

Study #10
502.219 vol.112

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

Study Summary: This study was an open-label follow-on study. There was no placebo group or randomized placebo-withdrawal phase. Long-term efficacy, therefore, cannot be established from this study. Since those who entered this study, completed a previous study, those intolerant to drug have already been discontinued during the previous exposure to telmisartan.

Patients who successfully completed a previous double blind telmisartan study (studies # 502.202, 502.203, 502.204, 502.206, 502.223) were eligible to enroll in this long term extension. The duration of the previous studies were 4-12 week long. The designs of the previous studies included placebo-controlled dose-ranging study (study # 502.203), placebo-controlled dose ranging study with a positive controlled arm (# 502.202, 502.206), a placebo controlled study with a positive control arm (# 502.223) or a factorial design study (#502.204). When employed, the positive controls were generally angiotensin converting enzyme inhibitors (enalapril or lisinopril).

Those who enrolled, therefore were treated either with telmisartan monotherapy (dose range 20-160 mg) or telmisartan 40-160 mg with 12.5 or 25 mg hydrochlorothiazide, daily during the previous lead-in study.

Patients who entered this study more than 30 days after completing the previous qualifying telmisartan study had baseline measurements including safety measurements re-established. All patients were started at 40 mg telmisartan, independent of the previous stable telmisartan dose. If the goal blood pressure was achieved, they remained at that dose. The protocol-stipulated goal blood pressure was initially < 95 mm Hg. However, this was altered by amendment # 2 to < 90 mm Hg. If the goal blood pressure was not achieved, the dose was raised to 80 mg once daily of telmisartan. After 2-4 weeks if blood pressure control was inadequate, hydrochlorothiazide at dose of 12.5 mg daily was added. After an additional 2- 4 weeks if blood pressure control was inadequate the dose of hydrochlorothiazide was increased to 25 mg daily. If after an additional 4 weeks blood pressure control was inadequate other antihypertensive medications could be added. All medications were taken before breakfast (approximately 1 hour).

The specifics of the procedures are diagramed below.

Table 10.1 Procedures During Study 502.219

Visit #	Open-Label Titration visits q 4 weeks				Open-Label Treatment				Final/yearly	Interim*
	1	2	3	4	5	6	7	8		
weeks on treatment	-	4	8	12	20	28	36	42	52	
Procedures										
Informed Consent; Inclusion/Exclusion	x									
Vital Signs, Concomitant Therapies, Study drug dispense, Adverse Events	x	x	x	x	x	x	x	x	x	x
Compliance, Global Evaluation of Efficacy		x	x	x	x	x	x	x	x	x
Laboratory Evaluations (and q 6 months after 1 year), K+ checked 2 weeks post addition of HCTZ CPKs to be obtained if patient complained of myalgia.				x		x			x	
12-Lead ECG						x			x	
Pregnancy Test for women						x			x	

* A visit is scheduled after 2-weeks for any change in antihypertensive therapy

Study outcome:

The study design prevents any usable efficacy conclusion about the combination of hydrochlorothiazide and telmisartan. Some safety data, however, can be extracted about the concurrent use of telmisartan with hydrochlorothiazide.

598 patients were enrolled from the 6 prespecified studies plus from 1 non-prespecified study (4 Patients enrolled from study # 502.214). The studies for which the Patients were enrolled as well as their disposition during the study are shown in Table 10.2 and 10.3, respectively.

Table 10.2 Study of origin for patients enrolled in study 502.219

Previous Trial	Number Enrolled
502.202	8
502.203	85
502.204	320
502.206	173
502.214	4
502.223	8
Total= 598	

The final treatments, the status at the end of the study and the reason for discontinuation are shown below.

Table 10.3 Final treatments and outcomes study 502.219

	Telmisartan Monotherapy	Telmisartan + Any HCTZ	Combination Therapy	Total
Total at Last Treatment*	315 (100%)	216 (100%)	65 (100%)	596 (100%)
Completed	195 (61.9%)	149 (69.0%)	42 (64.6%)	386 (64.5%)
Discontinued	120 (38.1%)	67 (31%)	23 (35.4%)	210 (35.5%)
Adverse Events	45 (14.3%)	23 (10.7%)	9 (13.8%)	77 (12.9%)
Lack of Efficacy	5 (1.6%)	12 (5.6%)	5 (7.7%)	22 (3.7%)
Non-Compliance with Protocol	9 (2.9%)	10 (4.6%)	2 (3.1%)	21 (3.5%)
Lost to Follow-Up	26 (8.3%)	6 (2.8%)	2 (3.1%)	35 (5.9%)
Consent Withdrawn	19 (6.0%)	9 (4.2%)	5 (7.7%)	34 (5.7%)
Other	16 (5.1%)	7 (3.2%)	0	23 (3.8%)

* 2 subjects who enrolled never received medication, and therefore have no final treatment

Overall 64% of those who entered the study completed. The demographics of those enrolled is shown Table 10.4.

Table 10.4 Demographics among those entering Study 502.219

	Telmisartan Monotherapy	Telmisartan + Any HCTZ	Combination Therapy	Total
Gender (Male/Female) [% Male]	185/130 [59%]	137/79 [63%]	42/23 [65%]	364/232 [61%]
Race(Caucasian/Black/Other) [% Black]	259/46/10 [14.6%]	151/56/9 [25.9%]	46/16/3 [24.6%]	456/118/22 [19.8%]
Age (mean) [Range]	52.6 [23-79]	55.0 [29-79]	53.1 [31-74]	53.5 [23-79]
Blood Pressure at baseline	150/98	156.7/101.4	162.1/103.8	154/100.4

Among those who were required diuretics with or without additional add-on therapies were more likely to have higher blood pressures at baseline, more likely to be black and slightly older. The duration of exposure for each of the doses is shown in Table 10.5. This table includes exposure during the titration period and is not limited to the final treatment.

Table 10.5 –Duration of Exposure study 502.219

Exposure	T40	T80	T80 + H12.5	T80 + H25	T40 + H12.5	T40 + H25	Combination	Total
N	596	396	272	186	3	3	69	596
Mean	197.8	162.3	167.5	312.4	237.7	137	392.2	527.1
Median [Range]	44 [1-977]	35 [1-956]	70 [5-868]	291 [2-891]	52 [45-616]	192[28-327]	410 [1-918]	641 [1-983]
Patient-years	322.8	176.0	124.73	159.1	2.0	1.1	74.09	860.1

Deaths/Dropouts/Discontinuations:

There was one death in the study.

Patient # 4157 a 62-year old white male died a **sudden death** after treatment with monotherapy telmisartan. The subject was treated for a total of 296 days of treatment with telmisartan 40-mg and telmisartan 80-mg.

There were a total of 210 discontinuations from the study.

These are listed in Table 10.6.

Table 10.6: Discontinuations study 502.219

Patient #	TX	Age	Race	Gender	Duration	Reason	Specifics	
1	0233	T40	52	W	M	5	AE	Severe headache. BP at termination 138/87
2	1282	T40	57	W	M	756	AE	Inferior wall MI
3	1330	T40	46	W	M	237	AE	Arthralgias
4	3021	T40	42	W	F	14	AE	Severe headache and hypertension. BP at end of study was 208/124
5	3051	T40	65	W	M	242	AE	Rash
6	3111	T40	36	W	F	47	Other	Stopped medication. of BP was normal > 2 weeks after discontinuation of BP medication
7	3171	T40	43	B	F	2	AE	Headache. BP at termination was 141/95
8	3269	T40	59	W	M	10	AE	Chest pain. Stabbing chest pain and congestion (chest?). Not hospitalized.
9	3291	T40	53	W	M	545	AE	Hypotension and dizziness. No BP values listed
10	3308	T40	51	W	F	6	AE	Headache. No BP listed
11	3348	T40	48	W	M	30	AE	Elevated blood glucose
12	3403	T40	40	W	M	220	AE	Elevated SGOT and SGPT. Maximum SGOT 38 IU/L ; maximal SGPT 84IU/L
13	4056	T40	57	W	F	34	AE	Worsening hypertension. Last BP 200/120
14	4092	T40	55	W	M	206	AE	PSVT.
15	4158	T40	67	W	M	183	AE	Fatigue
16	4194	T40	43	W	M	55	AE	Fatigue and lower back pain
17	4201	T40	66	W	M	35	AE	Rash
18	4363	T40	55	W	M	91	AE	Retinal infarct
	4396	T40	55	W	M	581	AE	Tachycardia (with palpitations)
	4431	T40	62	W	F	42	AE	Coronary artery disease. Underwent angioplasty

21	4465	T40	64	W	M	143	AE	Esophageal cancer
22	4493	T40	50	W	M	81	AE	Fatigue
	4543	T40	61	W	M	148	AE	Fatigue, leg edema, weight gain, loss of libido and gynecomastia
	4555	T40	47	W	M	4	AE	MI.
	4574	T40	47	W	M	112	AE	Elevated SGPT and SGOT. Max SGPT (81 IU/L) SGOT 50 U/L)
26	6011	T40	45	B	M	91	AE	Orthostatic hypotension. Supine BP 113/88 to standing 80/61
27	6099	T40	46	B	F	26	AE	Hypertension. BP 190/130
28	6108	T40	33	B	M	249	AE	Elevated CPK. Maximum CPK= 446 U/l
29	6231	T40	36	B	F	1	AE	Positive pregnancy test
30	4281	T40 + H25	35	W	F	415	AE	Kidney infection
31	1091	T80	40	B	F	164	AE	Rash
32	1177	T80	47	W	F	293	AE	Fatigue and itching
33	1325	T80	40	W	M	218	AE	MI. Underwent catheterization and PTCA
34	3084	T80	49	W	M	42	AE	Tiredness and insomnia
35	3220	T80	41	W	M	46	AE	Hypertension. BP 204/136. Had severe headache and one episode of vomiting
36	3235	T80	56	W	F	183	AE	Stroke. Left arm numbness BP 198/112
37	3350	T80	56	W	M	59	AE	Cough and blurred vision
38	4157	T80	62	W	M	297	AE	Died sudden death
39	4168	T80	51	W	M	199	AE	Fatigue and lethargy
40	4328	T80	37	W	M	83	AE	Abnormal ECG. Primary AV block, sinus bradycardia, Mobitz-1 block
41	4399	T80	42	W	M	178	AE	Diabetes mellitus.
42	4527	T80	53	W	M	441	AE	Cancer of the large intestine, hematochezia
43	4582	T80	59	W	M	38	AE	Coronary artery disease. Chest pain.
44	6091	T80	40	B	M		AE	Elevated CPK maximum 595 U/L
45	6101	T80	61	B	M	319	AE	Chest pain, coronary artery disease. Underwent CABG
46	6207	T80	46	B	F	48	AE	Dizziness.
47	1169	T80 + H12.5	65	W	M	163	AE	MI. Patient underwent CABG
48	3165	T80 + H12.5	38	W	M	229	AE	Epigastric pain and tingling scalp and tingling extremities
49	4095	T80 + H12.5	75	W	F	238	AE	Atrial fibrillation, treated with quinidine
	4297	T80 + H12.5	58	W	F	133	AE	Colon cancer and uterine fibroids.
	4347	T80 + H12.5	43	W	M	239	AE	Tremor, bilateral leg aches and right arm ache, CPK not stated
	4378	T80 + H12.5	75	W	M	334	AE	Renal cyst, cholelithiasis and fatty infiltration of the liver, based on CT
53	4488	T80 + H12.5	52	W	M	121	AE	Dizziness and nausea
54	4528	T80 + H12.5	30	W	F	154	AE	Chest pain. Pain resolved
55	4607	T80 + H12.5	47	W	F	225	AE	Coughing
56	6020	T80 + H12.5	59	B	F	134	AE	Malignant breast neoplasm
57	6021	T80 + H12.5	56	B	F	319	AE	Hyperthyroidism
58	6060	T80 + H12.5	45	B	F	273	AE	Syncope. BP at time of event 79/59
59	6119	T80 + H12.5	52	B	F	47	AE	Dizziness. BP did not appear to be consistent with orthostasis
60	1006	T80 + H25	72	W	M	209	AE	Hepatitis. Elevated LFTs. Alk Phos 153 U/L, SGPT 365 U/l; SGOT 272 U/l; Total Bili 2.3 mg/dl; LDH 345 U/l
61	1045	T80 + H25	60	W	M	540	AE	Delirium requiring hospitalization
62	1280	T80 + H25	58	W	M	974	AE	SVT
63	3178	T80 + H25	58	W	M	97	AE	Tingling in both arms
64	3218	T80 + H25	62	W	M	329	AE	Malignant melanoma
65	3285	T80 + H25	70	W	M	757	AE	Glioblastoma multiforme
66	4362	T80 + H25	53	W	F	390	AE	Adenocarcinoma of the Colon
67	4459	T80 + H25	59	W	M	273	AE	Irritability
68	4575	T80 + H25	64	W	M	294	AE	MI. The patient underwent cardiac catheterization and angioplasty.
69	4349	T80 + Other	55	W	M	126	AE	Increased diastolic blood pressure. Supine BP 161/115; Standing 169/121; Corresponding baseline 171/109 and 173/109
70	4197	T80 + H12.5 + Other	74	W	M	226	AE	Prostate cancer
71	1001	T80 + H25 + Other	56	B	M	290	AE	Sexual dysfunction.
72	1022	T80 + H25 + Other	60	W	F	587	AE	Dizziness, heart palpitations, lack of energy and weight gain.
73	3119	T80 + H25 + Other	68	W	M	363	AE	Constipation
74	3186	T80 + H25 + Other	66	W	M	148	AE	Bell's palsy
75	3300	T80 + H25 + Other	48	W	F	403	AE	Fatigue
76	4006	T80 + H25 + Other	52	W	M	365	AE	Diabetes mellitus. Glucose level 152 mg/dl
77	4565	T80 + H25 + Other	45	W	M	307	AE	Symptomatic orthostatic hypotension. BP on standing 84/50 with dizziness and lightheadedness
78	1066	T40	48	W	F	595	Withdr Cons	No AEs
79	1071	T40	60	W	M	87	Withdr cons	No AEs upon D/C
80	1092	T40	39	W	M	299	Withdr cons	No AEs
	1095	T40	49	W	F	578	Withdr cons	No AEs upon D/C
	1833	T40	53	O	F	1	Withdr cons	No AEs

