Center X Race:

Treatments were stratified by race. Blacks received randomization numbers in the 6000 series and non-blacks in the 4000 series. Despite the attempt to equally distribute black patients within the study. Six centers (# 6, 12, 17, 29, 36 and 39) did not enroll any black patients. These centers contained 13.3 % of the non-black enrollment. Five centers enrolled only one black patient (centers # 4, 5, 14, 22, and 2). One center (# 43) enrolled 20 black and one non-black patient. This study site accounted for 9% of the total black population.

Gender x Race.

With respect to gender, the male/female ratio differed by race. In the non-blacks, 64% of those enrolled were male. Among blacks 51% were male.

Number with data analyzed.

Although 828 patients were randomized, the intent-to-treat cohort for the entire study consists of 807 patients. The 21 patients were excluded for the following reasons. Nine patients discontinued with no on-treatment blood pressures. Two Patients discontinued with the only measurements available at less than 10 hours (this was an arbitrary cut-off); as well as the 10 patients from study center 48 were all excluded

The number of patients in each of the intent-to treat group is shown in Table 7.8. The racial make-up of the key treatment groups ia shown in Table 7.9.

Table 7.8 number of patients in the intent to treat analysis study 502.204

Total enrolled =808	Hydrochlorothiazide	Telmisartan 0	20	40	80	160
	0	**73**	23	**75**	**77**	33
	6.5	21	25	21	20	31
	12.5	**73**	21	**70**	**73**	33
	25	24	25	25	32	32

Table7.9 Racial distribution among key treatment groups study 502.204

Black/white/Hispanic/ot Key Groups	Telmisartan 0	20	40	80	160
	18/50/5/0		20/40/13/2	22/51/4/0	
	19/45/9/0		16/46/8/0	22//43/8/0	

The baseline blood pressures and heart rate for the groups are shown in Table 7.10 for supine and 7.11 for standing values. The individual groups appear to be well balanced with respect to systolic/diastolic blood pressures and heart rates both in the supine and standing positions.

Baseline Supine systolic/diastolic blood pressure (SE) and [heart rate]

Table 7.10 Baseline Supine Systolic ± SD/Diastolic ± SD Blood Pressure and [Heart Rate ± SD]. Pivotal groups are in bold. Study 502.204

Hydrochlorothiazide	Telmisartan 0	20	40	80	160
0	**153.7 (1.3)/100.3 (0.5) [71.9 (1.1)]**	154.4 (2.9)/100.2 (0.9) [71.7 (2.0)]	**153.8 (1.4)/101.4 (0.6) [70.5 (1.0)]**	**153.1 (1.3)/100.3 (0.5) [71.8 (1.0)]**	151.4 (1.8)/100.6 (0.8) [71.1 (1.8)]
6.5	149.8 (2.8)/99.9 (1.1) [69.3 (2.0)]	151.7 (2.0)/101.2 (0.9) [69,9 (1.7)]	155.0 (2.4)/100.2 (0.9) [69.1 (2.5)]	154.9 (2.6)/99.7 (0.7) [68.6 (1.9)]	152.5 (1.8)/100.7 (0.7) [70.3 (1.4)]
12.5	**153.4 (1.5)/100.7 (0.5) [71.4 (1.2)]**	158.0 (2.6)/101.8 (0.9) [73.0 (2.7)]	**157.2 (1.7)/100.9 (0.5) [70.8 (0.9)]**	**156.2 (1.4)/101.1 (0.5) [69.8 (1.1)]**	154.0 (1.8)/100.5 (0.7) [72.6 (2.0)]
25	156.2 (2.2)/101.1 (1.1) [70.9 (1.9)]	149.8 (2.1)/99.8 (0.6) [71.0 (1.8)]	150.8 (3.0)/99.7 (0.7) [71.6 (1.5)]	153.8 (2.3)/100.6 (0.8) [67.0 (1.1)]	154.5 (2.1)/101.1 (0.9) [71.6 (1.1)]

Table 7.11 Baseline Standing systolic/diastolic blood pressure (SE) and [heart rate]. Pivotal groups are in boldstudy 502.204

Hydrochlorothiazide	Telmisartan				
	0	20	40	80	160
0	**15.0 (1.2)/100.9 (0.6) [76.2 (1.1)]**	152.7 (3.4)/100.6 (1.4) [74.2 (1.7)]	**150.3 (1.6)/101.8 (0.8) [74.9 (1.0)]**	**149.6 (1.6)/1011 (0.7) [75.9 (1.1)]**	147.1 (2.5)/101.2 (0.9) [76.5 (1.8)]
6.5	148.4 (3.7)/100.7 (0.7) [72.9 (2.0)]	152.3 (2.3)/102.4 (1.3) [75.1 (1.3)]	154.4 (2.5)/102.8 (1.0) [73.1 (2.6)]	153.3 (3.1)/101.0 (1.3) [72.4 (1.9)]	147.8 (2.1)/101.5 (1.2) [75.7 (1.6)]
12.5	**152.1 (1.7)/100.7 (0.7) [74.5 (1.0)]**	157.5 (3.0)/103.9 (1.5) [78.7 (2.8)]	**153.7 (1.7)/102.2 (0.7) [74.9 (1.0)]**	**151.5 (1.6)/101.1 (0.6) [74.3 (1.1)]**	149.3 (2.3)/100.9 (1.0) [76.2 (1.9)]
25	152.5 (2.0)/101.6 (1.3) [74.5 (1.8)]	147.1 (2.3)/99.1 (1.0) [73.7 (1.5)]	148.5 (2.9)/100.4 (1.1) [77.1 (1.5)]	150.2 (2.8)/100.6 (1.2) [72.6 (1.3)]	152.6 (2.1)/101.9 (1.1) [75.6 (1.3)]

The change in supine diastolic and systolic blood pressures and heart rates are shown in Tables 7.12 and standing blood pressures and heart rate in table 7.13.

Table7.12 Change in Supine systolic/diastolic blood pressure (SE) and [heart rate]; shaded cells are the pivotal treatment groups study 502.204

Hydrochlorothiazide	Telmisartan				
	0	20	40	80	160
0	**-2.9 (1.4)/ -3.8 (0.88) [-1.2 (1.1)]**	-10.9(3.5)/-10.1 (1.6) [0.9 (1.9)]	**-12.2 (1.7)/-10.7 (1.0) [0.7 (1.3)]**	**-15.3 (1.7)/-11.5 (1.0) [-0.4 (1.0)]**	-15.0 (2.3)/-10.5 (1.7) [1.3 (1.5)]
6.5	-3.3 (2.2)/-4.6 (1.3) [7.8 (2.2)]	-13.3 (2.8)/-10.4 (1.4) [-1.1 (1.8)]	-24.1 (3.3)/-14.8 (1.6) [2.0 (1.7)]	-16.9 (3.2)/-10.8 (2.4) [0.9 (1.9)]	-17.4 (2.8)/-12.6 (1.5) [1.7 (1.9)]
12.5	**-6.9 (1.5)/-7.3 (0.9) [-0.3 (1.0)]**	-21.9 (2.1)/-11.7 (1.5) [-0.8 (2.2)]	**-18.8 (1.6)/-12.6 (0.8) [1.5 (1.0)]**	**-23.8 (1.7)/-14.9 (0.8) [1.5 (1.0)]**	-20.5 (1.9)/-12.7 (1.1) [0.0 (1.4)]
25	**-17.5 (2.3)/-10.2 (1.6) [2.5 (1.8)]**	-20.1 (2.7)/-14.7 (1.2) [-0.5 (1.2)]	-19.6 (2.8)/-13.0 (1.4) [-1.1 (1.4)]	-23.7 (2.4)/-14.4 (1.4) [2.1 (1.1)]	-26.2 (2.7)/-18.0 (1.3) [0.5 (1.5)]

Table 7.13 Change in Standing systolic/diastolic blood pressure (SE) and [heart rate]; shaded cells are the pivotal treatment groups study 502.204

Hydrochlorothiazide	Telmisartan				
	0	20	40	80	160
0	**-1.5 (1.4)/ -2.6 (0.9) [-1.1 (1.1)]**	-13.1(2.6)/-7.8 (1.3) [1.1 (1.4)]	**-10.4 (1.6)/-8.9 (1.1) [0.5 (1.0)]**	**-15.1 (1.7)/-9.7 (0.9) [0.3 (1.0)]**	-11.3 (2.4)/-10.5 (1.6) [-1.2 (1.5)]
6.5	-4.9 (1.6)/-4.0 (1.3) [7.6 (2.3)]	-14.2 (3.0)/-9.2 (1.3) [-0.1 (1.6)]	-19.8 (3.4)/-14.0 (1.7) [0.6 (1.8)]	-16.0 (2.7)/-11.7 (2.3) [1.8 (1.5)]	-16.5 (2.9)/-11.8 (1.8) [1.0 (1.6)]
12.5	**-7.3 (1.6)/-5.5 (0.8) [1.2 (0.9)]**	-20.5 (2.9)/-9.6 (1.3) [-2.4 (2.3)]	**-17.8 (1.9)/-12.0 (1.1) [1.4 (1.0)]**	**-22.1 (1.8)/-13.1 (0.9) [1.3 (1.0)]**	-20.1 (2.3)/-11.8 (1.2) [0.9 (1.4)]
25	**-16.7 (2.7)/-8.4 (1.6) [3.9 (1.9)]**	-20.9 (2.5)/-13.8 (1.3) [3.0 (1.5)]	-18.4 (2.9)/-12.6 (1.5) [-2.2 (1.4)]	-23.1 (2.4)/-12.8 (1.2) [1.1 (1.4)]	-27.0 (2.8)/-17.8 (1.6) [0.7 (1.6)]

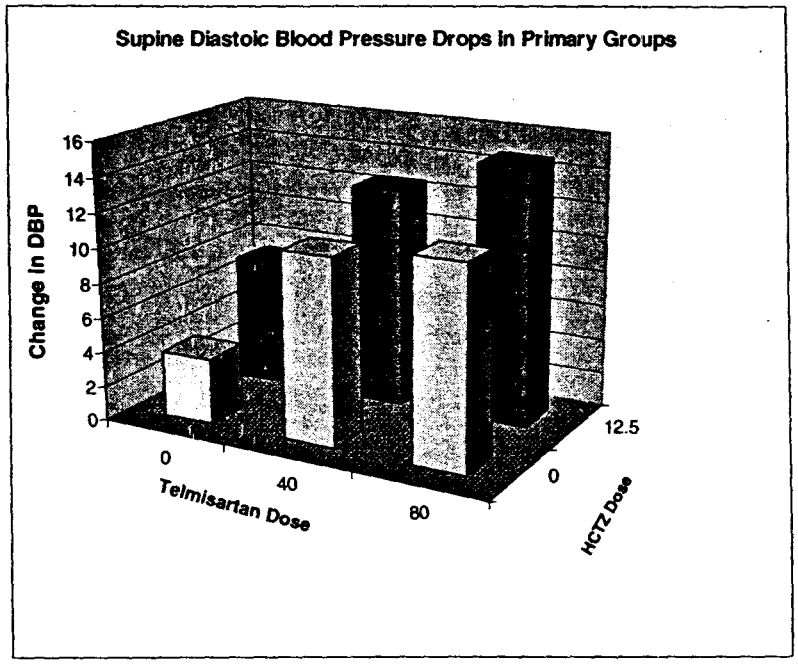
There was a dose response effect for both telmisartan and hydrochlorothiazide as monotherapy for both supine and standing systolic and diastolic blood pressures. Heart rates were only modestly altered. Considering the large number of dose groups, none of the heart rate changes appear to be different than zero.

The primary analysis of the study reflects the efficacy of the combination product for the six primary treatment groups. The change in diastolic blood pressure effect for the primary groups is shown in Table 7.14 and Figure 7.1 . The sponsor's analysis consisted of the following analyses. The variances of the treatment groups were not heterogenous (Levene's F-test). The global AVE test indicated that for the primary endpoint for at least one of the combination therapies was significantly ($p< 0.05$) superior to both of the individual monotherapies. From the MIN test, the combination therapy of telmisartan 80 mg and HCTZ 12.5 mg was significantly better ($p < 0.01$) than either of its components. The telmisartan 40 mg/HCTZ 12.5 was statistically superior to hydrochlorothiazide and marginally superior to telmisartan 40 mg monotherapy ($p=0.08$).

Table 7.14 Change in blood pressure for the combination therapy versus monotherapy for both supine and standing measurements at trough for intent to treat cohort for six primary treatment groups. Significant values are in bold.

	Supine		Standing	
Treatment Comparison	Diastolic	Systolic	Diastolic	Systolic
T40/HCTZ 12.5 versus T40	-1.9 (p=0.08)	**-6.6 (p<0.01)**	**-3.1 (p=0.01)**	**-7.4 (p <0.010**
T40/HCTZ 12.5 versus HCTZ 12.5	**-5.3 (P<0.01)**	**-11.9 (p<0.01)**	**-6.5 (p < 0.01)**	**-10.4 (p< 0.01)**
T80/HCTZ 12.5 versus T80	**-3.4 (p< 0.01)**	**-8.5 (p<0.01)**	**-3.4 (p < 0.01)**	**-6.9 (p < 0.01)**
T80/HCTZ 12.5 versus HCTZ 12.5	**-7.6 (p < 0.01)**	**-17.0 (p<0.01)**	**-7.5 (p < 0.01)**	**-14.7 (p < 0.01)**

Figure 7.1 Supine Diastolic Blood Pressure Decreases pivotal groups study 502.204



Additional Analyses:

The sponsor also performed several additional analyses using different cohorts. An analysis of those who had 8-week data available (n=413) (excludes those observation that were carried forward) were essentially the same as that for the entire cohort for the six key treatment groups (n=441). An analysis of covariance was performed (I don't believe that these covariates were prospectively declared), with age, race, gender, body mass index, baseline blood pressure and baseline plasma renin activity as the analytical covariates. The number of subjected included in the adjusted analysis of covariance (n=392) contained fewer subjects than the other analysis due to patient without baseline plasma renin levels.

Among the covariates that were non-trivial in the analysis of the primary end point response (for supine DBP as well as standing DBP response) were: baseline blood pressure, race and baseline plasma renin activity. Aside form the above covariate, age had a significant effect on standing systolic blood pressures but not standing diastolic blood pressure.

Race: The analysis of covariance for the six key treatment groups found that race (black versus non-black) was a significant covariate in defining the trough supine blood pressure effect. Caucasians had a much larger response to monotherapy with telmisartan than did blacks, with only a small numerical increase in the concurrent hydrochlorothiazide treatment. Blacks conversely responded less well to telmisartan but better to hydrochlorothiazide as monotherapy than Caucasians. The addition of hydrochlorothiazide had a lager effect on blacks than Caucasians. The data is shown in Table below and graphed in the figures below.

Table 7.15 Blood pressure effect at Trough for Race = Black or Caucasian study 502.204

			Telmisartan (Supine DBP)			Telmisartan (Supine SBP)		
	HCTZ Dose		0	40	80	0	40	80
Black		0	-3.4 (1.6)	-6.7 (2.2)	-4.6 (1.3)	-0.1 (3.5)	-2.0 (3.6)	-7.8 (3.0)
Caucasian			- 3.8 (1.1)	-13.5 (1.1)	-14.9 (1.1)	-4.1 (1.4)	-16.5 (2.2)	-19.9 (1.8)
Black		12.5	-5.2 (2.0)	-10.0 (2.6)	-13.3 (1.7)	-9.2 (2.8)	-14.3 (4.6)	-21.5 (3.1)
Caucasian			-8.1 (1.0)	-13.3 (1.4)	-16.4 (1.0)	-5.7 (2.1)	-19.9 (1.9)	-26.5 (2.2)

Table 7.16 Blood pressure effect at Trough for Race = Black or Caucasian Study 502.204

			Telmisartan (Standing DBP)			Telmisartan (Standing SBP)		
	HCTZ Dose		0	40	80	0	40	80
Black		0	-0.1	-4.2	-4.8	0.7	-2.0	-9.4
Caucasian			-3.5	-10.8	-11.7	-2.2	-13.4	-17.5
Black		12.5	-4.2	-8.1	-11.8	-11.5	-15.0	-17.0
Caucasian			-6.1	-13.2	-13.7	--5.9	-18.6	-24.2

Table 7.17 p-values (nominal) for black and non-black patients at trough:for supine and standing blood pressures study 502.204

	T40 + HCTZ 12.5 vs T40		T40 + HCTZ 12.5 vs HCTZ 12.5		T80 + HCTZ 12.5 vs T80		T80 + HCTZ 12.5 vs HCTZ 12.5	
Supine Diastolic Blood Pressure.		***Supine Systolic Blood Pressure***						
Black	0.2474	***0.0162****	0.0944	***0.32***	0.0007*	***0.0031****	0.0023*	***0.0100****
Non-Black	0.3975	***0.0863***	0.005*	***0.0001****	0.3937	***0.0097****	0.0001*	***0.0001****
Standing Diastolic Blood pressure		***Standing Systolic Blood Pressure***						
Black	0.11	*0.009**	0.11	*.26*	0.007*	*0.06*	0.005*	*0.14*
Caucasians*	0.04*	*0.02**	**0.0001***	***0.0001****	0.08	*0.005**	0.0001*	*0.0001**

* The sponsor sent in an analysis based on Caucasians. The number of non-caucasians, non-blacks were few (n=4). Hispanics were classified as either black or Caucasian

For the primary analysis i.e. supine diastolic blood pressure, the addition of hydrochlorothiazide to telmisartan for non-black patients showed than neither of the monotherapy groups (T40 or T80) was superior to combination therapy. For black patients, the combination therapy with T80 plus HCTZ was superior to the individual components (see table 7.17).

