CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20697

MEDICAL REVIEW(S)

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

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)

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1 MATERIALS USED IN REVIEW

Volume	*Submission Date*	*Material*
1	May 30, 1996	Index
2	May 30, 1996	Summary; Chemistry; Animal Toxicology; Human Pharmacokinetics/Pharmacodynamics; Labeling
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2 BACKGROUND

A. *Indication*

"TASMAR is indicated as an adjunct to levodopa/carbidopa in Parkinson's disease, in both nonfluctuating and fluctuating patients."

B. *Administrative History*

(i) Receipt of original IND . . . . . November 1, 1990
(ii) FDA letter: Phase II clinical hold . . . . . May 30, 1991
Additional preclinical data requested prior to the initiation of Phase II trials: in particular, data of Tolcapone administered concomitantly with Sinemet (one-month oral toxicity study in rats and dogs; and preclinical cardiovascular evaluation of the drug combination in rats and monkeys).
(iii) Phone conversation: clinical hold lifted . . . . . February 19, 1993
(iv) Safety Report . . . . . December 23, 1993
Possible ketamine-tolcapone interaction suggested by animal studies.
(v) Telecon . . . . . June 29, 1994
Addition of riboflavin to placebo tablets to cause yellow discoloration of the urine similar to that produced by the drug. According to the sponsor, "it was not expected that the blind would be compromised in Phase III, since the incidence of urine discoloration in Phase II studies was so low at the 200 mg tid dose" (v 1.2, p 153).
(vi FDA letter . . . . . August 16, 1994
FDA required the sponsor to conduct combination Segment II studies if the drug

combination was to be used in women of child-bearing potential.

(vii) End-of-Phase II Meeting . . . . . January 23, 1995
Combination Segment II studies with tolcapone and Sinemet should be performed in the rat and rabbits; mutagenicity testing should be performed on the combination regimen; further experiments on the possible interaction of tolcapone and ketamine be conducted.

(viii) Sponsor's response to statistical comments . . . . .April 6, 1995

(ix) Biopharm meeting with sponsor . . . . . .March 15, 1995

(x) Telecon with Biopharm . . . . . .July 20, 1995

(xi) Sponsor's statement on Tasmar tradename . . . . . .August 15, 1995
Response to the Labeling and Nomenclature Committee.

(xii)Pre-NDA meeting . . . . . December 12, 1995
Sponsor granted 2-year extension to expiry of Tasmar tablets packaged in OHDPE bottles as well as in PVDC blisters.

(xiii)Pre-NDA meeting . . . . . .February 15, 1996
Findings of renal tubulopathy and the incidence of renal tumors in 2-year carcinogenicity study would need to go into labeling.

(xiv)Telecon . . . . . .March 12, 1996
Sponsor should try to optimize the dissolution conditions used for tolcapone.

(xv)Follow-up IND Safety Report . . . . . March 20, 1996
According to the sponsor, "based on the large safety margin between the plasma levels that caused toxicity in animals and those at therapeutic doses in man, we do not consider the concomitant use of tolcapone and ketamine to represent a safety issue in man" (v 1.2, p 154).

C. *Related INDs and NDAs*

Entacapone, another COMT inhibitor proposed as an adjunct to levodopa/carbidopa therapy for the treatment of PD, is currently under file with the FDA as IND

D. *Proposed Directions for Use*

"Since TASMAR should be used with levodopa/carbidopa, the prescribing information for levodopa/carbidopa is also applicable to its concomitant use with TASMAR."

"TASMAR is contraindicated in patients with known hypersensitivity to tolcapone or any of its ingredients."

"DOSAGE AND ADMINISTRATION: TASMAR is administered orally tid. The first dose of the day . . . should be taken together with the first dose of the day of levodopa/carbidopa, and the subsequent doses of TASMAR should be given approximately 6 and 12 hours later.

"TASMAR may be taken with or without food.

"TASMAR can be combined with all pharmaceutical formulations of levodopa/carbidopa.

"Therapy with TASMAR should be initiated with 100 mg tid. . . .

"After adjustment of levodopa dose, an increase to 200 mg TASMAR tid is recommended, if, in the physician's opinion based upon the patient's response to 100 mg TASMAR tid, further benefit without limiting dopaminergic adverse reactions may be expected. After increasing to 200

mg TASMAR tid, a further readjustment of levodopa may be needed.

"The maintenance dose of TASMAR is 100 mg tid or 200 mg tid. . . .[T]he average reduction of daily levodopa dose was about 30% in those patients requiring a levodopa dose adjustment."

"PATIENTS WITH IMPAIRED RENAL OR HEPATIC FUNCTION: Patients with moderate cirrhosis of the liver should not be escalated to 200 mg TASMAR tid.

"No adjustment . . . is recommended for patients with mild to moderate renal impairment."

"CONTRAINDICATIONS: TASMAR should not be given in conjunction with non-selective monoamine oxidase (MAO) inhibitors (eg, phenelzine and tranylcypromine). Selective MAO-B inhibitors, such as selegiline, and selective MAO-A inhibitors are not contraindicated.

"Patients should be advised of the possible need to reduce levodopa dosage after the initiation of TASMAR therapy."

"INFORMATION FOR PATIENTS: If patients develop persistent or severe diarrhea, they should notify their physician. TASMAR can cause a harmless yellow urine discoloration."

"LABORATORY TESTS: It is recommended that transaminases be monitored before starting TASMAR treatment and approximately every 6 weeks for the first 6 months. If elevations occur, and a decision is made to continue to treat the patient, more frequent monitoring of complete liver function is recommended. Treatment should be discontinued is ALT exceeds 10 x ULN or if jaundice develops."

"SPECIAL POPULATIONS: Parkinson's disease patients with severe liver or severe renal impairment should be treated with caution. No information on the tolerability of tolcapone in these patients is available."

"DRUG INTERACTIONS: 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."

"EFFECT OF TOLCAPONE ON THE METABOLISM OF OTHER DRUGS: Due 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]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."

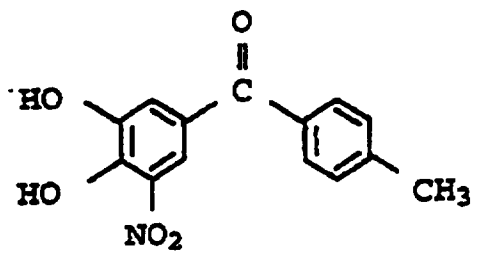
"There are no data available for the combination of TASMAR and MAO-A inhibitors, therefore this combination should be given with caution."

E. *Foreign Marketing Experience*

Tasmar is currently not commercially available in any part of the world.

3 CHEMISTRY

Tolcapone is a yellow, odorless, nonhygroscopic crystalline compound with a relative molecular mass of 273.24. Its chemical name is 3,4-dihydroxy-4'-methyl-5-nitrobenzophenone; its empirical formula, $C_{14}H_{11}NO_5$; and its structural formula:



Tasmar is supplied as film-coated tablets containing 100 mg or 200 mg tolcapone. The 100-mg beige tablet and 200-mg reddish-brown tablet are hexagonal and biconvex, imprinted in black ink on one side with "TASMAR" and the strength (100 or 200), and, on the other, with "ROCHE." Inactive ingredients include monohydrate, microcrystalline, cellulose, dibasic calcium phosphate anhydrous, povidone K-30, sodium starch glycolate, talc, and magnesium stearate. As to the film coating:

4 ANIMAL TOXICOLOGY

A. *General Information*

Tolcapone, at a dose of 15 and 30 mg/kg po, potentiated and prolonged the antiparkinson activity of levodopa/carbidopa in Rhesus monkeys rendered hemiparkinsonian by pretreatment with the neurotoxin MPTP. In rats, whose nigrostriatal neurons were lesioned with 6-OHDA, tolcapone at 30 mg/kg po prolonged the duration of response to levodopa/carbidopa.

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Tolcapone (10 mg/kg po) potentiated the ability of levodopa/carbidopa to reverse catalepsy induced by the dopamine antagonists pimozide, fluphenazine, and haloperidol in rats, and potentiated the effect of levodopa on locomotor activity in mice. When administered alone, tolcapone was inactive in these animal models.

Preclinical pharmacology and toxicology will be dealt with in detail in the review of Dr. Thomas Steele, and therefore only a brief overview will be attempted here. Acute- and multiple-dose toxicities of tolcapone are summarized in the following tables from the sponsor's NDA (v 1.2, pp 53, 55):

Table 10. Acute Toxicity Studies with Tolcapone

NDA Ref #	Species/ strain	#/ M/F	Age or weight	Doses (mg/kg)	Route/ vehicle	LD50 or HNLD[2] (mg/kg)	Time of death, toxic signs
[1001]	Mouse/ NMRI	5/5	22-26 g	1400-1800	p.o.[1]	LD50 1600-1800 HNLD <1400	< 30'; ataxia, slow breathing rate, reduced motor activity
[1002]	Mouse/ NMRI	5/5	22-27 g	45-90	i.p. [1]	LD50 56-71 HNLD 56	< 30'; ataxia, slow breathing rate, reduced motor activity
[1003]	Rat/ WIST	5/5	123-149 g	1600-2000	p.o. [1]	LD50 >2000 HNLD <1600	< 30'; ataxia, slow breathing rate, reduced motor activity
[1004]	Rat/ WIST	5/5	113-158 g	50-100	i.p. [1]	LD50 53-80 HNLD 63	< 30'; ataxia, slow breathing rate, reduced motor activity
[1005]	Dog/ Beagle	1/1	8.4-9.5 kg 15-21 months	10-300	p.o. in gel.- caps.	no mortalities	> 100: vomiting, watery faeces (in part with blood)

1 Administered in Standard Suspension Vehicle (SSV; 0.5% CMC, 0.4% Tween 80, 0.5% Benzyl Alcohol, in 0.9% Sodium Chloride)

2 Highest-non-lethal-dose

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Table 11. Multiple-Dose Toxicity Studies With Tolcapone

NDA Ref #	Species	#/ M/F	Duration	Route and vehicle	Doses (mg/kg/d)	Comment and Major Findings
[1009]	Mouse	12/12	8 weeks	feed-admix; prior to this study comp. study gavage versus feed-admix	0,100,300,800, 1200 feed-admix 100, 200, 300, 400 by gavage	Preparation for carc.study; previously 3 weeks comparison gavage versus feed-admix; detailed toxicokinetics; sudden deaths at ≥200 by gavage
[1063]	Mouse	50/50[4]	80-95 weeks	feed-admix	0, 0, 100, 300, 800	Increased forestomach epithelial hyperplasia with inflammation, increased incidence of spontaneously occurring slight-to-moderate granulocytosis, Kupffer cell proliferation, single cell necrosis and hepatocellular hypertrophy in the liver (carcinogenicity study) at ≥ 300
[1001]	Rat	10/10	4 weeks	daily gavage (SSV[1])	0,20,100, 400/300	400 reduced to 300 after 2 weeks due to cases of sudden death
[1013]	Rat	10/10	3 weeks	feed-admix	0,300,500	Comparison study feed-admix versus gavage; preparation for carc.study, detailed toxicokinetics
[1013]	Rat	10/10	6 weeks	daily gavage (SSV[1])	0,100,200,300, 400	In comparison with study above; detailed toxicokinetics; sudden deaths (at ≥ 300)
[1014]	Rat	26/26	6 months	feed-admix	0,20,100, 500	Retarded body-weight development and minor (reversible) reduction of RBC and Hgb (at 500)
[1014]	Rat	20/20	12 months	feed-admix	0,20,150, 450	Confirmation of findings from 6-month study. Minor histological changes in kidney (450), essentially in females, and in forestomach (150 and 450)
[1064]	Rat	50/50[4]	24 months	feed-admix	0, 0, 50, 250, 450	Kidney tubulopathy, secondary about 4% tumours, forestomach hyperplasia (at ≥250); increased spontaneous adenocarcinoma in uterus (at 450)
[1010]	Rat	10 M	2 weeks	iv (in mixed-micelles)	0,4,10,25	Threshold for sudden mortality at 25
[1020]	Dog	3/3	4 weeks	p.o. in gelatine capsules	0,10,40, 100/150	Vomiting at top dose
[1022]	Dog	4/4[2]	6 months	p.o. in gelatine capsules	0,10,40,75 b.i.d.	Vomiting and altered faeces (transient phases) at top dose, individual variation in severity and frequency
[1024]	Dog	4/4[2]	12 months	p.o. in gelatine capsules	0,10,40,75/90 b.i.d.[3]	Confirmation of data from 6-month study, no exacerbation of findings; top-dose increased in 2nd half of study; slight (reversible) reduction in RBC parameters at 2x90
[1019]	Dog	3 M	2 weeks	iv (in mixed micelles)	0,2,5,12/15	Vomiting due to vehicle (control and top dose), respiratory problems at higher doses and following rapid injection, no problems at slow injection rate