83	3025	T40	52	W	F	198	Withdr cons	No AEs
84	3088	T40	55	W	F	1	Withdr cons	No AEs
	3228	T40	31	W	F	519	Withdr cons	No AEs
	3365	T40	53	W	F	218	Withdr cons	Stopped taking meds
	4084	T40	52	W	M	44	Withdr cons	No AE s listed
88	4319	T40	53	O	F	376	Withdr cons	No AE s listed
89	4389	T40	48	W	F	25	Withdr cons	No AE s listed
90	4407	T40	69	W	F	276	Withdr cons	No AE s at D/C
91	4460	T40	65	W	F	36	Withdr cons	Felt BP was ok
92	4586	T40	42	W	F	266	Withdr cons	Failed to return for follow up
93	6038	T40	60	B	F	355	Withdr cons	No AE s listed
94	6114	T40	29	B	F	365	Withdr cons	Planned to D/C after 1 year
95	3189	T80	48	W	F	609	Withdr cons	Moved, No AE s
96	4279	T80	69	W	M	75	Withdr cons	BP at time of D/C was 177/100; PVT physician stopped use
97	3049	T80 + H12.5	67	W	F	68	Withdr cons	No AE s at time of D/C
98	4088	T80 + H12.5	64	W	M	360	Withdr cons	No AE s
99	6178	T80 + H12.5	45	B	M	330	Withdr cons	No AE s
100	4191	T80 + H12.5 + other	64	W	F	41	Withdr cons	
101	1041	T80 +H25	37	W	M	421	Withdr cons	Moved
102	1093	T80 +H25	46	W	M	589	Withdr cons	Wished to D/C
103	1317	T80 +H25	30	W	M	686	Withdr cons	Moved
104	3211	T80 +H25	50	O	M	330	Withdr cons	Moved
105	4094	T80 +H25	57	W	M	360	Withdr cons	
106	6015	T80 +H25	44	B	F	600	Withdr cons	
107	3046	T80 +H25 +other	51	W	F	205	Withdr cons	Had worsening depression and carpal tunnel syndrome
108	4151	T80 +H25 +other	49	W	F	250	Withdr cons	No AE s at D/C
109	4296	T80 +H25 +other	36	W	F	101	Withdr cons	Withdrew because on 3 medications
110	6228	T80 +H25 +other	33	B	F	128	Withdr cons	Refused follow-up
111	1256	T40	66	W	M	14	Lack of Eff	At termination 195/110; Pretreatment 160/102
112	1259	T40	43	O	M	23	Lack of Eff	At termination 168/110 at Baseline 158/101
113	1048	T80 + Other	61	W	M	637	Lack of Eff	At termination 169/100 at baseline 137/97
114	3172	T80	61	W	M	34	Lack of Eff	At termination 161/111 pre-treatment 160/106
115	4200	T80	65	W	M	223	Lack of Eff	At termination 161/92; pretreatment 167/100
116	6096	T80	52	B	M	27	Lack of Eff	At termination 157/100; Visit 1.1 157/93
	1068	T80 + H12.5	46	W	M	223	Lack of Eff	At discontinuation BP 127/94; penultimate BP 139/103
	3364	T80 + H12.5	42	B	F	90	Lack of Eff	At discontinuation 135/90; visit 2 189/119
	4021	T80 + H12.5	49	W	M	56	Lack of Eff	At discontinuation 138/97; pretreatment 148/99
120	4224	T80 + H12.5	59	O	M	84	Lack of Eff	At discontinuation BP 167/97; visit 2 170/100
121	1067	T80 + H25	57	W	F	197	Lack of Eff	At discontinuation BP 130/97; Pretreatment 167/101
122	3325	T80 + H25	42	B	F	440	Lack of Eff	At discontinuation BP 132/114; pretreatment 139/89
123	4380	T80 + H25	64	W	F	63	Lack of Eff	At discontinuation 174/99; pretreatment 136/91
124	4486	T80 + H25	70	W	M	114	Lack of Eff	At discontinuation 137/87; visit 1.1 137/96
125	4579	T80 + H25	58	W	M	234	Lack of Eff	Last 149/99; visit 1.1 135/89
126	6102	T80 + H25	49	B	F	272	Lack of Eff	Last 169/92; visit 2 175/93
127	6116	T80 + H25	58	B	M	63	Lack of Eff	last 160/95; pretreat185/102
128	6198	T80 + H25	56	B	M	83	Lack of Eff	last160/100; visit 2 159/105
129	3219	T80 + H25	41	W	M	121	Lack of Eff	Last 137/99; visit 2 176/111
130	3167	T80 + H25 + Other	58	W	F	291	Lack of Eff	Last 150/98; visit 2 153/104
131	4408	T80 + H25 + Other	68	W	M	254	Lack of Eff	Last 131/92; Visit 2 163/85
132	6177	T80 + H25 + Other	59	B	F	128	Lack of Eff	Last 160/110 Visit 2 153/103
133	1065	T40	38	W	F	1	Admin	Lost to follow up
134	1253	T40	47	B	F	1	Admin	Lost to follow up
135	3029	T40	41	W	M	434	Admin	Lost to follow up
136	3090	T40	56	W	M	55	Admin	Lost to follow up
137	3224	T40	57	W	M	1	Admin	Lost to follow up
138	3293	T40	51	W	F	1	Admin	Lost to follow up
139	3347	T40	45	W	M	1	Admin	Lost to follow up
140	3409	T40	27	W	M	344	Admin	Lost to follow up
141	4012	T40	39	W	M	313	Admin	Lost to follow up
142	4024	T40	39	W	M	1	Admin	Lost to follow up
143	4311	T40	59	W	M	8	Admin	Lost to follow up
144	4469	T40	26	W	M	201	Admin	Lost to follow up
145	4580	T40	60	W	F	245	Admin	Lost to follow up
146	4601	T40	55	W	M	247	Admin	Lost to follow up
147	6024	T40	36	B	M	1	Admin	Lost to follow up
148	6047	T40	43	B	M	1	Admin	Lost to follow up
149	6141	T40	45	B	F	88	Admin	Lost to follow up
150	6185	T40	41	B	M	215	Admin	Lost to follow up
	6193	T40	44	B	F	60	Admin	Lost to follow up
	6208	T40	36	B	F	129	Admin	Lost to follow up
	6215	T40	28	B	M	1	Admin	Lost to follow up

154	4073	T80	24	W	M	234	Admin	Lost to follow up
155	4272	T80	47	W	M	84	Admin	Lost to follow up
	4466	T80	55	W	F	90	Admin	Lost to follow up
	4602	T80	52	W	M	70	Admin	Lost to follow up
	6100	T80	37	B	M	252	Admin	Lost to follow up
159	3254	T80 + H12.5	57	W	M	681	Admin	Lost to follow up
160	3275	T80 + H12.5	52	W	M	84	Admin	Lost to follow up
161	3319	T80 + H12.5	45	W	M	584	Admin	Lost to follow up
162	4603	T80 + H12.5	51	W	M	90	Admin	Lost to follow up
163	1314	T80 + H25	43	W	M	365	Admin	Lost to follow up
164	4570	T80 + H25	64	W	M	515	Admin	Lost to follow up
165	4430	T80 + H25 + Other	60	O	F	55	Admin	Lost to follow up
166	6174	T80 + H25 + Other	47	B	F	197	Admin	Lost to follow up
167	1148	T40	52	W	F	538	Admin	Non-compliance
168	4176	T40	67	W	M	96	Admin	New investigational drug
169	4269	T40	51	W	M	70	Admin	Non-compliance
170	4442	T40	36	W	M	609	Admin	Non-compliance
171	4515	T40	59	W	F	289	Admin	Non-compliance
172	4023	T80	45	W	M	95	Admin	Non-compliance
173	4277	T80	43	W	F	596	Admin	Non-compliance - Started Verapamil per PMD
174	4451	T80	49	W	M	34	Admin	Non-compliant- increased own medication
175	6111	T80	35	B	F	83	Admin	Non-compliance
176	3109	T80 + Other	53	B	M	40	Admin	started on other antihypertensive by PMD
177	4152	T80 + H12.5	45	W	M	492	Admin	Non-compliance
178	6013	T80 + H12.5	49	B	M	191	Admin	Non-compliance
179	1072	T80 + H25	48	W	F	164	Admin	Non-compliance
180	3353	T80 + H25	59	W	M	163	Admin	Non-compliance
181	3356	T80 + H25	69	W	M	522	Admin	Non-compliance- started on Hytrin
182	4175	T80 + H25	65	W	M	356	Admin	Non-compliance
183	4390	T80 + H25	38	W	M	476	Admin	Non-compliance
184	4588	T80 + H25	37	O	M	302	Admin	Non-compliance
185	6016	T80 + H25	45	B	F	467	Admin	Non-compliance
186	6182	T80 + H25	46	B	F	373	Admin	Non-compliance
187	6167	T80 + H25 + Other	32	B	F	88	Admin	Non-compliance
	2051	T40	50	W	M	21	Other	Ineligibility
	3255	T40	66	W	F	364	Other	Moved
	4050	T40	48	W	M	362	Other	Stopped per PMD
191	4352	T40	64	W	M	36	Other	Leaving
192	4433	T40	39	W	F	386	Other	Significant weight loss with normalized BP
193	4567	T40	58	W	F	304	Other	Moving
194	4018	T80	64	W	F	70	Other	Per PMD request
195	4049	T80	48	W	F	250	Other	Moving
196	4202	T80	69	W	M	301	Other	Per investigator's discretion
197	4569	T80	69	W	M	225	Other	PMD requested discontinuation
198	6095	T80	37	B	F	81	Other	Moving
199	4161	T80 + H12.5	79	W	M	371	Other	Scheduled for surgery
200	4359	T80 + H12.5	68	W	F	551	Other	Own preference
201	6104	T80 + H12.5	77	B	M	245	Other	Moved
202	6173	T80 + H12.5	48	B	F	211	Other	D/C BY PMD- BP not controlled
203	1007	T80 + H25	54	B	M	396	Other	Moved
204	4083	T80 + H25	53	O	M	301	Other	Stopped per PMD- new medication started
205	6216	T80 + H25	76	B	M	117	Other	Moved
206	3055	T40	57	W	M	256	Other	Terminated study at site
207	3056	T40	44	W	M	178	Other	Terminated study at site
208	3058	T40	39	W	M	260	Other	Terminated study at site
209	3059	T40	45	W	F	215	Other	Terminated study at site
210	3060	T40	63	W	M	157	Other	Terminated study at site

Five of those who discontinued did so because of premature study termination in a site. There were 77 patients who discontinued the trial due to adverse events and 22 patients who discontinued due to lack of efficacy.

Most of the severe adverse events occurred among those who were treated with telmisartan monotherapy. Among those who were taking concurrent concomitant hydrochlorothiazide with

telmisartan, thee severe reactions included one patient with a syncopal episode (# 6060). Two patients (# 1169, # 4574) had myocardial infarctions. There were four patients (# 6020, 4297, 4362 and 3218) discontinued due to neoplasm. One patient (# 1006) discontinued due to hepatitis.

Serious adverse events per sponsor, (table 10.2.4:1) as Table 10.7.

Table 10.7 Serious adverse events study 502.219

	Telmisartan 40	Telmisartan 80	Telmisartan 80 + HCTZ 12.5	Telmisartan 80 + HCTZ 12.5	Total
Total Treated	596	396	273	176	596
Total with SAE	20 (3.4%)	15 (3.8%)	7 (2.6%)	8 (4.3%)	54 (9.1%)
Patient*years treated	322.8	176.0	124.7	159.1	860.1
SAE/Patient years Treated	0.062	0.085	0.056	0.050	0.062
Body as a Whole	4 (0.7%)	2 (0.3%)	1 (0.4%)	0	7 (1.2%)
Cardiovascular Disorders	1 (0.2%)	2 (0.5%)	0	0	3 (0.5%)
Central and Peripheral Nervous Systems	1 (0.2%)	1 (0.3%)	0	0	2 (0.3%)
Gastrointestinal Disorders	6 (1.0%)	1 (0.3%)	0	1 (0.4%)	8 (1.3%)
Liver and Biliary System	0	0	1 (0.4%)	0	1 (0.2%)
Musculoskeletal System	2 (0.3%)	9	0	0	2 (0.3%)
Myo-, Endo-, Peri-, Cardial and Valve Disorders	2 (0.3%)	4 (1.0%)	(0.4%)	1(0.4%)	9 (1.5%)
Neoplasm	2 (0.3%)	1 (0.3%)	3 (1.1%)	3 (1.6%)	11 (1.8%)
Psychiatric Disorder	0	0	0	1 (0.5%)	1 (0.2%)
Reproductive Disorders Male/Female	0 / 2 (0.3%)	1(0.3%)/1 (0.3%)	0/ 1 (0.4%)	1 (0.5)/0	6 (1.0%)/3 (0.5%)
Resistance Mechanism Disorders	1 (0.2%)	0	0	0	1 (0.2%)
Respiratory System Disorders	1 (0.2%)	0	1(0.4%)	0	4 (0.7%)
Urinary System Disorders	0	2 (0.5%)	0	1(0.5%)	1 (0.2%)
Vascular Extracardiac Disorders	1 (0.2%)	1 (0.3%)	0	0	2 (0.3%)

There did not appear to be any signal that overall serious adverse events were increased when telmisartan and hydrochlorothiazide were concurrently used. In particular, when normalized for duration of exposure there appears to be no major signal that any of the serious adverse events are increased with concurrent use of telmisartan and HCTZ.

Overall Adverse Events:

The sponsor tabulates the overall adverse events reported in > 2% of the patients treated (sponzor's table 10.2.3:1). Selected portions of this table are reproduced in Table 10.8.

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Table 10.8 Overall adverse events, study 502.219

	Telmisartan Monotherapy	Telmisartan + HCTZ	Combination
Total Treated	596	287	69
Total Adverse Events	432 (72.5%)	216 (75.3%)	54 (78.3%)
Exposure (days)	188	232	393
Body as a whole	31.8%	36.6%	39.1%
Chest Pain		3.7%	4.2%
Fatigue		6.0%	4.5%
Cardiovascular System	7.7%	5.6%	13.0%
Central & Peripheral Nervous System	29.2%	22.3%	33.3%
Dizziness		6.2%	9.4%
Headache		17.6%	11.1%
Gastrointestinal System	17.8%	21.3%	23.2%
Heart Rate and Rhythm	3.4%	4.9%	4.3%
Metabolic and Nutritional	5.7%	7.7%	4.3%
Musculoskeletal	9.9%	13.6%	13.0%
Neoplasm	0.7%	3.1%	4.3%
Psychiatric Disorder	5.0%	7.0%	14.5%
Reproductive Disorders	1.8%	2.1%	1.4%
Resistance Mechanisms	6.4%	5.9%	14.5%
Respiratory System Disorders	32.0%	34.1%	46.4%
Skin and Appendages	6.9%	6.3%	10.1%
Urinary System	6.0%	5.6%	8.7%
Vision Disorder	3.7%	1.0%	5.8%

It is difficult to interpret the overall adverse events.

ECGs: The sponsor lists a total of 36 "Clinically Significant ECG Changes". Of these, 13 were on concomitant telmisartan and hydrochlorothiazide.

Table 10.9 ECG abnormalities on combination telmisartan/Hydrochlorothiazide, study 502.219

Patient #	Treatment	Age	Race	Sex	ECG change
1169	T80 + H12.5	65	W	M	Anterior MI
4034	T80 + H12.5	51	W	M	Benign extra systoles present
4348	T80 + H12.5	59	W	M	Left axis deviation. Left anterior fascicular block/possible ischemia
6022	T80 + H12.5	32	B	M	Incomplete RBBB- no longer seen. Sinus bradycardia
4173	T80 H12.5 (&H25)	55	W	F	T-wave inversion in I, II,III, AVF, AVL, V2-V6 consistent with ischemia. WNL low voltage change from
1280	T80 + H25	56	W	M	SVT
3117	T80 + H25	74	B	M	Sinus tachycardia
3270	T80 + H25	49	W	F	Non-specific T wave abnormalities
4257	T80 + H25	57	W	M	Non-specific T wave abnormality absent
4380	T80 + H25	64	W	F	Enlarged heart? Hypertensive Cardiac myopathy
4575	T80 + H25	63	M	W	Suggested MI
6140	T80 + H25	57	B	M	PACs
3338	T80 + H25 +Other	50	B	M	LVH by Voltage

Since there is no reasonable control group it is difficult to interpret this data.

Vital Signs/Dizziness/Lightheadedness/Orthostasis.

The sponsor claims no significant clinical significant positional differences in blood pressure or heart rate (group means). There were three patients # 6011 (T40) and # 4565 (T 80 + H25 + other) and # 6061 (T80 + H12.5) who discontinued due to orthostasis. Patient #6061 discontinued due to syncope associated with a low BP. Six additional patients discontinued for dizziness or lightheadedness. Of these, four were on some form of telmisartan plus hydrochlorothiazide (# 4486, 6119, #1022, # 4565) two were on monotherapy (# 6207, #3291)

Laboratory:

There were 7 patients who discontinued from telmisartan monotherapy due to laboratory abnormalities. There were two patients on some combination therapy that included diuretic who discontinued due to adverse events (# 1006; treated with T80 + H25) discontinued due to increased LFTs; pt # 4006 (T80 + H25 + Other) who discontinued due to diabetes.

The number of subjects who had laboratory values classified as an adverse event is shown Tble 10.10

Table 10.10 Laboratory values classified as adverse events.

Treatment group	Telmisartan	Telmisartan + HCTZ	Combination	Comment
Hyperlipidemia	6	1	1	
Increase glucose	2	2		
Increased SGOT/SGPT	5	0?		# 1006 D/C'd due to abnormal LFTS on T + HCTZ?
Diabetes Mellitus	5			
Hypertriglyceridemia	2	4		
Increased LDH	1			
Increased Alkaline Phosphatase	2			
Hypokalemia	1	6		
Hypercholesterolemia	4	3		
Increased CPK	3			
Hyponatremia		1		

Conclusion: This is a relatively large open-label database, with some fraction of those who enrolled treated with concurrent telmisartan and HCTZ. Since there was no comparative group, there is no context by which to interpret either the safety or blood pressure effect of the combination therapy.

