone - Placebo	-0.08	0.17	23	-0.43	0.27	0.6343
2-4 :E-P	-0.22	0.26	23	-0.76	0.32	0.3991
5-10 :E-P	0.06	0.21	23	-0.37	0.49	0.7653

STUDY 2939063
Statistical table 2.1.4 UPDRS part I - Mentation, behavior, and mood for fluctuating patients (4.5 h OFF time over three home diary days at baseline) - PP-analysis (cont.)

Analysis of variance on month 6

Source	DF (nomin)	DF (denomin)	F-value	p-value
Baseline	1	126	110.17	0.0000
Stratif	1	126	0.65	0.4212
Treatment	1	22	0.58	0.4558
Stratif * Treatment	1	126	0.69	0.4065

Estimation of treatment differences

Comparison	Difference	Standard error	DF	95% CI lower	95% CI upper	p-value
Entacapone - Placebo	-0.14	0.18	22	-0.52	0.24	0.4558
2-4 :E-P	-0.29	0.29	22	-0.90	0.32	0.3314
5-10 :E-P	0.01	0.22	22	-0.44	0.47	0.9502

STUDY 2939063
Statistical table 2.1.7 UPDRS part II - Activities in daily living for all patients PP-analysis (cont.)

Analysis of variance on month 6

Source	DF (nomin)	DF (denomin)	F-value	p-value
Baseline	1	150	387.19	0.0000
Stratif	1	150	0.08	0.7785
Treatment	1	23	5.25	0.0314
Stratif * Treatment	1	150	0.84	0.3601

Estimation of treatment differences

Comparison	Difference	Standard error	DF	95% CI lower	95% CI upper	p-value
Entacapone - Placebo	-1.42	0.62	23	-2.71	-0.14	0.0314
2-4 :E-P	-0.97	0.86	23	-2.75	0.81	0.2719
5-10 :E-P	-1.88	0.72	23	-3.38	-0.38	0.0160

STUDY 2939063
Statistical table 2.1.8 UPDRS part II - Activities in daily living for fluctuating patients (4.5 h OFF time over three home diary days at baseline) - PP-analysis (cont.)

Analysis of variance on month 6

Source	DF (nomin)	DF (denomin)	F-value	p-value
Baseline	1	126	313.32	0.0000
Stratif	1	126	0.04	0.8493
Treatment	1	22	4.56	0.0440
Stratif * Treatment	1	126	0.14	0.7046

Estimation of treatment differences

Comparison	Difference	Standard error	DF	95% CI lower	95% CI upper	p-value
Entacapone - Placebo	-1.41	0.66	22	-2.78	-0.04	0.0440
2-4 :E-P	-1.20	0.96	22	-3.19	0.79	0.2248
5-10 :E-P	-1.62	0.76	22	-3.19	-0.05	0.0432

STUDY 2939063
Statistical table 2.1.11 UPDRS part III - Motor examination for all patients
PP-analysis (cont.)

Analysis of variance on month 6

Source	DF (nomin)	DF (denomin)	F-value	p-value
Baseline	1	148	309.09	0.0000
Stratif	1	148	0.42	0.5189
Treatment	1	23	6.34	0.0192
Stratif * Treatment	1	148	2.25	0.1361

Estimation of treatment differences

Comparison	Difference	Standard error	DF	95% CI lower	95% CI upper	p-value
Entacapone - Placebo	-2.91	1.16	23	-5.30	-0.52	0.0192
2-4 :E-P	-1.24	1.76	23	-4.89	2.40	0.4880
5-10 :E-P	-4.58	1.43	23	-7.54	-1.62	0.0040

STUDY 2939063
Statistical table 2.1.12 UPDRS part III - Motor examination for fluctuating patients (4.5 h OFF time over three home diary days at baseline)
PP-analysis (cont.)

Analysis of variance on month 6

Source	DF (nomin)	DF (denomin)	F-value	p-value
Baseline	1	124	245.51	0.0000
Stratif	1	124	0.17	0.6832
Treatment	1	22	5.36	0.0303
Stratif * Treatment	1	124	0.05	0.8275

Estimation of treatment differences

Comparison	Difference	Standard error	DF	95% CI lower	95% CI upper	p-value
Entacapone - Placebo	-2.82	1.22	22	-5.34	-0.29	0.0303
2-4 :E-P	-2.55	1.95	22	-6.60	1.49	0.2045
5-10 :E-P	-3.09	1.47	22	-6.14	-0.04	0.0476

STUDY 2939063
Statistical table 2.1.15 Total score of UPDRS (parts I, II, and III) for all patients
PP-analysis (cont.)

Analysis of variance on month 6

Source	DF (nomin)	DF (denomin)	F-value	p-value
Baseline	1	148	432.88	0.0000
Stratif	1	148	0.33	0.5682
Treatment	1	23	7.40	0.0122
Stratif * Treatment	1	148	2.05	0.1540

Estimation of treatment differences

Comparison	Difference	Standard error	DF	95% CI lower	95% CI upper	p-value
Entacapone - Placebo	-4.57	1.68	23	-8.04	-1.09	0.0122
2-4 :E-P	-2.57	2.36	23	-7.46	2.32	0.2881
5-10 :E-P	-6.56	1.98	23	-10.66	-2.46	0.0030

STUDY 2939063
Statistical table 2.1.16 Total score of UPDRS (parts I, II, and III) for fluctuating patients (4.5 h OFF time over three home diary days at baseline) - PP-analysis (cont.)

