

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: NDA 20850**

**STATISTICAL REVIEW(S)**

**STATISTICAL REVIEW AND EVALUATION**

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**NDA: 20-850.**

**Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.**

**Name of Drug: Telmisartan (CGP 48933)**

**Indication: Hypertension**

**Document Reviewed: CANDA for the submission,**  
volumes 1.001, 1.152, 1.153, 1.165, 1.166, 1.173, 1.174, 1.175, 1.176,  
1.207, 1.208, 1.209, 1.213, 1.214, 1.215, 1.246, and 1.247.  
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**1. INTRODUCTION**

This application consists of 7 placebo-controlled randomized multi-center studies 502.201, 502.202, 502.203, 502.204, 502.206, 502.207 and 502.208, and 6 active-controlled 502.209, 502.210, 502.211, 502.214, 502.215 and 502.216. Study 502.201 was a 7-day study, study 502.209 was for patients with severe hypertension, study 502.210 was for hypertensive elderly patients (age > 65 years), and study 502.211 was for hypertensive patients with renal impairment. The active controls used were either atenolol, enalapril, HCTZ, or lisinopril,

In this review the results of studies 502.202, 502.203, 502.204, 502.206, 502.207 and 502.208 will be discussed. The results of study 502.201 will not be discussed since it was a small 7-day study.

The primary efficacy endpoint in these studies was the change from baseline in supine diastolic blood pressure (SuDBP) at trough, using an intent-to-treat analysis as the primary analysis.

**2. STUDY 502.202**

This was a randomized, multicenter, placebo-controlled and active-controlled, double-blind study to determine the dose response of antihypertensive efficacy of once-daily (OD) administration of telmisartan in patients with mild to moderate hypertension. The study included 207 patients with diastolic blood pressures of 100 to 114 mmHg and without major hematologic, renal, hepatic, cardiac or endocrine abnormalities. After a 4-week placebo run-in period, patients were randomized to placebo, enalapril 20 mg or telmisartan (40, 80 or 120 mg) once daily for 4 weeks. To assess the antihypertensive effect of telmisartan over a 24-hour period, blood pressure at baseline (day 0), day 1 and day 28 of dosing was recorded at 12 hours after the dose and then again at 24 hours.

**3. STUDY 502.203**

This was a randomized, multicenter, placebo-controlled, double-blind study to evaluate the efficacy and safety of various doses of telmisartan compared to placebo and to assess the dose-response

relationship in patients with mild to moderate hypertension (mean supine diastolic blood pressure (SuDBP)  $\geq 100$  and  $\leq 114$  mmHg). After a four-week placebo run-in period, qualifying patients were entered into a four-week double-blind period and randomized to one of six treatment groups: placebo, or telmisartan 20, 40, 80, 120, or 160 mg (OD). Trough blood pressures (BP) and heart rates (HR) were measured weekly in the placebo run-in period and double-blind period, and daily during a seven day post-double-blind period (washout) at four centers. To assess the 24-hour BP effects of telmisartan, supine and standing BP and HR were measured approximately every hour for 12 hours and then again at 24-hours post-dose at baseline and at the end of the double-blind period. Two hundred seventy four patients (mean age 52.3 years, range 28 to 72 years, 69% males, 79.6% were white, 13.5% were black, 6.2% were Hispanic and 0.7% were of other races) were randomized and received double-blind study drug.

#### 4. STUDY 502.204

This was a multicenter, randomized, double-blind, parallel-group placebo-controlled study. Eight hundred and eighteen patients with mild to moderate hypertension, from 49 clinical centers, were randomized to a once daily dose of telmisartan (20, 40, 80, or 160 mg), hydrochlorothiazide (6.25, 12.5, or 25 mg), one of the 12 possible telmisartan/HCTZ combinations, or placebo. The primary combinations of interest were T40/H12.5 and T80/H12.5, where T stands for telmisartan and H for hydrochlorothiazide. Randomization to treatments was stratified according to race (black or non-black). Patients were treated double blind for eight weeks following a four week run-in period on single blind placebo. Change in trough supine and standing blood pressure was assessed at baseline, 2, 4, and 8 weeks, and clinical and laboratory safety were monitored.

#### 5. STUDY 502.206

This was a multicenter, randomized, double-blind, parallel-group placebo-controlled study to evaluate the efficacy and safety of telmisartan (40, 80, 120 and 160 mg (OD)) compared to placebo after three months of oral dosing in patients with mild to moderate essential hypertension (mean supine DBP  $\geq 95$  mmHg and  $\leq 114$  mmHg). Enalapril 20 mg (OD) was used as a reference standard. The dose response relationship of the antihypertensive effect of telmisartan was also assessed. Following a four-week placebo run-in period, qualifying patients were randomized to one of six treatment groups (40, 80, 120 or 160 mg telmisartan, 20 mg enalapril, or placebo) for 12 weeks of double-blind therapy. Patients were seen weekly during the placebo run-in phase, and at one, four, eight and twelve weeks during the double-blind phase. At eight selected sites, patients entered a placebo withdrawal phase following completion of double-blind treatment. Patients were seen twice weekly, and continued in this phase until their blood pressure was within 3 mmHg of their baseline measurements (3 mmHg below baseline or higher) or for a maximum of three weeks.

Four hundred forty patients (283 males, 157 females) were randomized and received double-blind drug. The majority (69%) of patients were white.

## 6. STUDY 502.207

This was a randomised, multicentre, placebo-controlled and active-controlled, double-blind study to evaluate the antihypertensive efficacy and safety of telmisartan 40 - 120 mg (OD) in comparison to placebo and atenolol 50 - 100 mg (OD) in patients with mild to moderate hypertension (mean SuDBP between 95 mmHg and 114 mmHg).

The treatment regimens were as follows:

1. Telmisartan 40 mg (OD) (titrated to telmisartan 80 mg (OD)).
2. Telmisartan 80 mg (OD) (titrated to telmisartan 120 mg (OD)).
3. Atenolol 50 mg (OD) (titrated to atenolol 100 mg (OD)).
4. Placebo (OD).

Titration in all four groups was a single step and response based (SuDBP  $\geq$  90 mmHg at visit 5, week 8).

During a placebo run-in period of four weeks, trough blood pressure and pulse rate were measured at bi-weekly intervals with the visit 3 (randomisation) values taken as baseline. Following randomisation, visits were performed at bi-weekly intervals at weeks 6, 8, 10, and 12 from study entry.

The primary efficacy endpoint for the study was the change from baseline in SuDBP at trough (24 hours post dosing) after eight weeks of randomised treatment (visit 7, day 56) or at the last available trough observation during the double-blind phase (ie last-trough carried forward).

Two hundred and fifty six (256) patients were randomised to the double-blind treatment phase. Twenty (20) patients from Centre 10 were excluded from all analyses, both safety and efficacy, because of unreliable data quality.

Two hundred and twenty nine (229) patients were included in the Intent-to-Treat efficacy analysis (all randomised patients who received at least one dose of double-blind medication and had a valid baseline and post dose trough measurement of diastolic blood pressure).

Forty two (42) patients had blood pressures measured in the sitting position instead of supine. Since a minimal difference is expected between sitting and supine, blood pressures were treated as supine in the 'intent-to-treat' dataset.

## 7. STUDY 502.208

This was a randomized, double-blind, placebo and active controlled, parallel group multicentre study. The objective of this trial was to describe the anti-hypertensive effect and safety of telmisartan in titrated doses of 40 to 80 to 120 mg compared to placebo and to amlodipine in

titrated doses of 5 to 5 to 10 mg by trough. The trial consisted of a three to 14 day wash-out period followed by a four week placebo run-in period with bi-weekly visits to establish a stable baseline DBP of  $\geq 95$  mmHg and  $\leq 114$  mmHg. Following randomization to either placebo, telmisartan 40 mg or amlodipine 5 mg, patients entered a twelve week double-blind treatment phase with bi-weekly visits. Titration occurred at Weeks 4 and 8 if mean SuDBP was  $\geq 90$  mmHg.

Twenty-four hour ABPM was done at baseline and at Week 12. After completing the ABPM at Week 12, patients entered a placebo wash-out period with a final visit scheduled one week after the Week 12 visit.

## 8. REVIEWER'S ANALYSIS AND DISCUSSION

This reviewer has used the data submitted by the sponsor to check the sponsor's results of statistical analyses and to provide the following analyses that were not provided by the sponsor as described below. First, analysis of covariance for the change from baseline in SuDBP at the end of study 502.204 for all the 20 treatment groups as opposed to the sponsor's analysis for the "six key treatment groups". Second, summary statistics for the change from baseline in diastolic BP by gender for the above six studies. Third, summary statistics for the change from baseline in diastolic BP by race for studies 502.202, 502.203, 502.204, and 502.206.

Note that, since this application is directed towards telmisartan monotherapy, this reviewer's results in analysing the data of study 502.204 are listed in Tables 1 and 2, and discussed in section 8.1 below, only for the monotherapy groups. The results for the telmisartan/HCTZ combination groups will be discussed in a future review whenever the sponsor submit an NDA for the combination therapy.

### 8.1. Telmisartan doses in parallel studies

The discussion below will be based on the results of studies 502.202, 502.203, 502.204, and 502.206, shown for the SuDBP in Table 1 and on the results for the SuSBP as shown in Table 2.

#### ✓ Telmisartan 20 mg (OD)

This dose level was investigated in studies 502.203 and 502.204, the results of which (listed in Table 1) show that telmisartan 20 mg(OD) has caused a significant ( $p \leq 0.0014$ ) reduction in SuDBP over that for placebo. Similar significant results ( $p \leq 0.0153$ ) as above are found for the SuSBP as shown in Table 2.

#### ✓ Telmisartan 40 mg (OD)

This dose level was investigated in studies 502.202, 502.203, 502.204 and 502.206, the results of

which (listed in Table 1) show that telmisartan 40 mg(OD) has caused a significant ( $p \leq 0.0059$ ) reduction in SuDBP over that for placebo. Similar significant results ( $p=0.0001$ ) as above are found for the SuSBP as shown in Table 2.

✓ Telmisartan 80 mg (OD)

This dose level was investigated in studies 502.202, 502.203, 502.204 and 502.206, the results of which (listed in Table 1) show that telmisartan 80 mg(OD) has caused a significant ( $p \leq 0.0002$ ) reduction in SuDBP over that for placebo. Similar significant results ( $p=0.0001$ ) as above are found for the SuSBP as shown in Table 2.

✓ Telmisartan 120 mg (OD)

This dose level was investigated in studies 502.202, 502.203, and 502.206, the results of which show that telmisartan 120 mg(OD) has caused significant ( $p=0.0001$ ) reductions in both the SuDBP and SuSBP over that for placebo (see Tables 1 and 2).

Telmisartan 160 mg (OD)

This dose level was investigated in studies 502.203, 502.204, and 502.206, the results of which show that telmisartan 160 mg(OD) has caused significant ( $p=0.0001$ ) reductions in both the SuDBP and SuSBP over that for placebo (see Tables 1 and 2).

The above results are summarized symbolically in Table A below.

Table A. The results of tests for the change from baseline in diastolic (and systolic) BP for telmisartan OD regimen versus that of placebo. These results are denoted by S=Significant, N=Non-significant, where capital letters are for the diastolic and small letters are for the systolic BP.

Study	Telmisartan (OD) Dose (in mg)				
	20	40	80	120	160
202		S, s	S, s	S, s	
203	S, s	S, s	S, s	S, s	S, s
204*	S, s	S, s	S, s		S, s
206		S, s	S, s	S, s	S, s

\* Listed only for telmisartan monotherapy groups

## 8.2. Titrated telmisartan OD regimen

Studies 502.207 and 502.208 were titration studies in which patients dose levels were titrated at specified visits to control their blood pressure as described above for each of the two studies. Tables 1 and 2 shows that for both studies 502.207 and 502.208 telmisartan groups have acquired significant ( $p=0.0001$ ) BP reductions compared to that of placebo in both the SuDBP and SuSBP. These results provide the overall effect of telmisartan versus placebo that was contributed by patients whose dose levels were titrated and patients who stayed on their original dose level. To get some insight into the responses of patients whether their doses were titrated or have stayed on their original dose level, this reviewer has carried out a descriptive analysis for both studies 502.207 and 502.208.