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Study # 11

Study 502.261. Vol 5.1-5.10

Title Of Study: An Eight Week Randomized, Double-Blind Study Comparing a Fixed Dose Combination of Telmisartan 80 mg Plus Hydrochlorothiazide 12.5 mg t Telmisartan 80 mg in Patients Who Fail to Respond Adequately to Treatment With Telmisartan 80 mg

Investigator and Sites: A total of fifteen Canadian Investigators enrolled a total of 781 subjects of which 491 were eventually randomized to 80 mg Telmisartan or 80 mg telmisartan/HCTZ 12.5 mg. Many of those involved in the clinical trial were not affiliated with academic centers and were novices to hypertension clinical trials.

Table 11.1 Investigators, sites and number/site enrolled.

Center 1 Dr. YvesLacurciere Centre Hospitalier Universitaire de Quebec Sainte-Foy, Quebec n=104	Center 2 Dr. William Booth Antigonish Clinical Trials Antigonish , Nova Scotia n=18	Center 3 Dr. Howard Conter MHSU Research Assoc. Inc Halifax, Nova Scotia n=19	Center 4 Dr. Denis O'Keefe Commenwealth Med Clinic Mount Pearl, Newfoundland n=43	Center 5 Dr. Donald Taylor Charlottetown, Prince Edward Island n=29
Center 6 Dr. Jacques Lenis Invascor Longueuil, Quebec n=36	Center 7 Dr Vyta Senikas Clinical Research Consultant Group Montreal, Quebec n=9	Center 8 Dr. Jean-Pascal Oullet Q & T Research Inc Sherbrooke., Quebec n=9	Center 9 Dr. Jeff Dalter Richmond Hill, Ontario n=14	Center 10 Dr. Ben Lasko Weston, Ontario n=29
Center 11 Dr. Richard Tytus Hamilton, Ontario n=83	Center 12 Dr. Joseph Ennett Jenny Trout Centre Stratford, Ontario n=18	Center 13 Dr. David Cavanaugh Wortley Villiage Medical Center London, Ontario n=15	Center 14 Dr. Robert Orchard Midtown Medical Centre Saskatoon, Saskatchewan n=33	Center 15 Dr. I Dan Dattani Acadia Medical Center Saskatoon, Saskatchewan n=12

Formulations:

Table 11.2 Formulations study 502.261

Substance (open-Label)	Unit Strength (mg)	Formula No.	Lot #	Expiry Date
Telmisartan 40 mg	40	1309	PD-1879	3/2000
Telmisartan 80 mg (open-label and double-blind)	80	1299	PD-1881	9/2000
Placebo Matching Telmisartan 80	NA	1176	PD-1880	2/2000
FDC 80/12.5	80 Telmisartan & HCTZ 12.5	1310	PD-1883	3/2000
Placebo matching FDC 80/12.5	NA	1325	PD-1882	9/2000

[Comment: The biopharmaceutical properties of the combination product used in this study have not been described. The relationship of this product to the proposed to-be marketed formulation is not described in this submission]

Blinding: For the double blind portion of the study a double-dummy format. The subject took two tablet either telmisartan 80 mg or matching placebo and either FDC 80/12.5 or matching placebo.

Randomization: Patients were randomized in blocks of 4, two subjects to receive telmisartan 80 + FDC 80/12.5-placebo and two patients to receive telmisartan 80-placebo plus FDC 80/12.5.

Protocol Amendments and Dates of Study:

A protocol and single amendment was submitted.

The protocol was dated 19 October 1998.

The amendment was dated January 1999. The changes brought about by this amendment required the termination of subject for seated DBP \geq 114 mm Hg or SBP \geq 200 mm Hg. The title of the study was changed for clarification by the inclusion of the word adequately, referring to the response on telmisartan monotherapy.

The first patient completed the study February 1999.

The last subject completed the study September 1999

Protocol:

Inclusion Criteria: Patients were eligible for enrollment if they were between 18-80 years old, were able to provide a written consent and had mild-moderate hypertension who did not adequately respond to telmisartan monotherapy.

Exclusion Criteria:

Subjects were excluded for:

- Inadequate pregnancy prevention (for women)
- Cardiovascular disease e.g. CHF (NYHA Class III-IV); unstable angina, MI, cardiac surgery or PTCA within (3 months); arrhythmias (sustained VT, Afib, Afl or other cardiac rhythm disturbances), valvular or obstructive cardiomyopathy or stroke (6 months).
- Secondary forms of hypertension (e.g. bilateral renal artery stenosis, stenosis in a solitary kidney, post renal transplant, functioning of only one kidney)
- Contraindicated medications e.g. recent investigational new drug use. (Those treated with telmisartan in the past could be enrolled if there was at least a one-month hiatus), concomitant medications known to alter blood pressure, digitalis or digoxin, alcohol or drug dependency (within one year).
- Other clinical condition that would make the participation in this study unsafe e.g. known hypersensitivity to any component, hepatic (SGPT or SGOT \cdot 3 x ULN); renal disease (serum creatinine $>$ 2.3 mg/dl), electrolyte abnormality,
- Known hypersensitivity to any component.

Statistical Issues:

Primary End point:

The primary measure of efficacy is the change in seated diastolic blood pressure at trough after eight weeks of treatment or at last trough during the double blind phase with the last observation carried forward. The change will be calculated from the end of fixed dose period i.e. week 4 measurements will be considered the baseline). Measurements not between 20-30 hours will be excluded.

The secondary efficacy variables are the following:

- Change in trough seated systolic blood pressure after eight weeks (with last observation carried forward) from week 4 baseline.
- Change in standing diastolic and systolic blood pressure after eight weeks with LOCF, week 4 as baseline
- Blood pressure control (seated DBP $<$ 90 mm Hg)
- Systolic blood pressure response (how defined?)

Power Considerations:

The sponsor calculates that assuming at 3.0 mm Hg as a clinically relevant change in BP and a SD of approximately 9 mm Hg, a sample size of 190 evaluable patients would have a 90% power to detect his difference.

Analytic Plan: The prospective analysis was the analysis of covariance with baseline as covariate.

The list of the procedures and timing is shown in Table 11.3.

Table 11.3 Procedures study 502.261

Day	Screening		Open-Label		Double-Blind Treatment	
	-66 to -60	-56	-28	0	28	56
Visit	1	2	3	4	5	6
Informed Consent	X					
Demographics, Medical History	X					
Inclusion Exclusion Criteria	X	X	X	X		
Physical Exam, 12-lead EKG, Routine Labs,	X			X		X
Concomitant Therapy, Adverse Events	X	X	X	X	X	X
Trough Seated and Standing BP and HR	X	X	X	X	X	X
Randomization					X	
Compliance			X	X	X	X
Open Label 40 mg =X; Open Label 80 mg =Y First Dose Double Blind Medications =Z		X	Y	Z		

Study Outcome:

A total of 781 patients were enrolled into this study from 15 Canadian sites. Two hundred ninety (290) patients were withdrawn prior to randomization. There were therefore 491 patients who were randomized to double-blind treatment: 245 to telmisartan and 46 patients to telmisartan/HCTZ. The outcome for those enrolled are shown in Table 11.4:

Table 11.4 Outcomes study 502.261

Disposition	Telmisartan 80 N (%)	Telmisartan 80/HCTZ 12.5 N (%)	Total
Enrolled			781 (100%)
Not Randomized			290 (37.1%)
Randomized and Treated	245 (100%)	246 (100%)	491 (100%)
Prematurely Discontinued	10 (4.1%)	6 (2.4%)	16 (3.3%)
Adverse Events	4 (1.6%)	2 (0.8%)	6 (1.2%)
Lack of Efficacy	3 (1.2%)	0	3 (0.6%)
Non-Compliance to Protocol	1 (0.4%)	0	1 (0.2%)
Lost to Follow-up	0	3 (1.2%)	3 (0.6%)
Consent Withdrawn	1 (0.4%)	1 (0.4%)	2 (0.4%)
Other	1 (0.4%)	0	1 (0.2%)
Completed	235 (95.9%)	240 (97.6%)	475 (96.7%)
Number with "relevant" protocol Violations	6 (2.4%)	3 (1.2%)	9 (1.8%)
Either Baseline or Final Measurement outside 20-30 hour post dose window	3 (1.2%)	2 (0.8%)	5 (1.0%)
Non compliance	3 (1.2%)	1 (0.4%)	4 (0.8%)
Analysis Cohorts			
Randomized	245	246	491
Safety	245	246	491
Intent-to Treat	245	246	491
Evaluable	239	243	482
Evaluable Completers	230	235	465

The vast majority of those who enrolled completed the study. The number of patients in each of the analyzable cohorts is also displayed in Table 11.4.

The Demographics of those randomized are shown Table 11.5. Since this was a non-USA study, the fraction of those who were randomized who were black was relatively small.

Table 11.5 Demographics of study 502.261

	Telmisartan		FDC 80/12.5		Total	
Age mean ± SD (% ≥ 65 years)	55 + 10.7	(23.7%)	55.6 + 10.0	(19.9%)	55.3 + 10.4	(21.8%)
Gender (Male/Female) [% Female]	149/96	[39.2%]	160/86	[35%]	309/182	[37.1%]
Race (Caucasian/Black/ Other) [%Black]	231/8/6	[3.3%]	235/9/2	[3.7%]	466/17/8	[3.5%]
Hypertension Duration Years	8.9		9.0		9.0	
Blood Pressure at baseline (week 4)	148.7/96.6		148.9/96.4		148.8/96.5	
Pulse Rate at week 4	96.6		96.4		96.5	

Primary End Point:

The adjusted mean change from baseline in trough diastolic blood pressure for the intent-to treat population is shown in Table 10.6:

Table 10.6 measurement of primary end point, study 502.261

Group	Baseline-(reference)	Change	Difference
Telm 80 (n=245)	96.6 + 0.3	-4.9 (+ 0.4)	
FDC 80/12.5 (n=246)	96.4 + 0.3	-8.0 + 0.4	-3.1 (P<0.01*) CI (-4.2, -2.0)

*Based on analysis of covariance with the effects of reference (week 4) DBP center and treatment. [note center was not prespecified, but it is clearly a reasonable covariate]

Selected Secondary End points:

The effect for seated systolic as well as standing diastolic and systolic blood pressures are shown in Table 11.6. All measurements indicate the combination product superior to the telmisartan monotherapy.

Table 11.6 measurement of secondary end point study 502.261

	N=	Seated Systolic Blood Pressure		Standing Diastolic Blood Pressure		Standing Systolic Blood Pressure	
		Reference	Change	Reference	Change	Reference	Change
Tel 80	245	148.7 (1.0)	-7.0 (0.8)	98.0 (0.4)	-3.9 (0.5)	148.6 (1.0)	-6.3 (0.8)
FDC 80/12.5	246	148.9 (0.9)	-12.6 (0.8)	98.0 (0.4)	-7.0 (0.5)	148.7 (0.9)	-12.1 (0.9)
Treatment effect mean 95% CI		-5.7 (-7.7, -3.6) [P<0.01]*		-3.2 (-4.3, -2.0) [P<0.01]*		-5.8 (-7.9, -3.7) [P<0.01]*	

*Based on analysis of covariance with the effects of reference (week 4) DBP center and treatment. [note center was not prespecified, but it is clearly a reasonable covariate]

Pulse rates for both seated and standing, were essentially unchanged from telmisartan monotherapy reference value.

Table 11.7 Pulse changes from reference seated and standing; study 502.261

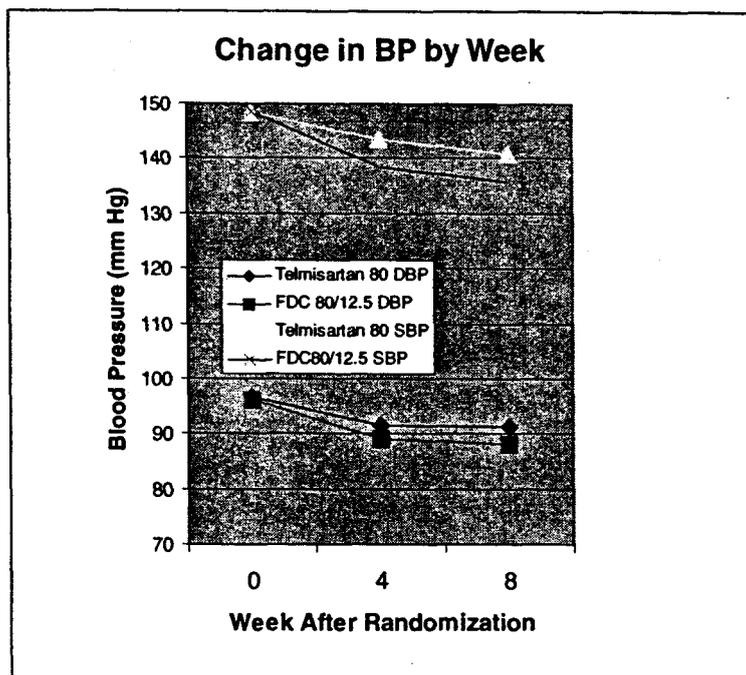
	N= (seated/standing)	Seated Pulse mean (SE)		Standing Pulse mean (SE)	
		Reference Rate	Mean Change	Reference Rate	Mean Change
Telmisartan 80 mg	245/244	72.9 (0.5)	0.6 (0.5)	75.7 (0.6)	0.1 (0.5)
FDC 80/12.5	245/246	72.9 (0.6)	-1.2 (0.5)	75.9 (0.6)	1.0 (0.5)
Difference across groups (95% CI)		-0.5 (-0.7, 1.8)		-0.8 (-0.5, 2.1)	

Not surprisingly, no change in pulse was detected during the course of the study.

Time to Effect

Among those patients who had complete blood pressure measurements (the evaluable completer cohort) there was only a small additional drop in blood pressure between week 4 and week 8.

Figure 11.1 Weekly change in blood pressure study 502.261



Secondary end point- blood pressure responses

As secondary end-points the sponsor looked at response rates for both diastolic and systolic blood pressures. Some of these values were prespecified in the protocol others were not. Combination product appears superior to monotherapy in less than adequate responders.

Table 11.9: Response rate and criteria for success, study 502.261

	Telmisartan 80; N=245	FDC 80/12.5; N=246
Diastolic BP response (seated DBP < 90 mm Hg)	87 (35.5%)	129 (52.4%)
Systolic BP Response (decrease from reference \geq 10 mm Hg)	167 (68.2%)	184 (74.8%)
Normalized Response seated (SBP < 140 mm Hg) and DBP (< 90 mm Hg)	64 (26.1%)	102 (41.5%)
Optimal BP control (seated (SBP < 130 mm Hg) and (DBP < 85 mm Hg)	23 (9.4%)	48 (19.5%)

Subgroups:

The sponsors analyzed the data by age (\geq 65 and < 65) as well as gender. There were too few non-Caucasians to analyze the data by race. The \geq 65 years had a numerically greater systolic blood pressure effect than those < 65 years old. Pulse rate amongst for those treated with FDC in those > 65 years were substantially greater than those treated with telmisartan monotherapy.

Table 11.10: Subgroup analysis those \geq 65 years and those < 65 years old, study 502.261

	Patients < 65 years				Patients \geq 65 years			
	N=	Δ SBP	Δ DBP	Δ HR	N=	Δ SBP	Δ DBP	Δ HR
Telmisartan 80	187	-7.2 (0.9)	-4.7 (0.5)	1.0 (0.6)	58	-6.3 (1.6)	-5.5 (0.9)	-0.6 (1.0)
FDC 80/12.5	197	-12.0 (0.9)	-7.6 (0.5)	1.2 (0.5)	49*	-15.4 (1.8)	-9.6 (0.9)	0.8 (1.0)
		-4.8	-2.9	0.2		-9.1	-4.1	1.4

* One patient had no seated heart rate, the N for this parameter is therefore 48.

