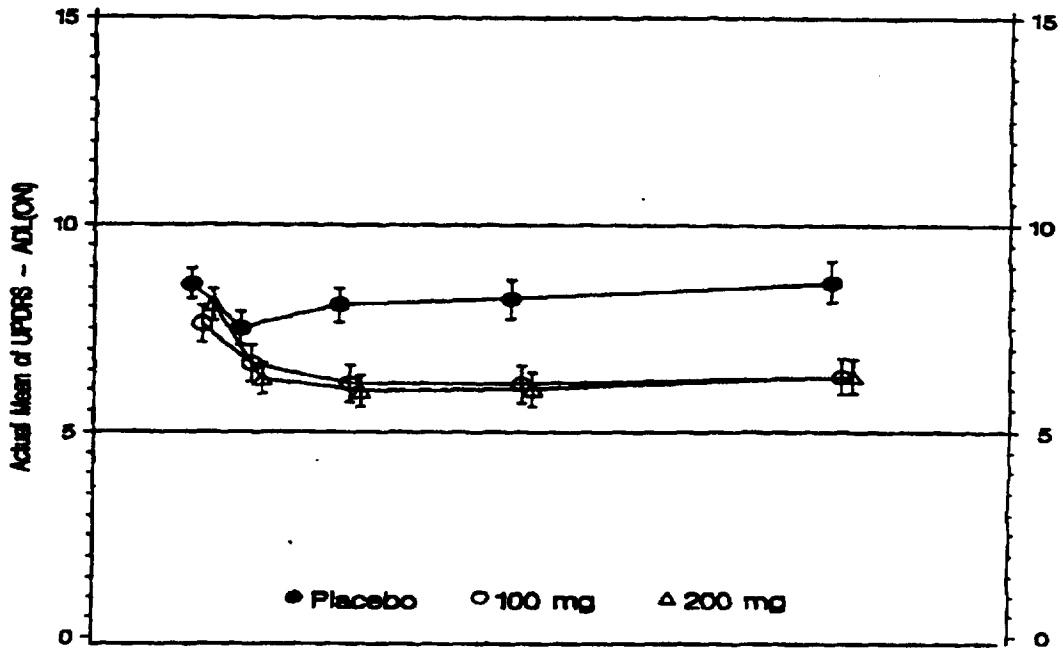
Figure 6. UPDRS Subscale II (ADL during ON) Score Over Time
ITT population; LOCF analysis. The figure shows actual means and SEM.



	BL	2	6	13	26
Placebo n =	102	102	102	102	102
100 mg n =	98	96	97	97	97
200 mg n =	98	98	98	98	98

According to the sponsor, treatment effects were demonstrated significantly for patients with greater ADL impairment at baseline, or an ADL score>6, but not for those with baseline scores <7 (v 1.268, p 40). Finally, it should be noted that only the *total* score for the UPDRS subscale II was found to be statistically significant; no single category on the ADL list stood out across the board (personal communication from Ernest E. Dorflinger, MD, director, International Clinical Research--CNS, Hoffmann-LaRoche).

Improvement in ADLs was also accompanied by significant improvements on several of the secondary outcome measures, namely, the Motor and Composite Index of Overall Severity of the UPDRS (see Table 5 above).

Table 10. Summary of Efficacy Results -Change from Baseline at Month 6 (Least-Squares Means ± SEM)

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

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

The SIP was significantly different from placebo only for the Physical score for both the 100- ($p<0.01$) and 200-mg ($p<0.05$) groups (v 1.268, p 45):

Table 9. Summary of SIP Scores (Change from Baseline at Month 6) - ITT LOCF, ITT Observed-Cases, and Evaluable-Patients Analyses

Data shown are least-squares means (SEM). * $P < 0.05$ and ** $P < 0.01$ for pairwise comparison with placebo after adjustment for multiple comparisons.

SIP Scale	Population (Analysis)	Placebo		Tolcapone tid			
				100 mg		200 mg	
		N	MEAN (SE)	N	MEAN (SE)	N	MEAN (SE)
Total	ITT (LOCF)	100	0.4 (0.5)	96	-0.9 (0.5)	96	-0.7 (0.5)
	ITT (Observed-Cases)	85	0.8 (0.5)	70	-0.9* (0.6)	71	-1.1* (0.6)
	Evaluable-Patients	78	0.6 (0.6)	60	-1.5* (0.7)	65	-1.4* (0.6)
Physical	ITT (LOCF)	100	0.5 (0.4)	96	-1.2** (0.5)	96	-1.0* (0.4)
	ITT (Observed-Cases)	85	1.0 (0.5)	70	-1.2** (0.6)	71	-1.6**(0.5)
	Evaluable-Patients	78	0.8 (0.5)	60	-1.4** (0.6)	65	-1.8* (0.6)
Psychosocial	ITT (LOCF)	100	0.0 (0.7)	96	-0.7 (0.7)	96	-1.2 (0.7)
	ITT (Observed-Cases)	85	0.5 (0.8)	70	-0.6 (0.9)	71	-1.4 (0.8)
	Evaluable-Patients	78	0.5 (0.8)	60	-1.6 (1.0)	65	-2.1 (0.9)

To assess the effect of dropouts on study results, the sponsor performs both an ITT-LOCF and observed cases analysis at the end of week 26. A statistically significant ($p<0.05$) effect of Tolcapone on ADL score was found, as well, in the observed-cases and evaluable-patients analyses (v 1.268, p 206-7):

Appendix 9 UPDRS Subscales I-III and Total

Appendix 9.1 Summary of Least Squares Mean Change of UPDRS Subscales I-III and Total Score for the ITT Observed Cases Analysis

UPDRS	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)
Total @	Baseline	84	30.4 (1.2)	70	25.5 (1.4)	71	25.3 (1.3)
	Month 6	84	30.0 (1.4)	70	20.9 (1.7)	71	20.9 (1.6)
	Change (Mo6-BL)	84	-0.1 (0.9)	70	-4.8 (1.1)	71	-4.7 (1.0)
	Treatment Difference				-4.7		-4.6
	95% CI				(-7.5, -1.9)		(-7.3, -1.8)
	P-value [<0.001]				0.0013 **		0.0012 **
Motor	Baseline	84	20.2 (0.9)	70	17.2 (1.0)	71	16.8 (1.0)
	Month 6	84	19.6 (1.0)	70	14.3 (1.2)	71	13.6 (1.1)
	Change (Mo6-BL)	84	-0.2 (0.7)	70	-3.1 (0.8)	71	-2.9 (0.8)
	Treatment Difference				-2.9		-2.7
	95% CI				(-5.0, -0.8)		(-4.8, -0.7)
	P-value [0.0085]				0.0068 **		0.0100 **

(Continued)

@ 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.

Appendix 9.1 (cont.) **Summary of Least Squares Mean Change of UPDRS Subscales I-III and Total Score for the ITT Observed Cases Analysis**

UPDRS	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)
ADL-On	Baseline	85	8.9 (0.4)	70	7.2 (0.5)	72	8.1 (0.4)
	Month 6	85	9.0 (0.5)	70	5.4 (0.6)	72	6.2 (0.5)
	Change (Mo6-BL)	85	0.2 (0.3)	70	-1.9 (0.4)	72	-1.9 (0.4)
	Treatment Difference				-2.0		-2.1
	95% CI				(-3.1, -1.0)		(-3.1, -1.1)
	P-value [<0.001]				< 0.001 **		< 0.001 **
Mood	Baseline	85	1.3 (0.1)	70	1.1 (0.2)	72	1.3 (0.1)
	Month 6	85	1.3 (0.1)	70	1.2 (0.2)	72	1.3 (0.2)
	Change (Mo6-BL)	85	0.0 (0.1)	70	0.1 (0.1)	72	-0.0 (0.1)
	Treatment Difference				0.0		-0.0
	95% C				(-0.3, 0.4)		(-0.4, 0.3)
	P-value [0.9297]				0.8162		0.8642

@ 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 overal 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.

As to secondary measures, a statistically significant of Tolcapone also found with respect to the UPDRS I-III Total and Motor scores, when the data were analyzed by the observed-cases and

evaluable-patients methods. Moreover, there was a statistically significant interaction of treatment effect with baseline motor score: treatment effects were greatest in patient with more impairment of motor functioning at baseline (motor score>16.5 for the 100-mg, and >14 for the 200-mg, group) (v 1.268, p 43). With respect to SIP scores, there was basically no difference in the results derived from either of the three statistical methods (v 1.268, p 42). Please see the Biometric Review by Dr. Dave Hoberman for a detailed statistical examination of the sponsor's efficacy claims.

In terms of change in L-Dopa usage, the mean change in daily L-Dopa dose and total number of daily L-Dopa intakes were statistically significant ($p<0.01$) for both Tolcapone groups at week 26 (for ITT-LOCF data, see v 1.268, pp 34-5; for observed cases data, see v 1.268, p 201):

Table 7. Summary of Total Daily L-DOPA Therapy at Baseline and Month 6

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

	Scheduled Assessment Visit	Placebo N mean (sem)	Tolcapone tid 100 mg N mean (sem)	Tolcapone tid 200 mg N mean (sem)
L-Dopa: Regular Number of Daily Intakes	Baseline	102 3.29(0.06)	98 3.13(0.06)	98 3.27(0.06)
	Month 6	102 3.47(0.07)	98 3.15(0.07)	98 3.23(0.07)
	Change (Mo6-BL)	102 0.20(0.06)	98 -0.01(0.05)	98 -0.03(0.05)
	Treatment Difference		-0.21	-0.23
	95% CI		(-0.4, -0.1)	(-0.4, -0.1)
	P-value [0.0027]		0.0049 **	0.0018 **
Total Daily Dose (mg)	Baseline	102 364.28(13.15)	98 370.65(13.33)	98 381.93(13.23)
	Month 6	102 412.81(13.82)	98 349.87(14.01)	98 347.03(13.90)
	Change (Mo6-BL)	102 46.58(9.58)	98 -20.82(9.70)	98 -32.30(9.64)
	Treatment Difference		-67.39	-78.88
	95% CI		(-94.2, -40.5)	(-105.7, -52.1)
	P-value [<0.001]		< 0.001 **	< 0.001 **

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.

Reduction in daily L-Dopa dosage was shown over time (v 1.268, p 36):

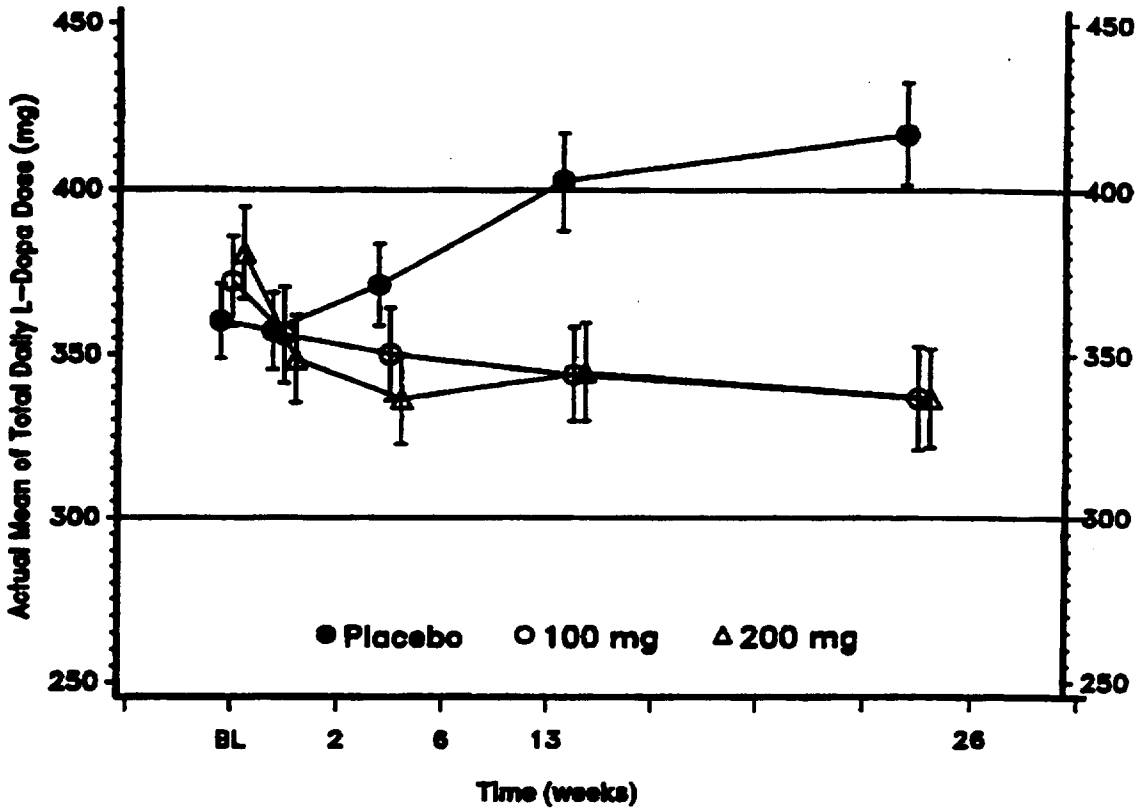
Appendix 8 L-DOPA Therapy

Appendix 8.1 Summary of Least Squares Mean Change in Total Daily L-DOPA Therapy for the ITT Observed Cases Analysis

	Scheduled Assessment Visit	Placebo N mean (sem)	Tolcapone tid 100 mg N mean (sem)	Tolcapone tid 200 mg N mean (sem)
L-Dopa: Regular Number of Daily Intakes	Baseline	88 3.33(0.06)	75 3.07(0.07)	79 3.31(0.07)
	Month 6	88 3.47(0.07)	75 3.08(0.08)	79 3.23(0.07)
	Change (Mo6-BL)	88 0.17(0.05)	75 -0.03(0.06)	79 -0.06(0.05)
	Treatment Difference		-0.20	-0.22
	95% CI		(-0.4, -0.0)	(-0.4, -0.1)
	P-value [0.0058]		0.0126 *	0.0033 **
Total Daily Dose (mg)	Baseline	88 371.52(14.73)	75 365.22(16.75)	79 385.29(15.30)
	Month 6	88 420.48(14.73)	75 337.06(16.75)	79 335.97(15.29)
	Change (Mo6-BL)	88 48.33(10.26)	75 -30.56(11.68)	79 -46.08(10.67)
	Treatment Difference		-78.89	-94.41
	95% CI		(-109.6, -48.2)	(-123.6, -65.2)
	P-value [<0.001]		< 0.001 **	< 0.001 **

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.