1 Administered in Standard Suspension Vehicle (SSV; 0.5% CMC, 0.4% Tween 80, 0.5% Benzyl Alcohol, in 0.9% Sodium Chloride)
2 5/5 in top dose group (1/1 for recovery)
3 90 mg/kg b.i.d. in the second half of the study
4 Satellite animals for toxicokinetics

Reproductive toxicity studies with tolcapone alone and segment II studies, in combination

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with Sinemet, in rats and rabbits showed no signs of teratogenicity or impairment of fertility or peri- and postnatal development in rats. The maternally lethal level in rats was 250 mg/kg/d, whereas 200 mg/kg was not lethal with repeated daily administration. An abortive potential was shown in rabbits at doses ≥100 mg/kg/d. Sinemet has been reported to cause visceral and skeletal malformations in the rabbit. When Tolcapone was given in combination with Sinemet to produce plasma levels of levodopa six times higher than those in humans under therapeutic conditions, maternal toxicity, but no teratogenicity, was observed in rabbits. A further elevation of the dose up to severe maternal toxicity led to a slight--though statistically insignificant--increase of malformed fetuses in rabbits. The following table summarizes these findings (v 1.2, p 66):

Table 14. Reproductive Toxicity Studies with Tolcapone

NDA Ref #	Species	Study type	Doses (mg/kg/d)	Route / vehicle	#/ M/F	Study design and guidelines	Comment
[1045]	Rat	Segment I	0,30,100, 300	p.o. gavage [2]	34/34	FDA, CSM, MHW; 1/2 C section, GD[1] 21; 1/2 rearing. Includes behaviour and reproductive performance of F1 generations	NOAEL 100 for parent animals; 300 for foetuses
[1046]	Rat	Segment II	0,50,150, 450	p.o. gavage [1]	36 F	FDA, DHSS; 20 for C section, GD[1] 20; remaining for rearing up to weaning (no behaviour of F1)	NOAEL 150 for mothers, foetuses and pups. No assessment at 450 due to high maternal mortality. Study was repeated [1048]
[1048]	Rat	Segment II (repeat)	0,50,150, 300	p.o. gavage [1]	36 F	FDA, DHSS; 20 for C section, GD[1] 20; remaining for rearing up to weaning (no behaviour of F1)	NOAEL 150 for mothers, 300 for foetuses and pups
[1047]	Rabbit	Segment II	0,25,100, 400	p.o. gavage [1]	18 F	FDA, DHSS, MHW; all females C section, GD[1] 29	NOAEL 100 for mothers and 25 for foetuses: not teratogenic but abortive at 100 and 400
[1049]	Rat	Segment III	0,40,100, 150/250	p.o. gavage [1]	24 F	FDA, DHSS, EC; includes behaviour	NOAEL 100 for mothers and pups

[1] Administered in Standard Suspension Vehicle (SSV; 0.5% CMC, 0.4% Tween 80, 0.5% Benzyl Alcohol, in 0.9% Sodium Chloride)
[2] Administered in CMC

The 3-0-methyl metabolite Ro 40-7591 has a long half-life that, although very long in man, is much shorter in animals. Studies in rats and dogs of four-week duration have demonstrated toxicities only in doses producing elevated plasma concentrations of the metabolite (50 mg/kg/d or >25 ug/ml), as presented in the following table (v 1.2, p 65):

Table 13. Multiple-Dose Toxicity Studies with Ro 40-7591 (3-O-Methyl Metabolite)

NDA Ref #	Species	#/ M/F	Duration	Route and vehicle	Doses (mg/kg/d)	Comment and major findings
[1025]	Rat	10/10	4 weeks	feed-admix	0,10,60, 300/400	Top dose increased due to good tolerance, slightly reduced body-weight gain at top dose
[1027]	Dog	2/2	4 weeks	p.o. in gelatine capsules	0,10,50, 150	Reduced to 0,5,25,75 after first application due to strong convulsions at 150; diarrhoea at 50, diarrhoea, salivation and vomiting at 75; generalized tonic/clonic seizures at > 75.

Mutagenicity studies of tolcapone and Sinemet showed one assay, the mouse lymphoma assay (ML/TK), that was marginally positive (v 1.2, p 67):

Table 16. Mutagenicity Studies with Tolcapone And Sinemet® (Carbidopa:L-Dopa = 1:4)

NDA Ref #	System	Protocol	Doses	Toxicity	Genotoxicity
[1055]	Ames, 5 strains	Standard +S9 Preincub. +S9	32 - 1000 µg/pl[1] 16 - 500 µg/pl[1]	≥ 1000 µg/pl ≥ 500 µg/pl	no increase of revert. colonies no increase of revert. colonies
[1060]	ML/TK	-S9: 3 h +S9: 3 h	6.25 - 200 µg/mL[1] 12.5 - 300 µg/mL[1]	200 µg/mL ≥ 50 µg/mL	no increase of the number of mutant colonies slight increase of mutant frequency due to tolcapone
[1062]	MNT, mouse	24 and 48	150, 300 and 600 mg/kg[1]	≥ 600 mg/kg	no induction of micronuclei

[1] Sinemet® (carbidopa:L-DOPA = 1:4) was tested at the same concentrations as tolcapone

However, Ames and micronucleus tests showed no evidence of genotoxicity (v 1.2, p 67):

Table 15. Mutagenicity Studies with Tolcapone

NDA Ref #	System	Protocol	Dose	Toxicity	Genotoxicity
[1054]	Ames, 7 strains	Standard +S9 Preincub.+S9	5 - 1000 µg/pl 5 - 1000 µg/pl	≥250 µg/pl ≥250 µg/pl	no increase of revert. colonies no increase of revert. colonies
[1056]	E.coli, WP2 uvrA	Standard +S9 Preincub.+S9	5 - 250 µg/pl 5 - 250 µg/pl	>250 µg/pl >250 µg/pl	no increase of revert. colonies no increase of revert. colonies
[1057]	V79/HPRT	-S9: 16h +S9: 5h	1 - 200 µg/mL 5 - 400 µg/mL	≥ 25 µg/mL 400 µg/mL	no increase of revert. colonies no increase of revert. colonies
[1058]	UDS, rat hepatocytes	18 h	1 - 5 µg/mL	> 4 µg/mL	no induction of UDS
[1059]	CA human lymphocytes	-S9: 3-46 h +S9: 3 h	5 - 400 µg/mL 400 µg/mL	≥30 µg/mL 400 µg/mL	no induction of chrom. damage no induction of chrom. damage
[1061]	MNT, mouse	24/48/72	150, 300 mg/kg	>300 mg/kg	no induction of micronuclei

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Tests for active systemic, or passive cutaneous, anaphylaxis were also negative (v 1.2, p 67):

Table 17. Antigenicity Studies With Tolcapone

NDA Ref #	Test	Species	Comment
[1065]	Active systemic anaphylaxis Passive cutaneous anaphylaxis	Mouse Guinea pig	No antigenic activity No antigenic activity

B. *Safety Pharmacology by Body System*

Cardiovascular:

At the high dose of 10 mg/kg iv (dosing range at least 1-10 mg/kg, with 1 mg/kg iv equal to the no toxic cardiovascular effect dose) in anesthetized dogs, tolcapone produced a moderate decrease in systolic and diastolic blood pressure and slightly shortened the QRS complex; the effects were reportedly transient, observed during or immediately after infusion when plasma levels were maximal, and disappeared rapidly 15-30 minute post infusion, when levels declined. At 10 mg/kg, the plasma concentration in dogs was 10- to 20-fold higher than that detected in humans after chronic administration of therapeutic doses.

In conscious dogs, tolcapone 10 and 30 mg/kg po, given alone and in combination with levodopa 4.4 mg/kg and carbidopa 1.1 mg/kg po, produced a modest decrease in heart rate but no ventricular arrhythmias or changes in EKG waveform (v 1.2, p51).

Very high doses (30 mg/kg iv; C_{max} 130 ug/ml) in rabbits led to cardiac arrhythmias and death; this dose is comparable to lethal plasma levels in the rat and is 20- to 40-fold higher than the C_{max} in patients (3-6 ug/ml) treated chronically with therapeutic doses (100-200 mg tid).

In doses up to 100 mg/kg po, tolcapone did not alter systolic arterial blood pressure or heart rate in rats in spontaneously hypertensive rats.

Nervous:

Tolcapone produced neither a direct nor a physical dependence after subchronic administration (4 weeks) at doses up to 600 mg/kg/d (fed admix) in the rat; and psychological dependence, in a self-administration paradigm in cymologous monkeys, was also not induced.

There is no proconvulsive or anticonvulsive activity in the DBAA/J2 mouse model of epilepsy (audiogenic seizure) at doses of 10, 100, and 300 mg/kg po; and it does not exhibit an antinociceptive effect in the hot-plate test in the mouse at doses of 10, 30, 50, and 100 mg/kg po. Administered at doses of 3, 30, and 300 mg/kg po, tolcapone had no effect on the ability of methylhexabital to induce loss of righting reflex in the mouse. While levodopa/benserazide (100/25 mg/kg po) increased the duration of the loss of the righting reflex induced by a hypnotic dose of methylhexabital (80 mg/kg ip), addition of tolcapone had no effect on levodopa.

With reference to the EEG, dose of 1, 3, and 10 mg/kg iv produced no abnormal morphology of spontaneous EEG in cats.

Respiratory:

In anesthetized dogs, doses of 1 and 3 mg/kg po had minimal to no effect on rate. At 10 mg/kg, the rate increased during dosing, returning to normal 60 minutes post dosing.

GU:

Renal tubulopathy occurred in male and female rats at 500 mg/kg/d x 6 months and 450 mg/kg/d x 12 months. In addition, there was an increased incidence (4%) of spontaneous renal adenocarcinomas in both male and female rats at 450 mg/kg/d x 24 months (dosing range 0-450 mg/kg/d).

Also observed in female rats was an increase (14%) in spontaneous uterine adenocarcinomas at the same high dose.

Gastrointestinal:

There was slight epithelial hyperplasia/acanthosis of the nonglandular part of the stomach (forestomach) of both male and female rats at ≥250 mg/kg/d (dosing range 0-450 mg/kg/d) x 12 months. Increased granulocytosis, Kupffer cell proliferation, single cell necrosis, and hepatocellular hypertrophy were detected on liver pathology at ≥300 mg/kg/d (dosing range 0-800 mg/kg/d) x 95 weeks.