### Titration study 502.207

Table B below shows that, for the three treatment groups, patients who continued on their initial dose levels had lower baseline SuDBP and had acquired a greater change from baseline in their SuDBP at the end of the study than those whose dose levels had to be titrated.

Table B. Change from baseline in SuDBP for patients whose dose levels were titrated and those who have stayed on their initial dose levels.

Starting Dose	Results	Ending Dose Level				
		Placebo	Placebo+	T40	T80	T120
Placebo	N	10	41			
	Baseline	97.4	100.8			
	Change	-11.5	-2.4			
Telmisartan 40 mg	N			22	32	
	Baseline			98.9	104.3	
	Change			-10.8	-6.8	
Telmisartan 80 mg	N				29	24
	Baseline				99.8	101.9
	Change				-12.6	-6.0

+ Titrated placebo dose level 2.

This means that the significant results for the telmisartan groups versus placebo, shown in Table 1, were contributed mainly by the groups of patients who responded positively to either

telmisartan 40 or 80 mg regimens without needing titration to higher dose levels during the study.

### Titration study 502.208

Table C below shows that the telmisartan group of patients who continued on their initial dose levels had lower baseline SuDBP and had acquired a relatively greater change from baseline in their SuDBP at the end of the study than those whose dose levels had to be titrated to either telmisartan 80 or 120 mg.

**Table C. Change from baseline in SuDBP for patients whose dose levels were titrated and those who have stayed on their initial dose levels.**

Starting Dose	Results	Ending Dose Level					
		Plac.	Plac+	Plac++	T40	T80	T120
Placebo	N	10	17	52			
	Baseline	103.2	98.8	101.8			
	Change	-5.7	-7.6	-3.6			
Telmisartan 40 mg	N				27	22	22
	Baseline				98.6	99.9	103.1
	Change				-15.3	-11.2	-9.9

+ Titrated placebo dose level 2.

++ Titrated placebo dose level 3.

By comparing the reductions in SuDBP, one can see that the significant result for telmisartan versus placebo, shown in Table 1, was contributed mainly by the group of patients who responded positively to telmisartan 40 mg regimen without needing titration to a higher dose level during the study.

### 8.3. Dose Response

This reviewer has constructed a logistic model and an  $E_{MAX}$  model for the change from baseline in SuDBP for study 502.203 and a logistic model for study 502.206. Figures 1 and 2 show the graphs for the constructed logistic model and the  $E_{MAX}$  model, respectively, for study 502.203. It is clear that both of these models well fit the data of the change from baseline in SuDBP, although the RMSE (7.76) for the logistic model is slightly smaller than that for the  $E_{MAX}$  model (RMSE=7.775). Note that a description of the estimated  $E_{MAX}$  model is given with Figure 2.

For study 502.206 the graph of the constructed logistic model is shown in Figure 3. The RMSE for this model is 7.776. Attempts were made by this reviewer to construct an  $E_{MAX}$  model for this study but, the estimation scheme have produced a negative value for the  $EC_{50}$  parameter.

The three dose response curves seem to have reached a plateau after telmisartan 20 mg and in particular the  $E_{MAX}$  model, shown in Figure 2, has reached plateau after telmisartan 80 mg.

#### 8.4. Telmisartan effect by gender

Table 3 summarizes the results of the change from baseline in SuDBP by gender for all the above described studies .

Table 3 shows that in studies 502.202, 502.203, 502.204, and 502.206 all telmisartan dose levels (except for 20, 80 and 160 mg in study 502.203, 40 mg in study 502.204, and 120 mg in studies 502.202 and 502.206) have resulted in greater changes from baseline in SuDBP for females over those for males.

In titration studies (studies 502.207 and 502.208) this table shows that female patients who started on telmisartan 40 mg, with a conditional titration to 80 mg (in study 502.207) or to 80 and 120 mg (in study 502.208), have acquired greater reductions in SuDBP over male patients.

#### 8.5. Telmisartan effect by race

Other than studies 502.202, 502.203, 502.204, and 502.206 there were very few or no black patients in other studies.

Although the number of black patients is small compared to the non-black patients, Table 4 shows that in all the studied telmisartan doses blacks show smaller change from baseline in SuDBP over that for the non-blacks.

### 9. SUMMARY AND CONCLUSION (WHICH MAY BE CONVEYED TO THE SPONSOR)

This reviewer has used the data submitted by the sponsor to check the sponsor's results of statistical analyses and to provide the following analyses that were not provided by the sponsor: First, analysis of covariance for the results of study 502.204 for all the 20 treatment groups as opposed to the sponsor's analysis for "the six key treatment groups". Second, summary statistics for the change from baseline in diastolic BP by gender for the above six studies Third, summary statistics for the change from baseline in diastolic BP by race for studies 502.202, 502.203, 502.204, and 502.206.

Telmisartan OD regimen was investigated in parallel groups for 20, 40, 80, 120, and 160 mg in studies 502.202, 502.203, 502.204, and 502.206 and as a titrated regimen in studies 502.207 and 502.208. For the four parallel studies, Table 1 shows that all the above mentioned dose levels of

telmisartan have resulted in significant ( $p < 0.0014$ ) changes from baseline in SuDBP over that of placebo. These significant results were also true for the change from baseline in SuSBP ( $p < 0.0153$ ) shown in Table 2.

Figures 1 and 2 show the graphs for a logistic and an  $E_{MAX}$  models, respectively, that this reviewer has constructed for the change from baseline in SuDBP in study 502.203. Figure 3 shows the graph for a logistic model that was constructed by this reviewer for study 502.206. The three dose response curves seem to have reached a plateau at some dose level between telmisartan 20 and 80 mg.

Table 3 shows that, in all the six studies, the studied telmisartan dose levels (except for 20, 80 and 160 mg in study 502.203, 40 mg in study 502.204, 120 mg in studies 502.202 and 502.206, and for 80-120 mg group in study 502.207) have resulted in greater changes from baseline in SuDBP for females over those for males.

Table 4 shows that, for studies 502.202, 502.203, 502.204, and 502.206 and for all the studied telmisartan dose levels, blacks show smaller change from baseline in SuDBP over that for the non-blacks.

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This review consists of 9 pages, 4 tables, and 3 figures.

Concur:

Dr. Mahjoob

Dr. Chi *Chi* 151 06/19/98  
6/19/98

cc: Orig. NDA 20-850

HFD-110/Dr.U

HFD-344/Dr. Barton

HFD-710/Dr. Chi

HFD-710/Dr. Mahjoob

HFD-710/Dr. Nuri

Chron:

W A Nuri: 594-5303 DB I: 06-19-98: DISC10/telm1.wpd

Table 1. Mean baseline value and mean change from baseline at endpoint for SuDBP(trough) in studies 202, 203, 204, 206, 207, and 208 (telmisartan).

Study	Regimen (mg)	N	Mean SuDBP (mmHg)		p-value	
			Baseline	$\Delta^{\#}$		$\Delta\Delta^{\$}$
202	Placebo	43	104.0	-1.5		
	40 mg telmisartan	40	102.4	-7.9	-6.4	0.0059
	80 mg telmisartan	41	101.7	-8.7	-7.2	0.0002
	120 mg telmisartan	41	102.7	-9.8	-8.3	0.0001
	20 mg Enalapril	42	102.5	-9.6	-8.1	0.0001
203	Placebo	46	102.5	-0.4		
	20 mg telmisartan	47	103.0	-6.9	-6.5	0.0001
	40 mg telmisartan	47	101.5	-8.6	-8.2	0.0001
	80 mg telmisartan	44	103.1	-10.5	-10.1	0.0001
	120 mg telmisartan	45	102.1	-8.9	-8.5	0.0001
	160 mg telmisartan	44	101.9	-9.4	-9.0	0.0001
204*	Placebo	73	100.3	-4.3		
	20 mg telmisartan	23	100.2	-10.4	-6.1	0.0014
	40 mg telmisartan	75	101.4	-11.1	-6.8	0.0001
	80 mg telmisartan	77	100.3	-11.8	-7.5	0.0001
	160 mg telmisartan	33	100.6	-11.3	-7.0	0.0001
206	Placebo	74	100.5	-1.8		
	40 mg telmisartan	72	100.4	-9.3	-7.5	0.0001
	80 mg telmisartan	71	100.1	-9.7	-7.9	0.0001
	120 mg telmisartan	72	100.3	-8.8	-7.0	0.0001
	160 mg telmisartan	73	100.3	-8.6	-6.8	0.0001
	20 mg Enalapril	71	100.5	-7.2	-5.4	0.0001
207	Placebo	60	100.4	-2.7		
	Telm 40 (to 80 mg)	59	102.0	-8.4	-5.7	0.0001
	Telm 80 (to 120 mg)	59	100.8	-9.1	-6.4	0.0001
	Aten 50 (to 100 mg)	59	101.2	-10.8	-8.1	0.0001
208	Placebo	81	101.4	-4.5		
	Telmisartan	73	100.6	-11.6	-7.1	0.0001
	Amlodipine	78	101.1	-11.6	-7.1	0.0001

#  $\Delta$  = Change from baseline (Least squares estimates)

\$  $\Delta\Delta$  = Placebo adjusted change from baseline

\* Listed for only the telmisartan and placebo groups

Table 2 Mean baseline value and mean change from baseline at endpoint for SuSBP(trough) in studies 202, 203, 204, 206, 207, and 208 (telmisartan).

Study	Regimen (mg)	N	Mean SuSBP (mmHg)		p-value	
			Baseline	$\Delta^{\#}$		$\Delta\Delta^{\$}$
202	Placebo	43	159.0	+3.5		
	40 mg telmisartan	40	155.0	-10.0	-13.5	0.0001
	80 mg telmisartan	41	150.0	-15.5	-19.0	0.0001
	120 mg telmisartan	41	156.1	-12.5	-16.0	0.0001
	20 mg Enalapril	42	152.4	-10.2	-13.7	0.0001
203	Placebo	46	152.9	+3.2		
	20 mg telmisartan	47	150.0	-3.3	-6.5	0.0153
	40 mg telmisartan	47	148.8	-7.8	-11.0	0.0001
	80 mg telmisartan	44	153.1	-9.8	-13.0	0.0001
	120 mg telmisartan	45	149.8	-9.1	-12.3	0.0001
160 mg telmisartan	44	152.7	-11.7	-14.9	0.0001	
204*	Placebo	73	153.7	-3.4		
	20 mg telmisartan	23	154.4	-11.5	-8.1	0.0149
	40 mg telmisartan	75	153.8	-13.3	-9.9	0.0001
	80 mg telmisartan	77	153.1	-16.1	-12.7	0.0001
	160 mg telmisartan	33	151.4	-16.0	-12.6	0.0001
206	Placebo	74	154.9	-0.8		
	40 mg telmisartan	72	155.2	-11.6	-10.8	0.0001
	80 mg telmisartan	71	153.8	-11.8	-11.0	0.0001
	120 mg telmisartan	72	152.1	-10.0	-9.2	0.0001
	160 mg telmisartan	73	153.4	-11.9	-11.1	0.0001
	20 mg Enalapril	71	153.8	-8.2	-7.4	0.0001
207	Placebo	60	164.2	-3.1		
	Telm 40 (to 80 mg)	59	164.9	-12.3	-9.2	0.0024
	Telm 80 (to 120 mg)	59	160.5	-16.2	-13.1	0.0001
	Aten 50 (to 100 mg)	59	159.6	-12.7	-9.6	0.0016
208	Placebo	81	153.1	-3.4		
	Telmisartan	73	153.4	-16.5	-13.1	0.0001
	Amlodipine	78	153.1	-17.4	-14.0	0.0001

#  $\Delta$  = Change from baseline (Least squares estimates)

\$  $\Delta\Delta$  = Placebo adjusted change from baseline

\* Listed for only the telmisartan and placebo groups

Table 3. Mean baseline value and mean change from baseline (by gender) at endpoint for SuDBP(trough) in studies 202, 203, 204, 206, 207, and 208 (telmisartan). The analysis was carried out by the reviewer.