Figure 4. Total Daily L-DOPA Dose over Time ITT population; LOCF analysis
Figure shows actual means and SEM.



Placebo	n = 102	102	97	91		86
100 mg	n = 98	98	95	90		75
200 mg	n = 98	98	95	88		79

Some imbalances between groups in baseline demographics and disease characteristics are notable. Compared with the placebo group, the 200 mg tolcapone group had a shorter mean duration of disease (placebo, 4.1 years; 100 mg, 4.2 years; 200 mg, 3.4 years); however, by the sponsor's calculations, no statistically significant treatment-by-duration of disease interaction was found (v 268, p 44). The tolcapone groups also demonstrated less impairment on the UPDRS motor subscale (placebo: 19.6; 100 mg, 17.9; 200 mg, 16.0). According to the sponsor, there was a statistically significant ($p<0.001$) treatment-by-baseline motor-score interaction. The sponsor states further that patients with more severe motor disability -- and hence a higher UPDRS motor subscale score -- showed greater improvement on the UPDRS ADL score in both tolcapone groups. Therefore, the sponsor concludes, "since the tolcapone groups had lower mean motor scores at baseline, there was no evidence that the imbalance of baseline motor scores could account for the improvement in ADL scores in the tolcapone groups" (v 1.260, p 44).

Finally, the sponsor analyzed patients as to tendency to develop fluctuations on study drug, compared to placebo. Fluctuations were defined in two ways: (1) having any types of OFF periods, as determined by UPDRS items #36 (predictable OFF periods), #37 (unpredictable OFF periods), or #38 (sudden OFF periods), and (2) having any amount of OFF time as determined by UPDRS item #39 (proportion of day spent OFF). Given criterion #1, 26% of placebo patients developed fluctuations, 19% of the 100-mg, and 17% of the 200-mg groups. Given criterion #2, for the respective groups 26%, 19%, and 14% developed fluctuations. The differences between groups failed to achieve statistical significance.

The ADL score served as a secondary efficacy parameter for the shorter six-week BZ14115 trial in nonfluctuators. The 200-mg -- but not the 400-mg -- group showed a statistically significant change at 6 weeks (baseline score, 8.2±0.9; 6-week score, 7.1±0.9; treatment difference -1.5 [p=0.0103, 95% confidence interval]).

8 SAFETY FINDINGS

A. *Methods*

Information for the safety evaluation of tolcapone has been derived from the sponsor's Integrated Summary of Safety (v 333-5); case reports forms and narrative summaries for deaths, serious adverse events, and withdrawals; and the individual study summaries for the trials described above. There were 2839 participants in the entire tolcapone program, a total of 2,333 subjects (both patients and volunteers) received at least one dose of tolcapone; of these, 1536 were PD patients.

The following table shows the number of *exposed* patients (in bold type) in each of the nine *Phase 2 and 3* "therapeutic" trials (placebo controlled, active control, and uncontrolled) discussed in the NDA:

Study Type	*Study No.*	*Enrolled at baseline* ($n_{treated}$ [$n_{placebo}$])	*Primary Efficacy Endpoint* ($n_{treated}$ [$n_{placebo}$])	*Maximum Duration* ($n_{treated}$ [$n_{placebo}$])
Placebo-controlled	NZ14316[1]	**119** [42]	Week 6 (**111** [41])	6 weeks (**111** [41])
	NZ14114[1]	**112** [42]	Week 6 (**104** [37])	6 weeks (**104** [37])
	NZ14115[1]	**64** [33]	Week 6 (**55** [31])	9 weeks (**54** [31])
	NZ14653[2]	**196** [102]	Week 26 (**150** [88])	65 weeks (**2** [2])
	NZ14654[2]	**136** [66]	Week 13 (**117** [59])	52 weeks (**42** [24])
	NN14971	**143** [72]	Week 6 (**136** [66])	6 weeks (**136** [66])
	NZ14655[1,2]	**119** [58]	Week 13 (**114** [56])	52 weeks (**22** [10])
Active-controlled (tolcapone vs bromocriptine)	NZ14656	**72** (tolcapone); 74 (bromocriptine)	Week 8 (**64** [65])	8 weeks (**64** [65])
Uncontrolled (ongoing)	NZ14657	**484**	231 days (**355**)	52 weeks (projected duration)

[1]Placebo-controlled studies which also had an uncontrolled extension segment, following the point of maximum duration of the placebo-controlled arm. Subjects (whether treated or given placebo) who completed the placebo-controlled arm

were given the choice of participating in the uncontrolled extension; there was a total of 309 subjects in all of the extension studies, and all participants received the same tolcapone dose of 200 mg tid.
[2]The three pivotal studies--two for fluctuators (NZ14654, 14655), one for nonfluctuators (NZ14653).

B. *Serious and Unexpected Adverse Events*

1. Deaths

A total of 15 deaths occurred during the "therapeutic" trials summarized above: nine in the placebo-controlled Phase 3 studies (4 [1.3%] in the placebo, 3 [1%] in the 100 mg, and 2 [0.7%] in the 200 mg groups) and six (0.8%) during the uncontrolled studies. No patients died during the placebo-controlled Phase 2 or the active-control studies (v 1.333, p 80). The mean age of those who died was 72 years (range: 55-84). All but one of the deaths were assessed by the investigator as unrelated or remotely related to tolcapone treatment; among the most frequent causes of death were MI, cardiac arrest/failure, and pneumonia (three cases each). Other causes included cerebral hemorrhage, hypoxia, cancer, asphyxia, and aortic stenosis.

Of the 15 deaths, the one that was rated as "possibly related" to tolcapone treatment concerned a women (patient 14654/14586/133) who had been out of town and not evaluated by the investigator during the period when she developed diarrhea and presumed jaundice. An autopsy was not performed; however, the investigator assumed the cause of death to be cardiac-related, because the patient had had a right-bunndle-branch-block on her baseline EKG (performed at entrance into the study).

Following is a list of patients who died during "therapeutic studies," adapted from the sponsor's Table 32, v 333, p 81 (quotations taken from case summaries in Appendix 20, v 335, pp 26-32):

Study/Pt (Tolcapone tid)	*Age Sex*	*Adverse Event*	*Onset (day)* [1]	*Death (day)*	*Primary cause of death*	*PI's Assessment (autopsy)*
14653 /14060/303 (100 mg)	72M	L. hemiparesis 2/to neck trauma (C4-5 disc herniation); also found to have brainstem infarct. Developed cerebral epidural hemorrhage and quadriplegia after iv heparin. Persistent quadriplegia post C4-5 corpectomy and hematoma resection; expired 1 hr after family requested extubation. PMH: RHD, HTN. Meds: Sinemet 25/100 tid, selegiline 5 mg qd, Lasix 40 mg qd, KCl 20 mEq qd, Elavil 25 qhs.	102	112	Cerebral hemorrhage	Unrelated; no autopsy.
14653 /14134/183 (200 mg)	75M	Acute MI. PMH: HTN, cataracts, lumbar stenosis. Meds: Sinemet 25/100 1.5 T qid, nifedipine 60 qd, Tenoretic 50 qd, paracetamol prn.	228	228	MI	Remote; no autopsy.
14654 /16444/213 (placebo)	74M	Acute MI. PMH: psychosis, L4-5 fusion, vit B12 deficiency, constipation. Meds: Sinemet 25/100 0.5 T bid, Sinemet CR 50/200 (freq?), risperidone 0.25 mg bid, B12 1000 ug/month, bisacodyl 10 mg.	420 (1 month post study completion)	420	MI	Unrelated; no autopsy.

14654 /14644/236 Placebo	59M	Hospitalized on day 237 after choking on piece of meat. PMH: DM, arthritis, postural dizziness, constipation. Meds: Sinemet 50/200 (9 tabs, divided into 6 intakes/d), selegiline, amantidine, insulin, ibuprofen, acetaminophen, Metamucil.	237	239	Asphyxia Hypoxic-ischemic encepha-lopathy	Unrelated; no autopsy
14654 /14587 /0185 (100 mg)	69F	Severe abdominal distention: colon/stomach/pancreas cancer. PMH: HTN, CVA, arthritis, H/A, asthma. Meds: Sinemet CR 50/200 qid, nifedipine 30 qd, diclo-fenac sodium 50 tid, enalapril 50 qd, estrogen qd. *1st complaint on day 183; sx resolved, no medical attention. 2nd complaint on day 324 + medical follow-up.	183 (1st com-plaint); 324 (2nd com-plaint)*	About 2 mo. later.	Cancer (stomach/ colon/ pancreas)	Unrelated; tolcapone discontinued day 330; no autopsy.
14654 /14644/236 (placebo)	59M	Asphyxia; brought to hospital after choking on piece of meat. PMH: DM, arthritis, "postural dizziness," constipation. Meds: Sinemet CR 50/200 9 T/d (6 intakes), sele-giline 5 mg qd?, amantidine 200 mg qd, insulin, ibuprofen, acetaminophen, metamucil.	329	331	Asphyxia	Unrelated; no autopsy.
14654 /14586/133 (200 mg)	55F	Diarrhea from day 53; yellowing of skin and eyes from day 57. Pt was out of state; her husband notified investigator who advised medical follow-up; pt decided to return home the next day. Near end of 12-hr car trip, pt had "prominent dyskinesia, not unlike dyskinesias she had experienced previously." She lay down on the car's back seat. On arrival home about 1 hr later, she was found unresponsive and pronounced dead by physician. Her husband was told that "she had been dead for awhile." No reported history of vascular or cardiac disease (but EKG: incomplete RBBB), liver disease or known exposure to hepatitis. PMH: torti-collis, back pain, insomnia. Meds: Sinemet 25/100 1 qd, pergolide 3 mg qd, selegiline 10 mg qd.	53	60	Cardiac re-lated?	Possibly related; no autopsy.

14971 /15938/319 (100 mg)	80F	Cough, high fever; dx: pneumonia, tx amoxicillin 250 mg tid. Three days later, found unresponsive, bent over in chair. Hospitalized with "empyema, pneumonia, resp arrest," placed on ventilator, tx cefuroxime 750 mg iv q8, clindamycin 600 mg iv q8. Attempted extubation on day 39 unsuccessfully, 2/to laryngeal edema. Extubation and trach on day 41. On day 46, medically stable, but unresponsive neurologically. On day 47, found pleuritic fistula; abdomen grossly impacted with stool. On day 48, Cheyne-Stokes breathing noted, with central and peripheral cyanosis; no response to pain,unreactive pupils. Pronounced dead, PMH: thyroid cancer (15-yr remission), nausea, blurred vision, constipation, insomnia. Meds: Sinemet 25/100 3.75 T/d (5 intakes), pergolide 0.25 mg tid, domperidone 10 mg qid, dicycloverine 10 mg tid, Lasix 20 mg prn, Citrotein.	33	48	Pneumonia	Unrelated; brain autopsy: changes c/w idiopathic PD; mild Alzheimer's; severe, diffuse hypoxia.
14971 /5929/57 (placebo)	63F	Found unresponsive at home on day 36, with Cheyne-Stokes respiration, pallor, cyanosis. In ER, glu=22; EKG=SR@100; CXR=RUL/RLL pneumonia. Tx: 5% dextrose, cefotaxime 750 mg iv + Unasyn 1.5 g iv q6. Intubated 2/to resp distress. Day 39, CXR: R pneumothorax; chest tube inserted. Extubated day 40; then developed aspiration pneumonia. Made DNR by family. PMH: pneumonia, insomnia. Meds: Sinemet 10/100 12.5 T/d, Larodopa 1700 mg/d, pergolide 1.25 mg tid, chloral hydrate 500-1000 mg hs.	36	?	Pneumonia	Unrelated; no autopsy.
14657 /15303/8 (200 mg)	81M	Day 81-8, hospitalized for repair of aortic aneurysm, but refused surgery. Day 91, rehospitalized for pneumonia and "cardiac decompensation:; tx: PCN, mefanamic acid, Lasix (doses?). Day 104, discharged. Day 106, died at home. PMH: aortic aneurysm, CAD, ankle edema. Meds: Madopar 125 1 T tid, Madopar HBS 1 T (freq?), selegiline 10 mg qd, lisuride 0.08 mg/d, isosorbide 0.02/d, oxazepam 15 mg/d.	81	106	"Suspected pneumonia"	Unrelated; no autopsy.

14657 /15303/8 (200 mg)	73M	Recurrent syncope and dyspnea, day 115-7; hospitalized for cardiac cath 2/to severe aortic stenosis. Day 117, tx isosorbide 40 mg, Dytide H 0.025 (freq?). On day 204, rehospitalized for CABG; CXR: cardiomegaly, bilat pleurral effusion, pulmonary congestion. Day 209, died prior to surgery. PMH: aortic stenosis, CAD, hypercholesterolemia, depression. Meds: Medopar 125 1 T tid, Madopar HBS 1 T (freq?), selegiline 10 mg, lisuride 0.8 mg (freq?), citalopram, Limbitrol.	115	209	Aortic stenosis	Unrelated; no autopsy.
14657 /5372/1505 (200 mg)	77M	Severe chest pain day 42; had complained of recurrent CP earlier at beginning of study as well. Day 42 hospitalized for worsening angina pectoris. Day 43, died 2/to "masssive MI." PMH: angina, lumbago. Meds: Sinemet 25/250 3 T/d, pergolide 3 mg qd, NTG o.4 mg, isosorbide 60 mg (freq?), caposide 12.5 mg (freq?), atenolol 50 mg qd?, carbasalate calcium.	42	43	MI	Unrelated; autopsy: severe stenosis LCA, obstructed LAD, hypertrophy, LV fibrosis.
14316ext /12809/10 (200 mg; previously on placebo)	84M	Hospitalized with aspiration pneumonia and dysphasia day 444. NGT placed; unspecified antibiotic started. Day 454, developed afib; EKG suggestive of MI (enzymes negative). Conversion to NSR after digoxin and quinidine. Found to have R LE embolus, unresponsive to urokinase; angioplasty unsuccessful; had AKA. Day 462, found unresponsive; not resuscitated. PMH unknown. Meds: diflunisal 500 mg, hydrocodone 7.5 mg, paracetamol 500 mg, diazepam 5 mg (freq?).	506 (444)= pneumonia; 516 (454)= afib; 524 (462)= cardiac arrest[2]	462	Cardiac arrest	Pneumonia, unrelated; afib, unrelated; cardiac arrest, remotely related.