In dogs, severe vomiting was observed at the highest doses (100 or 150 mg/kg/d or 75 or 90 mg/kg bid x 4 weeks; dosing range 0-150 mg/kg/d). Diarrhea also occurred at similar high doses at the beginning of the chronic studies, but allegedly improved when the drug was given bid.

5 DESCRIPTION OF CLINICAL SOURCES

A. *Study Type and Design/Patient Enumeration*

Table 1: Summary of Randomized Double-Blind, Placebo-Controlled, Multiple-Dose, Parallel-Group Trials

Study	*Phase*	*Duration*	*Patient Type*	*L-Dopa Type*	*Tolcapone Dose (no. subjects)*	*Placebo (no. subjects)*
NZ14316 (USA)	II	6 weeks	Fluctuating	Sinemet	50 mg = 41 200 mg = 40 400 mg = 38	42
BZ14114 (Europe, Australia)	II	6 weeks	Fluctuating	Sinemet/ Madopar	50 mg = 37 200 mg = 38 400 mg = 37	42
NZ14654 (USA, Canada)	III	13 weeks	Fluctuating	Sinemet	100 mg = 69 200 mg = 67	66
NZ14655 (Europe)	III	13 weeks	Fluctuating	Madopar	100 mg = 60 200 mg = 59	58
NN14971 (USA)	III	13 weeks	Fluctuating	Sinemet	100 mg = 69 200 mg = 74	72

BZ14115 (Europe, Australia)	II	6 weeks	Nonfluctuating	Sinemet/ Madopar	200 mg = 32 400 mg = 32	33
NZ14653 (USA, Canada)	III	26 weeks	Nonfluctuating	Sinemet	100 mg = 98 200 mg = 98	102

B. *Demographic Profile for Phase II and III Double-Blind, Placebo-Controlled Trials*

Table 2: **FLUCTUATORS**

	Placebo (n=280)	*Tolcapone (n=629)*
AGE (yrs; mean [SD])	63.9 (9.0)	63.0 (9.5)
GENDER Male Female	 186 94	 401 228
RACE (%) Caucasian Other	 97 3	 97 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 1.5-2.5 ≥3 missing	 8.9 64.3 25.7 1.1	 7.9 63.7 27.8 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)

Table 3: **NONFLUCTUATORS**

	Placebo (n=135)	*Tolcapone (n=260)*
AGE (yrs; mean [SD])	66.3 (9)	66.0 (9)

GENDER Male Female	 81 54	 164 96
RACE (%) Caucasian Other	 99 1	 98 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 1.5-2.5 ≥3 missing	 3.7 17.0 3.7 75.6	 4.6 16.9 3.1 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)

C. *Extent of Exposure*

The following table* shows the total number of subjects and their exposures in each treatment group for all *Phase I-III* trials, incluidng placebo-controlled, active control, and uncontrolled studies:

Duration on Tolcapone (tid dosing)	*50 mg (n)*	*100 mg (n)*	*200 mg (n)*	*400 mg (n)*	*800 mg (n)*
Total exposure	78	296	1188	135	16
1 week	78	295	1168	131	16
6 weeks	60	267	1046	85	
13 weeks		190	852		
26 weeks		157	619		
39 weeks		117	296		
52 weeks		46	160		

*Adapted from the sponsor's Table 32, v 1.2, p 117; information about the 800 mg dose from v 1.92, pp 9-10.

6 HUMAN PHARMACOKINETICS

Tolcapone is an orally active, potent, selective, reversible COMT inhibitor. The sponsor contends that, when administered concomitantly with levodopa and an aromatic amino-acid

decarboxylase inhibitor, it leads to more stable plasma levels of levodopa by reducing its metabolism to 3-methoxy-4-hydroxy-L-phenylalanine (3-OMD). Because 3-OMD has been associated, according to the sponsor, with poor response to levodopa, the decrease in 3-OMD may, in turn, result in an improvement in symptomatic response and may allow for a reduction of the daily dose of levodopa.

The systemic clearance of tolcapone is 7 l/h but, owing to its small volume of distribution, its elimination occurs rapidly ($t_{1/2}$=2 h). The AUC after a 200-mg dose is about 27 h·ug/ml, resulting in an average concentration of 4.5 ug/ml over six hours; and COMT inhibition is fairly constant during the waking day with tid dosing, according to a 6/6/12 schedule (EC_{50} erythrocyte COMT: 1 ug/ml). After oral administration, tolcapone is rapidly absorbed; it has an oral bioavailability of 75% in rats, 68% in dogs, and 60-70% in man. Incomplete oral absorption is due in part to the low solubility of the compound and in part to first-pass metabolism.

The main metabolic pathway is through irreversible conjugation to the inactive glucuronide. The drug is completely metabolized prior to excretion in the urine (60%) and feces (40%); an alternative route exists into the bile. With moderate cirrhosis, a two-fold increase in the average concentration of unbound tolcapone can be expected after multiple dosing. Since tolcapone's effects are believed to be related to its unbound concentration, the sponsor recommends that patients with moderate liver cirrhosis remain on 100 mg tid, which would result in unbound concentrations comparable to those after the maximally recommended dose (200 mg tid) in patients with normal liver function.

Tolcapone's oxidation is mediated by cytochrome P450 3A and 2A6; but it can also inhibit 2C9. Tolbutamide was not inhibited in a study of healthy volunteers; but the sponsor recommends caution with respect to warfarin, since it exhibits a narrow therapeutic window.

Tolcapone is highly bound to plasma albumin (>99.9%) and does not distribute widely to the tissues (V_{ss}>9 l). Free drug concentrations increase with decreasing albumin levels below 36 g/l, and drug levels may consequently be affected in the elderly. *In vitro* displacement studies demonstrate that, at therapeutic concentrations, tolcapone binding is not saturated; essentially no displacement of phenytoin, warfarin, tolbutamide, or digoxin was observed. No *in vivo* studies, however, have been performed.

As a result of COMT inhibition, tolcapone might also interfere with the elimination of other drugs, such as carbidopa, dobutamine, isoproterenol, methyldopa, and apomorphine. But, according to the sponsor, there was apparently no change in carbidopa plasma levels when administered with tolcapone in clinical trials.

Tolcapone's PK appear to be independent of the patient's age, sex, race, and body weight, and are also not influenced by the coadministration of Sinemet, dopamine-agonists, or selegiline (selegiline/tolcapone studies: NN14084, BZ14112, NN14927). The variability in AUC is consequently relatively small. The following sponsor's table shows Tolcapone PKs over the dosing range from 100 to 800 mg tid (v 1.92, p 17):

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Table 3. Pharmacokinetic Parameters of Tolcapone on Days 1 and 7 of Multiple Dosing (t.i.d.) with Tolcapone and Sinemet® 25-100 [4011]

Data are presented as means ± SD. Day 1 AUC is AUC(0→∞) after the first dose; day 7 AUC is AUC(0→6h) during the first dosing interval.

Tolcapone (mg)	Study day	C_{max}(0→6h) (µg/mL)	AUC (h·µg·mL^{-1})	$t_{1/2}$ (h)
100	1	2.8 ± 0.3	12.7 ± 1.9	2.2 ± 0.6
	7	3.5 ± 1.0	13.0 ± 1.6	2.2 ± 0.2
200	1	5.9 ± 1.9	25.1 ± 9.3	2.6 ± 0.9
	7	6.4 ± 1.7	26.7 ± 6.6	3.1 ± 1.0
400	1	9.9 ± 3.4	43.3 ± 5.7	3.3 ± 0.7
	7	9.9 ± 4.1	54.4 ± 18.9	6.6 ± 3.1
800	1	15.0 ± 4.4	102.5 ± 32.3	5.9 ± 3.4
	7	28.5 ± 5.4	200.8 ± 60.3	19.0 ± 3.1

Tolcapone PKs measured in PD patients and healthy volunteers are similar, even though a higher volume of distribution was observed in the target population (15-35 l) leading to an apparently longer elimination half-life of 4-8 h. With food intake, a statistically significant reduction of tolcapone bioavailability by 10-20% was observed in PD patients; but this may lie within the acceptance range for bioequivalence (Dr. Mahmood Iftekar will discuss this subject in his pharmacokinetics review).

The rationale for the tolcapone doses selected was based upon tolcapone's effect on L-DOPA pharmacokinetics (see v 1.333, p 11), which, according to the sponsor, is maximal at around 200 mg. The dosage regimen chosen, or tid, was determined not only by tolcapone's effect on the pharmacokinetics of L-DOPA, but also by its pharmacodynamic effect on eythrocyte COMT inhibition. After 200 mg, average concentrations over 6 hours are approximately 4.5 ug/ml, and a 6 am-6 pm-12 am dosing regimen results in relatively stable inhibition of COMT during the waking day (EC50 of eythrocyte COMT = 1 ug/ml).

For Phase II studies, selected doses were 50 mg (submaximal), 200 mg (maximal), and 400 mg (supramaximal). In trials NZ14316, BZ14114, and BZ14115, 200 mg tid was, according to the sponsor, "most frequently the most effective tolcapone dose among the efficacy parameters assessed (v 1.333, p 11). It was therefore the dose selected for Phase III trials. The sponsor further states that, as "50 mg tolcapone was also found to be effective in study NZ14316, therefore an intermediate dose of 100 mg tolcapone was included in the Phase III studies" (v 1.333, p 11).

Animal studies demonstrated that tolcapone has the potential to cross the blood brain barrier. However, the sponsor was not able to show, "due to methological reasons" (v 2.1, p 77), whether tolcapone exhibited a central -- in addition to its peripheral -- effect at therapeutic concentrations; PET scan data were not helpful (see study BZ14312, discussed below).

Further information can be found in detail in Dr. Iftekhar Mahmood's review. He will also discuss the difference between the two different formulations the sponsor used in various trials and any effect that might have on the results (information submitted 3/5/97 by the sponsor upon request):

	Number of Patients on Tolcapone in Double-Blind Studies	Number of Patients on Clinical Formulation Only in Double-Blind Studies	Number of Patients on Marketed Formulation Only in Double-Blind Studies	Number of Patients who Received Both Formulations During Extension Studies	Number of Patients who Received Marketed Formulation only During Extension Study
Phase II					
BZ14114	112	112		75*	
BZ14115	64	64		26*	
BZ14316	119	119		139*	
Phase III					
NN14927	42	42			
NZ14655 -	119	119		91*	
NZ14657	484	484		285*	
NZ14656	72	72		69*	
NZ14653 -	196	196			154
NZ14654 -	136	136		133*	
NN14971	143		143	197*	
Total	1,487	1,344	143	1,015	154

* These patients received both formulations during the course of the extension studies. As the supply of clinical formulatio was depleted, the marketed formulation was used.

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7 EFFICACY FINDINGS

A. *General Overview of All Studies*

In the following two tables (v 1.331, pp 9, 12), the sponsor summarizes the seven randomized double-blind, placebo-controlled studies submitted in support of the NDA:

Phase	Protocol no.	Location	L-DOPA medication	Treatment groups	No. of patients	Primary end-point	Maximum duration	Primary efficacy parameters
II	NZ14316 [1]	USA	Sinemet®	Placebo Tolcapone t.i.d.: 50 mg 200 mg 400 mg	42 41 40 38	week 6	6 weeks	Investigator-assessed OFF-time at 30-min intervals for 10 h. UPDRS III (motor) AUC (10 h).
	BZ14114	Europe, Australia	Sinemet®/ Madopar®	Placebo Tolcapone t.i.d.: 50 mg 200 mg 400 mg	42 37 38 37	week 6	6 weeks	Patient-assessed OFF/ON-time at 30-min intervals for 16 h.
III	NZ14654 [1]	USA, Canada	Sinemet® [2]	Placebo Tolcapone t.i.d.: 100 mg 200 mg	66 69 67	week 13	52 weeks	Patient-assessed OFF/ON-time at 30-min intervals for 18 h.
	NZ14655	Europe	Madopar®	Placebo Tolcapone t.i.d.: 100 mg 200 mg	58 60 59	week 13	52 weeks	Patient-assessed OFF/ON-time at 30-min intervals for 18 h.
	NN14971 [1]	USA, Canada	Sinemet® [2]	Placebo Tolcapone t.i.d.: 100 mg 200 mg	72 69 74	week 6	6 weeks	Patient-assessed OFF/ON-time at 30-min intervals for 18 h.

