

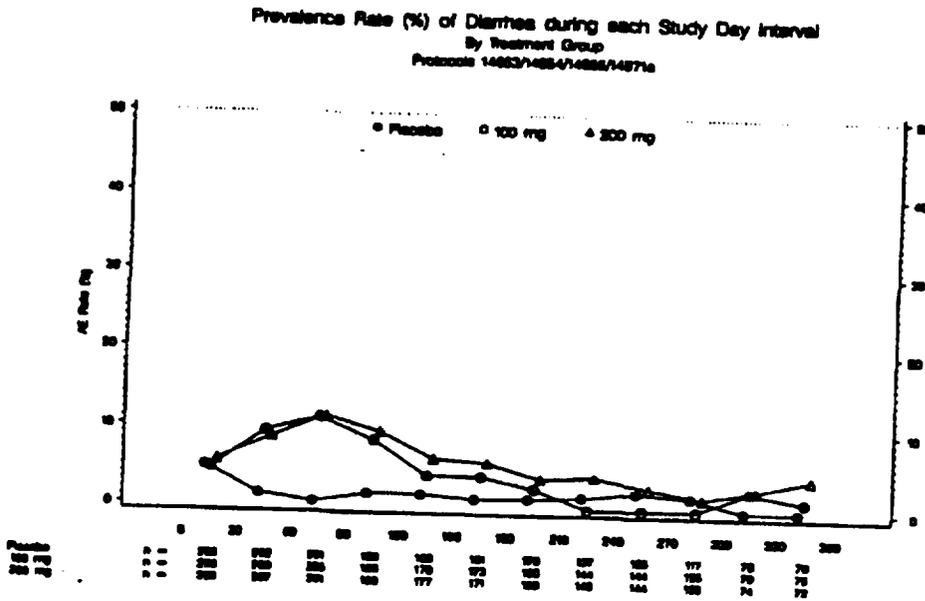
J3576-11A/265 (100 mg tid x 16 d)	54 F	PMH: unknown; meds: Neodopaston (levodopa/carbidopa), trihexyphenidyl, pergolide, arotinolol, teprenone, Vencoll, primidone. Developed anxiety, delusions, and worsening movements on Day 14. Neodopaston was stopped on Day 15; on Day 16 tolcapone was stopped. On Day 19, CPK was 981 (upper limit of normal), WBC 4300, temp 36.3°C. Considered a prodromal NMS due to discontinuation of anti-PD meds. By Day 23, she refused food and meds and received a Dopaston (levodopa) infusion. On Day 24, her CPK was 2026 and temp 38°C; there was "moderate" left-sided muscle rigidity. On Day 27, WBC was 8200 and CPK 985. The outcome is not yet known.	Probable NMS; possibly tolcapone related	Possibly related
J3576-06A/22-1 (200 mg tid x 152 d)	64F	PMH: gastric ulcer; meds: Madopar, bromocriptine, droxidopa, sucralfate. Six months after the patient was started on tolcapone, a family member abruptly discontinued the medication due to "aggravated hallucinations." Two days later, she developed visual hallucinations and "moderate" muscular rigidity and was emergently hospitalized. On admission her CPK was 4920 (peak; range: 50-190), LD 655 (range: 290-540), WBC 11,000 (peak), temp 37°C (peak: 37.7°C). Treated with cooling blanket, hydration, and antibiotics, she reportedly recovered 15 days later. No further information is available.	Probably NMS; possibly tolcapone related	Possibly related
J3576-08A/5-01 9100 mg tid x 85d, then 50 mg tid)	65 F	PMH: uterine leiomyoma; meds: Madopar, bromocriptine, trihexylphenidyl, sennoside, nitrazepam, digestive aid nos, ascorbic acid. On Day 86 developed "aggravated dyskinesia," and family member decreased dose from 100 to 50 mg tid (all other meds continued unchanged). Developed fever (39°C) on Day 87, in "OFF phase," with eating difficulties; hosp Day 90 for dehydration, resp failure. Died Day 91 of resp failure. Autopsy: depigmented substantia nigra and locus ceruleus, Lewy bodies in Meynert nuclei and hypothalamus as can be seen in PD; decreased neurons, atrophic pyramidal cells, hyperplasia of stellate glia in cortex, diapedesis in hypothalamus as can be seen in--but not specific for--NMS.	Probable NMS; possibly tolcapone related	Remote

## (c) Diarrhea

According to the sponsor, diarrhea was the most prevalent nondopaminergic adverse event in Phase III trials, associated with an 8-10% higher incidence among tolcapone-treated, than placebo, patients and occurring mainly during the second through fourth months of treatment (see the sponsor's Figure 32, v 1.333, p 60):

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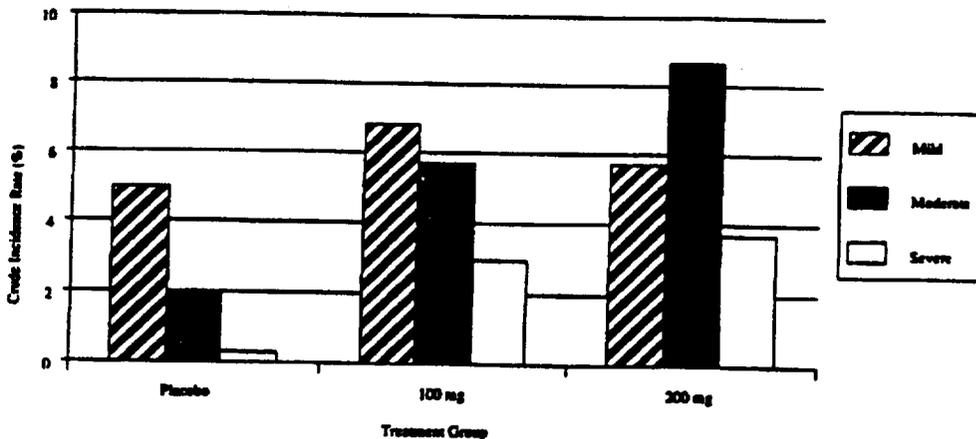
**Figure 32. Prevalence Rate (%) of Diarrhea in 30-day Intervals. Phase III placebo-controlled studies**



Note: No refer to the total number of patients at the beginning of each time interval

Furthermore, there was a clear shift toward more severe symptoms with increasing dose (see the sponsor's Figure 30, v 1.333, p 59):

**Figure 30. Intensity of Diarrhea in Phase III placebo-controlled Studies**



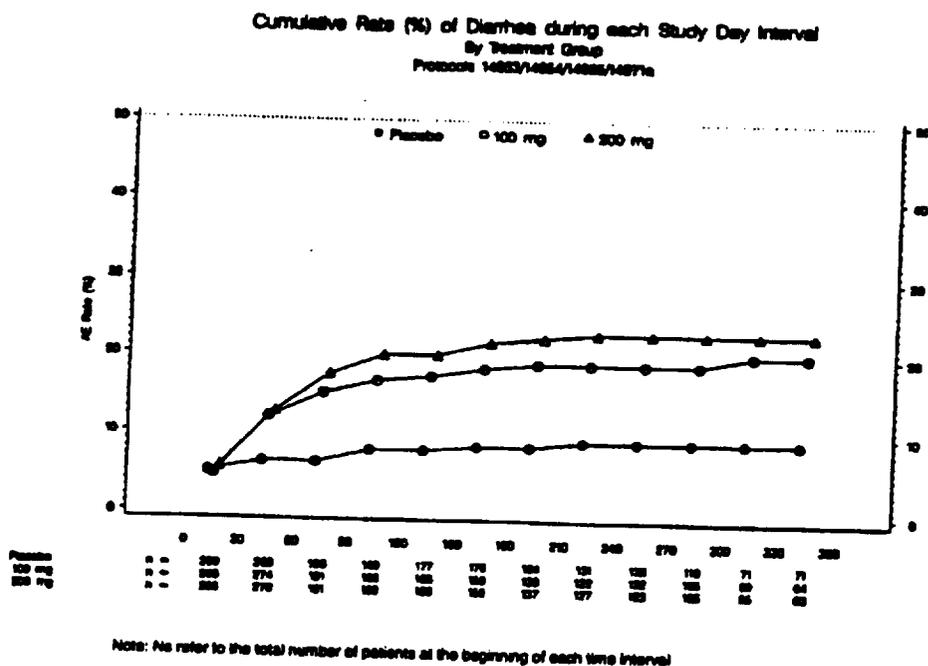
Diarrhea was also the most common adverse event leading to withdrawal: 16 (5.4%) of patients in the 100-mg, and 18 (6%) in the 200-mg, tolcapone groups; this compares with 3 patients (or 1%) in the placebo group. It was also the most frequently treated adverse event. Subgroup analysis showed that females were more likely to experience diarrhea. The treatment effects for female patients were 14% in the 100-mg, and 16% in the 200-mg, groups. Among

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males, the treatment effects were 4% and 7%. Over 75 years of age, the treatment effects were 23% and 19%, and 6% and 12% among younger patients.

Although diarrhea was the cause of 3% of the withdrawals and found to be dose-related, its onset was usually delayed and on average appeared 6-12 weeks after the start of tolcapone. The shortest time to onset was two weeks and the longest about nine months (see the sponsor's Figure 31, v 1.333, p 60):

**Figure 31. Cumulative Rate (%) of Diarrhea in 30-day Intervals. Phase III placebo-controlled studies**



According to the sponsor's submission, the diarrhea often terminated spontaneously 4-6 weeks later; it may also have resolved following antidiarrheal treatment or after temporary discontinuation of tolcapone. But no information has been provided to determine the potential for recurrence after reinstatement of tolcapone. The number of patients rechallenged with tolcapone, following a serious bout of diarrhea, is not known.

Overall, approximately 236 patients (12%), covering the entire spectrum of tolcapone exposure, have reported diarrhea. In six (0.3%), hospitalization was required for treatment. A total of 64 (3%) have discontinued tolcapone because of this adverse event. (The above follow-up information is from p 15 of the 5/30/96 IND Amendment submitted by the sponsor.) These results have not been challenged by subsequent data furnished in the Four-Month Safety Update (dated 10/3/96), covering the uncontrolled trials through 4/1/96.

Finally, according to the sponsor, the mechanism of the diarrhea is not clear, and no description of the diarrhea experienced by patients has been provided: the number of stools/day, the type (secretory, bloody, etc.), the severity. A search of case reports, narrative summaries, and NDA findings have not provided this information.

(d) Cardiac-related adverse events

Twenty-one (1%) patients over the entire spectrum of tolcapone exposure have experienced serious cardiac-related adverse events, including palpitations, arrhythmias, angina pectoris, myocardial infarction, and cardiac failure. To date, eight patients have discontinued treatment because of these events. The sponsor, however, has not established a clear connection with tolcapone in any of these instances.

(e) Syncope, postural hypotension, and increased risk of falls

While orthostatic hypotension (symptomatic as well as asymptomatic), dizziness, falling, and balance loss are symptoms frequently associated with PD (given autonomic disturbance and rigidity), an increased incidence of all of these symptoms were found in the tolcapone-treated patients. Moreover, from the sponsor's tabulated data, it appears that tolcapone is likely to aggravate pre-existing symptoms of orthostatic hypotension: "The incidence rates for orthostatic hypotension during the study among patients without orthostatic symptoms at baseline were 6%, 10%, and 18%, respectively. The corresponding rates for patients with mild orthostatic symptoms at baseline were 12%, 21%, and 18%, respectively; and for patients with moderate or severe orthostatic symptoms at baseline, they were 27%, 36%, and 50%" (v 1.333, p 69).

(f) Dyskinesias

Worsening dyskinesias led to one (0.3%) patient withdrawal in the 100-mg group and three (1%) in the 200-mg group; there were no dropouts in the placebo group for this adverse event. Tolcapone probably aggravated the dopaminergic side effects of Sinemet.

(g) Hallucinations

Hallucinations led to withdrawal from the study of one (0.3%) patient in the placebo group, four (1.4%) in the 100-mg group, and three (1%) in the 200-mg group. Tolcapone probably aggravated the dopaminergic side effects of Sinemet.

(h) Renal tumors

Preclinical animal data (chronic rat studies) have shown the growth of renal tumors at high mid-range doses (250 mg/kg in food admixture), yielding an AUC (500) that is approximately six-fold higher than the suggested human dose of 200 mg tid (AUC 80). No laboratory changes have been identified as diagnostic markers (except for nonspecific[?] small, round epithelial cells); the tumors were noted on necropsy. In view of these findings, the FDA has recommended that patients, who have completed the 12-month extension to Protocol NZ14653 and elect to continue tolcapone therapy in the additional two-year extension (by sponsor request on 8 Oct 1996), undergo renal ultrasound testing every six months.

There were no documented cases of agranulocytosis, Stevens-Johnson, clear instances of sudden death or serious cardiac abnormalities, or known cases of hepatic failure.

## 10. Demographic Subgroup Analysis

(a) Fluctuators vs Nonfluctuators

The sponsor proposes tolcapone as an adjunct to levodopa/carbidopa in two populations of PD patients, fluctuators and nonfluctuators. Clinical trials (NZ14654, NZ14655) in fluctuating

patients provide statistically significant evidence that tolcapone decreases the amount of OFF time at both the 100-mg tid and 200-mg tid doses. Study NZ14653 provides statistically significant evidence for improvement on the ADL/ON scale of the UPDRS (subscale 2) in nonfluctuating patients at the 200-mg dose; moreover, statistically significant evidence is also mustered for L-DOPA dose reductions after the addition of tolcapone.

Following is a summary of the characteristics of the two populations studied in Phase III NDA trials. About half the patients studied were female; few non-Caucasians were involved in clinical trials:

### FLUCTUATORS

	<i>Placebo (n=280)</i>	<i>Tolcapone (n=629)</i>
AGE (yrs; mean [SD])	63.9 (9.0)	63.0 (9.5)
GENDER		
Male	186	401
Female	94	228
RACE (%)		
Caucasian	97	97
Other	3	3
MEAN WEIGHT (kg [SD])	73.1 (14.5)	71.6 (14.7)
DISEASE DURATION (yrs [SD])	10.1 (4.9)	10.3 (5.2)
HOEHN/YAHR baseline score (%n)		
≤1	8.9	7.9
1.5-2.5	64.3	63.7
≥3	25.7	27.8
missing	1.1	0.6
L-DOPA THERAPY (yrs [SD])	8.4 (5.6)	8.5 (4.8)
MEAN L-DOPA DOSE (mg [SD])	849.1 (414.6)	786.2 (372.7)

### NONFLUCTUATORS

	<i>Placebo (n=135)</i>	<i>Tolcapone (n=260)</i>
AGE (yrs; mean [SD])	66.3 (9)	66.0 (9)
GENDER		
Male	81	164
Female	54	96
RACE (%)		
Caucasian	99	98
Other	1	2
MEAN WEIGHT (kg [SD])	73.2 (15.0)	75.1 (13.6)

DISEASE DURATION (yrs [SD])	6.6 (4.5)	5.5 (2.8)
HOEHN/YAHR baseline score (%n)		
≤1	3.7	4.6
1.5-2.5	17.0	16.9
≥3	3.7	3.1
missing	75.6	75.4
L-DOPA THERAPY (yrs [SD])	4.4 (2.8)	4.0 (2.5)
MEAN L-DOPA DOSE (mg [SD])	479 (146.2)	533.7 (168.3)

(b) Drug-Disease interactions

**HEPATIC:** Tolcapone is hepatically metabolized and administration has led to elevated transaminases. The drug is thus not recommended in patients with severe hepatic impairment: "No substantial effect was observed on the total tolcapone concentration, but the average concentration of unbound drug could be doubled in patients with moderate liver cirrhosis. Therefore, patients with moderate liver cirrhosis should not receive more than 100 mg tolcapone tid. An adjustment of the dosing interval is not warranted for these patients. Patients with severe liver and/or severe renal impairment should be treated with caution as no information in these populations is available" (v 1.2, p 144). The sponsor provides no laboratory cut-off points to determine when to initiate the drug in cases of mild hepatic impairment, but does recommend in labeling to discontinue the drug if "ALT exceeds 10x ULN or if jaundice develops." In the clinical trials, however, the sponsor classifies transaminase elevations into groups of  $\geq 2x$ ,  $3x$ ,  $5x$ , and  $8x$  ULN (see the addendum for ranges); far fewer patients were in the groups above  $3x$  ULN. Can one infer that most patients were terminated whose transaminases equalled or exceeded  $3x$  ULN? Caution is therefore advised. In labeling, the sponsor recommends that "transaminases be monitored before starting TASMAR treatment and approximately every 6 weeks for the first 6 months."