14114Ext /11899/805 (200 mg; previously on placebo)	77M	Day 93, primary mamma virilis carcinoma under local anesthesia. Days 184-315, hospitalized for "neuralgia" and given carbamazepine "200 or 400 mg" days 189-222; then given colecalciferol from day 201 and clozapine for "confusion and agitation" from day 203 until discharge. Per investigator, neuralgia unrelated, but psychiatric sx probably related to tolcapone. Days 218-60, given promethazine and flurazepam for sleep disorder. Day 271, found down in front of house (fall?) and hospitalized with femur fracture, hypothermia (32°C), hypotension (90/60). 2 h later had died 2/to cardiac arrest. PMH: HTN, 1° mam-ma virilis carcinoma, glaucoma?. Meds: lis-uride 0.4 mg tid, nifedipine 20 mg bid, enal-april 10 mg qd, HCTZ 12.5 mg qd, Ferro San-ol 100 mg tid, bisacodyl 10 mg qd, pilocarpine 2% 1 gt tid, apraclonidine (strength?) 1 gt/d.	465 (271)	465 (271)	Cardiac arrest	Hypotension, remotely related; cardiac arrest, remotely related.
14114Ext /11950 /1805 (200 mg; previously on 50 mg)	67F	History of low Hgb, HCT, RBC counts at baseline and all assessments; on day 69, Hgb 10 (reference range 13-18). Entered open-label ext 205 days after completing 40-day double-blind, placebo-controlled segment on tolcapone 50 mg tid. "Died unexpectedly" on day 431 (227); "primary cause of death was recorded as LV failure, with anemia and gastric ulcer as precipitating factors." PMH: anemia, no history gastric ulcer. Meds: disodium etiodronate 400 mg qd, dihydrocodeine 60 mg tid, paracodol 1 T/d.	431 (227)	431 (227)	Cardiac failure	Unrelated; autopsy: "no evidence of acute bleeding and there was no history of gastric ulcer."

[1]Days from start of double-blind randomized treatment.

[2]Numbers without parentheses indicate days on placebo or lower dose of tolcapone during the double-blind, placebo-controlled segment of the trial; and numbers within parentheses, days on tolcapone during the open-label extension period.

The mean age of subjects who died was 72 years (range: 55-84). In view of the advanced age of the study population and the duration of the studies, it would not be surprising to see deaths in the development program. Using data from the sponsor's Figure 13, "Duration of Exposure to Tolcapone" (v 1.2, p 117), one calculates 882.8 person-years for total study exposure. Factoring in the 15 study deaths yields a mortality ratio of 1.7 deaths per 100 person-years. This number may indeed be quite low for the PD population as a whole: very rough mortality rates for PD patients in general (with 63 as the mean age, similar to the Tasmar PD population [v 1.2, p 115]) would approximate 8.9 per 100 person-years (see Morens DM, Grandinetti A, Davis, JW, et al. Evidence against the operation of selective mortality in explaining the association between cigarette smoking and reduced occurrence of idiopathic Parkinson Disease. Am J Epidemiol 144;1966:400-4). However, the Tasmar PD population would appear to be healthier than the PD population as a whole. Tolcapone is highly protein bound, and the investigators therefore attempted to screen out

serious medical conditions necessitating medications that could potentially result in interactive complications. The general health of the tolcapone population can be gauged by the types of concomitant medications patients were taking (v 1.2, p 116): antihypertensives (13-19%), laxatives (15-17%), analgesics (38-40%), anti-inflammatories (21-25%), psycholeptics (eg, anxiolytics; 21-22%), and psychoanaleptics (eg, antidepressants; 15-21%).

Subsequent information, submitted 10/3/96 by the sponsor in the Four-Month Safety Update (covering the period through 4/1/96), discusses deaths in the uncontrolled trials. There have been 22 deaths after the cut-off date for the NDA to 9/27/96, or the date of publication of the Four-Month Safety Update (study cut-off date: 4/1/96). Case reports for 15 are included in the Four-Month Safety Update (the others presumably occurred duringthe period between the study cut-off date, 4/1/96, and publication date, 9/27/96): 9 in the uncontrolled extensions of the placebo-controlled studies [4 (1.3%) in the placebo, 3 (1%) in the 100 mg, and 2 (0.7%) in the 200 mg groups], and 6 (0.8%) in the uncontrolled studies. The remaining seven deaths occurred after the cut-off point of the Four-Month Safety Update, and case reports were therefore not submitted. The mean age of those who died was 70 years (range: 58-80; compare to the mean of 72 and range, 55-84, for the NDA studies). All of the deaths were assessed by the investigator as either unrelated or remotely related to tolcapone treatment. As in the NDA, the most frequent causes of death were cardiac arrest/failure and pneumonia. Again, there was little difference between the NDA and the Safety Update as to the other causes listed (cerebral hemorrhage, hypoxia, cancer, and atherosclerosis). Following is a list of patient deaths from the NDA cut-off date to the end of the period covered by the Four-Month Safety Update (from the sponsor's Table 13, v 7.1, p 31; patient information adapted from case summaries on pp 32-37):

Study/Pt (dose)	*Age Sex*	*Adverse Event*	*Onset (day)* [1]	*Death (day)*	*1 º cause of death*	*PI's assessment*
14657 /15392/400 (open label: 200 mg tid)	65M	**Carcinoma bowel:** diarrhea since day 400, hosp day 429, d/c'd after resolution day 434. Rehosp day 440 after dx of bowel carcinoma, mets to liver. Tolcapone d/c'd day 444. Died day 448.	440 (382)	448 (382)	Carcinoma bowel	Unrelated
14316Ext /12642/190 (double-blind and open-label ext studies: 200 mg tid)	79M	**Pneumonia:** hosp with pneumonia day 538, but recurrent aspiration pneumonia (Pseudomonas, Klebsiella, MRSA) resulted in prolongation of stay; s/p jejunostomy tube. Intubated for lethargy and resp failure. Made DNR by family, then extubated. Amphotericin added for recurrent fevers; pulm edema developed, then afib. Condition worsened; tolcapone d/c'd, pt withdrawn from study. Died day 638. PMH: HTN; meds: Sinemet, Verapimil, Quinapril.	584 (584)	684 (678)	Pneumo-nia	Unrelated

14316Ext /12849/102 (double-blind study: 400 mg tid x 42d; open-label ext: 200 mg tid)	78F	**Cardiac failure:** 1st seizure ("mild") day 384; DPH started day 446. Seizures ("moderate") recurred day 626; then "severe" seizure day 683, when seen by home-health aide and "determined to be stable." Found dead later that day by husband. PMH: severe LAE, HTN; meds: Sinemet, lisinopril, DPH, ranitidine, Tylenol prn, psyllium.	725 (725)	726 (726)	Probable cardiovas-cular event	Unrelated
14654Ext /14586/132 (double-blind study: 100 mg tid x 270d; open-label ext: 200 mg tid x 209d)	73F	**Cardiac failure:** hosp for R humerus fx day 128 due to multiple falls; R pleural effusion; ataxic gait; LE weakness; s/p ORIF day 135. D/c'd to rehab day 136. Developed progressive weakness day 202 transported by EMS to hosp day 209; died in ER. PMH: CHF, cardiomyopathy, MR, AR, bilateral pleural effusions, hypotension, edema, DJD, cellulitis; meds: Sinemet, pergolide, digoxin, Lasix, KCl, fludrocortisone, folate, Lac-Hydrin, simethicone.	81 (81)	479 (479)	Gen. ather-osclerosis and athero-sclerotic heart disease	Unrelated
14655Ext /14670/187 (double-blind study: placebo x 273 days; open-label ext: 200 mg tid)	66F	**Pneumonia:** hosp day 21 with R femur fx due to fall; s/p endoprosthesis day 22 and d/c'd day 35 to rehab. Day 103 rehosp for rectal prolapse; day 106 s/p perianal cerclage, d/c'd day 128. Rehosp day 203 for pneumonia and LV decompensation; also tx'd for UTI and anemia. Day 212 had resp failure and CV arrest; though resuscitated, artificial resp d/c'd and pt died day 212. PMH: osteoporosis, orthostasis, UTI; meds: Madopar, selegiline, pergolide, doxepin, domperidone, nitroxoline, ASA, Tridin, Mg^{++}, cholecalciferol, oxilofrine.	476 (203)	485 (212)	Pneumo-nia	Unrelated
14657 /15404/2907 (open label: 200 mg tid)	58F	**Sudden death:** day 360 found collapsed in chair; "EMS arrived 30 min late"; no vitals en route to hosp, failed resuscitation. PMH: orthostasis, hypokalemia, hemoptysis, R ear deafness, insomnia; meds: Sinemet, pergolide, fludrocortisone, oxazepam, temazepam.	360 (360)	360 (360)	Probably cardiac related	Remote

14657 /15391/305 (open label: 200 mg tid)	70M	**Ventricular hypertrophy left:** found down in NH day 279, cyanotic and asystolic; unsuccessful resuscitation. PMH: edema, cramps; meds: Madopar, Lasix, Kcl, docusate, folate, quinine. (*Autopsy:* LVH, pulm edema, atherosclerosis.)	279 (279)	279 (279)	LVH	Remote
14657 /15301/203 (open label: 200 mg tid)	73M	**Pneumonia:** hosp day 426 with pneumonia; died day 440 (no other information). PMH: pneumonia, cardiomyopathy; meds: amoxicillin, digotoxin.	426 (425)	440 (439)	Pneumo-nia	Unrelated
14657 /15323/1415 (open label: 200 mg tid)	75F	**Lymphoma** (incorrectly recorded; should probably be *multiple myeloma*): back pain starting day 157; hosp day 175 and d/c'd on analgesics day 181. Rehosp day 184 with dx multiple myeloma; tx'd with XRT and chemo. Tolcapone d/c'd day 285 and pt withdrawn from study. Chemo d/c'd day 294 because pt was terminal; died day 311. PMH: anxiety, intercostal neuralgia, vertebral disc, insomnia; meds: Madopar, selegiline, alprazolam, lorazepam, imipramine, indomethacin, diclofenac, ergoloid mesylate, picosulfate, sterculia, Agiolax, Ca^{++}, vit D, Antichloric.	205 (205)	311 (285)	Multiple myeloma	Unrelated
14971Ext /15928/29 (double-blind study: 200 mg tid x 43d; no med x 41d; open-label ext: 200 mg tid x 91d)	66M	**Pneumonia:** withdrew from tolcapone study day 194 to pursue pallidotomy, then increased Sinemet dose to baseline ("no different off tolcapone" day 197). Hosp day 201 for pneumonia; progressively deteriorated; died day 203. PMH: systolic murmur, papular rash, insomnia; meds: Sinemet, pergolide, selegiline, amantidine, clonazepam.	285 (237)	287 (237)	Pneumo-nia	Unrelated

14657 /15373/1708 (open label: 200 mg tid)	58M	**Pneumonia:** hosp day 372 for recurrent aspiration pneumonia; tx'd with gentamicin and piperacillin, later (when cx results available) changed to pen G and amphotericin (then switched to itraconazole on day 385). On day 388 developed **bradycardia**, followed by **cardiac arrest** with resuscitation; but suffered post-hypoxemic **coma**. Made DNR on day 395 by family and died. PMH: pleural effusion, anemia, DOE; meds: Sinemet, pergolide, amantidine, albuterol, acetylcysteine, lactulose, Tylenol, thiamine, vit C, vit B complex.	372 (363) 388 (363) 388 (363) 388 (363)	395 (363) 395 (363) 395 (363) 395 (363)	Pneumo-nia Bradycardia Cardiac arr Coma	Remote Unrelated Remote Unrelated
14657 /15380/3904 (open label: 200 mg tid)	75F	**Carcinoma ovary:** hosp day 203 with L LE cellulitis; tx'd with pen G and flucloxacillin and d/c'd day 206 when could, "ambulate well." Rehosp day 294 with abdominal and thigh edema; found to have malignant ascites and pelvic lesion, dx: ovarian carcinoma. Died day 323. PMH: hypothyroidism, dyspepsia, cramps, hernia, insomnia; meds: Madopar, selegiline, thyroxine, ranitidine.	294 (294)	323 (323)		Unrelated
14657 /15404/2901 (open label: 200 mg tid)	67M	**Cerebral hemorrhage:** completed tolcapone study day 370 and chose not to enter ext. Hosp day 371 for elective L pallidotomy; surgery day 372, during which developed speech difficulty, impaired comprehension, L H/A. CT: large L frontal bleed. Postop: resp problems; seizures day 375 (CT: R hydrocephalus). Tx: cefotaxime, DPH, mannitol; compassionate care because of poor prognosis. Died 380. PMH: hypotension, dyspnea, CP, tics, panic attacks, sciatica, pharyngitis, dry mouth, DJD, constipation; meds: Sinemet, Sinemet CR, bromocriptine, selegiline, domperidone, diclofenac, senna.	372 (370)	380 (370)	Brainstem death; cerebral hemor-rhage	Unrelated Unrelated (*autopsy:* brainstem death; cerebral hemor-rhage, undeter-mined etiology)
14971Ext /15937/289	73M	**Carcinoma pulmonary:** day 13 CXR showed bilateral lung shadows found to be masses on CT. WNL bone, brain, abd scans and PFTs; bx on day 32: poorly dif adenocarcinoma. Hosp day 42 for "unstable HTN," which resolved same day. Died day 56.	57 (57)	100 (86)	Carcinoma pulmo-nary; HTN	Unrelated Remote

14657 /15412/4506 (open label: 200 mg tid)	80M	**Cardiac failure:** hosp day 242 with femur fx. Day 261 developed agitation, tx'd with clozapine and clonazepam. Dx'd with DM and bronchopneumonia day 268, tx'd with cefotaxime, piperacillin, paracetamol, acetylcysteine, tolbutamide. Tx'd with piracetam and citicoline for confusion day 270. Progressively deteriorated; died day 309 due to "cardiac failure." PMH: HTN, SVT; meds: Sinemet, Lasix, amiodarone, Ca^{++}, NTG, clozapine, and later digitalis, cortisone, Agarol.	309 (309)	309 (309)	Cardiac failure	Unrelated (*autopsy:* cardiac failure)
NZ14567Ext /0111[2]	86M	Suicide	127 (127)	127 (127)	Suicide	Unrelated
NZ14657Ext /800[2]	67F	Asthma	549 (549)	557 (557)	Asthma[3]	Unrelated
NZ14655Ext /708[2]	49M	Abdominal Pain	247 (247)	247 (247)	Abdominal pain[3]	Remote
NZ14657Ext /25122[2]	79M	Cerebrovascular disorder	494 (494)	497 (497)	Cerebro-vascular disorder[3]	Remote
J357611 /114[2,4]	66F	Sudden death	57 (41)	57 (41)	Sudden death[3]	Remote
J347608 /1801[2,4]	71F	Pneumonia	111 (111)	113 (113)	Pneumonia[3]	Unrelated
J357608 /2701[2,4]	55M	Anoxic encephalopathy	92 (92)	92 (92)	Anoxic encephalo-pathy[3]	Unrelated

[1]Days from the start of the original study; numbers in parentheses indicate days on tolcapone.