[1] Study under US IND.
[2] Generic forms of L-DOPA/carbidopa were also permitted.

Phase	Protocol no.	Location	Type of patient	L-DOPA medication	Treatment groups	No. of patients	Primary end-point	Maximum duration	Primary efficacy parameters
II	BZ14115	Europe, Australia	Non-fluctuators	Sinemet®/ Madopar®	Placebo Tolcapone t.i.d.: 200 mg 400 mg	33 32 32	week 6	9 weeks	Daily L-DOPA therapy
III	NZ14653 [1]	USA/ Canada	Non-fluctuators	Sinemet®	Placebo Tolcapone t.i.d.: 100 mg 200 mg	102 98 98	week 26	65 weeks	UPDRS subscale II (ADL during ON)

[1] Study under US IND.

PD patients were divided into two groups: fluctuators and nonfluctuators. Fluctuators were defined as those with an "unstable" response to L-Dopa medications (Sinemet or Madopar) who experience "wearing off, characterized by the shortening of the duration of action of each [L-Dopa] intake" (v 1.2, p 77). Fluctuating patients thus require larger amounts of L-Dopa and ever-briefer intervals between doses. As the sponsor states, "the wearing-off phenomenon affects about 50% of PD patients after five years of treatment with L-Dopa" (v 1.2, p 77). In contrast, nonfluctuators, or those usually within the five-year period of starting L-Dopa, can be placed on a relatively "stable" regimen. Inclusion/exclusion criteria for patient selection were common to all studies: both males and females (amenorrheic, surgically sterile, or on reliable contraceptives) were

enrolled; at least 30 years old at the onset of PD symptoms and 40 at trial screening; diagnosed with idiopathic PD and on a stable dose of Sinemet or Madopar; not on any recent investigational agents; without history of drug or alcohol abuse, psychiatric disorder, or medical problems prior to treatment with tolcapone that would place the subject at increased risk; recent neurosurgery (Phase III); or on high protein-bound drugs (Phase II) (v 1.331, p 10).

There was, in addition, one Phase III multiple-dose, multicenter, parallel-group, open-label, randomized active-controlled study in fluctuating patients (NZ 14657), the objectives of which were: (1) to compare the effect of tolcapone to bromocriptine, in combination with Sinemet or Madopar, over an eight -week period; and (2) to determine the effect of tolcapone on levodopa regimen. Conducted in France, the trial enrolled 146 patients (tolcapone, 74; bromocriptine, 72). Patients continued their usual Sinemet or Madopar regimens, unless levodopa adjustment was deemed necessary by the investigator, but no increase above baseline levodopa dose was permitted in the study. Patients randomized to bromocriptine were titrated from 1.25 mg/d up to a maximum of 30 mg/d (mean of final dose = 22.4 mg/d) or until an adequate response was reached (balanced between efficacy and side effects); the tolcapone dose was 200 mg tid. With bromocriptine, a distinction was made between nonmotor and motor dopaminergic adverse events: whereas, for tolcapone, daily levodopa doses could be reduced only for motor adverse events, for bromocriptine they could be reduced for nonmotor as well.

Five open-label, uncontrolled multicenter studies were also conducted: one phase III study (NZ 14657, fluctuating and nonfluctuating subjects) to obtain exploratory long-term data on the efficacy of tolcapone, and four open-label extensions (to the Phase III active-controlled study [NZ 14656; 69 fluctuating subjects] and three Phase II placebo-controlled studies [NZ 14316, 139 fluctuating subjects; BZ 14114, 75 fluctuating subjects; BZ 14115, 26 nonfluctuating and fluctuating subjects]). The objectives of the open-label, uncontrolled trials were (1) to assess the effect of tolcapone on PD signs and symptoms, and (2) to determine the effect of tolcapone on levodopa dosage regimen. During the uncontrolled trials, subjects received 200 mg tolcapone tid in combination with Sinemet or Madopar, regardless of their treatment during the previous blinded segment of the studies; they could continue tolcapone 200 mg tid for up to 18 months. In all studies, adjustment of daily levodopa dose or other PD medications was allowed, based upon levodopa-related adverse events or PD symptoms. Patients from NZ 14656, who had received bromocriptine in the original randomized study, were allowed to continue bromocriptine therapy during the extension period. UPDRS and levodopa therapy were both evaluated in the uncontrolled open-label studies.

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

B. *Pivotal Trials:* Fluctuators *(13 weeks)*

1. Study NZ14654

This was a multicenter (11 centers: 7 in the US, 4 in Canada), randomized, double-blind, parallel-group, placebo-controlled study to evaluate, over a 13-week period, the efficacy, tolerability, and safety of two doses of tolcapone, 100 and 200 mg tid, in fluctuating PD patients on Sinemet. Inclusion criteria stipulated treatment with L-Dopa for ≥1 year; a stable regimen for ≥4 weeks, comprising a daily administation of ≥4 doses (or 3 , if at least 2 contained Sinemet CR), plus ≥70 mg carbidopa, with "predictable end-of-dose motor fluctuations which could not be eliminated by adjusting...current anti-PD treatment regimen....In other words, patients who were candidates to begin additional anti-PD drug therapy"; a stable regimen of other anti-PD drugs for ≥4 weeks (*eg*, dopamine agonists, amantadine, anticholinergics, selegiline, antihistamines, beta-

blockers, carbidopa, or Mysoline). Exclusion criteria were a history of sudden, unpredictab le ON/OFF fluctuations or DID pattern of dyskinesias (diabling choreiform dyskinesias shortly after taking L-Dopa and/or shortly before the next dose); Mini-Mental Status score ≤25; treatment with centrally acting dopamine antagonists (antipsychotics, metoclopramide, buspirone, amoxapine) ≤6 months, or antiemetics or MAOI (other than selegiline)≤2 months, prior to study entrance; or neurosurgery ≤1 year prior to study entrance. The study also prescribed that no adjustment in anti-PD drugs be made during the two weeks before the next clinic visits for week 6 and month 2 (and thereafter during the study extension for months 6, 9, and 12).

The outcome measure was the "percent change from baseline in proportion of ON or OFF time (average of up to 3 diaries), as determined by self-rating charts (patient diaries) based on a four-point scale of OFF, ON, INTERMEDIATE, and ASLEEP (v 1.233, pp 18-19). Secondary efficacy measures were the Investigator's Global Assessment of change, the UPDRS Subscales I, II, III, IVb, and VI (percent change from baseline in individual subscale scores and the total score of Subscales I, II, and III); the frequency and total daily L-Dopa dose (change from baseline); and the Beck Depression Inventory (change from baseline) to be filled out by the patient (v 1.233, pp 18-19). "Other" efficacy parameters were the quality of life assessment as measured on the Sickness Impact Scale (SIP; change from baseline) and the Medical Resource Assessment (distribution of responses), both completed by the physician with information garnered from not only his history and physical but also the patient, family, or caretaker. Criteria for study parameters were defined as follows (v 1.233, pp 26-7):

1. **Proportion of average ON or OFF time per day using the patient diaries (primary). The last 3 diaries during 10 days immediately before the given visit will be averaged. Percent change from baseline in the average proportion will be analyzed. Zero percent of ON or OFF hours at baseline with non-zero at postbaseline will be replaced with one entry on the diary (ie, 2.78%) in order to calculate the percent change from baseline.**

2. **Proportion of patients showing any improvements (ie, moderate/slight, marked, or very marked) on the Investigator's Global Assessment of Changes (secondary).**

3. **Subcategory total scores of the UPDRS mood/mentation, ADL, and motor items (secondary).**

4. **Total scores of the 3 UPDRS subcategories – mood/mentation, ADL, and motor items (secondary).**

5. **Total daily dose of levodopa and frequency of doses per day (secondary). Change from baseline will be analyzed.**

6. **Total score of the Beck Depression Inventory (secondary).**

7. **Total score (expressed as a percentage of total dysfunction) of the Sickness Impact Profile (other). Scores of the 2 dimensions (physical and psychosocial) and the 12 individual categories will be examined.**

8. **Distribution of responses on the Medical Resource Assessment (other).**

Efficacy analyses were to be performed on the ITT population of patients who received at least one dose of test medication and who had one post-baseline assessment. Excluded were patients who demonstrated protocol violations; were noncompliant (defined as <80% of test medication taken on an average during the first three months); or were terminated from the study before the month 3 assessment; or had data collected at any assessment less than 7 days after an adjustment in Sinemet (or other anti-PD) dose or frequency.

The sponsor projected the requisite sample size as follows:

The sample size required for this study was calculated considering the clinically relevant differences in the primary efficacy parameter (ie, proportion of ON or OFF hours per day). A 30% additional improvement of the status produced by tolcapone is considered clinically relevant for this study.

Based on the results of previous tolcapone studies in Parkinson patients with Sinemet or Madopar end-of-dose wearing-off, it was assumed that the standardized effect size (ie, mean divided by standard deviation) of treatment difference in reduction of average percent ON or OFF hours between placebo and tolcapone would be approximately 0.6. In order to detect such a difference (ie, effect size of 0.6 or greater), between the tolcapone and placebo groups, in mean percent change of ON or OFF hours from baseline, with 80% power at the Type I error level of 0.05 (2-sided), a total sample size of 180 (60 per treatment group) is required, with an expectation of 30% dropout and nonevaluable case rate.

Due to the "common closing date" design, the total target number of patients will complete 3 months of treatment and at least 30% of the total patients will complete 12 months of treatment.

The study was closed when all patients had been treated for three months, according to a common closing-date design. A total of 202 subjects were randomized, 62 of whom eventually withdrew: 65 to placebo (18 withdrawals, 27%), 69 to 100 mg (20 withdrawals, 29%), and 67 to 200 mg (24 withdrawals, 36%). Reasons for withdrawal (to be discussed later in greater detail) are listed by the sponsor (v 1.231, p 29) as:

Table 3. Summary of Reasons for Withdrawal from the Study

	Placebo	Tolcapone tid	
		100 mg	200 mg
	N = 66	N = 69	N = 67
	n (%)	n (%)	n (%)
Reasons for Withdrawal			
Entry Violation	0 (0)	1 (1)	0 (0)
Other Protocol Violation	1 (2)	1 (1)	0 (0)
Insufficient Response	3 (5)	2 (3)	1 (1)
AE / Intercurrent Illness	10 (15)	13 (19)	15 (22)
Withdrawal of Consent	2 (3)	3 (4)	4 (6)
Lost to Follow-up	2 (3)	0 (0)	3 (4)
Others	0 (0)	0 (0)	1 (1)
Total Patients Withdrawn from Treatment	18 (27)	20 (29)	24 (36)

Dr. Dave Hoberman (FDA biometric review, p 2) independently checked the results of the study with data provided by the sponsor. The number of patients Dr. Hoberman used in his calculations differed in two of the three groups (55 for placebo, 56 for the 200-mg group), because the sponsor supplied him with a data set regarded as complete that only contained information on those patients (personal communication).