**RENAL:** While no study investigated the effects of mild/moderate renal impairment on tolcapone pharmacokinetics was performed, the sponsor feels that "renal impairment should not affect tolcapone concentrations, and adjust of tolcapone dose in this situation is considered unnecessary. A review of the adverse event profile for patients with renal impairment (estimated renal clearance of  $<45$  ml/min) in the placebo-controlled Phase III studies did not identify any difference from patients without renal impairment. . . Patients with severe liver and/or severe renal impairment should be treated with caution as no information in these populations is available" (v 1.2, p 144).

An increased incidence in hematuria (1/58 placebo, 4/60 at 100 mg, 8/59 at 200 mg; marked proteinuria: 2/58 placebo, 1/60 at 100 mg, 1/59 at 200 mg) was found among tolcapone-treated patients in one placebo-controlled Phase III European study (NZ14655; see v 254, p 82). For the three placebo-controlled Phase III US studies, the incidence rates for marked hematuria were 2.1% (5/234) for placebo, 2.6% (6/287) for the 100-mg group, and 2.6% (6/291) for the 200-mg group. According to the sponsor, the episodes of hematuria were one-time events, and no patients dropped out of the study because of the symptom. But no information is provided about follow-up; and there is no indication that any attempt was made to investigate the etiology of the hematuria. The possibility of an interstitial nephritis or glomerulonephritis is not specifically mentioned. The sponsor speculates that the increase noted in the European study may have been due "to occasional delays in delivering samples" (v 1.333, p 75). However, this would appear

improbable: why, in a blinded study, would delays mainly affect the tolcapone-treated group and not the placebo? The sample size (about 60) and duration (13 weeks) of two of the US studies were similar to the European study in question; the third US study was 30% larger and lasted twice as long.

## 11. Drug-Drug Interactions

(a) *Tolcapone and protein binding*: Tolcapone is highly bound (99.9%) to serum protein, primarily albumin, in human plasma. *In vitro* displacement studies with other highly protein-bound drugs (such as tolbutamide, phenytoin, digitoxin, warfarin), according to the sponsor, have shown no relevant displacement.

(b) *Tolcapone and P450*: The main metabolic pathway for tolcapone is glucuronidation. The sponsor used desipramine, as an example, and reportedly found no pharmacokinetic interaction. Hydroxylation is a minor metabolic pathway mediated by cytochrome P<sub>450</sub> isozymes 3A4 (CYP 3A4) and 2A6 (CYP 2A6). Because *in vitro* interaction studies showed that tolcapone's affinity for these enzymes was at least 10-fold less than for midazolam, cyclosporine, terfenadine, and coumarin, the sponsor concluded that *in vivo* studies did not have to be done.

It was found, however, that tolcapone had a high affinity for the isoenzyme CYP2C9, even though it was not metabolized by this enzyme. An *in vitro* interaction study between tolcapone 200 mg and tolbutamide (mainly metabolized by this enzyme) did not, according to the sponsor, interfere with the pharmacokinetics of tolbutamide. Since interaction studies were not performed with warfarin and phenytoin, the sponsor cautions against their concomitant administration with tolcapone.

Additionally, the sponsor states that 33 patients in Phase III studies were taking diclofenac (also metabolized by the the 2C9 enzyme) and, though no *in vitro* interaction studies were done, "no appreciable difference in AE profile was found among patients receiving tolcapone and diclofenac concomitantly" (v 1.333, p 93).

In labeling, with respect to drugs metabolized by the cytochrome P450 pathway, the sponsor has indicated that, "[D]ue to its affinity to cytochrome P450 2C9 *in vitro*, tolcapone may interfere with drugs whose clearance is dependent on this metabolic pathway, such as tolbutamide and warfarin. In an interaction study, tolcapone did not change the PK of tolbutamide.

"Since clinical information is limited regarding the combination of warfarin and tolcapone, coagulation parameters should be monitored when these drugs are coadministered."

(c) *Tolcapone and the COMT enzyme*: The COMT enzyme is involved with the methylation of carbidopa and benzeride (coadministered with L-DOPA in the form of Sinemet and Madopar, respectively). Steady state levels of carbidopa, measured at baseline, after 1-2 weeks, and again at 6 weeks, of tolcapone treatment showed no difference in AUC or C<sub>max</sub>. Other drugs of similar class, such as methldopa, dobutamine, isopreterenol, and apomorphine, were not studied; the sponsor consequently suggests that "a reduction in their dose should be considered when they are administered with tolcapone" (v 1.333, p 93).

Endogenous compounds which contain the catechol moiety, like the monoamines, noradrenaline, and adrenaline, are also methylated by the COMT enzyme; and COMT inhibition could therefore potentiate their effects. Separate interaction studies were performed for ephedrine (at rest and during exercise) and desipramine, taken concomitantly with multidose treatment with Sinemet and tolcapone. Ephedrine and exercise had the *expected* hemodynamic effects on pulse rate and systolic blood pressure.

Furthermore, according to the sponsor, the tolcapone/Sinemet combination did not

potentiate the pharmacokinetics of desipramine or desipramine-mediated hemodynamic effects.

In labeling, the sponsor has indicated under "DRUG INTERACTIONS" that "TASMAR may influence the pharmacokinetics (PK) of drugs metabolized by COMT. However, no effects were seen on the PK of the COMT substrate carbidopa. The effect of tolcapone on the PK of other drugs of this class, such as alpha-methyldopa, dobutamine, apomorphine, and isoproterenol has not been evaluated. A dose reduction of such compounds should be considered when they are coadministered with TASMAR." Additionally noted: "[C]aution should be exercise when desipramine is administered to Parkinson's disease patients being treated with TASMAR and levodopa/carbidopa."

"Since tolcapone interferes with the metabolism of catecholamines, interactions with other drugs affecting catecholamine levels are theoretically possible.

"Tolcapone did not influence the effect of ephedrine . . . On hemodynamic parameters or plasma catecholamine levels, either at rest or during exercise."

(d) *Tolcapone, MAOIs, and selegiline:* The sponsor conducted a randomized placebo-controlled, double-blind trial (Protocol NN14927; v 1.325), in 83 US and Canadian patients ( $n_{\text{placebo}}=41$ ,  $n_{\text{treated}}=42$ ), to determine tolerability, safety, and efficacy of tolcapone alone and in combination with the MAO-B inhibitor selegiline in untreated PD patients. Participants had to have been diagnosed with the disease within five years prior to the study (Hoehn and Yahr  $\leq 2.5$ ). They were given either tolcapone 200 mg tid or placebo for four weeks; open-label selegiline 5 mg bid was then added to whichever regimen they were on for a second four-week period.

Primary objectives were safety (evaluated by the occurrence of adverse events, vital-sign changes, labs, and EKGs) and tolerability (evaluated by an investigator's "global assessment of tolerability") of tolcapone versus placebo. Secondary objectives were safety and tolerability of tolcapone in combination with selegiline in untreated PD patients; additionally, an "exploratory objective" was to compare the tolcapone and selegiline combination with selegiline, using the UPDRS (subscales II [ADLs] and III [motor score]) and the Purdue Pegboard (motor dexterity) to determine symptomatic improvement. Selegiline was not found to influence tolcapone pharmacokinetics (v 1.333, p 94).

There were five withdrawals (12%) from the tolcapone-treated, and none from the placebo, group, all of which took place during the second four-week period; no deaths occurred. During the first four-week period, a higher incidence of adverse events was seen with the tolcapone (62%), compared to placebo (37%); the five side effects with incidences 5% or greater than placebo were nausea (6/42 [14%] versus 0 for placebo), headache (4/42 [10%] versus 2/41 [5%]), diarrhea (4/42 [10%] versus 1/41 [2%]), dizziness (3/42 [7%] versus 1/41 [2%]), and urine discoloration (5/42 [12%] versus 0). During the second four-week period, when selegiline was added to the regimen, the incidence of adverse events increased in the tolcapone-treated group: diarrhea (10/42 [24%] versus 2/41 [5%]) and nausea, abdominal pain, and dizziness (each 3/42 [7%] versus 1/41 [2%]). Excessive dreaming (3/42 [7%] versus 0) was also a problem, but the sponsor's report does not specify whether it occurred during the first- or the second-half of the study. As to the five withdrawals (no patient profiles are available), all occurred during the second half of the study: three for diarrhea (on days 33, 52, and 59); one for angina (day 41), classified by the sponsor as a "serious adverse effect"; and one for dizziness, dyspepsia, somnolence, and vision blurred (day 42) (v 1.325, p 27). As to orthostatic hypotension, there were 3/42 cases in the tolcapone-treated, and 1/41 in the placebo, group; two patients on placebo-selegiline had significant EKG changes (LVH in one and afib in the other) and one in the tolcapone-selegiline group (afib with tachycardia and ST depression); patient profiles were not provided in the NDA. A table of lab abnormalities shows two instances of high ASAT and ASAT in the tolcapone-treated group during the first and the second (with selegiline) four-week periods and two instances of elevated fasting blood sugars during the second four-week period versus two instances of high ASAT and ALAT in the selegiline placebo group.

Not mentioned in this study, however, is the increased incidence of dyskinesias. The sponsor states elsewhere (v 1.333, p 94) that "approximately half the patients in the Phase III placebo-controlled studies were using selegiline concurrently with L-DOPA, and experienced 'a slightly higher incidence rate of dyskinesia and sleep disease.'"

In terms of symptomatic benefit in early PD patients, no difference was found between the placebo versus tolcapone and placebo-selegiline versus tolcapone-selegiline groups from the perspective of the investigator's global assessment of change, UPDRS II and III scores, and the results of Purdue Pegboard testing.

In labeling, tolcapone administration is contraindicated with non-selective MAO inhibitors (eg, phenelzine and tranylcypromine). Although labeling specifically states that "[S]elective MAO-B inhibitors, such as selegiline, and selective MAO-A inhibitors are not contraindicated," the sponsor states elsewhere that "[T]here is no data available for the combination of tolcapone and MAO-A inhibitors, therefore, this combination should be given with caution" (v 1.333, 94).

"[C]aution should be exercised when desipramine is administered to Parkinson's disease patients being treated with TASMAR and levodopa/carbidopa."

"Since tolcapone interferes with the metabolism of catecholamines, interactions with other drugs affecting catecholamine levels are theoretically possible.

"Tolcapone did not influence the effect of ephedrine . . . On hemodynamic parameters or plasma catecholamine levels, either at rest or during exercise."

(e) *Tolcapone and dopamine agonists:* "Approximately one-third" of the patients in the placebo-controlled Phase III studies were receiving concurrent dopamine agonists; the "safety profile" showed a higher incidence of orthostatic complaints and hallucinations (no numbers supplied) than among subjects receiving tolcapone only (v 1.333, p 94). It should be noted that the one patient, whose death was ascribed by the sponsor as "possibly related" to tolcapone, was also taking selegiline and pergolide concurrently with Sinemet and tolcapone. It is not known how many other patients were on a similar regimen.

## 9 CONCLUSIONS

In my opinion, based on a review of the data submitted by the sponsor, tolcapone appears to be reasonably safe and efficacious when used as directed in the defined patient population.

## 10 RECOMMENDATIONS

In this reviewer's opinion, NDA 20,697 should be made approvable pending resolution of several outstanding issues. These issues should be made an ACTION on the part of the sponsor in the approvable letter:

(1) **DIARRHEA:** There is no description of the diarrhea experienced by patients: the number of stools/day, the type (secretory, bloody, etc.), severity. A search of case reports, narrative summaries, and NDA findings have not provided this information.

(2) **LIVER TRANSAMINASES:** The sponsor should provide updates on patients with elevated transaminases in quarterly reports.

(3) **NEUROLEPTIC MALIGNANT SYNDROME:**

(a) The sponsor should provide follow-up on the three (possibly more) cases of neuroleptic malignant syndrome. Tom Watson (Hofmann-La Roche, Inc) has promised to submit more information about this adverse event, as it becomes available.

(b) The risk of neuroleptic malignant syndrome should be specifically indicated in labeling, in addition to instructions about altering the doses of other concomitant dopaminergic agents when tolcapone is tapered off.

(4) **RENAL:**

(a) An FDA renal consult has been sought for recommendations concerning hematuria in study NZ14655. The recommendations should be made part of the approvable letter.

(b) The sponsor should provide follow-up renal ultrasound data on patients in the extension to study NZ14653.

(5) **STATISTICS:**

(a) The sponsor needs to provide area-under-the-curve data for the UPDRS subscale 2 (ADL) for all PHASE III placebo-controlled studies comprising in the NDA.

(b) The sponsor needs to provide a description of dropouts for the three pivotal studies (NZ14654, NZ14655, and NZ14653).

(c) The sponsor needs to provide the total number of exposures to Tolcapone, broken down by single and multiple exposures and doses for each.

Richard Tresley, MD  
Medical Reviewer

NDA 20-697 div file/Katz R/Tresley R/Wheelous T/15 Nov 1996 (Revised 3/19/97)

**ADDENDUM**

**Table of Potential Tasmar-related Adverse Events, with Crude Incidence Rates,  
for Phase III Placebo-controlled studies (from the sponsor's proposed  
labeling)**

**Table of Other Adverse Events During Therapeutic Clinical Trials (from the  
sponsor's proposed labeling)**

**Sponsor Laboratory Reference Ranges**

**Sample Patient Diary**

**Sponsor Adverse Event Criteria**

**Mini-Mental Status Examination**

**Unified Parkinson's Disease Rating Scale**

**Hoehn & Yahr Criteria**

**Schwab and England Activities of Daily Living**

**Dyskinesia Rating Scale**

**Investigator's Global Assessment of Changes**

**Beck Depression Inventory**

**Sickness Impact Profile**

**Medical Resource Assessment**

A tabulated summary of potential Tasmalor-related adverse events, with crude incidence rates, for Phase III placebo-controlled studies has been provided by the sponsor in its proposed labeling. A further listing of other adverse events during therapeutic trials, also taken from the labeling, follows.

HLR Tasmalor March 27, 1997

**TASMAR™ (tolcapone) TABLETS**

Experience with TASMAR obtained in parallel, placebo-controlled, randomized studies in patients with Parkinson's disease are shown in the following table which lists adverse events, regardless of relationship, that occurred at an incidence rate that was at least two percentage points higher than the placebo group, suggesting a potential relationship to TASMAR.

**Summary of Potentially TASMAR-Related Adverse Events, with Crude Incidence Rates for the Phase III Placebo-Controlled Studies:**

Adverse Events	Placebo N=298 (%)	100 mg Tolcapone N=296 (%)	200 mg Tolcapone N=298 (%)
† Dyskinesia	19.8	41.9	51.3
† Nausea	17.8	30.4	34.9
† Sleep Disorder	18.1	23.6	24.8
† Dystonia	17.1	18.6	22.1
† Dreaming Excessive	17.1	21.3	16.4
† Anorexia	12.8	18.9	22.8
† Orthostatic Complaints	13.8	16.6	16.8
† Somnolence	13.4	17.9	14.4
Diarrhea	7.7	15.5	18.1
Dizziness	9.7	13.2	6.4
Headache	7.4	9.8	11.4
† Hallucination	5.4	8.4	10.4
† Vomiting	3.7	8.4	9.7
Constipation	5.0	6.4	8.4
Upper Respiratory Tract Infection	3.4	4.7	7.4
Sweating Increased	2.3	4.4	7.4
Xerostomia	2.3	4.7	6.4
Abdominal Pain	2.7	4.7	5.7
† Syncope	2.7	4.1	5.0
Urine Discoloration	0.7	2.4	7.4
Dyspepsia	1.7	4.1	3.0
Influenza	1.7	3.0	4.0
Chest Pain	1.3	3.4	1.0
Hypokinesia	0.7	0.7	2.7

HLR Tasmart March 27, 1997

## TASMAR™ (tolcapone) TABLETS

†Potentially L-DOPA-induced symptoms

### Other Adverse Events Observed During Therapeutic Clinical Trials.

The events listed below represent those experienced, regardless of relationship, on at least one occasion by a patient receiving TASMAR. Events are classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring in at least 1/100 patients; infrequent adverse events are those occurring in < 1/100 to 1/1000 patients; rare adverse events are those occurring in fewer than 1/1000 patients.

