CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-093

MEDICAL REVIEW/STATISTICAL REVIEW

TO: NDA 21-093, AstraZeneca

FROM: Stephen Fredd, M.D. and Kooros Mahjoob, Ph. D.

SUBJECT: Clinical and Statistical Review of Candesartan Cilexetil+HCTZ for the Treatment of Hypertension

1.0 Introduction

Candesartan Cilexetil was approved on June 4, 1998 for the treatment of hypertension, alone or in combination with other antihypertensive drugs. The usual starting dose was stated to be 16mg once daily, and a therapeutic dose range of 8 to 32 mg daily in either single or divided doses is noted.
Since marketing no labeling changes have been made.
The current application requests approval of two fixed combination of Candesartan Cilexetil(CC) and hydrochlorothiazide(HCTZ); one containing 16 mg of CC and 12.5mg of HCTZ, and the other 32mg and 12.5mg. The proposed indication "for the treatment of hypertension" is modified by the statement that the fixed combination is not for initial therapy.
While the combination has not been marketed abroad, the sponsor notes that the 16mgCC+12.5mgHCTZ combination has been submitted to 4 countries, and an 8mgCC/12.5mg combination has been approved in 9 countries, but not marketed as of May 1999. The UK application was withdrawn to await the results from a study of the 16mgCC+12.5mgHCTZ combination in patients uncontrolled on CC alone. That study (SH-AHK-0011) has been included in this NDA.
This NDA was submitted on 9/28/99 by AstraZeneca, and consists of 416 printed volumes with case report tabulations and case report forms in electronic format.
Administrative assurances, information, debarment and financial disclosure certifications as well as user fee payment are provided. A request for exclusivity under 21CFR 314.505(j) is made, noting that this product has not previously been approved under 505(b) of The Act.
The following index may help readers locate sections of particular interest.

2.0
Clinical Data Overview

6426 subjects were entered into the 19 clinical studies which constitute the Phase II/Phase III clinical trials submitted in support of the safety and efficacy of the CC+HCTZ fixed combinations requested for marketing. Of these the sponsor notes that 6303 were randomized and eligible for efficacy analysis.

Study	Drugs	Population	N	duration	Endpoint
SH-AHK-0004 Pg 5	Placebo, CC4mg, HCTZ6.25mg, CC4mg/HCTZ6.25	HTN SiDBP 95-114mmHG	371	12 weeks	Change in trough sdp
AM124 Pg 22	Placebo, CC8mg, CC16mg, HCTZ12.5,25mg, CC8mg+HCTZ 12.5mg	HTN SiDBP 95-114mmHg	602	12 weeks	Change in trough SiDBP
EC408 Pg 18	Placebo,CC16mg, HCTZ12.5mg CC16+HCTZ12.5	HTN SiDBP 95-110mmHG	693 -20 with non-verifiable data	12 weeks	Change in trough SiDBP
AM153 Pg 16	Placebo, CC32mg, HCTZ 12.5mg, CC32/HCTZ12.5	HTN SiDBP 95-114mmHG	275	8 weeks	Change in trough SiDBP
EC403 Pg 27	Placebo, CC2,4,8,16mg, HCTZ12.5,25mg, CC/HCTZ all poss. Combos,15cells.	HTN SiDBP 95-110mmHG	1096	8 weeks	Change in trough SiDBP
AM140 Pg 79	CC16mgto32mg± HCTZ12.5mg, Placebo±HCTZ 12.5mg	HTN SiDBP 91-105mmHg Black	304	12weeks	Change in trough SiDBP
AM117DB Pg 66	CC8mg to16mg+ HCTZ12.5mg, Placebo+HCTZ 12.5mg	HTN SiDBP ≥ 110mmHg	217 48week open label extension	4weeks	Change in trough SiDBP to week 4
AM117OL	CC8+HCTZ12.5, CC16+HCTZ12.5, CC16mg+HCTZ 25mg	HTN SiDBP≥110mmHg Titrated to response	143	48weeks	Change in trough SiDBP over time and for each dose group
EC016 Pg 73	Placebo+HCTZ 12.5, CC4mg+ HCTZ12.5, CC 8mg+HCTZ12.5	HTN SiDBP 95-109mmHg	234	8weeks	Change in trough SiDBP
SH-AHK-0011 Pg 43	CC16mg+HCTZ 12.5mg, CC16mg+ Placebo	HTN insufficiently responsive to CC alone, SiDBP 90-110mmHg	329	8weeks	Change in trough SiDBP

SH-AHK-0003 Pg 82	HCTZ6.25to12.5, CC4to8mg+pl, CC4to8mg+HCTZ 6.25to12.5, dose increase response dependent	HTN SiDBP 95-114mmHg Titrated up if SiDBP>90mmHg after 6 weeks	69 12weeks 3 way crossover	Not used in support of efficacy
AM116OL Pg 91	CC8mg,CC16mg, CC16mg+HCTZ 12.5mg	HTN SiDBP 95-109mmHG,titrated to response	187 44weeks 19 titrated to combination	Little value for efficacy
EC406 Pg 75	CC4+HCTZ6.25, CC8+HCTZ12.5	HTN SiDBP 95-110mmHg, titrated to response	559 12months	Change from baseline SiDBP %titrated up
EC015 Pg 90	CC8,CC16mg, CC16+Amlod5mg, CC16+Amlod5mg +HCTZ25mg. Placebo added to each group for DB	HTN SiDBP 100-114mmHg	185 12week open label titration 4weekDB	Little value for efficacy
EC033 Pg 84	Placebo,CC4mg, CC8mg,CC12mg, Enalapril10mg HCTZ12.5to25mg could be added	HTN Reponsive patients from EC011	193 40weeks	Little value for efficacy
SH-AHK-0012 Pg 86	CC16mg+HCTZ 12.5mg, Losartan 50mg+HCTZ12.5 QD	HTN SiDBP 90-110mmHG	300 12weeks	Change in trough SiDBP
EC407 Pg 85	Placebo,CC8mg+ HCTZ12.5, Enalapril10mg+ HCTZ25mg QD	HTN SiDBP 95-110mmHg	279 12weeks	Change in trough SiDBP
SH-AHK-0006 Pg 87	CC8+HCTZ12.5, Lisinopril 10+ HCTZ 12.5mg QD	HTN SiDBP 95-114mmHg	355 26weeks	Change in trough SiDBP
EC415 Pg 93	CC16+HCTZ25, HCTZ 25mg Single dose	HTN SiDBP 95-110mmHg	23 24-36hours	Clin pharm study

Efficacy data for a fixed combination antihypertensive drug is derived from studies that show that the fixed combination is superior to each component, and that each component is superior to placebo. Studies SH-AHK-0004, AM124, EC408, AM153 and EC403 are studies that can provide these data. In that doses of 4-32 mg of Candesartan Cilexetil and 6.25 to 25 mg of hydrochlorothiazide were evaluated in these studies, but not all within a single study, pooling of the studies seems reasonable to get an estimate of dose response.

The sponsor has provided such a pooled analysis with response surface displays using an Emax model, or a quadratic model. That analysis does not include study EC403, because, they reason, no peak blood pressure measurements were done and blood pressure was assessed by automated devices. Since these are not compelling arguments to omit a study with over 1000 patients and also study AHK-0004 which the sponsor did include did not measure peak blood pressures and used an automated device, we will do a pooled analysis with study EC403 included.

These 5 studies contain 2940 ITT patients, approximately 50% of those involved in the 19 clinical trials listed above.
Safety data will be derived from the entire cohort of 6426 patients.

3.0
EFFICACY

The 5 informative clinical studies will be reviewed individually, followed by pooled analyses to explore dose response. The order of review for these 5 studies will be first those that evaluated one dose strength of the combination versus placebo and the components (AHK-004, EC 408, AM153, AM124), followed by the trial that explored some dose range (EC403). After this, other trials will be summarized.

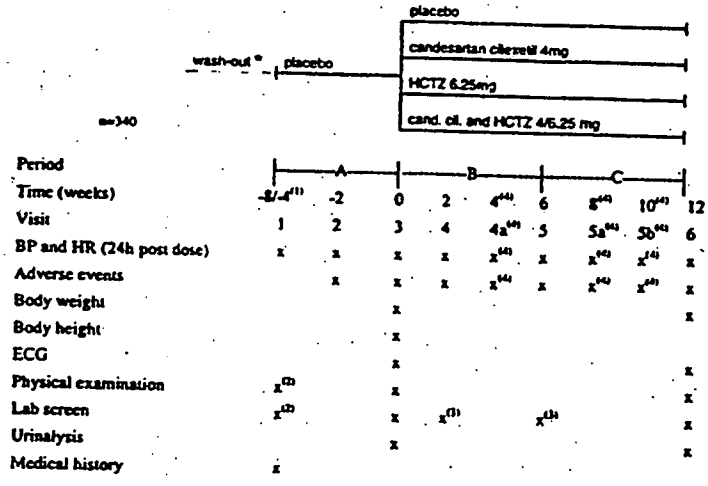
3.1
Study SH-AHK-0004

Antihypertensive effect of the fixed combination of candesartan cilexetil and hydrochlorothiazide, 4/6.25 mg once daily, in comparison with the individual components once daily, and placebo.

The protocol for this study called for 340 male or female patients with sitting diastolic blood pressures (SiDBP) of 95-114 mmHg to be randomized to placebo Candesartan Cilexetil(CC) and placebo Hydrochlorothiazide(HCTZ), CC 4mg plus placebo HCTZ, 6.25mg HCTZ plus placebo CC, or CC 4mg/6.25HCTZ combination plus placebo HCTZ. It is seems that the placebo used in the latter group matched CC, not the combination tablet, but both were to be identical in appearance.

Exclusions included women of child bearing potential, malignant hypertension, sitting systolic blood pressure (SiSBP) ≥180mmHg, and serious cardiovascular disease.

The study design was as follows:



(1) The time between visits 1 and 2 is flexible and was depended on the BP value two weeks after visit 1

(2) To check for inclusion/exclusion criteria

(3) Only creatinine

(4) Visits 4a, 5a and 5b were performed in Hungary, Poland and the Czech Republic. The blood pressure measurement determined if the patient continued the study or not (DBP ≥110 or SBP ≥180 mmHg caused discontinuation) and the values were not entered in the CRF. Any adverse event observed at these visits were entered in the CRF at the next visit, i.e. at visit 5 or 6.

* Wash-out visit for patients treated with more than one antihypertensive drug or a β-blocker. Patients will be asked to give written informed consent to participate before any antihypertensive medication is withdrawn.

The primary endpoint was the change in SiDBP from baseline (week 3) to week 12, comparing the true mean difference for the combination to each individual active and placebo. Additionally, each active was to be compared to placebo. Blood pressure was measured at trough (24 hours±2 hours) by a fully automated device (

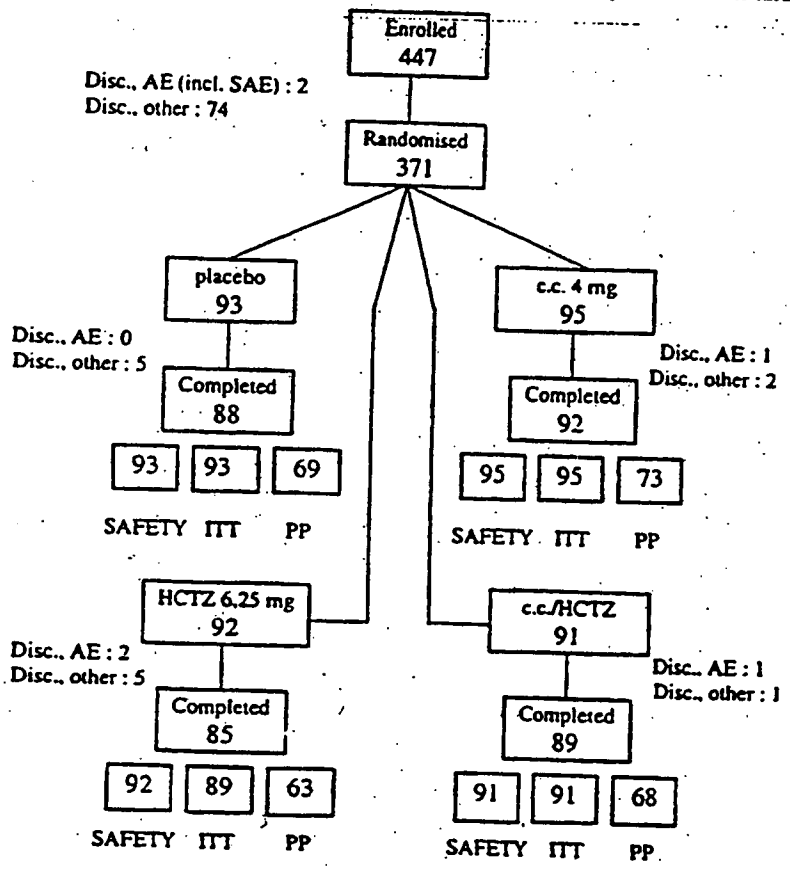
Estimating a delta of 7.5mmHg +/- 2.5mmHg for the primary variable a sample size of 70 patients per treatment group was thought to be needed. Other secondary parameters such as proportion of responders,

hemodynamic variables were to be evaluated as well. Safety assessments included EKGs, laboratory assessments and clinical evaluations were to be done.

The protocol was finalized on 12/18/1995 with some local protocol amendments incorporated such as restricting age to 20-70 years in Hungary.

The visit schedule of patients involved in this study was depicted in the following figure.

260 males and 108 females were randomized, all caucasian. 90% of patients were 64 years of age or younger. 101 patients had not been on previous antihypertensive therapy, while 78 had been on 2 or more antihypertensive drugs prior to entrance.
60 randomized patients were from the Czech Republic, 74 from France, 115 from Hungary, and 122 from Poland. Only 3 patients (all in the HCTZ arm) were excluded from the randomized population for the ITT analysis which included all patients who took some study medication and had some post-dose efficacy data.