Analysis of variance on month 6

Source	DF (nomin)	DF (denomin)	F-value	p-value
Baseline	1	124	341.51	0.0000
Stratif	1	124	0.03	0.8580
Treatment	1	22	6.82	0.0159
Stratif * Treatment	1	124	0.13	0.7182

Estimation of treatment differences

Comparison	Difference	Standard error	DF	95% CI lower	95% CI upper	p-value
Entacapone - Placebo	-4.45	1.70	22	-7.98	-0.92	0.0159
2-4 :E-P	-3.89	2.57	22	-9.22	1.45	0.1449
5-10 :E-P	-5.01	2.00	22	-9.15	-0.87	0.0200

STUDY 2939063
Statistical table 2.2.1 Proportion of daily ON time (%) on 24-hour Home diary for patients with 5-10 levodopa doses - PP-analysis

		Statistic	Baseline	Month 0.5	Month 1.5	Month 4	Month 6
5-10 doses	Entacapone	MEAN	64.3	70.0	71.6	70.8	72.6
		SD	15.5	17.3	16.6	17.0	17.4
		SEM	1.8	2.0	1.9	1.9	2.0
		MIN	[illegible]				
		MAX					
		N	77.0	76.0	76.0	77.0	77.0
	Placebo	MEAN	61.6	67.2	65.7	64.5	67.9
		SD	16.5	18.3	20.6	19.9	19.8
		SEM	2.5	2.8	3.1	3.1	3.0
		MIN	[illegible]				
		MAX					
		N	43.0	43.0	43.0	41.0	43.0

Analysis of variance on month 6

Source	DF (nomin)	DF (denomin)	F-value	p-value
Baseline	1	73	126.31	0.0000
Treatment	1	20	1.03	0.3224

Estimation of treatment differences

Comparison	Difference	Standard error	DF	95% CI lower	95% CI upper	p-value
5-10 :E-P	-2.46	2.43	20	-7.53	2.60	0.3224

STUDY 2939063
Statistical table 2.2.2 Proportion of daily ON time (%) on 24-hour Home diary for fluctuating patients (4.5 h OFF time over three home diary days at baseline) - PP-analysis (cont.)

Analysis of variance on month 6

Source	DF (nomin)	DF (denomin)	F-value	p-value
Baseline	1	120	43.32	0.0000
Stratif	1	120	0.36	0.5507
Treatment	1	22	2.75	0.1115
Stratif * Treatment	1	120	0.01	0.9245

Estimation of treatment differences

Comparison	Difference	Standard error	DF	95% CI lower	95% CI upper	p-value
Entacapone - Placebo	4.48	2.70	22	-1.13	10.09	0.1115
2-4 :E-P	4.74	4.34	22	-4.25	13.74	0.2862
5-10 :E-P	4.23	3.25	22	-2.50	10.96	0.2063

STUDY 2939063
Statistical table 2.2.5 ON time (hours) on 24-hour Home diary for patients with 5-10 levodopa doses - PP-analysis

		Statistic	Baseline	Month 0.5	Month 1.5	Month 4	Month 6
5-10 doses	Entacapone	MEAN	10.5	11.5	11.6	11.6	12.0
		SD	2.4	2.6	2.5	2.7	2.7
		SEM	0.3	0.3	0.3	0.3	0.3
		MIN	[illegible]				
		MAX					
		N	77.0	76.0	76.0	77.0	77.0
	Placebo	MEAN	10.1	11.1	10.6	10.5	11.2
		SD	2.6	3.2	3.3	3.1	3.1
		SEM	0.4	0.5	0.5	0.5	0.5
		MIN	[illegible]				
		MAX					
		N	43.0	43.0	43.0	41.0	43.0

Analysis of variance on month 6

Source	DF (nomin)	DF (denomin)	F-value	p-value
Baseline	1	73	93.36	0.0000
Treatment	1	20	1.65	0.2133

Estimation of treatment differences

Comparison	Difference	Standard error	DF	95% CI lower	95% CI upper	p-value
5-10 :E-P	-0.52	0.41	20	-1.37	0.33	0.2133

STUDY 2939063
Statistical table 2.2.6 ON time (hours) on 24-hour Home diary days for fluctuating patients (4.5 h OFF time over three home diary days at baseline) - PP-analysis (cont.)

Analysis of variance on month 6

Source	DF (nomin)	DF (denomin)	F-value	p-value
Baseline	1	120	47.18	0.0000
Stratif	1	120	0.00	0.9521
Treatment	1	22	1.86	0.1862
Stratif * Treatment	1	120	0.10	0.7576

Estimation of treatment differences

Comparison	Difference	Standard error	DF	95% CI lower	95% CI upper	p-value
Entacapone - Placebo	0.59	0.44	22	-0.31	1.50	0.1862
2-4 :E-P	0.46	0.70	22	-0.99	1.91	0.5180
5-10 :E-P	0.73	0.52	22	-0.35	1.81	0.1767

STUDY 2939063
Statistical table 2.2.9 OFF time (hours) on 24-hour Home diary for patients with 5-10 levodopa doses - PP-analysis

		Statistic	Baseline	Month 0.5	Month 1.5	Month 4	Month 6
5-10 doses	Entacapone	MEAN	6.0	5.0	4.7	4.9	4.6
		SD	2.8	3.0	2.8	3.0	3.1
		SEM	0.3	0.3	0.3	0.3	0.4
		MIN					
		MAX					
		N	77.0	76.0	76.0	77.0	77.0
	Placebo	MEAN	6.4	5.4	5.6	5.8	5.3
		SD	2.9	3.1	3.6	3.4	3.2
		SEM	0.4	0.5	0.5	0.5	0.5
		MIN					
		MAX					
		N	43.0	43.0	43.0	41.0	43.0

Analysis of variance on month 6

Source	DF (nomin)	DF (denomin)	F-value	p-value
Baseline	1	73	128.60	0.0000
Treatment	1	20	0.88	0.3582

Estimation of treatment differences

Comparison	Difference	Standard error	DF	95% CI lower	95% CI upper	p-value
5-10 :E-P	0.39	0.41	20	-0.48	1.26	0.3582

STUDY 2939063
Statistical table 2.2.10 OFF time (hours) on 24-hour Home diary for fluctuating patients (4.5 h OFF time over three home diary days at baseline) - PP-analysis (cont.)