Table 11.11 Subgroup analysis gender -male versus female, study 502.261

	Gender Male				Gender Female			
	N=	ΔSBP	ΔDBP	Δ HR	N=	ΔSBP	ΔDBP	Δ HR
Telmisartan 80	149	-6.1 (1.0)	-4.1 (0.6)	0.1 (0.6)	96	-8.3 (1.2)	-6.2 (0.7)	1.4 (0.7)
FDC 80/12.5	160*	-12.6 (1.0)	-7.3 (0.5)	1.9 (0.6)	86	-12.6 (1.4)	-9.2 (0.7)	-0.5 (0.8)
		-6.5	-3.2	1.8		-4.3	-3.0	-1.9

* One patient had no seated heart rate, the N for this parameter is therefore 159.

With respect to gender numerically there was a slightly greater effect for FDC 80/12.5 for SBP. Pulse rate in males also increased. With respect females, the pulse rate among those who treated with FDC 80/12.5 was actually lower than those treated with monotherapy.

Safety:

Duration of Exposure:

Table 11.12: Duration of exposure; study 502.261.

	Telmisartan 80 N=245			FC 80/12.5 N=246			Total N=491		
	Open Label	Double Blind		Open Label	Double Blind		Open Label	Double Blind	
Mean (SD)	27.9 (2.2)	28.5 (1.7)	56.6 (7.0)	27.9 (2.6)	28.6 (2.4)	57.5 (5.9)	27.0 (2.4)	28.5 (.2)	57.1 (6.5)
Patient Years	18.7	19.11	37.96	18.79	19.26	38.73	36.30	38.3	76.6

The demographics among those enrolled are displayed in Table 11.5.

Deaths/ Dropouts/ Serious Adverse Events/severe adverse events.

There was one death that occurred during the telmisartan 40-mg dose open-label portion of the study.

The 16 dropouts are listed in Table 11.13

Table 11.13 Dropouts of study 502.261

Patient #	Treatment	Age	Gender	Days	Reason	Specifics
14071	FDC 80/12.5	50	M	28	Lost to FU	Last BP 150/91
14326	Telm 80	54	M	32	AE	worsening chest pain on exertion, ECG showed PVC and SV premature beats. No follow up supplied.
14355	FDC 80/12.5	33	M	28		Consent Withdrawn
14503	FDC 80/12.5	55	M	28	Con With	Last BP 111/84
14505	FDC 80/12.5	51	M	41	AE	Sexual dysfunction
14512	Telm 80	47	M	4	LOE	last BP 183/120. Reference baeline = 187/113
14523	FDC 80/12.5	48	M	29	Lost to FU	Last BP 170/99
14528	FDC 80/12.5	36	M	29	Patient non-compliant.	Had episode of kidney stones requiring hospitalization. Last BP 132/87
14628	Telm 80	54	M	46	AE	Paroxysmal AF
14634	Telm 80	72	M	27	LOE	last 170/102
14815	Telm 80	43	M	32	Non- Comp	Stopped taking medication. Had worsening of diabetes. Hospitalized for syncope and severe headache. Patient also complained of increased sweating, urination and fatigue. Last BP 163/105
15005	Telm 80	52	M	33	Other	Hodgkins Disease. Last BP 146/103
15008	FDC 80/12.5	62	M	47	AE	Nausea, increased sweating, pallor, fatigue and anorexia
15127	Telm 80	48	F	35	AE	Dizziness and nausea
15330	Telm 80	66	M	34	AE	Memory loss (TIA)
15410	Telm 80	54	F	29	LOE	Last 1203/101; Reference 201/96.

One additional patient during the double blind phase had a serious adverse event but did not discontinue.

Patient # 15105, a 38 year old female patient, who was randomized to telmisartan 80 mg. On day 37 the patient was feeling unwell and took two Atasol 30 tablets (acetaminophen). Approximately 20 minutes later the patient developed chest pain and had a syncopal episode with loss of consciousness, The patient had a negative stress test.

There were a total of nine patients; three in the monotherapy and six in the combination therapy in the combination treatment who had events classified as severe in intensity. Of these patients # 14815, #14505 and #14528 discontinued; patient # 15105 had an event listed as serious, these patients are described above.

The other 5 patients are listed in Table 11.14

Table 11.14 Patients with severe intensity adverse events who did not discontinue, study 502.261

telm 80 mg		FDC 80/12.5	
Pt # 14415	Back pain	#14803	toothache
		#14814	Heat Stroke. Dixxiness, Hypoaesthesia
		#14816	Headache
		#14818	Somnolence

Overall Adverse Events:

The sponsor tabulates the most common events (. 2%) during the double-blind treatment period.

Table 11.5 most common (> 2%) adverse events

WHO Term	Telm 80 n=245	FDC 80/12.5 N=246	WHO Term	Telm 80 n=245	FDC 80/12.5 N=246
Diarrhea	0	10 (4.1)	Headache	8 (3.3%)	6 (2.4%)
Edema*	9 (3.7%)	2 (0.8%)	Back Pain	6 (2.4%)	4 (1.6%)
Dizziness	8 (3.3%)	14 (5.7%)	Bronchitis	7 (2.9%)	0
Fatigue	5 (2.0%)	7 (2.8%)			

*combines all types of edema

Diarrhea was much more frequent in the combination treatment. All but two of the ten were mild in intensity. The two remaining cases of diarrhea were moderate in intensity. One of the patients had stool positive for campylobacter jejuni -coli. The other patient with diarrhea, the sponsor appears to attribute to a recent episode of sun stroke.

Edema was more frequent in the monotherapy group 9 versus 2.

Laboratory: Blood was collected for laboratory evaluations at baseline, a the end of open label and at the end of treatment The sponsor claims no abnormalities were of note.

ECG: The sponsor lists two events under ECGs (measured at end of study). Patient # 14326 had ventricular and supraventricular premature beats. Patient # 14057 had atrial fibrillation.

Vital Signs: The sponsor defined orthostatis as either 10 mm drop in systolic or diastolic blood pressure upon standing greater than the same effect seen during the reference period, or a increase in heart rate of >

10 BPM greater than those seen during the reference period. The frequency of such events were slightly greater in the combination than monotherapy groups.

Table 11.16 Orthostatic vital signs, study 502.261

	Systolic Blood Pressure	Diastolic Blood Pressure	Heart Rate
Telm 80	8 (3.3%)	6 (2.4%)	6 (2.4%)
FDC 80/12.5	12 (4.9%)	7 (2.8%)	8 (3.2%)

Conclusion. This study supports the contention that telmisartan plus hydrochlorothiazide is superior in decreasing both systolic and diastolic blood pressure in a nearly exclusively Caucasian population. The study was not designed to test that other portion of the hypothesis that telmisartan plus hydrochlorothiazide is superior to hydrochlorothiazide monotherapy.

There is no description of the combination product used in this study.

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Integrated Safety Review.

The safety data-base for this combination product is derived from 10 studies included in this submission. A summary of each of the studies is Table ISS.1. Only one of the studies # 502.204 was a placebo-controlled study in which the combination product could be directly compared to both placebo and its individual components with respect to safety. The safety of study # 502.204 is outlined on pages 54-64 of this review and will not be reproduced in this section. All other studies had hydrochlorothiazide added to telmisartan when there was inadequate blood pressure control on telmisartan monotherapy. As part of one study # 502.261 telmisartan was also added a low dose hydrochlorothiazide treatment when there was an inadequate response to diuretic monotherapy.

Table ISS.1 Studies in the integrated summary.

Study #	Design	Treatment groups	N	End point
Placebo-Controlled Trial				
502.204	Factorial 4 x 5 design. Random; Double-Blind; PBO-cont.; Active cont; parallel study; mild moderate HBP; stratified by race	Placebo, H6.25, H12.5, H25 Telm 20; Telm 40, Telm 80, Telm 160 Telm 20/H6.25; Telm 20/ H12.5, Telm 20/ H25 Telm 40/H6.25; Telm 40/ H12.5, Telm 40/ H25 Telm 80/H6.25; Telm 80/ H12.5, Telm 80/ H25 Telm 160/H6.25; Telm 160/ H12.5, Telm 160/ H25	74; 21 73; 24; 23; 75; 77; 33 25; 21; 25; 21; 70; 25; 20; 73; 32; 31; 33; 22	ITT –change in DBP LOCF also PK/Trough
Long Term Active Controlled Trials				
502.210	Random , Double-Blind, Parallel Titration study, HCTZ added PRN BP control 26 weeks in patients > 65 years	Tel 20-80 mg Plus as needed HCTZ 12.5 –25 Enalapril 20 Plus as needed HCTZ 12.5 –25	139 139	LOCF Change in DBP; SBP Safety
502.214	Random, Double-Blind; Active Controlled; Parallel 52 weeks in Mild/Mod HBP	Tel 40-160 mg Plus as needed H 12.5-25 mg Lisinopril 10-40 mg Plus s needed H 12.5-25mg	385 193	Responder (% < 90 mm Hg) Safety
502.215	Random , Double-blind, Active controlled Parallel study 26-weeks	Tel 40-160 mg Plus as needed H 12.5-25 mg H 12.5 to max 25 mg H12.5 Plus as needed Telm 80 mg	235 62 66	Responder (% DBP < 90 mm Hg), Safety
502.216	Random , Double-blind, Active controlled Parallel study 26-weeks	Tel 40-160 mg Plus as needed H12.5 to 25 mg Atenolol 50-100 mg Plus if needed H 12.5 to 25 mg	355 178	change in DBP Change in SBP QOL, ECHO study;
Long Term Uncontrolled Trials				
502.219	Open-Label	Tel 40-80 mg Plus H12.5 to 25 mg as needed	596	Safety ; BP
502.220*	Open –Label Follow-up study	Tel 40-80 with H12.5 to 25 mg added as needed	888	Safety; BP
502.221	Open-Label Follow-up study for participants in European studies	Telm 40-80 mg Plus H12.5 to 25 mg as needed	100	Safety BP
502.228	Open Label non-previously Treated	Telm 40-80 mg Plus H12.5 to 25 mg added as needed. Plus other medications added if needed	132	Safety, BP
502.260	Follow-up study	Tel 80 mg plus H12.5 to 25 plus other if necessary	490	Safety % patients < 90 mm Hg
502.261	Titration Open Label then HCTZ added for non-responders	T40-80 for titration H12.5 added to Telm 80 for inadequate responders	69	Seated trough DBP Seated trough SBP
Clinical Trials in Special Populations				
502.209	Random, double blind, active control parallel group 12-week study moderate-severe HBP	Telm 80 to 160 plus H25 if needed Enalapril 10-20 mg plus H 25 if needed	11 10	DBP, LOCF analysis SBP
502.238	Open label active control, 8-week study in Severe HBP	Telm 80 –160 plus H25 if needed plus Amlodipine if needed Enalapril 20-40 mg plus H25 if needed plus Amlodipine if needed	58 38	Change in DBP LOCF SBP
502.213	Safety double-blind parallel 8 week study; mild –moderate HBP	T80 T80 Plus HCTZ	15 15	Renal Function DBP SBP
* This study not submitted in conjunction with NDA 21-162 but reviewed by Dr. U in conjunction with telmisartan monotherapy NDA 20-850.				

The sponsor submits both an original ISS with a safety update (submitted with the NDA). The cutoff dates were NDA-ISS was 03 April 1998; four month Safety Update cutoff date 20 April 1999. The sponsor differentiates several overlapping populations from the database. Aside from a description of the nature of these overlapping populations, safety for the entire population (i.e. including the safety update) will be emphasized in this review.

Safety:

Table ISS.2 Patient Allocation in the initial ISS.

Total Number of patients who received any Telmisartan/HCTZ combination was 1495 during ISS and 1725 after Safety update (SUD)				
PBO Controlled study # 502.204 N=818	Long Term Controlled # 502.210, 502.214, 502.215, 502.216 N=1752	Long Term Uncontrolled #502.219, 502.220; 502.221; 502.228 N=1716 also added are those	Severe Hypertension #502.209, 502.238 N=107	Renal Hemodynamics #502.213 N=30
PBO=74	T monotherapy = 1114 of which ↓	Follow-up studies T monotherapy = 1450 of which ↓	T monotherapy N=69 Telmisartan + Ca antagonist	T monotherapy ↓ N=15
T/HCTZ= 414	T/HCTZ =536	T/HCTZ =557		T/HCTZ ↓ N=15
T Mono=209				
HCTZ monotherapy =128		De novo T monotherapy = 232 of which ↓ T/HCTZ =119	T/HCTZ= 52 Enalapril Monotherapy n=38 E /HCTZ N=31	
		Net T/HCTZ = 676 ISS Net T/HCTZ = 917 SUD		

The populations described in Table ISS.2 are not unique, patients may be counted both under the initial therapy as well as in follow up studies. The total number of unique patients per sponsor in the ISS who received a combination of telmisartan and HCTZ is 1495 unique patients. In the 4-month update, the number of such patients has increased to 1725 based on the inclusion of additional 230 patients from studies (#502.220; 502.228; 502.260). The patients, who are listed in the long term controlled database, are those who, because of an inadequate response, had HCTZ added to telmisartan regimen. Since those who had HCTZ added were not randomized to that treatment but were so treated as a consequence of an inadequate response to telmisartan, it is not clear how to compare this group to any other treatment group.

The long term uncontrolled subset increased from 676 to 917 (an additional 241 patient- note there were 11 patients who were inadvertently left out of this group in the analysis of the ISS but captured for this safety update. The 241 patients include these 11 patients, additional 230 patients who were exposed during the safety update period). These patients are those were initially treated as de novo patients and those who received telmisartan/hydrochlorothiazide after treatment with other regimens.

The demographics for the 1725 patients who enrolled in any of the studies as well those who were in the controlled data-base are shown in Table ISS-3:

Table ISS.3 Demographics

	Controlled Population*	Safety Updated Total T/H treated
N	1752	1725
Gender		
Male	(56.6%)	1026 (59.5%)
Female	(43.2%)	699 (40.5%)
Race		
Black	(6.4%)	241 (14%)
Non-black	(93.6%)	1448 (83.9%)
Missing		36 (2.1%)
Age Years Mean ± SD	58.5 ± 11.6	56.1 ± 11.1
number (%) > 65	(35.3%)	426 (24.7%)
Supine Sitting DBP Mean + SD	101.5 + 4.9	102.8 + 5.6
Supine Sitting SBP Mean + SD	163.2 + 18.1	162.1 + 16.3
Hypertension Duration (years) Mean + SD	8.4 + 8.3	9.2 + 8.5
Duration of Exposure		
* includes comparator and telmisartan groups		

The sponsor tabulates outcome for those treated. Below are tabulated the various outcomes for those who were treated with telmisartan/hydrochlorothiazide as well as all patients who were included in the controlled population database.

Table ISS.4 Outcomes.

	All T/H patients	T/H outcome in Controlled Studies *
Total	1725	1762 =all treatments Any T/H exposure 536 By last treatment 521
Ongoing	300 (17.4%)	0
Planned Time Reached	1062 (61.6%)	407 (78.1%)
Discontinued due to:	363 (21.0%)	104 (20.0%)
Adverse Events	106 (6.1%)	33 (6.3%)
Lack of Efficacy	67 (3.9%)	30 (5.8%)
Non-Compliance	33 (1.9%)	7 (1.3%)
Lost to Follow-up	18 (1.0%)	0
Consent Withdrawn	28 (1.6%)	1 (0.2%)
Other**	111 (6.4%)	43 (8.2%)
* Sponsor supplies data on a last treatment basis. Data derived from Sponsor's Table 10.2.2:2 (v29 p 85) and Tables B8-B12 v30p114-122		
** Other includes premature termination of study.		

Duration of Exposure:

The sponsor tabulates the duration of exposure for patients. Since a subject could be treated with different combinations of telmisartan/hydrochlorothiazide, the duration of exposure for each of the various combinations of telmisartan/HCTZ. Approximately 45% of the exposure was among patients who were treated with Telmisartan 40/HCTZ 12.5 and Telmisartan 80 /HCTZ 12.5 (397.5/957.4 patient –years).