All subjects were screened within four weeks of randomization; during this period, their anti-PD medications were stabilized, and each patient was given an opportunity to complete three ON/OFF self-rating scales. For the study itself, patient assessments were conducted in clinic for both efficacy and safety between weeks 1 and 2 and at the end of weeks 6 and 13. Demographic and baseline characteristics for patient groups were as follows (v 1.231, p 32):

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Table 6. Summary of the Key Baseline Characteristics of Parkinson's Disease

Parameter	Placebo	Tolcapone tid 100 mg	Tolcapone tid 200 mg
*Duration of disease			
Mean	10.5	11.0	11.1
SD	5.82	5.64	5.41
Range	[redacted]	[redacted]	[redacted]
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	[redacted]	[redacted]	[redacted]
N	66	69	67
Schwab and England Scale (ON)			
Mean	88.4	87.3	84.5
SD	10.19	11.88	12.02
Range	[redacted]	[redacted]	[redacted]
N	63	68	66
Schwab and England Scale (OFF)			
Mean	62.5	63.1	57.7
SD	19.90	20.02	18.36
Range	[redacted]	[redacted]	[redacted]
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	[redacted]	[redacted]	[redacted]
N	64	68	66

* Duration in years

The most frequent used previous and concomitant anti-PD medications (other than Sinemet) for the three patient groups (placebo, 100- and 200-mg patients) were selegiline (49%, 42%, and 54%), pergolide (30%, 42%, and 31%), and bromocriptine (26%, 29%, and 19%).

Patient diaries were completed over an 18-hour period on three typical days each week during the screening period and subsequently, during the trial, in the week prior to clinic visits; the subject himself performed the rating, then entered the information every hour for the two previous 30-minute periods. A four-point scale was used for the ratings: OFF, ON, INTERMEDIATE, and ASLEEP. The percent change from baseline of daily ON- and OFF-time was derived from the average of diary entries for the particular week.

The greatest increase in ON-time and decrease in OFF-time were observed at the 200-mg dose -- the changes (from baseline) significantly different from placebo -- as indicated in the sponsor's summary table below (for the ITT LOCF cohort); the results were not statistically significant for the 100-mg dose (see v 1.231, p 38):

Table 8. Summary of OFF/ON-Time

Rating	Scheduled Assessment Visit	Placebo N mean (SE)	Tolcapone tid 100 mg N mean (SE)	Tolcapone tid 200 mg 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 (Mn3-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 56.6 (2.2)
	Month 3	55 62.8 (2.9)	59 63.9 (2.9)	56 73.8 (2.9)
	Change (Mn3-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 *

Secondary outcome measures included (a) the investigator's Global Assessment of change; (b) change from baseline in UPDRS Subscales I, II, IVb, and VI; (c) total daily L-Dopa dose; and (d) quality of life evaluation (SIP) (v 1.231, p 46):

Table 11. 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 ± 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±22.5	8.6±2.5	-7.8±2.3	37	32	-0.4±0.9
100	-166.3±22.3**	12.6±2.5	-12.2±2.2	68**	60**	-1.9±0.9
200	-207.1±22.6**	18.2±2.6*	-18.8±2.3**	95**	79**	-2.0±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±0.5	0.0±0.2	-2.2±1.0	-2.4±1.1	-2.0±1.3	-0.8±0.8	-0.7±1.2	42
100	-0.8±0.4	0.3±0.2	-0.4±1.0	-0.1±1.1	-0.7±1.3	-0.3±0.7	-2.4±1.1	71**
200	0.2±0.4	0.2±0.2	-0.3±1.1	-0.8±1.2	0.8±1.3	0.4±0.7	-1.7±1.2	91**

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

Both the 100- and 200-mg doses produced statistically significant results for a decrease in L-Dopa usage (see above) and the Investigator's Global Assessment of efficacy at three months (v 1.231, p 41):

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Table 9. Summary of Investigator's Global Assessment of Efficacy

ITT population; LOCF analysis.

Parameter Scheduled Assessment Visit	Placebo	Tolcapone tid 100 mg	Tolcapone tid 200 mg
Severity of Parkinson's Disease			
Month 3			
Frequency Counts [n (%)]			
(1) Improvement	19 (32)	37 (60)	46 (79)
(0) No Improvement	41 (68)	25 (40)	12 (21)
Not Evaluable	0	0	0
P-value [<0.001]		0.0031 ** +	<0.001 **
Wearing Off-Phenomenon			
Month 3			
Frequency Counts [n (%)]			
(1) Improvement	22 (37)	42 (68)	55 (95)
(0) No Improvement	38 (63)	20 (32)	3 (5)
Not Evaluable	0	0	0
P-value [<0.001]		<0.001 **	<0.001 **
Overall Efficacy			
Month 3			
Frequency Counts [n (%)]			
(1) Improvement	25 (42)	44 (71)	53 (91)
(0) No Improvement	35 (58)	17 (27)	4 (7)
Not Evaluable	0	1 (2)	1 (2)
P-value [<0.001]		<0.001 **	<0.001 **

Mean was calculated based on the assigned scores printed in front of each category description.
NOTE: The unadjusted P-values are computed using the Cochran-Mantel-Haenszel test. The P-value for overall comparison is presented in brackets. '+' indicates P < 0.15 for Breslow-Day homogeneity test. '*' indicates P < 0.05 and '**' indicates P < 0.01 for pairwise comparison with placebo after adjusting for multiple comparisons.

Dr. Dave Hoberman's analysis concurs (FDA biometric review, p 2): "Between 60% and 80% of Tolcapone patients showed improvement in severity of PD symptoms, compared to 30% of placebo patients. The respective proportions, for treated and placebo groups, for Overall Wearing-Off Phenomenon were 70%-95% vs 37%, and for Overall Severity were Efficacy vs 42%. There were no statistical differences on quality of life (SIP) or the UPDRS (v 1.231, p 43):

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Table 10. Summary of UPDRS Subscales I-III, with Total Score

ITT population; LOCF analysis. The table shows least-squares means ± SEM based on ANOCOVA

UPDRS	Scheduled Assessment Visit	Placebo N mean (SE)	Tolcapone tid 100 mg N mean (SE)	Tolcapone tid 200 mg N mean (SE)
Total θ	Baseline	61 28.5 (1.9)	67 27.1 (1.8)	64 31.0 (1.8)
	Month 3	61 27.9 (1.9)	67 25.0 (1.9)	64 28.9 (1.9)
	Change (Mo3-BL)	61 -0.7 (1.2)	67 -2.4 (1.1)	64 -1.7 (1.2)
	Treatment Difference		-1.6	-1.0
	95% CI		(-4.9, 1.6)	(-4.3, 2.3)
	P-value [0.6059]+		0.3199	0.5534
Motor	Baseline	61 19.6 (1.3)	67 17.6 (1.2)	64 20.6 (1.3)
	Month 3	61 19.0 (1.4)	67 16.0 (1.3)	64 18.3 (1.3)
	Change (Mo3-BL)	61 -0.4 (0.9)	67 -1.9 (0.9)	64 -2.0 (0.9)
	Treatment Difference		-1.6	-1.6
	95% CI		(-4.1, 0.9)	(-4.2, 0.9)
	P-value [0.3583]+		0.2171	0.2103
ADL-On	Baseline	61 7.8 (0.7)	67 7.7 (0.6)	64 8.3 (0.7)
	Month 3	61 7.2 (0.7)	67 6.9 (0.7)	64 8.4 (0.7)
	Change (Mo3-BL)	61 -0.3 (0.5)	67 -0.8 (0.4)	64 0.2 (0.4)
	Treatment Difference		-0.4	0.5
	95% CI		(-1.7, 0.8)	(-0.7, 1.8)
	P-value [0.3057]		0.4872	0.4122
Mood	Baseline	61 1.6 (0.2)	67 1.8 (0.2)	64 2.1 (0.2)
	Month 3	61 1.6 (0.2)	67 2.1 (0.2)	64 2.2 (0.2)
	Change (Mo3-BL)	61 -0.0 (0.2)	67 0.3 (0.2)	64 0.2 (0.2)
	Treatment Difference		0.3	0.2
	95% CI		(-0.1, 0.8)	(-0.2, 0.7)
	P-value [0.3880]		0.1782	0.3498

θ 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 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. Included are patients with assessments at both baseline and month 3.

Note, finally, that statistical analyses were done on the ITT-LOCF population. There were a large number of dropouts in NZ14654, compared to the other placebo-controlled trials in fluctuators (v 1.2, p 87):

Table 23. Withdrawals from the Placebo-Controlled Studies in Fluctuators

The numbers of withdrawals shown are patients who withdrew prior to the time window for the primary end-point in each study.

Study	Primary end-point	Withdrawals by primary end-point - *n* (%)				
		Placebo	50 mg tolcapone	100 mg tolcapone	200 mg tolcapone	400 mg tolcapone
NZ14654	Week 13	7 (14%)	–	10 (20%)	9 (19%)	–
NN14971	Week 6	6 (8%)	–	2 (3%)	5 (7%)	–
NZ14316	Week 6	1 (2%)	1 (2%)	–	2 (5%)	5 (13%)
NZ14655	Week 13	10 (17%)	–	8 (13%)	7 (12%)	–
BZ14114	Week 6	5 (12%)	2 (5%)	–	2 (5%)	4 (11%)

The dropouts were presumably due to adverse events (see the sponsor's Table 3 above); these will be discussed in detail later. The sponsor has tried to adjust for the dropouts with an observed cases analysis. Despite the use of both ON- and OFF-time in the initial protocol as the primary outcome measure (see above), the present study report mentions only OFF-time (v 1.231, p 48). Nonetheless, as Dr. Hoberman has explained (personal communication), since the outcome measure can only be one of two possibilities (either ON-time or OFF-time), were one to be significant, the other must be signifcant too. For OFF-time, the observed cases analysis also shows significance (v1.231, p 49):

Appendix 9 ON/OFF-Time (Additional ITT LOCF and Observed Cases Analyses)

Appendix 9.1 Summary of Least-Squares Mean Change in ON/OFF-Time for the ITT Observed Cases

Rating	Scheduled Assessment Visit	Placebo N	Placebo mean (SE)	Tolcapone tid 100 mg N	Tolcapone tid 100 mg mean (SE)	Tolcapone tid 200 mg N	Tolcapone tid 200 mg mean (SE)
Percent OFF	Baseline	53	39.0 (1.9)	52	41.4 (1.9)	49	36.3 (2.0)
	Month 3	53	31.3 (2.5)	52	26.5 (2.6)	49	18.4 (2.6)
	Change (Mo3-BL)	53	-7.7 (2.3)	52	-13.7 (2.4)	49	-19.3 (2.4)
	Treatment Difference				-6.0		-11.6
	95% CI				(-12.7, 0.6)		(-18.3, -4.9)
	P-value [0.0035]				0.0747		< 0.001 **
Percent ON	Baseline	53	55.1 (2.2)	52	48.8 (2.3)	49	56.2 (2.3)
	Month 3	53	63.4 (3.0)	52	64.8 (3.1)	49	73.8 (3.1)
	Change (Mo3-BL)	53	8.9 (2.6)	52	14.7 (2.7)	49	18.6 (2.7)
	Treatment Difference				5.8		9.7
	95% CI				(-1.6, 13.3)		(2.3, 17.1)
	P-value [0.0365]				0.1254		0.0109 *

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 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.