In considering supine systolic blood pressure (Table 7.17) both non-blacks and blacks the combination of T80 + HCTZ was superior to the individual components for both black and non-black patients. Dr. Lu Cui analyze the data for the key treatment groups for standing measurements of blood pressure. Again at least one of the combination treatments is superior to the individual components.

Tables 7.18 and 7.19 contain the analysis of the supine and standing effects at peak i.e. 3 hours after the dose for both Caucasians and Blacks. Since there was no baseline measurement that corresponded to the measurement at peak, the trough measurement was used for determining change from baseline.

Table 7.18 Blood pressure effect at Peak for Race=black and race=caucasian

			Telmisartan (Supine DBP)			Telmisartan (Supine SBP)		
	HCTZ Dose		0	40	80	0	40	80
Black		0	-5.0	-11.9	-9.6	0.5	-10.8	-12.7
Caucasian			-8.5	-14.7	-19.3	-6.9	-19.4	-28.4
Black		12.5	-9.9	-15.6	-17.3	-10.9	-19.9	-24.7
Caucasian			-10.0	-19.1	-18.5	-9.1	-26.8	-28.4

Table 7.19 Blood pressure effect at Peak for Race=black and race=caucasian

			Telmisartan (Standing DBP)			Telmisartan (Standing SBP)		
	HCTZ Dose		0	40	80	0	40	80
Black		0	-2.2	-9..2	-9.7	-0.2	-7.3	-10.6
Caucasian			-7.7	-14.1	-16.3	-5.8	-15.8	-22.3
Black		12.5	-8.9	-15.2	-15.2	-13.6	-22.3	-19.4
Caucasian			-7.7	-18.5	-18.6	-7.4	-24.3	-29.3

Figure 7.2 These values represent observed values (uncorrected) supine diastolic blood pressure study 502.204.

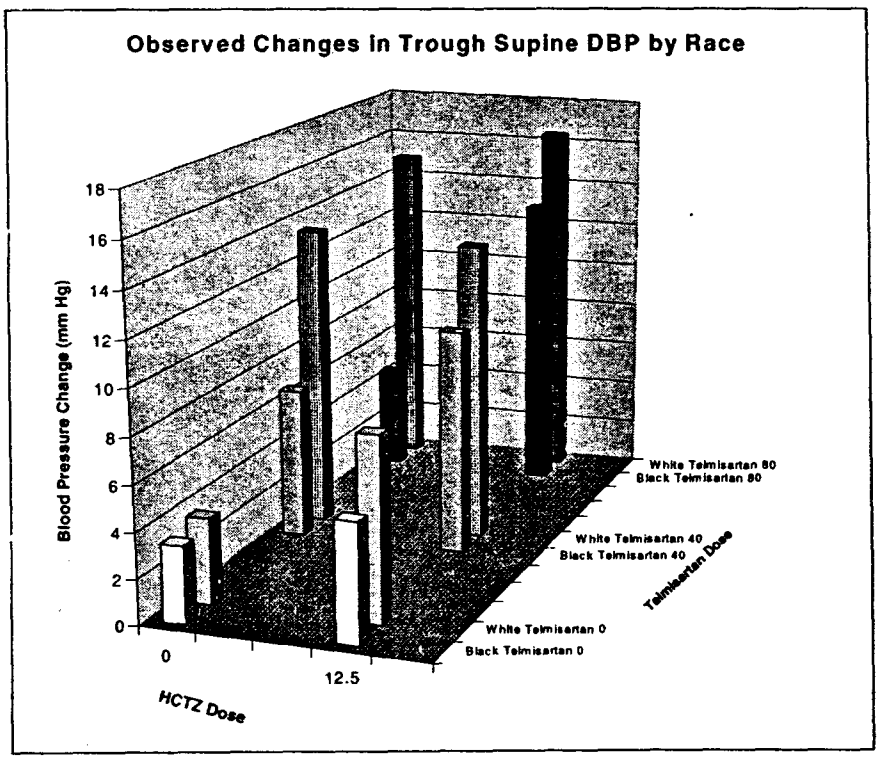
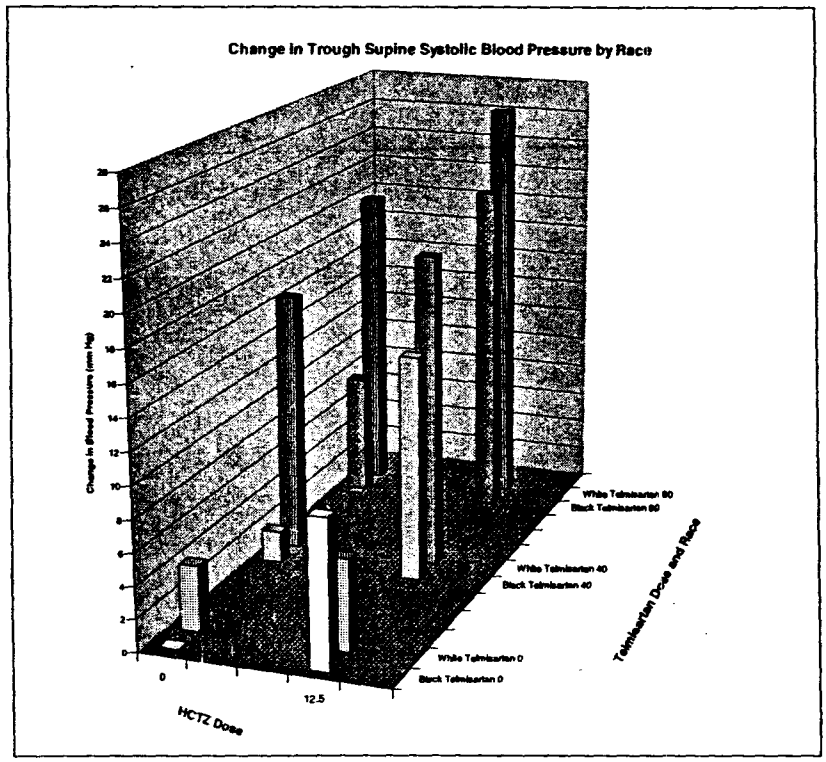


Figure These values represent observed values (uncorrected)stud 502.204



With respect to peak measurements, for Caucasians at least one of the combination doses was statistically superior to the individual components for both supine and standing diastolic and systolic blood pressures. For peak supine measurements the T40/H12.5 was superior to each of the components. For standing measurements both combination products were superior to the individual components. When the combination product was not superior to the individual components, the addition of hydrochlorothiazide to telmisartan was the treatment not significant.

For blacks, the sample size and consequently the power to detect differences of the combination therapy from the individual components was less than that of Caucasians. Nevertheless, for all peak measurements at least one of the combination products was superior to the individual components.

Response Surface Analysis.

The sponsor analyzed all the cells of the factorial study for supine trough diastolic blood pressure for the purposes of better defining the relationship between dose and blood pressure effect. The effect on blood pressure for each of the individual treatment groups for supine systolic and supine diastolic blood pressures are shown in Table 7.20 and graphed as Figures 7.4 and 7.5 .respectively. Supine heart rate is shown in Table7.21 . Heart rates, with the exception of HCTZ monotherapy (6.25 mg) showed no effects. The heart rate response for this cell appears anomalous.

Table 7.20 Adjusted (for Baseline BP and Baseline PRA) Supine Blood Pressure for the entire factorial study mean ± SE study 502.204

HCTZ Dose	Systolic					Diastolic				
	Telmisartan Dose									
	0	20	40	80	160	0	20	40	80	160
0	-2.7 (1.7)	-9.9 (2.9)	-12.1 (1.6)	-15.4 (1.6)	-17.2 (2.5)	-3.2 (1.0)	-9.9 (1.7)	-10.7 (0.9)	-11.3 (1.0)	-12.2 (1.5)
6.25	-3.7 (3.0)	-12.9 (3.0)	-23.3 (3.1)	-16.9 (3.3)	-16.0 (2.6)	-4.5 (1.8)	-10.8 (1.8)	-13.4 (1.8)	-11.0 (1.9)	-11.7 (1.5)
12.5	-8.1 (1.7)	-21.5 (3.1)	-18.8 (1.7)	-24.0 (1.7)	-21.0 (2.5)	-7.2 (1.0)	-12.1 (1.8)	-12.6 (1.0)	-15.1 (1.0)	-12.8 (1.5)
25	-17.9 (2.9)	-20.5 (2.9)	-19.6 (3.0)	-23.4 (2.4)	-25.8 (2.6)	-11.1 (1.7)	-14.5 (1.7)	-13.4 (1.7)	-14.1 (1.4)	-17.5 (1.5)

Table 7.21 Change in Supine heart rate at trough mean ± SD (Sponsor's table 4 p 225)

HCTZ Dose	Telmisartan Dose				
	0	20	40	80	160
0	-1.2 ± 9.5	0.9 ± 9.3	0.7 ± 11.7	-0.4 ± 9.0	1.3 ± 8.3
6.25	7.8 ± 10.3	-1.1 ± 9.1	2.0 ± 7.7	0.9 ± 8.4	1.8 ±10.4
12.5	-0.3 ±8.7	-0.8 ± 10.3	1.5 ± 8.1	1.5 ± 8.2	0.0 ± 7.8
25	2.5 ± 8.9	-0.5 ± 5.9	-1.1 ± 6.9	2.2 ± 6.1	0.5 ± 9.0

Figure. 7.4 Observed measurements of placebo-subtracted trough supine diastolic blood pressure. Study 502.204 full 20 cells

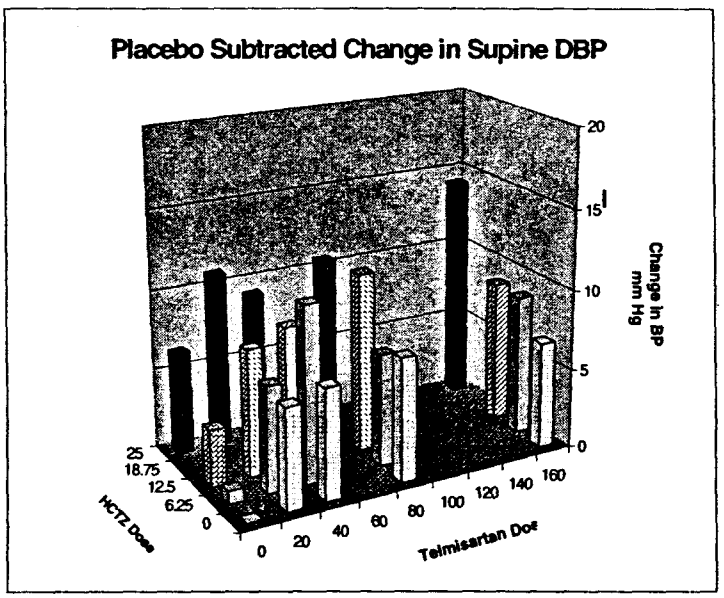
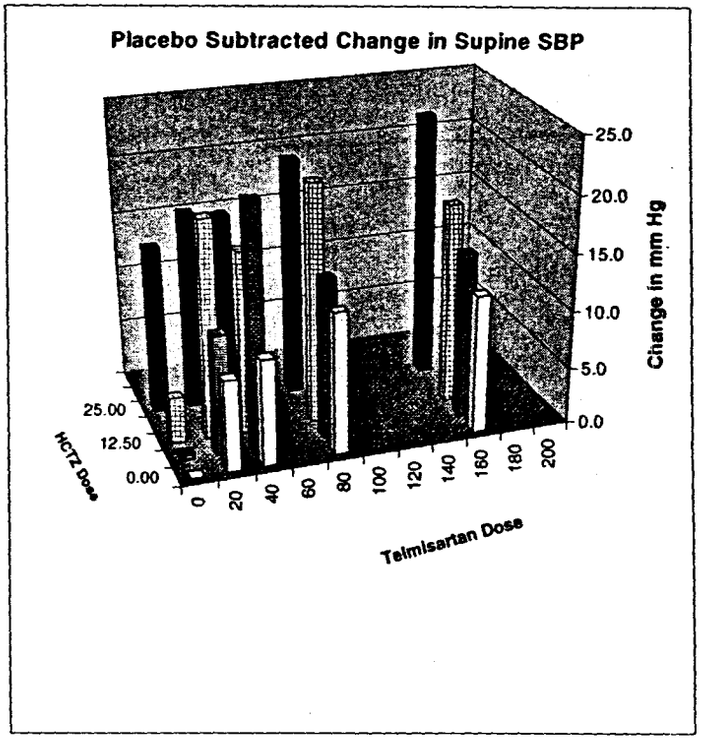


Figure Observed measurements of placebo-subtracted trough supine systolic blood pressure full 20 cells. Study 502.204 cells



The effect for all the treatment groups for trough standing measurements of diastolic and systolic blood pressures as well as heart rate are showed in Table 7.22 and 7.23, respectively. With respect to standing trough heart rates, HCTZ (6.25 as monotherapy) appears to be the only cell that indicates an increase in heart rate.

Table 7.22 Change in Standing Blood Pressure for the entire factorial study (uncorrected) mean (SD)

		Systolic					Diastolic				
		Telmisartan Dose									
HCTZ Dose		0	20	40	80	160	0	20	40	80	160
	0	-1.4 (12.1)	-13.1 (12.5)	-10.4 (14.0)	-15.2 (15.3)	-11.3 (2.5)	-2.6 (7.3)	-7.9 (6.1)	-9.0 (9.2)	-9.7 (7.9)	-10.5 (9.2)
	6.25	-5.0 (7.3)	-14.3 (14.9)	-19.8 (15.7)	-16.0 (12.3)	-16.5 (16.6)	-4.0 (6.0)	-9.2 (6.6)	-14.0 (8.0)	-11.7 (10.6)	-11.9 (10.1)
	12.5	-7.4 (13.6)	-20.5 (13.3)	-17.8 (15.7)	-21.1 (15.5)	-20.1 (13.2)	-5.6 (6.7)	-9.6 (5.8)	-12.1 (9.0)	-13.1 (8.1)	-11.8 (6.8)
	25	-16.7 (13.3)	-20.9 (12.7)	-18.3 (14.7)	-23.1 (13.6)	-27.0 (15.8)	-8.4 (7.7)	-13.9 (6.7)	-12.6 (7.6)	-12.8 (7.3)	-17.8 (9.2)

Table 7.23 Change in Standing heart rate at trough mean ± SD (Sponsor's table 4 p 225)

		Telmisartan Dose				
HCTZ Dose		0	20	40	80	160
	0	-1.1 ± 9.2	1.1 ± 6.7	0.5 ± 8.8	0.4 ± 9.7	-1.2 ± 8.9
	6.25	7.6 ± 10.5	-0.2 ± 8.0	0.6 ± 8.2	1.8 ± 6.8	1.0 ± 8.7
	12.5	1.3 ±7.9	-2.4 ± 10.5	1.4 ± 8.7	1.3 ± 9.0	0.9 ± 8.0
	25	4.0 ± 9.3	-3.0 ± 7.6	-2.2 ± 6.8	1.1 ± 7.9	0.7 ± 9.1

The data for supine measurements response surface model included linear, quadratic and linear interaction terms for both the telmisartan and hydrochlorothiazide doses as well as the following variables: baseline blood pressure, baseline PRA. Race was not included in the response surface analysis. The

sponsor addressed the issue of race by a separate analysis. The adjusted (for baseline PRA and baseline BP, the n=714 for this analysis) systolic and diastolic measurements.

For both supine diastolic and systolic measurements the model had a non-significant results of the goodness of fit test (p=0.25 and p=0.98, respectively), thus per sponsor indicating that the model fit well the data. The significance of the overall model was highly significant (p<0.001) for both supine systolic and diastolic blood pressures. The magnitude of the estimate of each of the parameters as well as the attendant error and statistical significance is shown in Table 7.24.

Table 7.24–Parameter Values Response surface analysis study 502.204.

	Diastolic Blood Pressure					Systolic Blood Pressure			
	Degree Freedom	Estimate	SE	Prob> [T]		Degree Freedom	Estimate	SE	Prob> [T]
Intercept	1	-19.975	6.848	0.0036		1	29.105	6.518	0.0000
HCTZ	1	-0.2625	0.1059	0.0134		1	-0.717	0.182	0.0001
Telm	1	-0.1436	0.018917	0.0000		1	-0.259	0.0324	0.0000
HCTZ^2	1	0.001635	0.004120	0.6917		1	0.01	0.00710	0.1571
Telm*HCTZ	1	0.000377	0.000628	0.5485		1	0.00083	0.00108	0.4414
Telm^2	1	0.000639	0.000110	0.0000		1	0.00114	0.00019	0.0000
BSU- DIA	1	0.15732	0.675	0.0201	BSU-SYS	1	-0.2006	0.04157	0.0000

For both trough systolic and diastolic measurements, the linear terms in the model for both HCTZ and telmisartan were both highly significant. The quadratic term for Telmisartan, but not HCTZ was significant. The interaction term was not significant. Baseline supine systolic or diastolic blood pressure was significant.

With respect to supine systolic blood pressures, both of the combination products were superior in blood pressure lowering than their individual components. Supine heart rates are shown below. With respect to heart rate, with the exception of the 6.25 mg dose, there did not appear to be a consistent increase in trough heart rates.

Subgroup Analyses:

Race:

The response of all treatment groups for balk/Caucasian race is shown in the figure below. For both trough systolic and diastolic blood pressures, there appears to be a small blood pressure response for blacks to monotherapy telmisartan. Whites seem to respond well to monotherapy telmisartan. Conversely whites respond quite well to HCTZ monotherapy, non-blacks less so.

