CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 21-162

MEDICAL REVIEW(S)

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Executive Summary:

This reviewer recommends the approval of the fixed combination of telmisartan/hydrochlorothiazide at doses of 40-mg telmisartan/12.5 mg hydrochlorothiazide and 80-mg telmisartan/12.5 mg hydrochlorothiazide. The telmisartan/hydrochlorothiazide product are one of several AT_1 blockers/diuretic combinations that have either already been approved or have been submitted for review. As such, there are few surprises within this submission. The combination product should only be considered as a product of convenience, and not as initial therapy.

Although, a total of 11 studies were also submitted either with the NDA or as an amendment to the NDA, this recommendation for approval rests almost entirely on the results of study # 502.204. These other studies with the exception of study 502.261 (see below), add little to establishing efficacy of the combination product for the treatment of hypertension. Patients who were treated in these studies received the combination of telmisartan and hydrochlorothiazide as stepped care when either telmisartan monotherapy or, for a few patients, when hydrochlorothiazide at 12.5 mg did not adequately control blood pressure. These studies, therefore, add little information with regards to the efficacy of the combination product, however, these studies support safety on the concurrent use of telmisartan with hydrochlorothiazide.

Study 502.204 was a large (n= 818) placebo-controlled, randomized, factorial design study of eight weeks duration. The study compared the effects of placebo to those of doses of telmisartan at 20, 40, 80 and 160 mg once daily as monotherapy or hydrochlorothiazide at doses of 6.25, 12.5 to 25 mg once daily as monotherapy or the factorial combinations of telmisartan/hydrochlorothiazide after eight weeks of treatment. Six of the cells in the factorial study were considered as pivotal for establishing efficacy (placebo, Telmisartan 40 and 80 mg monotherapy as well as hydrochlorothiazide 12.5 mg monotherapy and the combinations of telmisartan 40/hydrochlorothiazide 12.5 and telmisartan 80/hydrochlorothiazide 12.5).

The combination product T80/H12.5 was superior to the individual components at a $p<0.01$ for both trough supine and standing systolic and diastolic pressures. The combination product T40/H12.5 was superior to the individual components for standing and supine trough systolic blood pressure, as well as standing trough diastolic blood pressure. The T40/H12.5 combination, however, was superior to the HCTZ 12.5 mg monotherapy for supine diastolic blood pressure, but was only marginally superior to telmisartan monotherapy ($p=0.08$) (the pivotal measurement for this study). The superiority of the T80/H12.5 mg dose over its components is sufficient by itself to establish the efficacy of the combination product.

Although the overall effect of combination therapy was significant for the primary end-point of the study (trough supine diastolic blood pressure), the effects in blacks largely drove significance. For black patients, adding hydrochlorothiazide to telmisartan resulted in an additional drop in blood pressure response by 3.3 to 8.9 mm Hg for the 40- and 80- mg telmisartan treatments, respectively. Adding telmisartan at 40 and 80 mg, respectively to hydrochlorothiazide at 12.5 mg resulted in an additional blood pressure response of 4.8 to 8.1 mm Hg when compared to the hydrochlorothiazide 12.5 mg monotherapy.

For Caucasians, however, the addition of hydrochlorothiazide to telmisartan added minimal benefit of (-0.2 to + 1.5 mm Hg). Adding telmisartan to diuretics, however, for Caucasians resulted in a

substantial increase in blood pressure response (5.2 to 8.2 mm Hg). Caucasians apparently received little, if any, benefit in the addition of hydrochlorothiazide to any dose of telmisartan.

This reviewer does not believe that these small changes in Caucasians in study # 502.204 for the primary measurement (supine diastolic blood pressure) reflects anything more than the play of chance. Aside from supine diastolic blood pressure, other measurements of blood pressure responses within this study show a non-zero additive benefit upon adding hydrochlorothiazide to telmisartan monotherapy. Thus for supine systolic blood pressure the effect of adding diuretic to telmisartan in Caucasians produced an additional 3.4 to 6.5 mm Hg decreased in blood pressure.

For the Caucasian population the overall AVE test indicates that at least one of the combination doses is superior to the individual components for both standing diastolic and systolic blood pressures at trough. Peak measurements (3 hours post dose) for both supine and standing, systolic and diastolic blood pressures, also demonstrate measurable benefit, in Caucasians of adding hydrochlorothiazide to telmisartan.

Study 502.261 further supports the contention that hydrochlorothiazide when added to telmisartan, in Caucasians results in an additional blood diastolic blood pressure response when compared to telmisartan monotherapy. This study was carried out in Canada and blacks accounted for only 3% of those enrolled. The results of this study, therefore, reflect the additive benefit in a Caucasian population. Patients who had an insufficient blood pressure response to telmisartan at a dose of 80 mg as monotherapy were randomized to receive either add-on hydrochlorothiazide at a dose of 12.5 mg or placebo. Relative to no hydrochlorothiazide, the addition of diuretic resulted in an additional drop in supine diastolic blood pressure of 3.1 mm Hg ($p< 0.01$). These results support the concept that addition of hydrochlorothiazide to telmisartan affords benefit in decreasing supine diastolic blood pressure in Caucasians.

In summary, study 502.204 by itself supports the approval of the combination product. The combination product is superior to the individual components in the primary end-point of supine diastolic trough blood pressure. Although Caucasians appear to be respond with a lower additive diastolic trough blood pressure response to combination therapy when compared to telmisartan monotherapy than black subjects, the weight of data suggest that even this group receives added blood pressure response during combination therapy.

Safety of telmisartan/hydrochlorothiazide is supported by the safety of the individual components of this combination as well as the results of study 502.204. Additional safety on the use of telmisartan in conjunctior wi.h hydrochlorothiazide is derived from the large cumulative open-label database. A total of 1725 patients were exposed for a mean exposure of 146 days to some dose of telmisartan with some dose of hydrochlorothiaizde. There did not appear to be any unusual adverse events.

This approval recommendation however, is dependent on demonstrating that the pharmacokinetics of the proposed to-be marketed combination product is equivalent to the individual components which were used in the pivotal clinical study # 502.204. Please refer to the biopharmaceutic review for specifics of pharmacokinetics of the combination product.

Materials Reviewed.

The original submission of NDA 21-162 consisted of 161 volumes organized as follows.

Vol 1.01	General Information
Vol 1.02-1.05	Chemistry
Vol 1.06-1.19	Non-clinical Pharmacology and Toxicology Section
Vol 1.20-1.26	Human Pharmacokinetics and Bioavailability Section
Vol 1.27-1.136	Clinical Data Section
Vol 1.137-1.158	Statistical Section
Vol 1.159	Other Electronic Data Submission

In addition the following amendments were submitted and were appropriate were reviewed.

Vol 2.1	Dated 5 May 2000	Packaging Trade Name Issues
Vol 3.1-3.13	Dated 26 April 2000	Updated Safety Information.
Vol 4.1-4.2	Dated 9 May 2000	Bioequivalence Study U00-1275
Vol 5.1-5.10	Dated 15 May 2000	Study #502.261
Amendment # 15	Dated 5 September 2000	Response to Questions
Amendment # 17	Dated 26 September	Response to Questions

Chemistry/Manufacturing Controls. Please refer to the Chemistry Review

Animal Pharmacology/Toxicology:

Dr. G. Jagadeesh, Ph.D. reviewed this portion of the NDA submission. The submission included 26-week oral toxicity studies in rats and 26-week oral toxicity in dogs as well as an oral developmental toxicity study in rats. The key findings on pathological examination during the 26-week toxicology studies included hyperplasia/hypertrophy of the JGA apparatus in both rats and dogs and evidence of gastrointestinal tract ulceration.

Clinical Background.

Telmisartan is an angiotensin II (Type AT-1) receptor blocker. The drug is approved and marketed for use as an anti-hypertensive. The approved labeling class-specific contains a black box warning reflecting the teratogenic potential for use of drugs that block the renin-angiotensin system during middle to late pregnancy.

Hydrochlorothiazide is approved for use in hypertension. Hydrochlorothiazide promotes the secretion of sodium and water primarily by inhibiting their re-absorption in the cortical diluting segment of the distal renal tubule.

The combination product is the subject of this review. Approval of such a product is dependent on demonstrating that the product is superior in blood pressure response than the individual components. The approval therefore rests on the efficacy results of study # 502.204 and less so on the results of study #502.261.

Indication and Usage:

The combination is recommended for the treatment of hypertension as a product of convenience. This product is not intended for initial therapy.

Description of Clinical Data Sources (IND and Non-IND)

Efficacy is predominantly supported by the results of study 502.204, and partially confirmed by study # 502.261. Safety of concurrent administration of telmisartan and hydrochlorothiazide is the result of exposure of 1725 patients in clinical protocols as well as open-labeled studies.

Table of Clinical Trials

	Study ID Report #	Status	Population	Design	Duration of Treatment	Treatment Groups	#	Entered/ completed	Mean Age	%M/ %F	%B/%W/%O
Placebo-Controlled Study											
1	502.294 U97-3070	Comp	mild-mod HBP	Double-Blind, Randomized., PBO – Controlled , factorial Design	8 weeks	T20 T20/H6.25 T20/H12.5 T20/H25 T40 T40/H6.25 T40/H12.5 T40/H25 T80 T80/H6.25 T80/H12.5 T80/H25 T160 T160/H6.25 T160/H12.5 T160/H25 H6.25 H12.5 H25 PBO	23 25 21 25 75 21 70 25 77 20 73 32 33 31 33 32 21 73 24 73	818/749	53	60/40	27/73/0
Long Term Active Controlled Trials-											
1	502.210 U97-0059	Comp	elderly HBP	Double-blind, Double-Dummy, Randomized Parallel group, Titrate Dose	26	T20,40, 80 E5,10,20 HCTZ added if inadequate response	139 139	278/251	71	42/58	0/100/0
2	502.214 U97-3085	Comp	Mild-mod HBP	Double-blind, Double-Dummy, Randomized Parallel group, Titrate Dose	52-60	T40,80, 160 L10,20,40	385 193	578/352	53.5	66/34	18/75/7
3	502.215 U97-0052	Comp	mild-mod HBP	Double-Blind, Randomized, Parallel Group, Titrated Dose	26	T40-T40/H12.5 T80-T80/H12.5 H12.5-H12.5/T80 H12.5-H25	114 121 66 62	363/298	58	53/47	0/100/0
4	502.216 U96-2613	Comp	Mild-Mod HBP	Double-Blind, Double Dummy, Randomized, Parallel group Titrated Dose	26	T 40-80-120 Atenolol 50-100-100 HCTZ PRN as add on	355 178	533/489	57.9	56/64	2/98/0
Special population Studies											
1	502.209 U97-0064	Comp	Severe HBP	Double-Blind, Double Dummy, Randomized, Parallel group Titrated Dose	12	T80-160 E10-20 HCTZ PRN as add on	12/11	23/21	54.3	38/62	0/100/0
2	502.213	Comp	Mild-Mod	Double-Blind,	8	T80	15	30/27	54	60/40	33/63/4

	U97-3064		HBP	Randomized. Parallel Group		T80/H12.5	15				
3	502.213 U97-3210	Comp	Severe HBP	Open-Label Comparison With Enalapril	8	T80-160 E 20-40 HCTZ PRN as add on	58 28	86/73	51	76/24	28/63/9
4	502.261 U00-3112	Comp	Mild-Mod HBP	Double-Blind Randomized Add on HCTZ vs Placebo to T80	8	T40-80 T80/H12.5	245 246	491/475	55	63/37	995/3/2

Post-Marketing Experience: This combination product is not yet marketed.

Literature: There did not appear to be any submitted literature relating to the efficacy and safety of the combination telmisartan/hydrochlorothiazide.

APPEARS THIS WAY
ON ORIGINAL

Clinical Studies

Volumes 1.39 to 1.45
Study # 502.216

Title of Study: Double-blind trial on the long-term efficacy and safety of telmisartan (BIBR 277 SE) 40 to 120 mg once daily compared to atenolol 50 to 100 mg once daily alone and in combination with hydrochlorothiazide 12.5 to 25 mg once daily in patients with mild to moderate hypertension (THERESA).

Dr. Khin Maung U, M.D reviewed this study in conjunction with the review of Telmisartan (NDA-20-850) (p 114-120 of his review). Please refer to Dr. U's review for a complete analysis of the safety and efficacy results and conclusions of the entire study. Comments here are limited to the analysis of the safety of the combination of telmisartan/hydrochlorothiazide.

This study was a 26-week positive controlled study comparing regimens that contained telmisartan to regimens that contained atenolol in patients with mild to moderate hypertension.