The sponsor plotted the treatment effect for the observed cases over time (as for the ITT-LOCF cohort, the observed cases data show statistical significance for the 200-mg and not the 100-mg dose; v 1.231, p 49):

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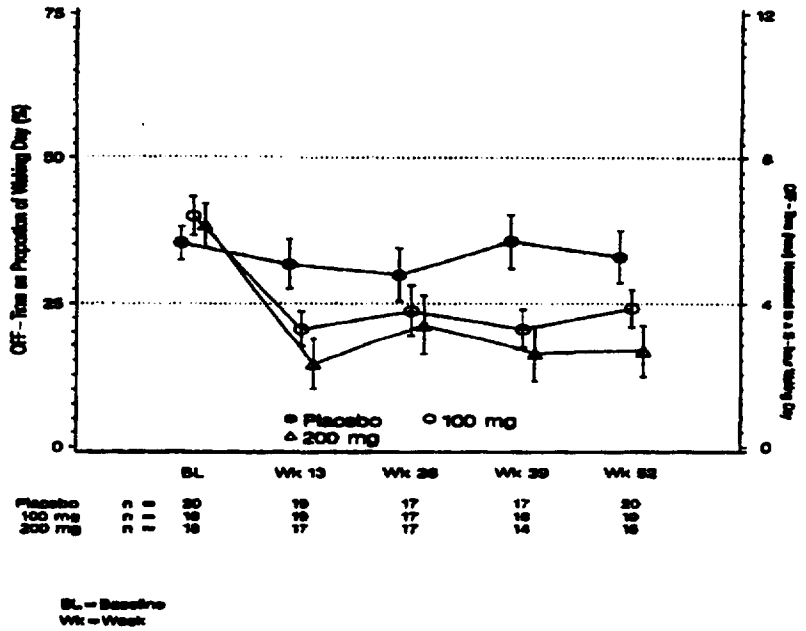
Figure 11. Completer Analysis of OFF-Time between Baseline and Month 12.
Patients with OFF-time assessments at week 52 and baseline; Observed cases.



Finally, the observed cases analysis of L-Dopa usage also shows significance; the plot below traces the effect over the time course (v 1.232, p 48):

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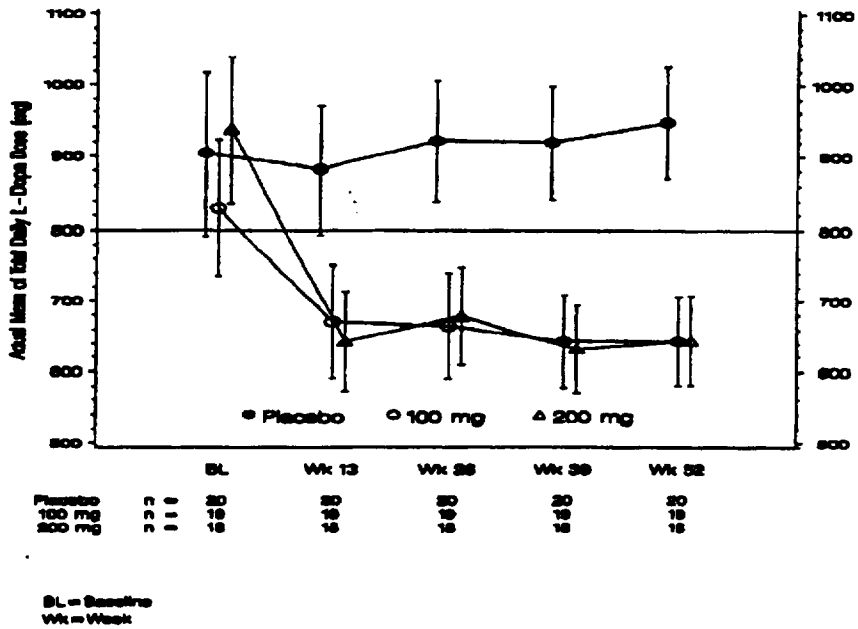
Figure 10. Completer Analysis of Change in Total Daily L-DOPA Dose between Baseline and Month 12

Patients with OFF-time assessments at week 52 and baseline; Observed cases.



BL = Baseline
Wk = Week

2. Study NZ14655

Also multicenter (18 European centers), randomized, double-blind, parallel-group, and placebo-controlled, this study aimed to evaluate the effect of two doses of tolcapone, 100 and 200 mg tid, over a 13-week period in fluctuating PD patients on Madopar.

As with NZ14654, the primary efficacy parameter was "the percent change from baseline in proportion of ON or OFF time (average of up to 3 diaries [patient self-rating charts])." Secondary outcome measures, efficacy analyses, criteria for study parameters, and statistical considerations for sample size were also identical. Screening and diary design were essentially the same as the requirements for study NZ14654.

A total of 177 subjects were randomized, with an eventual 53 withdrawals: 58 to placebo (18 withdrawals, 31%), 60 to 100 mg (21 withdrawals, 35%), and 59 to 200 mg (14 withdrawals, 24%). Reasons for withdrawal (to be discussed later) were shown as follows (v 1.254, p 28):

Table 4. Summary of Reasons for Withdrawal from the Study
All patients

	Placebo	Tolcapone tid	
	N = 58	100 mg N = 60	200 mg N = 59
	n (%)	n (%)	n (%)
Reasons for Withdrawal			
Entry Violation	1 (2)	0 (0)	1 (2)
Other Protocol Violation	1 (2)	2 (3)	1 (2)
Insufficient Response	9 (16)	4 (7)	1 (2)
AE / Intercurrent Illness	4 (7)	14 (23)	9 (15)
Withdrawal of Consent	3 (5)	1 (2)	1 (2)
Others	0 (0)	0 (0)	1 (2)
Total Patients Withdrawn from Treatment	18 (31)	21 (35)	14 (24)

Baseline demographics were similar for all three groups (ibid, p 30):

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Table 7. Summary of the Key Baseline Characteristics of Parkinson's Disease
ITT population

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

Percentages for the placebo, 100-mg, and 200-mg groups receiving concomitant anti-PD medications were roughly similar (84%, 73%, and 83%), as were percentages for the most common medications: selegiline (53%, 55%, and 59%), bromocriptine (24%, 18%, and 25%), and pergolide (19%, 22%, and 14%) (see v 1.254, p 31).

Unlike study NZ14654, the largest decrease in OFF time was observed with the 100-mg (and not the 200-mg) dose; the change from baseline for the 100-mg dose demonstrated a statistically significant difference from placebo. Mean increases in ON time were identical and statistically significant, when compared to placebo, for both doses of tolcapone (v 1.254, p 37; see also the sponsor's summary table below [v 1.254, p 46]):

Table 9. Summary of OFF/ON-Time

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

Rating	Scheduled Assessment Visit	Placebo N mean (SE)	Tolcapone tid 100 mg N mean (SE)	Tolcapone tid 200 mg 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.

For the observed cases analyses, the data show a similar pattern of significance (ibid, p 210):

Appendix 9 OFF/ON-Time

Appendix 9.1 Summary of OFF/ON-Time at Baseline and Month 3 for the ITT Observed-Cases Analysis

The table shows least-squares means ± SEM based on ANOCOVA. OFF/ON-time is presented as a percentage of the waking day.

Protocol: NZ14655 Report Date: 11DEC95

Table 8.1.1e.obs
Summary of Average* Percent Daily ON and OFF Time at Month 3
Based on Patient's Diary
Estimated Means and Standard Error of the Means
All Patients: Intent-to-Treat, Observed Cases

Rating	Scheduled Assessment Visit	Placebo N	Placebo mean (SE)	Tolcapone tid 100 mg N	Tolcapone tid 100 mg mean (SE)	Tolcapone tid 200 mg N	Tolcapone tid 200 mg mean (SE)
Percent OFF	Baseline	39	37.3 (2.7)	47	38.7 (2.4)	48	37.5 (2.3)
	Month 3	39	32.7 (3.4)	47	26.3 (3.1)	48	27.0 (2.9)
	Change (Mo3-BL)	39	-4.7 (2.8)	47	-13.1 (2.5)	48	-10.5 (2.4)
	Treatment Difference				-8.4		-5.8
	95% CI				(-16.9, -0.9)		(-13.1, 1.5)
	P-value [0.0824]+				0.0283		0.1159
Percent ON	Baseline	39	54.9 (3.1)	47	52.1 (2.8)	48	51.8 (2.7)
	Month 3	39	54.9 (3.9)	47	64.4 (3.6)	48	63.5 (3.4)
	Change (Mo3-BL)	39	0.4 (3.2)	47	11.9 (2.9)	48	11.2 (2.8)
	Treatment Difference				11.5		10.8
	95% CI				(2.9, 20.2)		(2.4, 19.3)
	P-value [0.0164]				0.0096 *		0.0128 *

* 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.

Withal, significance for the ITT-LOCF data is superior to the observed cases possibly suggesting that the placebo dropouts were clinically worse than the treated. This could not be verified because

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the sponsor did not provide a description of dropouts. Finally, when plotted over time, mean OFF- and ON-time for the observed cases analysis demonstrates a long-term treatment effect, most pronounced for the 200-mg dose (v 1.254, p 49):

Figure 11. Completer Time Course of Actual Mean OFF-Time between Baseline and Month 9

ITT population; observed-cases analysis. Patients are included with assessments at baseline and Month 9. BL, baseline; Wk, week.

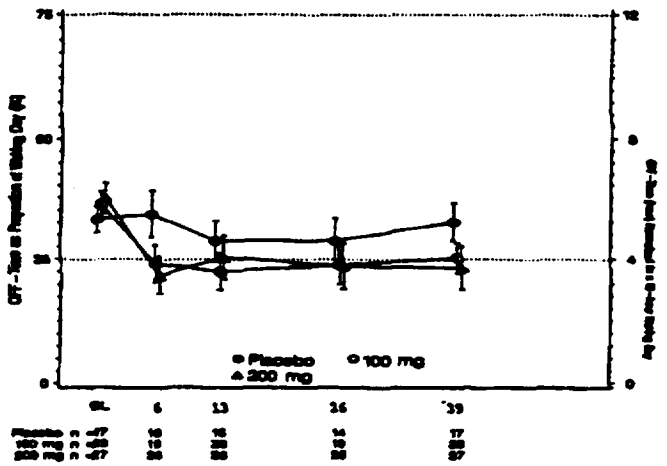
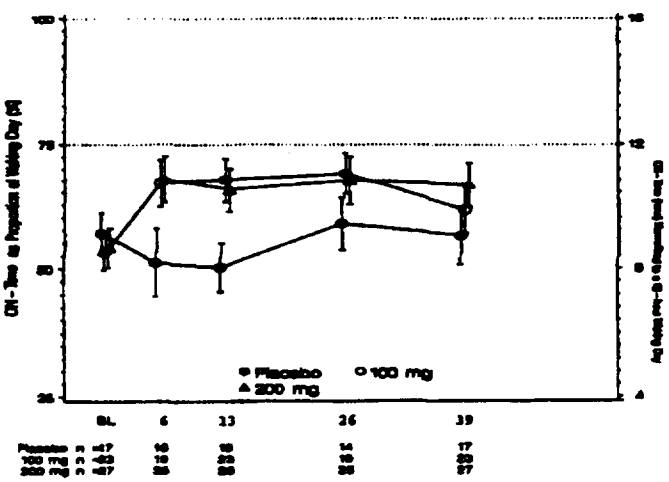


Figure 12. Completer Time Course of Actual Mean ON-Time between Baseline and Month 9

ITT population; observed-cases analysis. Patients are included with assessments at baseline and Month 9. BL, baseline; Wk, week.



As for secondary efficacy parameters, reductions in L-Dopa usage achieved statistical signficance for patients on Tolcapone, in contrast to placebo (v 1.254, p 46):

Table 13. 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 ± 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 x change/baseline.