Figure 7.6 Study 502.204 Effects of various treatments on race of DBP

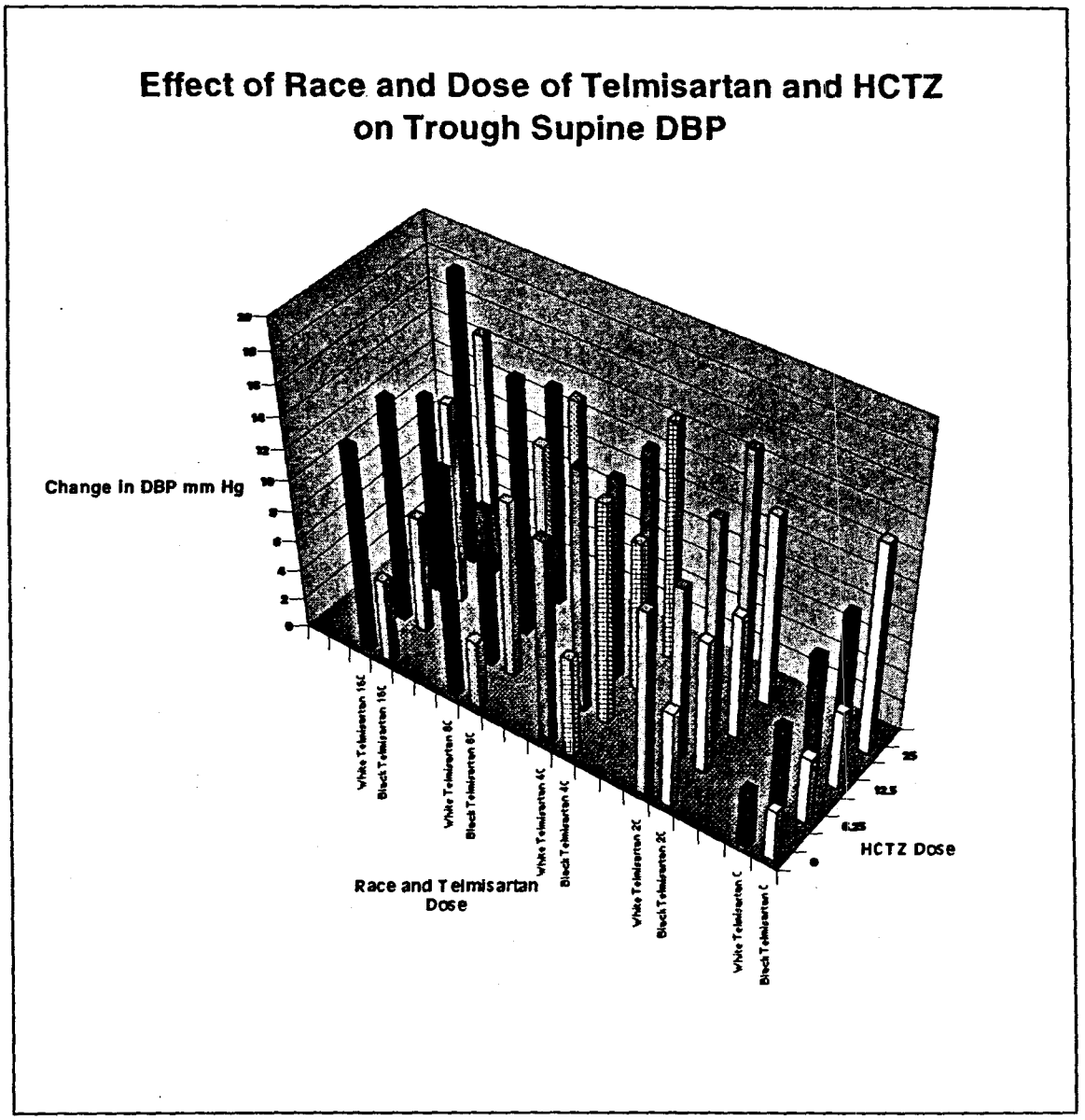


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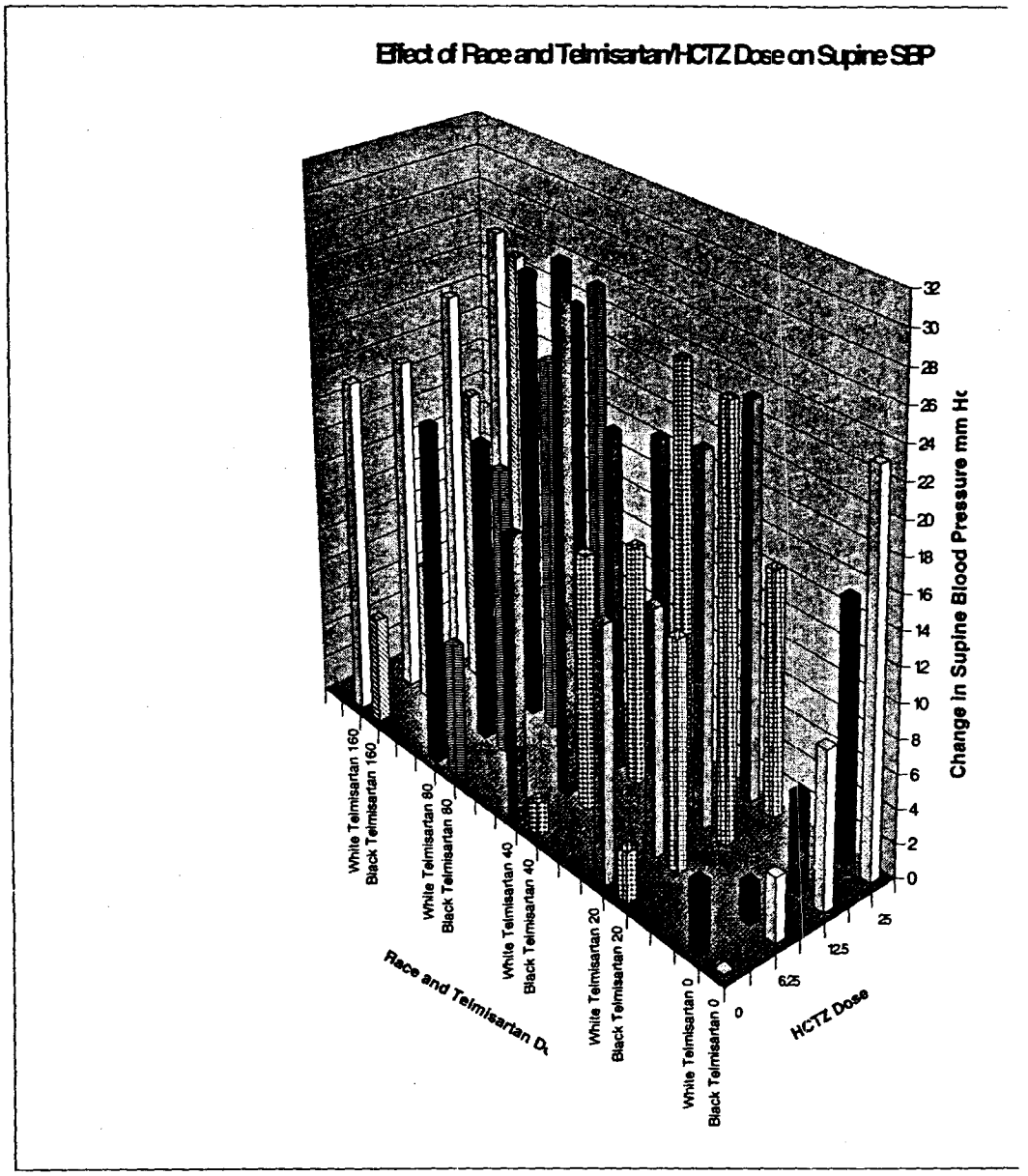
Figure 7.7 ffect of various treatments by race on supine systolic blood pressure study 502.204



Weekly dependence of Blood Pressure Response

Blood pressure measurements were taken at trough on weeks 2, 4 and 8. in general, there was a trend to increase in BP as the duration of treatment increased.

Effect of Duration of treatment on diastolic (Figure 7.8) and systolic (Figure 7.9) blood pressures study 502.204

Figure 7.8

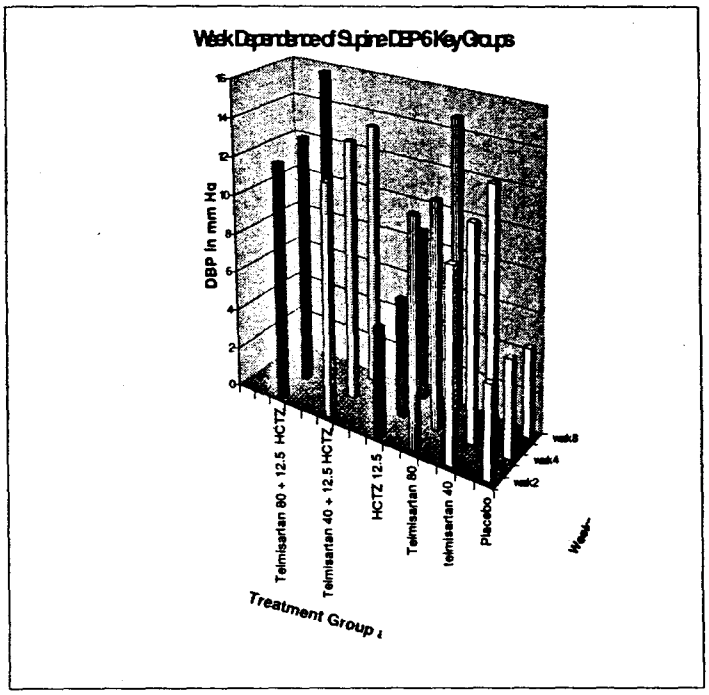
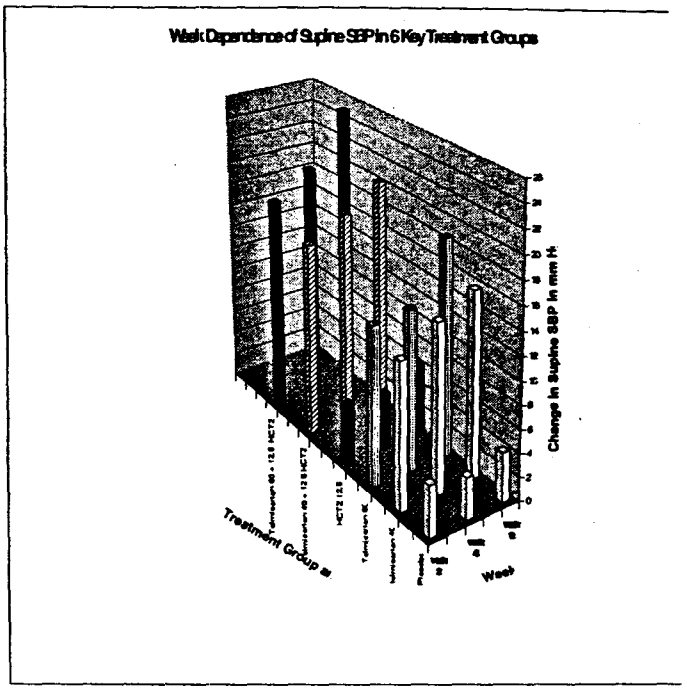


Figure 7.9



Time Dependence of Blood Pressure post dose.

Supine and standing vital were measured at week 8 at previous dose trough as well as 1, 3 and 4 hours after dosing. The data for supine diastolic blood pressure is shown below. At 4 hours, particularly for the monotherapy telmisartan dose, the effect at 3 and 4 hours appears greater than that at trough. Peak to trough measurements can be calculated and are shown in Table 7.25. Peak was defined as the 3 hour visit on Week 8 Trough the lowest value on either visit 8 or visit 9 (24 hours later). No peak baseline value was available, so trough baseline was subtracted from peak measurments.

Table 7.25 Study 502.204 trough and peak measurements as well as ratio of trough/peak

	Baseline	Week 8 peak	Week 8 Trough	placebo Pk	Placebo Trough	Delta peak	Delta trough	Delta Delta PK	Delta Delta Trough	Troug/PK
placebo	99.92	92.39	95.45	92.39	95.45	-7.53	-4.47			
Telmisartan 20	99.69	84.72	89	92.39	95.45	-14.97	-10.69	-7.44	-6.22	0.836022
Telmisartan 40	101.4	87.3	90.47	92.39	95.45	-14.1	-10.93	-6.57	-6.46	0.983257
Telmisartan 80	100.2	83.63	88.21	92.39	95.45	-16.57	-11.99	-9.04	-7.52	0.831858
Tel misartan 160	100.71	86.64	89.57	92.39	95.45	-14.07	-11.14	-6.54	-6.67	1.019878
HCTZ 6.25	99.4	93.51	94.38	92.39	95.45	-5.89	-5.02	1.64	-0.55	-0.33537
Telmis 20/H6.25	101.1	86.19	90.16	92.39	95.45	-14.91	-10.94	-7.38	-6.47	0.876694
Telmis 40/H6.25	100.4	83.2	85.8	92.39	95.45	-17.2	-14.6	-9.67	-10.13	1.04757
Telmis 80/H6.25	99.47	81.78	87.4	92.39	95.45	-17.69	-12.07	-10.16	-7.6	0.748031
Telmis 160/H6.25	100.69	82.75	87.49	92.39	95.45	-17.94	-13.2	-10.41	-8.73	0.838617
HCTZ 12.5	100.47	90.47	92.34	92.39	95.45	-10	-8.13	-2.47	-3.66	1.481781
Telmis 20/H12.5	102.03	88.72	90.1	92.39	95.45	-13.31	-11.93	-5.78	-7.46	1.290657
Telmis 40/H12.5	100.6	82.26	87.13	92.39	95.45	-18.34	-13.47	-10.81	-9	0.832562
Telmis 80/H12.5	100.92	82.77	85.39	92.39	95.45	-18.15	-15.53	-10.62	-11.06	1.041431
Telmis 160/H12.5	100.35	81.18	87.94	92.39	95.45	-19.17	-12.41	-11.64	-7.94	0.682131
HCTZ 25	100.39	87.61	89.91	92.39	95.45	-12.78	-10.48	-5.25	-6.01	1.144762
Telmis 20/H25	99.86	82.7	85.63	92.39	95.45	-17.16	-14.23	-9.63	-9.76	1.013499
Telmis 40/H25	99.68	82.8	86.67	92.39	95.45	-16.88	-13.01	-9.35	-8.54	0.913369
Telmis 80/H25	100.6	79.42	86.23	92.39	95.45	-21.18	-14.37	-13.65	-9.9	0.725275
Telmis 160/H25	101.36	79	82.96	92.39	95.45	-22.36	-18.4	-14.83	-13.93	0.939312

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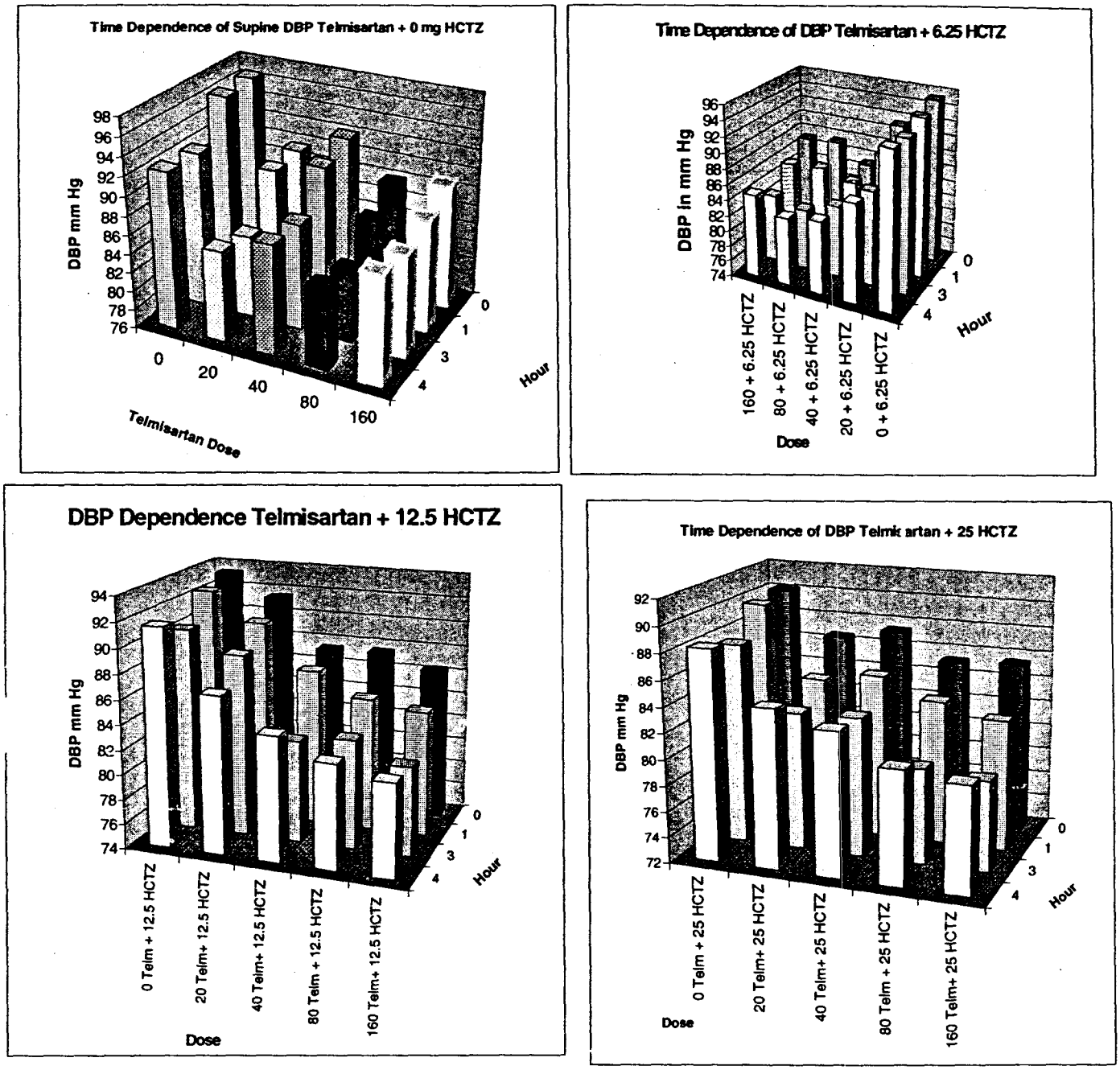

Figure 7.10 Hour Dependence of supine DBP. Each hydrochlorothiazide dose is treated in a separate panel

Safety:

Duration of Exposure and Compliance: The planned duration of exposure was 56 days. The actual mean ± SD exposure during the study was 54.6 ± 10.6 days. Patient compliance (based on pill counts at weeks 2, 4 and 8 was > 99.5%.