\* = AE frequency  $\leq$  to placebo

**Central and Peripheral Nervous System:** *Frequent:* dyskinesia, dystonia, somnolence, confusion, dizziness, headache, falling\*, tremor, balance loss, hypoesthesia\*, hyperkinesia, paresthesia, hypokinesia. *Infrequent:* neuralgia\*, burning, paresis\*, speech disorder, gait abnormal\*, memory disturbance, hypertonia, hyperactivity, parkinsonism aggravated\*, sensory disturbance\*, migraine\*, neuropathy\*, cerebral ischemia, stroke, voice disturbances\*, choreoathetosis, myoclonus\*, stuttering, twitching. *Rare:* encephalopathy\*, dementia, hemiplegia, mentation impaired, pain faciocranial, parkinsonian fluctuation, spasms, teeth-grinding.

**Gastro-intestinal System:** *Frequent:* nausea, anorexia, diarrhea, vomiting, constipation, abdominal pain, dyspepsia, flatulence, tooth disorder\*, abdominal discomfort\*. *Infrequent:* dysphagia\*, GI hemorrhage, gastrointestinal inflammation, canker sores oral, hernia inguinal, bowel movements frequent\*, esophagitis, hernia hiatal, burning throat, colitis, edema mouth, hemorrhoids, hiccup, tongue discoloration. *Rare:* gastric atony\*, intestinal obstruction\*, appetite disturbances, appetite increased, discoloration sputum, duodenal ulcer, duodenitis, ileus, tongue dryness.

**Psychiatric:** *Frequent:* sleep disorder, dreaming excessive\*, hallucination, depression, agitation, anxiety\*. *Infrequent:* asthenia\*, mental deficiency, emotional lability\*, impotence\*, panic reaction, irritability, euphoria, aggressive reaction, paranoid reaction\*, libido decreased\*, libido increased, delusion\*, nervousness, apathy\*, illusion\*, hypomania, mania, psychosis. *Rare:*

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delirium, oppression, behavior disturbances, cachexia, compulsive reaction, libido disorder, orgasm loss, personality disorder.

**Musculo-skeletal System:** *Frequent:* cramps muscle, back pain\*, arthralgia\*, pain limbs\*, fractures\*, stiffness, pain neck, myalgia\*, arthritis\*. *Infrequent:* sprains and strains, carpal tunnel syndrome, intervertebral disc disorder\*, bone spur, pain body\*, tendinitis, flank pain, joint dislocation, spasms vertebral column. *Rare:* fracture pathological, arthritis rheumatoid, arthropathy, calcium deficiency bone, hemarthrosis, leg discomfort, muscle disorder, synovitis.

**Autonomic Nervous System:** *Frequent:* orthostatic complaints, hypotension, xerostomia, sweating increased, syncope. *Infrequent:* hypertension\*, flushing\*, hot flushes\*, saliva increased\*. *Rare:* saliva altered.

**Urinary System:** *Frequent:* urine discoloration, urinary tract infection, micturition frequency\*. *Infrequent:* micturition disorder, urinary incontinence, urinary retention\*, urinary tract bleeding\*, dysuria, nocturia\*, polyuria, bladder disorder, renal calculus\*, oliguria. *Rare:* bladder calculus, bladder prolapse, kidney failure, pyelonephritis, renal function abnormal, vesical obstruction.

**Body as a Whole:** *Frequent:* fatigue\*, chest pain\*, edema peripheral\*, trauma\*, weight decrease. *Infrequent:* chest discomfort\*, lethargy\*, malaise, fever, allergic reaction\*, edema joint\*, surgical procedure, pain\*, shivering\*, edema\*, face edema. *Rare:* death, weight increase.

**Respiratory System:** *Frequent:* upper respiratory tract infection, dyspnea, pneumonia\*. *Infrequent:* bronchitis, sinusitis\*, pharyngitis, coughing\*, sinus congestion, asthma bronchial, epistaxis\*, pharynx dryness\*, rhinitis\*, rhinitis allergic atopic, hyperventilation\*, laryngitis\*. *Rare:* chest congestion\*, embolism pulmonary, wheezing, apnea, breathing abnormally shallow, hypoxia, irritation pharynx, phlegm, pulmonary edema, respiratory tract hemorrhage.

**Resistance Mechanism:** *Frequent:* Influenza. *Infrequent:* infection\*, herpes zoster\*, infection viral\*, infection bacterial\*, infection mycotic, abscess, herpes simplex. *Rare:* angina tonsillaris, encephalitis, HIV test positive, meningitis aseptic, otitis, otitis media.

**Skin and Appendages:** *Frequent:* rash. *Infrequent:* pruritus, skin discoloration\*, cellulitis\*, seborrhea, eczema, erythema\*, alopecia, dermatitis, furunculosis\*, urticaria. *Rare:* nail disorder,

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goose flesh, hair texture abnormal, neurodermatitis, nevus, psoriasis, rosacea, skin burns, skin warm, xeroderma.

**Vision:** *Frequent:* vision blurred. *Infrequent:* diplopia\*, cataract, visual disturbance, eye inflamed, eye pain, ocular hemorrhage, tear secretion increased, vision decreased. *Rare:* conjunctivitis, eye irritation, glaucoma, xerophthalmia\*, blepharitis, corneal abrasion, mydriasis, retinopathy.

**Heart Rate and Rhythm:** *Frequent:* palpitation. *Infrequent:* fibrillation atrial\*, tachycardia\*, arrhythmia\*, bradycardia, cardiac arrest.

**Hearing and Vestibular:** *Infrequent:* vertigo\*, tinnitus, pain ear. *Rare:* cerumen impacted.

**Metabolic and Nutritional:** *Infrequent:* hypercholesterolemia, thirst, dehydration, diabetes mellitus\*. *Rare:* gout\*, hyperglycemia, hypocalcemia, hypokalemia.

**Special Senses Other:** *Infrequent:* taste alteration\*, parosmia\*.

**Platelet, Bleeding and Clotting:** *Infrequent:* bleeding dermal, bleeding genital, cerebral hemorrhage\*. *Rare:* thrombocytopenia.

**Myo-, Endo-, Pericardial and Valve:** *Infrequent:* angina pectoris, aortic stenosis, coronary infarction. *Rare:* arteriosclerosis, coronary artery disorder.

**Cardiovascular, General:** *Infrequent:* cardiac failure\*. *Rare:* cardiovascular side effects, coronary stenosis, myocardial ischemia, pericardial effusion.

**Reproductive, Male:** *Infrequent:* prostate enlarged, prostatitis. *Rare:* prostatic disorder\*, unspecified transurethral resection of prostate.

**Neoplasm, Skin and Appendages:** *Infrequent:* tumor skin.

**Vascular (extracardiac):** *Infrequent:* stenosis arterial. *Rare:* ischemia\*, phlebitis\*, livedo reticularis, thromboembolic complications, thrombophlebitis, venous thrombosis.

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**TASMAR™ (tolcapone) TABLETS**

**Neoplasm, Reproductive System: Infrequent:** tumor uterus, carcinoma prostate, tumor breast.  
**Rare:** carcinoma ovary.

**Reproductive, Female: Infrequent:** hysterectomy, uterine prolapse, vaginal discharge. **Rare:** menstrual disorder, cervicitis, mastopathy.

**Neoplasm: Infrequent:** tumor, carcinoma renal. **Rare:** cyst popliteal, neuroma.

**Red Blood Cell: Infrequent:** anemia.

**Liver and Biliary System: Infrequent:** cholelithiasis. **Rare:** cholecystitis.

**Endocrine: Rare:** glands swollen, goiter.

**Neoplasm, Gastrointestinal System: Rare:** esophageal carcinoma, rectal carcinoma.

**Hemic and Lymphatic: Rare:** pain lymph nodes.

**Unclassified: Rare:** bleeding fibroid uterus.

**White Cell Disorders: Rare:** leukemia.

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

ADDENDUM TO CLINICAL REVIEW OF NDA

Generic (Brand) Name	Tolcapone (Tasmar)
Indication	Adjunct to Levodopa to treat Parkinson's Disease
NDA Classification	3P
NDA Number	20-697
Original Receipt Date	June 3, 1996
Clinical Reviewer	Richard M. Tresley, MD
Review Completed	November 15, 1996 (revised 3/19/97)
Addendum Completed	June 2, 1997

Response to comments from Robert Temple MD:

#5. DOSE-RELATED ADR

The company divides ADRs into two categories, dopaminergic (or "L-Dopa-induced" [v 1.333, p 29]) and nondopaminergic.

Following are dose-related *dopaminergic* events:

(1) **DYSKINESIA**: Dyskinesia was "the most commonly reported adverse event in the tolcapone program, and its incidence rate was clearly related to tolcapone dose" (v 1.333, p 30). The incidence of dyskinesias appeared dependent on the presence of fluctuations. The treatment differences (tolcapone minus placebo) in the three Phase III fluctuator studies (NZ14654, NN14971, NZ14655) were 31% in the 100-mg tolcapone group and 42% in the 200-mg group. Among patients in the Phase III nonfluctuator study (NZ14653), the differences were 4% and 10%, respectively.

(2) **DYSTONIA**: Incidence rates in Phase III studies were 17% (51/298) in the placebo group, 18.6% (55/296) in the 100-mg group, and 22.1% (66/298) in the 200-mg group.

(3) **NAUSEA AND VOMITING**: Nausea was "the second most frequently reported adverse event" (v 1.333, p 37). Incidence rates in Phase III studies were 17.8% (53/298) in the placebo group, 30.4% (90/296) in the 100-mg group, and 34.9% (104/298) in the 200-mg group. Incidences were similar for Phase II studies as well (see v 1.334, p 265-77).

Incidence rates for vomiting in Phase III studies were 3.7% (11/298) in the placebo group, 8.4% (25/296) in the 100-mg group, and 9.7% (29/298) in the 200-mg group.

(4) **ANOREXIA**: Incidence rates for anorexia in Phase III studies were 12.8% (38/298) in the placebo group, 18.9% (56/296) in the 100-mg group, and 22.8% (68/298) in the 200-mg group. "Body mass was not recorded at each assessment visit, so the occurrence of anorexia cannot be correlated with weight loss" (v 1.333, p 41).

(5) **ORTHOSTATIC COMPLAINTS**: Crude incidence rates for Phase III studies were 13.8% (41/298) for the placebo group, 16.6% (49/296) for the 100-mg group, and 16.8% (50/298) for the 200-mg group. Hypotension occurred infrequently in Phase III studies: 1.3% (4/298) in the placebo group, 1.7% (5/296) in the 100-mg group, and 2.3% (7/298) in the 200-mg group. Similarly with syncope: 2.7% (8/298), 4.1% (12/296) in the 100-mg group, and 5.0% (15/298) in the 200-mg group. The sponsor's discrete method of data collection does not allow for adequate correlation of the three adverse events.

(6) **SLEEP DISORDER** ("a preferred AE term which includes the L-Dopa-induced symptom of insomnia" [v 1.333, p 45]): Crude incidence rates for Phase III studies were 18.1% (54/298) for the placebo group, 23.6% (70/296) for the 100-mg group, and 24.8% (74/298) for the 200-mg group. "Sleep disorder was the second most commonly treated AE in the therapeutic studies, but it rarely led to withdrawal from study. Psycholeptics (eg., anxiolytics) and psychoanaleptics (e.g.,

anti-depressants) were the most commonly prescribed medications" (v 1.333, p 45).

(6) **HALLUCINATION:** Crude incidence rates in Phase III studies were 5.4% (16/298) in the placebo group, 8.4% (25/296) in the 100-mg group, and 10.4% (31/298) in the 200-mg group. Hallucinations led to withdrawal in the case of 1 (0.3%) patient in the placebo, and 4 (1.4%) in the 100-mg, and 3 (1.0%) in the 200-mg, groups.

(7) **EXCESSIVE DREAMING:** Incidence rates in Phase III studies were 17.1% (5/298) in the placebo group, 21.3% (63/296) in the 100-mg group, 16.4% (49/498) in the 200-mg group.

Following are dose-related *nondopaminergic* events:

(1) **DIARRHEA:** Diarrhea was the most prevalent *nondopaminergic* adverse event in Phase III trials (v 1.333, p 57). Crude incidence rates were 7.7% (23/298) in the placebo group, 15.5% (46/296) in the 100-mg group, and 18.1% (54/298) in the 200-mg group. The complaint led to the withdrawal of 3 (1.0%) patients in the placebo group, and 16 (5.4%) in the 100-mg, and 18 (6.0%) in the 200-mg, groups.

(2) **CONSTIPATION:** Incidence rates in Phase III trials were 5.0% (15/298) in the placebo group, 6.4% (19/296) in the 100-mg group, and 8.4% (25/298) in the 200-mg group.

(3) **HEADACHE:** Incidence rates in Phase III studies were 7.4% (22/298) in the placebo group, 9.8% (29/296) in the 100-mg group, and 11.4% (34/298) in the 200-mg group. "[A]bout half of the patients with headache received some form of treatment" (v 1.333, p 61).

(4) **HYPOKINESIA:** Incidence rates in Phase III studies were 0.7% (2/298) for the placebo, 0.7% (2/296) for the 100-mg, and 2.7% (8/298) for the 200-mg groups.

(5) **AUTONOMIC DISORDERS:** Incidence rates for "sweating increased" were 2.3% (7/298) for the placebo, 4.4% (13/296) for the 100-mg, and 7.4% (22/298) groups. For "xerostomia": 2.3% (298) for the placebo, 4.7% (14/296) for the 100-mg, and 6.4% (19/298) groups.

(6) **RESISTANCE MECHANISM DISORDERS:** Incidence rates for "upper respiratory tract infection" were 3.4% (10/298) for the placebo, 4.7% (14/296) for the 100-mg, and 7.4% (22/298) groups. For "influenza": 1.7% (5/298) for the placebo, 3.0% (9/296) for the 100-mg, and 4.0% (12/298) groups.

(7) **URINE DISCOLORATION:** Incidence rates in Phase III studies were 0.7% (2/298) in the placebo, 2.4% (7/298) in the 100-mg, and 7.4% (22/298) in the 200-mg groups.

## DEMOGRAPHIC SUBGROUP ANALYSES

### Safety:

#### (1) FEMALES:

(a) **nausea:** Phase III trial treatment differences (tolcapone minus placebo) for females were 17.7 (for males: 8.5) for the 100-mg, and 27.4 (for males: 11.5) for the 200-mg, groups (v 1.334, p 396). Nausea tended therefore to be a complaint more frequently found with female patients.

(b) **sleep disorder:** Phase III trial treatment differences (tolcapone minus placebo) for females were 16.4 (for males: -1.0) for the 100-mg, and 13.2 (for males: 3.3) for the 200-mg, groups (v 1.334, p 396). Sleep disorder tended therefore to be a complaint more frequently found with female patients.

(c) **increased LFTs:** "Females were found to be represented more among tolcapone-treated patients with elevated transaminases (61%, 19/31) than among those without elevated transaminases (36%, 540/1505). There were no obvious differences between patients with or without elevated transaminases in terms of previous or concomitant medical conditions or medications" (v 1.333, p 78; see also v 1.335, p 489).

(2) **AGE:** According to the sponsor, age had "little impact" on dopaminergic side effects (v 1.333, p 53; see also v 1.334, pp 392-4). No analysis of age on *nondopaminergic* side effects was provided.

(3) **RACE:** The "limited number [ 26] of non-Caucasian patients precludes making any meaningful statements about effects of race on the incidence of AEs" (v 1.333, p 53).