Tolcapone dose (mg)	L-DOPA dose (mg)	Wearing-off/Fluctuations					Motor function	
		OFF-time		ON-time		IGA Wearing-off (%)	IGA Severity (%)	UPDRS Motor
		% waking day	% baseline	% waking day	% baseline			
Placebo	-29±26.2	-4.2±2.3	-11.1	-0.7±2.8	-1.3	37	29	-2.1±1.1
100	-109±23.4*	-12.7±2.1*	-31.5	10.8±2.6**	21.3	74**	75**	-4.2±1.0
200	-122±23.9**	-9.8±2.1	-26.2	10.8±2.6**	20.6	75**	73**	-6.5±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±0.4	-0.2±0.2	-0.9±0.9	-2.2±1.2	1.2	-2.8± 1.4	37
100	-0.9±0.3	0.1±0.2	-1.9±0.9	-3.2±1.1	-1.3	-4.8± 1.3	70**
200	-1.3±0.3	-0.1±0.2	-4.2±0.8*	-5.0±1.1	-4.7**	-7.9± 1.3**	78**

* $P < 0.05$ for difference from placebo
** $P < 0.01$ for difference from placebo

Scores on the Investigator's Global Assessment were also significant for the treated groups. However, the 200-mg dose was significant on the SIP Total (ibid, p 43):

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Table 10. Summary of Investigator's Global Assessments of Efficacy
ITT population; LOCF analysis.

Parameter Scheduled Assessment Visit	Placebo	Tolcapone tid 100 mg	 200 mg
Severity of Parkinson's Disease			
Month 3			
Frequency Counts [n (%)]			
(1) Improvement	15 (29)	40 (75)	40 (73)
(0) No Improvement	36 (71)	13 (25)	15 (27)
Not Evaluable	0	0	0
P-value [<0.001]		<0.001 ** +	<0.001 **
Wearing Off-Phenomenon			
Month 3			
Frequency Counts [n (%)]			
(1) Improvement	19 (37)	39 (74)	41 (75)
(0) No Improvement	32 (63)	14 (26)	14 (25)
Not Evaluable	0	0	0
P-value [<0.001]		<0.001 ** +	<0.001 **
Overall Efficacy			
Month 3			
Frequency Counts [n (%)]			
(1) Improvement	19 (37)	37 (70)	43 (78)
(0) No Improvement	32 (63)	16 (30)	12 (22)
Not Evaluable	0	0	0
P-value [<0.001]		0.0026 ** +	<0.001 **

* Mean was calculated based on the assigned scores printed in front of each category description.
NOTE: The unadjusted P-values are computed using the Cochran-Mantel-Haenszel test. The P-value for overall comparison is presented in brackets. '+' indicates P < 0.15 for Breslow-Day homogeneity test. '*' indicates P < 0.05 and '**' indicates P < 0.01 for pairwise comparison with placebo after adjusting for multiple comparisons.

the UPDRS Total, and the UPDRS Motor Scores (ibid, p 42):

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Table 11. Summaries of UPDRS Subscales I - III and Total Score

ITT population; LOCF analysis. The table shows least-squares means ± SEM based on ANOCOVA

UPDRS	Scheduled Assessment Visit	Placebo N mean (SE)	Tolcapone tid 100 mg N mean (SE)	Tolcapone tid 200 mg N mean (SE)
Total @	Baseline	58 34.6 (2.5)	56 31.9 (2.3)	58 32.4 (2.3)
	Month 3	58 31.8 (2.5)	56 27.5 (2.3)	58 24.7 (2.3)
	Change (Mo3-BL)	58 -2.8 (1.4)	56 -4.8 (1.3)	58 -7.9 (1.3)
	Treatment Difference		-2.0	-5.1
	95% CI		(-5.9, 1.8)	(-9.0, -1.3)
	P-value [0.0300]		0.2892	0.0092 **
Motor	Baseline	58 24.0 (1.7)	57 22.4 (1.5)	58 22.4 (1.6)
	Month 3	58 21.8 (1.7)	57 18.6 (1.5)	58 16.2 (1.6)
	Change (Mo3-BL)	58 -2.1 (1.1)	57 -4.2 (1.0)	58 -6.5 (1.0)
	Treatment Difference		-2.1	-4.5
	95% CI		(-5.0, 0.9)	(-7.4, -1.5)
	P-value [0.0144]		0.1633	0.0038 **
ADL-On	Baseline	58 7.9 (0.9)	57 7.5 (0.8)	58 7.7 (0.8)
	Month 3	58 7.5 (0.9)	57 6.7 (0.8)	58 6.4 (0.8)
	Change (Mo3-BL)	58 -0.5 (0.4)	57 -0.9 (0.3)	58 -1.3 (0.3)
	Treatment Difference		-0.4	-0.9
	95% CI		(-1.4, 0.6)	(-1.9, 0.2)
	P-value [0.2507]		0.4077	0.0974
Mood	Baseline	58 2.8 (0.3)	56 2.0 (0.3)	58 2.3 (0.3)
	Month 3	58 2.5 (0.3)	56 2.2 (0.3)	58 2.2 (0.3)
	Change (Mo3-BL)	58 -0.2 (0.2)	56 0.1 (0.2)	58 -0.1 (0.2)
	Treatment Difference		0.3	0.0
	95% CI		(-0.3, 1.0)	(-0.6, 0.7)
	P-value [0.5591]		0.3356	0.8971

@ Total of Motor, ADL (during ON), and Mentation Subcategories Scores.
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.

(See Dr. Hoberman's biometric review, p 3 for further discussion.)

C. *Other Double-blind, Placebo-controlled Trials:* Fluctuators *(6 weeks)*

There were, in addition, three shorter double-blind, placebo-controlled trials in fluctuating PD patients, but their length -- a six-week period -- may not provide an adequate amount of time to assess efficacy in a chronic disease like PD. Following are the results:

(1) Decreased OFF-time achieved statistical significance for all doses in studies NZ14316 (50, 200, and 400 mg) and NN14971 (100 and 200 mg), but only for the 200 mg dose (compared to 50 and 400 mg) in study NZ14114.

(2) As to increased ON-time, statistical significance was demonstrated for all doses in studies NN14971 (100 and 200 mg) and BZ14114 (50, 200, and 400 mg); but no dose achieved statistical significance in prolonging ON-time in study NZ14114.

Table 28. Summary of Efficacy Results at the Primary End-Points from the Placebo-Controlled Studies with Fluctuating Patients

ITT population using LOCF data. Data for OFF/ON-time and daily L-DOPA dose are expressed as change from baseline as least-squares means ± SEM, except for the investigator's global assessments of efficacy which are shown as incidence of patients with improvement. Change in OFF-time as a percentage of baseline was calculated as 100 X change in OFF-time from baseline / OFF-time at baseline. OFF/ON-time in study NZ14316 was assessed by the investigator at the clinic over a 10-hour period. ON-time in study NZ14316 is ON without dyskinesia. In all other studies, OFF/ON-time was recorded by the patient using an OFF/ON self-rating chart.

Study no.	Tolcapone	OFF-time		ON-time	L-DOPA	IGA improvement incidence			UPDRS score				SIP score		
	dose (mg)	% waking day	% baseline	(%)	dose (mg)	Severity (%)	Wearing-off (%)	Efficacy (%)	I	II	III	Total	Physical	Psycho-social	Total
NZ14654	Placebo	-7.8	-20.1	8.6	15.5	32	37	42	0.0	-0.3	-0.4	-0.7	-2.4	-2.0	-2.2
	100	-12.2	-30.7	12.6	-166.0**	60**	68**	71**	0.3	-0.8	-1.9	-2.4	-0.1	-0.7	-0.4
	200	-18.8**	-51.1	18.2*	-207.0**	79**	95**	91**	0.2	0.2	-2.0	-1.7	-0.8	0.8	-0.3
NZ14971	Placebo	-2.2	-5.4	2.0	-0.5	21	27	27	-0.3	-0.7	-1.2	-2.2	-1.1	-2.2	-1.5
	100	-12.3**	-30.1	12.9**	-185.5**	69**	79**	74**	-0.2	-0.4	-2.3	-2.9	-2.9	-2.7	-2.7
	200	-15.6**	-36.7	14.1**	-251.5**	80**	78**	77**	0.0	-0.5	-2.4	-2.9	-2.6	-2.8	-3.0
NZ14316	Placebo	-0.4	-0.0	0.8	-2.9	19	17	19	0.2	-0.1	-	-	-	-	-
	50	-16.6**	-40.9	7.5	-130.0**	65**	63**	70**	-0.5	-0.7	-	-	-	-	-
	200	-16.1**	-39.0	2.0	-239.0**	79**	79**	82**	-0.2	-0.7	-	-	-	-	-
	400	-18.1**	-46.5	5.0	-202.0**	80**	69**	77**	-0.0	0.2	-	-	-	-	-
NZ14655	Placebo	-14.2	-11.1	-0.7	-28.9	29	37	37	-0.2	-0.5	-2.1	-2.8	-2.2	1.2	-0.9
	100	-12.7*	-31.5	10.8**	-108.9*	75**	74**	70**	0.1	-0.9	-4.2	-4.8	-3.2	-1.3	-1.9
	200	-9.8	-26.2	10.8**	-122.0**	73**	75**	78**	-0.1	-1.3	-6.5**	-7.9**	-5.0	-4.7**	-4.2*
BZ14114	Placebo	-0.7	-2.9	-2.1	2.4	24	32	-	0.0	-0.8	-0.3	-0.9	-	-	-
	50	-5.9	-20.0	10.3*	-56.0	64**	72**	-	-0.3	-0.6	-2.6	-3.7	-	-	-
	200	-11.1*	-41.6	13.0**	-79.7**	61**	82**	-	0.0	-1.4	-5.8	-6.9	-	-	-
	400	-7.2	-29.1	8.9*	-13.3	57**	59*	-	-0.5	-1.5	-3.7	-6.0	-	-	-

* $P < 0.05$ and ** $P < 0.01$ for pairwise comparison with placebo after adjustment for multiple comparisons.

These results are summarized in the sponsor's table in v 1.2, p 103.

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Finally, in the active-control trial comparing Tolcapone to bromocriptine, changes in L-Dopa usage and improvement in wearing-off were statistically significant with Tolcapone (v 1.2, p 113):

Table 31. Summary of Efficacy Results for Study NZ14656: Open-Label Active-Controlled Comparison of Tolcapone and Bromocriptine in Fluctuators

ITT population using LOCF data. Data for OFF/ON-time and daily L-DOPA dose are expressed as least-squares mean change between baseline and week 8. The investigator's global assessments (IGA) are given as incidence (%) of patients with improvement between baseline and week 8.

Treatment	Efficacy parameter					
	OFF-time) (% waking day)	ON-time (% waking day)	Daily L-DOPA dose (mg)	IGA (%)		
				Severity	Wearing-off	Efficacy
200 mg tolcapone t.i.d.	-18.8	17.6	-123.7**	72	83*	82
Bromocriptine t.i.d.	-14.9	13.4	-30.2	65	69	69

* $P < 0.05$ and ** $P < 0.01$ for comparison with bromocriptine.

D. *Pivotal Trials:* Nonfluctuators

There have been two multicenter randomized, double-blind, parallel-group, placebo-controlled trials in nonfluctuating PD patients: (1) study BZ14115 (six-week duration in Europe and Australia, comparing two doses of tolcapone, 200 and 400 mg tid, in patients on either Sinemet or Madopar); and (2) NZ14653 (26-week duration in the USA and Canada, comparing tolcapone 100 and 200 mg tid against placebo in patients on a stable Sinemet regimen). Of the two, only NZ14653 provides a satisfactory length of time for a chronic disease. For study BZ14115 (the smaller, shorter trial), daily L-DOPA therapy (change in both total daily milligrams and total daily intakes) served as the primary efficacy parameter but failed to reach statistical significance in either treatment group when compared to placebo. Study NZ14653 (the larger, longer trial), on the other hand, used the UPDRS subscale II (ADLs), and by this measure both treatment groups demonstrated statistically significant changes with respect to placebo (v 1.2, p 112):

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Table 30. Summary of Efficacy Results at the Primary End-Points of the Placebo-Controlled Studies with Non-Fluctuating Patients

ITT population using LOCF data. Data are expressed as change between baseline and the primary end-point as least-squares means ± SEM.