Deaths, Dropouts and Discontinuations:

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There were no deaths in the study. Of the 69 patients who prematurely discontinued, a total of 24 patients discontinued due to adverse events, the others for reason listed in Table 7.5. Twelve of those who discontinued for adverse events were among those in the six pivotal groups. The other twelve who discontinued for adverse events were among the 366 patients who were randomized to the peripheral dosing mono- or combination therapy. Discontinuations are summarized below.

Placebo:

1) Patient # 4017, a 64-year old white male was treated for 38 days prior to discontinuation. The patient reported **vomiting blood** that worsened the next day which was accompanied by rectal bleeding. A Barrett's ulcer was diagnosed on endoscopy.
2) Patient # 4096 a 69-year old white female was discontinued after 8 days for **headache**.
3) Patient # 4188, a 58-year old white male discontinued after 7 days because of an **infected laceration** .
4) Patient # 4059, a 72-year old white male was discontinued after 15 days due to **lack of efficacy**. The patients blood pressure at the time of discontinuation was 171/107. Baseline blood pressure was 162/103.
5) Patient # 4427, a 56-year old white female discontinued after 14 days discontinued due to **lack of efficacy**. At the time of discontinuation the measured blood pressure was 173/105. The baseline measurements were 171/103.
6) Patient # 4477, a 57-year old white male who discontinued after 28 days due to **lack of efficacy**. The measurement at the time of discontinuation was 153/107. Baseline measurement was 143/97. The patient also had **flipped T-waves** on the ECG at the time of discontinuation.
7) Patient # 4539, a 63-year old white male discontinued after 41 days of treatment due **to lack of efficacy**. Blood pressure measurement at the time of termination was 155/110. Baseline measurements were 169/107.
8) Patient # 6044, a 40-year old black female discontinued after 27 days due to lack of efficacy. At the time of termination blood pressure measurements were 163/117. Baseline measurement was 155/107.
9) Patient number 4553, a 77-year old white male discontinued after 36 days because the **patient was leaving the country**. The measurement at the time of termination was 150/95.
10) Patient # 6120, a 38-year old black male discontinued after 28 days of therapy because the patient **was moving**. Blood pressure at the time of termination was 149/85.

Telmisartan monotherapy:
Telmisartan 20 mg:

1) Patient # 4326 was a 65-year old white male discontinued after 14 days due to **worsening of systolic blood pressure**. At the time of discontinuation the blood pressure was 213/114. Baseline measurements was 213/114. The subject was treated with diltiazem and enalapril.

Telmisartan 40 mg

1) Patient # 4425, a 61-year old white male discontinued after 22 days because of **diabetes mellitus**. Although baseline fasting blood sugar and urine dipstick was consistent with diabetes, the patient was only discontinued after randomization. Baseline fasting blood sugar was 248 mg/dL. Fasting blood sugar at the time of discontinuation was 283 mg/dL.
2) Patient # 6176, a 47-year old black female discontinued after 14 days because of **lack of efficacy**. Baseline blood pressure measurement was 175/112. The blood pressure at the time of discontinuation was 165/121.
3) Patient # 6061, a 66-year old black male was discontinued after 62 days (the calculated last dose of medication) because the subject **could not meet the trial schedule** (listed as non-compliant). The blood pressure measurement a last on treatment visit was 141/91.
4) Patient # 2238, a 42-year old Hispanic male was discontinued after 53 days due to **inability to meet the study schedule** (labeled as consent withdrawn). The blood pressure at the last on treatment measurement was 172/110.
5) Patient # 4122, a 57-year old white male discontinued after 41 days because of a **planned trip**. At the termination of the study his blood pressure was 134/96.

Telmisartan 80

1) Patient # 6043, a 53-year old black female discontinued after 28 days due to **lack of efficacy**. Baseline measurement of blood pressure was 161/103. At last visit blood pressure was 163/110.

2) Patient # 4053 a 44-year old white female discontinued after 20 days because of **non-compliance**. At the final visit the patient was partially compliant with medication (64%). Baseline blood pressure was 155/100. The blood pressure at the time of discontinuation was 119/91
3) Patient # 4439, a 57-year old Hispanic female was **lost to follow up**. The patient completed the visit 6. There was no further contact with the patient. The patient apparently returned the residual pills by mail with no further clinic contact. The last blood pressure on treatment was 134/86.
4) Patient # 6037, a 43-year old black female discontinued on day 29. The patient **did not return** for the end of the study. The last measurement after 4 weeks was 152/99.
5) Patient # 4103, a 44year old white male discontinued at day # 35. The patient withdrew consent after his personal physician expressed **concern about blood pressure control**. The last measured blood pressure was 158/102. Baseline blood pressure was 154/101.
6) Patient # 4137, a 41-year old white male who discontinued on day 27 because he **relocated**. The last measurement was 130/84.

Telmisartan 160 mg

1) Patient # 4383, a 49-year old white male discontinued on day # 5 because of **bilateral back pain that radiated to the abdomen**. The patient was a smoker with a history of ankylosing spondylitis. The patient was referred for an IVP which showed prostatic hypertrophy.
2) Patient # 4074, a 51-year old white female discontinued after the first dose because of facial flushing, numb nose, chills and flushing of hands, neck and back. The following day the patient had periorbital edema. The diagnosis was **angioedema.**
3) Patient # 6166 a 65-year old black male discontinued on day 16 because of **CK elevation** (CK =753) baseline CK 22 to 198). The MB faction was 2.9%. Baseline ECG was notable for a right bundle branch block. I saw no reference to a termination visit ECG.
4) Patient # 6266, a 20-year old black female was discontinued on day 49 due to an **attempted suicide**. The patient had a history of previous suicide attempts. After the patient was admitted to the hospital the blind was broken.
5) Patient # 4412, a 76-year old white male discontinued after 28 days due to **lack of efficacy**. The blood pressure a termination was 165/114. The baseline blood pressure was 165/103. Compliance was 100%
6) Patient # 6129, a 52-year old black male discontinued on day 56 due to **loss to follow up**. The last visit was visit 7 (presumably around day # 28). Blood pressure a the last visit was 117/82.

Hydrochlorothiazide Monotherapy:
Hydrochlorothiazide 6.25 mg:

1) Patient # 4117, a 54-year old Hispanic male was discontinued after 14 days due to **loss to follow up**. Baseline measurements were 173/112. At visit 6, the blood pressure was 178/118.
2) Patient # 4346, a 45-year old Hispanic female discontinued after 31 days due to **non-compliance**. The blood pressure at termination visit (14 days off drug) was 130/90.

Hydrochlorothiazide 12.5 mg

1) Patient # 6191, a 19-year old black female was discontinued because of **worsening blood pressure**. The blood pressure at baseline was 149/99. Blood pressure at the time of discontinuation was 149/117.
2) Patient # 4317, a 69-year old white male discontinued after day 58 due to a **syncopal episode** that resulted in a motor vehicle accident. Apparently, the patient took 2 mg of Hytrin the morning of the episode.
3) Patient # 6109, a 52-year old black female discontinued after 2 days due to **weakness, lightheadedness, palpitations, nausea and headache.**
4) Patient # 4020, a 64-year old white male discontinued on day 3 due to **lack of efficacy**. The blood pressure at the termination visit was 179/110. baseline measurement was 183/109.
5) Patient # 4098, a 77-year old white male discontinued on day 14 due to **lack of efficacy**. The final blood pressure was 201/103. Baseline blood pressure was 185/97. The compliance was reported s 100%
6) Patient # 4192, a 61-year old Hispanic male discontinued after 37 days due to **lack of efficacy**. Blood pressure at the time of discontinuation was 165/105. Blood pressure at visit 7 was 169/111. Baseline blood pressure was 169/110.
7) Patient # 4531, a 67-year old white male discontinued after 28 days due to **lack of efficacy**. Baseline measurement was 181/101. Terminal blood pressure measurement was 196/100.
8) Patient # 4190, a 66-year old white male discontinued after 35 days due to **non-compliance**. The patient ran out of medication. Compliance was 100%.

Hydrochlorothiazide 25 mg

1) Patient # 4566, a 41-year old white male discontinued due to **non-compliance**. The patient was **incarcerated.**
2) Patient # 6250, a 47-year old black male **withdrew consent**. The patient received one dose from the wrong stratum and did not return for re-randomization.
3) Patient # 6187, a 46-year old black male discontinued after days due to **inability to make scheduled** visits. The last blood pressure was 132/103. The baseline measurement was 152/109.

Combinations Products:

Hydrochlorothiazide 6.25 + Telmisartan 20 mg

1) Patient # 6121, a 54-year old black male discontinued after 35 days because the patient **withdrew consent**. Visit 6 blood pressure was 147/104.

Hydrochlorothiazide 6.25 + Telmisartan 40.

1) Patient # 4268, a 55-year old white female discontinued after 1 day due to **lack of efficacy**. After the first dose the blood pressure because man supine systolic blood pressure was > 200 mm Hg.
2) Patient # 6203, a 40-year old black female discontinued after day 8 due to **relocation**. Blood pressure at the termination visit was 119/85.

Hydrochlorothiazide 6.25 + 80 Telmisartan:

1) Patient # 4147, a 64-year old Hispanic female, discontinued after 19 days due to **lack of efficacy**. Baseline blood pressure measurement was 162/105. Measurement at the time of discontinuation was 170/118. The patient had a history of systolic murmur, TIA, retrosternal mass and elevated LFTs.

Hydrochlorothiazide 6.25 + Telmisartan 160:

1) Patient # 4069, a 64-year old white male who discontinued after the first dose because of **postural hypotension**. At two hours post dose the blood pressure was 97/70. The patient was symptomatic with dizziness and sweating
2) Patient # 6097, is a 57-year old black male that discontinued after 28 days due to **loss to follow-up**. Blood pressure at least visit was 123/87.
3) Patient # 4265, a 54-year old white Hispanic discontinued after 10 days due to **withdrawal of consent**. The withdrawal of consent was due to personal problems. No additional information was supplied.

Hydrochlorothiazide 12.5 + Telmisartan 20

1) Patient # 6135, a 48-year old black male discontinued after the first dose due to **symptomatic orthostatic hypotension**, coincident with peak drug effect. Blood pressure at baseline was 157/107. Lowest measured blood pressure was 87/60. The patient complained of dizziness.
2) Patient # 4275, a 49-year old white male discontinued on day 21due to **non-compliance**. The patient could not make scheduled visits. The blood pressure at the time of the last visit was 131/89.

Hydrochlorothiazide 12.5 + Telmisartan 40

1) Patient # 6242, a 63-year old black female discontinued after 28 days due to **worsening blood pressure**. The blood pressure at the time of discontinuation was 161/111. Baseline blood pressure was 164/103
2) Patient # 4043, a 79-year old white male discontinued after 40 days due to **shortness of breath with sere cough**. The patient had a history of cardiac murmur and also reported an adverse event of URI. Supine blood pressure at the time of discontinuation was 137/88. The adverse event apparently resolved after approximately 4 weeks.
3) Patient # 4144, a 46-year old Hispanic male discontinued after 34 days due to a **positive hepatitis B screen**.
4) Patient # 6062, a 60-year old black male discontinued after15 days due to **lack of efficacy**. The blood pressure at the ti.ne of discontinuation was 186/120. Blood pressure at baseline was 191/113.
5) Patient # 6163, a 54-year old black female discontinued after 28 days due to **lack of efficacy**. The blood pressure at termination was supine was 185/107 (standing blood pressure was 198/124). The blood pressure measurement at baseline was 151/103.
6) Patient # 4051, a 40-year old white male discontinued after 58 days due to **loss to follow up**. The blood pressure measurement at visit 8 was 134/91.

Hydrochlorothiazide 12.5 + Telmisartan 80

1) Patient # 4038, a 51-year old white male discontinued after 1 dose because of a **cardiac arrhythmia**. The patient apparently complained of " heart racing at 70 minutes after the dose. The arrhythmia, however, was not documented on ECG. The physician however auscultated a **bigeminal rhythm**. The patient had a history of an enlarged heart.
2) Patient # 4242, a 44-year old white male discontinued after 29 days due to complaints of **decreased libido**. Last blood pressure measurement was 125/85. Baseline measurements was 159/104
3) Patient # 6068, a 41-year old black male discontinued after the first dose due to **lack of efficacy**. At 3 hours post dose the blood pressure was 158/123. At 4 hours post dose the blood pressure was 179/123. Baseline blood pressure was 177/112. The patient had an **elevated 1946 U/L** and 11.4% (27 U/L [is this a typo for 1,4%)) for MB band a retest showed a CK of 1403 ; 59 U/L MB (4.2%) . The screening ECG indicated left atrial enlargement, left ventricular hypertrophy and T-wave changes. I saw no evidence of a follow-up ECG. **Liver function studies** were also abnormal at visit 5.
4) Patient # 4315, a 56-year old white female discontinued after 14 days due **to non-compliance with birth control**. Supine blood pressure at the time of discontinuation was 135/93.

Hydrochlorothiazide 12.5 + Telmisartan 160.

1) Patient # 4159, a 40-year old white male discontinued after 11 days due to **symptomatic orthostatic hypotension**. Symptoms included lightheadedness on standing or walking and feeling faint. Blood pressure was 82/48. Blood pressure at termination was 117/84.

Hydrochlorothiazide 25 + Telmisartan 20

1) Patient # 4453, a 67-year old white male discontinued after 13 days due to **weakness , tiredness and tingling sensation**. There was evidence of excessive blood pressure response. At 3 hours during the first dose the blood pressure decreased to 98/63.
2) Patient # 6112, a 54-year old black male discontinued after 50 days was hospitalized due to **severe chest pain and anxiety**. The patient was treated with Nitropatch, Serax, Deseril and Tradazone. The event occurred one day after the last dose of study drug.
3) Patient # 4160, a 67-year old white male discontinued after 29 days because the patient **went on vacation**. The patient's last blood pressure was 143/86.

Hydrochlorothiazide 25 mg + Telmisartan 80 mg

1) Patient # 4087, a 53-year old white female discontinued after 2 days because of **symptomatic orthostatis** (diaphoresis, nausea and dizziness). Blood pressure decreased from 115/76 to 93/71.

2) Patient # 6064, a 59-year old black male discontinued after 36 days due to a **maculopapular skin eruption**. No trough blood pressure values were available.

Hydrochlorothiazide 25 + Telmisartan 160

1) Patient # 6122, a 47 year old black male discontinued after 57 days due to a death in the family. The last blood pressure was 129/89.
2) Patient # 4487, a 51-year old white female discontinued after 11 days, because the **consent was withdrawn**. The patient complained that her **blood pressure was too low and her pulse too fast** at home. Measurements at home (time relative to dose not stated was 100/60 pulse 98). On last clinic visit blood pressure was 139/85 pulse 96.
3) Patient # 4148, a 35-year old Hispanic female discontinued after 14 days **due to relocation**. No on therapy measurements were available.

Adverse Events listed as Severe:

There were a total of 18 adverse events listed as severe in intensity. Theses are listed below. (Derived from sponsor's 10.2.2:3 v 1.66 p 272)

Table 7.26 Study 502.204 severe adverse events

Treatment Group	# severe events	Patient #	Severe Adverse Events	Serious?	Dropout?	Recovered?
Placebo	2	# 4017	Esophageal ulceration	yes	Yes	yes
		# 4318	Sinusitis	no	No	yes
Monotherapy Telmisartan						
T20	0					
T40	1	# 4555	ECG abnormal specific	no	No	no
T80	3	# 4218	URI	no	No	yes
		# 6090	Abdominal Pain	no	No	yes
		# 6138	Diarrhea	no	No	yes
T160	1	# 6226	Suicide attempt	yes	No	yes
Monotherapy Hydrochlorothiazide						
6.25	2	# 4091	Diarrhea	no	No	yes
		# 6035	Uterine Fibroid	yes	No	yes
12.5	1	# 4317	Syncope	yes	Yes	yes
25	0					
Combination						
T20 /H6.25	0					
T40/H6.25	0					
T80/H6.25	1	# 4593	Abscess	no	No	yes
T160/H6.25	1	# 4016	Bronchitis	no	No	yes
T20/H12.5	1	# 6135	Postural hypotension	no	Yes	yes
T40/H12.5	3	# 4043	coughing	no	Yes	yes
		# 4433	sinusitis	no	No	yes
		# 4546	vision abnormal	no	No	yes
T80/H12.5	0					
T160/H2.5	1	# 6206	diabetes mellitus	no	No	no
T20/H25	1	# 6112	Chest pain	yes	No	yes
T40/H25	0					
T80/H25	0					
T160/H25	0					

The events are scattered across all treatment groups and do not appear to be concentrated in the groups of telmisartan mono-therapy, hydrochlorothiazide mono-therapy or combination therapy groups. Only four of those subjects with severe events discontinued.