The results were reported as follows.
Baseline SiDBP, SiSBP, and heart rate for the ITT population was:

		placebo n=93	c.c. n=95	HCTZ n=89	c.c./HCTZ n=91	Total n=368
DBP (mmHg)	Missing	0	0	0	0	0
	Mean	101.7	100.9	101.6	101.3	101.4
	SD	4.9	4.8	5.1	5	4.9
SBP (mmHg)	Missing	0	0	0	0	0
	Mean	161.2	156.3	158.3	154.8	157.6
	SD	12.1	12.7	12.4	12.2	12.6
HR (beats per minute)	Missing	0	0	0	0	0
	Mean	80.4	80.9	78.5	80	80
	SD	11	10.9	12	10.8	11.2

The primary endpoint was change in SiDBP from baseline to week 12 for the ITT population, and those results were:

Treatment Comparison	Adjusted Mean	Lower 95% CI	Upper 95% CI	P-value
c.c. vs placebo	-4.9	-7.5	-2.3	<0.001
HCTZ vs placebo	-1.1	-3.8	1.5	>0.200
c.c./HCTZ vs placebo	-9.3	-12.0	-6.6	<0.001
c.c./HCTZ vs c.c.	-4.4	-7.1	-1.8	0.001
c.c./HCTZ vs HCTZ	-8.2	-10.9	-5.5	<0.001

For the secondary endpoint of change from baseline to week 12 for sitting systolic blood pressure (SiSBP) for the ITT population, the results were:

Treatment Comparison	Adjusted Mean	Lower 95% CI	Upper 95% CI	P-value
c.c. vs placebo	-5.9	-10.2	-1.6	0.008
HCTZ vs placebo	0.1	-4.3	4.6	>0.200
c.c./HCTZ vs placebo	-12.2	-16.7	-7.8	<0.001
c.c./HCTZ vs c.c.	-6.4	-10.7	-2.0	0.004
c.c./HCTZ vs HCTZ	-12.4	-16.9	-7.9	<0.001

There was little change for any arm in sitting heart rate for the ITT population, and no significant differences between arms. The highest proportion of responders and controlled patients was in the combination arm (72.5% and 56% respectively), which results were significantly better than placebo or any monotherapy arm.

The time course to antihypertensive effect can be seen in the following chart of results for SiDBP 24 hours post-dose by visit for the ITT population.

Treatment	Statistics	Baseline	Week 2	Week 6	Week 12	Week 12 (LVCF)
placebo	N	93	93	90	88	93
	Missing	0	0	3	5	0
	Mean	101.7	98.1	96.5	96.4	97.5
	SD	4.9	8.3	8.4	8.6	9.9
	Min.	95.0	78.0	77.0	75.0	75.0
	Median	101.0	98.0	96.5	96.0	97.0
	Max	114.0	120.0	118.0	119.0	129.0
c.c.	N	96	94	92	92	95
	Missing	0	1	3	3	0
	Mean	100.9	93.8	92.7	91.8	92.3
	SD	4.8	8.0	8.0	8.5	9.0
	Min.	95.0	74.0	73.0	74.0	74.0
	Median	99.0	93.0	92.0	92.0	93.0
	Max	114.0	115.0	116.0	112.0	115.0

APPEARS THIS WAY ON ORIGINAL

Treatment	Statistics	Baseline	Week 2	Week 6	Week 12	Week 12 (LVCF)
HCTZ	N	89	89	88	85	89
	Missing	0	0	1	4	0
	Mean	101.6	96.9	95.9	95.6	96.3
	SD	5.1	8.3	9.1	8.6	9.1
	Min.	95.0	80.0	79.0	74.0	74.0
	Median	101.0	98.0	96.5	94.0	94.0
	Max	114.0	119.0	120.0	114.0	117.0
c.c./HCTZ	N	91	90	90	89	91
	Missing	0	1	1	2	0
	Mean	101.3	91.7	90.1	88.7	88.5
	SD	5.0	8.3	8.6	8.7	8.8
	Min.	95.0	72.0	70.0	62.0	62.0
	Median	100.0	92.0	91.0	89.0	89.0
	Max	114.0	112.0	108.0	108.0	108.0

A graphic display of sitting versus standing DBP and SBP did not demonstrate orthostatic hypotension for any arm or between arms.

The safety database consisted of all 371 randomized patients. No deaths occurred. 4 patients discontinued the assigned drug for an adverse experience (ae): 0 placebo, 1 CC, 2 HCTZ, and 1 CC/HCTZ.
The most frequent AE was headache. Which occurred with similar frequency for CC/HCTZ, HCTZ, and placebo. No headache was noted for those on CC monotherapy. Dizziness/vertigo occurred with similar frequency in all active groups, but none was noted for placebo.

Some changes in laboratory values were noted from baseline to week 12.
Hemoglobin declined numerically more in the CC/HCTZ arm compared to placebo and HCTZ, but not to abnormal levels. The combination drug did not produce hypokalemia, changes in renal function or HbA1c.

Hyperuricemia was reported in 1 HCTZ and 1 CC/HCTZ patient. ALAT elevations were noted for 3 patients receiving CC and 1 receiving CC/HCTZ, but 3 of these patients had elevated ALAT at baseline and 1 CC patient developed both an elevated ALAT and bilirubin. No patient was discontinued from drug assignment because of liver function abnormalities.

Comments:
While 6.25 mg HCTZ did not provide a statistically significant antihypertensive effect, when added to 4 mg CC there is a synergistic effect on both SiDBP and SiSBP without orthostatic hypotension or additive toxicity. Whether increased doses of either or both actives combined would give a greater effect without dose limiting toxicity will be evaluated in other studies and the pooled analysis.

3.2
Study EC 408
A Twelve Week Placebo-Controlled Study of Candesartan Cilexetil/HCTZ 16/12.5 mg Combination Versus the Individual Components in Patients with Mild to Moderate Essential Hypertension.

The protocol was finalized on 9/16/97 with a protocol amendment on 11/25/98. The amendment increased the number of safety evaluations to be done.There was additionally a post-hoc, but prior to unblinding, definition established for major protocol violations, which served mainly to establish eligibility for the per-protocol population.

650 patients, male or female, 18-80 years of age, with mild to moderate (≥95 mmHg and ≤ 110 mmHg SiDBP), either untreated or unsatisfactorily treated could enter this multicenter study to be done in Germany. Exclusion criteria included secondary hypertension, concomitent disease or metabolic abnormality, and women of childbearing potential not using an acceptable method of contraception. Those qualified would be randomized using a computer generated list to placebo, CC 16 mg, HCTZ 12.5 mg, or CC/HCTZ 16mg/12.5 mg combination tablet. The test medications and placebo were prepared by , and apparently were provided as capsules for blinding purposes.

The study design was as follows:

	Placebo run-in period				Double-blind treatment period			
Week	-4	-2	-1	0	1	4	8	12
Visit	1	2	3a	3b	4	5	6	7
Informed consent	X							
Demographic variables	X							
Medical history (including previous medication)	X							
Inclusion/exclusion criteria	X			X				
Concomitant medication	X	X		X	X	X	X	X
Extensive physical examination	X							X
Brief physical examination				X		X	X	
Blood pressure/heart rate	X	X		X	X	X	X	X
24-hour ABPM *				X				X
Adverse events		X		X	X	X	X	X
Clinical laboratory tests	X		X					X
Blood sampling for first dose pharmacokinetics *				X				
ECG at rest	X							X
Distribution of medication	X			X		X	X	
Drug accountability				X		X	X	X
Final evaluation (incl. global assessment of efficacy/safety)								X

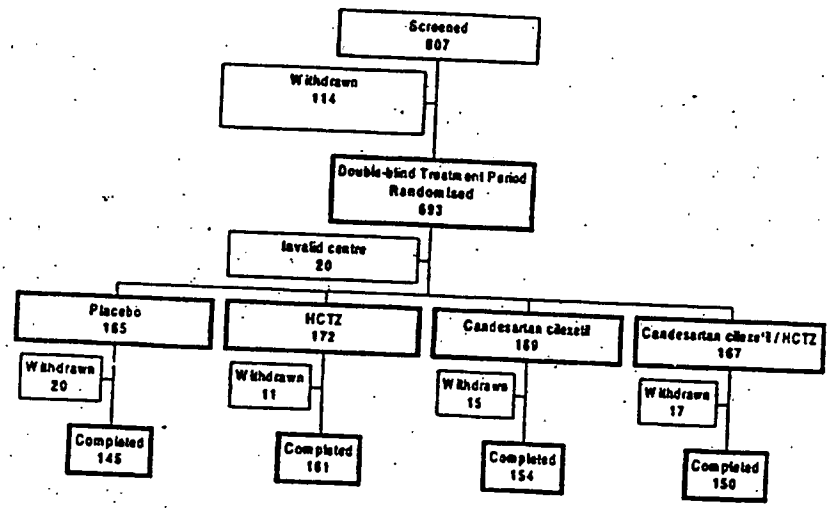
* at selected centres (24 to 32 patients per treatment group)

The primary endpoint was defined as change in SiDBP (24 hours post last dose) from baseline to 12 weeks of therapy. A subpopulation of 24-34 patients per treatment group were to have 24 hour ABPM. An ordered set of two-sided tests, each at the 5% significance level were to consider the null hypothesis for CC/HCTZ versus placebo, CC/HCTZ versus HCTZ, and then CC/HCTZ versus CC. Both ITT and per-protocol analyses were to be done. ITT patients were defined as all randomized who took at least 1 dose of medication and with baseline and at least 1 post-

baseline SiDBP measurement. The per-protocol population was to be the ITT population and absence of major protocol violations. As noted above, after the study was completed but before unblinding, a committee defined major protocol violations to include:
SiDBP or SiSBP outside the defined range for admission, but for those on prior antihypertensive medication with SiDBP <95 mmHg at visit 1.
Severe or malignant hypertension or hypertensive retinopathy.
Non-allowed concomitant medications taken for more than 1 week.
Compliance less than 75% or greater than 125%.
Serious deviations from the randomization procedure.
Duration of treatment less than 28 days.
And last study drug intake more than 24 hours before last visit.

For the ABPM substudy, mean 24 hour blood pressure results were analyzed.

Patient flow for the study was:



The populations for the various data analyses were:

Analysis population	Placebo	HCTZ	Candesartan cilexetil	Candesartan cilexetil/HCTZ	Total
Safety population	165	172	169	167	673
Efficacy					
Intent-to-treat population	163	172	165	165	665
ABPM subpopulation	43	41	41	45	170
Per-protocol population	146	156	145	149	596

Of the 673 randomized patients 307 were male and 366 female. The mean age was 58 years. Average duration of hypertension was 5.9±6.1 years. These characteristics were well balanced between cohorts.
436(64.8%) had been previously treated with antihypertensive drugs in the three months preceeding the trial. The distribution of the previously treated for placebo, CC, HCTZ, and the CC/HCTZ combination were respectively: 69.7%, 59.2%, 63.4%, and 67.1%.

Results for the mean change in SiDBP from baseline to week 12 for the ITT population were:

	Placebo	HCTZ	Candesartan cilexetil	Candesartan cilexetil/HCTZ
	n=163	n=172	n=165	n=165
Baseline (Visit 3b)	99.9 ± 4.0	100.1 ± 4.1	100.1 ± 4.9	99.8 ± 4.7
Last value	92.8 ± 9.4	91.3 ± 8.7	89.4 ± 8.2	87.5 ± 7.5
Change from baseline to last value	-7.1 ± 8.7	-8.7 ± 7.9	-10.7 ± 8.0	-12.4 ± 7.3

The combination of CC/HCTZ was statistically superior to placebo and to HCTZ (p=0.0001), but not to the CC monotherapy arm (p=0.0623). The results were similar for the per protocol population.

For the change in mean SiSBP from baseline to week 12 for the ITT population, the following results were provided:

	Placebo	HCTZ	Candesartan cilexetil	Candesartan cilexetil/HCTZ
	n=163	n=172	n=165	n=165
Baseline (Visit 3b)	161.0 ± 11.3	160.5 ± 11.3	159.4 ± 13.1	158.2 ± 13.4
Last value	153.5 ± 16.2	148.0 ± 14.4	143.4 ± 15.8	140.9 ± 16.9
Changes from baseline to last value	-7.5 ± 14.5	-12.5 ± 14.0	-16.0 ± 15.7	-17.4 ± 15.2

The analyses were similar to those for SiDBP in that the CC/HCTZ combination was statistically superior to placebo and to HCTZ, but not to CC monotherapy(p=0.2281).
The 24-hour ABPM results were also consistent with the above findings and also included data on daytime and nighttime effects.
For the ITT ABPM subpopulation mean 24-hour diastolic blood pressure results were:

	Placebo	HCTZ	Candesartan cilexetil	Candesartan cilexetil/HCTZ
	n=43	n=41	n=41	n=45
First drug intake (Visit 3b)	89.6 ± 11.7	89.1 ± 10.8	86.7 ± 9.8	84.2 ± 9.5
End of study (Visit 7)	87.9 ± 12.0	85.6 ± 9.8	81.8 ± 9.8	77.6 ± 8.8
Change from first drug intake to end of study	-1.8 ± 6.4	-3.5 ± 5.8	-6.0 ± 5.7	-7.5 ± 9.3

Results for daytime and nighttime are presented below.

	Placebo	HCTZ	Candesartan cilexetil	Candesartan cilexetil/HCTZ
	n=43	n=41	n=41	n=45
First drug intake (Visit 3b)	92.5 ± 11.9	92.0 ± 11.4	89.3 ± 10.1	87.1 ± 9.9
End of study (Visit 7)	90.5 ± 12.1	88.4 ± 10.3	84.1 ± 10.4	80.1 ± 9.0
Change from first drug intake to end of study	-2.0 ± 7.1	-3.7 ± 6.1	-6.3 ± 6.3	-7.8 ± 9.6

	Placebo	HCTZ	Candesartan cilexetil	Candesartan cilexetil/HCTZ
	n=43	n=41	n=41	n=45
First drug intake (Visit 3b)	78.0 ± 12.2	77.1 ± 10.9	76.6 ± 10.8	72.5 ± 9.9
End of study (Visit 7)	77.2 ± 13.3	74.1 ± 11.4	72.6 ± 9.3	67.2 ± 10.0
Change from first drug intake to end of study	-1.1 ± 7.2	-2.8 ± 8.3	-4.7 ± 5.8	-6.0 ± 10.0

The CC/HCTZ combination is statistically superior to placebo and HCTZ for each analysis, but only approached conventional statistical superiority compared to CC alone for the nighttime result (p=0.0535).
The findings for systolic blood pressure were similar.
Safety was evaluated for the 673 randomized patients who took at least 1 dose of the assigned treatment. Exposure was approximately 80 days in each group. No deaths occurred. 16 patients withdrew for an adverse experience (placebo-2, HCTZ-3, CC-5, CC/HCTZ-6).