Study	Regimen (mg)	Female				Male			
		N	Mean SuDBP (mmHg)			N	Mean SuDBP (mmHg)		
			Basln	$\Delta^{\#}$	$\Delta\Delta^{\$}$		Basln	$\Delta^{\#}$	$\Delta\Delta^{\$}$
202	Placebo	19	102.6	-2.1		24	105.1	-1.8	
	40 mg telmisartan	17	102.5	-8.1	-6.0	23	102.3	-7.9	-6.1
	80 mg telmisartan	15	100.5	-10.1	-8.0	26	102.4	-7.6	-5.8
	120 mg telmisartan	16	104.4	-9.3	-7.2	25	101.6	-10.0	-8.2
	20 mg Enalapril	11	98.8	-9.0	-6.9	31	103.8	-10.2	-8.4
203	Placebo	17	100.9	-3.5		29	103.4	-0.7	
	20 mg telmisartan	15	102.8	-5.9	-2.4	32	103.1	-8.4	-7.7
	40 mg telmisartan	15	101.3	-11.4	-7.9	32	101.6	-8.2	-7.5
	80 mg telmisartan	12	102.5	-10.1	-6.6	32	103.3	-10.5	-9.8
	120 mg telmisartan	14	100.6	-10.9	-7.4	31	102.4	-8.6	-7.9
	160 mg telmisartan	12	102.8	-8.6	-5.1	32	101.6	-10.0	-9.3
204*	Placebo	28	100.9	-2.8		45	100.0	-4.4	
	20 mg telmisartan	13	98.5	-12.2	-9.4	10	102.5	-7.5	-3.1
	40 mg telmisartan	31	102.3	-10.6	-7.8	44	100.8	-10.7	-6.3
	80 mg telmisartan	31	99.8	-11.8	-9.0	46	100.6	-11.3	-6.9
	160 mg telmisartan	16	101.3	-13.6	-10.8	17	100.0	-7.7	-3.3

#  $\Delta$  = Change from baseline (raw means)

\* Listed for only the telmisartan and placebo groups

\$  $\Delta\Delta$  = Placebo adjusted change from baseline

Table 3 (Continued)

Study	Regimen (mg)	Female				Male			
		N	Mean SuDBP (mmHg)			N	Mean SuDBP (mmHg)		
			Basln	$\Delta^{\#}$	$\Delta\Delta^{\$}$		Basln	$\Delta^{\#}$	$\Delta\Delta^{\$}$
206	Placebo	27	100.1	-2.1		47	100.7	-1.6	
	40 mg telmisartan	22	100.6	-10.3	-8.2	50	100.9	-9.0	-7.4
	80 mg telmisartan	30	99.4	-11.5	-9.4	41	100.5	-9.0	-7.4
	120 mg telmisartan	25	99.8	-6.8	-4.7	47	100.5	-9.9	-8.3
	160 mg telmisartan	24	99.4	-8.9	-6.8	49	100.8	-8.8	-7.2
	20 mg Enalapril	27	100.1	-10.3	-8.2	44	100.7	-5.4	-3.8
207	Placebo	19	100.3	-4.6		38	100.4	-2.9	
	Telm 40 (to 80 mg)	20	102.0	-9.1	-4.5	37	102.1	-7.1	-4.2
	Telm 80 (to 120 mg)	17	100.4	-7.9	-3.3	39	101.0	-10.3	-7.4
	Aten 50 (to 100 mg)	17	99.4	-9.2	-4.6	42	101.9	-11.5	-8.6
208	Placebo	29	100.4	-6.3		50	101.9	-3.8	
	Telmisartan	29	99.3	-13.8	-7.5	42	101.2	-11.3	-7.5
	Amlodipine	23	99.3	-13.3	-7.0	55	101.8	-11.1	-7.3

#  $\Delta$  = Change from baseline (raw means)

\$  $\Delta\Delta$  = Placebo adjusted change from baseline

Table 4. Mean baseline value and mean change from baseline (by race) at endpoint for SuDBP(trough) in studies 202, 203, 204, and 206 (telmisartan). The analysis was carried out by the reviewer.

Study	Regimen (mg)	Black				Non-Black			
		N	Mean SuDBP (mmHg)			N	Mean SuDBP (mmHg)		
			Basln	$\Delta^{\#}$	$\Delta\Delta^{\$}$		Basln	$\Delta^{\#}$	$\Delta\Delta^{\$}$
202	Placebo	5	104.2	+1.2		38	104.0	-2.3	
	40 mg telmisartan	0				40	102.4	-8.0	-5.7
	80 mg telmisartan	5	101.8	-1.0	-2.2	36	101.7	-9.6	-7.3
	120 mg telmisartan	5	104.4	-3.0	-4.2	36	102.6	-10.7	-8.4
	20 mg Enalapril	4	108.5	-7.8	-9.0	38	101.9	-10.1	-7.8
203	Placebo	5	104.8	+3.1		41	102.2	-1.3	
	20 mg telmisartan	8	104.2	-3.4	-6.5	39	102.8	-8.5	-7.2
	40 mg telmisartan	8	100.4	-7.0	-10.1	39	101.8	-9.7	-8.4
	80 mg telmisartan	4	105.3	-8.3	-11.4	40	102.9	-10.6	-9.3
	120 mg telmisartan	5	98.9	-6.4	-9.5	40	102.5	-9.7	-8.4
	160 mg telmisartan	7	105.9	-3.0	-6.1	37	101.2	-10.8	-9.5
204*	Placebo	18	101.2	-3.4		55	100.1	-3.9	
	20 mg telmisartan	7	100.8	-6.5	-3.1	16	100.0	-11.8	-7.9
	40 mg telmisartan	20	103.2	-6.7	-3.3	55	100.8	-12.1	-8.2
	80 mg telmisartan	22	99.7	-4.6	-1.2	55	100.5	-14.3	-10.4
	160 mg telmisartan	10	99.9	-5.6	-2.2	23	100.9	-12.7	-8.8

#  $\Delta$  = Change from baseline (raw means)

\* Listed only for the telmisartan and placebo groups

\$  $\Delta\Delta$  = Placebo adjusted change from baseline

Table 4 (Continued)

Study	Regimen (mg)	<u>Black</u>				<u>Non-Black</u>			
		N	Mean SuDBP (mmHg)			N	Mean SuDBP (mmHg)		
			Basln	$\Delta^{\#}$	$\Delta\Delta^{\$}$		Basln	$\Delta^{\#}$	$\Delta\Delta^{\$}$
206	Placebo	12	99.4	-0.2		62	100.7	-2.1	
	40 mg telmisartan	11	102.2	-5.6	-5.4	61	100.6	-10.1	-8.0
	80 mg telmisartan	7	101.7	-8.0	-7.8	64	99.9	-10.3	-8.2
	120 mg telmisartan	14	100.5	-6.9	-6.7	58	100.2	-9.3	-7.2
	160 mg telmisartan	13	100.7	-2.6	-2.4	60	100.3	-10.2	-8.1
	20 mg Enalapril	13	101.9	-6.2	-6.0	58	100.1	-7.5	-5.4

#  $\Delta$  = Change from baseline (raw means)

\$  $\Delta\Delta$  = Placebo adjusted change from baseline

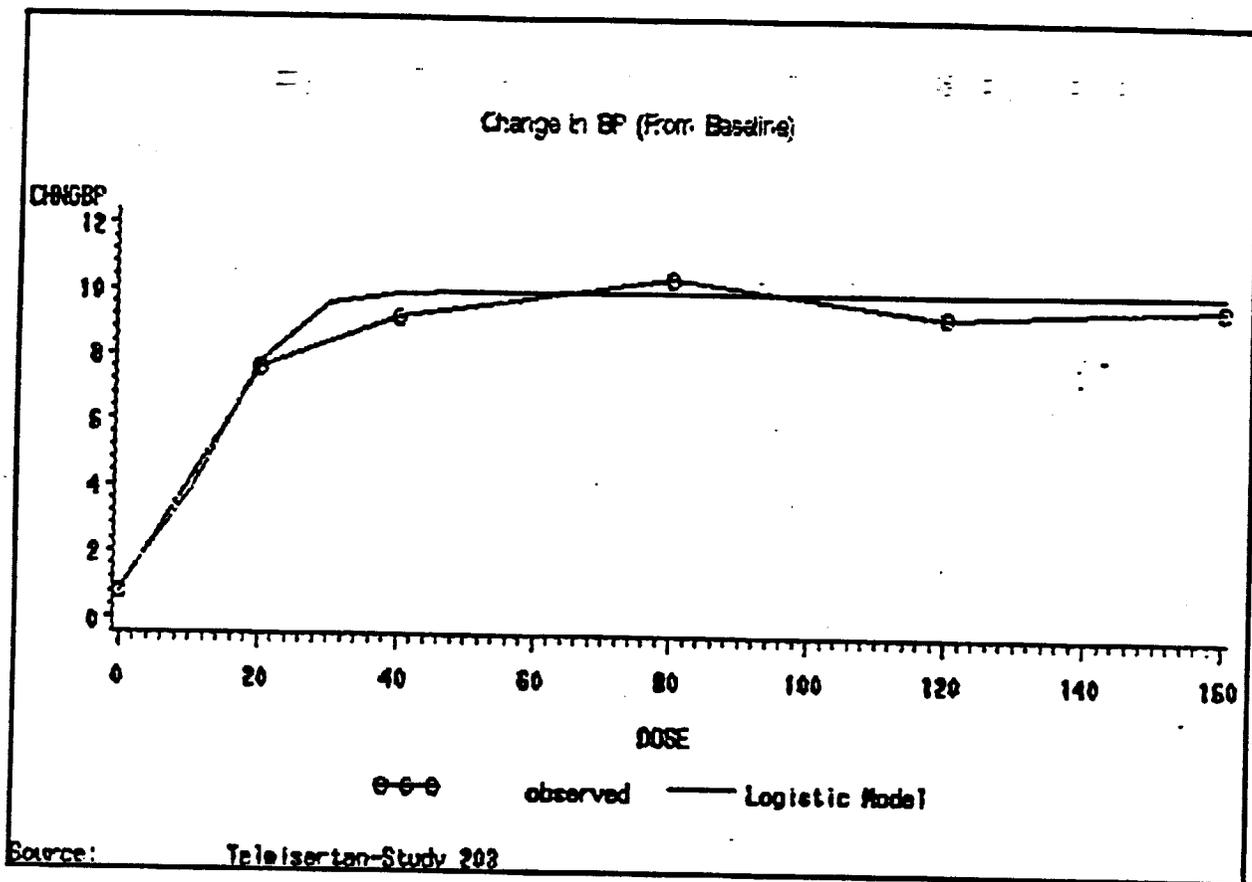


Figure 1. The observed changes from baseline in SuDBP and the estimated logistic model for dose response. (Study 502.203).

Model:  $\text{Change} = 10 / [1 + 4.7 \cdot \text{Exp}(-0.106 \cdot \text{dose})]$ .

RMSE=7.776.

The dose levels studied were 0, 20, 40, 80, 120, and 160 mg.