Analysis of variance on month 6

Source	DF (nomin)	DF (denomin)	F-value	p-value
Baseline	1	120	55.73	0.0000
Stratif	1	120	0.49	0.4864
Treatment	1	22	2.29	0.1445
Stratif * Treatment	1	120	0.02	0.8844

Estimation of treatment differences

Comparison	Difference	Standard error	DF	95% CI lower	95% CI upper	p-value
Entacapone - Placebo	-0.67	0.44	22	-1.58	0.25	0.1445
2-4 :E-P	-0.73	0.71	22	-2.20	0.73	0.3114
5-10 :E-P	-0.60	0.53	22	-1.70	0.49	0.2654

STUDY 2939063
Statistical table 2.2.13 ASLEEP time (hours) on 24-hour Home diary for patients with 5-10 levodopa doses - PP-analysis

		Statistic	Baseline	Month 0.5	Month 1.5	Month 4	Month 6
5-10 doses	Entacapone	MEAN	7.5	7.4	7.6	7.4	7.4
		SD	1.7	1.5	1.7	1.7	1.7
		SEM	0.2	0.2	0.2	0.2	0.2
		MIN					
		MAX					
		N	77.0	76.0	76.0	77.0	77.0
	Placebo	MEAN	7.5	7.4	7.7	7.6	7.5
		SD	1.6	1.7	1.6	1.3	1.7
		SEM	0.2	0.3	0.2	0.2	0.3
		MIN					
		MAX					
		N	43.0	43.0	43.0	41.0	43.0

Analysis of variance on month 6

Source	DF (nomin)	DF (denomin)	F-value	p-value
Baseline	1	73	105.70	0.0000
Treatment	1	20	0.57	0.4609

Estimation of treatment differences

Comparison	Difference	Standard error	DF	95% CI lower	95% CI upper	p-value
5-10 :E-P	0.22	0.29	20	-0.38	0.82	0.4614

STUDY 2939063
Statistical table 2.2.14 ASLEEP time (hours) on 24-hour Home diary for fluctuating patients (4.5 h OFF time over three home diary days at baseline) - PP-analysis (cont.)

Analysis of variance on month 6

Source	DF (nomin)	DF (denomin)	F-value	p-value
Baseline	1	120	141.89	0.0000
Stratif	1	120	1.37	0.2448
Treatment	1	22	0.04	0.8405
Stratif * Treatment	1	120	1.11	0.2950

Estimation of treatment differences

Comparison	Difference	Standard error	DF	95% CI lower	95% CI upper	p-value
Entacapone - Placebo	0.04	0.19	22	-0.36	0.44	0.8405
2-4 :E-P	0.24	0.31	22	-0.40	0.88	0.4424
5-10 :E-P	-0.16	0.23	22	-0.64	0.31	0.4845

STUDY 2939063
Statistical table 2.3.1 Global evaluation for all patients - PP-analysis (cont.)

Changes by category from Baseline to Month 6

Stratification		Worsened N	Worsened %	No change N	No change %	Improved N	Improved %	Total N	Total %
2-4 doses	Entacapone	10	19.6	17	33.3	24	47.1	51	100.0
	Placebo	3	10.0	11	36.7	16	53.3	30	100.0
5-10 doses	Entacapone	19	23.5	27	33.3	35	43.2	81	100.0
	Placebo	12	26.1	18	39.1	16	34.8	46	100.0
Total	Entacapone	29	22.0	44	33.3	59	44.7	132	100.0
	Placebo	15	19.7	29	38.2	32	42.1	76	100.0

Stratification	Comparison	Month	Mantel Haenszel test	p-value
2-4 doses	Entacapone - Placebo	Month 6	0.87	0.3520
5-10 doses	Entacapone - Placebo	Month 6	0.57	0.4490
Total	Entacapone - Placebo	Month 6	0.00	0.9744

STUDY 2939063
Statistical table 2.3.2 Global evaluation for fluctuating patients (4.5 h OFF time over three home diary days at baseline) - PP-analysis

Entacapone

i on		very poorly N	%	poorly N	%	rather poorly N	%	not well not poorl N	%	rather well N	%	well N	%	very well N	%	No. of pati ents
2-4 doses	Baseline	-	-	-	-	4	10.0	6	15.0	14	35.0	13	32.5	3	7.5	40
	Month 0.5	-	-	-	-	1	2.5	4	10.0	15	37.5	16	40.0	4	10.0	40
	Month 1.5	-	-	1	2.5	1	2.5	3	7.5	6	15.0	24	60.0	5	12.5	40
	Month 4	-	-	-	-	3	7.5	2	5.0	10	25.0	20	50.0	5	12.5	40
	Month 6	-	-	-	-	2	5.0	8	20.0	6	15.0	20	50.0	4	10.0	40
5-10 doses	Baseline	1	1.3	4	5.2	9	11.7	21	27.3	18	23.4	21	27.3	3	3.9	77
	Month 0.5	-	-	1	1.3	6	7.9	17	22.4	18	23.7	32	42.1	2	2.6	76
	Month 1.5	-	-	1	1.3	8	10.4	20	26.0	22	28.6	21	27.3	5	6.5	77
	Month 4	-	-	2	2.6	7	9.1	17	22.1	24	31.2	25	32.5	2	2.6	77
	Month 6	1	1.3	1	1.3	1	1.3	22	28.6	22	28.6	26	33.8	4	5.2	77
Total	Baseline	1	0.9	4	3.4	13	11.1	27	23.1	32	27.4	34	29.1	6	5.1	117
	Month 0.5	-	-	1	0.9	7	6.0	21	18.1	33	28.4	48	41.4	6	5.2	116
	Month 1.5	-	-	2	1.7	9	7.7	23	19.7	28	23.9	45	38.5	10	8.5	117
	Month 4	-	-	2	1.7	10	8.5	19	16.2	34	29.1	45	38.5	7	6.0	117
	Month 6	1	0.9	1	0.9	3	2.6	30	25.6	28	23.9	46	39.3	8	6.8	117

STUDY 2939063
Statistical table 2.3.2 Global evaluation for fluctuating patients (4.5 h OFF time over three home diary days at baseline) - PP-analysis (cont.)