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Table ISS.5 Exposure for entire population (data derived from sponsor's table)

HCTZ→	Telmisartan 20 mg			Telmisartan 40 mg			Telmisartan 80 mg					Telmisartan 120 mg		Telmisartan 160		
	6.25	12.5	25	6.25	12.5	25	6.25	12.5	25	37.5	50	12.5	25	6.25	12.5	25
N	25	25	25	22	238	52	21	900	484	1	2	47	17	32	122	137
Days†																
0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
1-14	0	2	1	2	3	1	0	57	28	0	2	1	0	2	2	7
15-31	0	1	1	0	15	1	1	185	30	0	0	11	0	1	30	43
32-61	24	19	19	19	81	28	18	151	54	0	0	8	10	26	47	43
62-91	1	3	4	1	33	4	1	74	43	0	0	22	7	3	7	6
92-182	0	0	0	0	73	7	0	185	55	1	0	5	0	0	9	9
183-335	0	0	0	0	28	10	1	119	80	0	0	0	0	0	26	29
336-364	0	0	0	0	0	0	0	9	19	0	0	0	0	0	1	0
365-547	0	0	0	0	3	1	0	64	101	0	0	0	0	0	0	0
>548	0	0	0	0	2	0	0	55	74	0	0	0	0	0	0	0
mean days	56.3	52.9	54.8	52.6	116.5	116.4	64.9	157	282.2	127	1	58.1	57.9	53.6	105.3	95
pt*years	3.9	3.6	3.8	3.2	75.9	16.6	3.7	386.9	373.9	0.3	0	7.5	2.7	4.7	35.1	35.6
Total patient -years of exposure to any T/H combination												957.4				

Exposure in Long Term controlled study:

The duration of exposure is shown below. Of the total duration of exposure, approximately 22% was derived from the long-term controlled database.

Table ISS.6 Duration of Exposure for Each of the cohorts of Patients

Days	Telmisartan Monotherapy	T/H Combination	H monotherapy	Comparator
N	1114	536	128	510
1-14	24	7	3	8
15-31	124	17	36	13
32-61	75	30	10	18
62-91	215	120	10	37
92-182	416	240	34	189
183-364	213	122	35	132
>365	47	0	0	113
mean Days Exposure	142.3	145.9	117.3	209.3
Pt *years	434.0	214.0	41.11	292

Deaths, Dropouts, Discontinuations:

Deaths: According to the summary table, only four patients in the combined Telmisartan/ HCTZ died.

Patient # **3023** (study 502.228), a 48 year old white male, **died suddenly** after enrollment in the trial for 13 months. He had been on a combination treatment of Telmisartan 8/ HCTZ 25 mg plus doxazosin 4 mg for approximately 61/2 months.

Patient # **4071** (study # 502.210) an 83 year old non-black male **died from cardiac failure**. The patient was taking Telmisartan 80/H25 at the time of death. The patient died on day 973 relative to treatment.

Patient # **4090** (study # 502.210) a 72 year old non-black male **died of a myocardial infarction** after 1003 days of treatment. The patient was taking telmisartan 80 /HCTZ 25.

Patient # **3569** (study # 502.216) a 48 year old non-black male **died a sudden death** after 1083 days of the study. The patient was taking Telmisartan 80/HCTZ 12.5.

The total number of patients who discontinued during the study for adverse events is shown in Table ISS.4 above. The specific reasons for discontinuation are shown In Table ISS.7.

Table ISS.7 Adverse Events leading to Discontinuations

	All Treated Patients for HBP Vol 2.3 Table M3		Long term Controlled Study Vol 1.29 p 118 (table 8.10.6.2:1). This part of the table is limited to events that occurred in more than one patient in any group			
			T/H Combination	T Monotherapy	H Monother	Total Comarpators
N	1725		536	1114	128	510
Total with any AE Leading to Discontinuation	90		31	52	12	50
Duration of Exposure. Pt years	957.4		214	434	41	292
Autonomic Nervous System	3		2	6	1	3
Impotence	3		2	5	0	2
Body as A Whole General Disorder	12		5	11	3	9
Allergic Reaction	1		0	0	0	0
Asthenia	2		0	0	0	0
Chest Pain	4		2	2	1	2
Death	1		0	0	0	0
Fatigue	2		1	5	1	4
Fever	1		0	0	0	0
Leg Pain	1		0	0	0	0
Syncope	1		0	0	0	2
Malaise	0		0	2	0	0
Cardiovascular Disorders, General	13		3	8	1	7
Cardiac Failure	2		0	0	0	0
Hypertension	2		1	5	1	3
Hypertension Aggravated	1		0	0	0	0
Hypotension	3		0	0	0	0
Hypotension Postural	4		0	0	0	0
Edema Peripheral	1		0	0	0	0
Central and Peripheral Nervous System Disorders	12		6	13	4	14
Dizziness	8		5	5	2	5
Headache	1		1	7	1	6
Paraesthesia	2		1	0	0	0
Paralysis	1		0	0	0	0
Somnolence	1		1	3	2	1
Tremor	1		0	1	0	2
Vertigo	1		0	0	0	0
Insomnia	0		0	2	0	0
Endocrine Disorders	2		0	0	0	0
Aldosterone Increased	1					
Hyperthyroidism	1					
Gastro-Intestinal System Disorders	9		7	11	1	3
Abdominal Pain	1		0	0	0	0
Diarrhea	7		6	2	0	0
Flatulence	1		0	0	0	0
Dyspepsia	0		0	3	0	2
Nausea	0		0	2	1	2
Heart Rate and Rhythm Disorders	10		4	3	1	2
Arrhythmia	2		0	0	0	0
Arrhythmia Ventricular	1		0	0	0	0
Fibrillation Atrial	5		2	1	0	1
Tachycardia Supraventricular	2		0	0	0	0
Liver and Biliary System Disorders	5		0	0	0	0
Cholecystitis	1					
Cholelithiasis	1					
Hepatic Enzyme Increase	1					
Hepatic Function Abnormal	1					
Heptitis Infectious Liver Fatty	1					
Metabolic and Nutritional Disorders	2		2	1	0	2
Diabetes Mellitus	1					
Diabetes Mellitus Aggravated	1					
Musculo-Skeletal System Disorders	2		1	2	1	2
Myalgia	2					
Myo-, Endo-, Pericardial and Valve Disorders	11		4	5	1	4

Angina Pectoris	3	1	2	1	2
Myocardial Infarction	8	3	2	0	1
Neoplasm	8	0	0	0	0
Brain neoplasm Malignant	1				
Breast Neoplasm Malignant (female)	1				
Carcinoma	1				
Colon Carcinoma	2				
Melanoma Malignant	2				
Neoplasm Malignant	1				
Psychiatric Disorders	4	1	3	0	3
Delirium	1	0	0		0
Depression	1	0	0		0
Libido Decreased	1	0	0		0
Nervousness	1	0	0		2
Agitation	0	0	2		0
Red Blood Cell Disorder	1	0	0	0	0
Anemia	1				
Respiratory System Disorders	5	1	4	0	16
Bronchitis	1	0	0		0
Bronchospasm	1	0	0		0
Coughing	3	1	1		10
Dyspnea	2	0	1		3
Sleep Apnea	1	0	0		0
Skin and Appendage Disorders	3	2	2	1	5
Pruritis	2	2	0	0	1
Rash	1	1	0	0	0
Rash Erythematous	1	1+	2+	0	1
Rash Maculopapular	1	1+	2+	0	0
Angioedema	0	0	0	0	3
Urinary System Disorders	2	0	4	1	0
Micturition Frequency	1		2	1	0
Dysuria	1		0	0	0
Renal Cyst			0	0	0
Vascular (Extracardiac) Disorders	3	0	0	0	0
Cerebrovascular Disorder	3				
Vision Disorders	1	1	4	0	0
Vision Abnormal	1	1	3		

+ Table lists rash as Rash (as Erythematous and Maculopapular rash). The events represent a single event.

There is no compelling signal from the causes of discontinuation with the possible exception of increased in coughing in the comparator groups (mostly ACE-inhibitors). Angioedema, as a cause for discontinuation all occurred in three patients all in the comparator group.

Serious Adverse Events:

Adverse events were defined as serious if: the event was fatal, immediately life-threatening, permanently or severely disabling, resulted in or prolonging in-patient hospitalization, resulted in cancer or a congenital anomaly, met comparable medical criteria or was due to an overdose. Specifics of the serious adverse events for all those who were treated with telmisartan/ hydrochlorothiazide preparations as well as those who were treated with this preparation in long-term controlled studies are shown in Table ISS.8.

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Table ISS.8 Serious Adverse events

	All Treated Patients for HBP \ Table M3; amended June 9,2000 Table 9.6.1:1	Long term Controlled Study Table K2 vole 1.32 p346			
		T/H Combination	T Monotherapy	H Monotherapy	Total Comparators
N	1725	536	1114	128	510
Total with any AE Leading to Discontinuation	109	17	33	4	24
Duration of Exposure (Patient*years)	957.4	214	434	41	292
Body as A Whole General Disorder	19	0	10	1	6
Back Pain	3	0	0	0	1
Chest Pain	7	0	5	0	2
Death	1	0	0	0	0
Pain	5	0	0	0	0
Sudden Death	1	0	0	0	0
Syncope	2	0	0	0	0
Abdomen Enlarged	0	0	0	0	1
Cyst	0	0	0	1	0
Fever	0	0	1	0	0
Pain	0	0	4	0	2
Cardiovascular Disorders, General	5	0	0	0	0
Cardiac Failure	2				
Hypertension	3				
Central and Peripheral Nervous System Disorders	4	1	0	0	1
Headache	2	1	0	0	0
Vertigo	0	0	0	0	1
Carpal Tunnel Syndrome	1	0	0	0	0
Neuralgia	1	0	0	0	0
Endocrine Disorders	1	0	0	0	0
Aldosterone Increased	1				
Hyperthyroidism	0				
Gastro-Intestinal System Disorders	10	1	3	0	3
Abdominal Pain	1	0	1	0	1
Diverticulitis	1	6	1	0	0
Enteritis	1	0	0	0	0
Gastroenteritis	1	1	0	0	0
Gastoesophageal Reflux	1	0	0	0	0
GI Hemorrhage	1	0	0	0	0
Hematemesis	1	0	0	0	0
Hemorrhoids	1	0	0	0	0
Mallory Weiss Syndrome	1	0	0	0	0
Vomiting	1	0	0	0	0
Diarrhea	0	0	0	0	1
Flatulence	0	0	0	0	0
Dyspepsia	0	0	0	0	0
Nausea	0	0	0	0	0
Constipation	0	0	1	0	1
Gastritis	0	0	0	0	0
Hearing And Vestibular	1	0	1	0	0
Deafness	1		1	1	
Heart Rate and Rhythm Disorders	6	1	2	0	4
Extrasystoles	0	0	0	0	1
A-V Block Complete	0	0	0	0	1
Fibrillation Atrial	3	1	1	0	3
Tachycardia Supraventricular	1	0	0	0	1
Bradycardia	1	0	0	0	0
Palpitations	1	0	0	0	0
Cardiac Arrest	0	0	1	0	0
Liver and Biliary System Disorders	3	1	2	0	2
Cholecystitis	2	1	2		1
Cholelithiasis	1	0	0		0
Gall Bladder Disorder	0	0	0		1
Metabolic and Nutritional Disorders	3	2	0	0	0
Dehydration	3	2			
Musculo-Skeletal System Disorders	13	2	2	1	0
Arthralgia	3	0	0	0	
Arthrosis	5	0	1	0	
Arthritis	1	0	1	1	
Arthritis Aggravated	3	2	0	0	

Osteoma	1	0	0	0	0	0
Osteoporosis	1	0	0	0	0	0
Myo-, Endo-, Pericardial and Valve Disorders	17	4	5	1	1	1
Angina Pectoris	4	1	2	1	1	1
Myocardial Infarction	12	3	2	0	0	0
Myocardial Ischemia	0	0	1	0	0	0
Coronary Artery Disease	1	0	0	0	0	0
Neoplasm	14	1	4	0	1	1
Basal Cell Carcinoma	1	1	2	0	0	1
Bladder Carcinoma	1	0	0	0	0	0
Brain neoplasm Malignant	1	0	0	0	0	0
Breast Neoplasm Malignant (female)	1	0	0	0	0	0
Carcinoma	1	0	0	0	0	0
Colon Carcinoma	2	0	1	0	0	0
Melanoma Malignant	2	0	0	0	0	0
Neoplasm Malignant	2	0	1	0	0	0
Neoplasm NOS	1	0	0	0	0	0
Pleural Mesothelioma	1	0	0	0	0	0
Skin Neoplasm Malignant	1	0	0	0	0	0
Bone Metastases	0	0	1	0	0	0
Hepatic Neoplasm	0	0	0	1	0	0
Psychiatric Disorders	2	0	0	0	1	0
Delirium	1	0	0	0	0	0
Depression	1	0	0	0	0	0
Confusion	0	0	0	0	0	1
Red Blood Cell Disorder	1	0	1	0	0	0
Anemia Hypochromic	1	0	1	0	0	0
Reproductive Disorders, female	3	0	1	0	0	0
Ovarian Cyst	2	0	0	0	0	0
Uterine Fibroid	1	0	0	0	0	0
Menorrhagia	0	0	1	0	0	0
Reproductive Disorders Male	2	1	2	0	0	0
Hernia Inguinal	1	0	0	0	0	0
Prostatic Disorder	1	1	2	0	0	0
Resistance Mechanism Disorders	2	1	0	1	1	0
Infection	1	0	0	0	0	0
Sepsis	1	1	0	1	1	0
Cellulitis	0	0	0	0	0	1
Respiratory System Disorders	6	1	1	0	2	0
Chronic Obstructive Airway Disease	1	0	0	0	0	0
Dyspnea	0	0	0	0	1	0
Epistaxis	1	1	0	0	1	0
Sinusitis	1	0	0	0	0	0
Sleep Apnea	1	0	0	0	0	0
Pneumonia	3	0	0	0	0	0
Pulmonary Edema	0	0	1	0	0	0
Urinary System Disorders	3	1	0	0	1	0
Renal Calculus	1	0	0	0	0	0
Urethral Disorder	1	0	0	0	0	0
Urinary Tract Infection	1	1	0	0	0	0
Cystitis	1	0	0	0	1	0
Vascular (Extracardiac) Disorders	5	1	1	0	4	3
Cerebrovascular Disorder	5	1	0	0	3	1
Thrombophlebitis	0	0	1	0	1	1
Vision Disorders	5	0	2	0	1	0
Cataract	5	0	0	0	0	0
Glaucoma	0	0	1	0	1	0
Strabismus	0	0	1	0	0	1
White Cell and Res Disorders	1	0	0	0	1	0
Myelomatosis Multiple	1	0	0	0	0	0
Lymphadenopathy	0	0	0	0	1	1

Severe Adverse Events

There were a total of 141 adverse events among the 1725 patients who were treated with the combination product that were labeled as severe in intensity. There was no equivalent table for those who were treated either with combination therapy or comparators in the Long-Term Controlled study database

Table ISS.9 Severe Adverse Events

vo13.2 p400		
Autonomic Nervous System Disorder	4	
Hot Flashes	1	
Impotence	3	
Body as A whole	29	
Allergic Reaction	1	
Back Pain	3	
Chest Pain	4	
Death	1	
Fatigue	2	
Influenza-Like Symptoms	3	
Malaise	1	
Pain	13	
Sudden Death	1	
Syncope	2	
Cardiovascular Disorders General	6	
ECG abnormal	1	
Hypertension	4	
Hypotension Postural	1	
Central and Periperal Nervous system	20	
Carpal Tunnel Syndrome	2	
Dizziness	2	
Headache	9	
Migraine	3	
Paralysis	2	
Somnolence	1	
Vertigo	2	
Endocrine Disorders	0	
Gastro-Intewstinal Disorders	13	
Abdominal Pain	1	
Diarrhea	4	
Dyspepsia	2	
Flatulence	1	
Gastro-Intestinal Disorder NOS	1	
Gastroenteritis	1	
Malory Weiss Syndrome	1	
Nausea	2	
Tooth Caries	1	
Hearing and Vestibular	2	
Deafness	1	
Earache	1	
Heart Rate and Rhythm Disorder	5	
Arrhythmia	1	
Fibrillation Atrial	3	
Tachycardia Supraventricular	1	
liver and Biliary System	1	
Cholecystitis	1	
Metabolic and Nutritional Disorders	3	
Dehydration	2	
Diabetes Mellitus	1	
Muscul-skeletal system disorders	12	
Arthralgia	3	
Arthritis	1	
Arthritis Aggravated	2	
Arthrosis	3	
Bone Disorder	1	
Myalgia	2	
Myopathy	1	
Myo Enoo Pericardial and Valve Disorders	10	
Angina Pectoris	1	