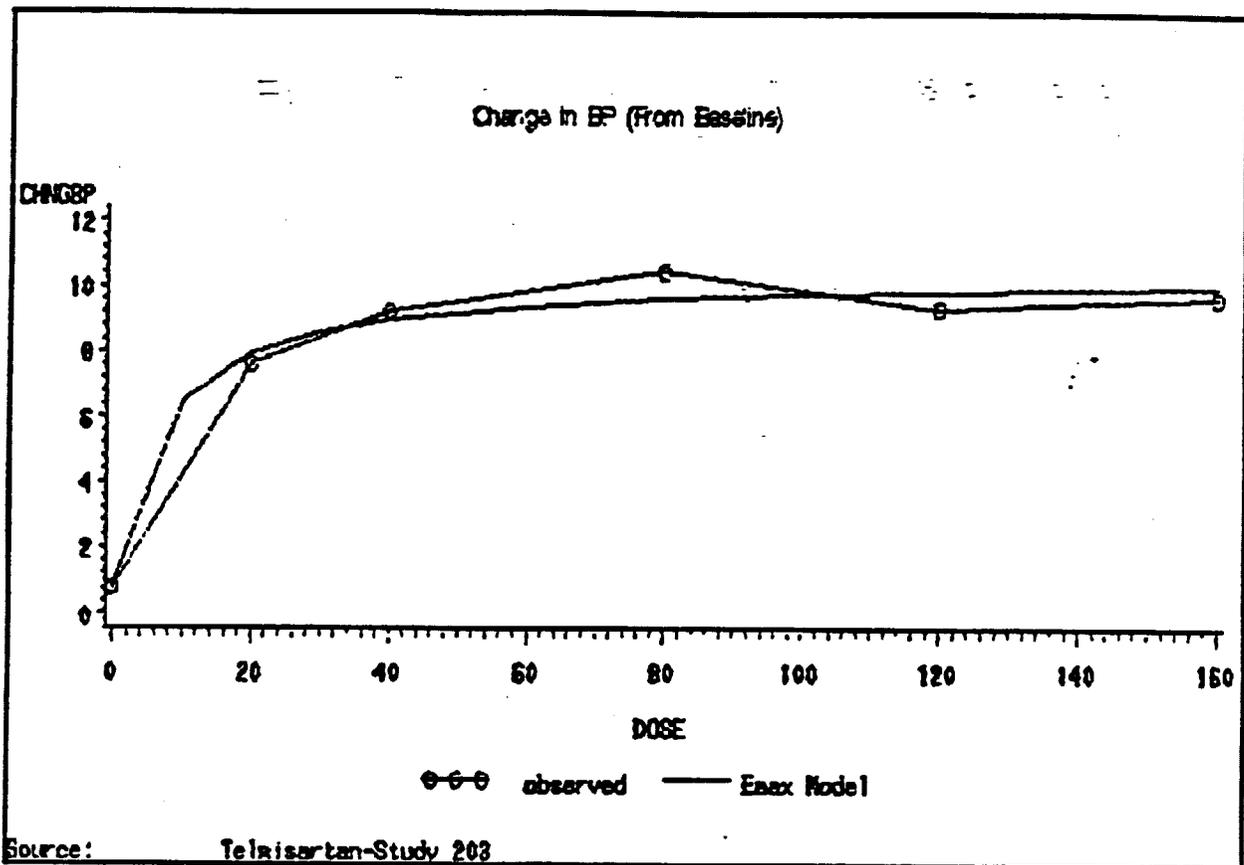


Figure 2. The observed changes from baseline in SuDBP and the estimated  $E_{MAX}$  model for dose response. (Study 502.203).

Model:  $Change = C + (E_{MAX} + Dose)/(EC_{50} + Dose)$ , where

$C$ =Unknown constant representing placebo effect,  
 $E_{MAX}$ =Maximum expected effect, and  
 $EC_{50}$ =Dose level producing an effect half of  $E_{MAX}$ .

Estimated Model :  $Change = 0.8 + (9.49) \cdot dose / (6.75 + dose)$ .

RMSE=7.775.

The dose levels studied were 0, 20, 40, 80, 120, and 160 mg.

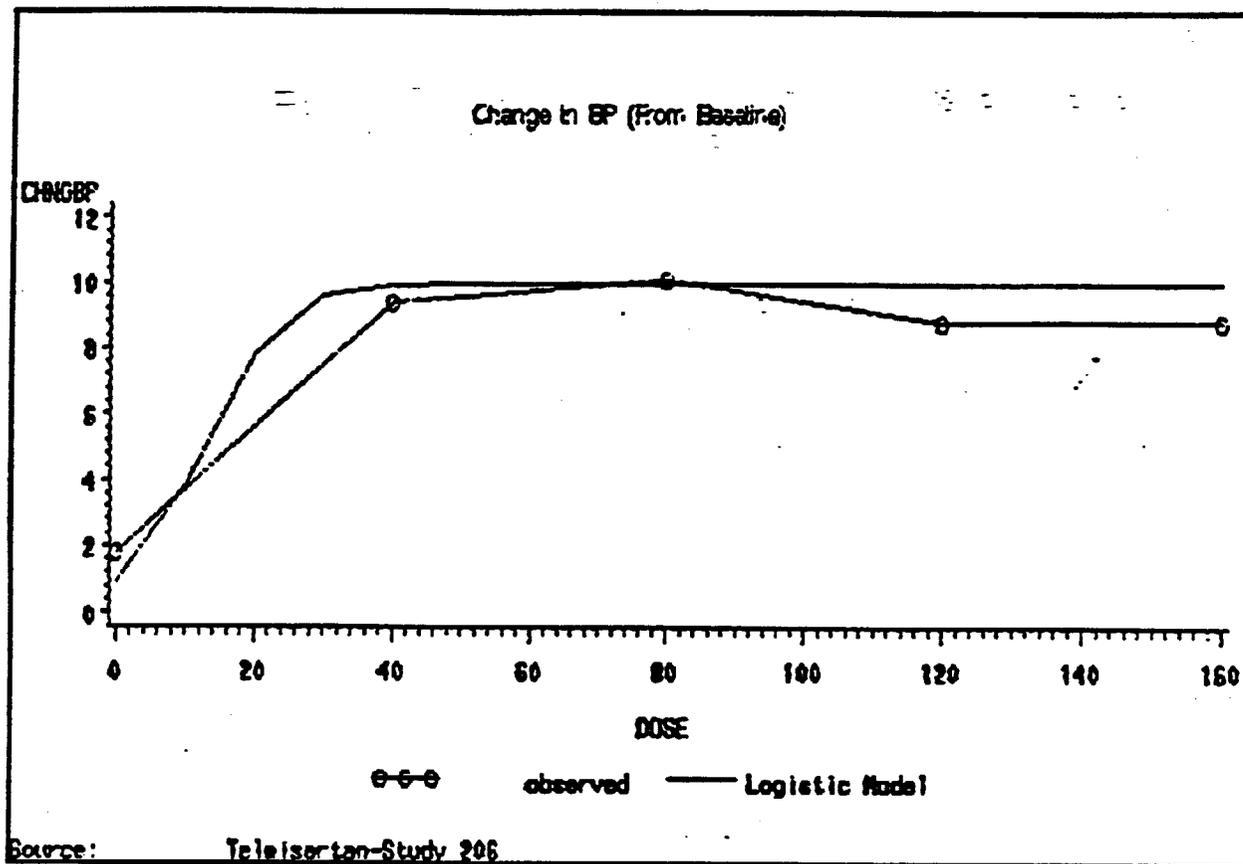


Figure 3. The observed changes from baseline in SuDBP and the estimated logistic model for dose response. (Study 502.206).

Model:  $\text{Change} = 10 / [1 + 9.94 \cdot \text{Exp}(-0.171 \cdot \text{dose})]$ .

RMSE=7.76.

The dose levels studied were 0, 40, 80, 120, and 160 mg.

STATISTICAL REVIEW AND EVALUATION  
(Addendum)

NDA: 20-850. Pre-Clinical Studies (Carcinogenicity Evaluation)  
Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.  
Name of Drug: Telmisartan (CGP 48933)  
Document Reviewed: Volumes 1.013, 1.051, 1.052, and 1.067, received 1/03/97  
Date of Review: 08/04/98

The sponsor's report of the results of the rat study has indicated that there was a significant (p-value=0.02) increase in the number of females of the high dose group (100 mg/kg/day) with cell adenoma (Thyroid gland) compared to females of control 2. Following Dr. Charles Resnick's (team leader/pharmacology) suggestion, this reviewer has conducted a comparison test for the incidence of the above mentioned tumor and the following results are found.

Number of females with cell adenoma tumor		
<u>Control 2</u>	<u>High dose</u>	<u>p-value</u>
3/50	11/50	0.0189

Since this is a common tumor, a p-value of 0.0189 is not significant under an 0.01 alpha level of significance according to FDA's rule.

/S/

Walid A. Nuri, Ph.D.  
Mathematical Statistician

Concur:

Dr. Mahjoob

Dr. Chi *Chi's*  
8/18/98

/S/ 08/18/98

cc: Orig. NDA 20-850, HFD-110

HFD-344/Dr. Barton

HFD-110/Dr. Resnick

HFD-110/Ms. Bongiovanni

HFD-710/Dr. Chi

HFD-710/Dr. Mahjoob

HFD-710/Dr. Nuri

Chron: W A Nuri: 594-5303 DB I: 08-17-98: DISC10/addtelm1.wpd

## STATISTICAL REVIEW AND EVALUATION

NDA: 20-850. Pre-Clinical Studies (Carcinogenicity Evaluation)

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.

AUG 4 1993

Name of Drug: Telmisartan (CGP 48933)

Document Reviewed: Volumes 1.013, 1.051, 1.052, and 1.067, received 1/03/97

### 1. INTRODUCTION

The sponsor has submitted a report containing details of the results of analyses of data collected for both mouse and rat studies together with diskettes containing this data. These two studies were intended to assess the carcinogenic potential of telmisartan in mice and rats. Telmisartan was administered orally in dietary mixture at some selected dose levels. The duration for both the mouse and the rat studies was 104 weeks.

### 2. MOUSE STUDY

#### 2.1. Design

In this study an experiment was conducted in which 300 female and 300 male CD-1 mice were observed for carcinogenicity under specified laboratory and dietary condition for 24 months. These animals were randomly divided into six groups of equal sizes to receive different dose levels (in dietary admixture): 0, 0, 0, 10, 100, and 1000 mg/kg/day. These dose levels were known as first control, second control, third control, low, medium, and high, respectively, where the first two controls were untreated diet and the third control was 20% lactose treated diet. The animals were observed daily for mortality and morbidity and were examined weekly for the presence of masses. At the end of the study all surviving animals were necropsied and microscopically examined.

#### 2.2. Sponsor's analysis

##### Survival analysis

The sponsor has applied log-rank test and Fisher's exact test to test for the difference in survival rates among treatment groups. The sponsor reported that no drug-related effect on survival were observed but, no p-values were provided for the results. A summary of the survival distribution for specific weeks and the mean time to death or sacrifice are given in Table 5.

Survival curves for male and female mice are shown in figures 1 and 2, respectively.

##### Tumor data analysis

The sponsor has applied Peto's test (Peto and al. 1980) and Armitage's test (Armitage, P., 1955).

Peto's trend test was carried out for the incidence of tumors for telmisartan doses versus each one of the three controls. The results of analysis indicate that there is no significant difference in tumor incidence, for all organs, between telmisartan and the three controls as shown in Table 6.

### 2.3. Reviewer's Analysis

#### FDA Statistical Decision Rules

FDA classifies a tumor as a "common" tumor if the incidence rate is  $>1\%$  and as a "rare" tumor if the incidence rate is  $\leq 1\%$ .

The decision rules which FDA statisticians follow are summarized below.

1. For common tumors, the level of significance used in pairwise comparisons is  $\alpha = 0.01$  and in trend analysis the level of significance used is  $\alpha = 0.005$ .
2. For rare tumors, the level of significance used in pairwise comparisons is  $\alpha = 0.05$  and in trend analysis the level of significance used is  $\alpha = 0.025$ .

#### Survival analysis

This reviewer has carried out a homogeneity analysis and a trend analysis on the survival data for male and female mice separately, using two statistical methods. The first method used Cox's statistic for life tables (see reference 2 or 5) and the second used Kruskal-Wallis statistic for survival data (see reference 2 or 5). Both Cox's and Kruskal-Wallis statistics use a Chi-square test, weighted with a calculated variance-covariance matrix, that is derived from an observed life table but, the difference between the two statistics is that the latter gives more weight to early deaths. The homogeneity analysis carries out the testing of the hypothesis of equality of survival distributions among the treatment groups and the trend analysis carries out the testing of the hypothesis of a linear trend in the survivals among the treatment groups of animals. The results of analyses are shown in Table 1.

The homogeneity tests in Table 1 show that, for both male and female mice, there is no significant difference ( $p\text{-values} \geq 0.1257$ ) in survival distributions among the treatment groups. Also, this table shows that there is no positive trend in mortality in the telmisartan treated groups when compared to the combined control group ( $p\text{-values} \geq 0.1083$ ).

Using the above two methods, pairwise comparisons were carried out for comparing the mortality between any two of the four tested groups, for male and female mice separately. The results are summarized in Table 2. According to the above decision rules, this table shows that, for both male and female mice, there is no significant difference ( $p\text{-values} \geq 0.0802$ ) in the mortality rates between the combined control group and the telmisartan treated groups. This

result was also true when comparing the mortality among any pair of telmisartan treated groups of mice ( $p$ -values  $\geq 0.0664$ ).