The reasons for withdrawal are listed in the following table:

Pat. No.	Age at onset [years]	Gender	Investigator's verbatim translated into English	Preferred Term
Placebo (n=2)				
0410	68	female	Preinfarction syndrome, angina pectoris gravis*	Angina pectoris
0581	54	male	Hypertensive crisis*	Hypertension
HCTZ (n=3)				
0513	33	female	Cardialgia	Angina pectoris
			Dizziness	Dizziness
			Episodes of profuse perspiration	Sweating increased
			Hypertension	Hypertension
			Intense back pain	Back pain
0585	57	female	Hypertensive crisis	Hypertension
0818	64	male	CK elevation	Creatine phosphokinase increased
Candesartan cilexetil (n=5)				
0303	68	male	Atrial fibrillation	Fibrillation atrial
0341	62	female	Cephalgias	Headache
			Subfebrile temperatures	Fever
0791	57	female	Gastric pains	Dyspepsia
			Skin reaction	Skin disorder
			Vomiting	Vomiting
0817	63	female	Dizziness	Dizziness
0841	64	female	Hypertensive dysregulation (220/110 mmHg)*	Hypertension
			Nose bleed*	Epistaxis
Candesartan cilexetil/HCTZ (n=6)				
0133	64	male	Cephalgia	Headache
0139	46	female	Supraventricular tachycardia due to blood pressure reduction	Tachycardia supraventricular
0199	57	female	Supraventricular tachycardia*	Tachycardia supraventricular
0204	67	male	Recurrent attacks of dizziness*	Dizziness
			Syncope*	Syncope
0449	54	female	Rotatory vertigo*	Vertigo
			Supraventricular tachycardia*	Tachycardia supraventricular
0895	49	female	Colon tumour (adenocarcinoma)*	Colon carcinoma

* reported as serious adverse event

Heart rate as measured by EKG from first visit to last visit increased slightly and variably in all arms with the largest numerical increase being found in the CC/HCTZ group (2.7±13.1 bpm). 3(1.8%) cases of supraventricular tachycardia were noted in the CC/HCTZ arm versus 0 in the other arms, although tachycardia was found in all arms but placebo with similar rare frequency. While no adverse experience called "hypotension", "dizziness"or "vertigo" or "syncope" was noted for 3 placebo patients, 1 HCTZ patient, 5 CC patients and 5 CC/HCTZ patients.

Differences between arms for laboratory parameters were noted for hemoglobin in the CC and CC/HCTZ groups (-2.70g/l±7.19, -3.58±7.40 respectively), and for mean potassium for the HCTZ group (-0.23 mmol/l).

Comments:
In this study the combination was not statistically superior to CC alone, although numerically the results ordered in the right direction. Since pooling of this and other studies is to be done to get some idea of dose response, it is not unreasonable to compare the results of the CC/HCTZ 16/12.5mg combination with those of 4/6.5mg seen in study AHK-0004. The following chart provides the deltas seen from baseline to endpoint for SiDBP for the ITT populations.

	4/6.25 mg	16/12.5 mg
placebo	-9.3 mmHg	-5.3mmHg
CC monotherapy	-4.4 mmHg	-1.7mmHg

While neither these nor the other studies were done in recidivistic populations where the dose response might be different, these results do not suggest an increased benefit with increased dose. From a safety perspective both combination products seemed well tolerated without increased toxicity compared to the active monotherapies.

3.4

Study AM 153

Comparison of the Safety and Antihypertensive Efficacy of the Fixed Combination of Candesartan Cilexetil and Hydochlorothiazide(32 mg/12.5 mg) Once Daily with the Individual Components Administered Once Daily: a Multicenter, Randomized, Double-blind, Placebo- controlled, Parallel-design Study.

The protocol called for randomization of 240(60 per group) male or female hypertensive (SiDBP 95-114 mmHg) patients 18 years of age or older to placebo or HCTZ 12.5 mg or CC 32 mg or a combination tablet of CC/HCTZ 32/12.5 mg to compare the antihypertensive efficacy and the safety of the combination to the monotherapies and placebo for change in trough SiDBP from baseline to week 8. Peak blood pressures (6±1.5 hours post-dose) were also to be evaluated. Patients with a life expectancy of less than 2 years, insulin dependent diabetes mellitus, orthostatic hypotension, or renal disease were to be excluded.

The visit schedule for the study was:

Procedure	Screening Week	Placebo Run-in Week					Double-blind Week			F/U
	-1	0*	1	2	3	4(5)/0**	2	4	8 or D/C	2
Informed Consent	X									
Medical History	X									
Chest X-ray					X‡					
12-lead ECG					X				X	
Complete Physical Exam	X				X				X	
Brief Physical Exam		X	X	X		X	X	X		X
Heart Rate/(Trough) BP	X	X	X	X	X	X	X	X	X	X
Peak BP Measurements (6h ± 1.5h post-dose)					X†	X†			X	
Laboratory Assessments	X				X				X	
Drug Accountability		X	X	X	X	X	X	X	X	
Current/Concomitant Medication Assessment	X	X	X	X	X	X	X	X	X	X
AE Assessment		X	X	X	X	X	X	X	X	X
Final Report									X	

APPEARS THIS WAY ON ORIGINAL

* If patient did not need washout of antihypertensive or other excluded medications, *Screening Week -1* and *Placebo Run-in Week 0* were combined into one visit. If these visits were combined, a complete physical exam was performed rather than a brief physical exam.

** If patient qualified for randomization at Placebo Run-in Week 4, Week 5 was not needed and Week 4 became Double-blind Week 0 (Baseline). If patient qualified for randomization at Placebo Run-in Week 5, this visit became Double-blind Week 0 (Baseline).

† Peak blood pressure was measured at first (Placebo Run-in Week 3 or Week 4) and second (whichever week was Double-blind Week 0) qualifying visits.

‡ Chest X-ray (PA view) performed within 3 months prior to admission into the study was an acceptable alternative.

Two primary questions were to be addressed:

1. Were there differences in antihypertensive efficacy between placebo and each active arm?
2. Were there differences in antihypertensive efficacy between the combination product and each other arm?

A sample size of 60 patients per group was thought needed to provide 95% power to detect a true mean difference in SiDBP change from baseline to week 8 of 5 mmHg assuming a standard deviation of 7.5 mmHg. Both ITT/LOCF and per protocol analyses were to be done, and a number of secondary endpoints (e.g. change in trough SiSBP, peak bp comparisons, proportions of responders and controlled patients) were to be analyzed. Blinding was done by administering three tablets daily to each patient:
placebo or dummy, HCTZ or dummy, CC or combination drug.

Patient disposition was noted in the following chart.

	Placebo	CC 32 mg	CC/HCTZ 32/12.5 mg	HCTZ 12.5 mg	Total
Patients Entered					381
Randomized to Double-blind	66(100.0%)	73(100.0%)	64(100.0%)	72(100.0%)	275(100.0%)
Discontinued	19(28.8%)	8(11.0%)	6(9.4%)	11(15.3%)	44(16.0%)
Lost to Follow-Up	2(3.0%)	0(0.0%)	0(0.0%)	1(1.4%)	3(1.1%)
Lack of Response	11(16.7%)	2(2.7%)	1(1.6%)	5(6.9%)	19(6.9%)
Adverse Event	2(3.0%)	1(1.4%)	4(6.3%)	3(4.2%)	10(3.6%)
Consent Withdrawn	4(6.1%)	4(5.5%)	1(1.6%)	0(0.0%)	9(3.3%)
Sponsor/Investigator Decision	0(0.0%)	1(1.4%)	0(0.0%)	2(2.8%)	3(1.1%)
Completed Study	47(71.2%)	65(89.0%)	58(90.6%)	61(84.7%)	231(84.0%)

30 centers participated, though 2 enrolled no patients. Also there was inadequate documentation of the data submitted from 2 sites (003-Dr. Bittar, and 016-Dr. Mersey), which contributed 10 and 8 patients respectively, to provide verification.

The sponsor after performing analyses with and without these centers provided their analysis with these data, since the results were little different.
The average age of those analyzed was 52.4 years, which included 152 men and 118 women of whom 57 were black. The mean duration of disease was 10 years. There were no significant differences in these demographic characteristics between arms. The mean trough sitting diastolic and systolic blood pressures at baseline were:

Baseline Trough Sitting DBP (mm Hg)	Mean (SD)	100.9 (4.8)	100.9 (5.1)	99.9 (3.5)	99.4 (3.7)	100.3 (4.4)
Baseline Trough Sitting SBP (mm Hg)	Mean (SD)	154.5 (13.8)	150.8 (14.3)	152.9 (13.2)	150.2 (12.9)	152.0 (13.6)

No data on antihypertensive treatment prior to entrance was provided.

The mean duration of time on randomized treatment was 53.4 days that ranged from 48.4 days on placebo to 56 days on the combination drug. The minimum number of days on therapy occurred in the CC alone and HCTZ alone arms (5 days each). Compliance was estimated above 96% for all groups.

The results as provided by the sponsor, including the two questionable centers, were
a) for the primary endpoint:

Least Squares Means (LSM) and Corresponding Confidence Intervals for Trough Sitting Diastolic Blood Pressure by Treatment (ITT/LOCF Population)

Treatment	N	LSM	95% CI	
			Lower	Upper
Placebo	62	-3.7	-6.0	-1.5
CC 32 mg	72	-10.6	-12.6	-8.5
CC/HCTZ 32/12.5 mg	63	-14.5	-16.6	-12.3
HCTZ 12.5 mg	70	-6.3	-8.4	-4.3

Test Results for Pairwise Treatment Group Comparisons Based on Trough Sitting Diastolic Blood Pressure (ITT/LOCF Population)

Treatment Comparison	LSM	95% CI		p-value
		Lower	Upper	
CC 32 mg vs. Placebo	-6.8	-9.9	-3.8	0.0001
CC/HCTZ 32/12.5 mg vs. Placebo	-10.7	-13.9	-7.6	0.0001
HCTZ 12.5 mg vs. Placebo	-2.6	-5.7	0.5	0.0987
CC/HCTZ 32/12.5 mg vs. CC 32 mg	-3.9	-6.9	-0.9	0.0115
CC/HCTZ 32/12.5 mg vs. HCTZ 12.5 mg	-8.1	-11.2	-5.1	0.0001

b) for trough sitting systolic blood pressure:

Test Results for Pairwise Treatment Group Comparisons Based on Trough Sitting Systolic Blood Pressure (ITT/LOCF Population)

Treatment Comparison	LSM	95% CI		p-value
		Lower	Upper	
CC 32 mg vs. Placebo	-5.4	-10.1	-0.8	0.0221
CC/HCTZ 32/12.5 mg vs. Placebo	-18.9	-23.7	-14.2	0.0001
HCTZ 12.5 mg vs. Placebo	-2.7	-7.4	2.0	0.2549
CC/HCTZ 32/12.5 mg vs. CC 32 mg	-13.5	-18.1	-8.9	0.0001
CC/HCTZ 32/12.5 mg vs. HCTZ 12.5 mg	-16.2	-20.8	-11.6	0.0001

c) for trough and peak sitting and standing blood pressures:

Least Squares Means for Changes From Baseline to Double-blind Week 8 (mm Hg) in Blood Pressure Measurements versus Combination Therapy and Placebo

Parameter	Placebo	CC/HCTZ 32/12.5 mg	CC 32 mg	HCTZ 12.5 mg
Trough Sitting DBP	-3.7	-14.5[c]	-10.6[b,c]	-6.3[a]
Trough Sitting SBP	-3.2	-22.1[c]	-8.6[a,d]	-5.9[a]
Peak Sitting DBP	-3.8	-15.3[c]	-9.6[a,c]	-6.2[a]
Peak Sitting SBP	-2.2	-22.8[c]	-11.4[a,c]	-5.5[a]
Trough Standing DBP	-3.2	-14.3[c]	-8.9[a,c]	-4.7[a]
Trough Standing SBP	-2.7	-21.3[c]	-8.5[a,d]	-6.1[a]
Peak Standing DBP	-2.9	-15.6[c]	-9.3[a,c]	-4.8[a]
Peak Standing SBP	-3.2	-24.1[c]	-12.3[a,c]	-4.2[a]

[a] Designates significantly different from the combination therapy, $p < 0.01$.

[b] Designates significantly different from the combination therapy, $p = 0.012$.

[c] Designates significantly different from placebo, $p < 0.01$.

[d] Designates significantly different from placebo, $p < 0.05$.

Placebo corrected trough to peak ratio for the combination product was 0.88.

Subgroup analyses for the primary endpoint showed consistent results for women and men, blacks and nonblacks, and age 65 or older and under 65 years of age, although CC alone performed somewhat better in females and those 65 years and older.

Population	Placebo (n)	CC 32 mg (n)	CC/HCTZ 32/12.5 mg (n)	HCTZ 12.5 mg (n)
Overall	-3.7 (62)	-10.6 (72)	-14.5 (63)	-6.3 (70)
Black	-3.5 (16)	-9.9 (16)	-13.1 (10)	-10.7 (11)
Nonblack	-3.8 (46)	-10.6 (56)	-15.1 (53)	-5.4 (59)
Age >= 65 yrs	-4.5 (6)	-13.2 (8)	-14.1 (11)	-6.6 (6)
Age < 65 yrs	-3.5 (56)	-10.6 (64)	-15.4 (52)	-6.2 (64)
Female	-4.5 (30)	-12.8 (31)	-15.4 (28)	-8.2 (29)
Male	-2.7 (32)	-9.5 (41)	-13.1 (35)	-5.2 (41)

The maximal effect on change from baseline to week 8 for SiDBP was similar for CC alone and CC/HCTZ(-34.0 and -37.3 mmHg respectively). However the maximal effect on SiSBP was much greater for CC/HCTZ(-64.0 mmHg) compared to CC alone(-37.3). The median results were also greater for the combination compared to CC alone(-23.3 versus -8.7 mmHg). As seen in other studies the majority of the effects were seen at 2 weeks. However, the only patient who experienced a change in systolic blood pressure of 30 mmHg or more going from the sitting to the standing position and was therefore counted as a case of orthostatic hypotension was on placebo.

Trough sitting heart rate changed little during the study, and no significant differences were noted between arms.

Safety was evaluated for the 275 patients who were randomized.
No deaths occurred.
Serious adverse experiences were reported in 5 patients: 4 placebo, 1 HCTZ. 3 of the placebo patients had neoplasms, 1 synovitis. The HCTZ patient has a "resistance mechanism disorder" or viral infection.

10 patients withdrew for adverse experiences as per the following table:

Patient	Treatment	Adverse Event (Preferred Term)	Days on Treatment
004/006	Placebo	Hives	6
		Lips Swelling	7
		Urticaria	38
004/013	Placebo	Gastric Carcinoma	25
010/004	CC 32 mg	Ankle Edema	18
009/009	CC/HCTZ 32/12.5 mg	Arthritis Aggravated	22
		Respiratory Disorder	29
		Thyroid Enlarged	29
012/004	CC/HCTZ 32/12.5 mg	Peripheral Edema	14
		Inflicted Injury	31
		Varicose Vein	31
013/006	CC/HCTZ 32/12.5 mg	Asthma	14
		Alcohol Problem	52
005/002	HCTZ 12.5 mg	Chest Pain	44
		Bite	59
011/003	HCTZ 12.5 mg	Accidental Overdose	1
		Headache (mild)	6
		Headache (moderate)	9
		Headache (moderate)	11
		Headache (severe)	28
		Headache (severe)	29
		Headache (severe)	30
028/006	HCTZ 12.5 mg	Joint Pain	28
		Infection Viral	42

The most frequently reported adverse experience was URI, and summating the cases of dizziness and lightheadedness that might suggest hypotensive episodes did not reveal a difference between groups.

While there were some numerical changes in laboratory parameters with the normal range, significant changes in BUN, creatinine, serum potassium, liver function tests were not found withing groups or between groups.