[2]Summary of deaths occurring in ongoing studies as of September 1, 1996, or after the cut-off date for the current Safety Update.

[3]No further information has been provided.

[4]Japanese studies.

2. Serious Nonfatal Adverse Events

The sponsor classifies a nonfatal adverse event as serious if it was life-threatening, permanently disabling ("incapacitating or interfering with the ability to resume usual life patterns"), or an overdose; required in-patient hospitalization or prolongation of hospitalization; or caused a congenital anomaly or cancer (v 1.333, p 12). The majority of these adverse events fell into the category of requiring hospitalization (v 1.2, p 139-40). Following is a list of nonfatal serious adverse events, with crude incidence, from the placebo-controlled studies (summarized from the sponsor's Appendix 21.3, v 335, pp 527-37):

Adverse Event 1	*Placebo (n=415)*	*50 mg (n=78)*	*100 mg (n= 296)*	*200 mg (n=408)*	*400 mg (n=107)*
<u>CNS/PNS</u>					
Dyskinesia	1 (0.2)	0	1 (0.3)	4 (1.0)	0
Falling	1 (0.2)	0	0	4 (1.0)	0
Confusion	0	0	2 (0.7)	2 (0.5)	0
Dystonia	1 (0.2)	0	0	2 (0.5)	0
PD aggravation	3 (0.7)	0	2 (0.7)	1 (0.2)	0
Encephalopathy	1 (0.2)	0	1 (0.3)	0	0
Neuralgia	1 (0.2)	0	1 (0.3)	0	0
Balance loss	0	0	0	1 (0.2)	0
Hemiballismus	0	0	1 (0.3)	1 (0.2)	0
Hemiplegia	0	0	1 (0.3)	0	0
Hyperkinesia	0	0	0	1 (0.2)	0
Hypertonia	0	0	0	1 (0.2)	0
Hypokinesia	0	0	0	1 (0.2)	0
PD fluctuation	0	0	0	1 (0.2)	0
Stroke					
<u>GI</u>					
Diarrhea	1 (0.2)	0	2 (0.7)	5 (1.2)	0
Abdominal pain	3 (0.7)	0	1 (0.3)	1 (0.2)	1 (0.9)
Gastric Atony	1 (0.2)	0	1 (0.3)	0	0
Nausea	0	0	1 (0.3)	1 (0.2)	0
Vomiting	1 (0.2)	0	0	1 (0.2)	0
Constipation	0	0	0	1 (0.2)	0
Dysphagia	0	0	1 (0.3)	0	0
GI infection	0	0	1 (0.3)	0	0
Hiatal hernia	0	0	1 (0.3)	0	0
Intestinal Obstr	1 (0.2)	0	0	1 (0.2)	0
<u>MUSCULO-SKELETAL</u>					
Fractures	4 (1.0)	0	1 (0.3)	0	1 (0.9)
Back pain	2 (0.5)	0	0	2 (0.5)	0
Intervert disc	1 (0.2)	0	1 (0.3)	0	0
Limb pain	1 (0.2)	0	1 (0.3)	0	0
Carpal tunnel	0	0	1 (0.3)	0	0
Stiffness	0	0	0	1 (0.2)	0
<u>RESPIRATORY</u>					
Pneumonia	3 (0.7)	0	3 (1.0)	3 (0.7)	0
Dyspnea	1 (0.2)	0	0	1 (0.2)	0
Apnea	0	0	1 (0.3)	0	0
Asphyxia	1 (0.2)	0	0	0	0
Hyperventilation	1 (0.2)	0	0	0	0
Hypoxia	0	0	1 (0.3)	0	0

GENERAL					
Chest pain	3 (0.7)	0	4 (1.4)	1 (0.2)	0
Trauma	1 (0.2)	0	0	2 (0.5)	0
Chest discomfort	0	0	0	2 (0.5)	0
Fever	1 (0.2)	0	0	0	0
PSYCHIATRIC					
Hallucination	0	0	5 (1.7)	0	0
Depression	1 (0.2)	0	0 (0.3)	1 (0.2)	0
Panic reaction	0	1 (1.3)	1 (0.3)	0	0
Paranoid reaction	0	0	1 (0.3)	1 (0.2)	0
Behavior disorder	0	0	1 (0.3)	0	0
HEART RATE/ RHYTHM					
Afib	4 (1.0)	0	0	0	1 (0.9)
Tachycardia	2 (0.5)	0	1 (0.3)	1 (0.2)	0
Palpitation	1 (0.2)	1 (1.3)	0	1 (0.2)	0
AUTONOMIC					
Syncope	2 (0.5)	0	3 (1.0)	3 (0.7)	0
Hypertension	1 (0.2)	0	0	0	0
Hypotension	1 (0.2	0	0	0	0
MYO-, ENDO-, PERICARDIAL					
Angina pectoris	1 (0.2)	0	1 (0.3)	0	0
MI	1 (0.2)	0	1 (0.3)	1 (0.2)	0
Aortic stenosis	0	0	0	1 (0.2)	0
Arteriosclerosis	0	0	1 (0.3)	0	0
Valve disorder	1 (0.2)	0	0	0	0
PLATELET, BLEEDING, CLOTTING					
Cerebral hemorr	1 (0.2)	0	1 (0.3)	1 (0.2)	0
Genital bleeding	0	0	1 (0.3)	0	0
Thrombocytopen	0	0	1 (0.3)	0	0
URINARY					
Bleeding	0	0	0	1 (0.2)	1 (0.9)
Infection	2 (0.5)	0	0	0	0
Bladder calculus	0	0	0	0	1 (0.9)
CARDIOVASC					
Cardiac failure	0	0	2 (0.7)	1 (0.2)	0
Pericardial effus	0	0	0	1 (0.2)	0

NEOPLASM					
Uterus	0	0	2 (0.7)	0	0
Prostate	0	0	1 (0.3)	0	0
Breast	0	0	1 (0.3)	0	0
Renal	0	0	1 (0.3)	0	0
Skin	1 (0.2)	0	1 (0.3)	0	0
Tumor (unspecif)	0	0	1 (0.3)	0	0
VASCULAR					
Arterial stenosis	0	0	1 (0.3)	2 (0.5)	0
Venous thromb	0	0	1 (0.3)	0	0
LIVER/BILIARY					
Cholecystitis	0	0	1 (0.3)	0	0
Jaundice	1 (0.2)	0	0	1 (0.2)[2]	0
SKIN					
Cellulitis	1 (0.2)	0	1 (0.3)	0	0
METABOLIC/ NUTRITIONAL					
Dehydration	0	0	0	1 (0.2)	0
REPRODUC-TIVE (FEMALE)					
Hysterectomy	0	0	0	1 (0.2)	0
RESISTANCE					
Infection (unspec)	1 (0.2)	0	0	0	0
VISION					
Cataracts	0	0	1 (0.3)	0	0
WHITE CELL					
Leukemia	0	0	1 (0.3)	0	0

[1]The sponsor's terms for adverse events has been used.

[2]Although omitted from the sponsor's table (v 335, p 534), this subject was reported to be "yellow" just prior to her death (14654/14586/133; see above table listing fatalities).

Following list gives totals, with crude incidence, for nonfatal *serious* adverse events for the tolcapone 200-mg dose from all studies in the NDA, including the active-control (N14656) and the large uncontrolled (NZ14657) trials (for which the 200-mg dose only was administered). The information is summarized from (1) Appendix 21, v 1.335, pp 50-74, and (2) v 1.281, p 52:

Serious Adverse Event	*200 mg (n=964)*
CNS/PNS	
Dyskinesia	12 (1.2)
Falling	6 (0.6)
Confusion	10 (1.0)
Dystonia	3 (0.3)
PD aggravation	4 (0.4)
Balance loss	1 (0.1)
Hypertonia	1 (0.1)
Hypokinesia	2 (0.2)
PD fluctuation	1 (0.1)
Stroke	4 (0.4)
Cerebral ischemia	2 (0.2)
Hyperkinesia	1 (0.1)
Memory disturbance	1 (0.1)
Somnolence	1 (0.1)
Speech disorder	1 (0.1)
Tremor	1 (0.1)
GI	
Diarrhea	6 (0.6)
Abdominal pain	2 (0.2)
Abdominal discomfort	1 (0.1)
Nausea	3 (0.3)
Vomiting	1 (0.1)
Constipation	1 (0.1)
Dysphagia	1 (0.1)
Hernia, hiatal	1 (0.1)
Hernia, inguinal	2 (0.2)
Duodenal ulcer	1 (0.1)
GI hemorrhage	1 (0.1)
MUSCULOSKELETAL	
Fractures	8 (0.8)
Back pain	5 (0.5)
Intervertebral disc disorder	1 (0.1)
Carpal tunnel	1 (0.1)
Arthralgia	1 (0.1)
Cramps	1 (0.1)
Stiffness	1 (0.1)
Myalgia	1 (0.1)
Pain, neck	1 (0.1)
RESPIRATORY	
Pneumonia	7 (0.7)
Dyspnea	5 (0.5)
Pulmonary edema	1 (0.1)
Sinusitis	1 (0.1)
Pulmonary embolism	1 (0.1)
Asthma (bronchial)	1 (0.1)

GENERAL	
Chest pain	4 (0.4)
Trauma	4 (0.4)
Chest discomfort	1 (0.1)
Edema, peripheral	1 (0.1)
Surgical procedure (unspecified)	4 (0.4)
PSYCHIATRIC	
Hallucination	8 (0.8)
Depression	1 (0.1)
Paranoid reaction	1 (0.1)
Agitation	2 (0.2)
Anxiety	1 (0.1)
Delirium	1 (0.1)
HEART RATE/RHYTHM	
Atrial fibrillation	2 (0.2)
Tachycardia	1 (0.1)
Palpitation	1 (0.1)
Cardiac arrest	2 (0.2)
AUTONOMIC	
Syncope	7 (0.7)
Hypertension	1 (0.1)
Hypotension	2 (0.2)
MYO-, ENDO-, PERICARDIAL	
MI	1 (0.1)
Aortic stenosis	2 (0.2)
PLATELET, BLEEDING, CLOTTING	
Cerebral hemorrhage	1 (0.1)
URINARY	
Bleeding	1 (0.1)
CARDIOVASCULAR	
Cardiac failure	4 (0.4)
Pericardial effusion	1 (0.1)
Coronary stenosis	1 (0.1)
NEOPLASM	
Esophageal	1 (0.1)
Rectal	1 (0.1)
Skin	2 (0.2)
Breast	1 (0.1)
Prostate	1 (0.1)
Uterus	1 (0.1)
VASCULAR	
Arterial stenosis	2 (0.2)
Thromboembolism, complications	1 (0.1)

LIVER/BILIARY	
Jaundice	1 (0.1)
Cholelithiasis	1 (0.1)
SKIN	
Cellulitis	1 (0.1)
Burns (unspecified)	1 (0.1)
METABOLIC/NUTRITIONAL	
Dehydration	2 (0.2)
REPRODUCTIVE (FEMALE)	
Hysterectomy	1 (0.1)
"???bleeding fibrois uterus" (no further description)	1 (0.1)
REPRODUCTIVE (MALE)	
Prostate, enlarged	1 (0.1)
RESISTANCE	
Abscess (unspecified)	1 (0.1)
Angina tonsillaris	1 (0.1)
Aseptic meningitis	1 (0.1)
VISION	
Glaucoma	1 (0.1)

Subsequent information for the uncontrolled trials through 4/1/96, furnished in the Four-Month Safety Update (dated 10/3/96), resembles the data presented for the NDA trials. The table below compares the nonfatal serious adverse events (with crude incidence), occurring at the 200-mg dose, for all NDA trials (placebo-controlled, active-control, and uncontrolled; summarized from the sponsor's Appendix 21.3, v 335, pp 527-37) with the results from the Safety Update (Appendix 17.1, v 7.3, pp 220-35):

Adverse Event [1]	NDA 200 mg (n=408)	Safety Update (n=1241)
AUTONOMIC		
Syncope	3 (0.7)	9 (0.7)
Hypertension	0	4 (0.3)
Hypotension	0	4 (0.3)
Sweating, increased	0	1 (0.1)
ENDOCRINE		
Hyperthyroidism	0	1 (0.1)
LIVER/BILIARY		
Cholecystitis	0	1 (0.1)
Jaundice	1 (0.2)[3]	0
PLATELET, BLEEDING, CLOTTING		
Cerebral hemorrhage	1 (0.2)	4 (0.3)