### Tumor data analysis

This reviewer has carried out a trend analysis, using FDA's approach (which is implemented in a SAS program) for analyzing the incidence of tumor for telmisartan doses versus the combined control (placebo). This program was also used to test for the incidence of tumors at the high dose of telmisartan versus that of placebo (pairwise comparison). This program employs the same statistical method the sponsor used in the trend analysis (Peto et al (1980)). The purpose of this analysis is to see if there is an increase (or decrease) in the number of animals who show tumors as the dose level increases from the lowest (control) to the highest dose. By comparison, the sponsor carried out the above mentioned Peto's trend analysis to compare tumor incidence in the telmisartan doses versus each one of the controls. Note that the decision to combine the three controls in this reviewer's analysis was based on the sponsor's analysis which shows that these controls do not significantly differ in the number of animals who had tumors.

The results of the reviewer's trend analysis show that there is no significant trend ( $p$ -values  $\geq 0.0061$ , for male mice, and  $\geq 0.0330$ , for female mice) in the number of animals who had tumors as the telmisartan dose level increases from 0 mg (control) to the highest dose, which is 1000 mg/kg/day. Similar non-significant results were found when comparing the high dose versus placebo, for which the  $p$ -value are  $\geq 0.0158$ , for male mice, and  $\geq 0.0724$ , for female mice). Note that the calculated  $p$ -values were compared to the specified levels of significance for "common" and "rare" tumors, according to FDA rules that are stated above.

## 3. RAT STUDY

### 3.1. Design

In this study an experiment was conducted in which 250 female and 250 male rats were studied for carcinogenicity under specified laboratory and dietary condition for 24 months. These animals were randomly divided into five groups of equal sizes to receive different dose levels (in dietary admixture): 0, 0, 3, 15, and 100 mg/kg/day. These dose levels were known as first control, second control, low, medium, and high, respectively, where the controls were 1.5% lactose treated diet. The animals were observed daily for mortality and morbidity and were examined weekly for the presence of masses. At the end of the 24 months all surviving animals were necropsied and microscopically examined.

### 3.2. Sponsor's analysis

#### Survival analysis

The sponsor has applied log-rank test and a nonparametric test (not specified) to test for the

difference in survival rates among treatment groups. The sponsor reported that no drug-related effect on survival were observed but, no p-values were provided for the results. A summary of the survival distribution for specific weeks and the mean time to death or sacrifice are given in Table 7.

Survival curves for male and female rats are shown in figures 3 and 4, respectively.

#### Tumor data analysis

The sponsor has applied Peto's test (Peto and al. 1980) and Armitage's test (Armitage, P., 1955). Peto's trend test was carried out for the incidence of tumors for telmisartan doses versus each one of the two controls. The results of analysis indicate that there is no significant difference in tumor incidence, for all organs, between telmisartan and the controls as shown in Table 8.

### 3.3. Reviewer's Analysis

#### Survival analysis

This reviewer has carried out a homogeneity analysis and a trend analysis on the survival data for male and female rats separately, using the statistical methods that were described above for the mouse study. The results of analyses are shown in Table 3.

The homogeneity tests in Table 3 show that, for both male and female rats, there is no significant difference ( $p\text{-values} \geq 0.5609$ ) in survival distributions among the treatment groups. Also, this table shows that there is no positive trend in mortality in the telmisartan treated groups when compared to the combined control group ( $p\text{-values} \geq 0.4901$ ).

Using the above two methods, pairwise comparisons were carried out for comparing the mortality between any two of the four tested groups, for male and female rats separately. The results are summarized in Table 4. According to the above decision rules, this table shows that, for both male and female rats, there is no significant difference ( $p\text{-values} \geq 0.3496$ ) in the mortality rates between the combined control group and the telmisartan treated groups. This result was also true when comparing the mortality among any pair of telmisartan treated groups of rats ( $p\text{-values} \geq 0.1749$ ).

#### Tumor data analysis

This reviewer has carried out the trend analysis for the tumor data, using the FDA's approach described above in the mouse study. The results of the reviewer's trend analysis show that there is no significant trend ( $p\text{-values} \geq 0.0544$ , for male rats, and  $\geq 0.0228$ , for female rats) in the number of animals who had tumors as the telmisartan dose level increases from 0 mg (combined control, or) to the highest dose, which is 100 mg/kg/day. However, there is a significant decrease in the number of females who had benign pheochromocytoma in the adrenal ( $p\text{-}$

value=0.0046) as the dose level increases to the high dose of telmisartan. Pairwise tests for comparing the high dose versus placebo (control), in the number of animals who had tumors, show non-significant results (p-values are  $\geq 0.0974$ , for male rats, and  $\geq 0.0298$ , for female rats). Note that the calculated p-values were compared to the specified levels of significance for "common" and "rare" tumors, according to FDA rules that are stated above.

#### 4. SUMMARY AND CONCLUSION

This reviewer has carried out an analysis for survival and a trend analysis for the incidence of tumors, for both the mouse and the rat studies.

For the mouse study, the sponsor had studied 300 mice (50 mice for each of the groups receiving 0, 0, 0 (three controls), 10, 100, and 1000 mg/kg/day) for carcinogenicity potential of telmisartan. The results of the survival analysis showed that there is no statistically significant positive linear trend and no significant increase in mortality among the treated groups when compared to the control group. Also, in the tumor analysis the results showed that none of the tested tumor type showed a statistically significant positive trend or an increase in incidence in the treated groups when compared with the (combined) control group.

For the rat study, the sponsor had studied 250 rats (50 rats for each of the groups receiving 0, 0 (two controls), 3, 10, and 100 mg/kg/day) for carcinogenicity potential of telmisartan. Similar non-significant results, in both the survival analysis and the tumor analysis, were found as those stated above for the mouse study.

/S/

Walid A. Nuri, Ph.D.  
Mathematical Statistician

This review consists of 6 pages, 8 tables, and 4 figures.

Concur:

Dr. Mahjoob

Dr. Chi

*[Signature]*  
8/4/98

cc: Orig. NDA 20-850  
HFD-110/Dr.U  
HFD-344/Dr. Barton  
HFD-710/Dr. Chi

HFD-110/Dr. Resnick  
HFD-110/Ms. Bongiovanni  
HFD-710/Dr. Mahjoob  
HFD-710/Dr. Nuri  
Chron: W A Nuri: 594-5303 DB I: 07-30-98: DISC10/cartelm1.wpd

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2. Breslow, N. A generalized Kruskal-Wallis test for comparing K samples subject to unequal patterns of censorship. *Biometrika* **57**, 579-594 (1970).
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4. Peto, R., et al. Guidelines for simple sensitive significance tests for carcinogenic effects in long-term animal experiments. IARC monographs on the long-term and short-term screening assays for carcinogens: A critical appraisal. Geneva: world Health Organization, Supplement 2, 311-426 (1980).
5. Thomas, D. G., Breslow, N., and Gart, J. Trend and Homogeneity Analysis of Proportions and Life Table data. *Comp. And Biom. Research* **10**, 373-381 (1977).

Table 1. Survival analysis for mouse study (Telmisartan).

a. Mortality data

No. of mice that died or had tumor	MALE				FEMALE			
	Dose (mg/kg/day)				Dose (mg/kg/day)			
	0	10	100	1000	0	10	100	1000
	79	22	27	22	79	21	23	18
Total No. Of mice	150	50	50	50	150	50	50	50

b. Test for homogeneity.

	P-value (Chi-Square)	
i. Cox's test	0.5465	0.2002
ii. Kruskal-Wallis	0.4113	0.1257

c. Test for positive trend.

	P-value (Chi-Square)	
i. Cox's test	0.3731	0.1083
ii. Kruskal-Wallis	0.2437	0.1302

Table 2. P-values for pairwise tests for the differences in mortality between treatment groups in mouse study. 0=Combined control, 1=Low dose, 2=Medium dose, and 3=High dose. (Telmisartan)

Male Mouse

PAIRWISE COMPARISONS (1 D.F. CHI-SQUARES, WITH CONT CORR)

GROUP		EXACT ONE TAIL TEST	2X2 CHI- SQUARE USING CSQ N IN DEN	DIRECTION	COX'S TEST		GEN.K/W ANALYSIS	
					EXACT/INV	CONSER	EXACT/INV	CONSER
0 VS. 1	CHISQ	.3419	.1671 .6827	NEG	.4747	.4745	1.0725	1.0721
	PROB				.4908	.4909	.3004	.3005
0 VS. 2	CHISQ	.3122	.2400 .6242	POS	.5613	.5611	1.0286	1.0281
	PROB				.4537	.4538	.3105	.3106
0 VS. 3	CHISQ	.3419	.1671 .6827	NEG	.1067	.1066	.0908	.0907
	PROB				.7440	.7440	.7632	.7632
1 VS. 2	CHISQ	.2119	.6403 .4236	POS	1.4039	1.4023	2.6226	2.6190
	PROB				.2361	.2363	.1053	.1056
1 VS. 3	CHISQ	.5798	.0000 1.0000	POS	.0084	.0084	.2569	.2567
	PROB				.9271	.9271	.6122	.6124
2 VS. 3	CHISQ	.2119	.6403 .4236	NEG	.8580	.8567	1.1723	1.1708
	PROB				.3543	.3547	.2789	.2792

Female Mouse

PAIRWISE COMPARISONS (1 D.F. CHI-SQUARES, WITH CONT CORR)

GROUP		EXACT ONE TAIL TEST	2X2 CHI- SQUARE USING CSQ N IN DEN	DIRECTION	COX'S TEST		GEN.K/W ANALYSIS	
					EXACT/INV	CONSER	EXACT/INV	CONSER
0 VS. 1	CHISQ	.1264	1.3067 .2530	NEG	1.5311	1.5302	2.1668	2.1695
	PROB				.2160	.2161	.1410	.1411
0 VS. 2	CHISQ	.2568	.4268 .5135	NEG	.0011	.0011	.2277	.2275
	PROB				.9730	.9731	.6332	.6334
0 VS. 3	CHISQ	.0297*	3.5298 .0603	NEG	3.0612	3.0586	3.0571	3.0553
	PROB				.0802	.0803	.0804	.0805
1 VS. 2	CHISQ	.4202	.0406 .8403	POS	.8222	.8195	2.7942	2.7839
	PROB				.3645	.3653	.0946	.0952
1 VS. 3	CHISQ	.3410	.1681 .6818	NEG	.0543	.0542	.0228	.0228
	PROB				.8158	.8159	.8801	.8801
2 VS. 3	CHISQ	.2081	.6614 .4161	NEG	1.6771	1.6733	3.3691	3.3604
	PROB				.1953	.1958	.0664	.0668

Table 3. Survival analysis for rat study (Telmisartan).

a. Mortality data

No. of mice that died or had tumor	MALE				FEMALE			
	Dose (mg/kg/day)				Dose (mg/kg/day)			
	0	3	15	100	0	3	15	100
	17	6	11	8	31	14	17	18
Total No. Of mice	100	50	50	50	100	50	50	50

b. Test for homogeneity.

	P-value (Chi-Square)	
i. Cox's test	0.5860	0.8301
ii. Kruskal-Wallis	0.5609	0.8335

c. Test for positive trend.