Angina Pectoris Aggravated	1	
Coronary Artery Disorders	2	
Myocardial Infarction	6	
Neoplasms	9	
Bladder Carcinoma	1	
Brain Neoplasm Malignant	1	
Carcinoma	1	
Colon Carcinoma	2	
Melanoma malignant	1	
Neoplasm Malignant	2	
Pleural Mesothelioma	1	
Platelet Bleeding and Clotting Disorders		
Psychiatric Disorders	2	
Anxiety	1	
Delirium	1	
Red Blood cell Disorders	1	
Anemia Hypochromic	1	
Reproductive Disorders Female	3	
Ovarian Cyst	2	
Uterine Fibroid	1	
Reproductive Disorders Male	0	
Resistance Mechanism Disorders	7	
Abscess	4	
Infection	1	
Infection Bacterial	1	
Sepsis	1	
Respiratory System Disorders	24	
Bronchitis	5	
Bronchospasm	1	
Chronic Obstructive Airways Disease	1	
Coughing	3	
Epistaxis	1	
Hyperventilation	1	
Pharyngitis	3	
Pneumonia	1	
Rhinitis	1	
Sinusitis	3	
Sleep Apnea	1	
Upper Respiratory Tract Infection	5	
Skin and Appendages Disorders	3	
Eczema	1	
Otitis Externa	1	
Psoriasis	1	
Special Senses Other, Disorders		
Urinary System Disorders	7	
Cystitis	1	
Dysuria	2	
Micturition Frequency	1	
Renal Calculus	2	
Renal Pain	1	
Urethral Disorder	1	
Vascular Extracardiac Disorders	5	
Cerebrovascular Disorder	3	
Peripheral Ischemia	1	
Vein Varicose	1	
Vision Disorders	3	
cataract	2	
Vision Abnormal	1	
White Cell and Res Disorders	0	

IND Safety Reports: There were a total of Five IND Safety reports between 29 May 1998 and 29 December 1999 Table ISS.10.

Table ISS.10 IND Reports

Study #/Country	Pt #	Date of Initial/Follow-up	Dose	Event (Preferred term)
502.220/UK	5798	7-1-98/7-15-98	T80/H12.5	Gastrointestinal Hemorrhage
502.220/UK	5530	12-9-98	T80/H25	Chest Pain, Palpitation
502.220/UK	5554	12-10-98	T80/H12.5	Angina pectoris
502.220/UK	5552	12-10-98	T80/H12.5	Tachycardia Supraventricular
502.220/UK	5590	12-10-98	T80/H12.5	Hematemesis.

Overall Adverse Events:

The most frequent reported adverse events (> 2%) for the all patient treated cohort include upper respiratory tract infection (9.8%); pain (9.4%); dizziness (8.0%); headache (7.1%); back pain (7.0%); bronchitis (5.5%); sinusitis 94.3%; diarrhea (4.2%); influenza-like syndrome (4.0%); coughing (3.7%); fatigue (3.5%); dyspepsia (3.2%); myalgia (2.9%); chest pain (2.7%); pharyngitis (2.5%); abdominal pain (2.4%); arthralgia (2.0%); nausea (2.0%) and UTI (2.0%).

Onset time:

The sponsor tabulates the mean as well as the upper and lower quartiles of both the time of onset and duration of these events for the entire exposed population. Since drug-related events are more likely detected if they occur shortly after the start of treatment, I've listed both the onset of the more common classes of adverse events as well as the duration of these events. There was overlap in the onset of various adverse events. In general, the median values for onset of any particular adverse event overlapped with the 25% or the 75% values of other adverse events. With respect to the duration of these events, there was no strong signal that any one event lasted longer than another event. Chronic problems such as fatigue and arthralgia appear to last longer than other adverse events (29 and 24 days, respectively). Myalgia, also appears to last long in this population (median 30 days).

Table ISS.11 Frequency, Onset and duration of adverse events in the cohort who received telmisartan/ hydrochlorothiazide.

	Frequency (% of Population)	Onset (days)*			Duration (days)*		
		median	25%	75%	median	25%	75%
Upper Respiratory Tract Infection	160 (9.8%)	62	26	178	11	7	17
Pain	162 (9.4%)	126	49	296	19	8	43
Dizziness	143 (8.3%)	58	15	176	20	8	46
Headache	123 (7.1%)	43	15	168	9	4	30
Back Pain	121 (7.0%)	118	43	244	15	6	33
Sinusitis	75 (4.3%)	105	24	206	11	8	22
Bronchitis	95 (5.5%)	157	55	361	11	8	15
Diarrhea	73 (4.2%)	49	16	173	5	2	15
Fatigue	61 (3.5%)	30	5	146	30	14	65
Influenza-like Symptoms	69 (4.0%)	173	51	480	10	7	14
Coughing	63 (3.7%)	142	31	368	23	13	57
Dyspepsia	55 (3.2%)	69	26	210	17	6	61
Myalgia	50 (2.9%)	86	25	177	29	8	80
Pharyngitis	43 (2.5%)	92	30	263	8	5	11
Chest pain	46 (2.7%)	110	25	443	8	3	22
Abdominal Pain	41 (2.4%)	133	42	313	10	5	54
Nausea	35 (2.0%)	19	3	69	9	3	29
Urinary Tract infections	34 (2.0%)	70	15	267	13	6	21
Arthralgia	35 (2.0%)	213	86	535	24	16	64

* The number of subjects to define median and upper and lower quartiles consisted of all patients with the adverse event. Occasionally a subject not having data available. These subjects were excluded from the calculations.

Laboratory Values. The sponsor tabulates the number of patients who had marked laboratory changes during exposure during combination telmisartan/hydrochlorothiazide treatment. the database excludes

patients who were enrolled in follow-up trials since the sponsor did not have adequate baseline measurements for such patients.

Table ISS.12 Metric of extreme values, and patients with extreme changes as well as median changes from baseline

Test	Range	#	# ↑	# ↓	Median Change From Baseline							
					Baseline		8 weeks		26 weeks		Last Available	
					N	Median Value	N	Change	N	Change	N	Change
Alkaline Phosphatase	-55 to +35 U/L	1087	26	10	1087	73.0	448	1.0	521	-3.0	1087	-1.0
BUN	-11.2 to +11.2 mg/dl	1088	48	1	1088	14.9	448	2.0	519	2.0	1088	2.0
Creatinine Phosphokinase	-300 to +300 U/L	1041	14	12	1041	98	448	0	490	5.0	1041	3.0
Creatinine	+0.5 to -0.5 mg/dl	1089	17	3	1089	0.9	442	-0.2	491	0.1	1089	0
Glucose	+60 to -60 mg/dl	1087	37	9	1087	96.0	447	2.0	519	2.0	1087	2.0
HDL	+33 to -33 mg/dl	583	3	3	583	46.4	22	0	484	-0.4	583	0
Hematocrit	+9% to -9%	1087	6	10	1087	43.0	441	0	519	-1.0	1087	0
Hemoglobin	+2.0 to -2.0 g/dL	1087	23	16	1087	14.4	444	-0.2	519	-0.2	1087	-0.2
LDH	+200 to -200 U/L	1080	4	1	1080	172.5	448	-5.0	514	-3.0	1080	-3.0
LDL	+77 to -77 mg/dL	557	5	7	557	145.4	21	15.0	458	3.0	557	3.0
Platelet Count	+134 to -134 x10 ³ u/L	1081	9	6	1081	235	442	5.0	517	7.0	1081	6.0
Potassium	+1.4 to -1.4 mEq/L	1084	11	1	1084	4.2	461	0	515	0	1084	0
SGOT	+35 to -35 U/L	1088	8	4	1088	20	447	0	521	0	1088	0
SGPT	+35 to -35 U/L	1084	24	7	1084	21	447	0	517	0	1084	0
Total Cholesterol	+90 to -90 mg/dL	1077	6	18	1077	214	446	6.0	514	4.0	1077	6.0
Total Protein	+1.4 to -1.4	1062	11	10	1062	7.1	448	0	493	-0.1	1062	0
Tnglycerides	+80 to -80 mg/dL	1076	233	107	1076	139	446	12.0	512	8.4	1076	10
Uric Acid	= 2.7 to -2.7mg/dl	1086	51	4	1086	5.9	448	0.6	517	0.6		

Trials 502.204, 502.209, 5502.210., 502.213, 502.214, 502.215, 502.216, 502.216, 502.218. Patients in follow-up studies were excluded by the sponsor. Data derived from Tables R1.2 and S1.2 Volume 3.2 P302 and 313, respectively.

Line listings for the 363 discontinuations are shown as Table ISS.13,

Table ISS.13 Discontinuations, reasons for discontinuation, baseline and last measured blood pressures –all exposures.

Symbols: o patient discontinued in the follow-up trial and was not on T/H in the initial trial
 x patient on T/H in both trials –total of days of T/H is listed as exposure
 # patient discontinued in original trial and not entered in long term treatment
 * Patient discontinued in initial trial and discontinued during monotherapy in long term trial
 + Patient had no blood pressure on last dose. Value is last available blood pressure.

Trial No	Pat No	Trial No FUP	Pat No FUP	Pat Detail	Last Dose	Age	Sex	Race	T/H Exposure (days)	Reason for Discont.	Base Mean Sys BP	Base Mean Dia BP	Last Mean Sys BP	Last Mean Dia BP
1	502.203	1001	502.219	1001 o	T080oth	55	male	black	62	AE-other	146	101	135	95
2	502.203	1006	502.219	1006 o	T080H25	72	male	white	148	AE-other	177	102	158	97
3	502.203	1007	502.219	1007 o	T080H25	54	male	black	341	other	164	109	112	81
4	502.203	1022	502.219	1022 o	T080oth	60	female	white	16	AE-other	139	98	129	89
5	502.203	1041	502.219	1041 o	T080H25	36	male	white	366	cons w/drawn	151	105	134	85
6	502.203	1045	502.219	1045 o	T080H25	60	male	white	490	AE-oth dis wors	155	100	139	87
7	502.203	1067	502.219	1067 o	T080H25	56	female	white	141	lack effic	151	106	130	97
8	502.203	1068	502.219	1068 o	T080H12.5	45	male	white	14	lack effic	151	108	127	94
9	502.203	1072	502.219	1072 o	T080H25	48	female	white	73	non comp	169	112	128	96
10	502.203	1093	502.219	1093 o	T080H25	45	male	white	534	cons w/drawn	155	109	143	105
11	502.203	1169	502.219	1169 o	T080H12.5	65	male	white	104	AE-other	171	110	148	81
12	502.203	1280	502.219	1280 o	T080H25	55	male	white	917	AE-other	159	101	133	81
13	502.203	1314	502.219	1314 o	T080H25	41	male	white	308	lost to fup	145	111	119	89
14	502.203	1317	502.219	1317 o	T080H25	29	male	white	597	cons w/drawn	146	97	145	89
15	502.204	4006	502.219	4006 x	T080oth	52	male	white	175	AE-oth dis wors	141	98	135	89

16	502.204	4021	502.219	4021	x +	T080H12.5	49 male	white	71 lack effic	155	103	157	101
17	502.204	4038			# +	T080H12.5	51 male	white	1 AE-other	181	106		
18	502.204	4043			#	T040H12.5	79 male	white	40 AE-other	149	103	137	88
19	502.204	4051			#	T040H12.5	40 male	white	58 lost to fup	143	101	134	91
20	502.204	4069			# +	T160H06.25	64 male	white	1 AE-other	130	98		
21	502.204	4083	502.219	4083	x	T080H25	52 male	white	324 other	160	109	143	87
22	502.204	4087			# +	T080H25	53 female	white	2 AE-other	151	101		
23	502.204	4088	502.219	4088	x	T080H12.5	63 male	white	376 cons w/drawn	170	101	143	83
24	502.204	4094	502.219	4094	x	T080H25	56 male	white	362 cons w/drawn	172	110	135	84
25	502.204	4095	502.219	4095	x	T080H12.5	75 female	white	204 AE-other	194	104	150	83
26	502.204	4144			#	T040H12.5	46 male	white	34 AE-other	149	101	132	91
27	502.204	4147			#	T080H06.25	64 female	white	19 lack effic	162	105	170	118
28	502.204	4148			# +	T160H25	35 female	white	14 other	144	103		
29	502.204	4151	502.219	4151	o	T080oth	48 female	white	209 cons w/drawn	154	99	112	85
30	502.204	4152	502.219	4152	o	T080H12.5	44 male	white	398 non comp	167	110	113	85
31	502.204	4159			#	T160H12.5	40 male	white	11 AE-other	135	106	117	84
32	502.204	4160	502.219	4160		T020H25	67 male	white	29 other	169	95	143	86
33	502.204	4161	502.219	4161	o	T080H12.5	75 male	white	324 other	181	105	126	79
34	502.204	4175	502.219	4175	x	T080H25	64 male	white	349 non comp	170	105	140	79
35	502.204	4197	502.219	4197	x	T080oth	74 male	white	63 AE-other	191	97	120	71
36	502.204	4200	502.219	4200	x	T080	64 male	white	85 lack effic	147	99	161	92
37	502.204	4202	502.219	4202	x	T080	68 male	white	71 other	148	98	143	83
38	502.204	4224	502.219	4224	x	T080H12.5	59 male	white	86 lack effic	166	104	167	97
39	502.204	4242			#	T080H12.5	44 male	white	29 AE-other	159	104	125	85
40	502.204	4265			#	T160H06.25	54 male	white	10 cons w/drawn	165	107	139	109
41	502.204	4268			# +	T040H06.25	55 female	white	1 lack effic	197	114		
42	502.204	4275			#	T020H12.5	49 male	white	21 non comp	147	97	131	89
43	502.204	4281	502.219	4281	x	T040H25	34 female	white	440 AE-other	153	103	121	89
44	502.204	4296	502.219	4296	o	T080oth	36 female	white	28 cons w/drawn	153	111	124	85
45	502.204	4297	502.219	4297	x	T080H12.5	57 female	white	139 AE-oth dis wors	154	99	136	87
46	502.204	4315			#	T080H12.5	56 female	white	14 non comp	147	97	135	93
47	502.204	4347	502.219	4347	o	T080H12.5	43 male	white	98 AE-other	143	96	138	88
48	502.204	4359	502.219	4359	o	T080H12.5	67 female	white	468 other	161	98	142	85
49	502.204	4362	502.219	4362	o	T080H25	52 female	white	349 AE-other	162	103	117	80
50	502.204	4378	502.219	4378	o	T080H12.5	75 female	white	262 AE-other	169	97	143	91
51	502.204	4380	502.219	4380	x	T080H25	64 female	white	76 lack effic	168	100	174	99
52	502.204	4390	502.219	4390	x	T080H25	38 male	white	477 non comp	151	101	127	85
53	502.204	4408	502.219	4408	x	T080oth	67 male	white	228 lack effic	167	101	131	92
54	502.204	4430	502.219	4430	x	T080oth	59 female	white	71 lost to fup	180	101	150	90
55	502.204	4451	502.219	4451	x	T080	49 male	white	70 non comp	155	97		
56	502.204	4453			#	T020H25	67 male	white	13 AE-other	143	96	102	75
57	502.204	4459	502.219	4459	o	T080H25	59 male	white	176 AE-other	151	99	132	90
58	502.204	4486	502.219	4486	x	T080H25	70 male	white	115 lack effic	157	99	137	87
59	502.204	4487			#	T160H25	51 female	white	11 cons w/drawn	138	96	139	85
60	502.204	4488	502.219	4488	x	T080H12.5	52 male	white	136 AE-other	161	103	122	91
61	502.204	4528	502.219	4528	x	T080H12.5	30 female	white	105 AE-other	141	101	129	88
62	502.204	4565	502.219	4565	x	T080oth	45 male	white	141 AE-other	147	107	139	97
63	502.204	4570	502.219	4570	x	T080H25	63 male	white	538 lost to fup	183	109	153	95
64	502.204	4575	502.219	4575	x	T080H25	63 male	white	91 AE-other	153	103	147	101
65	502.204	4579	502.219	4579	x	T080H25	58 male	white	82 lack effic	149	101	149	99
66	502.204	4588	502.219	4588	x	T080H25	36 male	white	319 non comp	141	98	146	105
67	502.204	4603	502.219	4603	o	T080H12.5	51 male	white	35 lost to fup	151	103	157	95
68	502.204	4607	502.219	4607	o	T080H12.5	46 female	white	88 AE-other	155	97	150	90