Comments:
This study clearly demonstrated that the combination of CC/HCTZ 32/12.5 mg was more effective than the components or placebo, but the marked effect on systolic pressure, the small number of subjects exposed to the combination (n=63) with only 11 of those subjects 65 years of age or older are concerns.

3.5

Study AM124

Comparison of the Safety and Antihypertensive Efficacy of the Fixed Combination of Candesartan Cilexetil and Hydrochlorothiazide(8 mg/12.5 mg) Once Daily with the Individual Components Given Once Daily: A Multicenter, Randomized, Double-blind. Placebo-controlled, Parallel-group Design Study

The protocol with its 7/9/96 amendment was finalized prior to the entrance of the first patient. It called for randomization of 560 patients, male or female, age 18 years or older with essential hypertension characterized by a mean SiDBP of 95-114 mmHg at randomization. There were to be 6 arms: placebo, HCTZ 12.5 mg, HCTZ 25 mg, CC 8 mg, CC 16 mg, and CC/HCTZ 8/12.5 mg. To assure blinding each patient was to take 4 tablets during the double-blind part of the study. All study drugs were manufactured by AstraHassle. Patients with secondary hypertension, systolic pressure ≥ 200 mmHg, or a life expectency of less than 2 years were excluded. An uneven randomization was planned with 140 patients in the combination and CC 8 mg arms, and 70 in each of the four remaining arms. The randomization was stratified for black, nonblack patients. 40 centers were to be involved, and the visit schedule of the study was presented in the following chart:

	Screening and Placebo Run-In Baseline					Double-Blind					Follow-Up
	Week					Week					Week
	1		2	3	4*	1	2	4	8	12	2
	Day					Day					Day
PROCEDURE	0	7	14	21	28	0	14	28	56	84	14
Informed Consent	X										
Medical History	X										
Chest X-ray				X							
12-lead ECG				X						X	
Complete Physical Exam	X									X	
Brief Physical Exam		X	X	X	X	X	X	X	X		X
Trough BP Measurements	X	X	X	X	X	X	X	X	X	X	
Peak BP Measurements				X		X			X	X	
Fasting Laboratory Assessments	X					X				X	
Drug Accountability		X	X	X	X	X	X	X	X	X	
AE Assessment		X	X	X	X	X	X	X	X	X	X

The primary endpoint of the study was change in trough SiDBP from randomization to 12 weeks of treatment. The fixed dose of CC/HCTZ was to be compared to placebo and each active treatment arm for the ITT population and the per protocol population. Other objectives were to compare peak trough ratios for the various regimens and assess safety and tolerability. Analyses of sitting and standing systolic blood pressures and proportions of responders were also to be done. The sample size was determined on the ability to detect a true mean difference in SiDBP change from baseline of 5 mmHg(assuming a standard deviation of 7.5 mmHg) between any two treatment groups with 95% power using a two-tailed test with an α=0.05.

602 patients were randomized to one of the six arms in an unbalanced manner as described above. 37 sites participated. One randomized patient (024/010) never returned and was not included in the analyses. Of the randomized population 55.5% were male, 26.6% were black. The average duration of hypertension was 9.5 years, and the mean trough SiDBP and SiSBP were 100.7 and 153.2 mmHg respectively at baseline. These characteristics were reasonably balanced between groups.

The disposition of those randomized was provided as follows:

	Placebo	CC 8 mg	CC 16 mg	CC/HCTZ 8/12.5 mg	HCTZ 12.5 mg	HCTZ 25 mg	Total
Patients Entered							892
Randomized to Double-Blind	78(100.0%)	137(100.0%)	76(100.0%)	157(100.0%)	73(100.0%)	81(100.0%)	602(100.0%)*
Discontinued	15(19.2%)	17(12.4%)	7(9.2%)	14(8.9%)	10(13.7%)	12(14.8%)	75(12.5%)
Lost to Follow-Up	1(1.3%)	3(2.2%)	1(1.3%)	0(0.0%)	0(0.0%)	2(2.5%)	7(1.2%)
Lack of Response	6(7.7%)	3(2.2%)	0(0.0%)	2(1.3%)	4(5.5%)	2(2.5%)	17(2.8%)
Adverse Event	2(2.6%)	5(3.6%)	2(2.6%)	7(4.5%)	3(4.1%)	5(6.2%)	24(4.0%)
Consent Withdrawn	3(3.8%)	3(2.2%)	2(2.6%)	1(0.6%)	2(2.7%)	0(0.0%)	11(1.8%)
Sponsor/Investigator Decision	3(3.8%)	3(2.2%)	2(2.6%)	4(2.5%)	1(1.4%)	3(3.7%)	16(2.7%)
Completed Study	63(80.8%)	120(87.6%)	69(90.8%)	143(91.1%)	63(86.3%)	69(85.2%)	527(87.5%)

The mean duration of treatment was 81.8 days, and treatment compliance was estimated above 96% for all groups. The sponsor noted that in the last phase of the study unused kits were broken up and medications redistributed because of a shortage of drugs. This resulted in some cases of non-sequential treatment assignment according to the randomization and incomplete blocks.
While 602 patients were randomized, 14 did not have baseline or other data recorded. Therefore the ITT analyses considered 588 patients data.
The results for the primary endpoint were provided in the following charts:

Trough Sitting Diastolic Blood Pressure (mmHg) by Treatment and Double-Blind (DB) Visit (ITT/LOCF Population)

Treatment		Baseline	DB 2	DB 4	DB 8	DB 12
Placebo	N	75	74	71	71	75
	Mean	100.2	94.5	92.7	93.4	94.8
	SD	4.9	9.5	9.4	9.0	10.3
CC 8 mg	N	136	135	131	121	136
	Mean	100.5	92.2	91.6	90.8	92.9
	SD	4.5	8.6	9.8	8.3	10.2
CC 16 mg	N	75	74	73	73	75
	Mean	100.7	92.1	90.5	89.9	90.3
	SD	4.5	9.0	9.7	9.4	9.1
CC/HCTZ 8/12.5 mg	N	154	150	151	144	154
	Mean	100.7	89.3	88.2	87.4	88.4
	SD	4.6	9.1	9.1	8.0	9.7
HCTZ 12.5 mg	N	72	70	70	64	72
	Mean	100.9	95.0	93.5	92.4	94.1
	SD	4.4	8.5	9.7	8.7	9.8
HCTZ 25 mg	N	76	75	74	69	76
	Mean	101.4	92.0	90.2	90.5	91.6
	SD	4.9	7.4	8.6	8.8	9.8

Test Results for Pairwise Treatment Group Comparisons Based on Trough Sitting Diastolic Blood Pressure (ITT/LOCF Population)

Treatment Comparison	LSM	95% CI		p-value
		Lower	Upper	
CC 8 mg vs. Placebo	-1.9	-4.6	0.7	0.1499
CC 16 mg vs. Placebo	-4.9	-7.8	-1.9	0.0012
CC/HCTZ 8/12.5 mg vs. Placebo	-7.4	-10.0	-4.9	0.0001
HCTZ 12.5 mg vs. Placebo	-1.0	-4.0	1.9	0.4925
HCTZ 25 mg vs. Placebo	-4.0	-7.0	-1.1	0.0077
CC/HCTZ 8/12.5 mg vs. CC 8 mg	-5.5	-7.7	-3.3	0.0001
CC/HCTZ 8/12.5 mg vs. HCTZ 12.5 mg	-6.4	-9.0	-3.8	0.0001

Subgroup results for sex, age and race were given in the following table:

Least Squares Means for Reductions from Baseline in Trough Sitting Diastolic Blood Pressure (mmHg) by Treatment and Subpopulation (ITT/LOCF Population)

Population	Placebo (n)	CC 8 mg (n)	CC 16 mg (n)	CC/HCTZ 8/12.5 mg (n)	HCTZ 12.5 mg (n)	HCTZ 25 mg (n)
Overall	-5.4(75)	-7.3(136)	-10.3(75)	-12.8(154)	-6.4(72)	-9.4(76)
Black	-7.6(18)	-5.0(34)	-7.5(15)	-13.5(48)	-9.1(19)	-12.8(21)
Nonblack	-4.7(57)	-7.8(102)	-10.7(60)	-12.5(106)	-5.7(53)	-8.6(55)
Age >= 65 yrs	-8.0(14)	-4.1(17)	-9.4(13)	-12.2(19)	-10.1(7)	-10.9(8)
Age < 65 yrs	-4.7(61)	-7.5(119)	-10.3(62)	-12.9(135)	-6.0(65)	-9.4(68)
Female	-6.9(33)	-7.0(63)	-10.0(27)	-15.1(72)	-9.3(33)	-12.7(36)
Male	-4.5(42)	-8.4(73)	-10.9(48)	-10.9(82)	-7.6(39)	-8.6(40)

For trough sitting systolic blood pressure the sponsor's table gave these results:

Test Results for Pairwise Treatment Group Comparisons Based on Trough Sitting Systolic Blood Pressure (ITT/LOCF Population)

Treatment Comparison	LSM	95% CI		p-value
		Lower	Upper	
CC 8 mg vs. Placebo	-3.7	-8.1	0.7	0.0973
CC 16 mg vs. Placebo	-10.9	-15.8	-6.0	0.0001
CC/HCTZ 8/12.5 mg vs. Placebo	-13.8	-18.1	-9.4	0.0001
HCTZ 12.5 mg vs. Placebo	-4.5	-9.5	0.5	0.0787
HCTZ 25 mg vs. Placebo	-9.3	-14.3	-4.4	0.0002
CC/HCTZ 8/12.5 mg vs. CC 8 mg	-10.0	-13.7	-6.4	0.0001
CC/HCTZ 8/12.5 mg vs. HCTZ 12.5 mg	-9.3	-13.6	-4.9	0.0001

For other parameters the sponsor provided a summary table:

Placebo-Corrected Least Squares Means for Reductions From Baseline to Double-Blind Week 12 (mmHg) in Blood Pressure Measurements by Treatment (ITT/LOCF Population)

Parameter	CC 8 mg	CC 16 mg	CC/HCTZ 8/12.5 mg	HCTZ 12.5 mg	HCTZ 25 mg
Trough Sitting DBP	-1.9	-4.9*	-7.4*	-1.0	-4.0*
Trough Sitting SBP	-3.7	-10.9*	-13.8*	-4.5	-9.3*
Peak Sitting DBP	-1.2	-1.4	-5.8*	+2.0	-0.2
Peak Sitting SBP	-4.0*	-5.6*	-11.6*	-0.5	-2.8
Trough Standing DBP	-1.4	-3.1*	-5.6*	-0.4	-2.4*
Trough Standing SBP	-5.6*	-12.8*	-14.3*	-5.2*	-8.8*
Peak Standing DBP	-3.2*	-2.4	-7.1*	+0.2	-0.5
Peak Standing SBP	-6.9*	-8.4*	-13.5*	-2.7	-6.0*

The * designates significantly different from placebo.

The placebo corrected peak trough ratio for the combination product was 1.06.

Safety was evaluated in 602 randomized patients.

There were no deaths. The most frequently reported adverse experience was URI.
Twenty-four patients withdrew for adverse experiences: placebo-2, CC 8mg-5, CC 16mg-2, HCTZ 12.5mg-3, HCTZ 25mg-5, and CC/HCTZ 8/12.5mg-7. Proportionally the highest rate of withdrawals was in the HCTZ 25mg group. The reasons for withdrawal from the CC/HCTZ group included gastroenteritis, fatigue, abnormal sexual function, but one patient withdrew for light-headedness(014/010) and another for kidney dysfunction((002/003).

Serious adverse reports were listed as follows:

Patient	Treatment Group	Body System	Preferred Term
027/001	Placebo	Musculo-Skeletal System Disorder	Pain in Calf Muscles
027/008	CC 8 mg	Gastro-Intestinal System Disorders	Hematemesis
021/001	CC 16 mg	Myo-, Endo-, Pericardial and Valve Disorders	Myocardial Infarction
022/019	CC 16 mg	Gastro-Intestinal System Disorders	Pancreatitis Chronic
		Gastro-Intestinal System Disorders	Pancreatic Cyst
029/003	CC 16 mg	Skin and Appendages Disorders	Cellulitis Skin
036/014	CC 16 mg	Neoplasm	Urinary Bladder Carcinoma
002/003	CC/HCTZ 8/12.5 mg	Metabolic and Nutritional Disorders	Dehydration
		Gastro-Intestinal System Disorders	Gastroenteritis
016/020	CC/HCTZ 8/12.5 mg	Body As A Whole-General Disorders	Chest Pain
030/012	CC/HCTZ 8/12.5 mg	Gastro-Intestinal System Disorders	Abdominal Pain Upper
017/036*	HCTZ 12.5 mg	Neoplasm	Basal Cell Carcinoma
006/005	HCTZ 25 mg	Vascular (Extracardiac) Disorders	Cerebrovascular Accident
019/007	HCTZ 25 mg	Skin and Appendages Disorders	Melanoma Malignant
020/005	HCTZ 25 mg	Vascular (Extracardiac) Disorders	Cerebrovascular Accident

CC/HCTZ patient 002/003 was 64 years old at randomization, and she was treated with the combination from 10/24/96 to 11/5/96. On 10/25/96 she developed diarrhea, although this may have been present during the placebo run-in phase. The diarrhea continued and prior to discontinuing the CC/HCTZ her blood pressure decreased and her BUN rose. After hydration these improved at discharge.

As had been noted in other studies there was a slight decrease from baseline for hemoglobin for all Candesartan containing arms, and a slight potassium decrease for all hydrochlorothiazide arms. Liver function and renal function did not show mean changes for CC/HCTZ or other arms in the study.

3.6

Study EC403

Dose-finding Study of Candesartan cilexetil/HCTZ combination(2,4,8,16 mg for Candesartan; 12.5, 25 mg for HCTZ) in Patients with Mild to Moderate Essential Hypertension(95-110 mmHg DBP)

The protocol, finalized in 1995, involved 120 centers in Germany to evaluate various strengths of CC, HCTZ, and the combination for efficacy and safety.

There were 4 protocol amendments, three of which occurred after the study had begun. Some changes involved the randomization and analytic methods where comparison of cells was specified for "exploratory statistics" including a quadratic equation to perform a response surface analysis.

The study objectives primarily were an evaluation of combination therapy compared to monotherapy. As stated in the clinical report:

Primary objectives:

- to evaluate whether treatment with Candesartan cilexetil (2, 4, 8 or 16 mg) and HCTZ (12.5 or 25 mg) in combination enhances the antihypertensive effect of monotherapy with each component in patients with mild to moderate essential hypertension.
- to investigate whether both components of the combination (Candesartan cilexetil (2, 4, 8 or 16 mg)/HCTZ (12.5 or 25 mg)) contribute to the therapeutic effect in patients with mild to moderate hypertension.
- to investigate whether the antihypertensive activity of the combination therapy (Candesartan cilexetil (2, 4, 8 or 16 mg)/HCTZ (12.5 or 25 mg) is greater than that of placebo in patients with mild to moderate essential hypertension.