	P-value (Chi-Square)	
i. Cox's test	0.9929	0.4901
ii. Kruskal-Wallis	0.9608	0.5119

Table 4. P-values for pairwise tests for the differences in mortality between treatment groups in rat study. 0=Combined control, 1=Low dose, 2=Medium dose, and 3=High dose. (Telmisartan)

Male Rat

PAIRWISE COMPARISONS (1 D.F. CHI-SQUARES, WITH CONT CORR)

GROUP	EXACT ONE TAIL TEST	2X2 CHI- SQUARE USING CSQ N IN DEN	DIRECTION	COX'S TEST		GEN.K/W ANALYSIS	
				EXACT/INV	CONSER	EXACT/INV	CONSER
0 VS. 1	CHISQ	.3145	NEG	.2856	.2855	.5218	.5217
	PROB	.5749		.5931	.5931	.4701	.4701
0 VS. 2	CHISQ	.2690	POS	.4114	.4113	.8749	.8747
	PROB	.6040		.5213	.5213	.3496	.3497
0 VS. 3	CHISQ	.0240	NEG	.0077	.0077	.0007	.0007
	PROB	.8769		.9300	.9300	.9791	.9791
1 VS. 2	CHISQ	1.1339	POS	1.2027	1.2023	1.8403	1.8396
	PROB	.2869		.2728	.2729	.1749	.1750
1 VS. 3	CHISQ	.0831	POS	.0991	.0991	.3496	.3495
	PROB	.7732		.7529	.7529	.5544	.5544
2 VS. 3	CHISQ	.2599	NEG	.3041	.3040	.6368	.6367
	PROB	.6102		.5813	.5814	.4249	.4249

Female Rat

PAIRWISE COMPARISONS (1 D.F. CHI-SQUARES, WITH CONT CORR)

GROUP	EXACT ONE TAIL TEST	2X2 CHI- SQUARE USING CSQ N IN DEN	DIRECTION	COX'S TEST		GEN.K/W ANALYSIS	
				EXACT/INV	CONSER	EXACT/INV	CONSER
0 VS. 1	CHISQ	.0357	NEG	.0093	.0093	.0162	.0161
	PROB	.8501		.9231	.9231	.8989	.8989
0 VS. 2	CHISQ	.0345	POS	.1510	.1510	.4798	.4796
	PROB	.8527		.6975	.6976	.4885	.4886
0 VS. 3	CHISQ	.1856	POS	.2303	.2302	.4295	.4293
	PROB	.6666		.6313	.6314	.5123	.5123
1 VS. 2	CHISQ	.1870	POS	.2095	.2094	.3640	.3639
	PROB	.6654		.6472	.6472	.5463	.5463
1 VS. 3	CHISQ	.4136	POS	.3152	.3151	.4026	.4025
	PROB	.5201		.5745	.5745	.5258	.5258
2 VS. 3	CHISQ	.0000	POS	.0062	.0062	.0000	.0000
	PROB	1.0000		.9373	.9373	.9952	.9952

TABLE 5.

Carcinogenicity study in mice: cumulative and per cent [%] survival in weeks 1 to 105 (males) and 100 (females)

Week	Dose level (mg/kg/day)											
	0		0		0		10		100		1000	
	Group 1		Group 2		Group 3		Group 4		Group 5		Group 6	
	Diet Control		Diet Control		Lactose Control		Low Dose		Mid Dose		High Dose	
	m	f	m	f	m	f	m	f	m	f	m	f
1	50	50	50	50	50	50	50	50	50	50	50	50
%	[100]	[100]	[100]	[100]	[100]	[100]	[100]	[100]	[100]	[100]	[100]	[100]
52	4	3	4	2	0	3	1	0	4	8	3	1
%	[92]	[94]	[92]	[96]	[100]	[94]	[98]	[100]	[92]	[84]	[94]	[98]
60	5	5	5	6	2	5	1	1	7	9	3	2
%	[90]	[90]	[90]	[88]	[96]	[90]	[98]	[98]	[86]	[82]	[94]	[96]
72	8	12	7	6	3	8	3	2	10	17	5	4
%	[84]	[76]	[86]	[88]	[94]	[84]	[94]	[96]	[80]	[66]	[90]	[92]
84	13	18	12	10	5	18	6	11	15	21	12	14
%	[72]	[64]	[76]	[80]	[90]	[64]	[88]	[78]	[70]	[58]	[76]	[72]
105/100	25	30	26	28	22	24	22	22	29	24	22	22
%	[50]	[40]	[46]	[44]	[56]	[52]	[56]	[56]	[42]	[52]	[56]	[56]

Table 5 (continued)

Carcinogenicity study in mice: mean time (weeks) to death or sacrifice

Dose level (mg/kg/day)											
Group 1 0		Group 2 0		Group 3 0		Group 4 10		Group 5 100		Group 6 1000	
Diet Control		Diet Control		Lactose Control		Low Dose		Mid Dose		High Dose	
m	f	m	f	m	f	m	f	m	f	m	f
92	85	91	90	98	86	98	92	90	81	93	91

TABLE 6:

## Carcinogenicity study in mice: incidence of primary neoplasms

Histopathological finding ORGAN SYSTEM Organ/Tissue Neoplasm	TD	Dose level (mg/kg/day)											
		0 Group 1		0 Group 2		0 Group 3		10 Group 4		100 Group 5		1000 Group 6	
		Diet Control		Diet Control		Lactose Control		Low Dose		Mid Dose		High Dose	
		m 50	f 50	m 50	f 50	m 50	f 50	m 50	f 50	m 50	f 50	m 50	f 50
<b>DIGESTIVE SYSTEM</b>													
Salivary glands Adenocarcinoma	MA	0	0	0	0	0	0	0	0	0	0	0	1
Cecum Mucinous carcinoma	MA	41	40	36	37	36	39	41	46	36	38	40	47
<b>ENDOCRINE SYSTEM</b>													
Pituitary Adenoma (small cell)	BE	48	49	43	46	48	48	48	45	47	48	48	50
Adenoma (acidophil cell)	BE	0	0	0	0	1	0	0	0	0	0	0	0
Thyroid gland Follicular cell adenoma	BE	50	50	46	49	47	49	49	49	46	50	48	50
Adrenal gland Spindle cell tumor (benign)	BE	50	50	47	48	48	50	48	50	49	50	48	49
Spindle cell tumor (malignant)	MA	0	0	0	1	0	0	0	1	0	1	0	0
<b>HEMATOPOIETIC/LYMPHOID SYSTEM</b>													
Generalized tumors													
Lymphoma (lymphoblastic)	MA	1	2	0	0	0	1	1	1	0	3	4	1
Lymphoma (heterogeneous)	MA	1	6	1	2	1	2	1	4	2	1	0	5
Lymphoma (lymphocytic)	MA	0	2	0	0	0	1	0	0	0	0	0	0
Myeloblastic leukemia	MA	0	0	1	1	0	0	0	1	0	0	0	0
Granulocytic leukemia	MA	3	2	3	1	3	1	4	2	3	2	0	0
Mesenteric lymph node Hemangiosarcoma	MA	42	44	42	42	44	43	45	46	38	42	43	49
Spleen Hemangioma	BE	49	50	46	49	48	49	49	50	48	50	50	50
Hemangiosarcoma	MA	1	0	0	0	1	0	0	0	0	0	0	0
Histiocytic sarcoma	MA	0	0	0	0	1	0	0	0	0	0	1	1
Thymus Thymoma, benign	BE	35	47	35	42	36	44	41	45	36	43	41	46
Thymoma, malignant	MA	0	3	0	2	0	2	0	1	0	2	0	1
<b>HEPATOPANCREATIC SYSTEM</b>													
Liver Hepatocellular adenoma	BE	50	50	48	48	49	49	50	50	50	48	50	50
Hepatocellular carcinoma	MA	7	4	7	5	10	0	7	2	9	1	8	0
Hemangioma	BE	1	0	4	1	5	0	2	1	1	0	3	0
Hemangiosarcoma	MA	0	0	2	1	1	0	1	0	2	0	2	1
	MA	1	0	1	0	0	1	0	0	1	0	2	1

TD Tumor designation (BE = benign; MA = malignant)

Note: No statistically significant increases or decreases in tumor frequency compared to controls

Table 6 (continued)

Histopathological finding ORGAN SYSTEM Organ/Tissue Neoplasm	TD	Dose level (mg/kg/day)											
		0 Group 1		0 Group 2		0 Group 3		10 Group 4		100 Group 5		1000 Group 6	
		Diet Control		Diet Control		Lactose Control		Low Dose		Mid Dose		High Dose	
		m 50	f 50	m 50	f 50	m 50	f 50	m 50	f 50	m 50	f 50	m 50	f 50
<b>HEPATOPANCREATIC SYSTEM (CONT)</b>													
Pancreas													
Islet cell carcinoma	MA	49 1	50 0	48 0	47 0	48 0	47 0	49 0	49 0	47 0	50 0	49 0	49 0
<b>INTEGUMENTARY SYSTEM</b>													
Skin													
Malig. fibrous histiocytoma	MA	50 1	50 0	47 1	49 0	49 0	50 0	49 1	50 1	49 1	50 1	50 0	49 0
Basal cell carcinoma	MA	0	0	0	0	0	0	0	0	0	0	0	0
Squamous cell carcinoma	MA	0	0	0	0	0	1	0	0	0	0	0	1
Mammary gland													
Adenoma	BE		50 0		49 1		50 0		50 0		50 1		49 0
Adenocarcinoma	MA		1		0		0		0		1		0
Adenoacanthoma	MA		0		0		2 0		0 0		2 1		1 0
Harderian gland													
Adenoma	BE	48 3	48 2	46 2	48 1	49 2	50 2	49 2	49 1	49 2	50 2	50 2	49 0
<b>MUSCULOSKELETAL SYSTEM</b>													
Femur													
Osteosarcoma	MA	50 0	49 1	46 0	48 0	47 0	50 0	49 0	49 0	49 0	50 0	50 0	48 0
Rib													
Chondrosarcoma	MA		1 0		0 0		0 0		0 0		1 1		0 0
Cranium													
Osteoma	BE	0 0	0 0	1 0	0 0	0 0	0 0	0 1	0 0	0 0	0 0	0 0	0 0
<b>RESPIRATORY SYSTEM</b>													
Lungs													
Bronchiolar adenoma	BE	50 2	49 0	50 0	50 1	50 1	50 1	50 1	50 3	50 2	50 0	50 1	50 1
Alveolar adenoma	BE	2	1	1	0	2	0	3	0	1	1	2	1
Bronchiolar/alveolar adenoma	BE	5	4	2	2	4	3	7	4	6	2	6	6
Bronchiolar/alveolar carcinoma	MA	4	2	4	3	5	0	2	0	4	1	0	0
<b>URINARY SYSTEM</b>													
Kidney													
Adenoma	BE	49 1	50 0	48 3	49 0	49 0	49 0	50 2	50 0	49 2	50 0	47 3	50 0
Tubular carcinoma	MA	1	0	0	0	0	0	0	0	0	0	0	0
Urinary bladder													
Carcinoma in situ	MA	50 0	45 0	41 0	43 0	46 0	44 0	45 0	46 0	48 1	44 0	49 0	49 0

TD Tumor designation (BE = benign; MA = malignant)

Note: No statistically significant increases or decreases in tumor frequency compared to controls

Table 6 (continued)

Histopathological finding ORGAN SYSTEM Organ/Tissue Neoplasm	TD	Dose level (mg/kg/day)											
		0 Group 1		0 Group 2		0 Group 3		10 Group 4		100 Group 5		1000 Group 6	
		Diet Control		Diet Control		Lactose Control		Low Dose		Mid Dose		High Dose	
		m 50	f 50	m 50	f 50	m 50	f 50	m 50	f 50	m 50	f 50	m 50	f 50
<b>REPRODUCTIVE SYSTEM</b>													
Testes													
Leydig (interstitial) cell tumor	BE	50 0		46 1		49 1		49 3		49 0		50 0	
Epididymides													
Fibroleiomyoma	BE	50		46		48		49		49		49	
Malig. fibrous histiocytoma	MA	0		0		0		1		0		0	
Seminal vesicles													
Anaplastic carcinoma	MA	50 1		47 1		50 0		49 0		48 0		50 0	
Ovary													
Granulosa-theca cell tumor	BE		49 1		47 0		46 0		50 1		50 0		49 0
Thecoma	BE		1		1		2		0		2		1
Luteoma	BE		1		0		0		0		0		0
Cystadenoma	BE		0		0		0		0		1		0
Papillary cystadenoma	BE		0		1		0		0		0		0
Tubular adenoma	BE		0		0		0		1		0		0
Sex cord stromal tumor (undiff.)	BE		0		0		0		1		0		1
Uterus													
Endometrial polyp	BE		49 0		48 1		49 1		50 0		49 2		50 1
Leiomyoma	BE		1		0		2		0		2		0
Leiomyofibroma	BE		1		0		0		0		0		1
Hemangioma	BE		2		1		1		0		0		0
Angiomyoma	BE		0		1		0		0		0		0
Granular cell tumor	BE		1		0		0		0		0		0
Endometrial carcinoma	MA		0		2		0		0		2		0
Malignant fibrous histiocytoma	MA		0		1		0		0		0		0
Squamous cell carcinoma	MA		1		0		0		0		0		0
Endometrial sarcoma	MA		1		3		4		3		1		1
Histiocytic sarcoma	MA		1		0		0		1		1		0
Leiomyosarcoma	MA		1		2		0		1		0		1
Vagina													
Leiomyofibroma	BE		46 0		46 0		46 0		48 1		48 0		48 0
<b>BODY CAVITIES</b>													
Abdominal Cavity													
Histiocytic sarcoma	MA	1	1	1	0	0	1	3	1	0	0	1	0
Liposarcoma	MA	1	0	1	0	0	1	1	1	0	0	1	0
Fibrosarcoma	MA	0	0	0	0	0	0	1	0	0	0	0	0
Adipose tissue													
Hemangioma	BE		2		2		1		1		1		1
			0		1		0		0		0		0

TD - Tumor designation (BE = benign; MA = malignant)

Note: No statistically significant increases or decreases in tumor frequency compared to controls

TABLE 7.