69	502.204	6013	502.219	6013 x	T080H12.5	48 male	black	195 non comp	158	99	165	101
70	502.204	6015	502.219	6015 o	T080H25	43 female	black	546 cons w/drawn	177	104	126	87
71	502.204	6016	502.219	6016 o	T080H25	44 female	black	397 non comp	165	103	146	89
72	502.204	6020	502.219	6020 o	T080H12.5	58 female	black	50 AE-other	164	98	131	85
73	502.204	6021	502.219	6021 x	T080H12.5	56 female	black	320 AE-other	170	107	145	89
74	502.204	6060	502.219	6060 o	T080H12.5	44 female	black	240 AE-other	149	105	102	71
75	502.204	6062		#	T040H12.5	60 male	black	15 lack effic	191	113	186	120
76	502.204	6064		#	T160H25	59 male	black	36 AE-other	162	97	123	78
77	502.204	6068		#	T080H12.5	41 male	black	1 lack effic	177	112	159	103
78	502.204	6097		#	T160H06.25	57 male	black	28 lost to fup	135	95	123	87
79	502.204	6102	502.219	6102 o	T080H25	48 female	black	203 lack effic	147	99	169	92
80	502.204	6104	502.219	6104 x	T080H12.5	76 male	black	219 other	177	101	179	78
81	502.204	6112		#	T020H25	54 male	black	50 AE-other	149	103	147	83
82	502.204	6116	502.219	6116 o	T080H25	58 male	black	25 lack effic	181	101	159	95
83	502.204	6119	502.219	6119 x	T080H12.5	51 female	black	62 AE-oth dis wors	163	103	158	91
84	502.204	6121		#	T020H06.25	54 male	black	35 cons w/drawn	156	101	147	104
85	502.204	6122		#	T160H25	47 male	black	57 lost to fup	145	96	129	89
86	502.204	6135		# +	T020H12.5	48 male	black	1 AE-other	157	107		
87	502.204	6163		#	T040H12.5	54 female	black	28 lack effic	151	103	185	107
88	502.204	6167	502.219	6167 x	T080oth	31 female	black	114 non comp	177	107	142	86
89	502.204	6173	502.219	6173 x	T080H12.5	48 female	black	219 other	141	99	127	86
90	502.204	6174	502.219	6174 o	T080oth	46 female	black	101 lost to fup	163	109	136	82
91	502.204	6177	502.219	6177 o	T080oth	59 female	black	80 lack effic	159	98	121	89
92	502.204	6178	502.219	6178 x	T080H12.5	44 male	black	330 cons w/drawn	155	104	133	99
93	502.204	6182	502.219	6182 x	T080H25	46 female	black	402 non comp	160	103	150	101
94	502.204	6198	502.219	6198 x	T080H25	56 male	black	99 lack effic	153	103	160	100
95	502.204	6203		#	T040H06.25	40 female	black	8 other	141	96	119	85
96	502.204	6216	502.219	6216 x	T080H25	75 male	black	131 other	161	99	139	87
97	502.204	6228	502.219	6228 o	T080oth	32 female	black	86 cons w/drawn	143	96	122	85
98	502.204	6242		#	T040H12.5	63 female	black	28 AE-st dis wors	164	103	161	111
99	502.206	3046	502.219	3046 o	T080oth	51 male	white	27 cons w/drawn	169	111	151	98
100	502.206	3049	502.219	3049 o	T080H12.5	67 female	white	14 cons w/drawn	163	96	154	91
101	502.206	3119	502.219	3119 o	T080oth	67 male	white	28 AE-other	170	103	143	89
102	502.206	3165	502.219	3165 o	T080H12.5	38 male	white	90 AE-other	153	100	138	87
103	502.206	3167	502.219	3167 o	T080oth	58 female	white	53 lack effic	163	106	150	98
104	502.206	3178	502.219	3178 o	T080H25	57 male	white	46 AE-other	163	95	154	90
105	502.206	3186	502.219	3186 o	T080oth	65 male	white	91 AE-other	162	108	159	95
106	502.206	3211	502.219	3211 o	T080H25	49 male	yellow	273 cons w/drawn	164	107	145	97
107	502.206	3218	502.219	3218 o	T080H25	61 male	white	274 AE-other	185	107	173	99
108	502.206	3219	502.219	3219 o	T080oth	40 male	white	65 lack effic	153	103	137	99
109	502.206	3254	502.219	3254 o	T080H12.5	56 male	white	672 lost to fup	150	95	141	93
110	502.206	3275	502.219	3275 o	T080H12.5	52 male	white	29 lost to fup	169	109	158	109
111	502.206	3285	502.219	3285 o	T080H25	67 male	white	700 AE-other	166	100		
112	502.206	3300	502.219	3300 o	T080oth	47 female	white	123 AE-other	142	102	124	86
113	502.206	3319	502.219	3319 o	T080H12.5	45 male	white	491 lost to fup	141	95	149	85
114	502.206	3325	502.219	3325 o	T080H25	41 female	black	247 lack effic	140	99	132	114
115	502.206	3353	502.219	3353 o	T080H25	58 male	white	99 non comp	175	105	165	97
116	502.206	3356	502.219	3356 o	T080H25	68 male	white	465 non comp	179	103	129	76
117	502.206	3364	502.219	3364 o	T080H12.5	41 female	black	37 lack effic	160	103	147	95
118	502.207	1003	502.22	5522 o	T080H12.5	62 male	white	18 AE-other	147	101	119	88
119	502.207	1006	502.22	5524 o	T080H25	42 male	white	605 other	157	108	129	89
120	502.207	1011	502.22	5585 o	T080H12.5	70 male	white	78 AE-other	143	99	126	77
121	502.207	1030	502.22	5590 o	T080H25	69 female	white	727 AE-other	165	99	151	89

122	502.207	1089	502.22	5568 o	T080oth	49 male	white	91 cons w/drawn	157	103	132	94
123	502.207	1104	502.22	5506 o	T080	48 male	white	77 lack effic	151	106	152	103
124	502.207	1115	502.22	5548 o +	T080oth	70 female	white	875 other	190	112	176	89
125	502.207	1121	502.22	5552 o	T080H12.5	56 male	white	20 AE-other	159	109	147	103
126	502.207	1123	502.22	5554 o +	T080H12.5	61 male	white	33 AE-other	164	103	165	96
127	502.207	1127	502.22	5581 o	T080H12.5	56 female	white	42 AE-other	183	105	129	89
128	502.207	1176	502.22	6326 o	T080H25oth	61 female	white	527 cons w/drawn	180	101	119	81
129	502.207	1193	502.22	6237 o	T080H25	68 male	white	75 AE-other	183	110	151	103
130	502.207	1221	502.22	5732 o	T080H25	43 female	white	290 non comp	153	97	123	79
131	502.207	1228	502.22	5739 o	T080H12.5	59 female	white	91 cons w/drawn	146	97	140	80
132	502.207	1286	502.22	6041 o +	T080oth	51 male	white	674 cons w/drawn	167	99	144	92
133	502.209	2011		#	T160H25	61 female	white	14 lack effic	147	107	145	109
134	502.21	4026	502.22	5902 o	T080H25	69 male	white	605 AE-other	173	102	142	89
135	502.21	4029	502.22	5906 x	T080H12.5	75 female	white	276 AE-other	155	109	147	89
136	502.21	4040	502.22	5638 x	T080	74 male	white	112 AE-other	178	100	156	77
137	502.21	4067	502.22	5618 o	T080H12.5	66 female	white	315 other	163	101	133	89
138	502.21	4071	502.22	5620 x	T080H25	83 male	white	986 AE-other	213	110	183	89
139	502.21	4076	502.22	5613 o	T080H12.5	68 female	white	274 non comp	167	98	150	85
140	502.21	4078		#	T080H12.5	70 female	white	29 AE-oth dis wors	187	107	168	93
141	502.21	4079	502.22	5755 o	T080H12.5	75 female	white	168 AE-other	185	105	160	87
142	502.21	4090	502.22	5882 o	T080H25	72 male	white	919 AE-other	170	97	168	69
143	502.21	4100	502.22	5764 o	T080H12.5	72 male	white	716 AE-other	188	100	175	83
144	502.21	4117	502.22	5754 x	T080H25	74 female	white	932 other	188	100	168	90
145	502.21	4122	502.22	5765 o	T080H25	66 female	white	202 other	192	102	149	87
146	502.21	4123	502.22	5774 o	T080H25	65 female	white	711 other	168	105	151	88
147	502.21	4173		# +	T020H12.5	76 male	white	1 lack effic	197	110	200	120
148	502.21	4188	502.22	5974 o	T080	68 female	white	447 non comp	193	102	167	81
149	502.21	4233	502.22	5964 o	T080H25oth	71 female	white	533 lack effic	165	110	159	106
150	502.21	4234		#	T080H12.5	81 female	white	33 other	164	99	171	89
151	502.214	1502		#	T160H25	54 male	white	98 AE-other	142	102	120	89
152	502.214	1538		#	T040H12.5	47 male	white	10 non comp	129	96	121	94
153	502.214	1547		#	T160H25	61 male	white	84 lack effic	131	105	129	94
154	502.214	1548		#	T040H25	43 male	white	247 lack effic	162	109	137	94
155	502.214	1554		#	T040H12.5	51 male	white	280 other	165	101	125	86
156	502.214	1557		#	T040H12.5	45 female	white	211 other	127	96	119	87
157	502.214	1572		#	T160H12.5	55 female	white	286 other	170	105	133	89
158	502.214	1579		#	T160H25	45 female	black	89 non comp	155	101	145	93
159	502.214	1584		#	T080H12.5	47 female	black	68 other	134	97	145	88
160	502.214	1603		#	T160H12.5	59 female	white	254 other	175	95	127	76
161	502.214	1604		#	T160H12.5	30 male	black	61 non comp	147	112	125	79
162	502.214	1608		#	T080H12.5	45 male	white	63 other	145	101	138	87
163	502.214	1614		#	T160H25	59 male	white	84 lack effic	177	111	143	93
164	502.214	1621		#	T160H25	67 male	white	210 lack effic	173	107	147	96
165	502.214	1625		#	T080H25	48 male	white	150 AE-other	143	97	123	87
166	502.214	1626		#	T040H12.5	66 male	white	228 other	139	99	115	83
167	502.214	1632		#	T080H12.5	73 male	white	28 other	144	95	140	85
168	502.214	1653		#	T160H12.5	41 male	white	31 AE-other	161	105	143	95
169	502.214	1665		# +	T040H25	58 male	white	195 AE-oth dis wors	141	101	121	93
170	502.214	1669		# +	T040H12.5	63 male	white	6 AE-other	135	95	127	91
171	502.214	1684		#	T080H25	65 male	white	98 AE-other	161	97	119	75
172	502.214	1691		#	T040H12.5	45 female	black	112 AE-other	144	103	152	97
173	502.214	1698		#	T160H25	54 male	black	320 other	152	99	125	83
174	502.214	1702		#	T040H12.5	74 male	black	161 other	159	99	131	81

175	502.214	1706	.	#	T160H12.5	62 male	black	175 AE-other	163	110	128	89
76	502.214	1707	.	#	T160H25	25 female	black	214 non comp	161	110	126	82
77	502.214	1710	.	#	T160H25	51 male	black	333 other	181	113	144	86
178	502.214	1711	.	#	T160H12.5	56 male	black	316 other	171	110	125	80
179	502.214	1713	.	#	T160H12.5	69 female	black	258 other	140	95	143	88
180	502.214	1714	.	#	T160H25	57 male	black	278 other	159	101	144	87
181	502.214	1732	.	#	T080H12.5	55 female	white	91 cons w/drawn	142	95	138	96
182	502.214	1733	.	#	T160H25	58 male	white	86 lack effic	162	111	173	99
183	502.214	1750	.	#	T160H25	58 female	white	271 other	155	109	138	87
184	502.214	1752	.	#	T080H25	47 female	white	286 other	164	107	108	78
185	502.214	1754	.	#	T160H25	56 male	white	293 lack effic	169	102	.	.
186	502.214	1757	.	#	T160H25	44 male	black	56 lack effic	166	105	149	99
187	502.214	1761	.	#	T160H25	53 male	white	296 other	158	103	120	81
188	502.214	1763	.	#	T080H12.5	33 male	white	265 other	130	97	110	71
189	502.214	1765	.	#	T080H12.5	52 male	white	85 AE-other	136	95	115	83
190	502.214	1775	.	#	T160H25	35 male	black	134 lack effic	151	103	132	99
191	502.214	1786	.	#	T040H12.5	63 female	black	112 AE-st dis wors	181	95	220	113
192	502.214	1799	.	#	T160H25	48 female	white	281 other	152	103	128	92
193	502.214	1800	.	#	T160H12.5	78 female	white	119 other	171	97	140	83
194	502.214	1809	.	#	T160H12.5	50 male	white	308 other	147	99	116	72
195	502.214	1810	.	#	T160H12.5	58 male	white	294 other	184	110	130	86
196	502.214	1817	.	#	T160H12.5	76 male	white	119 AE-other	161	107	116	82
197	502.214	1819	.	#	T160H12.5	44 male	white	45 AE-other	154	107	114	81
198	502.214	1824	.	#	T160H12.5	61 male	white	85 AE-other	161	108	135	87
199	502.214	1841	.	#	T080H25	63 male	white	154 non comp	160	100	119	72
200	502.214	1845	.	#	T080	36 female	white	182 cons w/drawn	134	97	123	85
201	502.214	1846	.	#	T040H12.5	41 male	white	250 other	170	101	139	77
202	502.214	1873	.	#	T040H25	62 female	white	74 AE-other	161	106	131	98
203	502.214	1897	.	#	T160H25	40 male	white	168 lack effic	135	102	133	97
204	502.214	1904	.	#	T160H12.5	62 male	white	287 other	165	105	139	92
205	502.214	1905	.	#	T160H25	61 male	white	316 other	191	101	177	97
206	502.214	1908	.	#	T080H12.5	40 male	white	238 other	155	96	111	81
207	502.214	1917	.	#	T040H25	56 male	black	166 other	156	99	137	87
208	502.214	1925	.	#	T160H12.5	60 female	white	227 other	165	97	127	74
209	502.214	1926	.	#	T040H12.5	72 male	white	253 other	161	97	107	65
210	502.214	1941	.	#	T160H25	39 male	white	77 AE-other	157	104	129	85
211	502.214	1961	.	#	T160H25	46 male	black	292 other	161	111	139	85
212	502.214	1975	.	#	T160H25	55 male	white	314 other	175	109	131	89
213	502.214	1976	.	#	T080	56 male	black	237 other	144	97	157	92
214	502.214	1979	.	#	T160	51 female	black	30 other	159	100	123	80
215	502.214	1985	.	# +	T080H25	55 male	yellow	65 other	151	96	136	91
216	502.214	1988	.	# +	T160H25	47 male	white	38 AE-other	156	107	156	91
217	502.214	1999	.	#	T160H25	50 male	white	323 other	141	105	123	81
218	502.214	2023	.	#	T160H12.5	58 female	white	28 lack effic	169	103	127	82
219	502.214	2030	.	#	T160H25	67 male	white	125 lack effic	185	107	167	96
220	502.214	2031	.	#	T160H25	54 female	white	84 lack effic	185	111	130	90
221	502.214	2033	.	#	T040H12.5	48 male	white	27 other	142	97	131	86
222	502.214	2043	.	#	T160H12.5	48 male	white	281 other	151	101	120	86
223	502.214	2051	502.219	2051	T040	49 male	white	77 other	133	95	111	79
224	502.214	2053	.	#	T160H12.5	70 male	black	3 lack effic	139	99	136	95
225	502.214	2059	.	#	T160H25	50 female	black	275 other	155	101	118	84
226	502.214	2063	.	#	T160H25	53 male	white	85 other	150	99	131	87
227	502.214	2067	.	#	T160H12.5	42 male	white	39 AE-other	160	105	120	83