After a two to three week placebo run in period, patients were randomized to either low dose telmisartan (40 mg daily) or low dose atenolol (50 mg daily). If at week 4 of treatment, the blood pressure was $\geq$ 95 mm Hg or the fall in blood pressure was $\leq$ 10 mm Hg, the patient was advanced to dose 2 (either 80 mg telmisartan or 100 mg atenolol). If both blood pressure criteria were met, the patient remained on the low dose.

If, at week 8, the diastolic blood pressure was $\leq$ 95 mm Hg and the decrease in diastolic blood pressure was greater than 7 but less than 10 mm Hg, hydrochlorothiazide at 12.5 mg/day was added. If, at week 8, the diastolic blood pressure was > 95 mm Hg or reduced less than 7 mm Hg the dose was increased to 100 mg atenolol (the same as the previous dose) or 120 mg telmisartan daily.

If, at week 16, at an interim visit between week 8 and 16, or at an interim visit between week 16 and 24, diastolic blood pressure was > 90 mm Hg, hydrochlorothiazide at 12.5 mg /day was added. If, however, the patient was already taking hydrochlorothiazide, the dose of hydrochlorothiazide was increased to 25 mg daily. All medications were taken 1 hour prior to breakfast with 120 cc of water.

Based on a description of the design of the study, there was no directly comparable group among those who received the combination of telmisartan and hydrochlorothiazide. The maximum exposure of the combination of hydrochlorothiazide and telmisartan was therefore limited to 16 weeks.

A total of 533 patients were enrolled. Of these patients, 355 were randomized to the telmisartan regimen and 178 to the atenolol regimen. There were a total number of 111 patients exposed to some combination of telmisartan and hydrochlorothiazide.

Table 1.1 Number of Patients who were treated with some dose telmisartan in combination with some dose of hydrochlorothiazide at last visit Study 502.216

Telmisartan → / Hydrochlorothiazide ↓	40 mg	80 mg	120 mg
12.5 mg	21	34	30
25 mg	1	8	17

Among the 111 subjects who received combination products, the mean duration of exposure was 77.7 days. The mean exposure during the entire study, for both those who received combination products and those who received monotherapy, with telmisartan was 182 days.

There were a total of 13 patients who had serious adverse events during the double-blind and post-treatment follow –up, among those who received telmisartan with /without HCTZ. There were a total of 4 patients who had serious adverse events while on combination treatment. The line listings of these 4 patients are shown in Table 1.2.

Table 1.2 Serious Adverse Events While on Combination Telmisartan/HCTZ therapy study 502.216

Treatment	Patients number	Gender	Age	Duration	Event
Telm 80/HCTZ12.5	3259	Female	69	147	Angina Pectoris
Telm 80/HCTZ 12.5	3393	male	68	111	Sepsis
Telm 80/HCTZ 12.5	3603	male	47	125	myocardial infarction
Telm 120/HCTZ 25	3395	male	58	follow-up	Angina pectoris [1]

[1] Patient successfully completed study but was referred for stress testing for chest pain post study.

With respect to laboratory adverse events, two patients who were receiving combination therapy were described as having hypokalemia. The specifics are shown in the Table below (Table 1.3). Although patient # 3533 had a potassium value within the normal region, he had a drop from the previous visit. Two patients who were treated with combination products had elevated uric acid levels.

Table 1.3. Laboratory Abnormalities while on combination HCTZ and Telmisartan Study 502.216

Treatment at end	parameter	Patient #	Value baseline (visit 3)	Week 8 (visit 5)	Week 16 (visit 6)	Week 26 (visit 7)
Telm 80/HCTZ 12.5	K+	3533	4.1	3.9	4.9	4.0*
Telm 80/HCTZ 25	K+	3501	3.9	4.1	3.1*	3.7
Telm 120/HCTZ 25	Uric Acid	3360	9.1	8.7	9.7	11.6*
Telm 120/HCTZ 25	Uric Acid	3414	7.3	7.6	7.7	9.9*
Telm 120/HCTZ 12.5	γGT	3361	43	49	45	136*
	SGPT		1	26	16	30*
	SGOT		9	22	11	13

* Visit for which hypokalemia was defined.

Conclusion: This study overall showed no statistically significant differences in regimens containing telmisartan when compared to a regimen containing atenolol. As part of the step regimen, patients from either group could be treated with a combination that included telmisartan (between 40-120 mg) and hydrochlorothiazide (12.5 or 25 mg). Since there were no concurrent comparable controls during the combination hydrochlorothiazide period, no definitive conclusion can be drawn from this study about the safety or efficacy of the combination telmisartan/hydrochlorothiazide.

Study #2. Volumes 1.46-1.50
Study # 502.215

Title of study: Safety and Efficacy of Long Term Exposure to monotherapy or Combination therapy with Telmisartan. (SELECT Study)

Dr. Khin Maung U, M.D. reviewed this study in conjunction with the review of Telmisartan (NDA-20-850) (p 109-114 of his review). This study was carried out in Great Britain. Please refer to Dr. U's review for a complete analysis of the safety and efficacy results and conclusions of the entire study.

The SELECT study is a positive controlled study in mild to moderate hypertensive patients (supine blood pressure $\geq$ 95 mm Hg and $\leq$ 114 mm Hg). The end-point was the comparison of the response rate after 26-weeks of treatment. After a 2-3 week run-in period, patients were randomized to receive one of four regimens. Each regimen consisted of an initial treatment and an add-on therapy for inadequate blood pressure response. The treatments are as follows:

- Telmisartan 40 mg (if the supine DBP blood pressure was inadequate, 12.5-mg hydrochlorothiazide could be added).
- Telmisartan 80 mg (if the supine DBP blood pressure was inadequate, 12.5-mg hydrochlorothiazide could be added).
- Hydrochlorothiazide 12.5 mg (if the supine DBP blood pressure was inadequate, the dose of HCTZ could be up-titrated to 25 mg)
- Hydrochlorothiazide 12.5 mg (if the supine DBP blood pressure was inadequate, telmisartan at 80 mg could be added).

Patients were asked to take the medication upon arising in the morning, on an empty stomach, approximately 1 hour prior to breakfast.

Patient's blood pressure was measured at weeks 4, 8, 12 and 16 during therapy prior to the pivotal measurement at the end of study at 26 weeks. If at any one visit the supine diastolic blood pressure of < 90-mm Hg was not achieved, additional treatment was added.

The end-point of the study was evaluated by a set of categorical response criteria, either full, partial or minimal/none. These responses were defined as follows (see Table 2.1). For those who prematurely discontinued, the last observation (assuming both baseline and on-therapy measurements were available) was used to calculate efficacy.

Table 2.1 Definition of Responses Study 502.215

Full	Reduction from baseline in mean supine BP diastolic at trough of > 10 mm Hg and/or a trough mean supine diastolic of > 90 mm Hg.
Partial	Reduction from baseline in mean supine diastolic blood pressure at trough of 7 to < 10 mm Hg with a trough mean supine diastolic blood pressure of > 90 mm Hg.
Minimal/None	Reduction from baseline in mean supine diastolic blood pressure at trough f < 7 mm Hg or any increase from baseline in mean supine diastolic blood pressure at trough or discontinuation due to lack of efficacy during the double-blind phase.

Statistical:

The original analysis was to discriminate between a pair of hypothesis.

Hypothesis 1: Adding hydrochlorothiazide to telmisartan does not change the probability of reaching the goal of a diastolic of < 90-mm Hg

Hypothesis 2: The alternative hypothesis is that adding HCTZ to telmisartan does change the probability of reaching the goal blood pressure of < 90-mm Hg.

The sponsor originally planned to analyze the study by a Markov chain model. This model classifies a patient as having one of three outcomes
-The goal DBP reached at interim visit and monotherapy continued with probability p1 (Defined as E1)
-Goal not reached at interim visit and HCTZ added with probability 1-p1
-Goal DBP reached (either on monotherapy or add-on therapy) with probability q1 (Defined as E2)
-Goal DBP not reached the probability is 1-q1. (Defined as E3)
-Dropcuts due to non-response after adding hydrochlorothiazide were counted as non responders (also defined as E3).

For each patient there were three mutually exclusive outcomes. E1, E2 or E3 with probabilities p1, p2 and p3 where p2=(1-p1) *q1 and p1 + p2 +p3=1.
Hypothesis 1 degenerates into the hypothesis p1=p2
Hypothesis 2 degenerates into the hypothesis p1<p2. .

This analysis compares the number of subjects who have achieved goal blood pressure with monotherapy when compared to the patients who overall achieved the goal DBP. (Comment: Unfortunately, the analysis is flawed by the dependence of those who go onto add-on therapy with whether they are considered successes to monotherapy. In effect some of those who respond after add on therapy may be regressors to the mean.).

This analysis was, therefore abandoned and a responder analysis was performed.

There were a total of 363 patients who were randomized. Patients were randomized to the 4 treatments in the study in a ratio of 2:2:1:1 [Telmisartan 40 mg (HCTZ 12.5 mg); Telmisartan 80 mg (HCTZ 12.5 mg); HCTZ 12.5 mg (HCTZ 12.5 mg); HCTZ 12.5 mg (telmisartan 80 mg). the doses in parenthesis represent the stepped dose add-on treatment]. The 365 patients represent the safety database for the study. Of these patients, there were a total of 353 patients who were considered the ITT efficacy group.

Table 2.2 Outcomes of Patients in Study 502.215

	Treatment group (add-on therapy)				
	Telm 40 mg (HCTZ 12.5 mg)	Telm 80 mg (HCTZ 12.5 mg)	HCTZ (12.5 mg) (HCTZ 12.5 mg)	HCTZ 12.5 mg (Telmisartan 80 mg)	Total
Randomized and Treated	114	121	62	66	363
Efficacy	112	117	60	64	353
Monotherapy	37	51	12	20	120
Combination	75	66	48	44	233
Withdrew	18	17	15	15	65
Adverse Events	7	8	7	10	32
Lack of Efficacy	8	5	6	3	22
Protocol Non-Compliance	1	3	0	0	4
Lost to follow up	0	0	1	0	1
Consent withdrawn	0	0	0	1	1
Other	2	1	1	1	5

The demographics of those enrolled into this study are shown below:

Table 2.3 Demographics

	T 40 (+H12.5)	T80 (+ H12.5)	H 12/5 (+ H12.5)	H12.5 (+ T80)
Age (years)	58	58	59	57
number < 65 (%)	80 (70%)	89 (74%)	43(69%)	49 (74%)
number > 65 (%)	34 (30%)	32 (26%)	19 (31%)	17 (26%)
Gender Male/Female (%male)	60/54 (53%)	62/59 (51%)	34/28 (55%)	37/29 (56%)
Duration of Hypertension (years)	2.7	3.3	5.2	4.4
Baseline BP	165.5/103.2	161.9/102.2	162.9/102.1	163.9/102.6
Race	data not collected			

The study did not collect racial data. (Comment: Blacks tend to be less responsive than Caucasians to angiotensin blockers, as such the relevance of this study to defining the response rate to a USA hypertensive population is unclear).

There are many possible comparisons with respect to response rate. I have reproduced the sponsor's analysis as Table 2.4. The nominal p-values are shown in Table 2.5

Table 2.4 –Outcome Measurements study 502.215

Did the Patient meet the Goal Response?		
	yes (%)	No (%)
Telm 40 mg (+ HCTZ 12.5 mg)	75 (67%)	37 (33%)
Telm 80 mg (+ HCTZ 12.5 mg)	81 (69%)	36 (31%)
HCTZ 12.5 mg (+ HCTZ 12.5 mg)	32 (53%)	28 (47%)
HCTZ 12.5 mg (+ Telm 80 mg)	40 (63%)	25 (37%)
Did the Patient Meet the Goal Response to Monotherapy?		
Telm 40 mg (+ HCTZ 12.5 mg)	34 (30%)	78 (70%)
Telm 80 mg (+ HCTZ 12.5 mg)	45 (38%)	72 (62%)
HCTZ 12.5 mg (+ HCTZ 12.5 mg)	10 (17%)	50 (83%)
HCTZ 12.5 mg (+ Telm 80 mg)	15 (24%)	49 (76%)
Among Titrated Patients, Who Met Goal Response?		
Telm 40 mg (+ HCTZ 12.5 mg)	41 (55%)	34 (45%)
Telm 80 mg (+ HCTZ 12.5 mg)	36 (55%)	30 (45%)
HCTZ 12.5 mg (+ HCTZ 12.5 mg)	22 (46%)	26 (54%)
HCTZ 12.5 mg (+ Telm 80 mg)	25 (57%)	19 (43%)

Table 2.5 Nominal p-value for efficacy comparisons

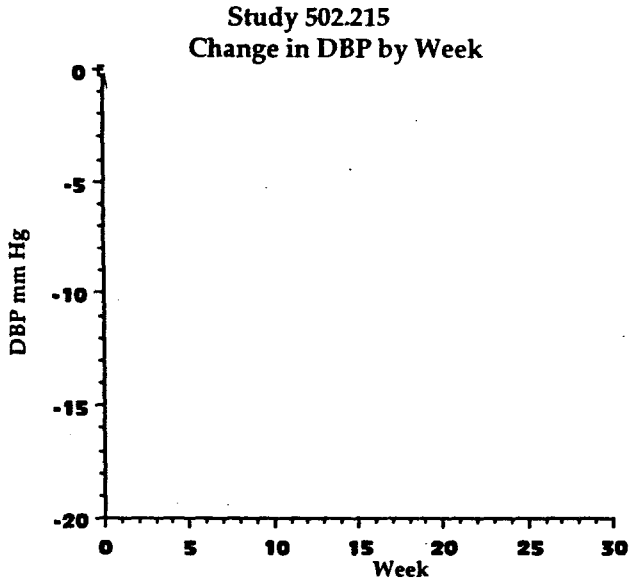
Comparison	Telm 40 (+ 12.5 HCTZ) vs Telm 80 (+12.5 HCTZ)	Telm 40 (+ 12.5 HCTZ) vs HCTZ 12.5 (+12.5 HCTZ)	Telm 80 (+ 12.5 HCTZ) vs HCTZ 12.5 (+12.5 HCTZ)	Telm 80 (+12.5 HCTZ) vs HCTZ 12.5 (+80 Telm)
Chi-square p-value	0.71	0.079	0.037	0.36

note p-values were 2 point comparisons with no correction for four comparisons.