Placebo

Strati fication		very poorly N	%	poorly N	%	rather poorly N	%	not well not poorl N	%	rather well N	%	well N	%	very well N	%	No. of pati ents
2-4 doses	Baseline	-	-	1	4.2	3	12.5	6	25.0	9	37.5	5	20.8	-	-	24
	Month 0.5	-	-	-	-	5	20.8	7	29.2	8	33.3	4	16.7	-	-	24
	Month 1.5	-	-	-	-	3	12.5	6	25.0	11	45.8	4	16.7	-	-	24
	Month 4	-	-	1	4.2	2	8.3	7	29.2	7	29.2	5	20.8	2	8.3	24
	Month 6	-	-	-	-	2	8.3	3	12.5	8	33.3	10	41.7	1	4.2	24
5-10 doses	Baseline	-	-	4	10.0	5	12.5	7	17.5	14	35.0	9	22.5	1	2.5	40
	Month 0.5	-	-	4	10.0	5	12.5	10	25.0	9	22.5	11	27.5	1	2.5	40
	Month 1.5	-	-	2	5.0	7	17.5	7	17.5	11	27.5	11	27.5	2	5.0	40
	Month 4	-	-	4	10.0	10	25.0	7	17.5	7	17.5	9	22.5	3	7.5	40
	Month 6	-	-	3	7.5	8	20.0	7	17.5	10	25.0	9	22.5	3	7.5	40
	Baseline	-	-	5	7.8	8	12.5	13	20.3	23	35.9	14	21.9	1	1.6	64
	Month 0.5	-	-	4	6.3	10	15.6	17	26.6	17	26.6	15	23.4	1	1.6	64
	Month 1.5	-	-	2	3.1	10	15.6	13	20.3	22	34.4	15	23.4	2	3.1	64
	Month 4	-	-	5	7.8	12	18.8	14	21.9	14	21.9	14	21.9	5	7.8	64
	Month 6	-	-	3	4.7	10	15.6	10	15.6	18	28.1	19	29.7	4	6.3	64

STUDY 2939063
Statistical table 2.3.2 Global evaluation for fluctuating patients (4.5 h OFF time over three home diary days at baseline) - PP-analysis (cont.)

Changes by category from Baseline to Month 6

Strati fication		Worsened N	%	No change N	%	Improved N	%	Total N	%
2-4 doses	Entacapone	9	22.5	15	37.5	16	40.0	40	100.0
	Placebo	2	8.3	9	37.5	13	54.2	24	100.0
5-10 doses	Entacapone	17	22.1	27	35.1	33	42.9	77	100.0
	Placebo	10	25.0	15	37.5	15	37.5	40	100.0
Total	Entacapone	26	22.2	42	35.9	49	41.9	117	100.0
	Placebo	12	18.8	24	37.5	28	43.8	64	100.0

Strati fication	Comparison	Month	Mantel Haenszel test	p-value
2-4 doses	Entacapone - Placebo	Month 6	2.17	0.1406
5-10 doses	Entacapone - Placebo	Month 6	0.29	0.5878
Total	Entacapone - Placebo	Month 6	0.20	0.6553

STUDY 2939063
Statistical table 2.4.1 Scheduled daily levodopa dose (mg) during the study period for all patients - PP-analysis (cont.)

Analysis of variance on month 6

Source	DF (nomin)	DF (denomin)	F-value	p-value
Baseline	1	138	177.77	0.0000
Stratif	1	138	11.54	0.0009
Treatment	1	23	2.23	0.1486
Stratif * Treatment	1	138	2.84	0.0945

Estimation of treatment differences

Comparison	Difference	Standard error	DF	95% CI lower	95% CI upper	p-value
Entacapone - Placebo	-40.89	27.36	23	-97.49	15.70	0.1486
2-4 :E-P	-75.36	36.63	23	-151.14	0.43	0.0512
5-10 :E-P	-6.43	31.51	23	-71.61	58.75	0.8401

STUDY 2939063
Statistical table 2.4.2 Scheduled daily levodopa dose (mg) during the study period for fluctuating patients (4.5 h OFF time over three home diary days at baseline) - PP-analysis (cont.)

Analysis of variance on month 6

Source	DF (nomin)	DF (denomin)	F-value	p-value
Baseline	1	119	145.24	0.0000
Stratif	1	119	9.72	0.0023
Treatment	1	22	1.90	0.1818
Stratif * Treatment	1	119	2.51	0.1158

Estimation of treatment differences

Comparison	Difference	Standard error	DF	95% CI lower	95% CI upper	p-value
Entacapone - Placebo	-42.30	30.68	22	-105.92	21.33	0.1818
2-4 :E-P	-78.75	41.92	22	-165.69	8.18	0.0736
5-10 :E-P	-5.84	34.41	22	-77.21	65.52	0.8667

STUDY 2939063
Statistical table 2.4.7 Dosing frequency of scheduled levodopa during the study period for all patients - PP-analysis (cont.)

Analysis of variance on month 6

Source	DF (nomin)	DF (denomin)	F-value	p-value
Baseline	1	138	554.26	0.0000
Stratif	1	138	1.10	0.2955
Treatment	1	23	4.93	0.0365
Stratif * Treatment	1	138	0.06	0.8046

Estimation of treatment differences

Comparison	Difference	Standard error	DF	95% CI lower	95% CI upper	p-value
Entacapone - Placebo	-0.23	0.10	23	-0.44	-0.02	0.0365
2-4 :E-P	-0.25	0.15	23	-0.57	0.06	0.1118
5-10 :E-P	-0.21	0.13	23	-0.47	0.05	0.1160

STUDY 2939063
Statistical table 2.4.8 Dosing frequency of scheduled levodopa during the study period for fluctuating patients (4.5 h OFF time over three home diary days at baseline) - PP-analysis (cont.)