Carcinogenicity study in rats: survival and % survival in weeks 1 to 107

Week/incidence	Dose level (mg/kg/day)									
	0 (Control 1)		0 (Control 2)		3		15		100	
	Group G 0		Group G 4		Group G 1		Group G 2		Group G 3	
	m	f	m	f	m	f	m	f	m	f
1	50	50	50	50	50	50	50	50	50	50
%	[100]	[100]	[100]	[100]	[100]	[100]	[100]	[100]	[100]	[100]
52	50	49	50	50	49	50	48	50	48	50
%	[100]	[98]	[100]	[100]	[98]	[100]	[96]	[100]	[96]	[100]
60	50	49	49	50	49	50	48	50	48	49
%	[100]	[98]	[98]	[100]	[98]	[100]	[96]	[100]	[96]	[98]
72	49	49	49	49	49	47	48	48	47	47
%	[98]	[98]	[98]	[98]	[98]	[94]	[96]	[96]	[94]	[94]
84	47	48	49	47	48	44	46	43	47	45
%	[94]	[96]	[98]	[94]	[96]	[88]	[92]	[86]	[94]	[90]
102	40	37	45	32	44	36	39	33	42	33
%	[80]	[74]	[90]	[64]	[88]	[72]	[78]	[66]	[84]	[66]
103-107*	39-38	37	44	32	44	36	39	33	42	33-32
%	[78-76]	[74]	[88]	[64]	[88]	[72]	[78]	[66]	[84]	[66-64]

\* Period of terminal sacrifice (one decedent each in the control 1 male and high dose female groups)

Table 7 (continued)

Carcinogenicity study in rats: mean survival time (weeks)

Dose (mg/kg)	0 (Control 1)	0 (Control 2)	3	15	100
Males	102.5	101.7	97.3	96.0	97.7
range	72-107	59-107	50-107	12-107	50-107
Females	98.0	96.9	96.0	94.7	97.9
range	51-107	62-107	64-107	65-107	55-107

Note: No statistically significant differences ( $p \leq 0.05$ ) between drug-treated and control groups

TABLE : 8

Carcinogenicity study in rats: incidence of primary neoplasms

Histopathological finding ORGAN SYSTEM Organ/Tissue Neoplasm	TD	Dose level (mg/kg/day)									
		0		0		3		15		100	
		Group 0		Group 4		Group 1		Group 2		Group 3	
		Ad lib diet		Restricted diet		Low Dose		Mid Dose		High Dose	
	m	f	m	f	m	f	m	f	m	f	
	50	50	50	50	50	50	50	50	50	50	
<b>DIGESTIVE SYSTEM</b>											
Tongue		50	50	50	50	50	50	49	50	50	50
Granular cell tumor	BE	0	1	0	0	0	0	0	0	0	0
Salivary glands		50	50	50	50	50	50	49	50	50	50
Parotid acinar cell adenoma	BE	2	0	2	2	0	0	1	1	1	2
Parotid acinar adenocarcinoma	MA	1	0	0	0	0	0	0	0	0	0
Parotid mixed tumor	BE	0	0	0	1	0	0	0	0	0	0
Sublingual carcinosarcoma	MA	1	0	0	0	0	0	0	0	0	0
Esophagus		50	50	50	49	50	50	48	50	50	50
Papilloma	BE	1	0	0	0	0	0	0	0	0	0
Stomach		50	50	50	50	50	50	49	50	50	50
Adenocarcinoma	MA	0	0	0	0	0	1	0	0	0	0
Duodenum		50	50	50	50	49	50	49	50	50	50
Leiomyoma	BE	0	1	0	0	0	0	0	0	0	0
Jejunum		50	50	50	50	49	49	50	50	50	50
Adenocarcinoma	MA	0	0	0	1	0	0	0	0	0	0
Leiomyosarcoma	MA	0	0	0	1	0	0	0	0	0	0
Colon		50	50	50	50	49	50	50	50	50	50
Adenocarcinoma	MA	1	0	0	0	1	0	0	0	1	0
Leiomyosarcoma	MA	0	0	0	0	1	0	0	0	1	0
Rectum		49	50	49	49	50	50	48	50	48	48
Squamous cell carcinoma	MA	0	1	0	0	0	0	0	0	0	0
Adenocarcinoma	MA	0	0	0	0	0	0	0	0	0	0
<b>ENDOCRINE SYSTEM</b>											
Pituitary		50	50	49	49	50	50	49	50	50	49
Adenoma	BE	10	38	12	40	10	38	6	33	9	28 <sup>ⓐ</sup>
Carcinoma	MA	0	0	0	1	0	0	0	0	0	1
Thyroid gland		50	50	49	50	50	50	50	50	49	50
Follicular cell adenoma	BE	1	1	2	0	4	0	1	2	2	1
Follicular cell carcinoma	MA	1	0	0	2	1	1	1	0	0	0
C cell adenoma	BE	7	7	4	3	6	6	2	6	10 <sup>ⓑ</sup>	11 <sup>ⓐ</sup>
C cell carcinoma	MA	1	0	0	0	2	1	0	0	1	1
Parathyroid		49	48	48	50	50	50	49	49	49	48
Adenoma	BE	1	1	1	2	2	0	2	1	4	1
Adrenal gland		50	50	50	50	50	50	50	50	50	50
Cortical adenoma	BE	4	3	4	3	2	5	4	3	5	5
Cortical adenocarcinoma	MA	2	0	0	0	1	2	1	0	2	1
Pheochromocytoma (benign)	BE	5	11	4	12	2	7	0	12	4	19
Pheochromocytoma (malignant)	MA	1	1	0	0	1	1	0	0	3	0

ⓐ Statistically significant decrease (p=0.0098, 0.0328) compared to both control groups

ⓑ Statistically significant decrease (p=0.0255) compared to control 1 group

ⓒ Statistically significant increase (p=0.02) compared to control 2 group

TD (Tumor designation)

BE Benign

MA Malignant

Table 8 (continued)

Histopathological Finding ORGAN SYSTEM Organ/Tissue Neoplasm	TD	Dose level (mg/kg/day)									
		0 Group 0		0 Group 4		3 Group 1		15 Group 2		100 Group 3	
		Ad lib diet		Restricted diet		Low Dose		Mid Dose		High Dose	
		m	f	m	f	m	f	m	f	m	f
		50	50	50	50	50	50	50	50	50	50
<b>HEMATOPOIETIC/LYMPHOID SYSTEM</b>											
Generalized tumors											
Lymphoma	MA	0	0	2	1	0	0	1	0	0	0
Histiocytic sarcoma	MA	1	1	1	0	2	0	0	0	0	0
Thymus											
Thymoma, benign	BE	50	49	48	49	48	48	44	49	49	50
Thymoma, malignant	BE	9	5	9	8	5	7	7	5	9	3
Carcinosarcoma	MA	1	0	0	0	0	0	0	0	0	0
Lymph node (all sites)	MA	1	0	0	0	0	0	0	0	0	0
Lymphangioma	BE	0	0	0	0	0	1	0	0	0	0
<b>HEPATOPANCREATIC SYSTEM</b>											
Liver											
Hepatocellular adenoma	BE	49	50	50	50	50	50	50	50	50	50
Hepatocellular carcinoma	MA	1	1	2	0	3	1	4	0	2	2
Bile duct adenocarcinoma	BE	2	0	0	0	3	0	3	0	1	0
	MA	0	0	0	0	0	0	1	0	0	0
Pancreas											
Islet cell adenoma	BE	50	50	50	50	50	50	49	50	50	49
Acinar cell adenoma	BE	0	0	2	2	2	0	2	1	3	0
	BE	0	0	1	0	0	0	0	0	0	1
<b>INTEGUMENTARY SYSTEM</b>											
Skin											
Keratoacanthoma	BE	2	1	0	1	4	1	1	0	2	0
Trichofolliculoma	BE	2	0	1	0	1	0	0	0	0	0
Eyelid adenoma	BE	0	0	1	0	0	0	0	0	0	0
Sebaceous adenoma	BE	1	0	0	0	0	0	0	0	0	0
Fibroma	BE	1	3	0	0	0	0	0	0	0	0
Lipoma	BE	1	0	0	0	0	0	1	0	0	0
Sebaceous carcinoma	MA	0	0	0	0	0	0	1	1	0	0
Basosquamous carcinoma	MA	0	1	0	0	0	0	0	0	1	0
Liposarcoma	MA	0	0	0	0	0	0	1	0	0	1
Malig. fibrous histiocytoma	MA	0	0	1	0	0	0	1	0	0	0
Mixed tumor	MA	0	0	0	1	0	0	0	0	0	1
Mammary gland											
Fibroadenoma	BE		49		49		49		49		50
Adenoma	BE		8		8		6		9		9
Adenocarcinoma	MA		1		1		0		2		1
	MA		2		1		2		3		5
<b>RESPIRATORY SYSTEM</b>											
Lungs											
Bronchiolar/alveolar adenoma	BE	50	50	50	50	50	50	50	50	50	50
Bronchiolar/alveolar carcinoma	MA	0	1	1	1	0	0	1	0	2	2
	MA	1	0	0	0	0	0	0	0	0	0

Tumor Designation: BE Benign; MA Malignant

No statistically significant increases or decreases in tumor frequency compared to control 1 or control 2 ( $p \leq 0.05$ )

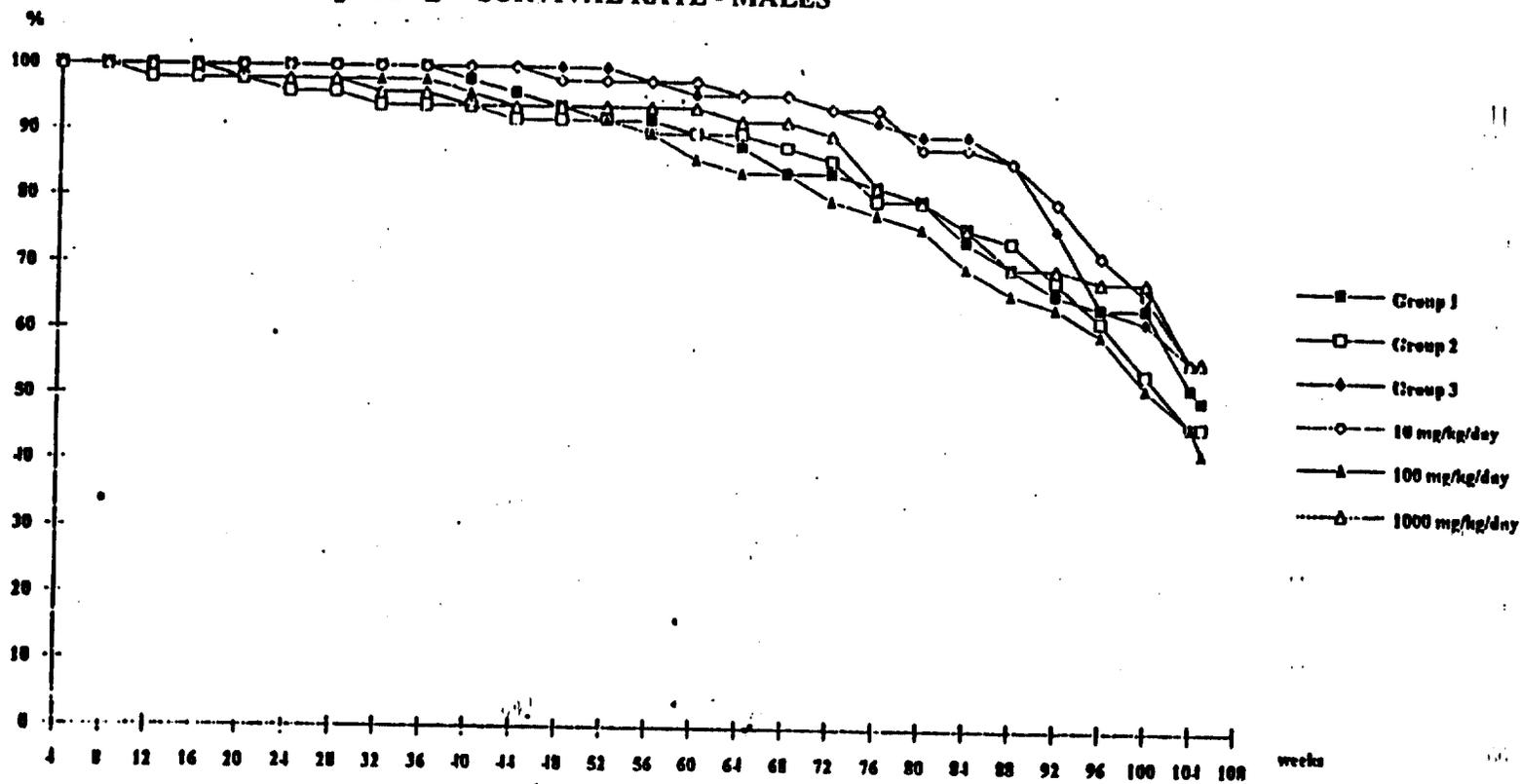
Table 8 (continued)