Secondary objectives:

- to obtain the safety profile of the combination (including adverse events, laboratory findings, ECG, etc.).
- to identify the optimal dose range of the combination.

The primary analysis was the sitting DBP difference from the end of the washout phase to the individual study end (last value) for the ITT population.

Sample size estimates for the different cells were:

		Candesartan cilexetil				
		0 mg	2 mg	4 mg	8 mg	16 mg
HCTZ	0 mg	0 mg/0 mg* 0 mmHg n=90	2 mg/0 mg 1 mmHg n=30	4 mg/0 mg 2 mmHg n=45	8 mg/0 mg 4 mmHg n=90	16 mg/0 mg 4 mmHg n=30
	12.5 mg	0 mg/12.5 mg 2 mmHg n=45	2 mg/12.5 mg 3 mmHg n=30	4 mg/12.5 mg 4 mmHg n=45	8 mg/12.5 mg 6 mmHg n=45	16 mg/12.5 mg 7 mmHg n=30
	25 mg	0 mg/25 mg 4 mmHg n=90	2 mg/25 mg 5 mmHg n=30	4 mg/25 mg 6 mmHg n=45	8 mg/25 mg 7 mmHg n=90	16 mg/25 mg 7 mmHg n=30

First line - definition of treatment groups
Second line - assumed difference of treatment effect to placebo
Third line - proposed sample size per cell
* 0 mg/0 mg also referred to as 'placebo'

For sample size estimation, differences between treatment groups concerning the target variable (decrease of diastolic blood pressure) of at least 3 mmHg were to be regarded as relevant. A standard deviation of 7 mmHg was to be assumed.

The initial protocol (October 12, 1994) included a 12 mg arm, and sample size projections were:

		CANDESARTAN				
		0	4 mg	8 mg	12 mg	16 mg
HCTZ	0	0.0 0 mmHg n=90	0.4 1 mmHg n=30	0.8 2 mmHg n=45	0.12 4 mmHg n=90	0.16 4 mmHg n=30
	12.5 mg	1.0 2 mmHg n=45	1.4 3 mmHg n=30	1.8 4 mmHg n=45	1.12 6 mmHg n=45	1.16 7 mmHg n=30
	25 mg	2.0 4 mmHg n=90	2.4 5 mmHg n=30	2.8 6 mmHg n=45	2.12 7 mmHg n=90	2.16 7 mmHg n=30

Fig. 1: Two factorial trial design to compare combined effects of CANDESARTAN and HCTZ to monotherapy. Naming of treatment groups, assumed difference of treatment effect to placebo, proposed sample size per cell.

One sided tests were used for planning and analysis.

An a priori specification of the order of a family group of testing was given. If one family was non-significant, no other family groups were to be tested.

The first family was a comparison of pooled combination means to placebo, pooled Candesartan monotherapy means to the combinations, pooled HCTZ means to the combinations, pooled placebo means to HCTZ pooled means, pooled placebo means to pooled Candesartan means.

The next family would involve factorial evaluation of "the most interesting combination" against the components and placebo.

Next one combination would be compared to placebo and each other. A series of these at each combination would be done.
For a combination to be judged effective, it would have to be significantly superior to each monotherapy component.

Although no interim analysis was noted, there was an increase in sample size based on greater variability of the target parameter noted on September 1995.

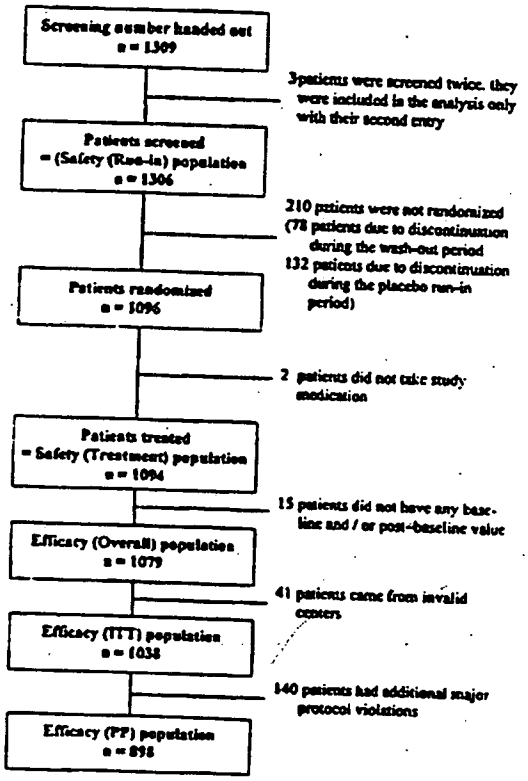
A computer generated randomization list was used as prepared by TAKEDA. There was unequal randomization and a block size of "51".

An automated device was used for the trough blood pressure readings.

The study visit schedule was:

Study Period		Wash-Out Period		Placebo Run-In Period				Treatment Period							
Week		1	2	3	4	5	6	7	8	9	10	11	12	13	14
Day	0		14				42	49	56		70				98
Visit	V1		V2				V3	V4	V5		V6				V7
Medical history	x														
Inclusion/Exclusion criteria	x		x				x								
Concomitant medication	x		x				x	x	x		x				x
Extensive physical examination	x														x
Brief physical examination			x				x	x	x		x				
Blood pressure/ Heart rate	x		x				x	x	x		x				x
Adverse events			(x)				x	x	x		x				x
Laboratory tests	x		(x)				x		x						x
ECG	x		x				x	x	x		x				x
Distribution of medication			x				x				x				
Drug accountability							x				x				x
Assessment of efficacy/safety															x

The disposition of those who entered the study was:



The invalid centers which included patients in the treatment period were centers 21, 48, 54, 124, 174 and 177. Reasons for concern leading to the exclusion of patient data were determined at a blind meeting on March 20, 1996 (last patient completed January 22, 1996). Irregularities, missing data, duplication of ECGs, and questionable blood pressure readings were noted as problems leading to invalidation.

Another concern was noted re 17 patients with high last DBP (i.e. > 120 mm Hg) readings. These were regarded as "medically implausible values" and were replaced with a previous value. 4 of these were placebo patients. 3 were 8/25 patients; 2 were 8/0 patients. None were 2, 4, or 16 monotherapy patients.

Re safety, a problem with potassium values was found due to the use of tubes containing potassium fluoride which were changed during the course of the study.

Baseline characteristics were:

Treatment group	Sex			Age [years]
	male (n)	female (n)	male/female	mean (min - max)
0 mg/0 mg	52/119 (43.7%)	67/119 (56.3%)	0.78	55.2 (23 - 80)
2 mg/0 mg	25/41 (61.0%)	16/41 (39.0%)	1.56	58.8 (37 - 75)
4 mg/0 mg	35/60 (58.3%)	25/60 (41.7%)	1.40	57.0 (26 - 74)
8 mg//0 mg	55/131 (42.0%)	76/131 (58.0%)	0.72	54.5 (32 - 78)
16 mg/0 mg	17/36 (47.2%)	19/36 (52.8%)	0.89	52.3 (22 - 73)
0 mg/12.5 mg	36/60 (60.0%)	24/60 (40.0%)	1.50	53.1 (21 - 75)
2 mg/12.5 mg	14/45 (31.1%)	31/45 (68.9%)	0.45	58.1 (34 - 74)
4 mg/12.5 mg	25/56 (44.6%)	31/56 (55.4%)	0.81	54.9 (33 - 75)
8 mg/12.5 mg	32/61 (52.5%)	29/61 (47.5%)	1.10	55.7 (26 - 72)
16 mg/12.5 mg	20/39 (51.3%)	19/39 (48.7%)	1.05	54.8 (29 - 72)
0 mg/25 mg	61/123 (49.6%)	62/123 (50.4%)	0.98	55.7 (29 - 74)
2 mg/25 mg	12/38 (31.6%)	26/38 (68.4%)	0.46	56.1 (33 - 73)
4 mg/25 mg	29/64 (45.3%)	35/64 (54.7%)	0.83	55.0 (31 - 74)
8 mg/25 mg	55/122 (45.1%)	67/122 (54.9%)	0.82	54.4 (22 - 74)
16 mg/25 mg	17/43 (39.5%)	26/43 (60.5%)	0.65	51.9 (28 - 72)

Treatment group	Duration of hypertension [years]		Pretreated patients	
	mean	(min - max)	n	%
0 mg/0 mg	2.8	(0.0-18.1)	43/119	36.1%
2 mg/0 mg	4.7	(0.0-16.0)	15/41	36.6%
4 mg/0 mg	4.0	(0.0-20.0)	25/60	41.7%
8 mg/0 mg	4.0	(0.0-29.0)	45/131	34.4%
16 mg/0 mg	2.7	(0.0-14.3)	13/36	36.1%
0 mg/12.5 mg	4.9	(0.0-30.0)	30/60	50.0%
2 mg/12.5 mg	4.6	(0.0-16.1)	20/45	44.4%
4 mg/12.5 mg	4.3	(0.0-20.0)	25/56	44.6%
8 mg/12.5 mg	3.6	(0.0-15.0)	26/61	42.6%
16 mg/12.5 mg	4.5	(0.0-24.0)	12/39	30.8%
0 mg/25 mg	4.8	(0.0-20.0)	49/123	39.8%
2 mg/25 mg	4.2	(0.0-35.0)	14/38	36.8%
4 mg/25 mg	3.8	(0.0-20.0)	25/64	39.1%
8 mg/25 mg	3.6	(0.0-29.0)	46/122	37.7%
16mg/25 mg	4.8	(0.0-35.0)	21/43	48.8%

The primary efficacy data as given was:

Treatment group	n	Median sitting diastolic blood pressure [mmHg]		
		Baseline (BL)	Last value (LV)	Absolute difference between BL and LV
		mean* ± s.d. median min - max	mean* ± s.d. median min - max	mean* ± s.d. median min - max
0 mg/0 mg	119	102.0 ± 6.0 101 88 - 125	98.0 ± 10.5 98 71 - 131	-4.0 ± 10.4 -4 -34 - +37
2 mg/0 mg	41	100.8 ± 5.1 101 89 - 110	93.9 ± 11.9 92 67 - 120	-6.9 ± 11.7 -6 -38 - +24
4 mg/0 mg	60	100.6 ± 6.4 100 73 - 114	95.3 ± 10.1 96 70 - 120	-5.3 ± 11.2 -2.5 -32 - +28
8 mg/0 mg	131	101.4 ± 5.0 101 86 - 115	93.3 ± 10.8 94 71 - 126	-8.2 ± 10.7 -8 -37 - +28
16 mg/0 mg	36	100.8 ± 5.7 100 85 - 112	90.8 ± 11.4 87.5 68 - 114	-10.0 ± 10.8 -11 -40 - +10
0 mg/12.5 mg	60	101.0 ± 5.2 100.5 88 - 118	95.6 ± 9.8 97 75 - 118	-5.5 ± 9.1 -5 -25 - +15
2 mg/12.5 mg	45	102.5 ± 4.4 103 93 - 109	96.5 ± 13.4 94 71 - 132	-6.0 ± 12.1 -7 -35 - +24
4 mg/12.5 mg	56	101.0 ± 3.8 101 93 - 112	91.1 ± 8.2 91 72 - 111	-9.9 ± 8.3 -11 -26 - +11
8 mg/12.5 mg	61	102.3 ± 5.1 103 94 - 119	91.6 ± 9.8 91 69 - 115	-10.7 ± 10.3 -11 -39 - +19
16 mg/12.5 mg	39	102.1 ± 6.2 100 95 - 127	85.2 ± 8.0 85 70 - 106	-17.0 ± 11.0 -16 -49 - +3
0 mg/25 mg	123	101.7 ± 5.2 101 83 - 119	94.3 ± 10.1 94 66 - 123	-7.4 ± 10.4 -7 -42 - +25
2 mg/25 mg	38	101.1 ± 5.2 101 85 - 113	93.8 ± 12.1 92 66 - 130	-7.2 ± 12.3 -7 -32 - +31
4 mg/25 mg	64	101.2 ± 4.9 101 87 - 112	94.1 ± 10.5 92 77 - 128	-7.1 ± 9.9 -7 -31 - +22
8 mg/25 mg	122	100.5 ± 5.1 100 86 - 116	90.2 ± 12.1 89.5 53 - 123	-10.2 ± 12.4 -12 -48 - +33
16 mg/25 mg	43	101.0 ± 5.9 101 86 - 115	88.0 ± 9.1 87 73 - 114	-12.9 ± 9.1 -16 -31 - +6

* mean from median values

Placebo adjusted least square means results were:

		Candesartan cilexetil				
		0 mg	2 mg	4 mg	8 mg	16 mg
HCTZ	0 mg	-	3.55	2.07	4.5	6.66
	12.5 mg	2.01	1.76	6.5	6.58	12.93
	25 mg	3.58	3.74	3.52	7.06	9.49

Results for change in SiDBP were:

		Candesartan cilexetil				
		0 mg	2 mg	4 mg	8 mg	16 mg
HCTZ	0 mg	4	6.9	5.3	8.2	10
		3.9	5	6	8.1	11.8
		4.3	5.3	6.3	8.3	12.2
	12.5 mg	5.5	6	9.9	10.7	17
		6.5	7.6	8.6	10.6	14.3
		5.6	6.5	7.5	9.5	13.4
	25 mg	7.4	7.2	7.1	10.2	12.9
		6.4	7.5	8.5	10.4	14
		6.8	7.8	8.7	10.7	14.7

First line: observed values
Second line: estimates under the quadratic model
Third line: estimates under the linear model

Response and normalization results were provided:

Treatment Group	Response		Normalisation	
0 mg/0 mg	36/119	30.3%	23/119	19.3%
2 mg/0 mg	17/41	41.5%	9/41	22.0%
4 mg/0 mg	23/60	38.3%	15/60	25.0%
8 mg/0 mg	62/131	47.3%	50/131	38.2%
16 mg/0 mg	25/36	69.4%	21/36	58.3%
0 mg/12.5 mg	22/60	36.7%	22/60	36.7%
2 mg/12.5 mg	18/45	40.0%	13/45	28.9%
4 mg/12.5 mg	33/56	58.9%	24/56	42.9%
8 mg/12.5 mg	34/61	55.7%	28/61	45.9%
16 mg/12.5 mg	33/39	84.6%	30/39	76.9%
0 mg/25 mg	52/123	42.3%	40/123	32.5%
2 mg/25 mg	18/38	47.4%	13/38	34.2%
4 mg/25 mg	31/64	48.4%	22/64	34.4%
8 mg/25 mg	76/122	62.3%	61/122	50.0%
16 mg/25 mg	30/43	69.8%	28/43	65.1%

Additional data re orthostatic change and systolic blood pressure were:

Treatment Group	DPB immediately upon standing mean ± s.d. (min - max)	DPB after 2 min. of standing mean ± s.d. (min - max)	Sitting SBP mean ± s.d. (min - max)	SBP immediately upon standing mean ± s.d. (min - max)	SBP after 2 min. of standing mean ± s.d. (min - max)
0 mg/0 mg	-2.5 ± 9.8 (-36 - +20)	-3.1 ± 12.3 (-56 - +33)	-4.6 ± 16.9 (-46 - +56)	-2.8 ± 18.0 (-60 - +39)	-2.9 ± 16.3 (-43 - +52)
2 mg/0 mg	-7.4 ± 12.3 (-36 - +24)	-7.4 ± 11.5 (-34 - +15)	-9.6 ± 23.6 (-57 - +43)	-2.5 ± 26.7 (-62 - +60)	-6.2 ± 25.2 (-61 - +57)
4 mg/0 mg	-8.3 ± 11.6 (-35 - +10)	-5.6 ± 11.3 (-36 - +17)	-7.9 ± 15.8 (-44 - +25)	-8.1 ± 21.6 (-62 - +39)	-8.5 ± 19.0 (-59 - +35)
8 mg/0 mg	-7.3 ± 14.3 (-66 - +35)	-7.7 ± 13.4 (-48 - +38)	-11.4 ± 19.1 (-58 - +42)	-11.9 ± 19.7 (-65 - +35)	-10.0 ± 22.0 (-67 - +84)
16 mg/0 mg	-11.6 ± 11.8 (-36 - +20)	-11.0 ± 12.9 (-35 - +18)	-12.6 ± 17.0 (-52 - +18)	-18.5 ± 23.0 (-78 - +21)	-13.8 ± 19.2 (-55 - +31)
0 mg/12.5 mg	-4.0 ± 10.8 (-29 - +31)	-2.8 ± 10.9 (-25 - +37)	-8.5 ± 13.4 (-36 - +47)	-6.8 ± 18.2 (-39 - +51)	-7.6 ± 17.2 (-38 - +71)
2 mg/12.5 mg	-5.9 ± 13.9 (-35 - +42)	-6.6 ± 11.0 (-27 - +30)	-12.1 ± 18.8 (-53 - +36)	-12.3 ± 17.8 (-42 - +43)	-9.2 ± 16.9 (-66 - +27)
4 mg/12.5 mg	-7.6 ± 10.8 (-31 - +28)	-7.1 ± 10.8 (-36 - +22)	-19.4 ± 14.6 (-58 - +20)	-17.9 ± 17.2 (-67 - +27)	-18.0 ± 17.4 (-70 - +21)
8 mg/12.5 mg	-9.4 ± 13.1 (-41 - +30)	-9.6 ± 12.1 (-34 - +29)	-20.6 ± 20.2 (-77 - +14)	-20.7 ± 20.4 (-96 - +15)	-20.6 ± 21.0 (-117 - +24)
16 mg/12 5 mg	-11.5 ± 13.4 (-37 - +19)	-12.5 ± 16.9 (-37 - +61)	-23.0 ± 17.8 (-61 - +13)	-21.5 ± 23.1 (-63 - +35)	-23.7 ± 17.9 (-69 - +24)
0 mg/25 mg	-5.7 ± 12.0 (-41 - +23)	-5.9 ± 11.8 (-44 - +22)	-10.3 ± 15.6 (-42 - +38)	-9.1 ± 20.6 (-56 - +87)	-8.4 ± 18.9 (-63 - +55)
2 mg/25 mg	-3.6 ± 14.1 (-32 - +39)	-6.0 ± 14.7 (-43 - +46)	-13.1 ± 17.8 (-50 - +21)	-10.6 ± 15.5 (-43 - +28)	-12.1 ± 19.8 (-41 - +50)
4 mg/25 mg	-6.0 ± 14.1 (-34 - +39)	-6.1 ± 11.6 (-40 - +31)	-12.9 ± 19.8 (-68 - +46)	-13.4 ± 23.1 (-102 - +50)	-11.1 ± 21.7 (-60 - +96)
8 mg/25 mg	-10.4 ± 13.8 (-59 - +27)	-9.0 ± 13.7 (-41 - +41)	-15.6 ± 19.3 (-78 - +49)	-16.2 ± 21.7 (-66 - +53)	-16.4 ± 23.4 (-95 - +82)
16 mg/25 mg	-13.8 ± 13.3 (-47 - +16)	-10.3 ± 11.4 (-28 - +29)	-21.5 ± 16.4 (-61 - +14)	-20.7 ± 17.9 (-66 - +34)	-21.9 ± 22.9 (-119 - +18)

Safety

1,094 patients comprised the original database, distributed among the 15 treatment groups as follows:

		Candesartan cilexetil				
		0 mg	2 mg	4 mg	8 mg	16 mg
HCTZ	0 mg	133	43	65	133	41
	12.5 mg	61	47	59	64	43
	25 mg	128	39	66	127	45

There was one death, a 78 year old woman (#53002) on 8 mg of Candesartan cilexetil died of a suspected pulmonary embolus on April 23, 1995. She had been started on Candesartan on April 3, 1995. On April 7, 1995 she developed tachycardia, dyspnea, malaise. Candesartan was discontinued on April 7, 1995, and patient was started on verapamil and nifedipine without response.

27 patients were withdrawn due to adverse events. Percentages in each group were:

		Candesartan cilexetil				
		0 mg	2 mg	4 mg	8 mg	16 mg
HCTZ	0 mg	0.8	9.3	1.5	3	0
	12.5 mg	0	0	5.1	3.1	0
	25 mg	2.3	2.6	1.5	3.9	2.2

Dizziness and hypotension was present in 8 of these cases, all on active drug. Cases occurred on monotherapy without clustering at any dose. There were two cases of myocardial infarction; one of 8 mg of Candesartan cilexetil and one on 4 mg of Candesartan cilexetil combined with 12.5 mg of HCTZ. Also one patient on 8 mg of Candesartan cilexetil developed severe CHF after 28 days on treatment.
Another patient (S3548) on 8 mg of Candesartan cilexetil had a "mild non-transmural myocardial infarction".

An overall listing of adverse events where there was an incidence in at least one group of > 1.0% was provided as follows:

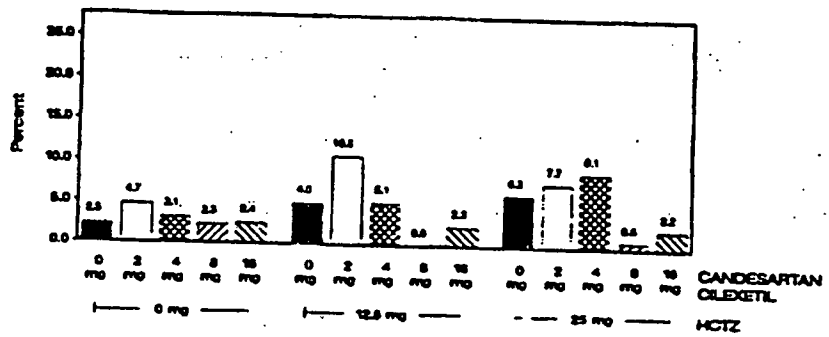
	Placebo n = 133		Candesartan Cilexetil only n = 282		HCTZ only n = 189		Combination n = 490	
	All AEs	Attrib AEs	All AEs	Attrib. AEs	All AEs	Attrib AEs	All AEs	Attrib. AEs
Body as a whole								
Influenza-like symptoms	2 (1.5%)	-	6 (2.1%)	-	9 (4.8%)	1 (0.5%)	17 (3.5%)	1 (0.2%)
Oedema peripheral	2 (1.5%)	2 (1.5%)	3 (1.1%)	2 (0.7%)	-	-	1 (0.2%)	-
Fatigue	-	-	1 (0.4%)	1 (0.4%)	4 (2.1%)	2 (1.1%)	3 (0.6%)	2 (0.4%)
Central and peripheral nervous system disorders								
Dizziness	3 (2.3%)	-	6 (2.1%)	5 (1.8%)	2 (1.1%)	2 (1.1%)	14 (2.9%)	2 (0.4%)
Headache	4 (3.0%)	1 (0.8%)	8 (2.8%)	4 (1.4%)	4 (2.1%)	2 (1.1%)	7 (1.4%)	2 (0.4%)
Paraesthesia	-	-	3 (1.1%)	1 (0.4%)	-	-	-	-
Gastrointestinal disorders								
Nausea	1 (0.8%)	-	4 (1.4%)	2 (0.7%)	-	-	7 (1.4%)	4 (0.8%)
Heart rate and rhythm disorders								
Tachycardia	2 (1.5%)	2 (1.5%)	2 (0.7%)	1 (0.4%)	1 (0.5%)	-	8 (1.6%)	4 (0.8%)
Liver and biliary system disorders								
Bilirubinaemia	1 (0.8%)	-	1 (0.4%)	1 (0.4%)	2 (1.1%)	1 (0.5%)	1 (0.2%)	-
Gamma-GT increased	1 (0.8%)	-	2 (0.7%)	1 (0.4%)	2 (1.1%)	1 (0.5%)	3 (0.6%)	2 (0.4%)
SGPT increased *	-	-	1 (0.4%)	1 (0.4%)	2 (1.1%)	1 (0.5%)	4 (0.8%)	1 (0.2%)
Metabolism and nutritional disorders								
Hyperglycaemia	-	-	4 (1.4%)	1 (0.4%)	2 (1.1%)	-	2 (0.4%)	-
Hypercholesterolaemia	2 (1.5%)	1 (0.8%)	3 (1.1%)	1 (0.4%)	1 (0.5%)	-	1 (0.2%)	1 (0.2%)
Hypertriglyceridaemia	2 (1.5%)	-	2 (0.7%)	-	1 (0.5%)	1 (0.5%)	2 (0.4%)	1 (0.2%)
CK increased	2 (1.5%)	-	1 (0.4%)	1 (0.4%)	3 (1.6%)	2 (1.1%)	5 (1.0%)	2 (0.4%)
Hyperuricaemia	-	-	1 (0.4%)	-	3 (1.6%)	3 (1.6%)	7 (1.4%)	2 (0.4%)
Hypokalaemia	-	-	1 (0.4%)	1 (0.4%)	4 (2.1%)	4 (2.1%)	3 (0.6%)	2 (0.4%)
Lipid metabolism disorder NOS	-	-	2 (0.7%)	1 (0.4%)	2 (1.1%)	-	1 (0.2%)	-
Musculo-skeletal system disorders								
Back pain	2 (1.5%)	-	6 (2.1%)	1 (0.4%)	5 (2.6%)	-	5 (1.0%)	2 (0.4%)
Accidental injury	-	-	1 (0.4%)	-	6 (3.2%)	-	3 (0.6%)	-

	Placebo n = 133		Candesartan Cilexetil only n = 282		HCTZ only n = 189		Combination n = 490	
	All AEs	Attrib. AEs	All AEs	Attrib AEs	All AEs	Attrib. AEs	All AEs	Attrib. AEs
Psychiatric disorders								
Sleep disorder	1 (0.8%)	1 (0.8%)	3 (1.1%)	1 (0.4%)	1 (0.5%)	1 (0.5%)	2 (0.4%)	2 (0.4%)
Respiratory system disorders								
Bronchitis	3 (2.3%)	-	3 (1.1%)	-	2 (1.1%)	1 (0.5%)	5 (1.0%)	-
Coughing	-	-	4 (1.4%)	1 (0.4%)	2 (1.1%)	1 (0.5%)	3 (0.6%)	3 (0.6%)
Pharyngitis	-	-	1 (0.4%)	-	2 (1.1%)	-	3 (0.6%)	2 (0.4%)
Resistance mechanism disorders								
Infection viral	-	-	-	-	2 (1.1%)	-	-	-
Skin and appendages disorders								
Rash erythematous	-	-	-	-	2 (1.1%)	-	-	-
Sweating increased	-	-	1 (0.4%)	-	-	-	7 (1.4%)	4 (0.8%)
Urinary system disorders								
NPN increased	2 (1.5%)	1 (0.8%)	-	-	1 (0.5%)	-	5 (1.0%)	2 (0.4%)
Urinary tract infection	-	-	3 (1.1%)	-	3 (1.6%)	-	4 (0.8%)	2 (0.4%)
Vision disorders								
Conjunctivitis	-	-	-	-	2 (1.1%)	-	-	-

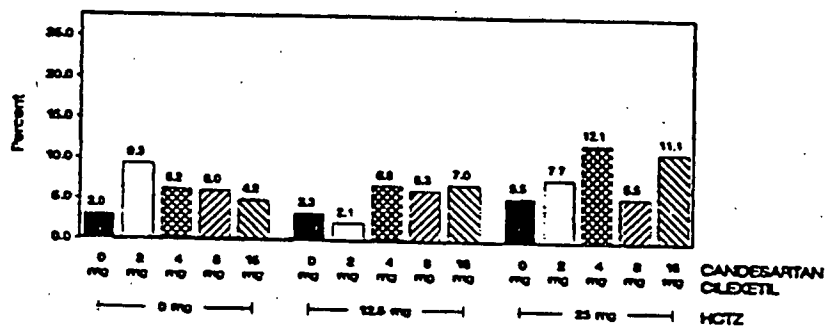
Laboratory Findings

Graphic displays of shifts from normal baseline to high final value for each treatment group were provided. Selected liver and renal chemistry displays were given as follows:

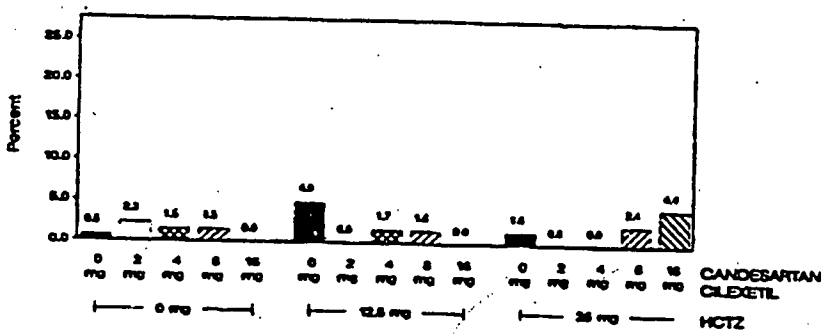
GOT (normal to high)

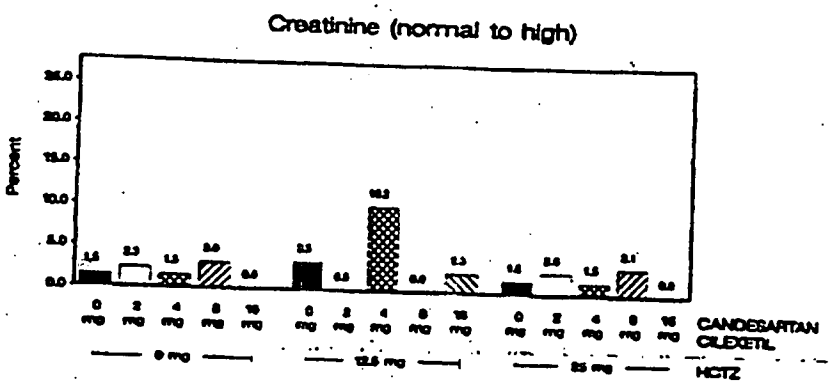


GPT (normal to high)



Total Bilirubin (normal to high)





The change in triglycerides was numerically greater for the 25 mg HCTZ combinations than for the 12.5 mg HCTZ combinations.
Numerous numerical differences were present for basophilia, eosinophilia, and glucose, but without pattern.
ECG interval changes were infrequent and small.