Study no.	Tolcapone	L-DOPA	UPDRS score				SIP score		
	dose (mg)	dose (mg)	II	I	III	Total	Physical	Psycho-social	Total
NZ14653	Placebo	46.6	0.1	0.0	0.1	0.1	0.5	0.0	0.4
	100	-20.8**	-1.4**	0.1	-2.0*	-3.1**	-1.2**	-0.7	-0.9
	200	-32.3**	-1.6**	0.1	-2.3**	-3.7**	-1.0*	-1.2	-0.7
BZ14115	Placebo	-113.9	0.4	0.3	-1.5	0.8	–	–	–
	200	-182.0	-1.1*	0.0	-3.4	-4.6	–	–	–
	400	-180.6	0.1	0.3	-1.0	-0.6	–	–	–

* $P < 0.05$ and ** $P < 0.01$ for pairwise comparison with placebo after adjustment for multiple comparisons.

1. Study NZ14653

This multicenter (20 US and Canadian centers) randomized, double-blind, parallel-group, and placebo-controlled study was conducted in the USA and Canada and compared tolcapone 100 and 200 mg tid to placebo over a 26-week period. Primary and secondary efficacy measures were defined as follows (v 1.270, p 24):

1. Total score of the UPDRS Activities of Daily Living (ADL) subscale items during "ON" period. [primary];
2. Total score of the UPDRS Mentation, Behavior and Mood subscale items [secondary];
3. Total score of the UPDRS Motor subscale items [secondary];
4. Combined scores of the three UPDRS subcategories – ADL, Mentation, Behavior and Mood, and Motor items [secondary];
5. Proportion of patients developing fluctuations based on the UPDRS–Clinical Fluctuation subscale subcategory section B. (Patients with "yes" response to any of the items will be considered to have developed fluctuations) [secondary];
6. Total daily dose of levodopa and frequency of dosing [secondary];
7. Total score (expressed as a percent of total dysfunction) of the Sickness Impact Profile [secondary]. Scores of the two dimensions (physical and psychosocial) and 12 individual categories will be examined.

For all subsequent assessments after any addition of antiparkinsonian medication, the scores at the time of the addition will be used in the analyses.

All subjects were screened within four weeks of randomization. Inclusion criteria insisted upon daily L-Dopa requirements of >2 intakes and 100 mg and <4 intakes and 600 mg; clear improvement of PD symptoms with Sinemet; stable Sinemet regimen for ≥4 weeks; L-Dopa treatment ≥3 months but ≤5 years; and a score of ≥3 on the UPDRS ADL Subscale. Exclusion criteria comprised (1) history of sudden on-off fluctuations, diphasic dyskinesias, peak-dose dyskinesias (score >1 on UPDRS item 33), or dystonia; (2) end-of-dose wearing-off; (3) chronic treatment within the previous 6 months with a centrally acting dopamine antagonist, MAOI (excluding selegiline, if on a stable dose for ≥4 months), adjunctive anti-PD drug (anticholinergic, amantadine, beta-blocker, primidone), or Sinemet CR; (4) history of stereotactic surgery to treat PD <1 year prior to baseline.

Baseline demographics for the three groups were similar (v 1.268, p 30):

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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	[redacted]	[redacted]	[redacted]
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	[redacted]	[redacted]	[redacted]
N	102	98	98
UPDRS: Total Score			
Mean	29.5	26.7	25.3
SD	13.19	13.91	11.47
Range	[redacted]	[redacted]	[redacted]
N	102	98	97
UPDRS: Mentation			
Mean	1.3	1.2	1.2
SD	1.14	1.13	1.34
Range	[redacted]	[redacted]	[redacted]
N	102	98	98
UPDRS: Motor			
Mean	19.6	17.9	16.0
SD	10.12	10.47	7.78
Range	[redacted]	[redacted]	[redacted]
N	102	98	97

* Duration in years

(Continued)

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

Parameter	Placebo	Tolcapone tid	
		100 mg	200 mg
UPDRS: ADL (ON)			
Mean	8.6	7.6	8.1
SD	3.80	4.26	3.90
Range	[redacted]	[redacted]	[redacted]
N	102	98	98
UPDRS Fluctuations (OFF): Predictable			
No	91 (90)	88 (90)	90 (92)
Yes	10 (10)	10 (10)	8 (8)
Total	101	98	98
UPDRS Fluctuations (OFF): Unpredictable			
No	98 (97)	95 (97)	95 (97)
Yes	3 (3)	3 (3)	3 (3)
Total	101	98	98
UPDRS Fluctuations (OFF): Suddenly			
No	99 (98)	98 (100)	97 (99)
Yes	2 (2)	0 (0)	1 (1)
Total	101	98	98
UPDRS Fluctuations (OFF): Proportion			
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
UPDRS Dyskinesias: Duration			
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
UPDRS Dyskinesias: Disability			
Not Disabling	100 (99)	98 (100)	95 (97)
Mildly Disabling	1 (1)	0 (0)	3 (3)
Total	101	98	98
UPDRS Dyskinesias: Painful Dyskinesias			
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
UPDRS Dyskinesias:Early Morning Dystonia			
No	84 (83)	86 (88)	84 (86)
Yes	17 (17)	12 (12)	14 (14)
Total	101	98	98
**Mini-Mental Status			
Mean	29.0	29.0	29.2
SD	1.15	1.18	0.98
Range	[redacted]	[redacted]	[redacted]
N	102	98	98

** Parameter was recorded at Screening

The percentages for the placebo, 100-mg, and 200-mg groups receiving concomitant anti-PD medications (other than Sinemet) were 64%, 54%, and 61%, and the most common medication used was selegiline (54%, 51%, and 59%) (v 1.268, p 31).

Sample size was determined as follows (v 1.270, p 23):

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Based on the results of a study in patients with Parkinson's disease who required levodopa treatment, and had a stable response to levodopa (lazabemide protocol N3564), it was assumed that placebo-treated patients would show a 10% improvement during the ON period in UPDRS-ADL score (ie., decrease of 0.84 with the standard deviation of 2.2 from baseline score of 7.6) over a 6-month period. In order to detect a 20% difference between the tolcapone and placebo groups in the change from baseline in UPDRS-ADL score (when ON) (ie., treatment group difference of 1.52 with the standard deviation of 3.8) with 90% power at the type I error level of 0.05 (2-sided), a total sample size of 300 is required, with an expectation of 15% dropout and nonevaluable case rate (Lachin, 1981).

Due to the "common closing date" design, the total target number of patients will complete 6 months of treatment and at least 30% of the total patients will complete at least 12 months of treatment.

Efficacy analyses centered on the ITT population, excluding those who "did not receive at least one dose of test medication or did not have any follow-up information" (v 1.270, p 24). Excluded from secondary analyses on evaluable patients were those who were noncompliant (<80% of the test drug taken), violated the protocol, or did not complete at least 6 months of threatment and did not have assessments at the 6-month visit.No privision was made for replacement of dropouts. The protocol proposed three types of analyses (ibid):

1. An "intent-to-treat" Cases Analysis with Last-Observation-Carry-Forward:

This analysis will include all randomized patients who received at least one dose of the study medication and had assessments at baseline [ie., randomization day] and at least one posttreatment visit. If the score at an assessment time is missing, the last posttreatment observation available (whether scheduled or unscheduled) will be used for the missing assessment point. For all subsequent assessments after any addition of antiparkinsonian medication(s), the scores at the time of the addition will be used in the analysis.

In addition, to examine effect of tolcapone administered with concomitant medications including additional antiparkinsonian medication(s), an exploratory analysis will be performed for the primary efficacy parameter at months 6 and 12, using actual assessment scores after taking additional antiparkinsonian medication(s).

2. An Observed Cases Analysis:

This will include all patients who were randomized and had the measurements at the given assessment times. All subsequent assessments after any addition of antiparkinsonian medication will be excluded from this analysis.

3. An Evaluable Cases ("Standard") Analysis:

This will include only the "evaluable" cases as defined in section 11.2 of the protocol. No imputation will be made for missing data. This subset will include data only from the "evaluable" patients who were randomized and completed the 6-month of treatment and were available for evaluation at the 6-month assessment time. Patients who started additional antiparkinsonian medication(s) before the 6-month assessment time will be excluded from this analysis.

The analyses of "intent-to-treat cases" and "observed cases" will be done for the primary and secondary efficacy parameters, with an exception of the intent-to-treat analysis of actual scores of the patients with additional antiparkinsonian medication(s). The "evaluable cases" analysis will be performed for the primary and secondary efficacy parameters at 6 months only when more than 15% of patients are determined to be non-evaluable.

A total of 298 subjects were randomized, with an eventual 14 withdrawals (for reasons to be discussed later): 102 to placebo (18 withdrawals by week 26, the primary endpoint, or 18%), 98 to 100 mg (26 withdrawals, 27%), and 98 to 200 mg (24 withdrawals, 24%). Reasons for withdrawal are summarized by the sponsor (v 1.268, p 27):

Table 3. Summary of Reasons for Withdrawal from Study

All Patients.

	Placebo	Tolcapone tid	
	N = 102	100 mg N = 98	200 mg N = 98
	n (%)	n (%)	n (%)
Reasons for Withdrawal			
Entry Violation	1 (1)	0 (0)	0 (0)
Other Protocol Violation	0 (0)	1 (1)	3 (3)
Insufficient Response	3 (3)	1 (1)	3 (3)
AE / Intercurrent Illness	11 (11)	20 (20)	18 (18)
Withdrawal of Consent	3 (3)	4 (4)	0 (0)
Total Patients Withdrawn from Treatment	18 (18)	26 (27)	24 (24)

During the actual trial, patients were evaluated for efficacy and safety once between weeks 1 and 2 and subsequently at the end of weeks 6, 13, and 26. Patients were to be assessed, by protocol prescription, by the same investigator and at the same time of day as on the initial baseline visit (v 1.271, p 23). The UPDRS subscale II (ADLs) was used as the primary efficacy measure and consisted of thirteen questions (see the appendix to this review for a photocopy), the responses to which were based on historical information provided by the patient for the ON phase only; only symptoms related to PD were to be considered when the investigator scored this section (v 1.268, p 16). The following table summarizes the results from the UPDRS Subscales 1-3 (v 1.268, p 39):

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Table 8. Summary of UPDRS Subscales I to III, together with Total Scores Analysis

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

UPDRS	Scheduled Assessment Visit	Placebo N mean (SE)	Tolcapone tid 100 mg N mean (SE)	Tolcapone tid 200 mg 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 **

@ 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.

When Subscale 2 (ADL while ON) is considered, both tolcapone dose groups, when compared to placebo, showed improved functioning in activities of daily living at the six-month primary endpoint, and the differences in total ADL scores between treated and placebo groups were statistically significant. The sponsor also plotted the UPDRS Subscale II scores over the time course of the study: the decrease in mean ADL impairment scores was noted by the first assessment timepoint (week 1-2) for both doses and then continued to decline, generally plateauing by week 6 (the second timepoint) and remaining somewhat stable through the end of the study at week 26 (v 1.268, p 40):