Histopathological finding ORGAN SYSTEM Organ/Tissue Neoplasm	TD	Dose level (mg/kg/day)									
		0 Group 0		0 Group 4		3 Group 1		15 Group 2		100 Group 3	
		Ad lib diet		Restricted diet		Low Dose		Mid Dose		High Dose	
		m 50	f 50	m 50	f 50	m 50	f 50	m 50	f 50	m 50	f 50
<b>CIRCULATORY SYSTEM</b>											
Hemangioma (all sites)	BE	9	1	6	1	8	1	8	2	10	2
Spleen		1	1	1	1	2	0	1	1	1	1
Lymph node		5	0	4	0	6	0	6	0	9	1
Adrenal gland (adjac. tissue)		0	0	0	0	0	0	1	0	0	0
Spinal cord		1	0	0	0	0	0	0	0	0	0
Bone / sternum / knee		2	0	1	0	0	0	0	0	0	0
Uterus		0	0	0	0	1	0	1	0	0	
Hemangiosarcoma (all sites)	MA	2	0	0	0	2	1	4	2	1	0
Spleen		2	0	0	0	2	0	0	0	1	0
Lymph node		0	0	0	0	0	0	3	0	0	0
Uterus		0	0	0	0	0	0	2	0	0	0
Ovary		0	0	0	0	1	0	0	0	0	0
Heart		0	0	0	0	0	1	0	0	0	
<b>MALE REPRODUCTIVE TRACT</b>											
Testis	BE	50		50		50		49		50	
Leydig cell tumor		19		16		19		18		16	
<b>FEMALE REPRODUCTIVE TRACT</b>											
Ovary	BE		50		50		50		50		50
Sex cord stromal tumor		3		4		4		2		5	
Granulosa cell tumor		0		0		0		1		0	
Granulosa / theca cell tumor		0		0		1		0		0	
Granulosa / theca cell tumor		0		1		0		0		0	
Theca cell tumor		0		1		0		0		1	
Theca cell tumor		0		0		1		0		0	
Sertoli cell tumor		0		0		1		1		0	
Lipoma	0		1		0		0		0		
Uterus	MA		50		50		50		50		50
Squamous cell carcinoma		1		1		0		0		0	
Adenocarcinoma		1		0		1		0		0	
Endometrial stromal sarcoma		3		2		3		1		1	
Vagina	MA		50		50		50		50		50
Endometrial stromal sarcoma		2		1		0		1		1	
<b>URINARY SYSTEM</b>											
Kidney	BE	50	50	50	50	50	50	50	50	50	50
Tubular adenoma		1	1	0	0	0	1	4	1	2	2
Lipomatous tumor (lipoma)		0	0	0	0	0	0	1	0	0	0
Urinary bladder	MA										
Transitional cell carcinoma		2	0	1	0	0	0	0	0	0	0

Tumor Designation: BE Benign; MA Malignant

No statistically significant increases or decreases in tumor frequency compared to control 1 or control 2 ( $p \leq 0.05$ )

Figure 1 SURVIVAL RATE - MALES



**Figure 2 SURVIVAL RATE - FEMALES**

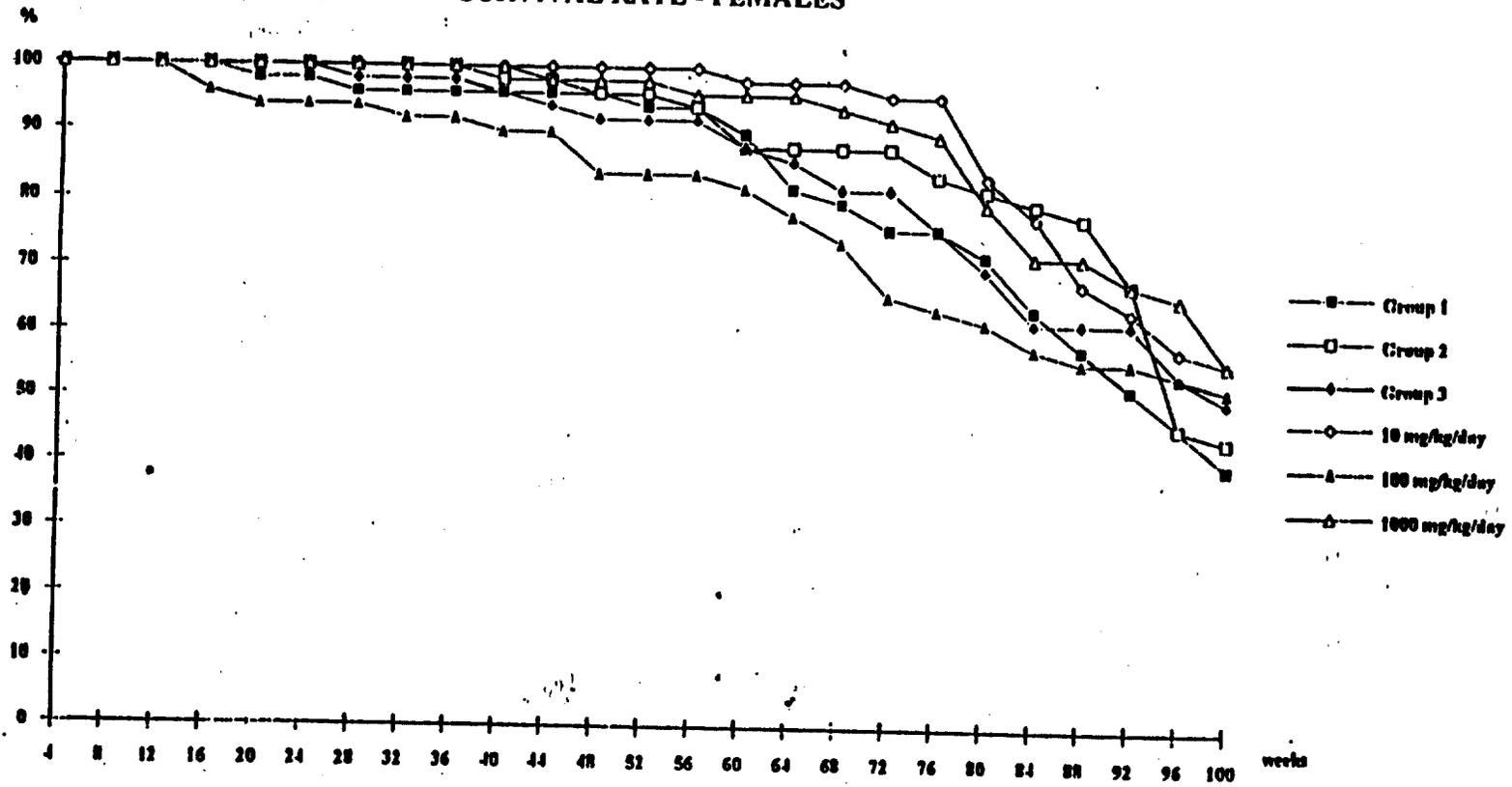


Figure 3 carcinogenicity 104 months rat  
survival rate - males

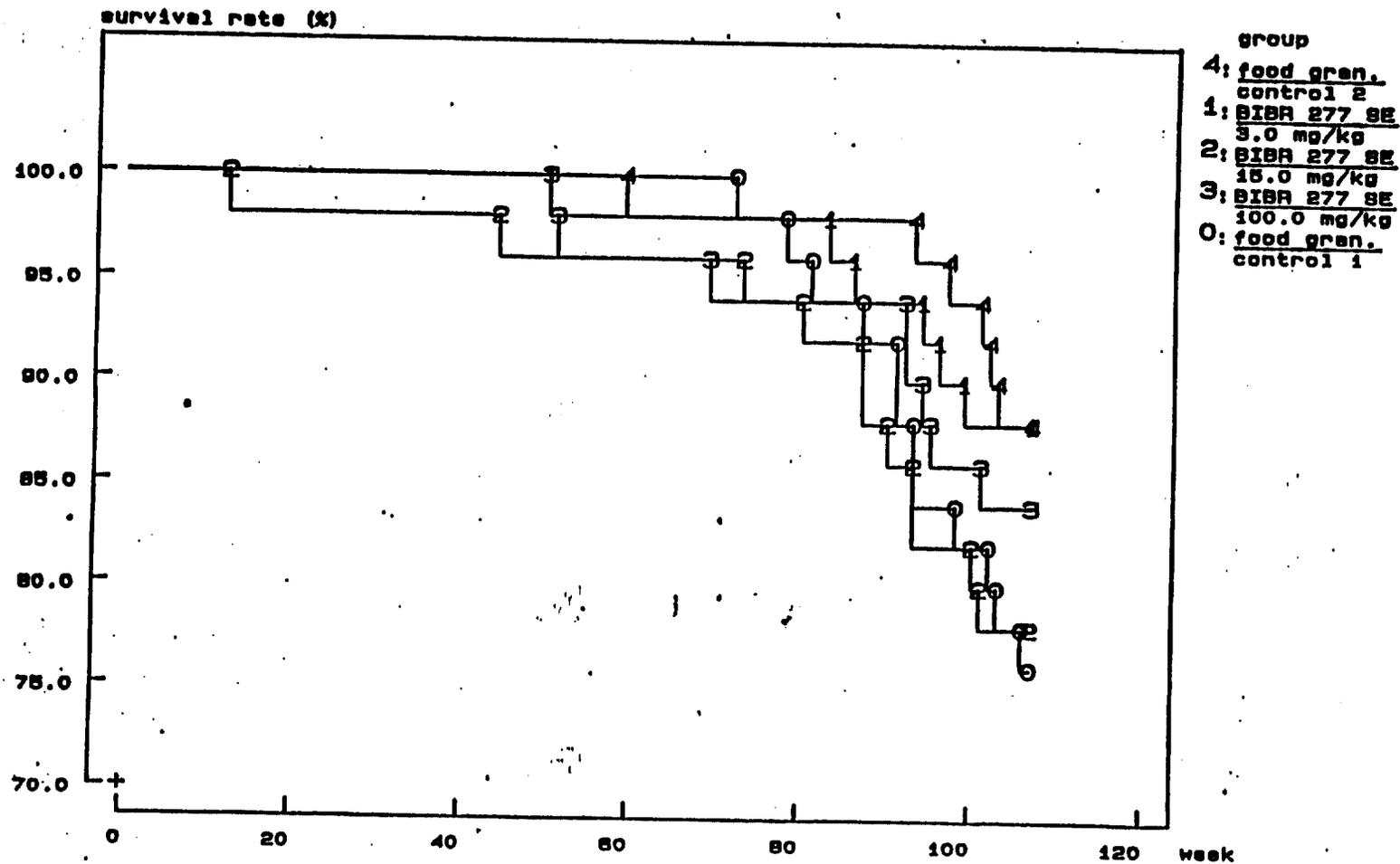


Figure 4 carcinogenicity 104 months rat survival rate - females