## Efficacy:

The sponsor has carried subgroup analyses for sex, age, and race with respect to the two primary endpoints, (1) OFF-time and (2) reduction in L-Dopa dose, in the three Phase III trials (NZ14654 [13 weeks], NZ14655 [13 weeks], and NN14971 [6 weeks]).

(1) For OFF-time: for females, *treatment differences* (tolcapone minus placebo) in OFF-time were significant with respect to both doses: 100 mg (-6.0 min,  $p < 0.0331$ ; for males: -9.9 min,  $p < 0.001$ ) and 200 mg (-8.1 min,  $p < 0.0070$ ; for males: -11.2 min,  $p < 0.001$ ). With respect to age: for the <65 and 65-75 categories, *treatment differences* were significant for both the 100-mg and 200-mg doses (100 MG: <65, -6.8 min,  $p < 0.0045$ , 109 subjects; 65-75 category, -10.7,  $p < 0.001$ , 59 subjects. 200 MG: <65, -8.0 min,  $p < 0.0011$ , 105 subjects; 65-75 category, -12.0 min,  $p < 0.001$ ; 64 subjects). For the >75 category, *treatment differences* were statistically significant only for the 200-mg dose (100 MG: -2.5 min,  $p = .6689$ , 16 subjects; 200 MG: -12.2,  $p = 0.0395$ , 15 subjects), but the numbers of subjects were small for both groups and, in the 100-mg group, may account for "the absence of a statistically significant difference from placebo with tolcapone" (v 1.331, p 42).

Selecting a  $p$  value of  $< 0.15$  to examine *treatment-by-subgroup*, the sponsor reports "[n]o statistically significant ( $p < 0.15$ ) treatment-by-subgroup interaction...for any of the subgrouping variables examined. No treatment-by-subgroup interaction was statistically significant for any subgrouping variable. The results of the subgroup analyses indicate that the mean decreases in OFF-time observed at the primary-end-point were greater with 100- and 200-mg tolcapone than placebo in all subgroups, and the magnitude of the treatment effects were comparable across all subgroups" (my emphasis, v 1.331, p 42; see also v 1.332, pp 225-7).

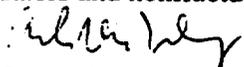
(2) For reduction in L-Dopa dose: "all subgroups exhibited mean reductions in daily L-Dopa dose that were greater with 100 and 200 mg tolcapone than placebo." Again, the sponsor adds that "[T]he absence of a statistically significant difference from placebo with tolcapone in some of the subgroups was generally due to the small number of patients included in these subgroups" (v 1.331, p 42):

(a) for females, the *treatment difference* (tolcapone minus placebo) at the 100-mg dose was -183.0 mg L-Dopa ( $p < 0.001$ ; for males: -131.7 mg,  $p < 0.001$ ), and at the 200-mg dose -252.6 mg L-Dopa ( $p < 0.001$ ; for males: 166.7 mg,  $p < 0.001$ ).

(b) with respect to age, for the <65 category, the *treatment difference* was -165.1 mg L-Dopa ( $p < 0.001$ ; 116 subjects) and, for the 200-mg dose, -200.4 mg L-Dopa ( $p < 0.001$ ; 115 subjects); for the 65-75 category, the respective *treatment differences* were -127.4 mg ( $p < 0.001$ ; 64 subjects) and -205.1 mg ( $p < 0.001$ ; 68 subjects); and for the >75 category, the respective *treatment differences* were -141.8 ( $p < 0.0180$ ; 18 subjects) and -115.3 (0.0588; 17 subjects).

With reference to *treatment-by-subgroup* analyses, "statistically significant three-way interactions were found between treatment, subgrouping variable, and baseline L-Dopa dose...Since baseline L-Dopa dose contributed to the change in daily L-Dopa dose to a much greater extent than any other variable, along with the significant three-way interaction mentioned above, the data were reanalyzed for each subgroup based on baseline daily L-Dopa dose <600, 601-900, and >900 mg. The results show that both interaction terms (treatment-by-subgroup and treatment-by-study) which were statistically significant ( $p < 0.15$ ) in the original overall group analysis were no longer statistically significant" (v 1.331, p 42).

As for race, there were only 7 non-Caucasian patients each in the 100- and 200-mg groups, too few to make "meaningful statements" about the efficacy of tolcapone in the non-Caucasian population. Finally, no comparisons are made between fluctuators and nonfluctuators with respect to treatment effect.

  
Richard M. Tresley MD  
Medical Reviewer

**Table 1. Reference Ranges and Clinically Relevant Changes from Baseline for Laboratory Data**

Laboratory Test	SI Unit	Significant Digits	Roche Standard Reference Range	Marked Reference Range	Direction of Change	Clinically Relevant Change from Baseline
<b>Hematology</b>						
Hematocrit	fraction	0/2			Increase Decrease	≥ 15 % ≥ 15 %
Hemoglobin	g/dL	2/1			Increase Decrease	≥ 15 % ≥ 15 %
Leucocytes	10 <sup>9</sup> /L	2/1			Increase Decrease	≥ 30 % ≥ 30 %
Platelets	10 <sup>9</sup> /L	4/0			Increase Decrease	≥ 50 % ≥ 30 %
+ MCH	pg/cell	2/1				
+ MCHC	g/L	3/0				
+ MCV	fL	3/0				
+ RBC	10 <sup>12</sup> /L	1/2			Increase Decrease	≥ 15 % ≥ 15 %
<b>Differentials</b>						
+ Bands	fraction	1/2			Increase	≥ 30 %
+ Basophils	10 <sup>9</sup> /L	1/2			Increase	≥ 100 %
+ Basophils	fraction	1/2			Increase	≥ 100 %
+ Lymphocytes	10 <sup>9</sup> /L	1/2			Increase Decrease	≥ 30 % ≥ 30 %
+ Lymphocytes	fraction	1/2			Increase Decrease	≥ 30 % ≥ 30 %
+ Monocytes	10 <sup>9</sup> /L	1/2			Increase Decrease	≥ 100 % ≥ 100 %
+ Monocytes	fraction	1/2			Increase Decrease	≥ 100 % ≥ 100 %
Neutrophils	10 <sup>9</sup> /L	2/2			Decrease	≥ 20 %
+ Neutrophils	fraction	1/2			Decrease	≥ 20 %
Eosinophils	10 <sup>9</sup> /L	1/2			Increase	≥ 100 %
+ Eosinophils	fraction	1/2			Increase	≥ 100 %

- \* Reference range replaces the corresponding investigator range.
- † Reference lower limit replaces the corresponding investigator lower limit (upper limit of investigator range used to transform a test result to the Roche standard).
- ^ Reference ranges expressed for females are used to transform data to conform to the male range for analytic and display purposes.
- ‡ A clinically relevant change here is a 2 unit increase over the Baseline (note that baseline values of 3 and 4 do not allow a subsequent clinically relevant change).
- § This test is not the recommended form for measure of T3 uptake but is included since many ongoing projects use this form of the test.

**Table 1 (cont.) Reference Ranges and Clinically Relevant Changes from Baseline for Laboratory Data**

Laboratory Test	SI Unit	Significant Digits	Roche Standard Reference Range	Marked Reference Range	Direction of Change	Clinically Relevant Change from Baseline
<b>Coagulation</b>						
Prothrombin time	seconds	2/0				
+ PT, Normalized Ratio	ratio	1/2			Increase -	≥ 30 %
PTT	seconds	2/0			Increase	≥ 30 %
+ Fibrinogen	μmol/L	2/1			Increase	≥ 40 %
					Decrease	≥ 30 %
<b>Heart Function</b>						
ASAT (SGOT)	U/L	3/0				
+ Lactic Dehydrogenase	U/L	3/0			Increase	≥ 50 %
+ CPK (MB Fraction)	μg/L	2/1			Increase	≥ 50 %
					Increase	≥ 50 %
<b>Liver Function</b>						
Alkaline Phosphatase	U/L	3/0				
ALAT (SGPT)	U/L	3/0			Increase	≥ 50 %
Total Bilirubin	μmol/L	3/1			Increase	≥ 50 %
+ Gamma-GT	U/L	3/0			Increase	≥ 75 %
					Increase	≥ 50 %
<b>Renal Function</b>						
BUN	mmol/L	2/1				
Creaunine	μmol/L	3/0			Increase	≥ 75 %
					Increase	≥ 75 %
<b>Thyroid Function</b>						
T3 Uptake, total	nmol/L	2/1				
					Increase	≥ 20 %
					Decrease	≥ 20 %
T3 Uptake, percent §	%	2/0				
					Increase	≥ 20 %
					Decrease	≥ 20 %
+ Reverse T3	nmol/L	1/2				
Thyroxine (T4)	nmol/L	3/0				
					Increase	≥ 20 %
					Decrease	≥ 20 %
+ Free T4	pmol/L	2/0				
					Increase	≥ 20 %
					Decrease	≥ 20 %
TSH	mU/L	2/1				
+ TSHS	mU/L	1/2				
					Increase	≥ 30 %
					Increase	≥ 30 %
					Decrease	≥ 30 %

\* Reference range replaces the corresponding investigator range.

† Reference lower limit replaces the corresponding investigator lower limit (upper limit of investigator range used to transform a test result to the Roche standard).

^ Reference ranges expressed for females are used to transform data to conform to the male range for analytic and display purposes.

‡ A clinically relevant change here is a 2 unit increase over the Baseline (note that baseline values of 3 and 4 do not allow a subsequent clinically relevant change).

§ This test is not the recommended form for measure of T3 uptake but is included since many ongoing projects use this form of the test.

**Table 1 (cont.) Reference Ranges and Clinically Relevant Changes from Baseline for Laboratory Data**

Laboratory Test	SI Unit	Significant Digits	Roche Standard Reference Range	Marked Reference Range	Direction of Change	Clinically Relevant Change from Baseline
<b>Protein</b>						
Total Protein	g/L	3/0			Increase	≥ 20 %
Albumin	g/L	2/1			Decrease	≥ 20 %
<b>Lipid Chemistry</b>						
Cholesterol	mmol/L	2/1			Increase	≥ 50 %
Triglycerides	mmol/L	2/2			Increase	≥ 100 %
<b>Electrolytes</b>						
Chloride	mmol/L	3/0			Increase	≥ 7 %
Potassium	mmol/L	1/1			Decrease	≥ 7 %
Sodium	mmol/L	3/0			Increase	≥ 20 %
					Decrease	≥ 20 %
Bicarbonate	mmol/L	2/0			Increase	≥ 7 %
					Decrease	≥ 7 %
<b>Miscellaneous</b>						
Calcium	mmol/L	1/2			Increase	≥ 10 %
					Decrease	≥ 10 %
Phosphate	mmol/L	1/2			Increase	≥ 30 %
					Decrease	≥ 30 %
+ Antithrombin 3	fraction	1/2			Increase	≥ 75 %
Blood Glucose (fasting)	mmol/L	2/2			Decrease	≥ 75 %
Uric Acid	μmol/L	4/0			Increase	≥ 50 %
<b>Urinalysis</b>						
+ Casts	/HPF	2/0				
Proteinuria	0 to 4+	1/0			Increase	‡
Glycosuria	0 to 4+	1/0			Increase	‡
Hematuria	0 to 4+	1/0			Increase	‡
WBCs	0 to 4+	1/0			Increase	‡
RBCs	0 to 4+	1/0			Increase	‡

- \* Reference range replaces the corresponding investigator range.
- † Reference lower limit replaces the corresponding investigator lower limit (upper limit of investigator range used to transform a test result to the Roche standard).
- ^ Reference ranges expressed for females are used to transform data to conform to the male range for analytic and display purposes.
- ‡ A clinically relevant change here is a 2 unit increase over the Baseline (note that baseline values of 3 and 4 do not allow a subsequent clinically relevant change).
- § This test is not the recommended form for measure of T3 uptake but is included since many ongoing projects use this form of the test.

**Table 2. Conversions for Urinalysis**

Values should be reported only on a scale ranging from 0 through 4. Those reported as noted below should be converted as indicated at left.

<b>Proteinuria</b>		
Should be reported as	Actual Range in mg/%	Alphabetic equivalents
0	0 to <30	negative, none, normal, not present, trace, slight, slight trace (ST)
1+	30 to <100	small
2+	100 to <500	moderate, positive
3+	500 to <1000	marked, large, strong, strongly positive (SP)
4+	1000 or more	
<b>Glycosuria</b>		
Should be reported as	Actual Range in mg/%	Alphabetic equivalents
0	0 to <100	negative, none, normal, not present
1+	100 to <250	small, trace, slight, slight trace (ST)
2+	250 to <1000	moderate, positive
3+	1000 to <2000	marked, large, strong, strongly positive (SP)
4+	2000 or more	
<b>Hematuria</b>		
Should be reported as	Actual Range in mg/%	Alphabetic equivalents
0	0 to <30	negative, none, normal, not present, trace, slight, slight trace (ST)
1+	30 to <100	small
2+	100 to <500	moderate, positive
3+	500 to <1000	marked, large, strong, strongly positive (SP)
4+	1000 or more	
<b>Red or White Blood Cells in Urine</b>		
Should be reported as	Actual Range (cell count)	Alphabetic equivalents
0	0-3 (M) 0-10 (F)	negative, none, normal, not present, trace, slight, slight trace (ST) absent, blank, not seen (ns) small, few, rare, occasional
1+	4-15 (M) 11-25 (F)	moderate
2+	16-40 (M) 26-50 (F)	severe, large
3+	41-100 (M) 51-100 (F)	high, numerous
4+	>100	many, loaded, full, packed, clumped, innumerable, too numerous to count (TNTC)

Note that, since the qualitative (dipstick) outcomes may be reported as 0 to 4+ or 0 to 5+ depending on the reporting laboratory, all outcomes of 5+ have been converted to 4+ for display and analytic purposes.

Alphabetic descriptions of results such as "increased" or "decreased" are ignored.

score as the covariate, treatment and center as main effects, and a treatment-by-center interaction term."

For multiple comparisons, the plan was to test each dose against placebo at .05 if the overall test was significant. If it was not, then a Bonferroni-Holm (closed testing) procedure using .025 and .05 as the nominal alphas would be followed.

## **Results**

A total of 202 patients were randomized among 11 centers to 3 treatment arms (N=66 placebo; N=69 100mg; N=67 200mg). **Figure 1** displays the patient flow during the trial. Approximately 60% of withdrawals were to adverse events and/or intercurrent illness. **Table 1** displays the baseline demographics and prognostic conditions of the groups. **All patients (18 with 6/group) in center 14588 were excluded from the analysis due to multiple protocol violations and insufficient self-rating of OFF/ON time.** In the intent-to-treat analysis, after exclusion of these 18, there were another (evenly distributed) 14 patients who did not have any diary data to carry forward to 3 months. Only 9 dropouts carried forward data to 3 months. Ultimately, there was data for 55 placebo, 59 100mg, and 56 200mg patients. **Table 2** and the accompanying figure display the results for ON and OFF time. Note the endpoint is % of waking day. The data indicate a treatment difference between the 200mg group and placebo of about 1.75 hours (11% x 16 waking hours) for OFF time and 1.5 hours for ON time. The 100mg group was not statistically different from placebo.

This reviewer checked these results by analyzing the simple change from baseline not taking into account sleep time and found similar results with low p-values for 200mg vs placebo, borderline results for 100mg and no statistical difference between 100mg and 200mg. Treatment differences were similar in that the estimates for both OFF and ON time were between 1.5 and 2 hours/day. The median sleep time at 3 months was 2 hours/day.

**Table 3** displays the results for all endpoints. Both doses produced statistically significant results for decrease in L-DOPA usage and the Investigator's Global Assessment of efficacy at 3 months. Between 60% and 80% of tolcapone patients showed improvement in Severity of Parkinson's Disease while 30% of placebo patients did. The respective proportions for improvement of Wearing-Off Phenomenon were 70%-95% vs 37% and the respective proportions for Overall Severity were Efficacy vs 42%. There were no statistical differences on quality of life (SIP) or the UPDRS.