Blood Pressure response with time:

The supine systolic and supine diastolic blood pressures are shown as Figures 2.1 and 2.2, respectively. In considering supine diastolic blood pressure, the value at week 4 reflects the sole direct comparison between telmisartan (2 groups at different doses) and hydrochlorothiazide (2 groups at 12.5 mg/day). One of the hydrochlorothiazide groups clearly appears to be the outlier (H12.5 + H12.5). Both telmisartan treatment groups differ from one of the HCTZ groups (H12.5 + H 12.5). At the end of the treatment (26 weeks) all treatment groups are superior to the H12.5 + H12.5 group ($p<0.002$ for all groups). The supine DBP effect at week 4 (the only directly comparative results for the four treatment groups: T40 (+H12.5), T80 (+H12.5), H12.5 (+H12.5), H12.5 (+T80) were respectively, -9.9; -9.5,-7.5, -9.1 mm Hg.

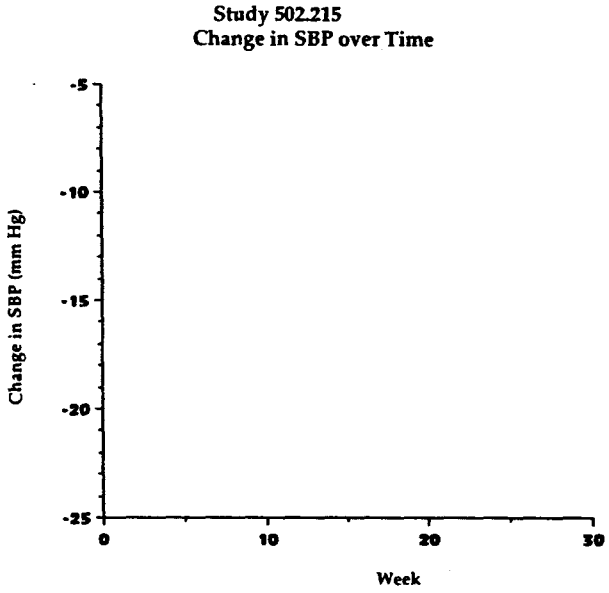
Figure 2.1



With respect to supine systolic blood pressure, the 4-week pre-titration point (to add-on therapy) shows that all the treatment regimens were equivalent. The change in supine systolic groups, at 4-weeks were respectively for the T40 (+ H12.5); T80 (+ H12.5); H12.5 (+ H12.5) and H12.5 (+ 80 Tel), -10.5; -9.2; -8.7 and –9.6 mm Hg. At the end of the 26-week treatment period all regimens, with the exception of the H 12.5 + H12.5 regimen, decreased supine SBP equivalently. The effect at the end of the 26-week treatment on SBP were –21.2, -18.6; -14.5 and –18.7 mm Hg, respectively.

With respect to supine pulse rates, there were small changes at 4 weeks. The two telmisartan regimens produced a small decrease in pulse and the two HCTZ doses producing some tachycardia. The pulse rates for T40 (+ H12.5); T80 (+ H12.5); H12.5 (+ H12.5) and H12.5 (+ 80 Tel) at 4-weeks (monotherapy) were –1.0; -1.4; +0.4; +2.4, respectively. At the end of treatment, the effect on pulse rate for the regimens were –2.6; -1.4; 0.7 and 2.0; respectively.

Figure 2.2



Safety:
Duration of Exposure:

Table 2.6 Total exposure during the clinical study (data derived from sponsor's Table 5.1.3.2 p SA 374-5) Study 502.215

Exposure Days			N	mean	SD	min-max	Total patient- days (years)
Telm 40 (+ HCTZ)	Telm 40	First level	38	169.3	7.7	5-217	6434 (17.61)
number enrolled = 114							
	Telm 40 + HCTZ 12.5	First level	76	35.3	2.4	21-120	2683 (5.6)
		Second level	76	137.6	4.9	4-184	10455 (28.6)
		Total	76	172.9	4.6	35-212	13138 (36.0)
Telm 80 (+ HCTZ)	Telm 80	First level	55	163	7.8	3-217	8966 (24.5)
number enrolled = 117							
	Telm 80 + HCTZ 12.5	First level	66	34.4	2.0	21-119	2269 (6.2)
		Second level	66	137.7	5.4	5-183	9090 (24.9)
		Total	66	172.1	5.3	39-211	11359 (31.1)
HCTZ 12.5 (+ HCTZ 12.5)	HCTZ 12.5	First level	13	128.5	21.5	1-204	1671 (4.6)
number enrolled = 62							
	HCTZ 12.5 + HCTZ 12.5	First level	49	37.1	3.0	21-113	1820 (5.0)
		Second level	49	132.4	6.1	15-188	6486 (17.75)
		Total	49	169.5	6.1	39-217	8306 (22.7)
HCTZ 12.5 (+ Telm 80)	HCTZ 12.5	First level	21	163.3	13.6	1-218	3430 (9.4)
number enrolled = 66							
	HCTZ 12.5 + Telm 80	First level	45	35.7	2.8	21-112	1607 (4.4)
		Second level	45	127.6	7.5	16-182	5743 (15.72)
		Total	45	163.3	7.4	43-212	7350 (20.12)

With respect to exposure, for the Telm 40 (+ HCTZ) group, 38 patients were treated with monctherapy with an average exposure to monotherapy in this group of 169.3 days. Among those who received both T 40 and HCTZ, the average exposure to monotherapy was 35.3 days. Patients usually had the HCTZ added at the first potential up-titration visit (the average first dose exposure was only approximately 5 weeks).

With respect to the Telm 80 + HCTZ cohort, fifty-five patients received monotherapy, with an average duration of exposure of 169.3 days. Among the 66 patients who were titrated to the second level drug, the majority were increased at approximately week 5 (probably week 4 visit). The duration of exposure to combination treatment in this group was 19.7 weeks.

With respect to the HCTZ 12.5 + HCTZ 12.5, there were 13 patients who were treated on low dose HCTZ, which reflects 21% of the cohort. There were 49 subjects who were eventually titrated to the higher HCTZ dose. The duration of those remaining on first level therapy was only 128.5 days (18.4 weeks). Titration usually took place at the 4-week visit (mean time of change slightly greater than weeks; 36.1 days). The duration of exposure to combination therapy averaged 18.9 weeks.

With respect to the HCTZ 12.5 + T 80 mg dose, 21 patients remained on monotherapy (32% of the cohort). Those who had telmisartan added had the additional medication added at the 4-week visit (mean time to up-titration 35.7 days). The duration to combination therapy was 127.6 days (18.22 weeks).

There were 363 patients exposed to any drug or drugs during this study. The total patient-days of exposure were 60,654 or an average of 167.1 days/subject. The extent of exposure to the combination of telmisartan and hydrochlorothiazide consist of those patients who were up titrated to the second level dose in the T40 + HCTZ, T80 + HCTZ regimens plus those up-titrated in the HCTZ 12.5 + T 80 group. There were a total of 187 patients (76 patients in T40 + HCTZ12.5; 66 in the T80 + HCTZ 12.5 and 45 patients in the H12.5 + T 80 groups) who received concurrent therapy with Telmisartan and hydrochlorothiazide. These patients were exposed for a sum of 25,288 days (69.2 patient-years; an average of 135.2 days /patient).

The only comparative data are the adverse events that occurred prior to the potential for up-titration to the add-on treatment.

The number of adverse events and their severity is shown in Table 2.7.

Table 2.7 Adverse events, by treatment regimen, up-titration regimen and severity study 502.215

Exposure Days			N	Any	Mild	Moderate	Severe
T 40 (+ HCTZ)	T40	First level	38	44	23	18	3
Number enrolled = 114	T40 + HCTZ 12.5	First level	76	52	23	25	4
Number of AEs=210		Second level	76	114	59	48	7
		Up-titrated total	76	166	82	73	11
T80 (+ HCTZ)	T80	First level	55	67	32	30	5
Number enrolled = 117	T80 + HCTZ 12.5	First level	66	48	27	19	2
Number of AEs=224		Second level	66	108	63	33	12
		Up-titrated total	66	156	90	52	14
H12.5 (+ HCTZ 12.5)	H12.5	First level	13	24	10	13	1
Number enrolled = 62	H12.5 + HCTZ 12.5	First level	49	21	10	11	0
Number of AEs= 116		Second level	49	71	36	29	6
		Up-titrated total	49	93	46	40	6
H12.5 (+ Telm 80)	H12.5	First level	21	98	51	37	10
Number enrolled = 66	H12.5 + Telm 80	First level	45	20	9	9	2
Number of AEs=98		Second level	45	51	29	20	2
		Up-titrated total	45	71	38	29	4

Deaths/Dropouts/Discontinuations/Serious Adverse Events.

One death occurred during the study. The death occurred on the H12.5 + T80 mg. A 63 year old female patient (#3067) with a history of TIAs was titrated from HCTZ 12.5 mg to HCTZ 12.5 mg + telmisartan 80 mg. She was discontinued after 77 days of treatment for lack of efficacy. Six days after withdrawal the patient suffered a stroke and died four days later.

Fifteen patients in the whole data-base experience serious adverse events while on therapy. One patient died shortly after discontinuation of therapy (see above) and one patient had a serious adverse event shortly after discontinuation of therapy. These events are summarized below (sponsor's table 10.2.4:1).

Table 2.8 Serous Adverse Event Study 502.215

Treatment	#	Sex/Age	Treat. Duration	Event	Outcome
T40	3380	F/61	90	Ankle Fracture requiring Surgery.	Not Recovered
T40	3252	M/75	28	Benign Prostatic Hypertrophy	Recovered
T40 +HCTZ 12.5	3461*	M/49	132	MI	Recovered
T80	3531	M/63	86	Prostate Ca-Pain in Thoracic Spine	Sequelae
T80	3273	M/70	63	Reduced Hearing	Sequelae
T80	3578*	M/57	27	Tight Chest Pain-No cardiac Abnormality	Recovered
T80	3162*	M/58	5	Intestinal Obstruction-Colonic CA with liver metastases	Not recovered
T80 + HCTZ 12.5	3045*	M/79	17	Cholecystitis	Recovered
T80 + HCTZ 12.5	3072	M/40	77	Dehydration	Recovered
T80 + HCTZ 12.5	3189	F/61	9	Epistaxis	Recovered
T80 + HCTZ 12.5	3238	M/74	12	Cerebrovascular Accident	Sequelae
HCTZ12.5 + H12.5	3293	F/69	19	Removal of Right Tonsillar Cyst	Recovered
HCTZ12.5 + H 12.5	3313*	M/71	14	Infected Right Heel	Not Recovered
HCTZ 12.5	3250*	M/57	run-in	Angina	Sequelae
HCTZ 12.5 + T80	3002	F/49	2	Urinary Tract Infection	Recovered
HCTZ 12.5 + T80	3067	F/63	6-days post D/C	CVA	Died
T80 + HCTZ 12.5	3238*	M/74	43 days post D/C	Carcinoma Prostate	Not Recovered

* Discontinued.