Overall Adverse Events: The sponsor does not separate out the adverse events for the 20 cells of the full factorial study. Adverse events, however, were tabulated for the six pivotal treatment groups and in a separate analysis for the monotherapies and the combination therapies. Both of these analyses are reproduced as 7.27 for events which occurred in > 2 % of those enrolled

Table 7.27 Adverse events for placebo, monotherapy and combination therapy groups as well as the six key treatment groups, study 502.204

		Treatment Group								
	Total	PBO	T mono	H Mono	T + H	T40	T 80	H12.5	T40/H12.5	80/H12.5
umber	818	74	209	121	414	75	77	75	70	74
Number with AE	384 (47%)	31 (42%)	96 (46%)	60 (50%)	197 (48%)	32 (43%)	36 (47%)	35 (47%)	30 (43%)	36 (49%)
Respiratory	128 (16%)	8 (11%)	30 (14%)	23 (19%)	67(16%)	10 (13%)	11 (14%)	14 (19%)	14 (19%)	10 (14%)
CNS + PMS	114 (14%)	16 (22%)	26 (12%)	24 (20%)	48(12%)	8 (11%)	11 (14%)	15 (20%)	15 (20%)	13 (18%)
Body as a Whole	109 (13%)	7 (10%)	30 (14%)	20(17%)	52(13%)	9 (12%)	10 (13%)	13 (17%)	6 (9%)	8 (11%)
GI	73 (9%)	1 (1%)	21 (10%)	9(7%)	42(10%)	5 (7%)	11 (14%)	3 (4%)	3 (4%)	7 (10%)
Musculoskeletal	20 (2%)	3 (4%)	8 (4%)	1(1%)	8(2%)	2 (3%)	4 (5%)	1 (1%)	1 (1%)	3 (4%)
Cardiovascular	21 (3%)	0 (0%)	9 (4%)	5(4%)	7(2%)	6 (7%)	2 (3%)	2 (3%)	2 31%)	0 (0%)
Urinary	22 (3%)	2 (3%)	7 (3%)	3(3%)	10(2%)	3 (4%)	2 (3%)	2(2%)	2 (3%)	0 (0%)
Hearing	10 (1%)	2 (3%)	1 (1%)	3(3%)	4(1%)	0 (0%)	1 (1%)	1 (1%)	2 (3%)	0 (0%)
Metabolic	19 (2%)	0 (0%)	3 (1%)	6(5%)	10(2%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	3 (4%)
Heart Rate and Rhythm	11 (1%)	0 (0%)	2 (1%)	2(2%)	7(2%)	1 (1%)	1 (1%)	1 (1%)	0 (0%)	2 (3%)
Psychiatric	10 (1%)	2 (3%)	3 (1%)	0 (0%)	1 (0%)	0 (0%)	1 (1%)	1 (1%)	0 (0%)	1 (1%)
Gynecologic	7 (1%)	0 (0%)	4 (2%)	2 (2%)	1 (0%)	0 (0%)	3 (4%)	3 (4%)	0 (0%)	0 (0%)
Resistance	11 (1%)	2 (3%)	1 (1%)	1 (1%)	7 (2%)	0 (0%)	1 (1%)	1 (1%)	0 (0%)	1 (1%)

Based on the data from sponsor's table 5.2.1, there were a total of 128 patients with respiratory adverse events 65 had upper respiratory tract infections and 32 patient had sinusitis. Coughing, as an adverse event, was reported in 13 patients. The other respiratory events were scattered among various symptoms with no strong signal.

With respect to 114 adverse events referring to the central and peripheral nervous system, headache was reported in 55 subjects and dizziness in 37 patients. Insomnia was reported in 6 patients.

Of the 109 patients with "body as a whole" adverse events, pain was reported in 28 patients, fatigue in 24 patients, back pain in 18 patients and influenza-like symptoms in 17 patients. No other adverse event were reported in two or more patients in any one of the 20 factorial groups.

Under gastro-intestinal disorders, there were 73 adverse events. Most frequently reported events were diarrhea (27 patients), nausea (13 patients), dyspepsia (13 patients) and vomiting (5 patients). Gastrointestinal events were more frequent in telmisartan and hydrochlorothiazide treated groups than placebo.

ECGs: ECGs were recorded at screening baseline (visit 5) and visit 8. The case report forms did not capture intervals. No analysis was available.

New abnormalities or significant changes in ECGs were reported in 41 of the 818 patients. Five events were considered as adverse events. Patient # 4266 (HCTZ 12.5) had anterior lateral ischemia; patients # 4555 (Telmisartan 40 had possible inferior infarction, Patient # 6024 (telmisartan 40 mg) sinus tachycardia; Patient # 6026 sinus arrhythmia (telmisartan 80/HCTZ 12.5), patients # 6184 and 6190 sinus had bradycardia during the placebo run-in period .

Cardiovascular rhythm as an adverse events were infrequent.

- Tachycardia was reported in one Telmisartan 40 monotherapy, 2 Telm 160/H 12.5 and 2 with T160/H25 patients.
- Palpitations were reported in one Telmisartan 80 and 1 Hydrochlorothiazide 12.5;
- Ventricular arrhythmias were reported in two patients with - Hydrochlorothiazide 25 mg.
- Atrial fibrillation in one T160/H6.25 patient;
- ECG abnormal one Telmisartan 40 patient and one Hydrochlorothiazide12.5 patient .

Orthostatic effects: Orthostatic effects were not separately analyzed. Syncope was reported in 1 patient Hydrochlorothiazide 12.5; and 1 T160/H6.25. Postural hypotension was observed in one patient T160/H6.25.

Table7.28 lists the orthostatic blood pressure measurements. Orthostatis was defined for diastolic or systolic blood pressure as a decrease in 10 mm Hg or an increase in 10 BBP in heart rate. I have also included a category of "any", which are unique patients with orthostasis by any of the three criteria.. Measurements for orthostasis were performed after the first dose and also at week 8 at approximately 3 hours post dose (peak effects). Baseline measurements were done at the clock time equivalent to trough measurements. The measurements for peak orthostasis do not therefore have an exact time equivalent measurement at baseline. Nevertheless, since there is a placebo-group, the results for orthostatics are interpretable. With respect to the first dose effect, relative to placebo there is no overwhelmingly convincing signal. At the two doses planned for marketing (Telm 40/H12.5 and Telm 80/H12.5), there is no particularly strong orthostatic signal. At the 8 week data, there is a higher percentage increase in orthostatis relative to placebo for the two marketed groups, 12.2% for placebo versus 17.8 and 17.1% respectively for e Telm 40/H 12.5 and Telm 80/H 12.5 treatments.

Table 7.28 First Dose-Flagged Orthostatic Effects, study 502.204

			Telmisartan Dose				
			0	20	40	80	160
Hydrochlorothiazide Dose	0	Diastolic BP	1/74 (1.4%)	0/23	0/75	0/77	0/34
		Systolic BP	4/74 (5.4%)	0/23	6/75 (7.8%)	6/77 (7.8%)	1/34 (2.9%)
		Heart Rate	5/74 (6.8%)	3/23 (13.0%)	3/75 (4.0%)	10/77 (13.0%)	0/34
		Any	**9/74 (12.2%)**	**3/23 (13.0%)**	**9/75 (12.0%)**	**15/77 (19.4%)**	**1/34 (2.9%)**
	6.25	Diastolic BP	0/20	0/25	0/22	0/20	0/32
		Systolic BP	1/20 (5.0%)	1/25 (4.0%)	0/22	2/20 (10%)	1/32 (3.1%)
		Heart Rate	1/20 (5.0%)	1/25 (4.0%)	1/22 (4.6%)	1/20 (5.0%)	3/32 (9.4%)
		Any	**2/20 (10%)**	**2/25 (4.0%)**	**1/22 (4.6%)**	**3/20 (15.0%)**	**4/32 (12.5%)**
	12.5	Diastolic BP	0/74	1/22 (4.6%)	1/69 (1.5%)	1/74 (1.4%)	0/33
		Systolic BP	2/74 (2.7%)	1/22 (4.6%)	3/69 (4.4%)	9/74 (12.2%)	3/33 (9.1%)
		Heart Rate	6/73 (8.2 %)	0/22	4/69 (5.8%)	5/74 (6.8%)	3/33 (9.1%)
		Any	**7/74 (9.5%)**	**1/22 (4.6%)**	**8/69 (11.5%)**	**13/74(17.6%)**	**6/33(18.2%)**
	25	Diastolic BP	0/24	0/25	1/25 (4.0%)	0/33	0/33
		Systolic BP	0/24	3/25 (12.0%)	0/25	3/33 (9.1%)	5/33 (15.2%)
		Heart Rate	4/24 (16.7%)	4/25 (16.0%)	1/25 (4.0%)	1/33 (3.0%)	3/33 (9.1%)
		Any	**4/24 (16.7%)**	**6/25 (24%)**	**2/25 (8.0%)**	**4/33 (12.1%)**	**7/33(21.2%)**

Table 7.29 Week 8 Peak Dose-Flagged Orthostatic Effects study 502.204

			Telmisartan Dose				
			0	20	40	80	160
Hydrochlorothiazide Dose	0	Diastolic BP	0/64	0/22	1/71 (1.4%)	0/71	1/28(3.6%)
		Systolic BP	364 (4.7%)	0/22	1/71 (1.4%)	4/71 (5.6%)	2/28 (7.1%)
		Heart Rate	1/64 (6.2%)	2/22 (9.1%)	7/71 (9.9%)	6/71 (8.5%)	0/28
		Any	**4/74 (12.2%)**	**2/22 (9.1%)**	**9/71 (12.6%)**	**10/71 (14.1%)**	**2/28 (3.6%)**
	6.25	Diastolic BP	0/19	0/24	0/21	0/19	1/29 (3.4%)
		Systolic BP	1/19 (5.3%)	1/24 (4.2%)	1/21 (4.7%)	1/19 (5.3%)	0/29
		Heart Rate	4/19 (21.1%)	2/24 (8.3%)	0/21	2/19 (10.5%)	2/29 (6.9%)
		Any	**5/19 (26.3%)**	**3/24(4.0%)**	**1/21 (4.8%)**	**3/19 (15.8%)**	**3/29 (10.3%)**
	12.5	Diastolic BP	1/68 (1.5%)	0/22	0/64	2/70 (2.8%)	1/32 (3.1%)
		Systolic BP	1/68 (1.5%)	1/20 (5.0%)	7/64 (10.9%)	5/70 (7.1%)	3/32 (9.4%)
		Heart Rate	7/67 (10.5 %)	1/20 (5.0%)	5/64 (7.8%)	5/70 (7.1%)	5/32 (15.6%)
		Any	**9/68 (13.2%)**	**2/20 (10.0%)**	**11/64 (17.8%)**	**12/70(17.1%)**	**6/32(18.8%)**
	25	Diastolic BP	0/22	0/23	0/25	0/32	2/33 (6.3%)
		Systolic BP	2/22 (9.1%)	0/23	1/25 (4.0%)	2/32 (6.3%)	3/30 (10.0%)
		Heart Rate	3/22 (13.6%)	3/23 (13.0%)	1/25 (4.0%)	2/32 (6.3%)	2/30 (6.7%)
		Any	**5/22 (22.3%)**	**3/23 (13.0%)**	**2/25 (8.0%)**	**4/32 (12.5%)**	**7/30(23.3%)**

Laboratory. Blood for laboratory tests were drawn at screening, randomization (visit 5), visit 6 (14 days), visit 7 (29 days) and visit 9 (after end of study). The measurements included hematology (hematocrit, hemoglobin, platelet count, RBC indices, and differential counts), chemistry (calcium, chloride, creatinine, glucose, inorganic phosphorus, potassium, sodium, BUN, Uric acid, cholesterol, triglycerides, SGOT, SGPT, Alkaline phosphatase, bilirubin, LDH, protein, Creatinine phosphokinase, plasma renin) and urine laboratory

At week 2 of treatment, several of the laboratory values that are known to be altered by thiazides were indeed changed during treatment (nominal p-values < 0.05) i.e. potassium decreases, uric acid increases BUN increases glucose increases and chloride increases. At two weeks of treatment, using linear regression analysis (I'm not sure how they handled the combination products in the linear regression). Telmisartan did not alter these parameters.

Table 7.30 Mean Change Laboratory values

Lab	PBO	Telmisartan monotherapy				HCTZ monotherapy			HCTZ 6.25 + Tel			
		20	40	80	160	6.25	12.5	25	20	40	80	160
Ca	-0.02	0.02	0.08	-0.05	0.13	0.02	0.15	0.09	0.02	0.13	0.09	0.05
Cl	1.42	0.52	0.25	0.01	1.03	-2.00	-1.41	-1.46	-0.12	-0.50	-0.55	-0.42
Cr	0.02	-0.02	0.02	0.00	-0.01	0.06	0.04	0.03	-0.04	0.01	0.06	0.04
Glucose	0.47	-0.87	-1.09	1.25	3.78	4.52	5.42	8.33	-0.64	5.50	6.30	0.20
Phosphorus	-0.01	0.08	0.05	0.03	0.11	0.00	0.06	-0.01	0.11	0.17	0.05	0.12
K+	0.05	0.02	0.03	0.10	0.19	-0.16	-0.11	-0.17	-0.02	0.16	0.02	0.11
Na+	0.96	-0.43	-0.41	-0.79	0.06	-1.76	-0.11	-0.54	-0.2	-0.55	-1.00	-1.06
BUN	0.25	0.17	0.77	0.18	1.34	0.071	0.70	2.13	-0.6	0.35	1.00	1.81
Uric Acid	-0.03	-0.21	-0.09	0.01	0.07	0.12	0.64	0.83	0.3	0.14	0.29	0.44
Cholesterol	-0.96	-4.74	0.64	-0.65	7.25	3.38	9.78	2.71	-0.80	2.95	-1.30	8.26
Triglycerdes	-12.8	1.83	14.2	9.88	37.0	-7.81	15.28	17.4	3.96	-3.9	12	12.58
SGPT	0.54	-2.17	0.93	-1.01	1.81	3.62	0.65	3.38	-1.92	1.35	3.85	0.13
SGOT	0.38	-1.04	-0.2	-1.23	0.81	1.62	0.45	2.13	-1.00	0.50	1.50	-0.87
Alk Phosp	0.27	3.17	1.72	2.90	1.28	-0.67	0.19	-3.67	0	3.30	1.30	2.03
LDH	3.03	2.52	0.77	-7.99	1.09	-0.33	2.88	-2.96	-0.36	-5.2	-4.8	-3.35
Protein	-0.04	0.01	-0.02	-0.09	0.05	0.13	0.12	0.13	0.10	0.03	-0.00	0.11
Creatinine P-Kinase	-11.7	8.52	-1.15	-24.67	34	-35.6	-12.0	50.3	2.91	-37	7.75	18.45
Hematocrit	0.69	0.17	0.36	0.20	-0.28	0.67	1.56	0.65	0.68	0.67	0.42	0.3
Hemoglobin	0.03	-0.29	-0.14	-0.22	-0.22	0.04	0.35	0.14	0.03	0.20	-0.17	-0.26
Platelets	-2.35	20.6	0.68	-4.83	4.28	17.81	0.68	-0.92	21.24	-4.55	-8.16	0.30

Table 7.30 Cont'd

Lab	HCTZ 12.5 + Tel				HCTZ 25 + Tel			
	20	40	80	160	20	40	80	160
Ca	0.08	0.09	0.06	0.11	0.07	0.32	0.04	0.12
Cl	0.38	-1.01	-0.96	-2.33	-3.40	-3.42	-1.36	-2.78
Cr	0.06	0.04	0.04	0.06	0.07	0.05	0.00	0.06
Glucose	1.71	2.97	2.93	9.00	14.6	5.75	6.18	-0.72
Phosphorus	0.06	0.12	0.04	0.02	0.13	0.10	0.08	0.02
K+	-0.09	-0.01	-0.05	-0.03	-0.27	-0.03	-0.17	-0.11
Na+	0.76	-0.43	-0.51	-1.27	-2.08	-1.13	-1.39	-1.63
BUN	0.86	2.40	2.08	2.06	3.68	2.67	2.00	2.28
Uric Acid	0.80	0.71	0.68	0.68	0.85	0.98	0.61	0.92
Cholesterol	1.48	8.89	1.96	8.88	4.60	16.25	4.61	10.7
Triglycerid	-21.8	15.1	4.47	29.9	11.1	39.7	16.8	30.8
SGPT	-2.29	15.0	0.01	1.24	1.92	1.71	1.12	0.81
SGOT	-0.71	8.24	-0.05	0.06	-0.20	-0.46	0.70	-0.22
Alk Phosp	-0.38	3.19	-0.75	4.53	1.88	1.88	-0.09	-0.72

LDH	-5.14	0.39	-5.54	-4.64	-7.48	-2.00	-7.27	-0.81
Protein	0.10	0.05	-0.03	0.05	0.14	0.23	0.05	0.01
Creatinine P-Kinase	-3.6	-1.85	-15.3	25.7	16.96	-27.8	-7.34	11.87
Hematocrit	-0.10	0.13	-0.28	-1.03	0.71	1.04	-1.22	-0.71
Hemoglobin	-0.09	-0.11	-0.18	-0.47	0.18	0.31	-0.46	-0.41
Platelets	-1.71	2.78	5.50	6.06	8.92	17.42	11.63	14.81

The sponsor tabulates the number of Patients who sustained treatment emergent laboratory abnormalities classified as adverse events.

Table 7.31 Derived from sponsor's Table 10.3.2:1-When no patient numbers are inserted next to a dose, there were no events classified as an adverse event.