## **Trial NZ14655D**

This trial was similar in design to NZ14654D. It randomized 177 patients among 24 centers in Europe. Endpoints were the same with the primary analysis also at 3 months. **Figure 2** displays the patient flow of the trial and **Table 4** displays the baseline prognostic and demographic factors

for each treatment group. Table 5 displays the results of the OFF/ON diary data. In this trial, 100mg was significantly different for both Off and On times, whereas 200mg was significant only for On time. Table 6 displays the results for all endpoints. As in the previous trial, L-DOPA was spared more while on tolcapone compared to placebo and the Investigator Global Assessment was significant. This time, however, the 200 mg dose was significant on the SIP total, the UPDRS total and the UPDRS motor score.

#### **Trial 14971D**

This trial was similar in design to the other two trials NZ19654D and NZ14655D. Two hundred fifteen (215) patients in the US were randomized among 15 centers. Endpoints were the same with the primary analysis at 6 weeks rather than 3 months. Figure 3 displays the patient flow of the trial and Table 7 displays the baseline prognostic and demographic factors for each treatment group. Table 8 displays the results of the OFF/ON diary data. In this trial, both doses (100mg, 200mg) were significantly different for both Off and On times. Table 9 displays the results for all endpoints. As in the previous trials, L-DOPA was spared more while on tolcapone compared to placebo and the Investigator Global Assessment was significant. There were no positive statistical results on either the UPDRS or the SIP.

#### **Trial BZ14115**

This European trial in non-fluctuating patients receiving l-dopa randomized 97 patients among 15 investigators in 7 countries to either placebo:N=33, 200mg:N=32 or 400mg:N=32. The change in l-dopa dose to week 6 was the primary endpoint. The sample size was planned for nearly a 100% chance of finding a 30% difference in the change of total daily l-dopa dose between placebo and each Tasmar dose group. Figure 4 displays the patient flow and Table 10 displays the baseline demographic and prognostic factors in the groups. Table 11 displays the protocol-specified analysis using ANOVA on the percent changes from baseline. An ANCOVA on the actual changes produced similar results. Although there was nominal significance for both dose groups, there were no statistically significant differences after using the multiple comparison procedure. Table 12 displays the results for number of daily intakes and Table 13 indicates no significance with respect to the total of scales I, II, and III of UPDRS or the components themselves except for ADL/ON at the 200mg dose.

#### **Trial NZ14653**

This US/Canadian trial randomized 298 patients among 20 centers to either placebo:N=102, 100mg: N=98, or 200mg: N=98. Patients had never experienced a wearing-off effect from l-dopa. The primary efficacy endpoint was the Subscale II (Activities of Daily Living/ON) of the UPDRS and the primary timepoint for analysis was six months. Other endpoints included Subscales I (Mentation, Behavior & Mood, III (Motor) and IVb(Clinical Fluctuations). Figure 5 and Table 14 display the patient flow and baseline characteristics of the treatment groups, respectively. Table 15 displays the results for the UPDRS. Both doses reached statistical

significance for total, ADL/ON and motor subscales. **Figure 6** displays the LOCF plot of the ADL/ON score over time. The sponsor found a treatment by baseline interaction which manifested itself by a larger treatment difference occurring among those with more ADL impairment at baseline (ADL score greater than 6). Treatment effects were not demonstrated for those with baseline score less than 7. **Table 16** summarizes results on all endpoints.

### Discussion and Conclusions

Taken together, the 3 trials in fluctuating patients (NZ14654, NZ14655, NN14971) provide statistical evidence that Tasmar decreases the amount of OFF time. It appears that both 100mg and 200mg are effective. However, these trials fail to demonstrate statistical evidence of improvement on any aspect of the UPDRS.

In non-fluctuating patients, **Trial BZ14115** produced nominal but not corrected statistical significance on its primary endpoint, reduction of l-dopa use but was only **6 weeks in duration**. **Trial NZ14653**, 3 times as large as the former and **6 months in duration**, provides statistical evidence of l-dopa reduction and its primary endpoint, improvement on the ADL/ON scale of the UPDRS. It is interesting to note that 200mg is statistically significant for ADL/ON in both studies, whereas the 400mg group in **Trial BZ14115** was essentially the same as placebo. It may also be relevant that in this smaller study, the significance for ADL/ON for the 200mg tid dose was the **only** statistical significance for any of the eight (8) UPDRS analyses. Recall that its primary endpoint was reduction of l-dopa. Consequently, it is doubtful that one can use study **Trial BZ14115** to support the efficacy of 200mg for three reasons: 1) a possibly spurious signal amid all the noise, 2) the disparity of length of treatment between the two trials, and 3) the lack of explanation of the complete failure of 400mg.

As a supplementary analysis, the division requested AUC analyses of UPDRS total, mood scale and motor scale for the 5 studies. By design, these analyses were appropriate for only studies NZ14653 (non-fluctuating patients), NZ14654 (fluctuating patients), and NZ14655 (fluctuating patients). **Results of all analyses were very similar to those which used only the last observation on each patient as reported in the study reports.**



David Hoberman, Ph.D.  
Mathematical Statistician

Concur: Dr. Sahlroot JTS 1/3/97

Dr. Chi *Chi*  
1/13/97

cc:

NDA#20-667

HFD-120/Dr. Leber

HFD-120/Dr. Katz

HFD-120/Dr. Tresley

HFD-120/Mr. Purvis

HFD-120/Ms. Wheelous

HFD-344/Dr. Lisook

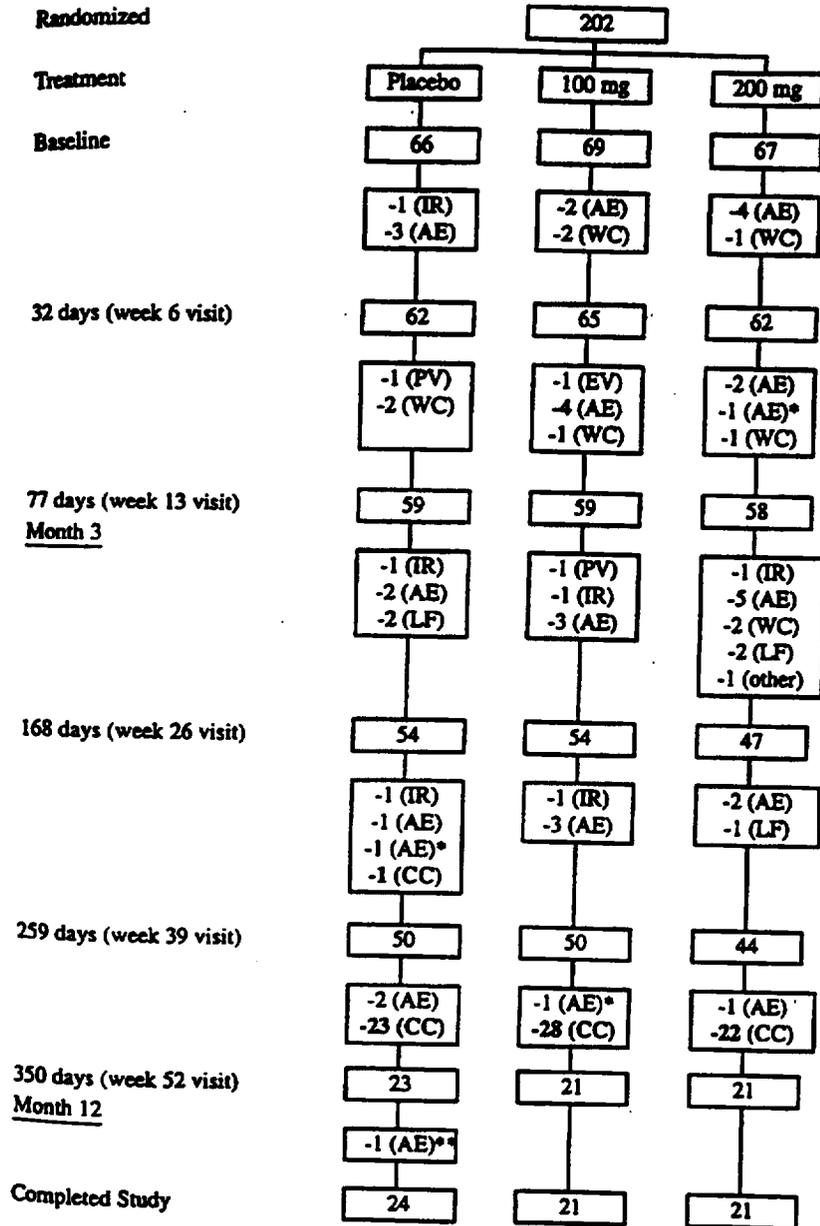
HFD-710/Dr. Chi

HFD-710/Dr. Sahlroot

HFD-710/Dr. Hoberman

HFD-710/chron

Figure 1 (654)



\*patient died after withdrawing from the study  
 \*\*patient withdrew during time window for week 52 visit.

Table 1 (654)

**BEST POSSIBLE COPY****Summary of Baseline Demographic Data for the ITT Population**

Parameter	Placebo N = 66	Tolcapone tid	
		100 mg N = 69	200 mg N = 67
Sex - No. (%)			
Males	47 ( 71)	40 ( 58)	52 ( 78)
Females	19 ( 29)	29 ( 42)	15 ( 22)
Age (years)			
Mean	65	63	64
SD	10	9	9
Range	42 - 87	44 - 85	43 - 84
Weight (kg)			
Mean	77	73	76
SD	14	19	14
Range	48 - 111	38 - 120	45 - 110
Height (cm)			
Mean	174	173	174
SD	11	12	11
Range	144 - 197	151 - 197	146 - 195
Race - No. (%)			
Caucasian	64 ( 97)	63 ( 91)	66 ( 99)
Oriental	0 ( 0)	2 ( 3)	0 ( 0)
Other	2 ( 3)	4 ( 6)	1 ( 1)

**Summary of the Key Baseline Characteristics of Parkinson's Disease**

Parameter	Placebo	Tolcapone tid	
		100 mg	200 mg
*Duration of disease			
Mean	10.5	11.0	11.1
SD	5.82	5.44	5.41
Range	<del>          </del>	<del>          </del>	<del>          </del>
N	66	69	67
*Duration of previous L-DOPA treatment			
Mean	8.2	8.9	8.7
SD	4.52	4.95	4.84
Range	<del>          </del>	<del>          </del>	<del>          </del>
N	66	69	67
Schwab and England Scale (ON)			
Mean	88.4	87.3	84.5
SD	10.19	11.88	12.02
Range	<del>          </del>	<del>          </del>	<del>          </del>
N	63	68	66
Schwab and England Scale (OFF)			
Mean	62.5	63.1	57.7
SD	19.90	20.02	18.38
Range	<del>          </del>	<del>          </del>	<del>          </del>
N	63	68	66
Hoehn and Yahr Stage (ON) - n (%)			
0	3 ( 5)	2 ( 3)	2 ( 3)
1	3 ( 5)	3 ( 4)	3 ( 4)
1.5	6 ( 9)	4 ( 6)	2 ( 3)
2	25 ( 38)	31 ( 45)	25 ( 37)
2.5	12 ( 18)	9 ( 13)	10 ( 15)
3	12 ( 18)	18 ( 26)	20 ( 30)
3.5	0 ( 0)	1 ( 1)	1 ( 1)
4	4 ( 6)	1 ( 1)	4 ( 6)
Total	65	69	67
UPDRS: Total Score			
Mean	28.0	26.6	31.6
SD	17.13	12.63	20.33
Range	<del>          </del>	<del>          </del>	<del>          </del>
N	64	68	66

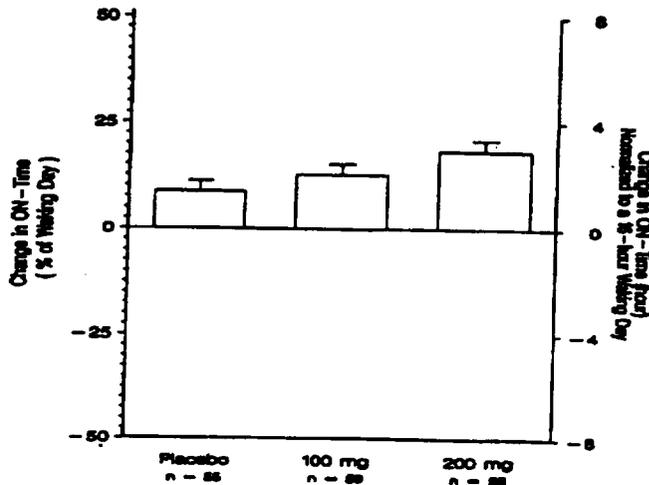
\* Duration in years

Table 2 (654)

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**Change in ON-Time between Baseline and Month 3.**

ITT population; LOCF analysis. The figure shows least-squares means + SEM based on ANCOVA. ON-time is presented as a percentage of the waking day. In order to visualize ON-time in hours, the right-hand y-axis has been labeled with a scale corresponding to a 16 hour waking day.



**Summary of OFF/ON-Time**

Rating	Scheduled Assessment Visit	Tolcapone t1d					
		Placebo	100 mg	200 mg			
		N	mean (SE)	N	mean (SE)	N	mean (SE)
Percent OFF	Baseline	55	38.9 (1.9)	59	39.8 (1.8)	56	36.8 (1.9)
	Month 3	55	31.1 (2.5)	59	27.1 (2.4)	56	19.0 (2.5)
	Change (Mo3-BL)	55	-7.8 (2.3)	59	-12.2 (2.2)	56	-18.8 (2.3)
	Treatment Difference			-4.4		-11.0	
	95% CI		(-10.8, 1.9)		(-17.5, -4.6)		
	P-value [0.0038]		0.1685		< 0.001 **		
Percent ON	Baseline	55	54.5 (2.2)	59	50.4 (2.1)	56	55.6 (2.2)
	Month 3	55	62.8 (2.9)	59	63.9 (2.9)	56	73.8 (2.9)
	Change (Mo3-BL)	55	8.6 (2.5)	59	12.6 (2.5)	56	18.2 (2.6)
	Treatment Difference			3.9		9.6	
	95% CI		(-3.0, 10.9)		(2.6, 16.7)		
	P-value [0.0282]		0.2665		0.0079 *		

Average of the last 3 diaries available prior to the given visits.  
 NOTE: The Treatment Difference is an estimate of the difference (Tolcapone - Placebo) in the change from baseline at month 3. 95% confidence intervals and P-values (unadjusted) are also provided for the treatment difference. The P-value for overall comparison is presented in brackets. '\*' indicates P < 0.15 for treatment-by-center interaction. '\*\*' indicates P < 0.05 and '\*\*\*' indicates P < 0.01 for pairwise comparison with placebo after adjustment for multiple comparisons.

Table 3 (654)

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**Summary of Efficacy and Total Daily L-DOPA Dose at Month 3**

The results show changes between baseline and month 3. ITT population, LOCF analysis. The values shown for L-DOPA, ON/OFF-time and the subscales of the UPDRS are least-squares means  $\pm$  SEM. The values for the investigator's global assessments (IGA) are % of patients showing improvement.