There were a total of 32 patients who experienced adverse events that led to discontinuation from the study. Of these, seven (6.1%) were from the T40 + HCTZ group; 8 (6.6%) were from the T80 + (HCTZ) group; 7 (11.3%) were from the HCTZ 12.5 + H12.5 group; and 10 (15.2%) were from the HCTZ

Table 2.10 Orthostatic events (derived from sponsor's tables study 502.215

		Flagged Changes-SBP				Flagged Changes -DBP				Flagged Changes Pulse			
		No		Yes		No		Yes		No		Yes	
Regimen	Dose	N	(%)	N	%	N	%	N	%	N	%	N	%
T40	T40	31	81.5%	7	18.4	38	100	0	0	36	100	0	0
T40 + HCTZ 12.5	T40	70	92.1%	6	7.8	75	98.6	1	1.3	72	97.2	2	2.7
	T40 + H12.5	61	80.2%	15	19.7	76	100	0	0	71	95.9	3	4.0
T80	T80	46	83.6%	9	16.3	54	98.1	1	1.8	50	90.9	5	9.0
T80 + HCTZ	T80	61	92.4%	5	7.5	66	100	0	0	62	95.3	3	4.6
	T80 + H12.5	51	78.4%	14	21.5	64	98.4	1	1.5	54	84.3	10	15.6
H12.5	H12.5	12	100%	0	0	12	100	0	0	11	91.6	1	8.3
H12.5 + H12.5	H12.5	48	97.9%	1	2.0	48	97.9	1	2	46	97.8	1	2.1
	H12.5 + H12.5	41	85.4%	7	14.5	48	100	0	0	43	93.4	3	6.5
H12.5	H12.5	16	76.1%	5	23.8	20	95.2	1	4.7	17	85.0	3	15
H12.5 + Telm 80	H12.5	41	91.1%	4	8.8	44	97.7	1	2.2	43	97.7	1	2.2
	H12.5 + T80	37	86.0%	6	13.9	43	100	0	0	42	97.6	1	2.3

Most events that the sponsor defined as orthostatic were derived form systolic blood pressure changes. There is no clear and consistent signal from these data. For example, the incidence of orthostasis in the H12.5 + H12.5 cohort appears different than the H12.5 + Telm 80, even during the monotherapy portion of the study. These subjects received the same treatment during that portion of the study.

One patient (# 3097) who was receiving H12.5 + T80, this event, however, was not associated with vital signs changes that fulfilled the criteria of orthostatic changes. Measurements of blood pressure were performed at trough and are likely underestimates peak drug effect.

Laboratory:

Marked changes in laboratory values (rather difficult to satisfy the definition of extreme was infrequently reported. Blood for laboratory chemistry and hematology were drawn at screening, run-in phase and at the end of the 26-week study. Line listings for all patients are not supplied. Changes of laboratory values, not reaching the rather generous criteria supplied by the sponsor were, therefore not frequently met.

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Table 2.11 Number of Marked Changes in Laboratory Parameters study 502.215

	Parameter	Marked change (units)	T40 (+ HCTZ)	T80 + (HCTZ)	H12.5 (+HCTZ 12.5)	H12.5 +(T80)
Hematology	Hemoglobin	≥ ± 2.0 g/dl	↑3 ↓0	↑ 5 ↓2	↑ 1 ↓0	↑0 ↓0
	Hematocrit	≥ ± 9 %	↑2 ↓0	↑ 0 ↓2	↑0 ↓0	↑0 ↓0
	Red Cell Count	≥ ± 9 (10^6/uL)	↑ ↓	↑ ↓	↑↓	↑↓
	White Cell Count	≥ ± 5 (10^3/uL)	↑ ↓	↑ ↓	↑↓	↑↓
	Neutrophils	≥ ± 20%	↑1 ↓0	↑ 1 ↓1	↑ 1 ↓0	↑ 2 ↓0
	Lymphocytes	≥ ± 16%	↑ 0 ↓1	↑4 ↓2	↑ 0 ↓1	↑0 ↓2
	Monocytes	≥ ± 7%	↑ 1 ↓0	↑ 2 ↓0	↑ 1 ↓0	↑ 0 ↓2
	Eosilophils	≥ ± 5%	↑ 0 ↓2	↑ 2 ↓0	↑ 0 ↓0	↑0 ↓2
	Basophils	≥ ± 2%	↑ 1 ↓0	↑ 1 ↓0	↑ 0 ↓1	↑1 ↓0
	Platelet Count	≥ ± 134 10^3/uL	↑ 1 ↓0	↑ 1 ↓0	↑ 0 ↓0	↑0 ↓0
Liver	SGPT	≥ ± 35 U/L	↑ 1 ↓1	↑ 2 ↓1	↑ 3 ↓0	↑ 1 ↓0
	SGOT	≥ ± 35 U/L	↑0 ↓4	↑ 1 ↓1	↑1 ↓1	↑0 ↓0
	Alk. Phosphatase	≤ -55 ≥ ±35 U/L	↑0 ↓2	↑1 ↓3	↑0 ↓0	↑0 ↓3
	Total Bilirubin	≥ ±0.8 mg/dl	↑0 ↓0	↑0 ↓0	↑0 ↓0	↑0 ↓2
	LDH	≥ ± 200 U/L	↑ ↓	↑↓	↑↓	↑↓
	Total Protein	≥ ± 1.4 g/dL	↑0 ↓1	↑0 ↓2	↑0 ↓0	↑0 ↓0
Electrolytes/ Renal	Sodium	≥ ± 10 mEq/L	↑0 ↓0	↑0 ↓6	↑0 ↓0	↑0 ↓1
	Potassium	≥ ± 1.4 mEq/L	↑↓	↑↓	↑↓	↑↓
	BUN	≥ ±11.2 mg/dL	↑↓	↑↓	↑↓	↑↓
	Creatinine	≥ ± 0.5 mg/dL	↑1 ↓3	↑3 ↓0	↑0 ↓1	↑2 ↓0
	Uric Acid	≥ ± 2.7 mg/dL	↑1 ↓1	↑1 ↓0	↑1 ↓0	↑0 ↓0
	Glucose (fasting)	≥ ± 60 mg/dL	↑2 ↓2	↑0 ↓1	↑2 ↓0	↑2 ↓0
Lipids	Total Cholesterol	≥ ± 90 mg/dl	↑↓	↑↓	↑↓	↑↓
	HDL	≥ ± 33 mg/dL	↑1 ↓0	↑0 ↓0	↑0 ↓0	↑0 ↓0
	LDL	≥ ± 77 mg/dL	↑0 ↓0	↑0 ↓1	↑0 ↓0	↑0 ↓0
	Triglycerides	≥ ± 80 mg/dL	↑16 ↓8	↑12 ↓6	↑10 ↓4	↑11 ↓5

Where no values are listed the sponsor did not supply any values.

Below is a list of laboratory values treated as adverse events.

Patient # 3137 (T40)- Elevated glucose level at visit 3 (run-in period).

Patient 3135 (T40 + HCTZ)- Elevated uric acid at end-of study was 383 umol/L. Run in period uric acid was 330 umol/l. Screening value was 381 umol/L.

Patient # 3019 (T80)- decrease neutrophil count both at run-in period (1.45 x 10^9/L) and end of study (1.93 x 10^9/L).

Patient # 3345 (T80)- BUN increased from 6 at run-in period to 11.3 at 26 weeks (normal 2.5-8.4 mol/l). The lab was repeated 15 days post-treatment was also outside the normal range (10.8 mmol/L).

Patient # 3136 (T80 + HCTZ 12.5).CPK was increased from 117 and 181 at baseline and run-in phase with end of-treatment measurement of 314 u/L (normal 24-195 U/L)

Patient # 3074. (T80 + HCTZ 12.5) SGPT increased from 19U/l at to 97 IU/L at end of treatment.
CPK increased to 282 u/l at end of the study from 126-136 at baseline and run in.
Creatinine increased from 7.3 at baseline and 5.4 at run-in to 7.9 post treatment.

Patient # 3025 (T80 + H12.5) Glucose increase to 12.7 mmol/L from baseline value of 8 and run-in value of 10.8 mmol/L.

Patient # 3344 (T80 + H12.5) Patient with low WBC count of 0.47x10^9/L. Repeat 5.6.

Patient #3352 (H12.5 + H12.5) Sodium post treatment of 124.7 baseline value 137.4.

Patient # 3283 (H12.5) Hyperglycemia at all visits last visit glucose 20.4 mmol/L (normal 2.8-5.8 mmol/L)

Patient # 3312 (H12/5 + T80) CPK increased post treatment to 263 u/L (normal 24-195 U/L.

Conclusion: Dr. U previously reviewed the efficacy of this study. This review predominantly dealt with the safety. The importance of the database, however, lies in that it defines the only safety information in which patients who were treated with hydrochlorothiazide were treated with telmisartan. The dose of hydrochlorothiazide was low (12.5 mg) , so that absent of profound orthostasis should not be extended to those who were taking higher doses of HCTZ.

Study #3. Volume 1.51 to 1.
Study Number 502.210

Title of Study: Telmisartan Enalapril Elderly Study-TESS: A double-blind evaluation of the efficacy and safety of telmisartan as compared to enalapril in elderly with essential hypertension alone and in combination with hydrochlorothiazide 12.5 mg to 25 mg once daily.

Study Summary: This study was reviewed in conjunction with the telmisartan( )by Dr. Khin Maung U. There is little information in this study that directly supports the use of the combination product telmisartan/ hydrochlorothiazide. There is, however, some safety data on the concurrent use of telmisartan with either 12.5 or 25 mg of hydrochlorothiazide. The safety database is uncontrolled and therefore, only descriptive.

This was a study on the use of one of two regimens either enalapril or telmisartan in elderly patients (> 65 years old) with mild-moderate diastolic hypertension (DBP $\geq$ 95 mm Hg to $\leq$ 114 mm Hg). Patients were excluded for the following reasons, excessive SBP ($\geq$ 220 mm Hg), excessive DBP (> 114 mm Hg); cardiovascular disease (i.e. heart failure –NYHA Class III-IV; MI-within 6 months, sustained VT, hypertrophic or valvular disease); electrolyte abnormality (hypokalemia, hyperkalemia or hyponatremia-Na+< 130 mmol/l); uncontrolled diabetes mellitus; administration of concurrent medications of concern (e.g. warfarin), secondary forms of hypertension, or renal or hepatic dysfunction.

After a 3-5 week run-in period, patients were enrolled into a 26-week study. Eligibility was established during screening and a 2-3 week run-in period (visits 1-3 and entry visit). The initial dose of those randomized to the telmisartan group was 20 mg daily. The initial dose for the enalapril group was 5 mg daily. At week 4 (visit 4), week 8 (visit 5) or week 12, if the DBP blood pressure was > 90 mm Hg, the dose could be increased to either 40 and then 80 mg daily of telmisartan for those in the telmisartan cohort or 10 mg and then 20 mg daily of enalapril for those in the enalapril cohort.

If at week 12 (visit 6), the subject was on the highest dose of either telmisartan or enalapril and the supine DBP was $\geq$ 90 mm Hg, hydrochlorothiazide at a dose of 12.5 mg daily was added.

At week 16 the dose of telmisartan or enalapril could not be further increased. If, however, the DBP was $\geq$ 90 mm Hg, hydrochlorothiazide could be added at a dose of 12.5 mg/day. If the subject's blood pressure was still not controlled and was already being treated with 12.5 mg of hydrochlorothiazide, the dose of hydrochlorothiazide was increased to 25 mg daily.

There were a total of 278 patients that were enrolled, of which 272 patients had data available for efficacy. These patients had both baseline and at least one on-treatment measurements. Those enrolled were elderly (> 65 years old, with 74% between the ages if 65-74 years), mostly female (58%) and entirely Caucasian. The population as a whole was fairly healthy with baseline diagnosis aside from hypertension in 60% of patients. Cardiovascular disease was concomitantly present in only 20% of the enrolled population (previous MI in only 3% of the population).

The number of subjects and duration of exposure to monotherapy and combination therapy are shown Table 3.1. Data derived from Sponsor's Appendix 15.9.2 Table 1.4.2.1 v54 p 124

Table 3.1 Exposure in the TESS study # 502.210

		N	mean	SD	min-max
Calculated time on Last Dose (days)	Telmisartan	139	110	51	1-203
	Enalapril	139	106	50	1-200
Calculated time on Monotherapy (Days)	Telmisartan	139	136	55	5-207
	Enalapril	139	131	54	2-222
Calculated time to Addition of HCTZ (days)	Telmisartan	56	56	17	13-147
	Enalapril	61	61	13	65-124
Calculated Time on Combination Therapy (days)	Telmisartan	139	35	45	0-113
	Enalapril	139	38	46	0-116
Calculated Time on Active Treatment (days)	Telmisartan	139	171	39	5-207
	Enalapril	139	169	42	2-222
Average Dose (mg/day)	Telmisartan	139	56	27	20-80
	Enalapril	139	14	6	5-20

The demographics of those enrolled are shown Table 3.2. The average age for each treatment was approximately 71 years. Since this study was carried out in Europe, no blacks were involved. Baseline blood pressures were approximately 178/101.