Analysis of variance on month 6

Source	DF (nomin)	DF (denomin)	F-value	p-value
Baseline	1	119	478.71	0.0000
Stratif	1	119	1.19	0.2785
Treatment	1	22	4.29	0.0504
Stratif * Treatment	1	119	0.10	0.7515

Estimation of treatment differences

Comparison	Difference	Standard error	DF	95% CI lower	95% CI upper	p-value
Entacapone - Placebo	-0.23	0.11	22	-0.46	0.00	0.0504
2-4 :E-P	-0.26	0.17	22	-0.62	0.09	0.1402
5-10 :E-P	-0.20	0.13	22	-0.47	0.08	0.1506

STUDY 2939063
Statistical table 2.5.1 Average daily levodopa dose (mg) on 24-hour Home diary for patients with 5-10 levodopa doses - PP-analysis

		Statistic	Baseline	Month 0.5	Month 1.5	Month 4	Month 6
5-10 doses	Entacapone	MEAN	535	511	477	460	482
		SD	330	319	303	302	282
		SEM	38.4	37.6	35.7	35.4	32.8
		MIN					
		MAX					
		N	74.0	72.0	72.0	73.0	74.0
	Placebo	MEAN	377	348	380	433	399
		SD	295	308	316	334	347
		SEM	45.1	47.0	48.8	52.8	54.1
		MIN					
		MAX					
		N	43.0	43.0	42.0	40.0	41.0

Analysis of variance on month 6

Source	DF (nomin)	DF (denomin)	F-value	p-value
Baseline	1	67	140.50	0.0000
Treatment	1	20	0.23	0.6351

Estimation of treatment differences

Comparison	Difference	Standard error	DF	95% CI lower	95% CI upper	p-value
5-10 :E-P	25.27	52.45	20	-84.13	134.68	0.6351

STUDY 2939063
Statistical table 2.5.2 Average daily levodopa dose (mg) on 24-hour Home diary for fluctuating patients (4.5 h OFF time over three home diary days at baseline) - PP-analysis (cont.)

Analysis of variance on month 6

Source	DF (nomin)	DF (denomin)	F-value	p-value
Baseline	1	111	125.08	0.0000
Stratif	1	111	0.87	0.3528
Treatment	1	22	1.04	0.3198
Stratif * Treatment	1	111	0.27	0.6060

Estimation of treatment differences

Comparison	Difference	Standard error	DF	95% CI lower	95% CI upper	p-value
Entacapone - Placebo	-43.08	42.33	22	-130.86	44.70	0.3198
2-4 :E-P	-60.32	58.76	22	-182.19	61.55	0.3158
5-10 :E-P	-25.85	48.48	22	-126.40	74.70	0.5993

STUDY 2939063
Statistical table 2.5.3 Dosing frequency of levodopa on 24-hour Home diary for fluctuating patients (4.5 h OFF time over three home diary days at baseline) - PP-analysis (cont.)

Analysis of variance on month 6

Source	DF (nomin)	DF (denomin)	F-value	p-value
Baseline	1	112	266.49	0.0000
Stratif	1	112	4.93	0.0284
Treatment	1	22	3.34	0.0813
Stratif * Treatment	1	112	0.50	0.4815

Estimation of treatment differences

Comparison	Difference	Standard error	DF	95% CI lower	95% CI upper	p-value
Entacapone - Placebo	-0.37	0.20	22	-0.80	0.05	0.0813
2-4 :E-P	-0.52	0.33	22	-1.20	0.16	0.1293
5-10 :E-P	-0.23	0.24	22	-0.73	0.28	0.3560

STUDY 2939063
Statistical table 2.6.3 UPDRS part I - Mentation, behavior, and mood for all patients during withdrawal period - PP-analysis (cont.)

Analysis of variance for withdrawal effect

Source	DF (nomin)	DF (denomin)	F-value	p-value
Baseline	1	346	130.23	0.0000
Stratif	1	346	0.17	0.6818
Treatment	1	23	0.45	0.5074
Time	1	346	0.37	0.5424
Stratif * Treatme	1	346	0.61	0.4344
Stratif * Time	1	346	1.04	0.3077
Treatment * Time	1	346	6.36	0.0121
Stra*Treat*Time	1	346	0.00	0.9643

Estimation of treatment differences

Comparison	Diffe-rence	Standard error	DF	95% CI lower	95% CI upper	p-value
Entacapone - Placebo	0.38	0.15	23	0.07	0.69	0.0190
2-4 doses:Entac-Place	0.37	0.24	23	-0.09	0.84	0.1128
5-10 doses:Entac-Plac	0.39	0.19	23	-0.00	0.78	0.0522

STUDY 2939063
Statistical table 2.6.4 UPDRS part I - Mentation, behavior, and mood for fluctuating patients (4.5 h OFF time over three home diary days at baseline) during withdrawal period - PP-analysis (cont.)

Analysis of variance for withdrawal effect

Source	DF (nomin)	DF (denomin)	F-value	p-value
Baseline	1	293	115.90	0.0000
Stratif	1	293	0.21	0.6510
Treatment	1	22	0.19	0.6671
Time	1	293	0.28	0.5993
Stratif * Treatme	1	293	0.33	0.5665
Stratif * Time	1	293	0.65	0.4192
Treatment * Time	1	293	5.64	0.0182
Stra*Treat*Time	1	293	0.04	0.8472

Estimation of treatment differences

Comparison	Diffe-rence	Standard error	DF	95% CI lower	95% CI upper	p-value
Entacapone - Placebo	0.41	0.17	22	0.05	0.76	0.0267
2-4 doses:Entac-Place	0.44	0.27	22	-0.09	0.97	0.1065
5-10 doses:Entac-Plac	0.37	0.21	22	-0.06	0.80	0.0873

STUDY 2939063
Statistical table 2.6.5 UPDRS part II - Activities in daily living for all patients during withdrawal period - PP-analysis (cont.)