Comments

This study with many cells provides evidence that 8 and 16 mg of CC are statistically superior to placebo to lower DBP in patients with mild to moderate essential hypertension. At CC doses of 8 mg to 16 mg, HCTZ adds to this effect. 4 mg CC plus HCTZ gave a variable result; an additive result when 12.5 mg of HCTZ was used, but not additive for the 25 mg HCTZ/4 mg CC combination. CC 16 mg/12.5 mg HCTZ appeared best.
Although same orthostatic reactions occurred, mean DBP and SBP changes from sitting to standing were not found.
Adverse events, a few of concern, appeared randomly distributed across all cells. The same seemed true for laboratory findings. The combinations appeared to be as well tolerated as monotherapy.

3.7
POOLED STUDIES

Since there were no factorially designed studies to evaluate dose response of the CC/HCTZ combination at doses of 16/12.5 and 32/12.5 mg (the strengths requested by the sponsor), we pooled the available placebo controlled, parallel, factorially designed studies to explore dose response of the various combination strengths.

The data being analyzed consists of the pooled data of five studies AM124, AM153, EC403, EC408, and SH-AHK-0004, for the Intent to Treat Patients, as they were identified in the demographic data set of each study; we will refer to this data set as the "**Pooled-Data**". The Pooled-Data set was constructed by using the SAS data sets electronically submitted to the FDA, by the sponsor, in a Compact Disk (**CD**) floppy. In the process, for each study the three SAS data sets Demographic (**DEMOG.SD2**), Treatment (**TREAT.SD2**), and Efficacy (**EFFIC.SD2**) were merged to generate the needed data set of that study. Then, the generated data of the five studies were pooled to create the Pooled-Data. **Table 1** presents the number of patients by Treatment-by-Study cross tabulation.

Table 1. Number of Patients by Treatment-by-Study Cross Tabulation

Treatment	Study					Treatment Total (n)
	AM124 (n)	AM153 (n)	EC403 (n)	EC408 (n)	SH-AHK-0004 (n)	
Placebo	78	63	118	163	93	515
HCTZ 6.25 mg	---	---	---	---	89	89
HCTZ 12.5 mg	73	70	59	172	---	374
HCTZ 25 mg	81	---	124	---	---	205
CC 2 mg	---	---	41	---	---	41
CC 4 mg	---	---	61	---	95	156
CC 8 mg	137	---	131	---	---	268
CC 16 mg	76	---	35	165	---	276
CC 32 mg	---	72	---	---	---	72
CC 2/HCTZ 12.5 mg	---	---	45	---	---	45
CC 2/HCTZ 25 mg	---	---	38	---	---	38
CC 4/HCTZ 6.25 mg	---	---	---	---	91	91
CC 4/HCTZ 12.5 mg	---	---	56	---	---	56
CC 4/HCTZ 25 mg	---	---	64	---	---	64
CC 8/HCTZ 12.5 mg	157	---	61	---	---	218
CC 8/HCTZ 25 mg	---	---	122	---	---	122
CC 16/HCTZ 12.5 mg	---	---	39	165	---	204
CC 16/HCTZ 25 mg	---	---	43	---	---	43
CC 32/HCTZ 12.5 mg	---	63	---	---	---	63
Study Total	602	63	1037	665	368	2940

As Table 1 shows, the Pooled-Data contains the information on demographic, treatment, and trough blood pressure data (baseline, endpoint or LOCF) from a total of 2940 patients. These data were analyzed for the trough reduction from baseline (reduction= -1x[postbaseline-baseline]) in sitting diastolic (**D_SiDBP**), sitting systolic (**D_SiSBP**), standing diastolic (**D_StDBP**), standing systolic (**D_StSBP**) blood pressures.

Due to the missing values, the number of patients analyzed were different from those reported in Table 1 and also different for one type of blood pressure to another. The number of patients analyzed are 2930 for the sitting and 2921 for the standing blood pressures instead of 2940 as reported in Table 1.

3.7.1 DESCRIPTIVE STATISTICS

The following tables present some descriptive feature (mean and sample sizes) of the data with respect to sitting, standing, diastolic and systolic blood pressures.

Reduction from Baseline

The means and sample sizes for the reduction from baseline in various blood pressures (D_SiDBP, D_SiSBP, D_StDBP, and D_StSBP) are presented in Tables 2 – 5.

Table 2: Mean ± SD and the Sample Size (n) for D_SiDBP (in mmHg)

		Candesartan (mg)					
		0	2	4	8	16	32
HCTZ (mg)	0	(514) 5.40 ± 9.19	(41) 6.81 ± 11.40	(156) 7.36 ± 9.32	(268) 7.95 ± 10.30	(276) 10.41 ± 8.56	(72) 10.85 ± 9.85
	6.25	(89) 5.25 ± 8.31	(0) —	(90) 12.85 ± 8.78	(0) —	(0) —	(0) —
	12.5	(373) 7.43 ± 7.43	(45) 4.04 ± 17.1	(55) 9.55 ± 8.18	(217) 11.42 ± 9.21	(203) 12.95 ± 8.12	(62) 14.32 ± 8.94
	25.0	(203) 7.72 ± 7.72	(38) 7.70 ± 12.40	(63) 6.59 ± 10.20	(122) 10.11 ± 12.50	(43) 12.54 ± 8.82	(0) —

Table 3: Mean ± SD and the Sample Size (n) for D_SiSBP (in mmHg)

		Candesartan (mg)					
		0	2	4	8	16	32
HCTZ (mg)	0	(514) 5.62 ± 15.00	(41) 9.01 ± 23.8	(156) 8.56 ± 14.0	(268) 9.67 ± 16.7	(276) 15.41 ± 15.7	(72) 9.29 ± 13.6
	6.25	(89) 4.09 ± 14.50	(0) —	(90) 14.01 ± 14.50	(0) —	(0) —	(0) —
	12.5	(373) 9.91 ± 15.10	(45) 12.90 ± 19.80	(55) 19.10 ± 14.20	(217) 17.70 ± 17.90	(203) 18.00 ± 15.70	(62) 21.20 ± 14.60
	25.0	(203) 11.00 ± 15.80	(38) 12.80 ± 16.90	(63) 10.70 ± 19.90	(122) 16.20 ± 19.80	(43) 21.00 ± 16.20	(0) —

Table 4: Mean ± SD and the Sample Size (n) for D_StDBP (in mmHg)

		Candesartan (mg)					
		0	2	4	8	16	32
HCTZ (mg)	0	(512) 4.22 ± 9.48	(41) 7.16 ± 11.40	(156) 5.88 ± 9.91	(266) 7.27 ± 11.10	(276) 10.20 ± 9.29	(72) 9.88 ± 9.56
	6.25	(89) 2.72 ± 10.00	(0) —	(89) 9.17 ± 9.67	(0) —	(0) —	(0) —
	12.5	(371) 6.57 ± 8.95	(45) 5.08 ± 14.2	(54) 7.25 ± 9.59	(217) 10.40 ± 9.95	(203) 11.40 ± 9.30	(62) 14.10 ± 8.40
	25.0	(202) 6.41 ± 10.50	(38) 4.80 ± 13.50	(63) 6.13 ± 12.70	(122) 9.68 ± 12.10	(43) 12.00 ± 10.50	(0) —

Table 5: Mean ± SD and the Sample Size (n) for D_StSBP (in mmHg)

		Candesartan (mg)					
		0	2	4	8	16	32
HCTZ (mg)	0	(512) 4.66 ± 16.00	(41) 3.45 ± 25.00	(156) 8.43 ± 17.00	(266) 9.88 ± 17.50	(276) 15.70 ± 17.20	(72) 9.92 ± 13.60
	6.25	(89) 5.09 ± 18.10	(0) —	(89) 13.00 ± 18.10	(0) —	(0) —	(0) —
	12.5	(371) 8.96 ± 14.80	(45) 11.90 ± 19.90	(54) 17.30 ± 16.00	(217) 17.40 ± 17.40	(203) 17.40 ± 16.90	(62) 20.60 ± 14.30
	25.0	(202) 9.84 ± 16.60	(38) 11.30 ± 15.70	(63) 11.30 ± 21.30	(122) 16.30 ± 20.90	(43) 20.80 ± 18.70	(0) —

Orthostatic Change

To evaluate the changes from sitting to standing positions in systolic blood pressures of the various drugs and doses. The mean difference of SiSBP and StSBP (**OH = SiSBP – StSBP**) was determined for each subject and then the mean was calculated by averaging the differences over the patients.

Table 6: Mean ± SD and the Sample Size (n) for OR = SiSBP – StSBP (in mmHg)

		Candesartan (mg)					
		0	2	4	8	16	32
HCTZ (mg)	0	(513) 0.53 ± 8.45	(41) -1.1 ± 8.98	(156) 9.98 ± 11.10	(266) 1.27 ± 8.65	(276) 0.37 ± 7.56	(72) 0.23 ± 6.38
	6.25	(89) 0.93 ± 10.20	(0) —	(90) -0.40 ± 10.00	(0) —	(0) —	(0) —
	12.5	(373) -0.18 ± 8.47	(45) 1.87 ± 11.00	(54) 0.79 ± 8.69	(218) 1.03 ± 7.73	(204 0.91 ± 7.96	(63) 0.59 ± 7.64
	25.0	(202) 0.22 ± 9.87	(38) 1.52 ± 8.15	(63) 1.45 ± 13.00	(122) 1.97 ± 11.60	(43) 4.55 ± 9.09	(0) —

From Table 6, the only noticeable change from sitting to standing systolic blood pressure is 4.55 mmHg, which is for the combination therapy of Candesartan 16/HCTZ 25 mg.

3.7.2 Between Treatment Comparisons

The pooled data was used to perform between treatment comparisons among the treatment groups. Since the pooled data was analyzed, the p-value results will differ from those provided for the individual studies. The treatments of interest consist of placebo, HCTZ 12.5, HCTZ 25, CC 4, CC 8, CC 16, CC 32 mg mono-therapies and their CC/HCTZ combinations therapies. The statistical methodology was one-way ANOVA, using D_SiDBP and D_SiSBP as the response and the treatment as the effect (factor). The SAS was used for the analysis and in addition the option LSMEAN/PDIFF was used to generate the Tables 8 and 10, which present the P-values for treatment pairs compared. In Tables 8 and 10 for the cells that the pairwise comparisons produced statistically significant difference (P-Value < 0.05) we used symbol "←" to indicate that the significance is in favor of the row treatment and the symbol "↑" was used to indicate that significance is in favor of the column treatment.

Table 7: Sample Size, Mean and Standard Deviation of D_SiDBP for the Pooled Data

	Placebo	CC 0/ HCTZ 12.5	CC 0/ HCTZ 25	CC 4/ HCTZ 0	CC 8/ HCTZ 0	CC 16/ HCTZ 0	CC 32/ HCTZ 0	CC 4/ HCTZ 12.5	CC 8/ HCTZ 12.5	CC 16/ HCTZ 12.5	CC 32/ HCTZ 12.5	CC 4/ HCTZ 25	CC 8/ HCTZ 25	CC 16/ HCTZ 25
N	514	373	203	156	268	276	72	55	217	203	62	63	122	43
MEAN	5.41	7.43	7.72	7.36	7.95	10.41	10.85	9.55	11.42	12.95	14.32	6.59	10.12	12.54
SD	9.19	8.63	9.64	9.32	10.29	8.56	9.87	8.18	9.21	8.13	8.94	10.15	12.47	8.82

Table 8: P-Values Resulting from the Pairwise Comparisons Among the Treatment with Respect to D_SiDBP, for the Pooled Data

Treatment i/j	Placebo	CC 0/ HCTZ 12.5	CC 0/ HCTZ 25	CC 4/ HCTZ 0	CC 8/ HCT Z 0	CC 16/ HCTZ 0	CC 32/ HCTZ 0	CC 4/ HCTZ 12.5	CC 8/ HCTZ 12.5	CC 16/ HCTZ 12.5	CC 32/ HCTZ 12.5	CC 4/ HCTZ 25	CC 8/ HCTZ 25	CC 16/ HCTZ 25
Placebo		↑0.0014	↑0.0028	↑0.0218	↑0.0003	↑0.0001	↑0.0001	↑0.0017	↑0.0001	↑0.0001	↑0.0001	0.3400	↑0.0001	↑0.0001
CC 0/HCTZ 12.5	←0.0014		0.7205	0.9392	0.4852	↑0.0001	↑0.0044	0.1152	↑0.0001	↑0.0001	↑0.0001	0.5103	↑0.0058	↑0.0007
CC 0/HCTZ 25	←0.0028	0.7205		0.7178	0.7908	↑0.0018	↑0.0144	0.1965	↑0.0001	↑0.0001	↑0.0001	0.4019	↑0.0251	↑0.0021
CC 4/HCTZ 0	←0.0218	0.9392	0.7178		0.5305	↑0.0011	↑0.0087	0.1343	↑0.0001	↑0.0001	↑0.0001	0.5809	↑0.0146	↑0.0013
CC 8/HCTZ 0	←0.0003	0.4852	0.7908	0.5305		↑0.0021	↑0.0191	0.2462	↑0.0001	↑0.0001	↑0.0001	0.2985	↑0.0337	↑0.0027
CC 16/HCTZ 0	←0.0001	←0.0001	←0.0018	←0.0011	←0.0021		0.7200	0.5333	0.2341	↑0.0032	↑0.0029	←0.0034	0.7713	0.1630
CC 32/HCTZ 0	←0.0001	←0.0044	←0.0144	←0.0087	←0.0191	0.7200		0.4363	0.6563	0.1004	↑0.0318	←0.0082	0.5949	0.3469
CC 4/HCTZ 12.5	←0.0017	0.1152	0.1965	0.1343	0.2462	0.5333	0.4363		0.1854	↑0.0165	↑0.0058	0.0857	0.7100	0.1152
CC 8/HCTZ 12.5	←0.0001	←0.0001	←0.0001	←0.0001	←0.0001	0.2341	0.6563	0.1854		0.0914	↑0.0305	←0.0003	0.2175	0.4694
CC 16/HCTZ12.5	←0.0001	←0.0001	←0.0001	←0.0001	←0.0001	←0.0032	0.1004	←0.0165	0.0914		0.3119	←0.0001	↑0.0079	0.7927
CC 32/HCTZ12.5	←0.0001	←0.0001	←0.0001	←0.0001	←0.0001	←0.0029	←0.0318	←0.0058	←0.0305	0.3119		←0.0001	↑0.0038	0.3362
CC 4/HCTZ 25	0.3400	0.5103	0.4019	0.5809	0.2985	↑0.0034	↑0.0082	0.0857	↑0.0003	↑0.0001	↑0.0001		↑0.0150	↑0.0013
CC 8/HCTZ 25	←0.0001	←0.0058	←0.0251	←0.0146	←0.0337	0.7713	0.5949	0.7100	0.2175	←0.0079	←0.0038	←0.0150		0.1422
CC 16/HCTZ 25	←0.0001	←0.0007	←0.0021	←0.0013	←0.0027	0.1630	0.3469	0.1152	0.4694	0.7927	0.3362	←0.0013	0.1422	

Generated from a one-way ANOVA with treatment as the factor, using Proc GLM and the option LSMEAN/PDIFF of SAS.