Table 3.2 Demographics at baseline Study 50.210

	Telmisartan	Enalapril
Age mean ± SD	71.2 ± 5.3	70.9 ±4.5
Gender M/F (% M)	57/82 (41%)	61/78 (44%)
Race Caucasian/other (% Caucasian)	139/0 (100%)	139/0 (100%)
Baseline BP (mean ± SD/mean ± SD)	180 ± 18.4/101.9 ± 5.2	177.4 + 16.6/100.7 ± 5.1

Combination therapy was required in 56 telmisartan and 61 enalapril patients. For those who were exposed to hydrochlorothiazide, the average duration of exposure was approximately 86.9 and 86.6 days for those on telmisartan and enalapril, respectively. The total exposure to combination therapy for telmisartan and enalapril was 4865 and 5282 patient*days, respectively.

The effects of the telmisartan and enalapril regimens on systolic and diastolic blood pressures, as measured by trough cuff-measurements, are shown as Figure 3.1 and Figure 3.2, respectively. The sponsor included all dropouts and discontinuations in a last observation-carried forward analysis. Since there was no placebo group, the absence of a any superiority of any of these regimens, precludes deriving any efficacy conclusions and no estimate of the magnitude of the effect of any of the two regimens ascertained. There was some imbalance in baseline blood pressures so that the change from baseline when corrected for baseline blood pressure, country of origin and center was still not significant. The overall ANCOVA for supine diastolic pressure or systolic blood pressures at trough was not statistically significant ($P > 0.05$). The lack of a substantial off- treatment effect suggests a substantial portion of the change from baseline may represent effects other than drug effect.

Ambulatory measurements at baseline and 26-week visit were available for 79 and 68 patients in the telmisartan and enalapril groups respectively. Among the several parameters measured including daytime and nighttime mean diastolic or systolic pressures. There was no difference in between those randomized to the telmisartan and those randomized to the enalapril regimens. (see sponsor's table 9.3.4.2; not reproduced here).

The additional effect of hydrochlorothiazide is also difficult to quantify, since hydrochlorothiazide was added as an adjunct treatment to inadequately controlled patients. Any change in blood pressure in blood pressure as a consequence of adding hydrochlorothiazide has a component of "regression to the mean" in its measurement.

Figure 3.1

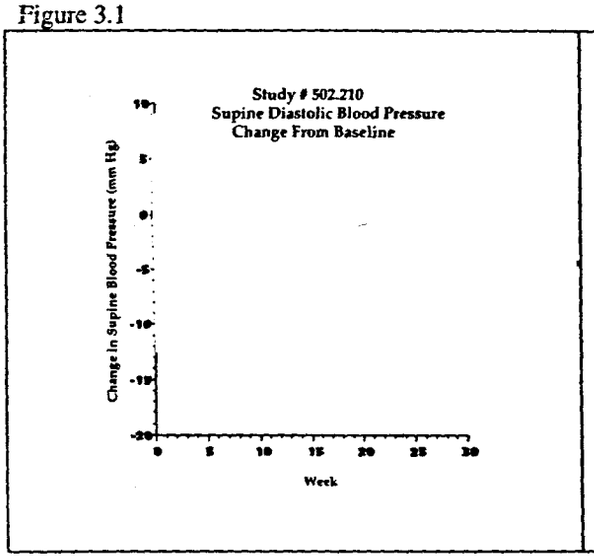
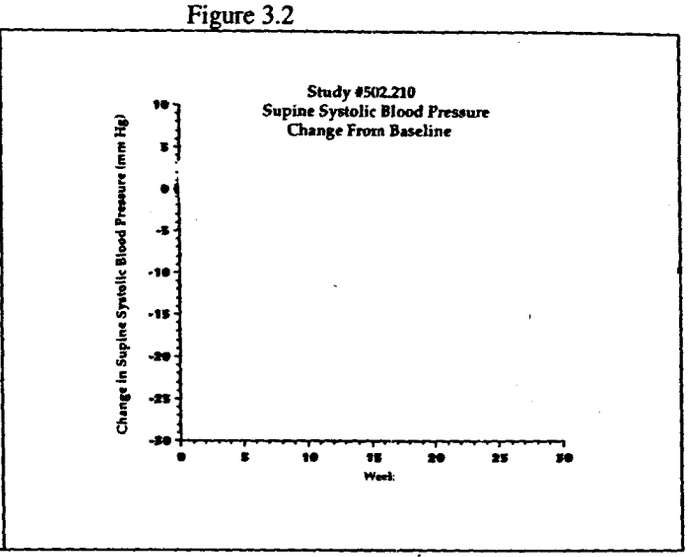


Figure 3.2



With respect to pulse rates, there was little difference in the change from baseline in end treatment (LOCF), trough measurement. There was a net drop in pulse rate at end-of therapy of –1.9 and -2.4 bpm for the telmisartan and enalapril regimens, respectively. Peak pulse effects were not captured.

Safety:

There were a total of 278 patients who received at least one dose of medication (either telmisartan or enalapril) and these patients represent the safety cohort of this study. There were 81patients who received concurrent hydrochlorothiazide and telmisartan for an average of 60.6 days. The total duration of exposure was 13.44 patient years for those treated with telmisartan plus hydrochlorothiazide. There were a total of 85 patients in the enalapril cohort who were treated with concurrent hydrochlorothiazide for an average of 62.2days. The cumulative duration of concurrent exposure of enalapril and hydrochlorothiazide was 15.87 patient years.

Deaths, Dropouts , Discontinuations and Serious Adverse Events:

There were no deaths in this study.

There were a total of 20 serious adverse events during the trial. Nine of these serious events were in the telmisartan cohort and 11 among those treated with enalapril. Two events occurred in those who were receiving concomitant telmisartan and hydrochlorothiazide during the study. Capsular summaries were supplied by the sponsor and are summarized:

Patient # 4299 a 67 year old male was hospitalized after 177 days of treatment for a aggravation of headache (maximum dose was 80 mg telmisartan plus 25 mg hydrochlorothiazide). The patient was loss to follow-up.

Patient # 4320 a 72 year old female developed pneumonia within one week after discontinuing therapy.

There were, in addition, 14 patients in this study who discontinued treatment due to non-serious adverse events. Of these, six were in the telmisartan regimen and eight were in the enalapril regimen. Of those telmisartan patients, only one patient was on concomitant telmisartan and hydrochlorothiazide. **Patient # 4078** a 70 year old female discontinued after 106 days after enrollment due to aggravation of diabetes mellitus, coughing bronchitis and vertigo.

There were four patients assigned to telmisartan and three patients assigned to enalapril that temporarily withdrew but finished the study. None of the telmisartan patients were on concomitant hydrochlorothiazide at the time of temporary discontinuation.

Overall Adverse Events:

The overall adverse event profile is derived from Appendix 15.9.3 Table 5.2.1. and reproduced as table 3.3. The events were classified based on the dose that subjects were taking at the time of the event. There did not appear to be an overall pattern that suggests a relationship to combination treatment.

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Table 3.3 Adverse events and dose that they occurred Study 502.210

	Tel 20 +H12.5	Tel 40 +H12.5	Tel 80 +H12.5	Tel 80 +H 25
Number	3	3	50	25
Number with ADR	1	2	10	8
Autonomic nervous system			1	1
Flushing			1	
Impotence				1
Body as a Whole			0	3
Allergy				1
Back Pain				1
Malaise				1
Central and Peripheral Central and Peripheral			4	2
Dizziness			1	0
Headache			1	1
Vertigo			2	1
Respiratory Disorder	1	1	4	3
Coughing	1		2	0
Pneumonia		1	0	0
Bronchitis			1	1
Epistaxis			0	1
Pharyngitis			2	0
Upper Respiratory Tract Infection				1
Gastrointestinal Disorders	0	1	4	0
Abdominal Pain	0	1	0	0
Constipation	0	1	1	0
Diarrhea	0	0	2	0
Disease of the Esophagus	0	0	1	0
Dyspepsia	0	0	1	0
Metabolic and Nutritional			1	
Diabetes Mellitus Aggravated			1	
Urinary System Disorders		1	1	
Cystitis		1	0	
Urinary Tract Infection		0	1	
Vascular Extracardiac Disorders	0	0	0	1
Cerebrovascular Disorder				1
Vision Disorder	0	0	1	0
Conjunctivitis			1	

Vital Signs:

Symptomatic orthostasis (syncope, or near syncope) was not reported among those treated with the combination of telmisartan and hydrochlorothiazide. Dizziness was reported in only one patient that was treated with concurrent telmisartan and hydrochlorothiazide.

Asymptotic orthostatis was defined as a greater than 10 mm Hg drop in systolic or diastolic blood pressure, in excess of that observed during baseline upon assuming the standing position. For pulse rate, orthostasis required a greater than 10 BPM pulse increase over that observed during baseline upon assuming the standing position.

Orthostasis events were determined at trough drug levels and are therefore, likely to underestimate the true frequency of these events. No listing for orthostasis was submitted based on concurrent hydrochlorothiazide treatment.

ECGs:

Twelve-lead ECGs were performed at screening (visit 1), visit 3 (run-in phase), week 12 (visit 6) and at week 26 (end-of study). The sponsor did not submit line listing of ECG results. The sponsor in a summary table (Appendix 15.9.2; Table 5.1.2) lists no new or worsened ECG changes among those who were treated with concurrent telmisartan and hydrochlorothiazide.

Laboratory:

Blood for laboratory values was measured during the placebo run-in, week 12 (visit 6) at end of study, and if there was an abnormal value a follow-up blood sample to be collected 5-9 days post study. No line listings were supplied.

Conclusion:

This study compared the efficacy of two antihypertensive regimens, one based on telmisartan and one based on enalapril in elderly patients with mild-moderate hypertension. There were no discernable differences between the two treatment groups in either efficacy or safety. Hydrochlorothiazide, as adjunctive therapy was allowed for those with inadequate blood pressure response.

APPEARS THIS WAY
ON ORIGINAL

Study # 4. Vol 1.59
Study # 502.209

Title of Study: Double-blind trial on long-term efficacy and safety of Telmisartan versus Enalapril in SEVerely hypertensive patients who are uncontrolled on a therapeutic dose of dihydropyridine calcium antagonist as background therapy (TESEV study).

Study Summary: This study was truncated prematurely because of inadequate enrollment. There were a total of 23 patients enrolled; One study site that enrolled 2 patients was excluded both from considerations of safety and efficacy. Of the remaining 21 patients, 11 that were treated with a regimen that featured telmisartan and 10 to a regimen that featured enalapril.

Eligible patients were those who were still hypertensive while on a dihydropyridine calcium channel blocker or those who were controlled on double or triple therapy, of which, one component was a dihydropyridine calcium channel blocker and were discontinued from the regimen due to adverse events (presumably caused by one of the other medications and not the calcium channel blocker). After a four week baseline period or washout period, subjects whose blood pressure at the final visit was bounded by 105 and 130 mm Hg (inclusive) were randomized to either telmisartan 80 mg or enalapril 10 mg administered once daily in the morning.

Patients were titrated at two–week intervals if supine diastolic blood pressure was $\geq$ 95 mm Hg. The first titration was to either 160-mg telmisartan or 20 mg enalapril. If the patient was still not adequately controlled, hydrochlorothiazide at a dose of 25 mg daily was added. The planned duration of exposure was 12 weeks.

Since there was no direct comparison between telmisartan/ hydrochlorothiazide therapy and individual components, this study does not support the efficacy of the combination product. There is a modicum of safety that is derived from the small number of patients on telmisartan who, because of an inadequate response required hydrochlorothiazide (25 mg daily).

With respect to safety, the eleven-telmisartan patients were treated for an average of 81.6 $\pm$ 15.1 days (range 41-106 days). Five patients received concurrent telmisartan and hydrochlorothiazide. These patients were treated for a mean ($\pm$ SD) duration of 34.6 ($\pm$ 20.1) days with concurrent therapies.

There were two telmisartan monotherapy patients who, based on blood pressure criteria, developed orthostasis (blood pressure criteria was defined as a standing minus supine measurement of either diastolic or systolic blood pressure that was in excess of 10 mm Hg greater than the same measurements at baseline). There was one additional telmisartan patient who had orthostasis based on pulse criteria (a greater than 10-bpm increase in assuming the standing position when compared to the increase measured at baseline). Orthostasis, however, were not measured at peak drug effect but was measured at trough (23-25 hours after the last dose). Orthostatic measurements, furthermore, were not measured when a new treatment was added or when a dose was increased, the most likely time to detect orthostatic effects. There is therefore, little comfort in the minimal occurrence of detectable orthostasis.