Treatment	Pt #	Adverse Event	Severity	Duration	Treatment Days
Placebo					
T20					
T40	4555	Hyperlipidemia	mild		58
T80					
T160	4485	Inc Triglycerides	Moderate		56
H6.25	4385	Anemia hyperchromic	moderate		36
H12.5					
H25					
H6.25/T20					
H6.25/T40					
H6.25/T80					
H6.25/T160					
H12.5/T20	4144	Hepatitis	mod		15
H12.5/T40					
H12.5/T80					
H12.5/T160	6206	Diabetes Mellitus	severe		15
H25/T20	4537	Diabetes mellitus	mild		
H25/T30					
H25/T80					
H25/T160	4159	Hyperuriciemia	mild		
	4454	Hyperuricemia	moderate		

Conclusions: This study supports the approvability of the combination telmisartan/HCTZ as treatment for hypertension. The overall study demonstrates that at least one of the combination products is superior to its individual components with respect to supine diastolic blood pressure response. The T 80 /HCTZ 12.5 mg was superior to the individual components for this parameter. Race, however, appears to be a dominant factor for demonstrating efficacy for this parameter. In considering non-black patients (the majority of those enrolled), there was no evidence that the combination product was superior to the individual components for trough supine diastolic blood pressure.

In considering other measurements reflecting blood pressure effect, that is the supine systolic blood pressure as well as the standing diastolic and systolic blood pressures, the effect of telmisartan/HCTZ at least for the telmisartan 80/HCTZ 12.5 mg appears to be superior to the individual components. Peak measurements of blood pressure effect also indicate that there is a benefit in the combination product over each of its components.

Safety appears tolerable. There was one case of angioedema (160 mg Telmisartan). Orhtostasis, though common based on blood pressure and heart rate measurements did not appear to translate into a excessive number of symptomatic events. With the exception of gastrointestinal symptoms, there was no apparent exacerbation of adverse events upon combining telmisartan and hydrochlorothiazide.

Study # 8
502.214 vol. 77

Title of Study: Long Term Trial of the Efficacy and Safety of Telmisartan (BIBR 277SE) Compared with Lisinopril in Patients with Mild-to Moderate hypertension.

Investigator and Sites. Dr. Khin Maung U previously reviewed this study in conjunction with the NDA for Telmisartan monotherapy (20-850). The efficacy results of this study will not be re-reviewed here. Only information pertinent to the safety of the combination product will be summarized.

Study Design: This was a positive-controlled, double dummy format. No placebo group was included. The study planned to enroll approximately 600 Patients, randomized in a 2: 1 ratio to telmisartan or lisinopril. Patients, who are mild-moderate hypertensives, as defined by a morning mean DBP of between 95 to 114 mm Hg (inclusive) entered this study. Blood pressure must be reproducible. No more than 7 mm Hg difference in supine diastolic blood pressure between adjacent run-in visits (there were three such visits) and no more than 10 mm Hg across all three baseline visits.

Patients were excluded if they

- Were or could potentially become pregnant.
- Had hypertension secondary to other disease process.
- Had excessive systolic blood pressure measurements (> 210 mm Hg).
- Had either hepatic or renal dysfunction.
- Had CHF (NYHA class III-IV).
- Had clinically relevant arrhythmias.
- Had valvular disease or obstructive cardiomyopathy.
- Had electrolyte abnormalities such as hyper- or hypokalemia or hyponatremia.
- Had diabetes mellitus that was erratically controlled.
- Required or used certain concomitant medications.

The study consisted of several phases; 1) screening visit; 2) a placebo run-in phase 3) a titration period and 4) a maintenance phase.

During the screening period eligibility will be determined, informed consent obtained, baseline measurements and physical exams performed and labs collected. Patients were weaned from concurrent therapies.

The placebo run-in phase was a single-blind period to last 4 weeks. Visits occurred weekly. Eligibility of blood pressures as well as compliance was determined during the placebo period.

The duration of the titration period was between 4 and 12 weeks. Eligible patients were randomized either to lisinopril 10-mg or to telmisartan 40-mg, administered once daily in the morning on an empty stomach. If after 4 weeks of initial dose, the supine diastolic blood pressure was still $\geq$ 90 mm Hg, the dose of telmisartan was increased to 80-mg or the dose of lisinopril to 20-mg. After an additional 4-weeks, if the blood pressure was inadequately controlled, the dose was increased to either 160-mg telmisartan or 40- mg lisinopril. If after the twelve weeks of the titration period, the blood pressure was above 90 mm Hg but had decreased by > 10 mm Hg, hydrochlorothiazide at 12.5 mg daily was added.

Any patient whose blood pressure was > 90 mm Hg and did not decrease at least 10 mm Hg at the end of the titration period was discontinued.

The maintenance phase was to last 48 weeks. Those who were controlled at any dose of either lisinopril or telmisartan during the titration phases (even if only on treatment for 4 weeks), as well as those who were partially controlled who required hydrochlorothiazide were advanced to this phase of the study. Patients were seen every 4 weeks for 3 visits and every six weeks for the last 4 visits. If at any time blood pressure control was lost, hydrochlorothiazide initially at 12.5 mg daily was added. If already on this dose of hydrochlorothiazide, the dose was increased to 25 mg daily. If blood pressure control was lost, on two sequential visits the subject was prematurely discontinued. Subjects were to be on stable doses of hydrochlorothiazide for two visits (approximately 12 weeks). If that the penultimate visit, it was necessary to add or to increase the dose of hydrochlorothiazide, an additional visit was added.

Efficacy: The primary end-points of the study were the maintenance of patients on monotherapy as well as the time when hydrochlorothiazide as add-on therapy was required. Since efficacy was described in Dr, U's review and since this study adds little information on the efficacy of the combination telmisartan/ hydrochlorothiazide, efficacy will not be further considered in this review.

Safety: the remainder of this review will deal with the safety among those who received both telmisartan and hydrochlorothiazide. This group consists of those who were partially controlled at the highest monotherapy dose as well as those who lost blood pressure control during the maintenance phase. The dose of hydrochlorothiazide could be either 12.5 or 25 mg.

There were a total of 385 patients who were randomized to received Telmisartan and 193 Patients who received lisinopril. The disposition of those who entered the study are reproduced as Table 8.1(derived from sponsor's Table 8.1:2)

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Table 8.1 Patient Disposition Study 502.214

	Telmisartan	Lisinopril
	N (%)	N (%)
No. Randomized all Received Drug	385 (100%)	193 (100%)
No. Discontinued During or at the End of Titration	82 (21.2%)	48 (24.9%)
Adverse Event	15 (3.8%)	16 (8.3%)
Unexpected Disease Worsening	0 (0%)	2 (1.0%)
Unexpected Worsening of Preexisting Disease	3 (0.78%)	0 (0%)
Other Adverse Events	9 (2.3%)	14 (7.3%)
Lack of Efficacy	53 (13.8%)	27 (14.0%)
Administrative	12 (3.1%)	4 (2.1%)
Other	2 (0.5%)	1 (0.5%)
Number Entering Maintenance	303 (78.7%)	145 (75.1%)
Number Discontinuing During Maintenance	125 (32.5%)	55 (28.5%)
Adverse Event	30 (7.8%)	16 (8.3%)
Unexpected Disease Worsening	1 (0.3%)	1 (0.5%)
Unexpected Worsening of Preexisting Disease	3 (7.8%)	2 (1%)
Other Adverse Events	26 (6.8%)	13 (6.7%)
Lack of Efficacy	13 (3.4%)	5 (2.6%)
Administrative	12 (3.1%)	3 (1.6%)
Other	13 (3.4%)	3 (1.6%)
sponsor's early termination	57 (14.8%)	27 (13.9%)
Number who received Hydrochlorothiazide	180 (47%)	84 (44%)
Number (% of those Randomized) who completed	178 (46.2%)	90 (46.6%)

One hundred eighty patients received hydrochlorothiazide at some time during the study. The demographics for the monotherapy and combination groups are shown as Table 8.2.

Table 8.2 Demographics study 502.214

Parameter	Monotherapy		Combination With HCTZ	
	Telmisartan	Lisinopril	Telmisartan	Lisinopril
Total	205	109	180	84
Gender (Male/Female)(% female)	130/75 (36.5%)	74/35 (32.1%)	127/52 (28.8%)	52/32 (38.1%)
Race (Black/White/Other) (% black)	35/166/4 (17%)	15/92/2 (15%)	38/141/1 (21%)	15/68/1 (17%)
Age (mean ± SD)	53.6 ± 11.6	53.0 ± 10.3	53.4 ± 9.9	53.9 ± 9.3

Duration of Exposure: The duration of exposure, for those who received specific doses of Telmisartan and hydrochlorothiazide is shown below (derived form sponsor's Table 5.1.2. page SA 466). The Table below only considers the duration of exposure while on a specific dose.

Table 8.3: Duration of exposure study 502.214 Telmisartan group

	Telmisartan Monotherapy			Telmisartan Combination					
	T 40	T 80	T 160	T40 + H 12.5	T40 + H 25	T80 + H 12.5	T80 + H 25	T160 + H 12.5	T160 + H25
Number	385	234	171	57	20	33	14	89	53
Duration of Treatment	96.12	76.89	73.82	154.93	161.8	141.91	110.07	123.57	185.45
Patient*Years	101.3	49.3	34.6	24.2	8.9	12.8	4.2	30.1	26.9
Sum	185.2			107.1					

Table 8.4 Duration of exposure study 502.214Lisinopril randomized patients

	Lisinopril Monotherapy			Lisinopril Combination					
	L 10	L 20	L 40	L10 + H 12.5	L10 + H 25	L20 + H 12.5	L20 + H 25	L40 + H 12.5	L40 + H25
Number	193	124	86	22	7	15	7	46	20
Duration of Treatment	93.3	75.02	76.12	164.82	193.57	133.07	146.14	154.37	178.35
Patient*Years	49.3	25.5	17.9	9.93	3.7	5.46	2.8	19.5	9.77
Sum	92.7			51.16					

Demographics: I do not have specific demographics among those who received specific doses.

Safety Outcomes:

Deaths: There were two deaths during the study. One patient died during the trial a second patient discontinued after an MI and after discontinuation of treatment.

Patient # 2018 was a 53-year old white male who on day 12 of the titration period (dose level 1) complained of **chest pain**. On arrival to the hospital he was noted to have **VT which progressed to VF** and asystole. The patient could not be resuscitated. The dose was Telmisartan 40 mg

Patient # 1706 was a 62-year old black male who during the maintenance phase complained of chest pain. He remained in the trial for a total of 258 days. The final dose was telmisartan 160 with 12.5 mg HCTZ. The patient was discontinued from the trial and died three months later.

Discontinuations:

There were a total of 203 Telmisartan and 103 Lisinopril patients who discontinued during the study, either during the titration or maintenance phase. As noted in Table , a substantial proportion of those patients who discontinued did so because the sponsor terminated the study early o submit the data with telmisartan as monotherapy (NDA 20-850. Of these patients 57 and 27 were from the telmisartan and lisinopril groups, prospectively. For either treatment regimen the fraction of patients who prematurely discontinued were similar (approximately 14-15%).

A larger fraction of blacks discontinued for lack of efficacy during the titration period. Twenty-one of the 35 black patients who enrolled into the telmisartan group discontinued during the titration period because of lack of efficacy. There were, therefore, few blacks that entered the maintenance phase for telmisartan. For lisinopril only 4 of 15 blacks discontinued during the titration portion of the study.

Among those who discontinued due to lack of efficacy, the vast proportion had some decrease in blood pressure, however, the decrease for these patients was insufficient to allow continuation in the study.

Table 8.5 List of Discontinuations:

	Treatment	Patient #	Age	Gender	Race	Reason	days	Details
1	Lis 40	1501	63	M	W	Admin	92	Patient withdrew consent
2	Tel 160 + H 25	1502	54	M	W	Adverse Event	211	Atrial fibrillation
3	Tel 40	1504	49	M	W	Adverse Event	154	Impotence, fatigue orthostatic hypotension, nausea, dizziness and headache
4	Lis 40	1510	54	M	W	Adverse Event	84	Lack of Efficacy. Last on-treatment BP was 129/92. Baseline BP was 144/97
5	Tel 160	1511	60	W	M	Lack of Efficacy	84	Last BP 147/97
6	Tel 80	1512	45	M	W	Administrative	36	Withdrew consent. Sponsor claims due to scheduling
7	Lis 40	1514	51	M	W	Adverse Event	140	Nervousness
8	Tel 40	1522	48	M	W	Adverse Event	284	Diarrhea
9	Tel 160	1523	44	F	W	Adverse Event	210	Fatigue
10	Tel 40	1936	75	M	W	Adverse Event	73	Cholecystitis followed by postural hypotension
11	Lis 20	1937	44	F	W	Adverse Event	183	Fatigue
12	Tel 160	1526	63	F	W	Lack of Efficacy	84	Last BP was 144/94
13	Lis 40	1527	29	M	B	Lack of Efficacy	77	Last BP 156/98
14	Tel 40 + H12.5	1538	47	M	W	Admin	66	Non-Compliant

15	Lis 40	1539	60	M	W	Lack of Efficacy	83	Last BP 147/91
16	Lis 10	1543	44	F	W	Adverse Event	50	Coughing
17	Tel 160 + H 25	1547	61	M	W	Lack of Efficacy	168	Last BP 136/96; previous 127/92
18	Tel 40 + H25	1548	43	M	W	Lack of Efficacy	305	Last visit 137/94; previous 140/91
19	Tel 160	1549	69	F	W	Lack of Efficacy	84	Last titration BP 153/95
20	Lis 40	1552	53	M	W	Lack of Efficacy	82	Last BP on Titration was 133/96
21	Tel 160	1553	58	F	W	Lack of Efficacy	82	Last titration measurement was 167/96
22	Tel 40	1570	64	F	W	Administrative	1	Preferred old medication
23	Lis 160 + H25	1578	47	M	B	Administrative	335	Declined follow-up due to work schedule
24	Tel 160 + H 25	1579	45	F	B	Administrative	171	Non-compliant with protocol
25	Lis 40	1581	43	M	B	Adverse Event	84	Worsening of disease
26	Tel 40	1586	55	M	B	Other	189	Moved out of country
27	Tel 160	1592	56	M	W	Lack of Efficacy	81	Last at end of titration163/103
28	Lis 40	1602	51	M	W	Lack of Efficacy	109	End of titration BP was 193/109 Baseline was 199/107
29	Tel 160 + H12.5	1604	30	M	B	Administrative	88	Non-compliance
30	Tel 160	1606	38	M	O	Adverse Event	228	Worsening of asthma and GE reflux
31	Lis 40	1607	51	M	W	Lack of Efficacy	78	Last BP 191/119. Baseline was 188/111
32	Tel 160	1609	50	F	B	Lack of Efficacy	84	Last BP 148/93
33	Lis 10	1612	61	M	W	Adverse Event	21	Worsening of disease under study
34	Tel 160	1613	57	M	W	Lack of Efficacy	84	Last BP 143/109; baseline 143/109
35	Tel 160 + H 25	1614	59	M	W	Lack of Efficacy	168	Last visit 150/98
36	Tel 160 + H 25	1621	67	M	W	Lack of Efficacy	294	Last 147/96
37	Tel 160	1622	64	F	B	Lack of Efficacy	84	Last measurement 180/119; Baseline was 159/101
38	Lis 10 + H 12.5	1634	57	F	W	Adverse Event	62	Tremor
39	Lis 20	1642	42	M	W	Adverse Event	120	Impotence
40	Tel 160	2053	70	M	B	Lack of Efficacy	86	Last BP Measurement 137/95
41	Lis 10	2058	38	M	W	Adverse Event	39	Rhinitis and coughing
42	Tel 80	2060	46	M	B	Adverse Event	51	Chest pain
43	Lis 10	1652	58	F	B	Adverse Event	4	Angioedema and headache
44	Tel 80	1653	41	M	W	Adverse Event	115	Impotence
45	Tel 40	1655	69	F	W	Adverse Event	56	Ankle edema, malaise
46	Lis 40	1656	51	M	W	Lack of Efficacy	84	Last BP 159/101
47	Lis 20 + H 5	1939	43	M	W	Other	217	Scheduled for endoscopy
48	Tel 160	1940	54	M	W	Lack of Efficacy	84	Last measurement 166/93
49	Tel 160 + H 25	1941	39	M	W	Adverse Event	160	Myalgia
50	Lis 40 + H 25	1658	46	M	B	Adverse Event	126	Worsening of disease under study
51	Lis 10	1660	57	F	W	Adverse Event	15	Increased sweating, asthenia, leg pain, headache, tremor tachycardia and leg cramps
52	Tel 160	1663	46	M	B	Lack of Efficacy	82	Last 151/103. Baseline was 167/111
53	Tel 40 + H 12.5	1665	58	M	W	Adverse Event	281	Worsening of preexisting arrhythmia
54	Lis 10	1667	62	M	W	Adverse Event	22	Headache and dizziness
55	Lis 40	2077	61	M	W	Lack of Efficacy	92	Last BP was 155/99
56	Tel 40 + H 12.5	2078	45	M	B	Adverse Event	85	Impotence
57	Tel 80	2079	62	M	O	Adverse Event	56	Hot flushing micturition frequency impotence and flatulence
58	Tel 160	2080	62	M	B	Lack of Efficacy	88	Last BP 146/101
59	Tel 40 + H 12.5	1669	63	M	W	Adverse Event	94	Asthenia and dizziness
60	Lis 40	1671	46	F	W	Lack of Efficacy	85	Last BP 167/101
61	Tel 40	1673	46	M	W	Adverse Event	7	Atrial fibrillation
62	Tel 160	1676	30	M	W	Administrative	335	Lost to follow up
63	Lis 40	1679	67	M	W	Lack of Efficacy	83	Last 141/91
64	Tel 80	1680	42	M	W	Adverse Event	52	Retinal disorder
65	Tel 160	1682	57	F	W	Lack of Efficacy	4	Last 155/99