Tolcapone dose (mg)	L-DOPA change (mg)	Wearing-off / Fluctuations			Motor function	
		ON-time (%)	OFF-time (%)	IGA Wearing-off (%)	IGA Severity (%)	UPDRS Motor
Placebo	15.5 $\pm$ 22.5	8.6 $\pm$ 2.5	-7.8 $\pm$ 2.3	37	32	-0.4 $\pm$ 0.9
100	-166.3 $\pm$ 22.3**	12.6 $\pm$ 2.5	-12.2 $\pm$ 2.2	68**	60**	-1.9 $\pm$ 0.9
200	-207.1 $\pm$ 22.6**	18.2 $\pm$ 2.6*	-18.8 $\pm$ 2.3**	93**	79**	-2.0 $\pm$ 0.9

Tolcapone dose (mg)	Quality of life						Additional measures of efficacy	
	UPDRS ADL-ON	UPDRS Mood	SIP Total	SIP Physical	SIP Psychosocial	BDI	UPDRS Total	IGA Efficacy (%)
Placebo	-0.3 $\pm$ 0.5	0.0 $\pm$ 0.2	-2.2 $\pm$ 1.0	-2.4 $\pm$ 1.1	-2.0 $\pm$ 1.3	-0.8 $\pm$ 0.8	-0.7 $\pm$ 1.2	42
100	-0.8 $\pm$ 0.4	0.3 $\pm$ 0.2	-0.4 $\pm$ 1.0	-0.1 $\pm$ 1.1	-0.7 $\pm$ 1.3	-0.3 $\pm$ 0.7	-2.4 $\pm$ 1.1	71**
200	0.2 $\pm$ 0.4	0.2 $\pm$ 0.2	-0.3 $\pm$ 1.1	-0.8 $\pm$ 1.2	0.8 $\pm$ 1.3	0.4 $\pm$ 0.7	-1.7 $\pm$ 1.2	91**

\*P < 0.05, \*\*P < 0.01. For pairwise comparison with placebo after adjusting for multiple comparisons

Table 4 (655)

**BEST POSSIBLE COPY****Summary of Baseline Demographic Data for the ITT Population**

Parameter	Placebo	Tolcapone tid	
	N = 58	100 mg N = 60	200 mg N = 59
Sex - No. (%)			
Males	35 (60)	31 (52)	33 (56)
Females	23 (40)	29 (48)	26 (44)
Age (years)			
Mean	64	62	63
SD	8	10	9
Range	42 - 81	39 - 81	37 - 78
Weight (kg)			
Mean	68	70	70
SD	12	14	13
Range	43 - 94	44 - 115	44 - 100
Height (cm)			
Mean	169	169	169
SD	10	9	10
Range	148 - 201	154 - 190	149 - 195
Race - No. (%)			
Caucasian	58 (100)	60 (100)	58 (98)
Black	0 (0)	0 (0)	1 (2)

**Summary of the Key Baseline Characteristics of Parkinson's Disease ITT population**

Parameter	Placebo	Tolcapone tid	
		100 mg	200 mg
*Duration of disease			
Mean	10.5	9.3	10.2
SD	5.54	5.02	4.79
Range			
N	58	60	59
*Duration of previous L-DOPA treatment			
Mean	9.1	7.8	8.6
SD	5.10	5.07	4.54
Range			
N	58	60	59
Hoehn and Yahr Stage (ON) - n (%)			
0			
1	3 (5)	2 (3)	0 (0)
1.5	3 (5)	6 (10)	1 (2)
2	3 (5)	1 (2)	3 (5)
2.5	14 (24)	22 (37)	26 (44)
3	13 (22)	10 (17)	7 (12)
4	20 (34)	18 (30)	20 (34)
Total	2 (3)	1 (2)	2 (3)
	58	60	59
Hoehn and Yahr Stage (OFF) - n (%)			
1			
1.5	1 (2)	1 (2)	1 (2)
2	0 (0)	3 (5)	1 (2)
2.5	1 (2)	4 (7)	1 (2)
3	7 (12)	9 (15)	6 (10)
4	15 (26)	14 (23)	23 (39)
5	28 (48)	25 (42)	20 (34)
Total	6 (10)	4 (7)	7 (12)
	58	60	59
UPDRS: Total Score			
Mean	35.5	33.4	33.9
SD	18.13	16.70	17.97
Range			
N	58	58	59
UPDRS: Mentation			
Mean	2.8	2.2	2.4
SD	2.14	1.60	
Range			
N	58	58	59

Table 4 (cont) (655)

Parameter	Placebo	Telcapone tid	
		100 mg	200 mg
UPDRS: Motor			
Mean	24.4	23.3	23.6
SD	11.76	12.18	13.01
Range	<del>          </del>	<del>          </del>	<del>          </del>
N	58	58	59
UPDRS: ADL (ON)			
Mean	8.3	7.9	7.9
SD	6.99	5.20	5.54
Range	<del>          </del>	<del>          </del>	<del>          </del>
N	58	58	59
UPDRS: ADL (OFF)			
Mean	21.7	20.6	20.2
SD	8.71	8.17	7.97
Range	<del>          </del>	<del>          </del>	<del>          </del>
N	58	58	59

\* Duration in years

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Figure 2 (655)

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**Patient Disposition Flowchart**

The numbers of days completed on the left of the flowchart are the lower limits of the time windows for the assessment visits shown in parentheses. Patients withdrawn from the study are indicated as negative numbers. Reasons for withdrawal from the study are given using the following abbreviations: AE, adverse event/intercurrent illness; EV, entry violation; IR, insufficient response; PV, other protocol violation; WC, withdrawal of consent; LF, lost to follow-up; CC, common closing date.

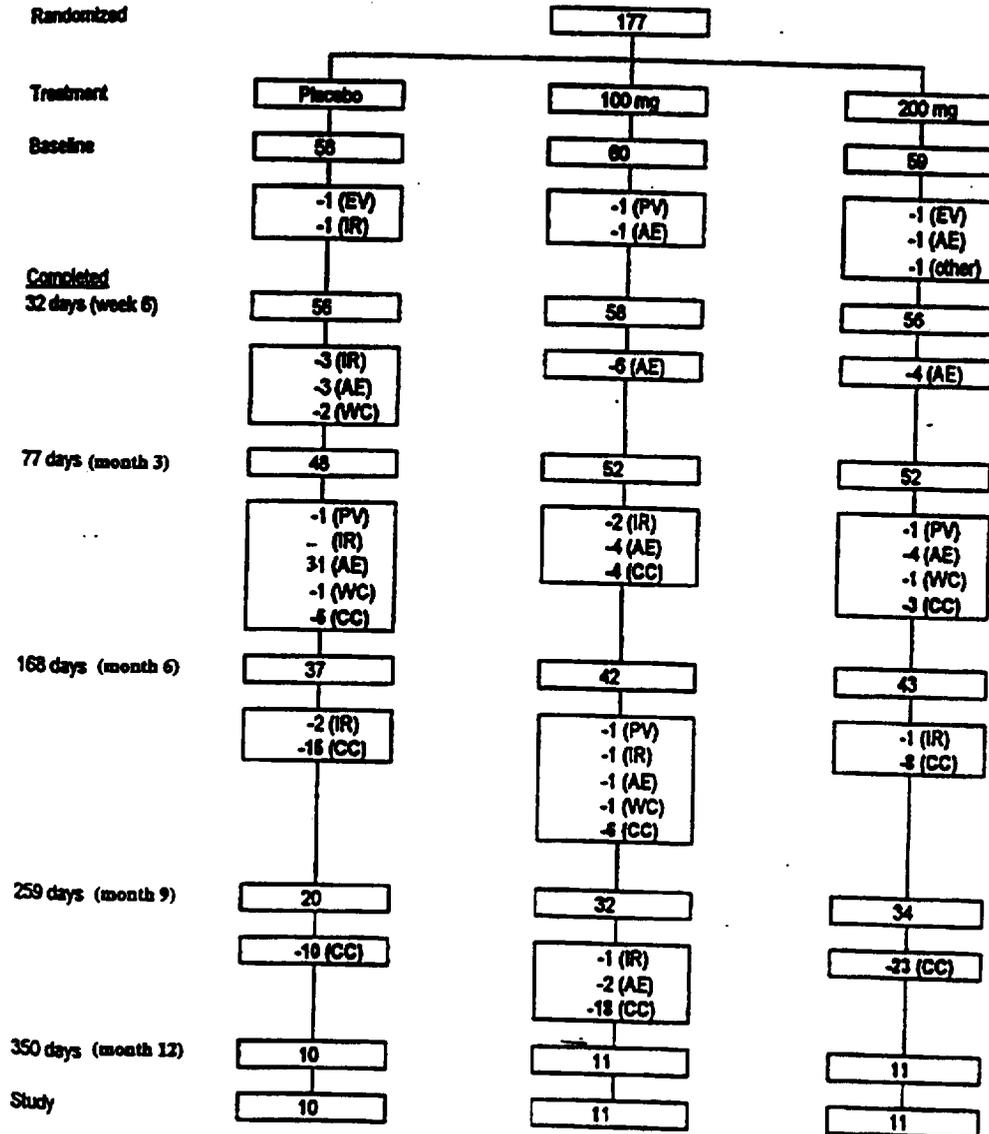


Table 5 (655) —

**BEST POSSIBLE COPY****Summary of OFF/ON-Time**

ITT population; LOCF analysis. The table shows least-squares means  $\pm$  SEM based on ANCOVA. OFF/ON-time is presented as a percentage of the waking day.

Rating	Scheduled Assessment Visit	Placebo		100 mg		200 mg	
		N	mean (SE)	N	mean (SE)	N	mean (SE)
Percent OFF	Baseline	51	37.8 (2.4)	56	40.3 (2.1)	55	37.4 (2.2)
	Month 3	51	33.5 (3.0)	56	27.0 (2.7)	55	27.7 (2.7)
	Change (Mo3-BL)	51	-4.2 (2.3)	56	-12.7 (2.1)	55	-9.8 (2.1)
	Treatment Difference			-8.5		-5.5	
	95% CI			(-14.7, -2.3)		(-11.8, 0.7)	
	P-value [0.0270]+			0.0077 *		0.0811	
Percent ON	Baseline	51	53.4 (2.8)	56	50.8 (2.5)	55	52.4 (2.5)
	Month 3	51	52.6 (3.6)	56	62.0 (3.3)	55	63.3 (3.3)
	Change (Mo3-BL)	51	-0.7 (2.8)	56	10.8 (2.6)	55	10.8 (2.6)
	Treatment Difference			11.5		11.5	
	95% CI			(4.0, 19.1)		(4.0, 19.1)	
	P-value [0.0037]			0.0031 **		0.0032 **	

\* Average of the last 3 diaries available prior to the given visit.

NOTE: All p-values shown are unadjusted. Statistical significance of treatment differences (tolcapone-placebo) was determined after adjustment for multiple comparisons and is indicated by asterisks placed beside treatment difference p-values: '\*' indicates statistical significance at the  $p < 0.05$  level and '\*\*' indicates statistical significance at the  $p < 0.01$  level. The p-value for the overall comparison is presented in brackets.

'+' indicates  $p < 0.15$  for treatment-by-center interaction.

Table 6 (655)

**Summary of Efficacy and Total Daily L-DOPA Dose**

The values shown for total daily L-DOPA dose, OFF/ON-time (primary parameters), UPDRS and SIP are least-squares means  $\pm$  SEM. The values for the investigator's global assessments (IGA) are incidences of patients showing improvement. OFF-time presented as % baseline was calculated as  $100 \times \text{change/baseline}$ .

Tolcapone dose (mg)	L-DOPA dose (mg)	Wearing-off/Fluctuations				IGA Wearing-off (%)	Motor function	
		OFF-time		ON-time			IGA Severity (%)	UPDRS Motor
		% waking day	% baseline	% waking day	% baseline			
Placebo	-29 $\pm$ 26.2	-4.2 $\pm$ 2.3	-11.1	-0.7 $\pm$ 2.8	-1.3	37	29	-2.1 $\pm$ 1.1
100	-109 $\pm$ 23.4*	-12.7 $\pm$ 2.1*	-31.5	10.8 $\pm$ 2.6**	21.3	74**	75**	-4.2 $\pm$ 1.0
200	-122 $\pm$ 23.9**	-9.8 $\pm$ 2.1	-26.2	10.8 $\pm$ 2.6**	20.6	75**	73**	-6.5 $\pm$ 1.0**

Tolcapone dose (mg)	Quality of life					Additional measures of efficacy	
	UPDRS ADL-ON	UPDRS Mood	SIP Total (%)	SIP Physical (%)	SIP Psychosocial (%)	UPDRS Total	IGA Overall efficacy (%)
Placebo	-0.5 $\pm$ 0.4	-0.2 $\pm$ 0.2	-0.9 $\pm$ 0.9	-2.2 $\pm$ 1.2	1.2	-2.8 $\pm$ 1.4	37
100	-0.9 $\pm$ 0.3	0.1 $\pm$ 0.2	-1.9 $\pm$ 0.9	-3.2 $\pm$ 1.1	-1.3	-4.8 $\pm$ 1.3	70**
200	-1.3 $\pm$ 0.3	-0.1 $\pm$ 0.2	-4.2 $\pm$ 0.8*	-5.0 $\pm$ 1.1	-4.7**	-7.9 $\pm$ 1.3**	78**

\*  $P < 0.05$  for difference from placebo

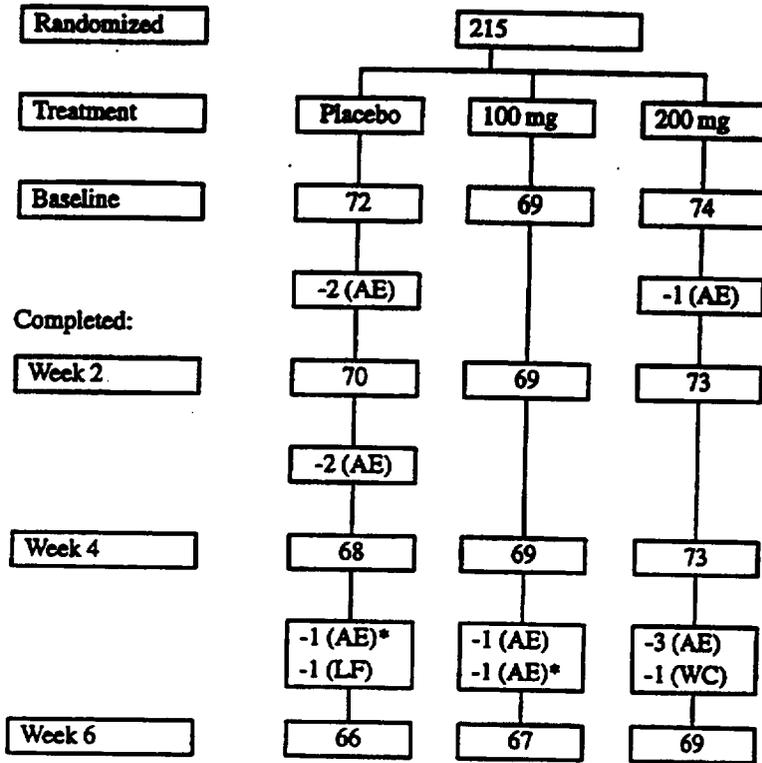
\*\*  $P < 0.01$  for difference from placebo

Figure 3 (971)

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**Patient Disposition Flowchart**

*Patients completing the study as assessed by the investigators. Withdrawals are indicated as negative numbers. AE, adverse event/intercurrent illness; LF, lost to follow-up; WC, withdrawal of consent;*



\* patient died (within 28 days) after withdrawing from study

Table 7 (971)

**BEST POSSIBLE COPY****Summary of Baseline Demographic Data for the ITT Population**

Parameter	Placebo N = 72	Telcapone tid	
		100 mg N = 69	200 mg N = 74
Sex - No. (%)			
Males	52 ( 72)	46 ( 67)	51 ( 69)
Females	20 ( 28)	23 ( 33)	23 ( 31)
Age (years)			
Mean	64	62	61
SD	8	12	10
Range	44 - 81	32 - 83	39 - 85
Weight (kg)			
Mean	74	72	75
SD	14	16	17
Range	42 - 102	41 - 107	42 - 142
Height (cm)			
Mean	174	173	175
SD	9	9	11
Range	151 - 195	154 - 192	146 - 197
Race - No. (%)			
Caucasian	68 ( 94)	68 ( 99)	69 ( 93)
Black	1 ( 1)	0 ( 0)	0 ( 0)
Oriental	1 ( 1)	0 ( 0)	2 ( 3)
Other	2 ( 3)	1 ( 1)	3 ( 4)

**Summary of the Key Baseline Characteristics Parkinson's Disease**

Parameter	Placebo	Telcapone tid	
		100 mg	200 mg
*Duration of disease			
Mean	10.6	10.5	10.6
SD	5.24	4.77	4.64
Range			
N	72	69	74
*Duration of previous L-DOPA treatment			
Mean	8.6	8.3	8.7
SD	5.19	4.63	4.83
Range			
N	72	69	74
Hoehn and Yahr Stage (ON) - n (%)			
0	0 ( 0)	1 ( 1)	0 ( 0)
1	2 ( 3)	2 ( 3)	1 ( 1)
1.5	4 ( 6)	2 ( 3)	3 ( 4)
2	44 ( 61)	42 ( 61)	48 ( 66)
2.5	10 ( 14)	10 ( 14)	10 ( 14)
3	11 ( 15)	10 ( 14)	9 ( 12)
4	0 ( 0)	2 ( 3)	2 ( 3)
5	1 ( 1)	0 ( 0)	0 ( 0)
Total	72	69	73
UPDRS: Total Score			
Mean	26.5	25.9	27.4
SD	13.50	13.92	14.24
Range			
N	72	69	73

\* Duration in years

Table 8 (971)

BEST POSSIBLE

**Summary of ON/OFF-Time**

ITT population; LOCF analysis. The table shows least-squares means (SEM) based on ANCOVA. ON/OFF-time is presented as a percentage of the waking day.