There were no deaths or serious adverse events among those treated with telmisartan either as monotherapy or with concurrent hydrochlorothiazide. One patient # 2045who was randomized to

telmisartan had progressive renal insufficiency (increases in both BUN and creatinine) while on telmisartan that appeared to worsen while on combination therapy:

Table 4.1 Observed Laboratory abnormalities. For study 502.209

Day	Period	Treatment	Creatinine	Urea
0	run-in	Placebo/ Calcium antagonist	138 umol/L	8.6 mmol/L
28	run-in	Placebo/ Calcium antagonist	137 umol/L	12.6 mmol/L
week 4	double blind	160 mg Telmisartan	155 umol/L	12.8 mmol/L
week 12	double blind	160 mg Telmisartan plus 25 mg Hydrochlorothiazide	198 umol/L	20.5 mmol/L

Among the five patients treated with concurrent telmisartan and hydrochlorothiazide, there were 4 adverse events all classified as mild. There were 1 episode each of headache, myalgia, upper respiratory tract infection and fungal infection.

APPEARS THIS WAY
ON ORIGINAL

Study # 5 v. 61 p 118
Study # 502.221

Title of Study: A De Novo, Open-Label Evaluation of the Safety of Chronic Administration of Telmisartan as Monotherapy or in Combination with Other Antihypertensive Medications.

Summary: Dr. Khin Maung U previously reviewed this study in the process of approval of Telmisartan as monotherapy (NDA 20-850). This study, however, does not bear direct importance to the approval of the telmisartan/hydrochlorothiazide combination product. There is, however, a small amount of safety data on concurrent exposure of patients to the components of the combination product.

The study proposed to enroll a total of 100 patients with mild-moderate hypertension (BP $\geq$ 95 mm Hg and $\leq$ 114 mm Hg) that were to receive in an open-label fashion, antihypertensive treatment. The goal of the study was to titrate patients to a goal supine diastolic blood pressure of < 90 mm Hg (originally, the protocol stipulated < 95 mm Hg). The duration of exposure was to be 52 weeks.

There were three phases to this study, a placebo run-in phase, an open-label dose-titration phase and an open-label treatment phase. Patients were enrolled after a two or three week placebo run-in period. Those patients, who satisfied the enrollment criteria were randomized to receive telmisartan at an initial dose of 40 mg daily, administered 1 hour before breakfast on an empty stomach. Each of the patients was to be seen at two-week intervals where vital signs were measured. Changes in medications, however, were limited to every other visit during the dose titration phase. The dose change was predicated on not achieving a goal blood pressure of < 90 mm Hg. The sequence of increasing regimens were: 1) 80 mg telmisartan daily; 2) 80 mg telmisartan plus hydrochlorothiazide 12.5 mg/day; 3) followed by 80 mg telmisartan plus 25 mg hydrochlorothiazide daily; 4) followed by the addition of other therapies to telmisartan plus hydrochlorothiazide.

There were two study sites that enrolled patients. In one of the study sites, the study was prematurely stopped, so that the full duration of exposure was less than 52 weeks. Since only a subset of patients were treated with concurrent hydrochlorothiazide and telmisartan and since these patients were treated with this combination for only a portion of study, there is no direct group for comparison either of the safety or efficacy of the combination treatment.

The demographics of those enrolled are shown below

Table –5.1 Demographics of those enrolled. Study 502.221

	Total (n=100)	Monotherapy	+ HCTZ/± other medications
Age mean ± SD	52 ± 11. 0	52.1	52.3
Gender (%male)	68/32 (68%)	30/22 (58%)	38/10 (79%)
Race: Caucasian/Black/Other (%Black)	60/25/15 (25%)	31/10/11 (19%)	29/15/4 (31%)
Baseline Measurements.	152/101	149/100	157/103

Those who required some additional therapy either hydrochlorothiazide or other antihypertensives were more likely to have higher baseline measurements (not surprising), and were more likely to be male and black.

The duration of exposure at each dose level is shown Table 5.2:

Table 5.2–Duration of Exposure at Various Doses Study 502.221

	Tel 40	Tel 80	Tel 80 + HCTZ 12.5	Tel 80 + HCTZ 25	Tel 40 + HCTZ 12.5	Combination
# Exposed	100	69	45	26	1	11
Mean Exposure	115.6	89.26	96.2	146.65	168	173.18
patient years	31.67	16.87	11.86	10.45	0.5	5.21
Total patients with ADRs	28	18	8	9	1	7
Total with Serious ADRs	0	1	1	1	0	0
Total with ADRs leading to Discontinuations	0	0	0	0	0	0

There were no deaths in the study.

There were a total of three patients who sustained serious adverse events, two of these patients discontinued. Of these patients, two were treated with concurrent telmisartan and hydrochlorothiazide. One patient a 56 year old male (patient #3696) was diagnosed with malignant melanoma. The second patient a 58 year-old white male (patient # 3671) discontinued due to a herniated disc.

There were, in addition, four patients who discontinued for non-serious adverse events. None of these Patients were taking the mixture of hydrochlorothiazide plus telmisartan, although one patient had been treated with telmisartan plus hydrochlorothiazide till 10 days prior to event

Laboratory:

According to the sponsor there were three patients who had laboratory values that were listed as adverse events.
Patient # 3617 who was treated with telmisartan was hypokalemic (K+=3.1) on the first day of treatment. A repeat measurement at day 29 showed a normal K+=4.1meq/l on potassium supplements.
Patient #3627 was hypokalemic (3.3 meq/l) on the first day of active treatment. The potassium remained low throughout the study with values reported as 3.1, 2.9, 3.2 and 3.1 meq/l. The patient received potassium supplements. The low potassium was, however, reported as an adverse event only after hydrochlorothiazide was added.
Patient # 3642 was reported as hypokalemic beginning at week 2 (placebo run-in phase)(K+= 3.2 meq/l). .

One patient # 3603 had an elevated CPK at baseline that remained elevated throughout the study. Fractionation of the baseline CPK (521 IU/L) indicated 100% CK-MM. Re-fractionating at visit 11(open-label treatment) indicated CPK fractionation at 2% CK-MB, the rest being CK-MM (MI cut-off was 4% CK-MB).

ECGs. ECGs were recorded at visits 1 (screening), 3 (or 3.1)(placebo-run-in), 11 (treatment) and 14 (treatment). One patient receiving telmisartan monotherapy had sinus bradycardia.

Conclusion: This was an open-label study that adds no useful information with respect to the efficacy of the combination telmisartan/hydrochlorothiazide product. There is some safety data in adding hydrochlorothiazide to telmisartan. The cumulative exposure was approximately 28 patient-years. No alarming unusual adverse events were reported.

Study 6: vol. 64 p 56
Study # 502.213

Title of Study: Effects of Telmisartan Alone and in Combination with Hydrochlorothiazide on Renal Function and Blood Pressure in Patients with Mild to Moderate Essential Hypertension.

Table 6.1 Investigator and Sites:

Garry P. Reams, MD University of Missouri Colombia , MO	William B. Smith, MD Louisiana Cardiovascular Research Center New Orleans, LA

Study Summary: This study was submitted in conjunction with the Telmisartan NDA by Dr. Khin Maung U. This study adds little support for the efficacy of the combination product telmisartan/hydrochlorothiazide.

This was a two-center randomized study comparing the renal and hemodynamic effects of telmisartan 80 mg daily versus telmisartan 80 mg plus 12.5 mg hydrochlorothiazide daily in patients with mild-moderate hypertension (blood pressure $\geq$ 95 to $\leq$ 114 mm Hg). Medication was taken 1 hour prior to breakfast on an empty stomach.

The study consisted of three phases, a screening phase, a placebo run-in period and a treatment period. Patients with mild-moderate hypertension (based on measurements during the run-in period) without concurrent medical conditions were eligible for enrollment. Patients with confounding medical problems (i.e. patients with severe renal dysfunction i.e. Cr clearances > 2.3 mg/dL, patients with electrolyte abnormalities i.e. Na+ < 230 meq/l or K+ < 3 meq/l or > 6 meq/L) were excluded.

A total of 30 patients were randomized, fifteen to receive telmisartan 80 mg and 15 to receive telmisartan 80 mg plus 12.5 mg hydrochlorothiazide. Data was available for 13 patients who received telmisartan monotherapy and 14 patients who received the combination treatment. The following measurements were performed at the end of week 5 (end of placebo run –in period) and end of week 12 (end of 8 week treatment period): Creatinine Clearance, plasma creatinine, GFR, effective renal plasma flow, urinary albumin excretion, 24-hour sodium excretion, 24-hour potassium excretion, 24-hour creatinine excretion, 24-hour protein excretion, serum Na+, serum K+, serum uric acid, serum phosphate, plasma renin activity and plasma aldosterone. Measurements were performed at trough drug effect. There was no placebo group.

Relative to baseline, there was a change in systolic/diastolic blood pressures of -13.8/-10.2 for the telmisartan monotherapy and -11/-9.5 for the telmisartan/hydrochlorothiazide therapy regimens. The effect of treatment on renal function is shown in Table 6.2.

Table 6.2 Renal Function and Blood Pressure Study 502.213.

	Telmisartan			Telmisartan + HCTZ		
	Baseline Mean ± SD (Range)	Final Mean ± SD (Range)	Change Mean ± SD (Range)	Baseline Mean ± SD (Range)	Final Mean ± SD (Range)	Change Mean ± SD (Range)
Serum Creatinine mg/dL	0.94 ± 0.22 (0.7 to 1.4)	0.97 ± 0.27 (0.6-1.5)	0.03 ± 0.12 (-0.2 to 0.2)	1.1 ± 0.21 (0.8-1.6)	1.13 ± 0.21 (0.7-1.3)	0.03 ± .13 (-0.2 to 0.2)
Creatinine Clearance ml/min	91.1 ± 25.3 (24-124)	101.4 ± 35.9 (23-149	10.0 ± 23.4 (-21 to 49)	85.8 ± 22.8 (48.4-125)	88.4 ± 27.6 (35-139)	2.56 ± 17 (-48 to 23)
DTPA Clearance ml/min	89.6 ± 31.3 (46-155.2)	77.6 ± 27 (36-143)	-12.03 ± 30.14 (-85-33.2)	85.3 ± 27.4 (52.7-144.9)	82.6 ± 23.9 (49.8-126)	-2.7 ± 21.5 (-26 to 36)
PAH Clearance ml/min	359 ± 135 (115-5730	328 ± 141 (118-533)	-31 ± 194 (-454 to 167)	372 ± 84 (231-499)	357 ± 116 (174-500)	-14.5 ± 97 (-176 to 175)
Albumin Excretion ug/min	43.9 ± 63 (0-206)	17.25 ± 19.2 (1-51)	-26.7 ± 47 (-159 to 3)	89 ± 128 (3-432)	57.2 ± 115 (0-435)	-31.8 ± 47.5 (-107 to 3.6)
DBP Supine mm Hg	103.1 ± 5.8 95-114	92.8 ±8.8 74-106.7	-10.2 ±8.0 (-21.3 to 3.3	101.74 ± 4.6 (95.3 –108.6)	90.3 ±12 (71.3-112.7)	-9.5 ± 10.7 (-24 to +3)
SBP Supine mm Hg	157.1 ± 19.2 (130-193)	143.3 ±16.8 (120-170.7)	-13.8 ± 17 (-50 to 6.7)	159.7 ±15.6 (132-189.3)	148.7 ±29.1 (122-222)	-11 ± 23 (-38 to 34.7)

(data derived from sponsor's listing 4.1 and 4.2 vol 65 p SA124-SA139.

With respect to renal function, there did not appear to be a consistent finding. It should be appreciated that the patients in whom the measurements were performed had normal or near normal renal function. One patient, however, had a creatinine clearance of 24 ml/min at baseline and 23 ml/min at end of treatment, despite what appeared to be a normal serum creatinine (0.9 mg/dl) and DTPA clearance (110 ml/min at baseline and 143 ml/min at the end of treatment.). There were several subjects who had fairly large decreases in PAH clearance (renal blood flow); patient # 2569 had a decrease of 454 ml/min (from 572-118 ml/min) on telmisartan monotherapy and patient #2561 had a decrease of 394 ml/min from 573-179 ml/min.

In summary, given the absence of a placebo group, the absence of substantial renal disease, the targeting of measurements to trough concentration and the small sample size, any conclusions from the small changes in renal function and blood pressure difficult to interpret.

Safety.