Analysis of variance for withdrawal effect

Source	DF (nomin)	DF (denomin)	F-value	p-value
Baseline	1	346	413.63	0.0000
Stratif	1	346	1.07	0.3021
Treatment	1	23	2.54	0.1244
Time	1	346	15.91	0.0001
Stratif * Treatme	1	346	0.03	0.8634
Stratif * Time	1	346	2.68	0.1025
Treatment * Time	1	346	8.66	0.0035
Stra*Treat*Time	1	346	3.39	0.0666

Estimation of treatment differences

Comparison	Diffe-rence	Standard error	DF	95% CI lower	95% CI upper	p-value
Entacapone - Placebo	1.30	0.44	23	0.39	2.21	0.0073
2-4 doses:Entac-Place	0.49	0.69	23	-0.87	1.84	0.4795
5-10 doses:Entac-Plac	2.11	0.55	23	0.97	3.26	0.0009

STUDY 2939063
Statistical table 2.6.6 UPDRS part II - Activities in daily living for fluctuating patients (4.5 h OFF time over three home diary days at baseline) during withdrawal period - PP-analysis (cont.)

Analysis of variance for withdrawal effect

Source	DF (nomin)	DF (denomin)	F-value	p-value
Baseline	1	293	341.12	0.0000
Stratif	1	293	0.82	0.3664
Treatment	1	22	2.30	0.1440
Time	1	293	10.99	0.0010
Stratif * Treatme	1	293	0.08	0.7711
Stratif * Time	1	293	1.59	0.2081
Treatment * Time	1	293	7.37	0.0070
Stra*Treat*Time	1	293	2.72	0.1003

Estimation of treatment differences

Comparison	Diffe-rence	Standard error	DF	95% CI lower	95% CI upper	p-value
Entacapone - Placebo	1.37	0.51	22	0.32	2.42	0.0127
2-4 doses:Entac-Place	0.54	0.80	22	-1.04	2.12	0.5022
5-10 doses:Entac-Plac	2.21	0.62	22	0.93	3.49	0.0017

STUDY 2939063
Statistical table 2.6.7 UPDRS Part III - Motor examination for all patients during withdrawal period - PP-analysis (cont.)

Analysis of variance for withdrawal effect

Source	DF (nomin)	DF (denomin)	F-value	p-value
Baseline	1	342	354.93	0.0000
Stratif	1	342	0.53	0.4650
Treatment	1	23	1.06	0.3148
Time	1	342	18.43	0.0000
Stratif * Treatme	1	342	0.01	0.9133
Stratif * Time	1	342	0.47	0.4921
Treatment * Time	1	342	6.27	0.0128
Stra*Treat*Time	1	342	7.93	0.0051

Estimation of treatment differences

Comparison	Diffe-rence	Standard error	DF	95% CI lower	95% CI upper	p-value
Entacapone - Placebo	2.47	0.99	23	0.43	4.51	0.0199
2-4 doses:Entac-Place	-0.31	1.53	23	-3.32	2.70	0.8403
5-10 doses:Entac-Plac	5.24	1.24	23	2.67	7.81	0.0003

STUDY 2939063
Statistical table 2.6.8 UPDRS Part III - Motor examination for fluctuating patients (4.5 h OFF time over three home diary days at baseline) during withdrawal period - PP-analysis (cont.)

Analysis of variance for withdrawal effect

Source	DF (nomin)	DF (denomin)	F-value	p-value
Baseline	1	289	285.23	0.0000
Stratif	1	289	0.03	0.8666
Treatment	1	22	0.69	0.4153
Time	1	289	13.69	0.0003
Stratif * Treatme	1	289	1.78	0.1827
Stratif * Time	1	289	0.94	0.3320
Treatment * Time	1	289	4.33	0.0383
Stra*Treat*Time	1	289	6.97	0.0087

Estimation of treatment differences

Comparison	Diffe-rence	Standard error	DF	95% CI lower	95% CI upper	p-value
Entacapone - Placebo	2.32	1.12	22	0.01	4.64	0.0492
2-4 doses:Entac-Place	-0.62	1.76	22	-4.09	2.84	0.7239
5-10 doses:Entac-Plac	5.27	1.37	22	2.43	8.11	0.0009

STUDY 2939063
Statistical table 2.6.9 Total score of UPDRS (parts I, II, and III) for all patients during withdrawal period - PP-analysis (cont.)

Analysis of variance for withdrawal effect

Source	DF (nomin)	DF (denomin)	F-value	p-value
Baseline	1	342	479.29	0.0000
Stratif	1	342	0.79	0.3734
Treatment	1	23	1.44	0.2430
Time	1	342	20.39	0.0000
Stratif * Treatme	1	342	0.02	0.8865
Stratif * Time	1	342	1.40	0.2372
Treatment * Time	1	342	10.21	0.0015
Stra*Treat*Time	1	342	7.61	0.0061

Estimation of treatment differences

Comparison	Difference	Standard error	DF	95% CI lower	95% CI upper	p-value
Entacapone - Placebo	4.19	1.31	23	1.48	6.90	0.0040
2-4 doses:Entac-Place	0.57	2.03	23	-3.43	4.57	0.7792
5-10 doses:Entac-Plac	7.80	1.65	23	4.38	11.22	0.0001

STUDY 2939063
Statistical table 2.6.10 Total score of UPDRS (parts I, II, and III) for fluctuating patients (4.5 h OFF time over three home diary days at baseline) during withdrawal period - PP-analysis (cont.)

Analysis of variance for withdrawal effect

Source	DF (nomin)	DF (denomin)	F-value	p-value
Baseline	1	289	383.95	0.0000
Stratif	1	289	0.07	0.7887
Treatment	1	22	1.06	0.3155
Time	1	289	14.57	0.0002
Stratif * Treatme	1	289	1.22	0.2699
Stratif * Time	1	289	1.55	0.2147
Treatment * Time	1	289	7.62	0.0061
Stra*Treat*Time	1	289	6.37	0.0122

Estimation of treatment differences

Comparison	Difference	Standard error	DF	95% CI lower	95% CI upper	p-value
Entacapone - Placebo	4.13	1.50	22	1.03	7.24	0.0114
2-4 doses:Entac-Place	0.36	2.36	22	-4.30	5.01	0.8807
5-10 doses:Entac-Plac	7.91	1.84	22	4.10	11.73	0.0003

STUDY 2939063
Statistical table 2.7.1 Global evaluation for all patients during withdrawal period - PP-analysis