Rating	Scheduled Assessment Visit	Placebo		Tolcapone tid			
		N	mean (SE)	100 mg N mean (SE)	200 mg N mean (SE)		
Percent OFF	Baseline	72	40.8 (1.6)	69	40.8 (1.6)	73	42.5 (1.6)
	Week 6	72	30.8 (2.2)	69	28.7 (2.2)	73	26.6 (2.2)
	Change (Wk6-BL)	72	-2.2 (1.9)	69	-12.3 (1.9)	73	-15.6 (1.9)
Treatment Difference				-10.1		-13.4	
95% CI				(-15.5, -4.8)		(-18.7, -8.1)	
p value [ $<0.001$ ]				$<0.001$ **		$<0.001$ **	
Percent ON	Baseline	72	56.1 (1.6)	69	56.7 (1.6)	73	56.1 (1.6)
	Week 6	72	58.1 (2.2)	69	69.5 (2.3)	73	70.2 (2.2)
	Change (Wk6-BL)	72	2.0 (1.8)	69	12.9 (1.8)	73	14.1 (1.8)
Treatment Difference				10.9		12.1	
95% CI				(5.9, 15.8)		(7.2, 17.0)	
p value [ $<0.001$ ]				$<0.001$ **		$<0.001$ **	

Average of the last 3 diaries available prior to the given visit.

NOTE: The Treatment Difference is an estimate of the difference (Tolcapone - Placebo) in the change from baseline at week 6. 95% confidence intervals and p values (unadjusted) are also provided for the treatment difference. The p value for overall comparison is presented in brackets. '+' indicates  $P < 0.15$  for treatment-by-center interaction. '\*\*' indicates  $P < 0.05$  and '\*\*\*' indicates  $P < 0.01$  for pairwise comparison with placebo after adjustment for multiple comparisons.

Table 9 (971)

**Summary of Efficacy Results**

The results show changes between baseline and week 6. ITT population, LOCF analysis. The values shown for L-DOPA, ON/OFF-time and the subscales of the UPDRS are least-squares means  $\pm$  SEM. The values for the investigator's global assessments (IGA) are % of patients showing improvement.

Tolcapone dose (mg)	L-DOPA dose change (mg)	Wearing-off/Fluctuations			Motor functions	
		ON-time (%)	OFF-time (%)	IGA wearing-off (%)	IGA severity (%)	UPDRS III (motor)
Placebo	-0.5 $\pm$ 20.1	2.0 $\pm$ 1.8	-2.2 $\pm$ 1.9	27	21	-1.2 $\pm$ 0.7
100	-185.5 $\pm$ 20.6**	12.9 $\pm$ 1.8**	-12.3 $\pm$ 1.9**	79**	69**	-2.3 $\pm$ 0.7
200	-251.5 $\pm$ 19.9**	14.1 $\pm$ 1.8**	-15.6 $\pm$ 1.9**	78**	80**	-2.4 $\pm$ 0.7

Tolcapone dose (mg)	Quality of Life (QOL)					Other	
	UPDRS II (ADL-ON)	UPDRS I (Mood)	SIP (Total)	SIP (Physical)	SIP (Psycho social)	UPDRS (Total)	IGA Efficacy (%)
Placebo	-0.7 $\pm$ 0.4	-0.3 $\pm$ 0.2	-1.5 $\pm$ 0.8	-1.1 $\pm$ 0.9	-2.2 $\pm$ 1.1	-2.2 $\pm$ 0.9	27
100	-0.4 $\pm$ 0.4	-0.2 $\pm$ 0.2	-2.7 $\pm$ 0.9	-2.9 $\pm$ 0.9	-2.7 $\pm$ 1.1	-3.0 $\pm$ 0.9	74**
200	-0.5 $\pm$ 0.4	0.0 $\pm$ 0.2	-3.0 $\pm$ 0.8	-2.6 $\pm$ 0.9	-2.8 $\pm$ 1.1	-3.1 $\pm$ 0.9	77**

\*\* $P < 0.01$ . For pairwise comparison with placebo after adjusting for multiple comparisons

Figure 4 (115)

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**Patient Disposition Flowchart**

Patients withdrawn from the study are indicated as negative numbers. NR, not randomized; AE, adverse event/intercurrent illness; IR, insufficient response; WC, withdrawn.

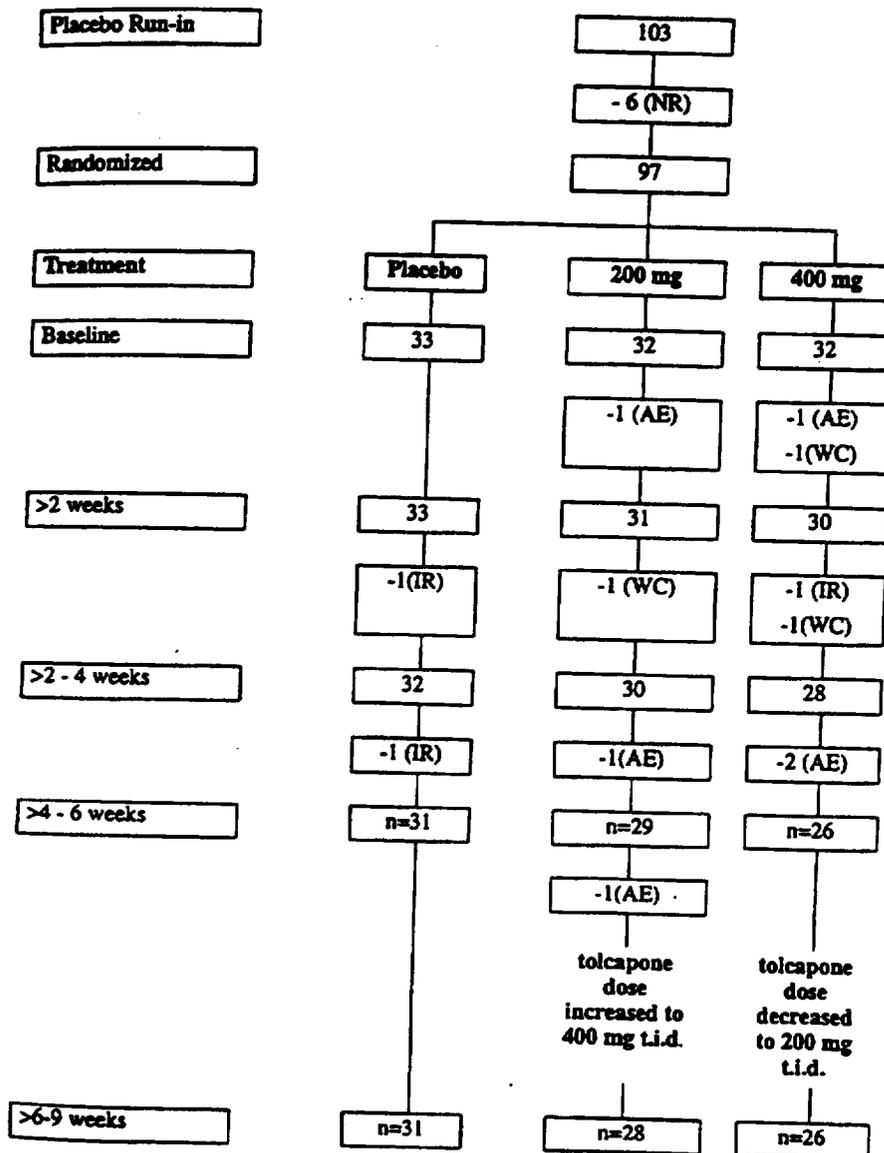


Table 10 (115)

Summary of Baseline Demographic Data  
ITT Population

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Parameter	Placebo N = 33	Tolcapone tid	
		200→400 mg N = 32	400→200 mg N = 32
Sex - No. (%)			
Males	19 (58)	17 (53)	26 (81)
Females	14 (42)	15 (47)	6 (19)
Age (years)			
Mean	66	66	68
SD	8	9	7
Range	48 - 83	47 - 83	49 - 79
Weight (kg)			
Mean	71	76	72
SD	16	14	12
Range	44 - 107	56 - 110	49 - 95
Height (cm)			
Mean	170	170	172
SD	10	9	10
Range	150 - 188	146 - 186	153 - 188
Race - No. (%)			
Caucasian	33 (100)	31 (97)	31 (97)
Black	0 (0)	0 (0)	1 (3)
Oriental	0 (0)	1 (3)	0 (0)

Summary of Key Baseline Characteristics of Parkinson's disease  
ITT Population

Parameter	Placebo	Tolcapone tid	
		200→400 mg	400→200 mg
*Duration of disease			
Mean	9.1	7.4	6.8
SD	6.46	2.89	3.68
Range			
N	33	32	32
*Duration of previous L-DOPA treatment			
Mean	6.6	6.1	5.5
SD	3.87	2.80	3.14
Range			
N	33	32	32
Hoehn and Yahr Stage (ON) - n (%)			
1	5 (15)	4 (13)	8 (25)
1.5	2 (6)	3 (9)	1 (3)
2	11 (33)	10 (31)	11 (34)
2.5	10 (30)	10 (31)	9 (28)
3	5 (15)	5 (16)	3 (9)
Total	33	32	32
Hoehn and Yahr Stage (OFF) - n (%)			
1	1 (9)	0 (0)	0 (0)
1.5	0 (0)	1 (7)	3 (19)
2	1 (9)	2 (14)	2 (13)
2.5	3 (27)	5 (36)	6 (38)
3	6 (55)	6 (43)	5 (31)
Total	11	14	16
UPDRS: Total Score			
Mean	34.8	31.3	28.4
SD	15.77	11.75	13.98
Range			
N	33	32	32
UPDRS: Mentation			
Mean	1.8	1.7	1.8
SD	1.92	1.35	1.63
Range			
N	33	32	32
UPDRS: Motor			
Mean	23.3	21.1	19.0
SD	11.68	9.96	9.68
Range			
N	33	32	32
UPDRS: ADL (ON)			
Mean	9.7	8.4	7.6
SD	5.06	3.54	4.80
Range			
N	33	32	32

\* Duration in years

Table 11 (115)

Table 5.2.2e.anova  
 Summary of L-DOPA Therapy [regular and MBS/CR combined] at Baseline and Follow-Up  
 Estimated Number of Daily Intakes and Total Dose (mg)  
 Estimated Means and Standard Error of the Means Based on Analysis of Variance  
 Intent-to-Treat Analysis: Last Observation Carried Forward

Scheduled Assessment Visit	Placebo N mean (sem)	Tolcapone tid	
		200→400 mg N mean (sem)	400→200 mg N mean (sem)
Overall (Madopar and Sinemet Combined)			
Total Daily Dose (mg)			
Baseline	33 597.1(33.4)	32 668.3(35.5)	32 715.3(35.5)
Week 6	33 499.3(32.9)	32 483.9(35.0)	32 520.0(35.0)
%Change (Wk6-BL)	33 -18.1( 3.1)	32 -27.1( 3.3)	32 -28.1( 3.3)
Treatment Difference		-9.0	-10.0
95% CI		( -18.0, -0.1)	( -18.9, -1.1)
P-value [0.0510]		0.0472	0.0285

NOTE : The Treatment Difference is an estimate of the difference (Tolcapone - Placebo) in the change from baseline at week 6. 95% confidence intervals and P-values (unadjusted) are also provided for the treatment difference. The P-value for overall comparison is presented in brackets. '+' indicates P < 0.15 for treatment-by-center interaction. '\*\*' indicates P < 0.05 and '\*\*' indicates P < 0.01 for pairwise comparison with placebo after adjustment for multiple comparison. Included are patients with assessments at both baseline and week 6.

Table 12 (115)

Table 5.2.2e.cmh  
 Summary of L-DOPA Therapy [regular and MBS/CR combined] at Week 6  
 Changes in the Number of Daily Intakes  
 All Patients: Intent-to-Treat, Last Observation Carried Forward

Parameter Scheduled Assessment Visit	Placebo	Tolcapone tid	
		200→400 mg	400→200 mg
Change in Number of Intakes			
Week 6			
Mean	-1.03	-1.28	-1.59
SD	1.07	1.05	1.04
N	33	32	32
Frequency Counts [n (%)]			
-4	0	0	1 ( 3)
-3	2 ( 6)	1 ( 3)	4 (13)
-2	12 (36)	16 (50)	14 (44)
-1	5 (15)	9 (28)	7 (22)
0	13 (39)	4 (13)	6 (19)
1	1 ( 3)	1 ( 3)	0
2	0	1 ( 3)	0
3	0	0	0
P-value [0.1116]		0.3207	0.0407

The P-values are computed using the Cochran-Mantel-Haenszel test and test the null hypothesis of no difference between each tolcapone group and placebo. The overall P-value appears in brackets. A '\*\*' indicates that the difference between treatment and placebo is significant at 0.05, and '\*\*' indicates a difference significant at 0.01. The Bonferroni-Holm method is used to adjust for multiple comparisons.

Table 13 (115)

Table 8.1.4e.anova  
 Summary of UPDRS I, II, and III (Mentation, ADL, and Motor) Items Subtotal Scores  
 Estimated Means and Standard Error of the Means  
 Based on Analysis of Variance  
 Intent-to-Treat: Last Observation Carried Forward

UPDRS	Scheduled Assessment Visit	Placebo		Tolcapone tid			
		N	mean (SE)	200→400 mg N	mean (SE)	400→200 mg N	mean (SE)
Total *	Baseline	31	35.1 (2.5)	30	31.5 (2.6)	28	28.0 (2.6)
	Week 6	31	33.9 (2.6)	30	26.9 (2.7)	28	27.7 (2.7)
	Change (Wk6-BL)	31	-1.2 (1.4)	30	-4.6 (1.5)	28	-0.3 (1.5)
	Treatment Difference				-3.4		0.9
	95% CI				( -7.5, 0.7)		( -3.2, 5.1)
	P-value [0.1033]				0.1055		0.6469
Motor	Baseline	31	23.1 (1.7)	30	21.7 (1.8)	28	18.4 (1.8)
	Week 6	31	21.4 (2.0)	30	18.2 (2.0)	28	17.8 (2.0)
	Change (Wk6-BL)	31	-1.7 (1.3)	30	-3.5 (1.4)	28	-0.7 (1.4)
	Treatment Difference				-1.8		1.1
	95% CI				( -5.5, 2.0)		( -2.7, 4.8)
	P-value [0.3313]				0.3514		0.5649
ADL-On	Baseline	31	10.1 (0.9)	30	8.2 (0.9)	28	7.8 (0.9)
	Week 6	31	10.4 (0.9)	30	7.1 (0.9)	28	8.0 (0.9)
	Change (Wk6-BL)	31	0.3 (0.4)	30	-1.1 (0.4)	28	0.1 (0.4)
	Treatment Difference				-1.4		-0.1
	95% CI				( -2.5, -0.2)		( -1.3, 1.0)
	P-value [0.0486]				0.0238 *		0.8134
Mentation	Baseline	31	1.9 (0.2)	30	1.6 (0.2)	28	1.7 (0.2)
	Week 6	31	2.2 (0.3)	30	1.6 (0.3)	28	2.0 (0.3)
	Change (Wk6-BL)	31	0.3 (0.2)	30	-0.0 (0.2)	28	0.3 (0.2)
	Treatment Difference				-0.3		-0.0
	95% CI				( -0.8, 0.3)		( -0.5, 0.5)
	P-value [0.5640]				0.3474		0.9965

\* Total of Motor, ADL (during ON), and Mentation Item Scores.  
 NOTE: The Treatment Difference is an estimate of the difference (Tolcapone - Placebo) in the change from baseline at week 6. 95% confidence intervals and P-values (unadjusted) are also provided for the treatment difference. The P-value for overall comparison is presented in brackets. '+' indicates P < 0.15 for treatment-by-center interaction. '\*\*' indicates P < 0.05 and '\*\*\*' indicates P < 0.01 for pairwise comparison with placebo after adjustment for multiple comparison. Included are patients with assessments at both baseline and week 6.