66	Tel 80 + H 25	1684	65	M	W	Adverse Event	210	Atrial fibrillation
67	Tel 160	1685	40	M	W	Lack of Efficacy	86	Last Measurement 147/111. Baseline 144/104
68	Lis 20	1686	49	F	B	Administrative	36	Withdrew consent
69	Tel 40 + H 12.5	1691	45	F	B	Adverse Event	196	Dizziness
70	Tel 160	2084	60	M	W	Lack of Efficacy	76	Last BP 156/97
71	Tel 160	2085	44	M	B	Lack of Efficacy	81	Last BP 172/115. Baseline was 159/107
72	Lis 20	1693	69	M	B	Adverse Event	56	Atrial fibrillation
73	Tel 40	1695	46	M	W	Adverse Event	34	Worsening of pre-existing disease, fatigue, somnolence
74	Tel 40	1700	71	M	B	Adverse Event	155	Worsening of arthritis
75	Tel 40	1701	79	M	W	Adverse Event	274	Diverticulitis, ileus, sepsis and urinary retention.
76	Lis 40	1623	55	M	B	Adverse Event	57	Angioedema
77	Tel 160 + H 12.5	1706	62	M	B	Adverse Event	258	Myocardial infarction
78	Tel 160 + H 25	1707	25	F	B	Administrative	298	Non-compliant
79	Tel 160	1715	34	F	B	Administrative	84	Non-compliant used diaphragm for birth control
80	Tel 80 + H 25	1625	48	M	W	Adverse Event	237	Peripheral edema, erythematous rash and pruritis
81	Tel 40	1717	48	F	W	Adverse Event	15	Tremor (preexisting disease)
82	Lis 40	1720	56	F	W	Lack of Efficacy	82	Last BP 148/97
83	Tel 160	1723	74	M	W	Lack of Efficacy	82	Last BP 161/109. Baseline 159/101
84	Lis 40	1724	58	F	W	Lack of Efficacy	84	Last 126/95
85	Tel 160	1726	72	M	W	Lack of Efficacy	83	Last 181/103
86	Tel 80 + H12.5	1732	55	F	W	Administrative	181	Potential interaction between study and anti-anxiety drugs
87	Tel 160 + H 25	1733	58	M	W	Lack of Efficacy	170	Last BP 173/99; penultimate 161/91
88	Tel 40	1735	50	M	W	Other	28	Moving
89	Tel 160	1737	61	M	B	Lack of Efficacy	85	Last 153/119. Baseline 159/107
90	Tel 40	1738	31	M	W	Other	104	Due to internship schedule
91	Lis 10	1739	57	F	O	Adverse Event	13	Headache, dizziness and anxiety
92	Tel 40	1740	35	M	W	Administrative	83	Lost to follow-up
93	Tel 160	1745	73	M	W	Lack of Efficacy	84	Last BP 155/95
94	Tel 160 + H 25	1754	56	M	W	Lack of Efficacy	380	Last visit 161/101. Penultimate 166/96
95	Tel 160	1755	67	M	B	Adverse Event	62	Hyperuricemia, increased BUN and non-protein nitrogen
96	Tel 160	1756	44	F	B	Lack of Efficacy	85	Last BP 170/99
97	Tel 160 + H25	1757	44	M	B	Lack of Efficacy	140	Last BP 149/97. Penultimate 148/94
98	Lis 10	1758	60	F	W	Adverse Event	326	Fatigue, paresthesia, increased CPK, hyperkalemia and myalgia
99	Lis 20	1759	43	M	W	Administrative	29	Withdrew consent- did not like time commitment
100	Tel 40	1760	44	F	B	Administrative	354	Non-compliance
101	Lis 40	1762	59	M	W	Lack of Efficacy	84	Last BP 180/105
102	Lis 40	1843	50	M	W	Lack of Efficacy	84	Last BP 167/111
103	Tel 160	1844	37	M	W	Lack of Efficacy	84	Last BP 133/101
104	Tel 80	1845	36	F	W	Administrative	308	Withdrew consent, study closing early
105	Lis 40	1630	48	M	W	Lack of Efficacy	84	Last BP 151/106. Baseline 151/1113
106	Tel 40	1631	48	M	W	Other	181	Moving
107	Tel 80 + H 12.5	1765	52	M	O	Adverse Event	322	Impotence, coughing diarrhea, micturition disorder and nocturia
108	Lis 40 + H 25	1766	49	M	O	Lack of Efficacy	306	Last BP 139/95. Penultimate 139/95
109	Tel 40	1768	57	M	W	Adverse Event	13	Worsening of headache
110	Lis 40 + H 25	1769	59	F	O	Administrative	154	Entered maintenance phase
111	Lis 40 + H 25	1774	71	M	W	Lack of Efficacy	142	Last 152/10. Penultimate 143/99
112	Tel 160 + H 25	1775	35	M	B	Lack of Efficacy	239	Last BP 142/99. Penultimate 151/106
113	Tel 160	1778	56	F	W	Lack of Efficacy	83	Last 175/112. Baseline 179/107
114	Tel 160	1783	53	M	B	Lack of Efficacy	84	Last 159/100
115	Tel 40 + H 12.5	1786	63	F	B	Adverse Event	196	Unexpected worsening of disease
116	Tel 40	1847	70	M	W	Administrative	282	Lost to follow up

117	Lis 40	1848	67	M	W	Lack of Efficacy	84	Last BP 152/99
118	Lis 10	1977	5	F	W	Adverse Event	235	Abdominal pain
119	Lis 20	1789	51	M	W	Other	57	Inability to attend clinic- new job
120	Tel 40	1790	59	M	W	Adverse Event	6	Worsening of headache
121	Lis 10	1792	53	M	W	Administrative	11	Didn't think he needed medications
122	Tel 160	1794	40	M	B	Lack of Efficacy	84	Last 166/109. Baseline 139/102
123	Tel 160	1795	64	M	W	Lack of Efficacy	84	Last 161/104
124	Tel 160	1802	56	F	W	Other	117	Refusal to come for visits
125	Lis 40	1803	73	M	W	Lack of Efficacy	84	Last 134/100
126	Lis 20	1813	80	M	W	Adverse Event	176	Chest pain
127	Tel 40	1815	40	F	B	Administrative	26	Withdrew consent
128	Tel 160 + H 12.5	1817	76	M	W	Adverse Event	204	Neoplasm malignant
129	Lis 40	1818	56	F	W	Lack of Efficacy	84	Last 148/95
130	Tel 160 + H 12.5	1819	44	M	W	Adverse Event	130	Dizziness and diarrhea
131	Lis 40	1820	56	M	W	Lack of Efficacy	85	Last 147/93
132	Lis 40 + H 12.5	1822	47	M	W	Adverse Event	324	Dizziness, syncope and hypotension
133	Tel 160	1823	38	M	W	Lack of Efficacy	85	Last 155/103
134	Tel 160 + H 12.5	1824	61	M	W	Adverse Event	253	Ventricular arrhythmia
135	Tel 160	2086	76	F	W	Adverse Event	11	Asthenia, fatigue dizziness, headache and abnormal vision
136	Lis 10 + H 25	1825	40	F	B	Lack of Efficacy	322	at Visit 133/95. Penultimate 136/90
137	Tel 160	1826	40	F	B	Lack of Efficacy	83	Last 151/110. Baseline 150/105
138	Tel 40	1827	77	M	W	Adverse Event	11	Colon carcinoma
139	Tel 160	1829	68	F	O	Lack of Efficacy	84	Last 163/100. Baseline 160/99
140	Tel 160	1830	80	M	W	Lack of Efficacy	83	Last 178/103 .Baseline 174/107
141	Tel 40	1831	49	M	W	Adverse Event	49	Impotence
142	Lis 40	1832	36	F	B	Lack of Efficacy	84	Last 145/100. Baseline 139/103
143	Lis 20	1980	54	F	O	Lack of Efficacy	84	Last 155/97
144	Tel 160	2096	41	F	O	Other	23	Wrong medication dispensed
145	Tel 40	2097	46	F	W	Adverse Event	23	Rash
146	Tel 160	1837	40	M	B	Lack of Efficacy	86	Last 147/100
147	Tel 160	1838	29	M	W	Administrative	126	Did not keep appointments
148	Lis 40	1839	58	M	W	Lack of Efficacy	84	Last 151/100. Baseline 140/00
149	Tel 80 + H 25	1841	63	M	W	Administrative	266	Elevated glucose
150	Lis 40	1852	65	M	W	Lack of Efficacy	84	Last 160/109. Baseline 183/111
151	Tel 160	1853	52	F	B	Lack of Efficacy	87	Last 177/104. Baseline 180/109
152	Tel 160	1854	49	F	B	Lack of Efficacy	85	Last 150/101. Baseline 157/109
153	Tel 40	1855	42	M	W	Other	58	Left area
154	Lis 40	1856	44	F	B	Lack of Efficacy	84	Last 165/95
155	Tel 160	1534	54	M	W	Lack of Efficacy	83	Last 160/109. Baseline 167/105
156	Tel 160	1535	46	M	W	Lack of Efficacy	84	Last 147/99
157	Tel 40	1862	46	F	W	Administrative	14	Non-compliant with birth control
158	Tel 160	1863	75	F	W	Lack of Efficacy	84	Last 159/110. Baseline 200/109
159	Lis 10	1869	68	M	W	Adverse Event	68	Cellulitis and lymphadenopathy
160	Lis 40	1944	70	M	W	Lack of Efficacy	77	Last 142/99. Baseline 157/107
161	Tel 40 + H 25	1873	62	F	W	Adverse Event	130	Diabetes mellitus
162	Lis 10	1880	43	F	W	Adverse Event	27	Breast carcinoma
163	Lis 10	1883	44	F	B	Adverse Event	14	Headache
164	Tel 40	1884	48	F	B	Adverse Event	3	Malaise, dizziness, headache, diarrhea, dyspepsia, nausea and abnormal vision
165	Lis 40 + H 12.5	1885	70	M	W	Lack of Efficacy	112	Last visit end of titration was 169/95
166	Tel 160	1886	63	M	W	Lack of Efficacy	98	Last 159/91
167	Tel 160	1889	49	M	O	Lack of Efficacy	80	Last 143/104. Baseline 141/109
168	Tel 40	1892	52	M	W	Adverse Event	28	Worsening of SGOT and SGPT(pre-existing)

169	Lis 40 + H 12.5	1896	54	M	O	Other	389	Error in scheduling
170	Tel 40	2044	62	F	W	Administrative	26	Non-compliance
171	Tel 40	2046	55	M	W	Administrative	7	Used hyperglycemic medications at baseline
172	Lis 10 + H 12.5	2047	61	M	W	Adverse Event	112	Worsening of peripheral edema (pre-existing)
173	Tel 160	2049	70	M	W	Lack of Efficacy	96	Last 213/110. Baseline 197/95
174	Lis 20	2050	48	W	M	Other	360	Error in scheduling
175	Tel 40	2051	49	W	M	Other	322	Error in scheduling
176	Tel 160	1860	58	M	W	Lack of Efficacy	84	Last 168/101. Baseline 157/96
177	Tel 160 + H 25	1897	40	M	W	Lack of Efficacy	252	Last 135/92; Penultimate 136/93
178	Tel 160	1898	66	M	W	Lack of Efficacy	84	Last 169/101. Baseline 190/104
179	Lis 40	1899	72	M	W	Lack of Efficacy	84	Last 158/101. Baseline 166/101
180	Lis 40	1902	49	M	W	Lack of Efficacy	82	Last 145/96. Baseline 154/99
181	Lis 10	1903	58	F	W	Adverse Event	28	Worsening of cardiac failure (pre-existing)
182	Lis 40	1906	45	M	W	Adverse Event	83	Fatigue and somnolence
183	Tel 160	1907	45	M	W	Lack of Efficacy	84	Last 131/93
184	Tel 160	1910	47	M	B	Lack of Efficacy	83	Last 169/103. Baseline 179/105
185	Tel 160	1911	77	M	B	Lack of Efficacy	84	Last 190/103
186	Tel 160	1914	68	M	B	Lack of Efficacy	90	Last 188/111. Baseline 169/104
187	Lis 10 + H 12.5	1915	41	M	B	Adverse Event	90	Coughing
188	Tel 40 + H 25	1917	56	M	B	Other	221	Moving out of the country
189	Tel 160	1918	47	M	B	Lack of Efficacy	84	Last 163/110. Baseline 142/99
190	Lis40	1919	68	M	B	Lack of Efficacy	85	Last 197/108. Baseline 201/105
191	Tel 160	1930	63	M	B	Lack of Efficacy	90	Last 167/99
192	Tel 160	2098	58	M	B	Lack of Efficacy	84	last 150/102. Baseline 159/105
193	Lis 20	2100	58	M	W	Adverse Event	46	Coughing
194	Tel 40	1923	55	M	W	Adverse Event	36	Neurosis
195	Tel 40	1950	59	F	W	Administrative	19	Withdrew consent
196	Tel 40	1952	52	F	W	Adverse Event	49	Pain
197	Tel 160	1953	57	F	W	Administrative	84	Non-compliant with visits
198	Tel 160	1954	51	F	H	Lack of Efficacy	84	Last 177/97
199	Lis 20	1955	58	M	O	Adverse Event	55	Chest pain
200	Tel 160	1956	44	M	O	Other	80	Moving out of state
201	Tel 40	2062	31	M	W	Administrative	7	Discontinued medication on own
202	Tel 160 + H 25	2063	53	M	W	Other	170	Unable to dispense medication
203	Tel 40	1981	44	M	W	Administrative	20	Withdrew consent
204	Tel 40	1983	48	M	W	Administrative	2	Withdrew consent
205	Tel 80 + H 25	1985	55	M	O	Other	145	Site error; no drug received
206	Tel 160 + H 12.5	1988	47	M	W	Adverse Event	151	Chest pain
207	Tel 160	1989	63	F	O	Lack of Efficacy	77	Last 167/95
208	Lis 10	1990	47	M	W	adverse Event	101	Headache and coughing
209	Tel 40	2003	60	M	W	adverse Event	68	Angina pectoris
210	Tel 160	2010	51	M	W	Lack of Efficacy	83	Last 63/110. Baseline 153/103
211	Tel 40	2018	53	M	B	Adverse Event	12	Cardiac arrest
212	Lis 20	2020	45	M	B	Adverse Event	47	Coughing
213	Tel 160	2023	58	F	W	Lack of Efficacy	112	Last 165/99 (end of titration)
214	Tel 160	2025	52	F	B	Lack of Efficacy	66	End of titration 81/100. Baseline 209/113
215	Lis 40 + H 12.5	2027	61	F	W	Adverse Event	95	Hyponatremia
216	Tel 160 + H 12.5	2067	42	M	W	Adverse Event	123	Headache, abnormal vision, dizziness and fatigue
217	Tel 160 + H 25	2030	67	M	W	Lack of Efficacy	209	Last 167/96. Penultimate 151/92
218	Tel 160 + H 25	2031	54	F	W	Lack of Efficacy	168	Last 130/90. Penultimate 136/93
219	Tel 160	2032	64	M	W	Other	63	Moving
220	Tel 40 + H 12.5	2033	48	M	W	Other	84	Error in study drug accountability

221	Tel 160	2038	72	F	W	Lack of Efficacy	84	Last 167/100. Baseline 169/104
222	Lis 10	2039	44	F	W	Administrative	28	Did not show for visit
223	Tel 160	2040	47	F	B	Lack of Efficacy	84	Last 154/102. Baseline 140/99
224	Lis 20 + H 12.5	2068	74	F	W	Adverse Event	343	Coughing and bronchitis
225	Tel 160	2070	41	M	W	Other	353	Protocol deviation; not started on diuretics
226	Lis 20	2071	47	F	W	Adverse Event	56	Coughing

Serious/Severe Adverse Events;

The incidence of serious adverse events that occurred during the double-blind period was 20/385 (5.2%) in the telmisartan and 10/193 (5.2%) in the lisinopril group. Seven of the 20 (35%) subjects with serious adverse events in the telmisartan group were taking combination product, closely proportional to the duration of exposure.