SKIN		
Cellulitis	0	4 (0.3)
Rash	0	1 (0.1)
Skin burns	0	1 (0.1)
METABOLIC/NUTRITIONAL		
Dehydration	1 (0.2)	3 (0.2)
CNS/PNS		
Dyskinesia	4 (1.0)	21 (1.7)
Falling	4 (1.0)	12 (1.0)
Confusion	2 (0.5)	13 (1.0)
Dystonia	2 (0.5)	2 (0.2)
PD aggravation	1 (0.2)	12 (1.0)
Neuralgia	0	2 (0.2)
Balance loss	1 (0.2)	1 (0.1)
Hemiballismus	1 (0.2)	0
Hyperkinesia	1 (0.2)	0
Hypertonia	1 (0.2)	3 (0.2)
Hypokinesia	1 (0.2)	2 (0.2)
PD fluctuation	1 (0.2)	2 (0.2)
Stroke	0	7 (0.6)
Cerebral ischemia	0	3 (0.2)
Speech disorder	0	2 (0.2)
Coma	0	1 (0.1)
Convulsions	0	1 (0.1)
Encephalopathy	0	1 (0.1)
Hemiplegia	0	1 (0.1)
Hypoesthesia	0	1 (0.1)
Memory disturbance	0	1 (0.1)
Neuroleptic malignant syndrome	0	1 (0.1)[2]
Somnolence	0	1 (0.1)
Spinal cord disorder	0	1 (0.1)
Tremor	0	1 (0.1)

GI		
Diarrhea	5 (1.2)	5 (0.4)
Abdominal pain	1 (0.2)	7 (0.6)
Gastric Atony	0	1 (0.1)
Nausea	1 (0.2)	5 (0.4)
Vomiting	1 (0.2)	1 (0.1)
Constipation	1 (0.2)	4 (0.3)
Dysphagia	0	3 (0.2)
Hiatal hernia	0	3 (0.2)
Intestinal Obstruction	1 (0.2)	3 (0.2)
Inguinal hernia	0	10 (0.8)
GI hemorrhage	0	3 (0.2)
GI inflammation	0	5 (0.4)
Duodenal ulcer	0	3 (0.2)
Esophageal ulceration	0	2 (0.2)
Anus disorder	0	1 (0.1)
Colitis	0	1 (0.1)
Hernia, umbilical	0	1 (0.1)
Ileus	0	1 (0.1)
Abdominal discomfort	0	1 (0.1)
MUSCULOSKELETAL		
Fractures	0	24 (1.9)
Back pain	2 (0.5)	11 (0.9)
Intervertebral disc disorder	0	3 (0.2)
Pain, limbs	0	6 (0.5)
Carpal tunnel	0	5 (0.4)
Stiffness	1 (0.2)	0
Arthralgia	0	3 (0.2)
Cramps, muscle	0	3 (0.2)
Fracture, pathological	0	2 (0.2)
Pain, neck	0	2 (0.2)
Arthropathy	0	1 (0.1)
Joint dislocation	0	1 (0.1)
Myalgia	0	1 (0.1)
RESPIRATORY		
Pneumonia	3 (0.7)	12 (1.0)
Dyspnea	1 (0.2)	5 (0.4)
Pulmonary edema	0	4 (0.3)
Embolism, pulmonary	0	2 (0.2)
Sinusitis	0	2 (0.2)
Asthma, bronchial	0	1 (0.1)
Pleural effusion	0	1 (0.1)
Upper respiratory tract infection	0	1 (0.1)

GENERAL		
Chest pain	1 (0.2)	11 (0.9)
Trauma	2 (0.5)	2 (0.2)
Chest discomfort	2 (0.5)	1 (0.1)
Fever	0	1 (0.1)
Surgical procedure	0	4 (0.3)
Fatigue	00	2 (0.2)
Weight decrease	0	2 (0.2)
Edema, peripheral	0	1 (0.1)
Lethargy	0	1 (0.1)
PSYCHIATRIC		
Hallucination	0	12 (0.1)
Depression	1 (0.2)	8 (0.6)
Panic reaction	0	2 (0.2)
Paranoid reaction	1 (0.2)	4 (0.3)
Behavior disturbances	0	1 (0.1)
Psychosis	0	2 (0.2)
Aggressive reaction	0	1 (0.1)
Anxiety	0	1 (0.1)
Asthenia	0	1 (0.1)
Delirium	0	1 (0.1)
Delusion	0	1 (0.1)
Impotence	0	1 (0.1)
HEART RATE/RHYTHM		
Fibrillation, atrial	0	5 (0.4)
Tachycardia	1 (0.2)	3 (0.2)
Palpitation	1 (0.2)	0
Cardiac arrest	0	3 (0.2)
Atrial flutter	0	1 (0.1)
Bradycardia	0	1 (0.1)
MYO-, ENDO-, PERICARDIAL AND VALVE		
Angina pectoris	0	5 (0.4)
MI (or Coronary infarction)	1 (0.2)	2 (0.2)
Aortic stenosis	1 (0.2)	2 (0.2)
Arteriosclerosis	0	2 (0.2)
Cardiomyopathy	0	1 (0.1)
URINARY		
Urinary tract bleeding	1 (0.2)	1 (0.1)
Urinary tract infection	0	2 (0.2)
Renal calculus	0	1 (0.1)
Urinary incontinence	0	1 (0.1)
Urinary retention	0	1 (0.1)

CARDIOVASC		
Cardiac failure	1 (0.2)	6 (0.5)
Pericardial effusion	1 (0.2)	1 (0.1)
Coronary stenosis	0	1 (0.1)
Ventricular hypertrophy, left	0	1 (0.1)
NEOPLASM		
Tumor uterus	0	3 (0.2)
Tumor prostate	0	4 (0.3)
Tumor breast	0	3 (0.2)
Rectal carcinoma	0	2 (0.3)
Tumor skin	0	7 (0.6)
Carcinoma ovary	0	2 (0.2)
Carcinoma pulmonary	0	1 (0.1)
Cyst popliteal	0	1 (0.1)
Lymphoma	0	1 (0.1)
Neoplasm pharynx malignant	0	1 (0.1)
VASCULAR (EXTRACARDIAC)		
Stenosis, arterial	2 (0.5)	2 (0.2)
Venous thrombosis	0	3 (0.2)
Ischemia	0	1 (0.1)
Thromboembolic complications	0	1 (0.1)
REPRODUCTIVE		
Hysterectomy	1 (0.2)	2 (0.2)
Prostate, enlarged	0	2 (0.2)
Prostatic disorder	0	1 (0.1)
Prostatism, aggravated	0	1 (0.1)
Prostatitis	0	1 (0.1)
Unspec transurethral resection of prostate	0	1 (0.1)
RESISTANCE		
Infection	0	3 (0.2)
Angina tonsillaris	0	1 (0.1)
Infection, bacterial	0	1 (0.1)
Infection, viral	0	1 (0.1)
Meningitis, aseptic	0	1 (0.1)
VISION		
Eye movement disorder	0	1 (0.1)
Glaucoma	0	1 (0.1)
UNCLASSIFIED		
???Acute brain syndrome	0	1 (0.1)
???Tumor or the liver	0	1 (0.1)
HEARING, VESTIBULAR		
Labyrinthine disorder	0	1 (0.1)

[1]The sponsor's terms for adverse events have been used.

[2]There has been a total of four patients diagnosed with neuroleptic malignant syndrome, three of whom participate in the Japanese trials and therefore were not part of the sponsor's list.

[3]Although omitted from the sponsor's table (v 335, p 534), this subject was reported to be "yellow" just prior to

her death (14654/14586/133; see above table listing fatalities).

C. *Assessment of Dropouts*

Adverse events leading to withdrawal from double-blind, placebo-controlled studies are listed in the table below, followed by crude incidence (adapted from v 335, pp 75-79; additional information from v 1.333, p 82 [four adverse events "inadvertently left off the CFR"]). Patients are counted once for each adverse event that caused withdrawal; however, more than one adverse event may have caused the patient's withdrawal. (*Key to abbreviations:* inc = increased; dec = decreased; unsp = unspec = ? = unspecified.)

Adverse Event	*Placebo (n=415)*	*50 mg (n=78)*	*100 mg (n= 296)*	*200 mg (n=408)*	*400 mg (n=107)*
Abdominal pain	2 (0.5)	3 (3.8)	1 (0.3)	4 (1.0)	7 (6.5)
Aggressive reaction	0	1 (1.3)	0	0	0
Agitation	1 (0.2)	0	1 (0.3)	1 (0.2)	0
Anorexia	0	0	2 (0.7)	3 (0.7)	0
Anxiety	1 (0.2)	0	0	0	0
Apathy	0	0	1 (0.3)	0	0
Apnea	0	0	1 (0.3)	0	0
Arrhythmia	1 (0.2)	0	0	0	0
Asphyxia	1 (0.2)	0	0	0	0
Asthenia	0	1 (1.3)	0	0	0
Atrial fibrillation	2 (0.7)	0	0	0	0
Back pain	1 (0.2)	0	0	0	0
Balance loss	0	0	0	0	1 (0.9)
Behavioral disturb	0	0	1 (0.3)	0	0
Bleeding (dermal)	0	0	0	1 (0.2)	0
Breathing, shallow	0	0	1 (0.3)	0	0
Cerebral hemorrhage	1 (0.2)	0	1 (0.3)	1 (0.2)	0
Chest discomfort	0	0	1 (0.3)	0	0
Chest pain	0	0	2 (0.7)	0	0
Confusion	3 (0.7)	0	4 (1.4)	3 (0.7)	0
Cramps (muscle)	3 (0.7)	0	4 (1.4)	1 (0.2)	0
Depression	0	0	2 (0.7)	0	0

Death	0	0	0	1 (0.2)	0
Delusion	0	0	1 (0.3)	0	0
Diarrhea	30 (7.0)	0	48 (16.2)	47 (11.5)	1 (0.9)
Dizziness	1 (0.2)	0	3 (1.0)	0	0
Dyskinesia	0	0	1 (0.3)	3 (0.7)	0
Dysphagia	0	0	1 (0.3)	0	0
Dyspnea	0	0	0	1 (0.2)	0
Dystonia	3 (0.7)	0	3 (1.0)	1 (0.2)	0
Encephalopathy	1 (0.2)	0	0	0	0
Eye inflamed	0	0	1 (0.3)	0	0
Excessive dreaming	0	0	2 (0.7)	2 (0.5)	1 (0.9)
Falling	0	0	1 (0.3)	0	0
Fatigue	0	0	2 (0.7)	0	0
Fever	0	0	0	1 (0.2)	0
Flatulence	0	0	0	1 (0.2)	0
Flushing	0	0	1 (0.3)	0	0
Fractures	1 (0.2)	0	0	0	0
Gait, abnormal	1 (0.2)	0	1 (0.3)	0	0
Gastric atony	1 (0.2)	0	0	0	0
Glaucoma	1 (0.2)	0	0	0	0
Hallucination	1 (0.2)	0	4 (1.4)	5 (1.2)	1 (0.9)
Headache	1 (0.2)	0	1 (0.3)	1 (0.2)	1 (0.9)
Hemarthrosis	0	0	0	1 (0.2)	0
Hiatal hernia	0	0	1 (0.3)	0	0
Hyperkinesia	1 (0.2)	0	0	1	0
Hypertension	1 (0.2)	0	0	0	0
Hyperventilation	1 (0.2)	0	1 (0.3)	1 (0.2)	0
Hypoesthesia	0	0	0	1 (0.2)	0
Hypokinesia	0	0	0	1 (0.2)	0
Hypotension	0	0	2 (0.7)	1 (0.2)	0
Intervertebral disc	0	0	1 (0.3)	0	0
Liver enzymes (inc)	1 (0.2)	0	1 (0.3)	5 (1.2)	0

Malaise	0	0	1 (0.3)	1 (0.2)	0
Mental deficiency (?)	0	0	1 (0.3)	0	0
MI	0	0	0	1 (0.2)	0
Nausea	6 (1.5)	0	5 (1.7)	6 (1.5)	2 (1.9)
Nervousness	0	0	1 (0.3)	0	0
Orthostatic compl	0	0	2 (0.7)	0	0
Palpitation	0	1 (1.3)	0	0	0
Panic reaction	0	1 (1.3)	0	0	0
Paresis	0	0	0	0	1 (0.9)
Pain, body	1 (0.2)	0	0	0	0
Pain, neck	0	0	0	1 (0.2)	0
Paranoid reaction	0	0	0	1 (0.2)	0
Paresis	1 (0.2)	0	0	0	0
PD aggravated	0	1 (1.3)	0	0	0
Photosensitivity	1 (0.2)	0	0	0	0
Pneumonia	1 (0.3)	0	1 (0.3)	0	0
Prostate (enlarged)	0	0	0	1 (0.2)	0
Sensory disturbance	0	0	0	0	1 (0.9)
Sleep disorder (unsp)	2 (0.5)	0	0	1 (0.2)	0
Somnolence	0	0	0	2 (0.5)	0
Stiffness	0	0	0	1 (0.2)	0
Sweating	0	0	0	1 (0.2)	0
Syncope	2 (0.5)	0	1 (0.3)	1 (0.2)	0
Tachycardia	1 (0.2)	0	0	1 (0.2)	0
Tinnitus	0	0	0	1 (0.2)	0
Trauma	1 (0.2)	0	0	0	0
Tremor	0	0	0	1 (0.2)	0
Tumor	0	0	1 (0.3)	0	0
Tumor, uterus	0	0	1 (0.3)	0	0
Urinary incontinence	0	0	1 (0.3)	0	0
Urinary retention	1 (0.2)	0	0	0	0
Vertigo	1 (0.2)	0	0	0	0

Vomiting	2 (0.5)	0	2 (0.7)	2 (0.5)	2 (1.9)
White count (dec)	0	0	0	1 (0.2)	0
Xerostomia	0	0	0	1 (0.2)	0

The next table summarizes adverse events leading to withdrawal for all the trials in the NDA, including the active-control and uncontrolled; it has been adapted from (1) Appendix 22, v 1.335, pp 75-83, and (2) Table 17, v 1.281, p 55. Two hundred milligrams is the one dose that is common to all the studies in question:

Adverse Event	*200 mg (n=964)*
Abdominal discomfort	1 (0.1)
Abdominal pain	4 (0.4)
Aggressive reaction	1 (0.1)
Agitation	7 (0.7)
Anorexia	11 (1.1)
Anxiety	5 (0.5)
Aortic stenosis	1 (0.1)
Back pain	1 (0.1)
Balance loss	1 (0.1)
Bleeding (dermal)	1 (0.2)
Bowel movements, frequent	1 (0.1)
Cachexia	1 (0.1)
Canker sores (oral)	1 (0.1)
Cardiac failure	1 (0.1)
Cerebral hemorrhage	1 (0.2)
Chest pain	1 (0.1)
Confusion	3 (0.7)
Constipation	1 (0.1)
Cramps (muscle)	7 (0.7)
Dehydration	1 (0.1)
Delirium	1 (0.1)
Depression	4 (0.4)
Diarrhea	83 (8.6)
Dizziness	5 (0.5)

Dreaming (excessive)	4 (0.4)
Duodenal ulcer	1 (0.1)
Duodenitis	1 (0.1)
Dyskinesia	27 (2.8)
Dysphagia	1 (0.1)
Dyspnea	1 (0.2)
Dystonia	9 (0.9)
Edema, peripheral	1 (0.1)
EKG -- bundle branch block (no details)	1 (0.1)
Esophageal carcinoma	1 (0.1)
Fever	1 (0.1)
Flatulence	1 (0.1)
Flushing	1 (0.1)
Hallucination	5 (1.2)
Headache	1 (0.2)
Hemarthrosis	1 (0.2)
Hyperactivity	1 (0.1)
Hyperkinesia	5 (0.5)
Hypertension	2 (0.2)
Hyperventilation	1 (0.1)
Hypoesthesia	2 (0.2)
Hypokinesia	2 (0.2)
Hypotension	2 (0.2)
Illusion	1 (0.1)
Influenza	1 (0.1)
Liver enzymes, increased	12 (1.2)
Libido, increased	1 (0.1)
Malaise	1 (0.2)
Mental deficiency (not specified)	1 (0.1)
MI	1 (0.2)
Nausea	20 (2.1)
Nervousness	1 (0.1)

Orthostatic compl	6 (0.6)
Pain, neck	1 (0.1)
Paranoid reaction	1 (0.1)
Paresthesia	1 (0.1)
PD aggravated	2 (0.2)
Pneumonia	1 (0.1)
Prostate, enlarged	1 (0.1)
Psychosis	1 (0.1)
Pulmonary edema	1 (0.1)
Rash (unspecified)	1 (0.1)
Skin burns	1 (0.1)
Stroke	3 (0.3)
Sleep disorder (unspecified)	8 (0.8)
Somnolence	8 (0.8)
Stiffness	1 (0.1)
Sweating, increased	2 (0.2)
Syncope	5 (0.5)
Tachycardia	1 (0.1)
Taste alteration	1 (0.1)
Tinnitus	1 (0.1)
Trauma	1 (0.1)
Tremor	1 (0.1)
Urine discoloration	1 (0.1)
Urinary tract infection	1 (0.1)
Vertigo	1 (0.1)
Vomiting	6 (0.6)
Weight decrease	1 (0.1)
White count, decreased	1 (0.1)
Xerostomia	5 (0.5)

D. *Late-onset Adverse Events (uncontrolled studies)*

The sponsor has defined late-onset adverse events as those occurring after 120 days of treatment: "this relatively arbitrary definition was selected primarily to provide sufficient patients for analysis" (v 1.333, p 65). Late-onset adverse events were gleaned from both the three long-term placebo-controlled (NZ14653, NZ14654, NZ14655) and the uncontrolled trials. The following table catalogues only those adverse events with incidence rates greater than 1% and either twice the incidence rate, or at least two percentage points higher than the incidence rate, for the entire study (see Table 22, v 1.333, p 66):

Adverse Event	*Occurrence During Study (n=793)*	*Occurrence After 120 Days While on Tolcapone (n=280)*
Anemia	4 (0.5%)	4 (1.4%)
Hernia, inguinal	5 (0.6%)	4 (1.4%)
Hypotension	62 (7.8%)	32 (11.4%)
Intervertebral disc disorder	3 (0.4%)	3 (1.1%)
Mental deficiency (unspecified)	4 (0.5%)	3 (1.1%)
Neuralgia	7 (0.9%)	5 (1.8%)
Sinusitis	4 (0.5%)	3 (1.1%)
Tumor, skin	6 (0.8%)	6 (2.1%)
Urinary tract infection	30 (3.8%)	17 (6.1%)

According to the sponsor, "when focusing on adverse events that occurred late in placebo-controlled studies, most of the adverse events in Table 22 occurred in the placebo group [ie, the group originally on placebo in the placebo-controlled arm, which, in the extension, was subsequently placed on tolcapone] more than the tolcapone groups. Urinary tract infection and skin tumors occurred after 120 days with identical frequencies in the placebo and 200-mg tolcapone groups" (v 1.333, p 66).

E. *Other Safety Findings*

1. **Vital Signs**

Vital signs were collected at baseline and scheduled clinic visits, as precribed by the protocol (generally between weeks 1 and 2, week 6, and week 13 for the three month studies); the sponsor has not specified whether they were taken at any particular time during the day, in relation to dose, or whether they were taken at the same time for each visit. The sponsor employs the following criteria to identify abnormalities in vital signs:

	low	*high*
pulse rate	<40 bpm	≥120 bpm
blood pressure - diastolic (DBP)	≤55 mmHg	≥100 mm Hg
systolic (SBP)	≤90 mmHg	≥200 mmHg

and orthostatic hypotension than placebo patients. The sponsor asserts that, in combination with dopamine agonists, tolcapone appears to be associated with an increased incidence of orthostatic hypotension (less L-DOPA is metabolized and more is consequently made available?), whereas, in their absence, tolcapone appears to have had only a marginal effect on orthostasis (v 1.333, p 70; 1.334, pp 215-6):

	Placebo	*50 mg*	*100 mg*	*200 mg*	*400 mg*
Placebo-controlled trials	(n=200)* (n=97)** 19 (10%) 26 (27%)	(n=78) 12 (15%)	(n=106)* (n=190)** 14 (13%) 27 (14%)	(n=101)* (n=197)** 17 (17%) 22 (11%)	(n=104) 8 (8%)
Active-control trials (bromocriptine vs tolcapone)	(bromo; n=74) 8 (11%)			(tolc; n=72 3 (4%)	
Uncontrolled trials				(n=771) 99 (13%)	

*With dopamine agonists at baseline, Phase III trials. **Without dopamine agonists at baseline, Phase III trials.

Subgroup analyses, according to the sponsor, has revealed no age or sex differences.

Significant autonomic disturbances may result from PD (*eg*, large blood pressure drops on postural changes which may remain asymptomatic for the patient), and it is therefore important to define whether the blood pressure changes are indeed associated with symptoms. As a result, the sponsor also provides a table correlating orthostatic hypotension (as defined by blood pressure criteria) with the most common orthostatic-like symptoms in patients in phase III placebo-controlled trials (v 1.333, p 69):

Symptoms	*Placebo*	*100 mg*	*200 mg*
Patients with orthostatic hypotension[1]	(n=24)	(n=41)	(n=39)
Dizziness	6 (25%)	6 (15%)	4 (10%)
Syncope	1 (4%)	3 (7%)	4 (10%)
Balance loss	1 (4%)	4 (10%)	1 (3%)
Falling	1 (4%)	1 (2%)	4 (10%)
Hypotension	0	2 (5%)	4 (10%)
Patients without orthostatic hypotension	(n=274)	(n=255)	(n=259)
Dizziness	23 (8%)	33 (13%)	15 (6%)
Syncope	7 (3%)	9 (4%)	11 (4%)
Balance loss	6 (2%)	6 (3%)	6 (2%)
Falling	12 (5%)	12 (5%)	14 (5%)
Hypotension	4 (2%)	3 (1%)	3 (1%)

[1] "Orthostatic Hypotension, as determined from vital sign measurements, recorded at any post-baseline time during the study" (v 1.333, p 69).

The sponsor states that "Patients with orthostatic hypotension were likely to experience syncope and falls than patients without orthostatic hypotension and this was slightly exacerbated with Tolcapone treatment" (v 1.333, p 70). However, given the small numbers of patients and the data variability, it would be difficult to derive any conclusions about Tolcapone's effects with respect to placebo. The sponsor has been asked to provide a time course for these symptoms, if the data are available: when do the symptoms occur in relation to medication dosing, how long they last, and whether they dissipate with time (if patients grow tolerant to the them).

whether they dissipate with time (if patients grow tolerant to the them).

There are two caveats about the data as presented in both the paper and the electronic NDA submissions:

(1) a review of case summaries, randomly selected from those presented in the sponsor's CANDA, shows that blood pressure data appear to have been collected (at each scheduled clinic visits prescribed by the protocol, as, for instance, week 1-2, 6 and 13) independently of symptoms of orthostasis, which were elicited by patient questionnaire; at least the entry dates for vital-sign information and symptoms tend to differ. The sponsor explains that, "To correlate orthostatic hypotension, detected by vital sign measurements, and orthostatic symptoms from [adverse event] summaries, separate [adverse event] summaries were prepared for patients with or without orthostatic hypotension at any time during the study" (v 1.333, p 69). There is thus no way for the reviewer to corroborate any of the above observations with the information supplied by the sponsor (personal communication from Cheryl Altieri, CANDA process manager, Hoffmann-La Roche, Inc.).

(2) orthostasis is defined by the sponsor only in terms of BP changes when moving from a supine to a standing position (namely, a decrease in DBP$\geq$15 and in SBP$\geq$25 [v 1.333, p 14]). Heart rate is not considered, yet the component of pulse change (e.g., fixed heart rate or tachycardia) is an important manifestion of orthostasis and sometimes integral to the definition (see *Harrison's Principles of Internal Medicine,* 13th ed. [1994], v 2, pp 2344-5); and patients might be classified as orthostatic by pulse alone even though the absolute changes in BP may not meet the above criteria. The frequency of true orthostasis (BP changes associated with patient complaints) may therefore have been either over- or under-represented.

Finally, although the individual patient data were not presented, one might possibly surmise that tolcapone is likely to aggravate pre-existing symptoms of orthostatic hypotension: "The incidence rates for orthostatic hypotension during the study among patients [classified by placebo, 100-mg, and 200-mg groups] 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).

2. Heart Rhythm and Electrocardiogram

EKGs were generally recorded at baseline and every six months after starting treatment, and additional recordings were made at six weeks or three months depending on the study. The sponsor provides a table of "treatment-emergent EKG abnormalities or worsening of existing abnormalities" (v 1.333, p 71). It is not clear from this description whether the sponsor means regularly scheduled EKGs which were found to be abnormal and required treatment, EKGs performed outside the protocol schedule when patients were symptomatic, or both; in any case, at least one of the so-called "treatment-emergent EKG abnormalities," the ventricular premature contraction, was not treated (see below). The following table of "treatment-emergent EKG abnormalities" has been adapted from the sponsor's Tables 25-27, v 1.333, pp 72-3):

	Placebo	*50 mg*	*100 mg*	*200 mg*	*400 mg*

Placebo-controlled trials (Phases 2 and 3)	(n=394)	(n=75)	(n=398)	(n=397)	(n=97)
1° AV block	2 (0.5%)	0	0	1 (0.3%)	1 (1%)
Incomplete heart block	1 (0.3%)	0	0	1 (0.3%)	0
Bundle branch block (right)	0	0	1 (0.3%)	0	0
Prolonged QT interval (unspecified)	0	0	2 (0.5%)	0	0
Sinus bradycardia (unspecified)	3 (0.8%)	0	2 (0.5%)	0	1 (1%)
Sinus tachycardia (unspecified)	1 (0.3%)	0	1 (0.3%)	2 (0.5%)	0
Supraventricular tachycardia	0	0	1 (0.3%)	0	0
Ventricular premature contractions	1 (0.3%)	0	1 (0.3%)	5 (1.7%)	2 (2%)
Supraventricula premature contractions	1 (0.3%)	0	1 (0.3%)	2 (0.5%)	0
Atrial fibrillation/flutter	2 (0.5%)	0	1 (0.3%)	1 (0.3%)	2 (2%)
ST-T changes	2 (0.5%)	0	2 (0.5%)	2 (0.5%)	1 (1%)
Evidence of MI	2 (0.5%)	0	0	1 (0.3%)	0
RVH	1 (0.3%)	0	0	0	0
Active-control trials (bromocriptine vs tolcapone)	*Bromocriptine* (n=74)			*Tolcapone* (n=72)	
ST-T changes	0			1 (1.4%)[1]	
Uncontrolled trials				(n=793)	
1° AV block				3 (0.4%)	
Incomplete heart block				2 (0.3%)	
Bundle branch block (left)				2 (0.3%)	
Bundle branch block (right)				1 (0.1%)	
Intraventricular conduction block				2 (0.3%)	
Sinus bradycardia (unspecified)				7 (0.9%)	
Sinus tachycardia (unspecified)				1 (0.1%)	
Ventricular premature contractions				5 (0.6%)	
Supraventricula premature contractions				3 (0.4%)	
Atrial fibrillation/flutter				5 (0.6%)	
Nodal rhythm (unspecified)				1 (0.1%)	
ST-T changes				7 (0.9%)	
Other findings/unknown				3 (0.4%)	

[1]The changes occurred 3 weeks post-angioplasty.

The most frequent abnormality among tolcapone-treated patients, as compared to placebo, appears to be the ventricular premature contraction (PVC). According to the sponsor, PVCs were first detected in patients in the Phase III studies "after at least three months of treatment" (v 1.333, p 71): "For three of the patients, subsequent EKGs were recorded as normal, while for the other three, follow-up information is not available. Of two patients in the Phase II studies, one had frequent nonconsecutive PVCs at the last assessment visit, while the other patient had 'rare' PVCs at the last assessment visit" (*ibid*). (However, because automatic EKG machines collect data for only one minute and, without a rhythm strip, their tracings may show no more than two or three complexes per lead, it is very possible to underestimate, or miss altogether, potential PVCs.)

According to the sponsor's report, none of the patients in the placebo-controlled studies received treatment for PVCs (*ibid*).