Figure 5 (653)

**Patient Disposition Flowchart**

Patients withdrawn from the study are indicated as negative numbers. AE, AE/intercurrent illness, D, death; EV, entry violation; IR, insufficient response; PV, other protocol violation; WC, withdrawal of consent; CC, common closing. Asterisks (\*) indicate those patients that were regarded by investigator as having completed the study despite their not having reached observed-cases time window for month 6 visit.

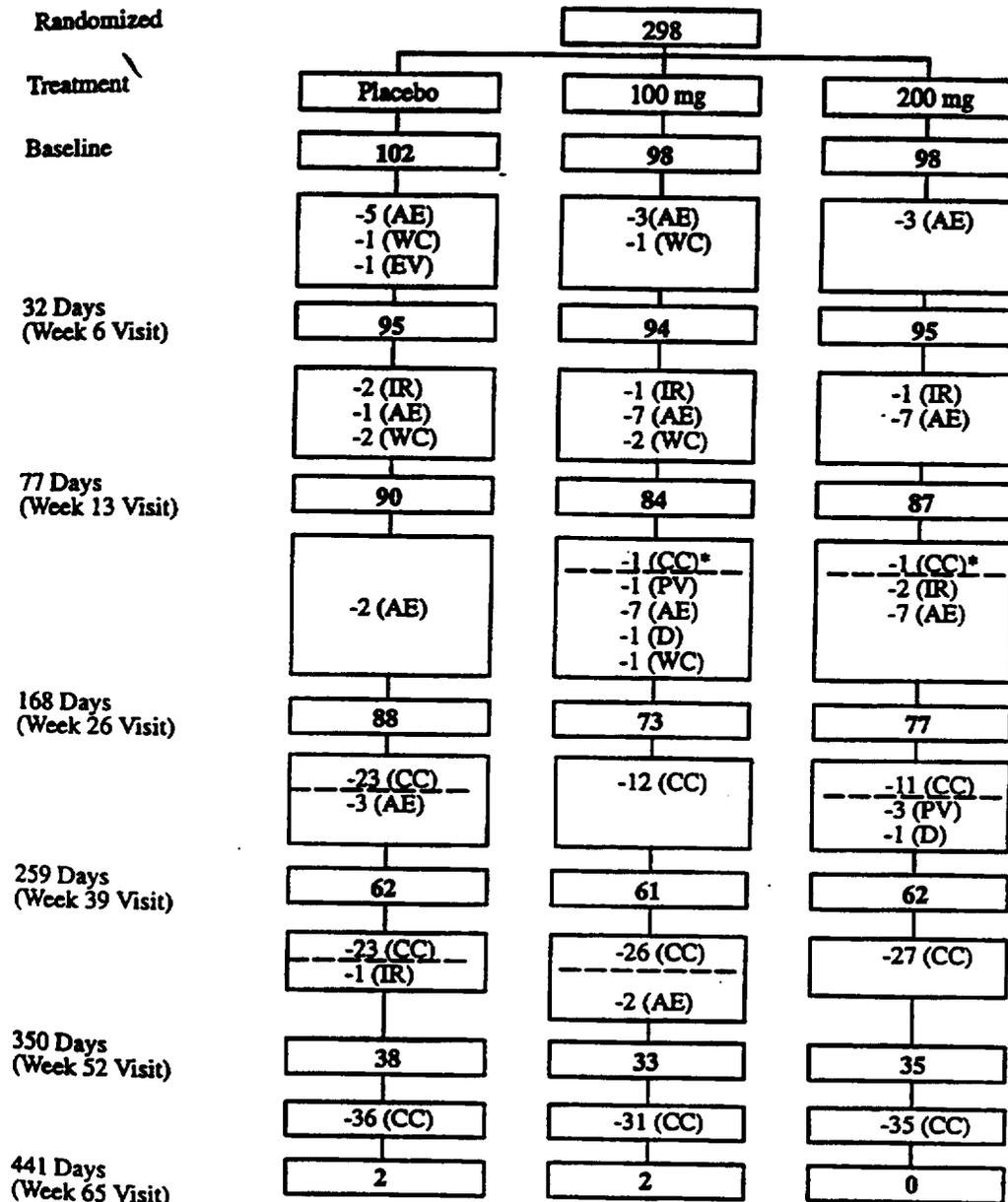


Table 14 (653)

Summary of Demographic Data - ITT Population

Parameter	Placebo N = 102	Tolcapone tid	
		100 mg N = 98	200 mg N = 98
Sex - No. (%)			
Males	62 (61)	63 (64)	58 (59)
Females	40 (39)	35 (36)	40 (41)
Age (years)			
Mean	67	67	63
SD	10	9	11
Range	38 - 84	39 - 84	35 - 83
Weight (kg)			
Mean	75	75	76
SD	15	12	17
Range	37 - 116	44 - 112	42 - 152
Height (cm)			
Mean	172	173	173
SD	9	11	11
Range	151 - 195	138 - 197	136 - 195
Race - No. (%)			
Caucasian	100 (98)	96 (98)	96 (98)
Black	0 (0)	1 (1)	1 (1)
Oriental	1 (1)	0 (0)	1 (1)
Other	1 (1)	1 (1)	0 (0)

Table 6. Summary of Key Baseline Characteristics of Parkinson's Disease - ITT Population

Parameter	Placebo	Tolcapone tid	
		100 mg	200 mg
*Duration of disease			
Mean	4.1	4.2	3.4
SD	2.44	2.51	2.00
Range			
N	102	98	98
*Duration of previous L-DOPA treatment			
Mean	2.2	2.3	2.0
SD	1.56	1.67	1.49
Range			
N	102	98	98
UPDRS: Total Score			
Mean	29.5	26.7	25.3
SD	13.19	13.91	11.47
Range			
N	102	98	97
UPDRS: Mentation			
Mean	1.3	1.2	1.2
SD	1.14	1.13	1.34
Range			
N	102	98	98
UPDRS: Motor			
Mean	19.6	17.9	16.0
SD	10.12	10.47	7.78
Range			
N	102	98	97

(Continued)

Table 14 (cont) (653)

**Summary of Key Baseline Characteristics of Parkinson's Disease - ITT Population**

Parameter	Placebo	Telcapone tid	
		100 mg	200 mg
<b>UPDRS: ADL (ON)</b>			
Mean	8.6	7.6	8.1
SD	3.80	4.26	3.90
Range			
N	102	98	98
<b>UPDRS Fluctuations (OFF): Predictable</b>			
No	91 ( 90)	88 ( 90)	90 ( 82)
Yes	10 ( 10)	10 ( 10)	8 ( 8)
Total	101	98	98
<b>UPDRS Fluctuations (OFF): Unpredictable</b>			
No	98 ( 97)	95 ( 97)	95 ( 97)
Yes	3 ( 3)	3 ( 3)	3 ( 3)
Total	101	98	98
<b>UPDRS Fluctuations (OFF): Suddenly</b>			
No	99 ( 98)	98 (100)	97 ( 99)
Yes	2 ( 2)	0 ( 0)	1 ( 1)
Total	101	98	98
<b>UPDRS Fluctuations (OFF): Proportion</b>			
None	76 ( 75)	77 ( 79)	80 ( 82)
1% - 25% of day	25 ( 25)	21 ( 21)	17 ( 17)
26% - 50% of day	0 ( 0)	0 ( 0)	1 ( 1)
Total	101	98	98
<b>UPDRS Dyskinesias: Duration</b>			
None	86 ( 85)	88 ( 90)	84 ( 86)
1% - 25% of day	13 ( 13)	10 ( 10)	13 ( 13)
26% - 50% of day	1 ( 1)	0 ( 0)	0 ( 0)
51% - 75% of day	0 ( 0)	0 ( 0)	1 ( 1)
76% - 100% of day	1 ( 1)	0 ( 0)	0 ( 0)
Total	101	98	98
<b>UPDRS Dyskinesias: Disability</b>			
Not Disabling	100 ( 99)	98 (100)	95 ( 97)
Mildly Disabling	1 ( 1)	0 ( 0)	3 ( 3)
Total	101	98	98
<b>UPDRS Dyskinesias: Painful Dyskinesias</b>			
None	101 (100)	98 (100)	95 ( 97)
Slight	0 ( 0)	0 ( 0)	2 ( 2)
Moderate	0 ( 0)	0 ( 0)	1 ( 1)
Total	101	98	98
<b>UPDRS Dyskinesias: Early Morning Dystonia</b>			
No	84 ( 83)	86 ( 88)	84 ( 86)
Yes	17 ( 17)	12 ( 12)	14 ( 14)
Total	101	98	98
<b>**Mini-Mental Status</b>			
Mean	29.0	29.0	29.2
SD	1.15	1.18	0.98
Range			
N	102	98	98

\*\* Parameter was recorded at Screening

ITT population; LOCF analysis. Tables shows least squares means and SEM based on ANCOVA.

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UPDRS	Scheduled Assessment Visit	Placebo		Tolcapone 100 mg		Tolcapone 200 mg	
		N	mean (SE)	N	mean (SE)	N	mean (SE)
Mood	Baseline	102	1.3 (0.1)	97	1.2 (0.1)	98	1.2 (0.1)
	Month 6	102	1.3 (0.1)	97	1.3 (0.1)	98	1.3 (0.1)
	Change (Mo6-BL)	102	0.0 (0.1)	97	0.1 (0.1)	98	0.1 (0.1)
	Treatment Difference			0.1		0.1	
	95% CI			(-0.2, 0.4)		(-0.2, 0.4)	
	P-value	[0.7983]		0.5570		0.5675	
ADL-On	Baseline	102	8.5 (0.4)	97	7.5 (0.4)	98	7.9 (0.4)
	Month 6	102	8.5 (0.4)	97	6.2 (0.4)	98	6.3 (0.4)
	Change (Mo6-BL)	102	0.1 (0.3)	97	-1.4 (0.3)	98	-1.6 (0.3)
	Treatment Difference			-1.4		-1.7	
	95% CI			(-2.3, -0.6)		(-2.6, -0.9)	
	P-value	<0.001		<0.001 **		<0.001 **	
Motor	Baseline	101	19.7 (0.8)	94	17.3 (0.8)	96	16.0 (0.8)
	Month 6	101	19.3 (0.9)	94	15.4 (0.9)	96	14.2 (0.9)
	Change (Mo6-BL)	101	0.1 (0.6)	94	-2.0 (0.6)	96	-2.3 (0.6)
	Treatment Difference			-2.1		-2.4	
	95% CI			(-3.9, -0.4)		(-4.2, -0.6)	
	P-value	[0.0143]		0.0183 *		0.0076 **	
Total †	Baseline	101	29.5 (1.1)	94	25.7 (1.1)	96	25.1 (1.1)
	Month 6	101	29.2 (1.2)	94	22.8 (1.3)	96	21.7 (1.2)
	Change (Mo6-BL)	101	0.1 (0.8)	94	-3.1 (0.8)	96	-3.7 (0.8)
	Treatment Difference			-3.2		-3.9	
	95% CI			(-5.6, -0.9)		(-6.2, -1.6)	
	P-value	[0.0024]		0.0069 **		0.0011 **	

Table 15 (653)

† Total of Motor, ADL (during ON), and Mentation Subcategories Scores.  
 NOTE: The Treatment Difference is an estimate of the difference (Tolcapone - Placebo) in the change from baseline at month 6. 95% confidence intervals and P-values (unadjusted) are also provided for the treatment difference. The P-value for overall comparison is presented in brackets. \* indicates P < 0.15 for treatment-by-center interaction. \*\* indicates P < 0.05 and \*\*\* indicates P < 0.01 for pairwise comparison with placebo after adjustment for multiple comparisons. Included are patients with assessments at both baseline and month 6.

**UPDRS Subscale II (ADL during ON) Score Over Time**

ITT population; LOCF analysis. The figure shows actual means and SEM.

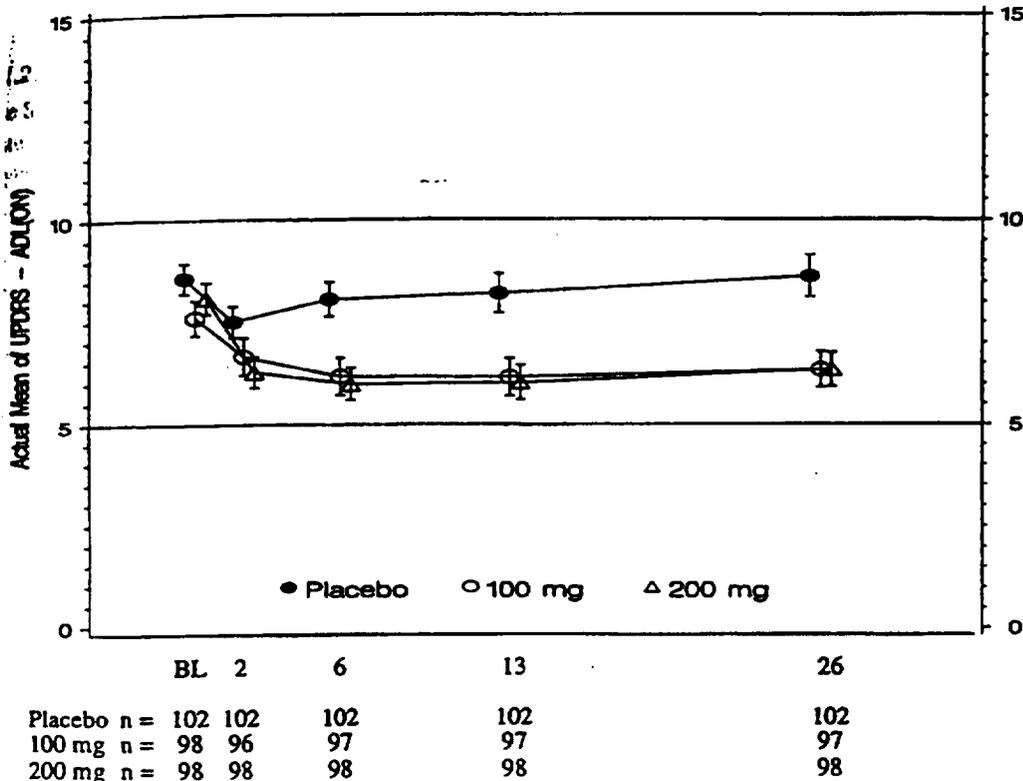


Figure 6 (653)

Table 16 (653)

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**Summary of Efficacy Results -Change from Baseline at Month 6 (Least-Squares Means  $\pm$  SEM)**

Ticagresor Dose (mg)	L-DOPA Dose change (mg)	ADL and QOL				Motor	Overall Severity
		ADL-ON (UPDRS II)	SIP Total	SIP Physical	SIP Psychosocial	Motor (UPDRS III)	Total (UPDRS I+II+III)
Placebo	46.6 $\pm$ 9.6	0.1 $\pm$ 0.3	0.4 $\pm$ 0.5	0.5 $\pm$ 0.4	0.0 $\pm$ 0.7	0.1 $\pm$ 0.6	0.1 $\pm$ 0.8
100	-20.8 $\pm$ 9.7**	-1.4 $\pm$ 0.3*	-0.9 $\pm$ 0.5	-1.2 $\pm$ 0.5**	-0.7 $\pm$ 0.7	-2.0 $\pm$ 0.6*	-3.1 $\pm$ 0.8**
200	-32.3 $\pm$ 9.6**	-1.6 $\pm$ 0.3**	-0.7 $\pm$ 0.5	-1.0 $\pm$ 0.4*	-1.2 $\pm$ 0.7	-2.3 $\pm$ 0.6**	-3.7 $\pm$ 0.8**

\*  $P < 0.05$ , \*\*  $P < 0.01$  for pairwise comparison with placebo after adjustment for multiple comparisons