Table 8.6 Serious adverse events for Telmisartan ± HCTZ

	Dose	Center- Pt Number	Demographics	Exposure (days)	Reason	Action /Outcome
1	Tel 40	2-1936	M/75	71-74	Abdominal Pain, Fever, Cholecystitis	Disc/Nrec
2	Tel 40	4-1544	M/61	260	Prostatic Disorder	Cont/Rec
3	Tel 40	15-1673	M/46	7	Atrial Fibrillation	Disc/Rec
4	Tel 40	17-1700	M/71	5	Arthritis	Disc/Nrec
5	Tel 40	17-1701	M/79	274-288	Diverticulitis, Ileus, Sepsis. Urinary Retention	
6	Tel 40	35-1914	M/68	12	Chest Pain	Cont/Rec
7	Tel 40	38-1952	F/52	41	Pain	Disc/Seq
8	Tel 40	42-1998	M/65	25	Basal Cell Carcinoma	Cont/Rec
9	Tel 40	44-2018	M/53	13	Cardiac Arrest	Fatal
10	Tel 40	42-2003	M/60	62	Angina Pectoris	Disc/Rec
11	Tel 40 + HCTZ 12.5	14-1661	M/57	252	Arthritis Aggravated	Cont/Rec
12	Tel 40 + HCTZ 12.5	26-1661	M/59	158	Arthritis Aggravated	Cont/Rec
13	Tel 80	12-2060	M/46	51	Chest Pain	Disc/Rec
14	Tel 80	19-1625	M/48	50	Basal cell Carcinoma	Cont/Rec
15	Tel 80 + HCTZ 25	16-1684	M/65	211	Atrial Fibrillation	Disc/Rec
16	Tel 80 + HCTZ 25	35-1916	M/62	58	Prostatic Disorder	Cont/Rec
17	Tel 160	23-1775	M/35	72	Chest Pain	Cont/Rec
18	Tel 160 + HCTZ 12.5	18-1706	M/62	258	Myocardial Infarction	Disc /Rec
19	Tel 160 + HCTZ 12.5	19-1721	F/51	288	Dehydration Gastroenteritis	Cont/Rec
20	Tel 160 + HCTZ 12.5	27-1817	M/76	157	Neoplasm Malignant	Disc/Nrec
Lisinopril						
1	Lis 10	31-1869	M/68	69	Cellulits/Lymphadenopathy	Disc/Red
2	Lis 10	21-1751	F/55	33	Gallbladder Disorder	Cont/Rec
3	Lis 10	43-2009	M/51	55	Back Pain	Cont/Rec
4	Liss 10 + HCTZ 12.5	28-1828	F/55	85	Abdominal Enlargement	Cont/Rec
5	Lis 10 + HCTZ 12.5?	16-1690	M/59	166	Confusion	Cont/Re
6	Lis 20	17-1693	M/69	57	Atrial Fibrillation, Dyspnea, Supraventricular Tachycardia	Disc/Rec
7	Lis 20	27-1813	M/80	169	Chest Pain Cerebrovascular Disorder	Cont/Rec
8	Lis 40 + HCTZ 12.5	6-1561	M/62	200	Cholecystitis	Cont/Rec
9	Lis 40 + HCTZ 12.5	39-1958	F/49	108	Pain	Cont/Rec
10	Lis 40 + HCTZ 25	3-1531	M/45	168	Basal Cell Carcinoma	Cont/Rec

Rec=recovered; Nrec = Not recovered

Overall Adverse Events:

The number of subjects with individual adverse events that occurred in the telmisartan and lisinopril regimens were summarize in sponsor's table 10.2.3:1. The table (not reproduced here) does not differentiate among those who were taking concurrent hydrochlorothiazide. As such, the table does not address potential safety concerns upon adding hydrochlorothiazide to telmisartan. Overall adverse events in the telmisartan group and lisinopril group were similar (80.5 and 83.4% respectively). Coughing was

increased in the lisinopril regime versus telmisartan group (14.0 versus 7.5%). No other adverse event appeared to substantially differ between the two groups.

Adverse events of Orthostasis or Dizziness:

Vital sign measurements were made at trough, consequently, the maximal effect of drug on vital signs may (peak) may not be adequately captured. Orthostatic events are shown in Table 8.7. There were two patients who discontinued the study due to orthostatis or syncope.

The sponsor tabulates a total of 25 patients who had orthostatis/postural events listed s adverse events. The sponsor also tabulates the 46 patients who had dizziness listed as a component of the adverse events. The proportion of such events is relatively consistent with the randomization rate of telmisartan and lisinopril and not inconsistent with the duration of exposure to combination telmisartan and hydrochlorothiazide.

Table 8.7 (Adapted from Sponsor's Table 10: 4.1:1) Orthostatic symptoms study 502.214

	Telmisartan (n=385)	Lisinopril (n=193)		Telmisartan (n=385)	Lisinopril (n=193)
Orthostatis/Postural	16 (4.2%)	9 (4.7%)	Dizziness	31 (8.1%)	15 (7.8%)
HCTZ Used	7	5	HCTZ Used	12	6
Moderate Intensity	1	3	Moderate Intensity	13	3
Permanently Discontinued	3	1	Permanently Discontinued	5	2

Among the patients enrolled three telmisartan patients discontinued due to dizziness and 5 patients discontinued due to Dizziness. Four of the telmisartan discontinuations (# 1819, #1669, #1691 and # 2067) were taking concurrent HCTZ with telmisartan.

#1819- complained of lightheadedness
1669- Symptoms began day after HCTZ was added
#1691-BP too low (98/76-standing) secondary to HCTZ.
2067- Complained of dizziness.

The sponsor also tabulated those patients who vital sign changes upon standing satisfied their criteria for orthostatis. For this table the definition of orthostasis required a greater than 10 mm drop in either systolic or diastolic blood pressure upon standing relative to the same changes at baseline. For heart rate the criteria required an increase in 10 BPM from the greatest value observed during the run-in period. The number of such Patients is shown in Table 8.8. The sponsor did not separate those with these orthostatic events based on the concurrent use of diuretics.

Table 8.8 Orthostatic by vital sign measurements (Table 10.4.1:2). Study 502.214

	Telmisartan (n=381)	Lisinopril (n=192)
Diastolic Blood Pressure	13 (3.4%)	3 (1.6%)
Systolic Blood Pressure	37 (9.7%)	20 (10.4%)
Heart Rate	5 (1.3%)	1 (0.3%)

The sponsor did not further classify these subjects with respect to the concurrent use of diuretics.

Laboratory:

The sponsor's criteria for flagging laboratory values as "marked" were rather generous. These criteria for defining a laboratory value as a "marked" change and the number per each randomized group is shown in Table 8.9.

Table 8.9 Criteria for defining a laboratory as marked and number of those treated with marked laboratory changes.

Laboratory Parameter	Marked Change Criterion	Telmisartan (n and % 379)	Lisinopril (n% 0f 188)
BUN	+ 11.2 mg/dl	9 (2%)	6 (3%)
Creatinine	+ 0.5 mg/dl	2 (<1%0	3 (2%)
Creatinine P-Kinase	+ 300 IU/l	13 (3%)	6 (3%)
Total Protein	+ 1.4 g/dl	6 (2%)	0
Potassium	± 1.4 meq/dl	inc= 2 (< 1%); dec =0	inc = 3 (2%); dec =0
Sodium	-10 meq/l	1 (< 1%)	3 (2%)
Glucose	+ 60 mg/dl	9 (2%)	1 (<1%)
Hematocrit	- 9%	4 (1%)	0
Hemoglobin	-2 gm/dl	5 (1%)	2 (1%)
Platelet count	-134,000	1 (<1%)	0
Cholesterol	+ 90 mg/dl	5 (1%)	1 (<1%)
LDL	+ 77 mg/dl	1 (< 1%)	2 (1%)
Triglycerides	+ 80 mg/dl	106 (28%)	45 (24%)
ALT	+ 35 IU/l	8 (2%)	3 (2%)
AST	+ 35 IU/l	2 (< 1%)	2 (1%)

There were 32 patients in the telmisartan (8.3%) and 14 patients in the lisinopril groups (7.3%) whose treatment emergent laboratory abnormality was classified as an adverse event. The sponsor lists patients (table 10.3.2.2:1).

Table 8.10 Laboratory events labeled as adverse events study 502.214

Parameter	Telmisartan	Lisinopril	Parameter	Telmisartan	Lisinopril
Elevated BUN	1755*		Elevated WBC count	1934	
Elevated Creatinine	1701,1755*		Low WBC count	1934	
Elevated CPK		1758*	Diabetes	1672, 1615	2061
Low Potassium	**1564, 1742, 1905,1943**, 1989	1805	Elevated Cholesterol	1750	1671, 1896
Elevated Potassium		1758*	Elevated triglycerdes	1617, 1763, 1985	1641, 1896
Low Sodium		1650,	Gout	1961, 1967, 1988	1963
Low Calcium		1855	Elevated ALT	1545, 1846, 2010, 2022	
Elevated Uric Acid	**1657, 1684, 1689**, 1755*, **1985**	1944, 1994	Elevated AST	1545, 2010, 2022	
Elevated Glucose	1593, **1873***, 2035, 2046	1875	Proteinuria	1525	
			Hematuria	1541, 1698	1944

* Discontiued; **Bold are on concurrent HCTZ + Telmisartan**

There did not appear to be any surprises. The nature of the abnormalities was mild.

ECGs: 12-lead ECGs were scheduled at screening visit, at the end of the placebo run-in period at the end of the titration period and after 12, 24 nd 36 weeks of maintenance as well as at the end of the study. There were seven patients on telmisartan and 5 patients on lisinopril who had changes in ECG. Of the telmisartan patients, four were taking concurrent diuretics.

Patient # 1502- a 54 y/o male discontinued for symptomatic atrial fibrillation (telmisartan 160 + HCTZ 25).

Patient # 1684- a 65 year old male discontinued for atrial fibrillation (telmisartan 80 mg HCTZ 25 mg)

Patient # 1824- 61 year old male discontinued for premature ventricular contractions (bigeminy and trigeminy;160 mg + HCTZ 12.5)
Patient # 1897- Sinus bradycardia with occasional premature atrial contractions (telmisartan 160 + HCTZ 25 mg).

Kinetics- The sponsor collected trough serum concentrations of telmisartan at baseline, at each titration period and at week 18 and 30 and at end of study. There were a total of 693 values for telmisartan levels during the course of the study. The sponsor tabulates the data without an analysis of patient related changes. The data is tabulated below. The coefficients of variation are sufficiently large that it is difficult to determine whether the concurrent use of HCTZ alters the concentration of telmisartan.

Table 8.11 kinetics of telmisartan study 502.214

Telmisartan↓ HCTZ→		0	12.5	25
40	Mean ± SD	60.4 ± 67.6	56.4 ± 52	34.12 ± 32
	N=	191	85	37
	Geometric mean	40.2	36.5	24.0
80	Mean ± SD	73.0 ± 65	112.7 ± 203	83.37 ± 71
	N=	85	51	16
	Geometric mean	54	71	77
160	Mean ± SD	131.9 ± 96	207 ± 323	137.7 ± 155
	N=	53	81	94
	Geometric means	97	133	93

Summary: This was a rather large and long-term study comparing telmisartan to lisinopril. Patients who were not well controlled on either telmisartan or lisinopril could have hydrochlorothiazide added. Since those who received hydrochlorothiazide did not represent a randomized population, no efficacy conclusions can be drawn either about adding hydrochlorothiazide to telmisartan or comparing telmisartan plus hydrochlorothiazide to lisinopril plus hydrochlorothiazide.

Blacks were apparently did not do particularly well on telmisartan. Among the 35 black subjects who were randomized to telmisartan 21 discontinued due to inefficacy.

There were no major safety issues.

Study # 9
#502.238; vol 108

Title of Study: Open-Label Comparison of the Antihypertensive Efficacy and Safety of telmisartan vs Enalapril in Patients with Severe hypertension.

Study Summary. This study was reviewed y Dr. Khin Maung U in conjunction with the review of telmisartan monotherapy. The study does not add additional information with respect to the combination product. The only useful information is some safety data on the concurrent administration of telmisartan with hydrochlorothiazide.

This study was an open-label positive controlled study in patients with severe hypertension as defined by a supine diastolic blood pressure of ≤ 115 to ≤ 130 mm Hg. Patients were excluded for the following reasons: potential for pregnancy, cardiovascular disease (e.g. NYHA Class III or IV, recent MI, PTCA, obstructive cardiac or valvular disease, arrhythmias including sustained VT, unstable angina), electrolyte abnormalities (Na+ < 130 meq/l; K+ < 3.0 meq/l; K+ > 6.0 meq/ml); poorly controlled diabetes, hypertension at risk (DBP > 130 mm Hg or SBP > 200 mm Hg) secondary reasons for hypertension, hepatic or renal disease, use of certain proscribed medications.

Patients were withdrawn from present therapy from between one and 14 days. Those who satisfy the study criteria were randomized in a 2: 1 ratio to receive either telmisartan at a dose of 80 mg daily or a dose of enalapril at 20 mg once daily, as open label therapy. If after one week of treatment the supine diastolic blood pressure was not < 115 mm Hg, the dose would be doubled to either 160 mg daily of telmisartan or 40 mg daily of enalapril. After one additional week, if the supine diastolic blood pressure is > 90 mm Hg, those on the initial dose would be increased to either 160 mg telmisartan or 80 mg enalapril. At this point, the dose of the initial drug i.e. telmisartan or enalapril becomes fixed. After an additional week of treatment, if the patient's blood pressure is ≥ 90 mm Hg hydrochlorothiazide at a dose of 25 mg daily was added. If after a further week, blood pressure was > 90 mm Hg those not already receiving hydrochlorothiazide received 25 mg hydrochlorothiazide daily. For those already on hydrochlorothiazide, amlodipine at 5 mg daily was added.

Following this titration period, patients were maintained at the titrated dose for two visits, at two-week intervals (4 weeks). If there was loss of control, however, hydrochlorothiazide, if not already on hydrochlorothiazide, was added. If already on hydrochlorothiazide, amlodipine at 5 mg daily was added. Patients could therefore, be on combination of telmisartan and hydrochlorothiazide for a maximum of 4 weeks.

A total of 86 patients were randomized, 58 to telmisartan and 28 to enalapril. The outcome of the Patients are shown below:

Table 9.1 Disposition of Patients study 502.238

Disposition	Telmisartan	Enalapril	Total
Randomized	58	28	86
Completed	49	24	73
Discontinued	9	4	13
Adverse Event	4	3	7
Lack of Efficacy	2	0	2
Non-Compliant	2	1	3
Lost to Follow-up	1	0	1

Key Demographics for those enrolled are shown in Table 9.2

Table 9.2 Demographics of study 502.238

Demographic	Telmisartan	Enalapril
Gender (Male/Female)	47/11	18/10
Age (mean ± SD)	51.1 ± 8.7	50.5 ± 9.1
Race (White/Black/Other)	36/16/6	18/8/2
Supine Vital Signs Systolic (± SD)/Diastolic (± SD) Heart Rate (± SD)	 172.9 (± 14.7)/117.1 (± 3.5) 73.8 (± 11.9)	 169.9 (± 14.0)/117.0 (± 2.0) 68.9 (± 11.5)
Standing Vital Signs Systolic (± SD)/Diastolic (± SD) Heart Rate (± SD)	 167.4 (± 15.5)/115.6 (± 5.6) 77.4 (± 11.4)	 167.5 (± 13.4)/117.6 (± 5.5) 73.1 (± 11.8)

Safety:

Exposure: The duration of exposure is shown in Table 9.3

Table 9.3 Exposure of patients to Different Doses

Treatment	N	Days Mean (SD) ; Range	Treatment	N	Days, Mean (SD); Range
Telmisartan 80	58	14.0 (9.0); 3-56	Enalapril 20	28	12.9 (3.0); 7-18
Telmisartan 160	53	15.5 (8.4); 1-44	Enalapril 40	28	15.1 (5.1) ;7-33
Telmisartan 80 + HCTZ25	1	28.0 (NA); 28	Enalapril 40 + HCTZ 25	27	16.0 (7.1); 4-29
Telmisartan 160 + HCTZ 25	46	18.0 (5.8); 12-33	Enalapril 40 + HCTZ 25 + Amlodipine 5	19	13.3 (4.0); 3-21
Telmisartan 160 + HCTZ 25 + Amlodipine 5	30	13.4 (2.7); 7-21			

The duration of exposure to concurrent telmisartan and hydrochlorothiazide with or without amlodipine was 5.15 patient-years. The duration of exposure to telmisartan monotherapy was 4.47 patient*years.

Deaths/Dropouts/Discontinuations:

There were no deaths during the study.

There were seven dropouts in the study; four in the telmisartan group and 3 in the enalapril group. Two of those who discontinued were on concomitant telmisartan and hydrochlorothiazide (and amlodipine). Patient (#8002) was a 50-year old white male who developed diarrhea when started on amlodipine. A second patient (# 8012) developed mild orthostatic hypotension while on telmisartan 160 mg + HCTZ 25 mg (supine BP 120/82- standing 99/74). Hydrochlorothiazide was discontinued, and the patient was back-titrated to telmisartan 160 monotherapy. The symptoms persisted and the patient discontinued after an additional 3 days.

None of the telmisartan patients had a serious adverse event. One enalapril-treated patient (a 58 year old black male treated for 32 days developed angioedema, without respiratory compromise. He was treated with antihistamines, steroids and pseudoephedrine, and recovered.

Other Adverse events: The most common adverse event was headache, reported among 11 telmisartan monotherapy and 3 telmisartan/hydrochlorothiazide with or without amlodipine.

Dizziness /Hypotension: There were two episodes of hypotension and 1 episode of dizziness among those who received telmisartan monotherapy. Among those who received telmisartan with hydrochlorothiazide with or without amlodipine, there were 4 episodes of dizziness or hypotension. Per sponsor, there were

only two patients who sustained orthostatic changes. One patient was taking telmisartan + HCTZ. The other patient was taking telmisartan + HCTZ + Amlodipine. The first patient # 8029 had a blood pressure drop from 130/90 to 94/68 (heart rate not reported) and complained about dizziness. The second patient # 8087 had a drop of 25-mm Hg in systolic blood pressure upon standing.

Chest Pain/cardiac ischemia: There were four patients in the telmisartan arm who developed chest pain or cardiac ischemia. One of these patients was on concurrent diuretic with telmisartan; the other was on telmisartan + HCTZ + amlodipine. The last patient eventually had angiography and angioplasty.

Arrhythmias: Four telmisartan patients had arrhythmias noted as an adverse event. Only one of these patients was on concurrent hydrochlorothiazide at the time of the arrhythmia. This patient had an abnormal heart rate on auscultation with no concurrent ECGs.

Laboratory:

According to the sponsor there were five patients who had an abnormal laboratory value of sufficient severity to qualify as an adverse event. One patient (#8076-randomized to enalapril) discontinued due to non-compliance with drug. The patient had hematuria at baseline that persisted during the 32 days the subject was in the study. Of the four other patients with laboratory measurements classified as adverse events, only one was on concomitant telmisartan and hydrochlorothiazide. This patient (# 8016) was a known diabetic who apparently stopped the oral hypoglycemic. His glucose increased from 166 at baseline to 386 at the end of titration.

Conclusion: This study adds little to defining the safety or efficacy of the combination product of telmisartan + Hydrochlorothiazide.

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