Subsequent information, submitted 10/3/96 by the sponsor in the Four-Month Safety Update (covering the period through 4/1/96), provides more data on "treatment-emergent EKG abnormalities" in the uncontrolled trials. The following table compares the type and incidence of

treatment-emergent EKG abnormalities as presented in the NDA and the Safety Update (adapted from the sponsor, NDA Tables 25-27, v 1.333, pp 72-3, and Update Table 10, v 7.1, p 27):

Adverse Event	*Placebo*	*50 mg*	*100 mg*	*200 mg*	*400 mg*
Placebo-controlled trials	(n=394)	(n=75)	(n=398)	(n=397)	(n=97)
1° AV block	2 (0.5%)	0	0	1 (0.3%)	1 (1%)
Incomplete heart block	1 (0.3%)	0	0	1 (0.3%)	0
Bundle branch block (right)	0	0	1 (0.3%)	0	0
Prolonged QT interval (unspecified)	0	0	2 (0.5%)	0	0
Sinus bradycardia (unspecified)	3 (0.8%)	0	2 (0.5%)	0	1 (1%)
Sinus tachycardia (unspecified)	1 (0.3%)	0	1 (0.3%)	2 (0.5%)	0
Supraventricular tachycardia	0	0	1 (0.3%)	0	0
Ventricular premature contractions	1 (0.3%)	0	1 (0.3%)	7 (1.7%)	2 (2%)
Supraventricular premature contractions	1 (0.3%)	0	1 (0.3%)	2 (0.5%)	0
Atrial fibrillation/flutter	2 (0.5%)	0	1 (0.3%)	1 (0.3%)	2 (2%)
ST-T changes	2 (0.5%)	0	2 (0.5%)	2 (0.5%)	1 (1%)
Evidence of MI	2 (0.5%)	0	0	1 (0.3%)	0
Right ventricular hypertrophy	1 (0.3%)	0	0	0	0
Active-control trials	*Bromocriptine*			*Tolcapone*	
(bromocriptine vs tolcapone)	(n=74)			(n=72)	
ST-T changes	0			1 (1.4%)[1]	
Uncontrolled trials				*NDA* (n=793) / *Update* (n=1241)	
1° AV block				3 (0.4%) / 6 (0.5%)	
Incomplete heart block				2 (0.3%) / 6 (0.5%)	
Bundle branch block (left)				2 (0.3%) / 3 (0.2%)	
Bundle branch block (right)				1 (0.1%) / 3 (0.2%)	
Intraventricular conduction block				2 (0.3%) / 4 (0.3%)	
Sinus bradycardia (unspecified)				7 (0.9%) / 12 (1%)	
Sinus tachycardia (unspecified)				1 (0.1%) / 3 (0.2%)	
Ventricular premature contractions				5 (0.6%) / 15 (1%)	
Supraventricular premature contractions				3 (0.4%) / 10 (0.8%)	
Atrial fibrillation/flutter				5 (0.6%) / 11 (0.9%)	
Nodal rhythm (unspecified)				1 (0.1%) / 2 (0.2%)	
ST-T changes				7 (0.9%) / 17 (1%)	
Other findings/unknown				3 (0.4%) / 7 (0.6%)	
Prolonged QT interval				0 / 1 (0.1%)	
Left axis deviation				0 / 2 (0.2%)	
Evidence of myocardial infarction				0 / 4 (0.3%)	
Left ventricular hypertrophy				0 / 3 (0.2%)	

[1]The changes occurred 3 weeks post-angioplasty.

The most frequent abnormality among tolcapone-treated patients in the Safety Update, as in the NDA, appears to be the ventricular premature contraction (PVC).

3. Clinical Laboratory Values

Roche standard reference ranges for all laboratory tests (chemistry, hematology, and urinalysis) can be found in the attachments at the end of this review.

(a) Clinical Chemistry

	Placebo (n/N)	*100 mg (n/N)*	*200 mg (n/N)*
High BUN	0/285	2/287 (1%)	1/293 (0.3%)
High creatinine	0/252	3/255 (1%)	0/254
High fasting glucose	2/237 (1%)	1/233 (0.4%)	2/236 (1%)
High total protein	0/264	1/263 (0.4%)	0/261

(b) Hematology

	Placebo (n/N)	*100 mg (n/N)*	*200 mg (n/N)*
Low hematocrit	5/289 (2%)	4/291 (1%)	3/291 (1%)
Low hemoglobin	4/290 (1%)	6/294 (2%)	3/291 (1%)
High platelets	0/290	0/293	1/291 (0.3%)
Low platelets	0/290	2/293 (1%)	3/291 (1%)
Low RBC	0/57	1/66 (2%)	1/64 (2%)
High WBC	1/290 (3%)	2/294 (1%)	1/292 (0.3%)
High eosinophils	0/176	0/175	1/168 (1%)
Low lymphocytes	3/176 (2%)	3/175 (2%)	1/168 (1%)
High monocytes	1/176 (1%)	0/175	0/168
Low moncytes	3/176 (2%)	3/175 (2%)	1/168 (1%)
Low neutrophils	2/176 (1%)	2/175 (1%)	1/168 (1%)

(c) Liver Enzymes

A "markedly high enzyme elevation" was defined, by Roche standards, as twice the ULN value.

	Placebo	*100 mg*	*200 mg*
***PHASE III* CONTROLLED TRIALS**	(n=292)	(n=294)	(n=293)
High SGPT (ALAT)			
≥2x ULN			
>3x ULN	0	3 (1%)	8 (3%)
>5x ULN	0	2 (0.7%)	3 (1%)
>8x ULN	0	1 (0.3%)	1 (0.3%)
High SGOT (ASAT)			
≥2x ULN			
>3x ULN	0	4 (1%)	6 (2%)
>5x ULN	0	2 (0.7%)	3 (1%)
>8x ULN	0	0	2 (0.7%)
High alkaline phosphatase	2 (1%)	0	1 (0.3%)
UNCONTROLLED TRIAL			(n=729)
High SGPT (ALAT)			
≥2x ULN			
>3x ULN			19 (3%)
>5x ULN			8 (1%)
>8x ULN			3 (0.4%)
High SGOT (ASAT)			
≥2x ULN			
>3x ULN			9 (1%)
>5x ULN			4 (0.5%)
>8x ULN			1 (0.1%)
High alkaline phosphatase			

The sponsor reports that only one patient in the Phase II placebo-controlled trials -- and none in the active-control study -- had an ALAT >3x ULN (the patient is not identified and it is not known whether he had any other enzyme abnormalities). The sponsor attributes the small number of identified irregularities to the short duration of the studies.

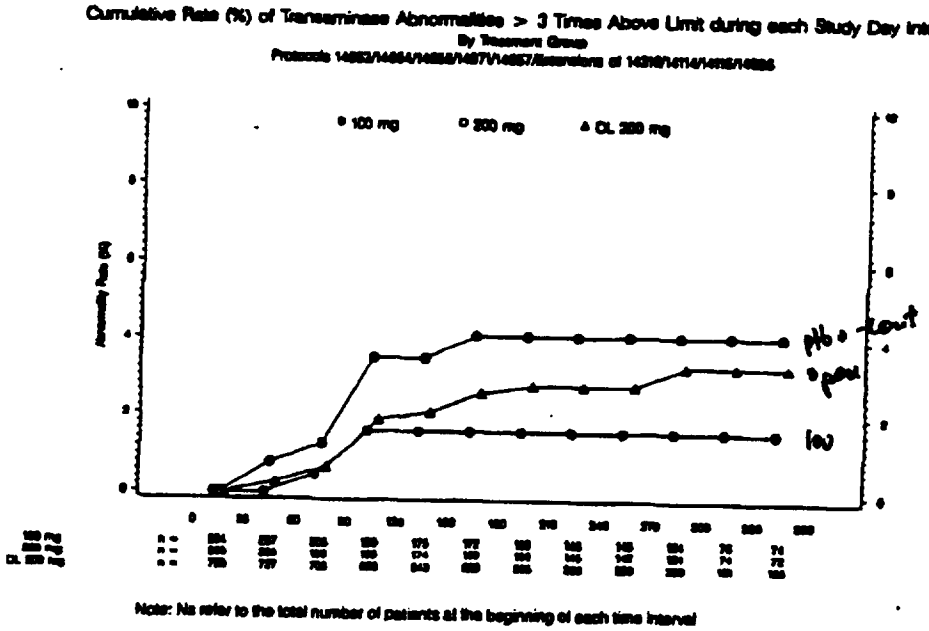
In Phase III controlled trials, for which the sponsor has catalogued data, the incidence rate of elevated transaminases (>3x ULN of ALAT or ASAT) for tolcapone 200 mg tid is about twice that of 100 mg tid; and the percentage of patients (3%) with elevated transaminases in the uncontrolled trial is almost identical to the 200-mg group in the controlled trials.

Liver problems, possibly resulting from tolcapone, may have played a part in the death of one of the patients in a Phase III controlled trial (narrative summary, v 1.335 p 28; case report, v 1.420 pp 1-115 [labs, p 8; extended summary report by investigator, pp 114-5]). Patient #14654/14586/133, a 55-year-old female in the 200 mg tid group, developed diarrhea on day 53 and "yellowing of skin and eyes" on day 57. She was apparently out of state at the time; her husband notified the investigator, who advised medical follow-up, but the patient decided to return home the next day before seeing a physician. Near the end of the 12-hour car trip, she was described as having "prominent dyskinesias, not unlike the dyskinesias she had experienced previously." She lay down on the car's back seat. On arrival home about one hour later on day 60, she was found unresponsive and pronounced dead by a physician. Her husband was told that "she had been dead for awhile." According to the sponsor, there was no reported history of vascular or

cardiac disease; however, her EKG showed an incomplete right bundle branch block. There was also no history of liver disease or known exposure to hepatitis. Her past medical history was remarkable only for torticollis, back pain, and insomnia; her medications, in addition to tolcapone, included Sinemet 25/100 1 qd, pergolide 3 mg qd, and selegiline 10 mg qd. There was no autopsy, and the sponsor claims to have only inital lab reports on the patient (dated 7/30/94), which were normal; no further medical information is avaliable closer to the date of death (10/13/94). Her death was attritbuted to a "cardiac-related" causes, and the investigator assessed it as possibly related to treatment with tolcapone. The patient was also on pergolide and selegiline; the influence of these drugs in the etiology of her condition is also not known.

The sponsor has prepared a life table to assess both the onset and risk of developing elevated liver transaminases for patients with ALAT values greater than 3x ULN. As can be seen below, the majority of cases occurred during the second through fourth months of treatment (see the sponsor's Figure 33, v 1.333, p 76):

Figure 33. Cumulative and Hazard rates for Elevated Transaminase in Placebo-controlled Phase III and Uncontrolled Studies.



For about one-third of the patients, the elevated value was initially detected at the last study assessment; no follow-up information was available for them at the time of NDA submission. Of the 22 patients for whom follow-up information is available, about half continued on treatment, with the enzyme reportedly returning to normal, and the other half withdrew from tolcapone treatment, with the enzyme returning to baseline or declining at the last assessment. The sponsor plans to submit more information in its four-month safety updates.

Gender differences were noted with respect to lab abnormalities: females were more likely to be found among tolcapone-treated patients with elevated transaminases (61%; 19/31) than without (36%; 540/1505). There were no differences among patients with or without transaminase elevations with respect to previous or concomitatnt medical conditions or medications (v 1.333, p 78).

In terms of associated adverse events, patients with elevated transaminases had higher

incidences of GI complaints (*eg*, nausea, anorexia, diarrhea, and abdominal pain). Nonetheless, the presence of GI side effects did not serve as a useful predictor for subsequent transaminase elevations: only 3-5% of patients with GI complaints eventually were found to have transaminases in the >3x ULN range.

Subsequent information on elevated transaminases has been provided by the Four-Month Safety Update, covering Tolcapone usage in the uncontrolled trials through 4/1/96. Thirty patients are listed with elevated transaminases (highest ALAT, 20x ULN; highest ASAT, 25x ULN; Appendix 16.2, v 7.3, pp 212-19).

Adverse Event	*Placebo*	*100 mg*	*200 mg*	
PHASE III CONTROLLED TRIALS	(n=292)	(n=294)	(n=293)	
High SGPT (ALAT)				
≥2x ULN				
>3x ULN	0	3 (1%)	8 (3%)	
>5x ULN	0	2 (0.7%)	3 (1%)	
>8x ULN	0	1 (0.3%)	1 (0.3%)	
High SGOT (ASAT)				
≥2x ULN				
>3x ULN	0	4 (1%)	6 (2%)	
>5x ULN	0	2 (0.7%)	3 (1%)	
>8x ULN	0	0	2 (0.7%)	
High alkaline phosphatase	2 (1%)	0	1 (0.3%)	
UNCONTROLLED TRIALS			*NDA* (n=729)	*Update* (n=1205)
High SGPT (ALAT)				
≥2x ULN				
>3x ULN			19 (3%)	29 (2%)
>5x ULN			8 (1%)	12 (1%)
>8x ULN			3 (0.4%)	7 (0.6%)
High SGOT (ASAT)				
≥2x ULN				
>3x ULN			9 (1%)	16 (1%)
>5x ULN			4 (0.5%)	7 (0.6%)
>8x ULN			1 (0.1%)	3 (0.2%)

Of the 30 patients, according to the sponsor, follow-up information was available on 29, and of these, 19 remained on treatment and 10 withdrew. Lab values for seven patients in the latter group were either "falling at the last assessment" or had "returned to normal," and for the other three remained markedly elevated, and rising, at least eight days--and, in one, 42 days (ALAT, 10x ULN; ASAT, 25x ULN)--after discontinuation (v 7.1, p 30). However, no episode of frank hepatic failure has been identified by the sponsor.

Finally, the Safety Update offered no further information on any gender differences with respect to elevated transaminases.

(d) Urinalysis

	Placebo	*100 mg*	*200 mg*
High hematuria (0-4+)*	5/234 (2%)**	4/287 (3%)**	6/291 (5%)**
High proteinuria (0-4+)	4/234 (1%)**	6/287 (2%)**	5/291 (2%)**
High RBC in urine (0-4+)*	5/199 (3%)**	4/193 (2%)**	3/201 (1%)**
High WBC in urine (0-4+)	7/218 (3%)**	4/212 (2%)**	11/216 (5%)**

*The difference between these two categories cannot be explained at present. It is not known whether a microscopic analysis was done on the urine.