228	502.214	2074	.	#	T160H25	44 male	black	239 other	154	104	146	87
229	502.214	2075	.	#	T160H12.5	55 female	white	111 other	150	105	131	85
230	502.214	2078	.	#	T040H12.5	45 male	black	28 AE-other	134	95	141	100
31	502.214	2092	.	#	T160H25	47 male	white	254 other	143	103	124	92
232	502.215	3001	502.22	5867 x	T080H12.5	72 female	white	394 AE-other	169	109	139	89
233	502.215	3008	.	#	T080H12.5	73 female	white	58 lack effic	166	108	180	109
234	502.215	3009	.	#	T040H12.5	69 male	white	44 lack effic	165	109	170	117
235	502.215	3010	.	#	T080H12.5	64 male	white	42 lack effic	164	101	169	101
236	502.215	3014	.	#	T080H12.5	68 female	white	30 AE-other	171	103	162	103
237	502.215	3015	.	#	T040H12.5	57 male	white	28 lack effic	180	112	171	115
238	502.215	3020	.	# +	T080H12.5	66 female	white	5 non comp	162	110	180	110
239	502.215	3028	.	# +	T080H12.5	61 female	white	16 AE-other	181	104	157	99
240	502.215	3038	.	#	T080H12.5	52 male	white	32 lack effic	167	105	157	100
241	502.215	3039	.	#	T040H12.5	67 female	white	56 lack effic	155	109	162	97
242	502.215	3040	.	#	T080H12.5	39 male	white	28 lack effic	143	100	133	93
243	502.215	3041	.	#	T080H12.5	53 male	white	28 lack effic	168	100	143	99
244	502.215	3045	.	# +	T080H12.5	79 male	white	20 AE-other	207	102	192	92
245	502.215	3055	.	#	T040H12.5	43 male	yellow	4 AE-other	147	100	143	102
246	502.215	3067	.	#	T080H12.5	63 female	white	78 lack effic	186	103	177	103
247	502.215	3111	.	#	T080H12.5	48 male	white	135 other	149	99	149	95
248	502.215	3113	.	#	T040H12.5	49 female	white	92 other	150	100	141	89
249	502.215	3125	.	#	T040H12.5	49 male	white	61 lack effic	180	108	170	112
250	502.215	3126	.	#	T080H12.5	54 male	white	28 AE-other	156	106	140	88
251	502.215	3135	.	#	T040H12.5	51 male	white	58 AE-oth dis wors	175	105	144	95
252	502.215	3139	502.22	5824 o	T080H12.5	50 female	white	835 non comp	155	95	117	73
253	502.215	3238	.	# +	T080H12.5	74 male	white	11 AE-other	171	103	159	95
254	502.215	3247	.	#	T040H12.5	59 male	white	91 lack effic	179	113	173	111
255	502.215	3250	.	#	T080H12.5	57 male	white	19 AE-oth dis wors	169	109	150	90
256	502.215	3271	.	#	T080H12.5	36 female	white	55 lack effic	167	106	160	102
257	502.215	3275	.	#	T080H12.5	62 male	white	65 lack effic	169	99	150	96
258	502.215	3282	.	#	T080H12.5	71 female	white	49 AE-other	180	101	145	93
259	502.215	3294	502.22	6252 x	T080H12.5	65 female	white	322 other	159	99	150	87
260	502.215	3304	.	# +	T080H12.5	44 male	white	16 AE-other	155	108	149	91
261	502.215	3338	502.22	5797 x	T080	53 male	white	193 AE-other	171	111	139	89
262	502.215	3359	.	#	T040H12.5	63 female	white	54 lack effic	209	114	202	121
263	502.215	3437	.	#	T040H12.5	56 female	white	56 lack effic	165	101	149	100
264	502.215	3461	.	#	T040H12.5	48 male	white	136 AE-other	138	105	130	85
265	502.215	3463	.	#	T040H12.5	65 male	white	53 lack effic	190	108	163	103
266	502.215	3465	.	#	T040H12.5	56 male	white	82 AE-other	150	97	135	88
267	502.215	3486	502.22	6302 x	T080H25	82 female	white	231 AE-other	187	112	137	79
268	502.215	3524	502.22	6191 x +	T080	72 female	white	219 AE-oth dis wors	174	108	165	102
269	502.215	3559	502.22	6304 x	T080H25	82 male	white	458 AE-other	177	99	127	73
270	502.215	3560	502.22	6249 x	T080H25oth	72 male	white	553 AE-other	155	104	159	101
271	502.216	3074	502.22	5307 x	T080H25	74 male	white	1088 other	200	103	153	77
272	502.216	3094	502.22	5034 x	T080H25oth	61 male	white	492 lack effic	168	105	182	99
273	502.216	3137	502.22	5124 x +	T080H12.5	63 female	white	75 non comp	160	112	169	115
274	502.216	3189	502.22	5157 o	T080H12.5	23 male	white	33 non comp	173	105	159	97
275	502.216	3190	502.22	5159 x	T080H12.5	57 female	white	371 cons w/drawn	175	102	143	84
276	502.216	3193	502.22	5213 o	T080	53 female	white	245 other	213	114	140	84
277	502.216	3222	502.22	5056 o	T080	64 female	white	213 lost to fup	173	102	154	83
278	502.216	3259	.	# +	T080H12.5	69 female	white	39 AE-other	167	99	154	100
279	502.216	3263	502.22	5133 x	T080H12.5	67 male	white	313 AE-other	175	100	134	81
280	502.216	3357	502.22	5321 x	T080H25oth	57 male	white	330 cons w/drawn	185	113	181	110

281	502.216	3360	502.22	5324 x	T080H25oth	60 male	white	357 lack effic	189	114	155	111
282	502.216	3367	502.22	5170 x	T080H25	55 female	white	742 cons w/drawn	171	107	139	85
283	502.216	3400	502.22	5533 o	T080H25	57 male	white	172 lack effic	167	111	160	108
284	502.216	3439		# +	T120H12.5	59 male	black	32 non comp	167	98	181	110
35	502.216	3452	502.22	5827 x	T080H25	61 female	white	475 other	191	104	173	99
286	502.216	3454	502.22	5818 x	T080H25	63 female	white	442 lost to fup	181	104	143	89
287	502.216	3456	502.22	5825 o	T080H12.5	58 male	white	29 other	161	96	155	93
288	502.216	3488	502.22	5819 o +	T080H12.5	61 male	white	15 AE-other	165	107	151	95
289	502.216	3532	502.22	5701 o	T080H25	55 male	white	331 AE-other	150	98	178	115
290	502.216	3569	502.22	5735 o	T080H12.5	48 male	white	1027 other	178	98	142	89
291	502.216	3603		#	T080H12.5	47 male	white	39 AE-other	155	99	139	89
292	502.221	3601		#	T080H25	58 male	white	258 other	166	109	120	81
293	502.221	3603		#	T080oth	53 male	white	56 other	155	95	126	80
294	502.221	3604		#	T080H12.5	62 male	white	252 other	191	101	169	93
295	502.221	3605		#	T080H25	65 male	black	261 other	158	99	127	85
296	502.221	3607		#	T080oth	59 male	white	58 other	175	109	125	80
297	502.221	3608		#	T080H12.5	55 male	white	252 other	146	100	117	74
298	502.221	3609		#	T080H12.5	33 male	white	238 other	137	101	130	89
299	502.221	3613		#	T080oth	52 male	white	56 lack effic	173	107	169	95
300	502.221	3614		#	T080H25	73 male	white	252 other	161	99	137	86
301	502.221	3616		#	T080oth	56 male	black	56 other	166	104	122	83
302	502.221	3617		# +	T080H12.5	42 female	black	1 lost to fup	162	101	160	91
303	502.221	3620		#	T080H12.5	75 male	white	252 other	155	99	134	89
304	502.221	3623		#	T080H25	57 male	white	206 other	149	107	133	87
305	502.221	3625		#	T080oth	47 male	white	28 other	171	106	154	97
306	502.221	3626		#	T080H12.5	39 female	white	197 other	141	103	125	75
307	502.221	3627		#	T080oth	47 male	black	14 other	179	112	162	102
308	502.221	3629		#	T080H12.5	35 male	black	21 lost to fup	153	103	137	89
309	502.221	3630		#	T080H12.5	35 male	black	217 other	143	99	137	95
310	502.221	3631		#	T080oth	47 male	black	93 other	153	111	138	93
311	502.221	3633		#	T080H25	41 male	black	198 other	136	101	119	89
312	502.221	3634		#	T080H12.5	37 male	black	55 other	139	101	131	89
313	502.221	3635		#	T080H12.5	45 female	black	199 other	157	101	107	72
314	502.221	3637		#	T080H25	44 male	black	195 other	161	110	120	81
315	502.221	3639		#	T080H25	52 female	white	219 other	159	96	123	79
316	502.221	3642		#	T080H25	55 male	white	91 other	168	104	123	84
317	502.221	3646		#	T080	57 male	white	14 AE-other	183	112	186	109
318	502.221	3647		#	T040H12.5	58 female	white	168 other	170	97	127	83
319	502.221	3650		#	T080H25	42 male	black	140 other	149	109	136	87
320	502.221	3655		#	T080	59 male	white	28 cons w/drawn	147	103	111	81
321	502.221	3656		#	T080H12.5	55 male	white	14 lack effic	141	103	133	97
322	502.221	3673		#	T080H25	48 male	white	112 lack effic	166	106	155	97
323	502.221	3679		#	T080H25	59 male	white	252 lack effic	169	105	171	105
324	502.221	3696		#	T080H12.5	56 male	white	177 AE-other	149	101	146	92
325	502.221	3700		#	T080H12.5	67 male	white	196 non comp	153	103	139	89
326	502.228	3002		#	T080H25	40 male	white	582 non comp	205	110	157	86
327	502.228	3008		#	T080H12.5	71 female	white	173 non comp	190	98	143	70
328	502.228	3009		#	T080H25	81 female	white	968 non comp	197	108	119	73
329	502.228	3023		#	T080H25oth	48 male	white	326 other	165	108		
330	502.228	3025		#	T080H12.5	66 male	white	134 AE-other	178	110	144	89
331	502.228	3046		#	T080	55 male	white	282 other	168	101	153	85
332	502.228	3047		#	T080H25oth	56 male	white	855 lack effic	179	113	180	109
333	502.228	3048		#	T080H25oth	59 male	white	924 other	170	109	141	85

334	502.228	3049	.	.	#	T080H25oth	65 female	white	82 lost to fup	178	112	151	106
35	502.228	3058	.	.	#	T080H12.5	58 female	white	154 lost to fup	181	96	151	87
36	502.228	3099	.	.	#	T080H25oth	56 male	white	311 lack effic	175	105	161	99
337	502.228	3100	.	.	#	T080	59 male	white	26 other	154	96	146	91
338	502.228	3101	.	.	#	T080H25oth	40 female	white	481 lack effic	169	96	144	105
339	502.228	3102	.	.	#	T080H25oth	51 male	white	447 lost to fup	180	98	147	87
340	502.228	3103	.	.	#	T080H25oth	52 female	white	930 other	164	114	121	85
341	502.228	3104	.	.	#	T080H25	48 male	white	830 other	162	103	112	87
342	502.228	3105	.	.	# +	T080	41 male	white	265 AE-other	155	99	135	89
343	502.228	3107	.	.	#	T080	56 female	white	72 other	173	99	147	89
344	502.228	3108	.	.	#	T080H12.5	67 male	white	644 other	157	96	143	89
345	502.228	3135	.	.	#	T080H25	82 female	white	461 other	168	100	133	70
346	502.228	3150	.	.	#	T080oth	54 male	white	91 other	155	97	132	90
347	502.228	3157	.	.	#	T080H25oth	64 male	white	379 other	159	100	145	88
348	502.228	3184	.	.	#	T080H12.5	87 female	white	7 non comp	193	100	130	80
349	502.238	8002	.	.	#	T160H25oth	50 male	white	22 AE-other	195	117	138	97
350	502.238	8012	.	.	# +	T160	48 female	white	21 AE-other	178	120	116	81
351	502.238	8028	.	.	#	T160H25	56 male	white	14 non comp	160	117	151	100
352	502.257	5408	502.26	5408 o +		T080H25	27 female	white	39 other	180	110	143	102
353	502.257	6585	502.26	6585 o		T080H25	53 female	white	99 lack effic	173	109	171	122
354	502.257	6586	502.26	6586 o		T080H12.5	57 female	white	41 cons w/drawn	159	101	151	83
355	502.257	6587	502.26	6587 o		T080H12.5	40 female	white	28 cons w/drawn	152	101	125	83
356	502.257	6593	502.26	6593 o		T080H25	44 female	white	99 lack effic	147	103	149	99
357	502.257	7270	502.26	7270 o		T080H25	74 male		103 AE-other	154	100	148	86
358	502.257	7402	502.26	7402 o		T080H12.5	58 male	white	61 other	169	104	147	91
359	502.257	7407	502.26	7407 o		T080H12.5	56 male	white	35 other	150	101	141	89
360	502.257	7605	502.26	7605 o		T080H12.5	66 female	white	139 other	149	103	127	88
361	502.257	7607	502.26	7607 o		T080	64 female	white	65 other	164	99	150	95
362	502.257	7617	502.26	7617 o		T080H12.5	66 male	white	69 other	185	99	132	89
363	502.257	8041	502.26	8041 o		T080H25	53 female	white	46 other	170	102	167	99

ECG. No formal ECG analysis of intervals was presented. Among those with serious adverse events, four patients had serious adverse events that were described as atrial fibrillation or atrial flutter.

Subgroup Analysis: The sponsor submits a subgroup analysis with the initial safety review. No re-analysis was included with the safety update. The overall adverse event profile was not corrected for difference in duration of exposure. Since, however, the overall adverse event profile was not distressing, little information can be gleaned from a subgroup analysis.

Race: The overall adverse event profile showed no gross difference in the overall adverse event profile among black and non-black patients (60.5% versus 63.6%). Chest pain was more frequent in black than non-black patients 4.6 versus 1.8%. Other adverse events more frequent in the black population were pain of unspecified origin (13.0 versus 8.8%); headache (8.8% versus 6.8%) and cough (3.7 versus 1.3%).

Gender: The frequency of adverse events in females was higher than males (69 versus 61%). Differences in adverse events between females and males include: UTI (4.0 versus 0.4%) bronchitis (6.7 versus 3.2%) and sinusitis (6.7 versus 3.5%).

Age: There was actually a lower incidence of adverse events among those over 65 years when compared to those younger than 65 years (64.2 versus 61.1%).

Safety in Volume depleted patients. This database adds little safety among those patients who were volume contracted when started on telmisartan. Only study #502.215 had patients who were on diuretics when telmisartan was introduced. One of the four treatments in this study was on diuretics (12.5 mg hydrochlorothiazide) when telmisartan could be introduced. Since the dose of hydrochlorothiazide was relatively low, it is not likely that substantial numbers of those who received concurrent diuretic (n=40) were substantially volume depleted.

Safety Conclusion: This was an adequately sized database for the approval of a combination product when the two components are already approved.

The safety profile from the one controlled database (study # 502.204) did not reveal any unusual interactions between the two components. The sum of the adverse events appears to be the approximate those of the individual components.

The long term data base consisted of 1725 unique patients who were treated for a total of 957.4 patient *years. No unusual or interpretable signals are seen from this data base.

**APPEARS THIS WAY
ON ORIGINAL**

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20 pages redacted from this section of
the approval package consisted of draft labeling