The duration of exposure is shown in Table 6.3:

Table 6.3 Duration of Exposure study 502.203

	Telmisartan 80 mg	Telmisartan 80 + Hydrochlorothiazide 12.5 mg
Number	15	15
Extent of exposure Mean ± SD (Range) days	51.6 ± 1.1 (14-58)	54.8 ± 1.3 (52-57)

There were no deaths in the study. The sponsor notes no serious adverse events among those who received randomized treatment. Two non-randomized patients withdrew during the placebo run in period for adverse events, one patient for an acute anterior MI and one for atrial fibrillation.

There were three dropouts in the study. The explanations are per sponsor. Patient # 2501 discontinued because of an illegal entry criteria, patient #2513 discontinued because the subject moved out of state and patient # 2559 discontinued due to non-compliance with medication.

Table 6.4 Number of Adverse events as well as those adverse events which occurred in two or more patients.

	Telmisartan 80 mg	Telmisartan 80 mg + Hydrochlorothiazide 12.5 mg
Number with ADR	7	8
Dizziness	2	3
Headache	3	1
Fatigue	0	2
Pain	2	0
Sinusitis	2	0

Laboratory Values:

The laboratory values were collected at baseline and end of week 8.
Mean values for selected laboratory parameters are show in Table 6.5.

Table 6.5 Mean laboratory values at baseline and final measurements study 502.203

Parameter →	Calcium	Chloride	glucose	Potassium	Sodium	BUN	Uric Acid	CPK
Telm								
baseline	9.33	104.47	0.91	4.0	141	11.9	5.28	120.4
final	9.21	102.64	0.94	4.21	138	12.4	5.36	198.9
Telm + HCTZ								
baseline	9.41	103.67	1.09	4.12	141	17	5.52	130.3
final	9.48	102.27	1.12	4.10	139	19.4	5.99	167.1
Parameter →	Cholesterol	LDL	SGOT	SGPT	Hgb	Hct	Platelets	
Telm								
baseline	197.6	133.3	33.1	46	13.63	40.69	242.4	
final	202.0	137.2	29.0	24.6	13.19	39.11	233.9	
Telm + HCTZ								
baseline	212.3	138.1	22.2	22.2	14.63	43.24	245.3	
final	224.7	152	22.8	22.6	14.45	42.35	251.1	

The sponsor's analysis of extreme changes in laboratory values is shown in Table 6.5 below. I've added other patients whose changes did not quite rise to the sponsor's rather generous criteria to flag a value as "marked" in Table 6.6.

Table 6.6 Reviewer's additions to laboratory measurements as marked.

Parameter (Extremes)	Telmisartan		Telmisartan + HCTZ		Parameter (Extremes)	Telmisartan		Telmisartan + HCTZ	
	# inc	# dec	# inc	# Dec		# inc	# dec	# inc	# Dec
Potassium ± 1.4 meq/l	1	0	0	0	SGPT ± 35	0	1	0	0
Sodium ± 10 meq/l	0	1	0	0	LDH± 200 U/l	1	0	0	0
Triglyceride ± 80 mg/dl	2	2	2	2	Protein ± 1.4 g/dl	0	0	1	0
SGOT ± 35 U/l	0	1	0	0	CPK ± 300 U/l	1	0	1	0

Table 6.6 Specific laboratory abnormalities

Parameter	Pt #	Treatment	Value Change	Parameter	pt #	Treatment	Value Change
Calcium	2560	T	9.3 to 8.0	Hematocrit %	2501	T	44.3 to 37.8
Calcium	2562	T	9.1 to 7.9	Hematocrit %	2508	T	49.5 to 43.9
Calcium	2569	T	9.2 to 10.5	Hematocrit %	2566	T	39 to 33.9
Chloride	2560	T	106 to 95	Hematocrit %	2563	T + H	44.8 to 39.1
Chloride	2567	T	95 to 88	Hemoglobin g/dL	2508	T	16.6 to 15.4
Potassium	2562	T	4.3 to 5.6	Hemoglobin g/dL	2566	T	12.6 to 10.7
Potassium	2566	T	3.2 to 3.0	Hemoglobin g/dL	2512	T	15.6 to 14.8
Potassium	2569	T	4.1 to 5.5	Hemoglobin g/dL	2513	T	15.3 to 14.4
Sodium	2560	T	143 to 123	Cholesterol mg/dL	2558	T + H	194 to 266
Sodium	2567	T	130 to 121	Cholesterol mg/dL	2568	T + H	284 to332
BUN	2563	T + H	23 to 31	Triglycerides mg/dL	2501	T	145 to 245
BUN	2565	T + H	22 to 31	Triglycerides mg/dL	2512	T	91 to 270
LDH U/L	2569	T	194 to 458	Triglycerides mg/dl	2556	T	165 to 216
LDH U/L	2565	T + H	188 to 350	Triglycerides mg/dL	2565	T + H	197 to 338
Creatinine P-Kinase U/L	2513	T	132 to 964				
Creatinine P-Kinase U/L	2506	T + H	150 to 235				
Creatinine P-Kinase U/L	2565	T + H	146 to 481	CPK MB %	2565	T + H	0 to 4

- Calcium, chloride was not analyzed

This reviewer, without a prospective cut-off point, chose the values shown in the above table.

Conclusion: This study adds little information with respect to the safety or efficacy of telmisartan/ hydrochlorothiazide combination product.

Title of Study: A Randomized, Double-blind, Placebo-Controlled, 4 x 5 Factorial Trial of Telmisartan and Hydrochlorothiazide I Patients with Mild to Moderate Essential Hypertension

Dr Khin Maung U previously reviewed this study in conjunction with telmisartan as monotherapy (NDA 20-850). Since, however, this study is pivotal to the approval of the combination telmisartan/HCTZ, the study will be reviewed here in its entirety.

Investigator and Sites:

The investigator and sites as well as the number of subjects enrolled per site are shown I Table 7.1:

Table 7.1 Investigators and Sites and number of subjects/site:

Center #1 John Angelo, DO New Orleans Institute of Clinical Investigations New Orleans, LA (n=15)	Center #2 Michael Azorr, MD Portland, OR (n=16)	Center #3 Dale Terell, MD Cheryl Miller, Pharm. D Deaconess Hospital St Louis, MO (n=16)	Center # 4 Luis Campos, MD Med-Tech., Inc Houston TX. (n=6)	Center #5 Ralph Billrebeck, MD Billerbeck Clinical Research, Inc Carmichael, CA (n=16)
Center # 6 Steven Bowman, MD Tampa Bay Medical Research Clearwater, Fl (n=18)	Center #7 Steven Dorfman, MD Research Institute of Dallas Dallas TX (n=20)	Center # 8 Larry Gilderman, DO University Clinical Research Associates, Inc. Pembroke Pines, Fl (n=15)	Center # 9 John Flack, MD Bowman Gray Schl Med Winston-Salem, NC (n=14)	Center # 10 Thomas Garland, MD Lawrenceville, NJ (n=18)
Center # 11 Bruce Garrett, MD The Medical Research Center Inc Washington, DC (n=17)	Center # 12 David Goldstein Tampa Medical Research Associates Tampa Fl (n=14)	Center # 13 Stephen Green, MD Hampton Roads Med .Specialists Hampton VA (n=18)	Center # 14 Treva Watkins Tyson, MD Hampton Roads Med .Specialists Hampton VA (n=5)	Center # 15 James R Herron, MD Herron Medical Center Ltd Chicago, Il (n=17)
Center # 16 Dean Kereiakes, MD Linden center for Cardiovascular Research Cincinnati, OH (n=21)	Center # 17 John Kostis, MD UMDNJ-Robert Wood Johnson Med School New Brunswick, NJ (n=7)	Center # 18 Robert D Lesser, MD Robert Lesser & Assoc New Orleans ,LA (n=9)	Center # 19 Jon Levine, MD Clinical Research Associates Nashville, TN (n=5)	Center # 20 Thomas Marbury, MD Orlando Clinical Research Center Orlando, Fl (n=33)
Center # 21 Douglas Owens, MD Greer, SC (n=19)	Center # 22 Stephen Richard, MD Associated Medical Research Richmond, VA (n=8)	Center # 23 Randall Stolz, MD GFI Pharmaceuticals Evansville, IN (n=24)	Center # 24 Julian Colton, MD Synergy in Clinical Research Inc St. Petersburg, FL (n=23)	Center # 25 Duane Wombolt, MD Clin Research Ass of Tidewater Norfolk, VA (n=16)
Center # 26 Kenneth Blaze Internal Medicine Pembroke Pines, FL (n=13)	Center # 27 Andrew Lewin, MD National Research Institute Los Angeles, CA (n=48)	Center # 28 Jerrold Glassman, MD Center for Clinical Research of San Diego Sand Diego, CA (n=14)	Center # 29 Joel Neutel, MD Orange County Heart Inst and Research Center Orange, CA (n=14)	Center # 30 Alan Niederman, MD The Greater Fort Lauderdale Group Research Fort Lauderdale, FL (n-21)
Center # 31 Harry M Serfer, DO Hollywood FL (n=48)	Center # 32 David Smith, MD Memorial Research Medical Clinic Long Beach , CA (n=17)	Center # 33 Danny Sugimoto, MD The Chicago Center for Clinical Research Chicago, IL (n=12)	Center # 34 William J Grossman, MD Charleston Cardiology Charleston, SC (n=7)	Center # 35 Fred E Karch Rochester, NY (n=12)

Center # 36 Robert Detrano, MD Harbor UCLA Med Center Torrance CA (n=17)	Center # 37 James Wilson, MD Clinical Investigation Specialists, Inc Littlerock, AR (n=36)	Center # 38 Naynesh Patel, MD Dayton Area Research Associates Dayton, OH (n=14)	Center # 39 David Williams, MD Atlantic Inst of Clinical Research Daytona Beach, FL (n=9)	Center # 40 Ronald P Karlsberg, MD Cardiovascular Research Inst Beverly Hills, CA (n=0)
Center # 41 Thomas W. Littlejohn, MD Piedmont Research Associates Winston Salem, NC (n=20)	Center # 42 William Mroczek, MD Cardiovascular Center of N. VA Falls Church, VA (n=15)	Center # 43 Vasilios Papedemetriou, MD Hypertension and Cardiovascular Research Clinic VA Med Center Washington, DC (n=21)	Center # 44 Boris Kerzner, MD Baltimore, MD (n=13)	Center # 45 John Matlock, MD Diagnostic Clinic of San Antonio San Antonio, TX (n=15)
Center # 46 Jane McGill, MD Wash U. School of Medicine St Louis, MO (n-24)	Center # 47 Robert S. Rosenstein, MD Decatur Memorial Hospital Decatur, IL (n=23)	Center # 48 Kathleen Spreen, DO Medical Center of Delaware Newark DE (10)	Center # 49 Andrew J King, MD New England Med Center Boston, MA (n=15)	Center # 50 Carlos Arroyo Beaumont, Tx (n=0)

Protocol Amendments and Key Dates:

The protocol was written June 6, 1995 and revised July 24, 1995. The revision pre-dated the enrollment of any patient. The earliest date of enrollment was 23 October 1995. Most subjects enrolled during 1996. The database was locked on 21 November 1996.

No interim analyses were planned or performed.

Nature of Study: This was a placebo-controlled, factorial designed study.

Primary endpoint: The primary end point of this study was the change from baseline in supine diastolic blood pressure (DBP) 24 hour post-dose at the last visit of the double blind period when compared to baseline (pre dose measurement on visit 5). (see further under statistics)

Protocol:

The study proposed to enroll a total of 780 patients. These patients are to be of either gender, whose age is between 18-80 years. These patients are to have mild to moderate uncomplicated essential hypertension, defined as a morning mean DBP of $\geq$ 95 and $\leq$ 114 mm Hg after triplicate measurements, five minutes after assuming the supine position. The degree of hypertension must be reproducible, with no more than a 7 mm Hg difference between supine DBP measurements at two consecutive run-in periods and no more than 10 mm Hg between the first and third run-in visit.

Subjects will be excluded for the following reasons. The reasons generally can be categorized as either potential risk of pregnancy, concurrent cardiovascular disease, concurrent other diseases, hypertension due to secondary causes or requirement for concurrent therapies or drugs.

Patients will be excluded for:

- Inadequate methodology of birth control (women).
- Subjects who have secondary forms of hypertension (e.g. bilateral renal artery stenosis, renal artery stenosis in a solitary kidney, post-renal transplant); or evidence of profound hypertension (e.g.

evidence of retinal hemorrhages/exudates upon ophthalmologic exam; supine DBP > 115 mm Hg or supine systolic blood pressure > 200 mm Hg).