**The numerator and denominator, as presented by the sponsor, include participants for US Phase III studies only.

An increased incidence in hematuria (1/58 pacebo, 4/60 at 100 mg, 8/59 at 200 mg) was found among tolcapone-treated patients in one placebo-controlled Phase III European study (NZ14655; see v 254, p 82). Only one of the cases (100-mg group; the patient had a permanent urinary catheter, see v 1.255, p 203 [#14648/0029]) also had "marked proteinuria"; the other cases of proteinuria ocurred independently of hematuria (in the study, "marked proteinuria was seen in 2/58 placebo, 1/60 at 100 mg, 1/59 at 200 mg). 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. The possibility of an interstitial nephritis or glomerulonephritis is not specifically mentioned, and there is no indication of follow-up or investigation into the causes of the hematuria. 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.

For IND Protocol NZ14653, the sponsor has recently requested an additional two-year extension (or until the drug is commercially available) to enable patients who have completed the first 12-month extension of the trial to continue treatment. 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 as well as of the results from European study NZ14655 discussed above, 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.

4. PET Scan Data

A randomized double-blind, placebo-controlled, crossover study (BD14312) was performed to determine, by PET scan examination, whether COMT inhibition slows the rate of dopamine loss (k_4). Sixteen subjects were enrolled, comprising six normal volunteers and 10 PD patients (male:female::1:1). There were no serious adverse events. There were three withdrawals: one because of "problems. . .encountered with the analysis" of blood samples (electronic submission for Protocol BD14312 [BD], p 27); one because of an inability to tolerate the PET scanner; and one due to an abnormal screening EKG who was inadvertently allowed to continue with the study for a brief time. All were subsequently replaced.

The objectives of the dosage regimen, namely to provide relatively constant plasma

The objectives of the dosage regimen, namely to provide relatively constant plasma tolcapone concentrations around 8 ug/ml and relatively constant erythrocyte COMT activity around 10% of baserline, were not achieved. Mean tolcapone concentration and erythrocyte COMT activity over the whole PET scan period (0-4 h) were approximately 4.4 ug/ml and 39%, respectively. Tolcapone concentrations were considerably lower than expected, especially in the first part of the PET scan (0-2 h), but increased in most subjects after two hours. The mean tolcapone concentrations and erythrocyte COMT activities over the first two hours of the scan (3.5 ug/ml and 43%) were different from those during the second part of the scan (5.2 ug/ml and 34%). According to the sponsor, the average tolcapone concentrations correlated reasonably well with the average erythrocyte COMT activities for the corresponding time intervals.

In the placebo scans, the striatal/background ratio was significantly lower in the PD patients (0.36±0.08) than in healthy volunteers (0.66±0.06). Following tolcapone, the striatal/backgound signal ratio increased in all subjects (PD group, by 49% on average; normals, 38%). For the placebo treatment, the mean constant of uptake (k_i) was lower in the PD group (0.14±0.03; normals, 0.23±0.03). Following tolcapone, it did not change significantly in either group compared to placebo. As to k_4, the mean value was greater in the PD group (PD, 0.0035±0.0006; normals, 0.0028±0.0004).

Although the PET scans showed that higher plasma levels of ^{18}F-L-DOPA were observed with tolcapone compared to placebo, resulting in increased striatal accumulation of 6-[^{18}F]fluorodopamine, no decrease in central 6-[^{18}F]fluorodopamine metabolism -- as reflected by the loss rate constant (k_4) -- was detected. The sponsor offers two possible explanations, neither of which appears wholly adequate: (1) the tolcapone concentration in the brain may not have been sufficient for complete inhibition of both COMT; or (2) 6-[18F]fluorodopamine may have been converted to MAO, thus combined central inhibition of both COMT and MAO may be needed to preserve striatal dopamine. Tolcapone did not influence the rate of the constant of uptake (k_i).

5. Literature Safety Review

A worldwide safety review, undertaken by the sponsor and including reports on . has turned up no reports of deaths. The spectrum and profile of adverse events in the literature was similar to that documented by the sponsor in its placebo-controlled studies.

6. Private INDs and Additional Trials Associated with IND (original TASMAR IND)

7. Foreign Studies

JAPAN

Seven studies have been completed in Japan: four clinical pharmacology studies in which 69 healthy voluneers received at least one dose (J3576-01, J3576-02, J3576-09, and J3576-10), and three therapeutic studies in 232 PD patients (J3576-03/04 open label; J3576-10 double-blind, parallel group). As to the clinical pharmacology trials, there was one patient withdrawal (J3576-01) because of "cardiac arrhythmias" (v 1.333, p 88); no other information is available in the NDA submission.

Minimal safety reports only are available in the NDA submission for the three therapeutic studies:

(1) *N138821 (J-3576-06):* Phase II 6-week, multicenter, double-blind, comparison group trial (three doses: 50 mg, 100 mg, 200 mg) in PD patients on Sinemet or Madopar, with end-of-dose wearing off, to determine optimal tolcapone dose. Patients may also have been taking additional PD medications concurrently (bromocriptine, pergolide, trihexyphenidyl, droxidopa, and amantidine were cited). One-hundred-forty-six patients were enrolled (almost equally split among the three doses); 9 patients withdrew (3 in the 150-mg group, 1 in the 300-mg group, and 5 in the 600-mg group). Reasons for withdrawal included (by complaint; some patients had more than one): hypotonia (1), paresthesia (1), dizziness (2), nausea/vomiting/abdominal discomfort (4), somnolence (2), dyskinesia (1), taste alteration/tongue discoloration (1). There was one death due to infection in a 73-year-old female with esophageal cancer; the death was not considered related to tolcapone (complications to a urinary tract infection treated with "cefotiam" [cefotetan?]; the patient withdrew from the study on day 37 because of "an aggravated complication [or occurrence] of accidental symptom" [v 1.333, p 89]). The most common adverse events were dyskinesia (7%), nausea (6%), abdominal discomfort (3%), anorexia (5%), hallucination (5%), and somnolence (5%). Eight patients had at least one instance of vital-sign abnormalities (mostly low SBP or DBP; unspecified). Two patients, with normal baseline EKGs, had abnormal tracings (not described) at the end of the study, but one subsequently normalized; five patients had abnormal EKGs at baseline and at the end of the study. Thirteen patients had abnormal hepatic transaminases, the most serious were AST (16 to 50; normal to 25), LDH (220 to 384; normal to 250), alkaline phosphatase (89 to 121; normal to 100), ALT (9 to 32; normal to 30), GGT (32 to 98; normal to 60), bilirubin (16.7 to 21.3; normal to 17.1); thrombocytopenia (159 to 137, 133 to 119); 2 patients had glucosuria (2+). It is not known whether all the abnormalities eventually returned to normal.

(2) *N138825 (J3576-03/04):* Phase II 8-week, open label study in fluctuating PD patients on Sinemet or Madopar (Hoehn and Yahr 1-4), comparing three doses of tolcapone (150 mg, 300 mg, 600 mg tid) in an ascending dose escalation; patients who were deemed to be responding well (criteria not specified) had their tolcapone dose increased every two weeks. Patients may also have been taking additional PD medications concurrently (bromocriptine, pergolide, trihexyphenidyl, droxidopa, and amantidine were cited). Eighty-six patients were enrolled; at completion (including withdrawals), 10 patients were at the 150-mg dose, 21 at the 300-mg dose, 53 at the 600-mg dose, and 3 at unspecified doses (200 mg or 450 mg). There were no deaths; 10 patients withdrew (5 in the 150-mg group; 3 in the 300-mg group, and 2 in the 600-mg group). No adverse event was classified as "serious." Thirty-three out of the 86 patients

reported at least one adverse event, most frequently hallucinations (7%), somnolence (6%), and abdominal discomfort, dyskinesia, and nausea (each with 5%). A higher percentage of adverse events occurred at the 300-mg dose (57%); withdrawals occurred for hallucinations (3), dizziness/headache (2), headache (2), abdominal pain (1), rash (1), diarrhea/liver disease (1; not specified but listed as "treated"). Six instances of (unspecified vital-sign abnormalities occurred). Three patients had a normal EKG at baseline, but abnormal at the end of the trial (not specified), 12 had abnormals EKGs at baseline and the trial's conclusion; and 1 had an abnormal EKG at baseline which normalized at the trial's end. Among lab abnormalities, two instances of transaminase elevations, at the 600-mg dose, were mentioned in the text as being in the "marked" range, but only one was located in the table of data (AST of 26 [upper limit 25]). There was one bilirubin of 18.4 (upper limit: 17.7). All abnormalities "returned to normal after the trial was completed" (v 1.328, p 4).

The sponsor notes that the "incidence of adverse events is lower overall than is reported in studies outside of Japan, but this is not uncommon and probably reflects a difference in reporting practice" (v 1.329, p 4; v 1.328, p 4).

In addition to the above completed studies, there are three ongoing trials in Japan: J3576-07, an open-label extension of J3576-06 (87 patients enrolled); J3576-08, an open-label study with doses of 100 or 200 mg tid (92 patients enrolled); and J3576-11, a double-blind, placebo-controlled study of 100 mg tid (81 patients enrolled). Of particular note in these ongoing studies is the incidence of neuroleptic malignant syndrome which will be discussed below (see section 8.9.2).

EUROPE

There is, in addition to the placebo-controlled trials discussed above, at least one ongoing trial in Europe and the US (NN15175): a randomized open-label, parallel- group, multicenter trial in the US and UK comparing tolcapone to pergolide, when administered in combination with Madopar or Sinemet; 200 PD patients, who exhibit end-of-dose wearing off, are expected to participate (about 33 patients in the US and two in Europe have been enrolled to date, according to personal communication from Tom Watson, Hoffmann-La Roche, Inc., 10/18/96).

8. Drug Abuse and Overdose Experience

The highest dose investigated in humans was 800 mg tid x 1 week, or four times the highest recommended dose of 200 mg tid and leading to a 16-fold higher exposure after one week of treatment; on 800 mg tid, C_{max} on day 1 = 15.0+4.4, and on day 7 = 1.5±0.3 (in comparison, toxicology studies in rats have shown that the minimal lethal plasma concentration is greater than 100 ug/ml).

The 800-mg dose led to an increase in GI complaints (nausea and vomiting) and dizziness (v 1.92, p 10); in a cohort of eight healthy volunteers, there was one case of elevated LFTs ("ALT>3x ULN, AST>ULN, GGT>2x ULN") in combination with diarrhea (v 1.92, p 9).

Dependency studies in rats and monkeys have shown no evidence to date of any potential for physical or psychological dependence; Dr. Tom Steele, Pharmacology, will review this data. Finally, the sponsor claims not to have found "any evidence of dependency or withdrawal effects upon discontinuation of tolcapone treatment in therapeutic studies" (v 1.333, p 97). However, the sponsor documents three possible case of neuroleptic malignnt syndrome as a result of abrupt withdrawal of the drug (see the next section).

9. Summary of Potentially Important Adverse Events Considered Drug Related

(a) Liver toxicity

Elevated transaminases led to the withdrawal of one (0.3%) patient in the 100-mg, and 5 (1.7%) patients in the 200-mg, group in Phase III studies; there were no dropouts from the placebo group for this reason. As discussed above (see section 8.3.iii), elevated transaminases were often associated with other GI side effects. Overall, 26 (1.25%) of patients in all studies have had elevated transaminases exceeding three time the upper limit of normal; five (0.2%) discontinued the drug for this reason. "Except for one patient" (not further described by the sponsor), all cases of elevated transaminases (>3x ULN) were first detected 6-12 weeks after tolcapone initiation and "generally returned to normal" following tolcapone discontinuation, about 2-4 weeks later "in most cases" (see the 5/30/96 IND Amendment submitted by the sponsor, v 41.1, p 15).

The sponsor suggests a possible link with one study death (discussed in full above); however, the actual cause of death really remains unknown. A 55-year-old female, without a history of hepatic disease, developed diarrhea and "yellowing of the skin and eyes" after six weeks of tolcapone 200 mg tid. She died six days later before coming to medical attention; no autopsy was done and there are, according to the sponsor, no recents labs on her. The patient was also on pergolide and selegiline; the influence of these drugs in the etiology of her condition is also not known.

(b) Neuroleptic malignant syndrome

Large decreases in, or the abrupt discontinuation of, L-DOPA or dopamine agonists have been "reported to induce a symptom complex known as neuroleptic malignant syndrome. . . . Therefore, when discontinuing tolcapone treatment, the sponsor recommends that "concomitant L-DOPA therapy should probably be increased so as to maintain dopaminergic stimulation" (v 1.333, p 96).

Three potential cases of NMS (two in Japan, one in Great Britain) are mentioned. Because, according to the sponsor, the patients were thought to have developed NMS after the clinical cut-off for this NDA, their case reports were not made part of the document (personal communication from Tom Watson, program manager, Drug Regulatory Affairs, Roche Pharmaceuticals, October 18, 1996). The sponsor has subsequently furnished this material upon request..

Subsequent information from the sponsor (the Four-Month Safety Update, dated 10/3/96 and covering Tolcapone up through 4/1/96) has recognized a total of four cases of NMS (the case report forms were sent under separate cover, dated 11/18/96, in response to FDA request). Three have occurred in Japan and were classified by the investigator as possibly related to test medication; a fourth case, reported in the United Kingdom and described by the investigator as "possible" NMS and probably attributable to tolcapone withdrawal, was nonetheless considered by the sponsor to be a questionable case ("remotely likely to be NMS").

Study/Pt (tolcapone dose)	*Age Sex*	*Adverse Event*	*PI's assessment*	*Sponsor's assessment*
NZ14657/3606 (200 mg tid x 361 d)	65M	PMH: HTN, anxiety/neurotic disorder, enlarged prostate; Madopar, Madopar CR, selegiline, dothiepin, pergolide, ventolin nebulizer, prothiaden. Hosp Day 361 in order to discontinue tolcapone after study completion. On Day 368 developed fever (37.4°C), confusion, CPK 1463 IU (admission CPK 234). Treated with bromocriptine with improvement by Day 375 (CPK 120).	NMS suspected; probably tolcapone related	Possibly related