Entacapone

Stratification		very poorly N	%	poorly N	%	rather poorly N	%	not well not poorl N	%	rather well N	%	well N	%	very well N	%	No. of patients
2-4 doses	Baseline	-	-	-	-	4	7.8	7	13.7	21	41.2	15	29.4	4	7.8	51
	Month 6	-	-	-	-	2	3.9	8	15.7	9	17.6	25	49.0	7	13.7	51
	Post-study	-	-	1	2.0	5	9.8	13	25.5	14	27.5	17	33.3	1	2.0	51
5-10 doses	Baseline	1	1.3	4	5.0	10	12.5	20	25.0	20	25.0	22	27.5	3	3.8	80
	Month 6	1	1.3	1	1.3	1	1.3	23	28.8	23	28.8	27	33.8	4	5.0	80
	Post-study	2	2.5	10	12.5	22	27.5	16	20.0	17	21.3	13	16.3	-	-	80
Total	Baseline	1	0.8	4	3.1	14	10.7	27	20.6	41	31.3	37	28.2	7	5.3	131
	Month 6	1	0.8	1	0.8	3	2.3	31	23.7	32	24.4	52	39.7	11	8.4	131
	Post-study	2	1.5	11	8.4	27	20.6	29	22.1	31	23.7	30	22.9	1	0.8	131

STUDY 2939063
Statistical table 2.7.1 Global evaluation for all patients during withdrawal period - PP-analysis (cont.)

Placebo

Stratification		very poorly N	%	poorly N	%	rather poorly N	%	not well not poorl N	%	rather well N	%	well N	%	very well N	%	No. of patients
2-4 doses	Baseline	-	-	1	3.4	3	10.3	6	20.7	11	37.9	8	27.6	-	-	29
	Month 6	-	-	-	-	2	6.9	5	17.2	8	27.6	13	44.8	1	3.4	29
	Post-study	-	-	-	-	4	13.8	7	24.1	8	27.6	10	34.5	-	-	29
5-10 doses	Baseline	-	-	5	11.6	4	9.3	9	20.9	13	30.2	11	25.6	1	2.3	43
	Month 6	-	-	4	9.3	9	20.9	7	16.3	10	23.3	10	23.3	3	7.0	43
	Post-study	1	2.3	4	9.3	8	18.6	10	23.3	11	25.6	6	14.0	3	7.0	43
Total	Baseline	-	-	6	8.3	7	9.7	15	20.8	24	33.3	19	26.4	1	1.4	72
	Month 6	-	-	4	5.6	11	15.3	12	16.7	18	25.0	23	31.9	4	5.6	72
	Post-study	1	1.4	4	5.6	12	16.7	17	23.6	19	26.4	16	22.2	3	4.2	72

STUDY 2939063
Statistical table 2.7.2 Global evaluation for fluctuating patients (4.5 h OFF time over three home diary days at baseline) during withdrawal period - PP-analysis

Entacapone

Stratification		very poorly N	%	poorly N	%	rather poorly N	%	not well not poorl N	%	rather well N	%	well N	%	very well N	%	No. of patients
2-4 doses	Baseline	-	-	-	-	4	10.0	6	15.0	14	35.0	13	32.5	3	7.5	40
	Month 6	-	-	-	-	2	5.0	8	20.0	6	15.0	20	50.0	4	10.0	40
	Post-study	-	-	1	2.5	4	10.0	12	30.0	9	22.5	14	35.0	-	-	40
5-10 doses	Baseline	1	1.3	4	5.3	9	11.8	19	25.0	19	25.0	21	27.6	3	3.9	76
	Month 6	1	1.3	1	1.3	1	1.3	21	27.6	22	28.9	26	34.2	4	5.3	76
	Post-study	2	2.6	10	13.2	22	28.9	14	18.4	16	21.1	12	15.8	-	-	76
Total	Baseline	1	0.9	4	3.4	13	11.2	25	21.6	33	28.4	34	29.3	6	5.2	116
	Month 6	1	0.9	1	0.9	3	2.6	29	25.0	28	24.1	46	39.7	8	6.9	116
	Post-study	2	1.7	11	9.5	26	22.4	26	22.4	25	21.6	26	22.4	-	-	116

STUDY 2939063
Statistical table 2.7.2 Global evaluation for fluctuating patients (4.5 h OFF time over three home diary days at baseline) during withdrawal period - PP-analysis (cont.)

Placebo

Stratification		very poorly N	%	poorly N	%	rather poorly N	%	not well not poorl N	%	rather well N	%	well N	%	very well N	%	No. of patients
2-4 doses	Baseline	-	-	1	4.2	3	12.5	6	25.0	9	37.5	5	20.8	-	-	24
	Month 6	-	-	-	-	2	8.3	4	16.7	8	33.3	9	37.5	1	4.2	24
	Post-study	-	-	-	-	4	16.7	7	29.2	8	33.3	5	20.8	-	-	24
5-10 doses	Baseline	-	-	4	10.8	3	8.1	7	18.9	13	35.1	9	24.3	1	2.7	37
	Month 6	-	-	3	8.1	8	21.6	5	13.5	10	27.0	8	21.6	3	8.1	37
	Post-study	1	2.7	3	8.1	6	16.2	9	24.3	11	29.7	4	10.8	3	8.1	37
Total	Baseline	-	-	5	8.2	6	9.8	13	21.3	22	36.1	14	23.0	1	1.6	61
	Month 6	-	-	3	4.9	10	16.4	9	14.8	18	29.5	17	27.9	4	6.6	61
	Post-study	1	1.6	3	4.9	10	16.4	16	26.2	19	31.1	9	14.8	3	4.9	61

STUDY 2939063
Statistical table 2.7.2 Global evaluation for fluctuating patients (4.5 h OFF time over three home diary days at baseline) during withdrawal period - PP-analysis (cont.)