- Cardiovascular or cardiac conduction diseases [e.g. NYHA Class III-IV, recent MI (6 months) or PTCA (3 months); sustained VT or clinically relevant cardiac arrhythmias; recent unstable angina (within 3 months); valvular disease (hypertrophic obstructive cardiomyopathy, aortic stenosis, hemodynamically relevant stenosis of aortic or mitral valves).
- Concurrent medications or drugs e.g. known drugs of abuse or alcohol dependency; patients taking drugs known to affect blood pressure such as chronic administration of NSAIDS; chronic use of high dose acetaminophen or chronic use of salt substitutes; recent use of investigational therapy; known hypersensitivity to one of the treatment components; previous exposure to telmisartan in a telmisartan trial; concurrent lithium or cholestyramine or colestipol resins.
- Other medical problems i.e. hepatic (SGPT or SGOT > 2 x ULN) or renal dysfunction (serum creatinine >2.3 mg/dl. insulin dependent diabetes mellitus or non-insulin dependent diabetes requiring anti-hyperglycemics.

Doses:

This is a 4 x 5 unbalanced factorial designed study. The doses as well as the number of patients that were planned for enrollment are shown below:

Table 7.2 Proposed size of groups study 502.204

Hydrochlorothiazide	Telmisartan				
	0	20	40	80	160
0	**75**	20	**75**	**75**	30
6.5	20	20	20	20	30
12.5	**75**	20	**75**	**75**	30
25	20	20	20	20	30

There are six cells of the factorial design are pivotal for the primary end point, these are in bold. These cells reflect the pivotal dose groups for he primary analysis.

Formulations:

Table 7.3 Drugs and Lot numbers study 502.204

Substance (all Are Tablets)	Lot # (Expiration Date)	Substance	Lot # (Expiration Date)
Telmisartan 20 mg	PD 1550 (3/31/97)	PBO Telmisartan 20 mg	PD 1554(3/31/97)
Telmisartan 40 mg	PD 1551 (3/31/97)	PBO Telmisartan 40 mg	PD 1555(3/31/97)
Telmisartan 80 mg	PD 1552 (3/31/98)	PBO Telmisartan 80 mg	PD 1556 (3/31/97)
Hydrochlorothiazide 6.25	PD 1526 (1/31/97)	PBO Hydrochlorothiazide	PD-1507 (10/31/99)
Hydrochlorothiazide 12.5 mg	PD 1505 (10/31/96)		
Hydrochlorothiazide 25 mg	PD 1506 (10/31/96)		

[Comment: The hydrochlorothiazide is the placebo for the three different doses of hydrochlorothiazide and reflects adequate blinding only if all doses of HCTZ appeared equivalent].

Procedures. The procedures for the studies are outlined Table 7.4:

Table 7.4 Study Procedures study 502.204

	screening period*	Placebo Run-in period				Double-blind period				
Visit number	1	2	3	4	5#	5#	6	7	8#	9
Day in study	1	8	15	22	30	30	43	58	86	87
Days between periods	-	7	7	7	8	0	13	15	28	1
Informed consent, demographics, medical history, discontinue medications	X									
Inclusion and Exclusion criteria	X	X	X	X	X					
Physical Examination	X									X†
Blood Pressure and Heart Rate	X	X	X	X	X	X	X	X	X	X†
Concomitant Medication	X	X	X	X	X	X	X	X	X	X†
Randomization						X				
Clinical Laboratory Assessment/includes plasma renin activity and pregnancy testing for women	X				X		X	X		X†
Dispense/ Administer Study Drug	X	X	X	X		X	X	X	X	
Adverse Event Monitoring		X	X	X	X	X	X	X	X	X†
Compliance		X	X	X	X		X	X	X	
12-Lead ECG	X				X			X		X†
Body Weight	X				X		X	X		X

* Visit 1 covers the duration of this period and may include more than one visit
† To be conducted if patient pre-maturely discontinues once randomized
# Visits 5 and 8 are to be 4- hours long to obtain peak drug effects.

Blinding/ Randomization: The study reports states that the investigator, site personnel and patients were blinded to treatment allocation. All members of the trial monitoring team were blinded until data lock. No statement is made that the sponsor was also blinded to treatment.

Patients were randomized based on race. Subjects who had characteristics that were predominantly African in origin were defined as black and received randomization numbers in the 6000 series. Non-black patients were assigned numbers in the 4000 series.

The large number of potential treatments, as well as the prespecified racial stratification, made the randomization procedure complex. The randomization schedule was generated in a blinded manner by a third party, . Each study site was initially shipped a total of 10 kits. The number of kits in the 6000 series (reserved for blacks) and the 4000 series (reserved for non-blacks) for each site was at first estimated. Upon the need for additional kits, the number of kits in the 6000 series that was already disbursed was determined. The next allocation group was sent with the frequency of black patients already enrolled was known. In addition, the particular treatments in previous disbursed lots was considered in supplying the next set of treatments so that no one site was over-weighted in a particular treatment.

Towards the end of the study, supplies were transshipped between study centers as the need arose. Numerical sequencing within a study site was therefore not reflective of the time of enrollment.

There were several five patients who were allocated to the wrong series. Three black patients received initial allocation numbers in the 4000 series and two non-blacks who received numbers in the 6000 series.

Statistical:

Power calculations: The study size of 780 patients would be sufficient to detect at the 0.05 level (one sided) will be able to detect a 4 mm Hg average minimum gain [global AVE test of the two combinations over their components] with a power of 86%. The power to detect superiority in the black population,

assuming that these subjects constitute 30% of those enrolled is 45%. The power to detect superiority in the non-black population is 73%.

End points:
Primary endpoint:

The primary end point of this study was the change from baseline (pre dose measurement on visit 5) in supine diastolic blood pressure (DBP) to the measurement at 24 hour post-dose at the last visit of the double blind period. The main focus for the primary end point is limited to the 2 x 3 factorial array consisting of placebo (telmisartan), telmisartan 40 mg, telmisartan 80 mg with placebo (HCTZ) or HCTZ 12.5 mg. The other dose combinations will only be utilized to define the response surface. A last observation carried forward method based on trough measurements will be used to estimate the effect for those who prematurely discontinue.

For the primary analysis, the study plans to show that at least one of the two combination products is superior to the individual components. The process of showing superiority is a two-stage analysis. The first stage is demonstrating that the arithmetic average of the minimum gain in blood pressure effect is greater than 0. Then, of the two combination products, any combination that is superior to its components will be selected by the MIN test.

The sponsor proposed to model the blood pressure effects to define a response surface with the data from the full 20 cell factorial study. The data is to be fit by published methodologies. The sponsor proposed performing piecemeal exploration of the response surface using a set of regression models to fit sub-regions of the surface (e.g. the dose-response of telmisartan, given a specific hydrochlorothiazide level, the dose-response of hydrochlorothiazide given a specific telmisartan level, and the dose-response of patients at or above specific levels of each treatment will all be explored). Final descriptive dose response models will be selected on the significance of the model as well as the lack of fit tests.

The primary data sets consist of all patients who took at least one dose. For those who prematurely discontinue a last observation carried forward analysis will be utilized.

[Comment: I could find no prespecified analysis that defined which, if any, covariates are to be included within the analysis.]

Secondary end points:

Secondary endpoint analyses include: the change from baseline in supine systolic blood pressure and supine heart rate as well as the change from baseline in standing diastolic and systolic blood pressures and heart rate.

A categorical response rate (how defined) will also be employed by the Mantel-Haenzsel test].

Peak to trough ratios will be analyzed. Peak will be defined as the measured effect four hours post dose at visit 8. Trough will be defined as the effect at visit 9 (24 hours after the dose on visit 8).

Safety Analysis.

These include adverse events, change in laboratory parameters, physical examination and ECGs. Analysis will also be done of the first dose postural effects at visit 5. Postural effects on treatment is defined as effects on blood of at least 10 mm Hg in assuming the standing position on treatment when compared to the same measurement at baseline. For heart rate, orthostasis is defined as an increase of at least 10 BPM greater than the same measurement at baseline.

Results:

A total of 828 patients were randomized among 50 centers (see Table 7.1). The sponsor terminated center # 48 on 19 January 1996 (prior to breaking the study blind) because of inadequate source documentation and drug accountability. The 10 patients who were enrolled in this site were excluded from analysis. There were, therefore a total of 818 Patients who were randomized and evaluable.

The outcomes of these patients, (per sponsor's table 8.1:2) are shown in Table 7.5.

Table 7.5 Outcomes study 502.204

Randomized	**818 (100%)**
Discontinued during double-blind period	69 (8.4%)
Adverse events	24 (2.9%)
Unexpected Worsening of Hypertension	3 (0.4%)
Worsening of Other Disease	2 (0.2%)
Other Adverse Events	19 (2.3%)
Lack of Efficacy	18 (2.2 %)
Non Compliance	7 (0.9%)
Lost to Follow-up	6 (0.7%)
Consent Withdrawn	6 (0.7%)
Other	8 91.0%)
Completed Study	**749 (91.6%)**

Protocol Violations:

The sponsor defined 12 patients as having major protocol violations. Four patients (# 4192, # 4317, # 6109 and # 6112) used another antihypertensive medication prior to study related measurements. Four patients (# 4053, # 4275, # 4566 and # 6061) discontinued for non-compliance. Three patients (# 4097, # 4098 and # 6064) had their blood pressures measurements at times inconsistent with trough measurements (< 10 hours post dose). One patient (# 4315) was using an inadequate method of birth control.

Most other deviations were considered as minor and the values not excluded from analysis .The sponsor adjudicated the criteria in a "blinding report" planning meeting of 20 November 1996. The data was locked the following day. Among the violations which the sponsor deemed minor were those measurements outside the prespecified 22-30 hour post-dose window. (There were 19 such events whose

measurement was outside the pre-specified window but not as extreme as those defined as "major" violations). Also included were patients with extremes in blood pressures (outside the upper limits of systolic or diastolic pressure at baseline). There were two whose baseline blood pressure exceeded 200-mm Hg supine systolic blood pressure. There were additionally 34 patients whose baseline supine systolic blood pressure were < 140 mm Hg. There were eight patients who had baseline measurements consistent with the entry requirement of ≥ 95 mm Hg, nevertheless at one or more of the run-in visits of < 95 mm Hg.

Demographics:

The sponsor tabulated the demographic characteristics in two different ways. Sponsor's table 8.3:2 lists the demographic characteristics for the six primary efficacy groups. Sponsor's table 8.3:1 lists the demographics for those on monotherapy telmisartan, monotherapy HCTZ, combination treatment (all combination treatments collapsed as a single group) as well as placebo. [Comment: The demographics for the full factorial treatments were not listed.]. I've reproduced selective demographics for the six primary treatment groups below:

Table Demographics of those in study 502.204 pivotal treatment groups

	Placebo	T40	T80	H12.5	T40/H12.5	T80/H12.5
Number	74	75	77	75	70	74
Age median (years) (25/75 quartiles)	55(44/62)	51 (42/61)	50 (44/58)	53 (44/51)	56 (49/65)	53 (44/62)
Race						
Black (%)	18 (24%)	20 (27%)	22 (29%)	20 (27%)	16 (23%)	22 (30%)
Non-black (%)	56 (76%)	55 (73%)	55 (71%)	55 (73%)	54 (77%)	52 (70%)
Gender						
Male (%)	45 (61%)	44 (59%)	46 (60%)	53 (71%)	39 (56%)	48 (65%)
Female (%)	29 (39%)	31 (41%)	31 (40%)	22 (30%)	31 (44%)	26 (35%)
Duration of Hypertension (yrs) (25/75 quartiles)						
Black	5.5 (3/12)	4.0 (2/14.5)	6.0 (3/10)	5.0 (2/8)	17 (7/21.5)	4.5 (3/7)
Non-black	6.0 (3.5/11)	6.0 (2/11)	9.0 (2/13)	6.0 (3/13)	7.5 (3/15)	10 (5/16)
Antihypertensive use in previous six months						
None	20 (27%)	29 (39%)	25 (33%)	21 (28%)	19 (27%)	27 (37%)
One drug	35 (47%)	32 (43%)	36 (47%)	33 (44%)	34 (49%)	32 (43%)
Two or more drugs	19 (26%)	14 (19%)	16 (21%)	21 (28%)	17 (24%)	15 (20%)

Slightly more black (77%) than non-black patients (65%) were treated with antihypertensive therapy within one-month of enrollment- primarily monotherapy. More black patients (34%) were on combination therapy than non-black Patients (20%). The distribution with respect to the treatment groups was not stated.

Target organ damage: The sponsor (sponsor's Table 8.3;3) lists the number of patients with target end-organ damage. The sponsor did not list these subjects by treatment group.

Table 7.7 Concurrent medical problems in patients enrolled in study 502.204

Organ System	Number of patients (%) 818 patients (100%)
Ophthalmologic	86 (10.5%)
Cardiac	81 (9.9%)
Peripheral Vascular	16 (2.0%)
Renal	10 (1.2%)
Cerebrovascular	8 (1.0%)
One or more of the above	**187 (22.9%)**