Changes by category from Month 6 to Post-study

Stratification		Worsened N	%	No change N	%	Improved N	%	Total N	%
2-4 doses	Entacapone	20	50.0	16	40.0	4	10.0	40	100.0
	Placebo	10	41.7	12	50.0	2	8.3	24	100.0
5-10 doses	Entacapone	50	65.8	20	26.3	6	7.9	76	100.0
	Placebo	13	35.1	17	45.9	7	18.9	37	100.0
Total	Entacapone	70	60.3	36	31.0	10	8.6	116	100.0
	Placebo	23	37.7	29	47.5	9	14.8	61	100.0

Stratification	Comparison	Month	Mantel Haenszel test	p-value
2-4 doses	Entacapone - Placebo	Month 6	0.16	0.6933
5-10 doses	Entacapone - Placebo	Month 6	8.99	0.0027
Total	Entacapone - Placebo	Month 6	7.19	0.0073

STUDY 2939063
Statistical table 2.7.1 Global evaluation for all patients during withdrawal period - PP-analysis (cont.)

Changes by category from Month 6 to Post-study

Stratification		Worsened N	%	No change N	%	Improved N	%	Total N	%
2-4 doses	Entacapone	24	47.1	23	45.1	4	7.8	51	100.0
	Placebo	10	34.5	16	55.2	3	10.3	29	100.0
5-10 doses	Entacapone	51	63.8	22	27.5	7	8.8	80	100.0
	Placebo	14	32.6	22	51.2	7	16.3	43	100.0
Total	Entacapone	75	57.3	45	34.4	11	8.4	131	100.0
	Placebo	24	33.3	38	52.8	10	13.9	72	100.0

Stratification	Comparison	Month	Mantel Haenszel test	p-value
2-4 doses	Entacapone - Placebo	Month 6	1.04	0.3075
5-10 doses	Entacapone - Placebo	Month 6	8.84	0.0029
Total	Entacapone - Placebo	Month 6	9.02	0.0027

STUDY 2939063

Statistical table 2.8.1 Scheduled daily levodopa dose (mg) for all patients during withdrawal period - PP-analysis (cont.)

Analysis of variance for withdrawal effect

Source	DF (nomin)	DF (denomin)	F-value	p-value
Baseline	1	327	185.37	0.0000
Stratif	1	327	12.30	0.0005
Treatment	1	23	1.06	0.3144
Time	1	327	14.86	0.0001
Stratif * Treatme	1	327	3.91	0.0488
Stratif * Time	1	327	2.60	0.1079
Treatment * Time	1	327	7.73	0.0057
Stra*Treat*Time	1	327	3.95	0.0477

Estimation of treatment differences

Comparison	Difference	Standard error	DF	95% CI lower	95% CI upper	p-value
Entacapone - Placebo	20.82	7.49	23	5.33	36.30	0.0106
2-4 doses:Entac-Place	5.94	11.76	23	-18.40	30.27	0.6186
5-10 doses:Entac-Plac	35.70	9.27	23	16.53	54.86	0.0008

STUDY 2939063

Statistical table 2.8.2 Scheduled daily levodopa dose (mg) for fluctuating patients (4.5 h OFF time over three home diary days at baseline) during withdrawal period - PP-analysis (cont.)

Analysis of variance for withdrawal effect

Source	DF (nomin)	DF (denomin)	F-value	p-value
Baseline	1	288	152.27	0.0000
Stratif	1	288	10.21	0.0016
Treatment	1	22	0.92	0.3481
Time	1	288	13.44	0.0003
Stratif * Treatme	1	288	3.41	0.0658
Stratif * Time	1	288	1.61	0.2056
Treatment * Time	1	288	6.45	0.0116
Stra*Treat*Time	1	288	2.90	0.0895

Estimation of treatment differences

Comparison	Difference	Standard error	DF	95% CI lower	95% CI upper	p-value
Entacapone - Placebo	21.23	8.36	22	3.90	38.56	0.0186
2-4 doses:Entac-Place	6.99	13.39	22	-19.36	33.35	0.6020
5-10 doses:Entac-Plac	35.47	10.00	22	14.73	56.21	0.0018

STUDY 2939063
Statistical table 2.8.3 Dosing frequency of scheduled levodopa for all patients during withdrawal period - PP-analysis (cont.)

Analysis of variance for withdrawal effect

Source	DF (nomin)	DF (denomin)	F-value	p-value
Baseline	1	327	601.83	0.0000
Stratif	1	327	0.36	0.5516
Treatment	1	23	3.38	0.0790
Time	1	327	3.19	0.0749
Stratif * Treatme	1	327	0.60	0.4390
Stratif * Time	1	327	0.00	0.9647
Treatment * Time	1	327	2.05	0.1529
Stra*Treat*Time	1	327	2.27	0.1326

Estimation of treatment differences

Comparison	Difference	Standard error	DF	95% CI lower	95% CI upper	p-value
Entacapone - Placebo	0.11	0.08	23	-0.05	0.27	0.1654
2-4 doses:Entac-Place	-0.01	0.12	23	-0.25	0.23	0.9620
5-10 doses:Entac-Plac	0.23	0.10	23	0.03	0.43	0.0263

STUDY 2939063
Statistical table 2.8.4 Dosing frequency of scheduled levodopa for fluctuating patients (4.5 h OFF time over three home diary days at baseline) during withdrawal period - PP-analysis (cont.)

Analysis of variance for withdrawal effect

Source	DF (nomin)	DF (denomin)	F-value	p-value
Baseline	1	288	522.37	0.0000
Stratif	1	288	0.40	0.5294
Treatment	1	22	3.19	0.0880
Time	1	288	3.05	0.0820
Stratif * Treatme	1	288	0.66	0.4164
Stratif * Time	1	288	0.02	0.8763
Treatment * Time	1	288	1.80	0.1807
Stra*Treat*Time	1	288	1.98	0.1602

Estimation of treatment differences

Comparison	Difference	Standard error	DF	95% CI lower	95% CI upper	p-value
Entacapone - Placebo	0.12	0.09	22	-0.06	0.30	0.1934
2-4 doses:Entac-Place	-0.01	0.14	22	-0.28	0.27	0.9669
5-10 doses:Entac-Plac	0.24	0.11	22	0.02	0.46	0.0315