Table 9: Sample Size, Mean and Standard Deviation of D_SiSBP for the Pooled Data

	Placebo	CC 0/ HCTZ 12.5	CC 0/ HCTZ 25	CC 4/ HCTZ 0	CC 8/ HCTZ 0	CC 16/ HCTZ 0	CC 32/ HCTZ 0	CC 4/ HCTZ 12.5	CC 8/ HCTZ 12.5	CC 16/ HCTZ 12.5	CC 32/ HCTZ 12.5	CC 4/ HCTZ 25	CC 8/ HCTZ 25	CC 16/ HCTZ 25
N	514	373	203	156	268	276	72	55	217	203	62	63	122	43
MEAN	5.62	9.91	10.95	8.56	9.67	15.36	9.29	19.09	17.66	18.03	21.19	10.71	16.25	21.09
SD	15.04	15.12	15.78	14	16.74	15.74	13.65	14.23	17.87	15.7	14.58	19.95	19.78	16.25

Table 10: P-Values Resulting from the Pairwise Comparisons Among the Treatment with Respect to D_SiSBP, for the Pooled Data

Treatment i/j	Placebo	CC 0/ HCTZ 12.5	CC 0/ HCTZ 25	CC 4/ HCTZ 0	CC 8/ HCTZ 0	CC 16/ HCTZ 0	CC 32/ HCTZ 0	CC 4/ HCTZ 12.5	CC 8/ HCTZ 12.5	CC 16/ HCTZ 12.5	CC 32/ HCTZ 12.5	CC 4/ HCTZ 25	CC 8/ HCTZ 25	CC 16/ HCTZ 25
Placebo		↑0.0001	↑0.0001	↑0.0438	↑0.0008	↑0.0001	0.0676	↑0.0001	↑0.0001	↑0.0001	↑0.0001	↑0.0170	↑0.0001	↑0.0001
CC 0/HCTZ 12.5	←0.0001		0.4522	0.3766	0.8493	↑0.0001	0.7639	↑0.0001	↑0.0001	↑0.0001	↑0.0001	0.7131	↑0.0001	↑0.0001
CC 0/HCTZ 25	←0.0001	0.4522		0.1593	0.3853	↑0.0028	0.4473	↑0.0008	↑0.0001	↑0.0001	↑0.0001	0.9145	↑0.0038	↑0.0002
CC 4/HCTZ 0	←0.0438	0.3766	0.1593		0.4927	↑0.0001	0.7487	↑0.0001	↑0.0001	↑0.0001	↑0.0001	0.3680	↑0.0001	↑0.0001
CC 8/HCTZ 0	←0.0008	0.8493	0.3853	0.4927		↑0.0001	0.8598	↑0.0001	↑0.0001	↑0.0001	↑0.0001	0.6409	↑0.0002	↑0.0001
CC 16/HCTZ 0	←0.0001	←0.0001	←0.0028	←0.0001	←0.0001		←0.0040	0.1130	0.1113	0.0698	↑0.0093	←0.0366	0.6092	↑0.0283
CC 32/HCTZ 0	0.0676	0.7639	0.4473	0.7487	0.8598	↑0.0040		↑0.0006	↑0.0001	↑0.0001	↑0.0001	0.6069	↑0.0034	↑0.0001
CC 4/HCTZ 12.5	←0.0001	←0.0001	←0.0008	←0.0001	←0.0001	0.1130	←0.0006		0.5531	0.6624	0.4764	←0.0044	0.2718	0.5372
CC 8/HCTZ 12.5	←0.0001	←0.0001	←0.0001	←0.0001	←0.0001	0.1113	←0.0001	0.5531		0.8125	0.1242	←0.0023	0.4319	0.1975
CC 16/HCTZ 2.5	←0.0001	←0.0001	←0.0001	←0.0001	←0.0001	0.0698	←0.0001	0.6624	0.8125		0.1718	←0.0015	0.3278	0.2528
CC 32/HCTZ12.5	←0.0001	←0.0001	←0.0001	←0.0001	←0.0001	←0.0093	←0.0001	0.4764	0.1242	0.1718		←0.0002	←0.0467	0.9746
CC 4/HCTZ 25	←0.0170	0.7131	0.9145	0.3680	0.6409	↑0.0366	0.6069	↑0.0044	↑0.0023	↑0.0015	↑0.0002		↑0.0252	↑0.0010
CC 8/HCTZ 25	←0.0001	←0.0001	←0.0038	←0.0001	←0.0002	0.6092	←0.0034	0.2718	0.4319	0.3278	↑0.0467	←0.0252		0.0865
CC 16/HCTZ 25	←0.0001	←0.0001	←0.0002	←0.0001	←0.0001	←0.0283	←0.0001	0.5372	0.1975	0.2528	0.9746	←0.0010	0.0865	

Generated from a one-way ANOVA with treatment as the factor, using Proc GLM and the option LSMEAN/PDIFF of SAS.

For the CC combinations with 12.5 & 25 mg HCTZ, the following pairwise comparisons relative to D-SiDBP are of particular interest.

Comparison of CC 8/HCTZ 12.5 with placebo and its individual components resulted in:

- CC 8/HCTZ 12.5 vs. Placebo (11.42 vs. 5.41 mmHg), P-Value = 0.0001, in favor of CC 8/HCTZ 12.5,
- CC 8/HCTZ 12.5 vs. CC 8/HCTZ 0; (11.42 vs. 7.95 mmHg), P-Value = 0.0001, in favor of CC 8/HCTZ 12.5,
- CC 8/HCTZ 12.5 vs. CC 0/HCTZ12.5; (11.42 vs. 7.43 mmHg), P-Value = 0.0001, in favor of CC 8/HCTZ 12.5.

Thus, CC 8/HCTZ 12.5 combination is superior to placebo as well as to both of its individual components.

Comparison of CC 8/HCTZ 25 with placebo and its individual components resulted in:

- CC 8/HCTZ 25 vs. Placebo; (10.12 vs. 5.41 mmHg), P-Value = 0.0001, in favor of CC 8/HCTZ 25,
- CC 8/HCTZ 25 vs. CC 8/HCTZ 0; (10.12 vs. 7.95 mmHg), P-Value = 0.0337, in favor of CC 8/HCTZ 25,
- CC 8/HCTZ 25 vs. CC 0/HCTZ 25; (10.12 vs. 7.72 mmHg), P-Value = 0.0251, in favor of CC 8/HCTZ 25.

Thus, the CC 8/HCTZ 25 combination is superior to placebo as well as to both of its individual components.

Comparison of CC 16/HCTZ 12.5 with placebo and its individual components resulted in:

- CC 16/HCTZ 12.5 vs. Placebo; (12.54 vs. 5.41 mmHg), P-Value = 0.0001, in favor of CC 16/HCTZ 12.5,
- CC 16/HCTZ 12.5 vs. CC 16/HCTZ 0; (12.54 vs. 10.41 mmHg), P-Value = 0.0032, in favor of CC 16/HCTZ 12.5,
- CC 16/HCTZ 12.5 vs. CC 0/HCTZ12.5; (12.54 vs. 7.43 mmHg), P-Value = 0.0001, in favor of CC 16/HCTZ 12.5.

Thus, the CC 16/HCTZ 12.5 combination is superior to placebo as well as to both of its individual components.

Comparison of CC 16/HCTZ 25 with placebo and its individual components resulted in:

- CC 16/HCTZ 25 vs. Placebo; (12.95 vs. 5.41 mmHg), P-Value = 0.0001, in favor of CC 16/HCTZ 12.5,
- CC 16/HCTZ 25 vs. CC 16/HCTZ 0; (12.95 vs. 10.41 mmHg), P-Value = 0.1630, no significant difference ,
- CC 16/HCTZ 25 vs. CC 0/HCTZ 25; (12.95 vs. 7.72 mmHg), P-Value = 0.0021, in favor of CC 16/HCTZ 12.5.

Thus, the CC 16/HCTZ 25 combination is superior to placebo but only is superior to CC 0/HCTZ 25 but not to HC 16/HCTZ 0.

Comparison of CC 32/HCTZ 12.5 with placebo and its individual components resulted in:

- CC 32/HCTZ 12.5 vs. Placebo; (14.32 vs. 5.41 mmHg), P-Value = 0.0001, in favor of CC 32/HCTZ 12.5,
- CC 32/HCTZ 12.5 vs. CC 32/HCTZ 0; (14.32 vs. 10.85 mmHg), P-Value = 0.0318, in favor of CC 32/HCTZ 12.5,
- CC 32/HCTZ 12.5 vs. CC 0/HCTZ 12.5; (14.32 vs. 7.72 mmHg), P-Value = 0.0001, in favor of CC 32/HCTZ 12.5.

Thus, the CC 32/HCTZ 12.5 combination is superior to placebo as well as to both of its individual components.

To following three comparisons investigate the effect of going from low CC doses to higher CC doses if they are added to 12.5 mg of HCTZ.

- CC 16/HCTZ 12.5 vs. CC 8/HCTZ 12.5; (12.95 vs. 11.42 mmHg), P-Value = 0.0914, no significant difference,
- CC 32/HCTZ 12.5 vs. CC 8/HCTZ 12.5; (14.32 vs. 11.42 mmHg), P-Value = 0.0305, in favor of CC 32/HCTZ 12.5,
- CC 32/HCTZ 12.5 vs. CC 16 HCTZ 12.5; (14.32 vs. 12.95 mmHg), P-Value = 0.3119, no significant difference,

The above three comparisons indicate that for the 8, 16, and 32 mg CC doses in combination with 12.5 mg of HCTZ, no significant increase in D_SiDBP from 8 mg CC to 16 mg CC and also from 16 mg CC to 32 mg CC was found. However, there is significant increase in D_SiDBP by going from the 8 mg CC to the 32 mg CC combination.

To following two comparisons investigate the effect of going from 12.5 mg HCTZ to 25 mg HCTZ dose for the CC doses of 8 and 16 mg.

- CC 8/HCTZ 25 vs. CC 8/HCTZ 12.5; (10.12 vs. 11.42 mmHg), P-Value = 0.2175, no significant difference,
- CC 16/HCTZ 25 vs. CC 16/HCTZ 12.5; (12.54 vs. 12.95 mmHg), P-Value = 0.7927, no significant difference,

The above two comparisons indicate that for the 8, 16 mg CC doses in combination with HCTZ, there would be no significant difference with respect to D_SiDBP by increasing the HCTZ from 12.5 mg to 25 mg.

3.7.3 RESPONSE SURFACE ANALYSIS

To further evaluate antihypertensive dose response of the various combination strengths, response surface analyses were conducted to further investigate the antihypertensive dose response relationship of the Candesartan/HCTZ therapy. The analysis consists of fitting quadratic regression models to the trough values of reductions from baseline in sitting diastolic (D_SiDBP), sitting systolic (D_SiSBP), standing diastolic (D_StDBP) and standing systolic (D_StSBP) blood pressures. The analysis used the Pooled-Data for the ITT patients.

Mathematical Model:

The mathematical equation for the fitted model is:

$$\textbf{Model (1):}\ R_i = \alpha + \beta*CC + \delta*HCTZ + \theta*CC^2 + \lambda*HCTZ^2 + \rho*CC*HCTZ + \epsilon_i$$

where:

CC = Magnitude of the Candesartan dosage (0 mg to 32 mg),

HCTZ = Magnitude of the HCTZ dosage (0 mg to 25 mg),

R_i = Response of i^{th} patients on CC/HCTZ combination (CC: 0 to 32 mg, HCTZ: 0 to 25 mg).

Response = D_SiDBP, D_SiSBP, D_StDBP or D_StSBP, depending on the analysis.

ϵ_i = Error term due to model specifications contributed by the response of i^{th} patients on CC/HCTZ.

Goodness of Fit:

For fitting the quadratic surface, the procedure "Response Surface Regression" of SAS (PROC RSREG) version 6.12 for Windows was used. Technically, the procedure is just a multivariate regression analysis. The option "LACKFIT" was selected to test the goodness of fit (or in another terminology "lack of fit"), namely the null and alternative hypotheses:

(Test a): Ho: Model is Quadratic vs. Ha: Model is not Quadratic .

A summary of the PROC RSREG output will be presented. This summary consists of the parameters' point estimates, standard error of the estimates, the P-Value of the "Lack of Fit" test and the P-Values of the tests of null and alternative hypothesis on the coefficients (parameters) of the quadratic surface:

(Test b): Ho: Coefficient = 0 vs. Ha: Coefficient $\neq$ 0.

Fitting Results:

The results of fitting model (1) to the data of D_SiDBP, D_SiSBP, D_StDBP and D_StSBP are presented below.

Results on D_SiDBP:

The following table gives the analysis results with respect to parameter estimates:

Table 11: Summary of Quadratic Response Surface Analysis on D_SiDBP

Variable	Parameter (Coefficient)	Parameter Estimate	Standard Error	P-Value for Testing Ho: Para. = 0 vs. Ha: Para. $\neq$ 0
Intercept	α	5.3764	0.3618	0.0000
Candesartan	β	0.4601	0.0619	0.0000
HCTZ	δ	0.3048	0.0666	0.0000
Candesartan*Candesartan	θ	-0.0089	0.0020	0.0000
HCTZ*HCTZ	λ	-0.0099	0.0026	0.0001
Candesartan*HCTZ	ρ	0.0018	0.0030	0.5414
Lack of Fit P-Value = 0.1915 Hence, the null hypothesis of quadratic fit (Test a) cannot be rejected, at α = 0.05				

Table 11 shows that:

- The statistical test for testing "Lack of Fit" (Test a) produced a P-Value = 0.1915, indicating that the null hypothesis of quadratic fit cannot be rejected at α = 0.05 (fitted model is not a poor fit).
- Except for the coefficient of the interaction term (ρ), the P-values of the statistical tests (Test b) on the other parameters (α, β, δ, θ, and λ) suggest that the parameter estimates are statistically significantly different from zero (P-Values = 0.0001, for all parameters). With respect to the interaction, the P-Value = 0.5414 suggests that there was no statistical evidence for a Candesartan-HCTZ interaction.

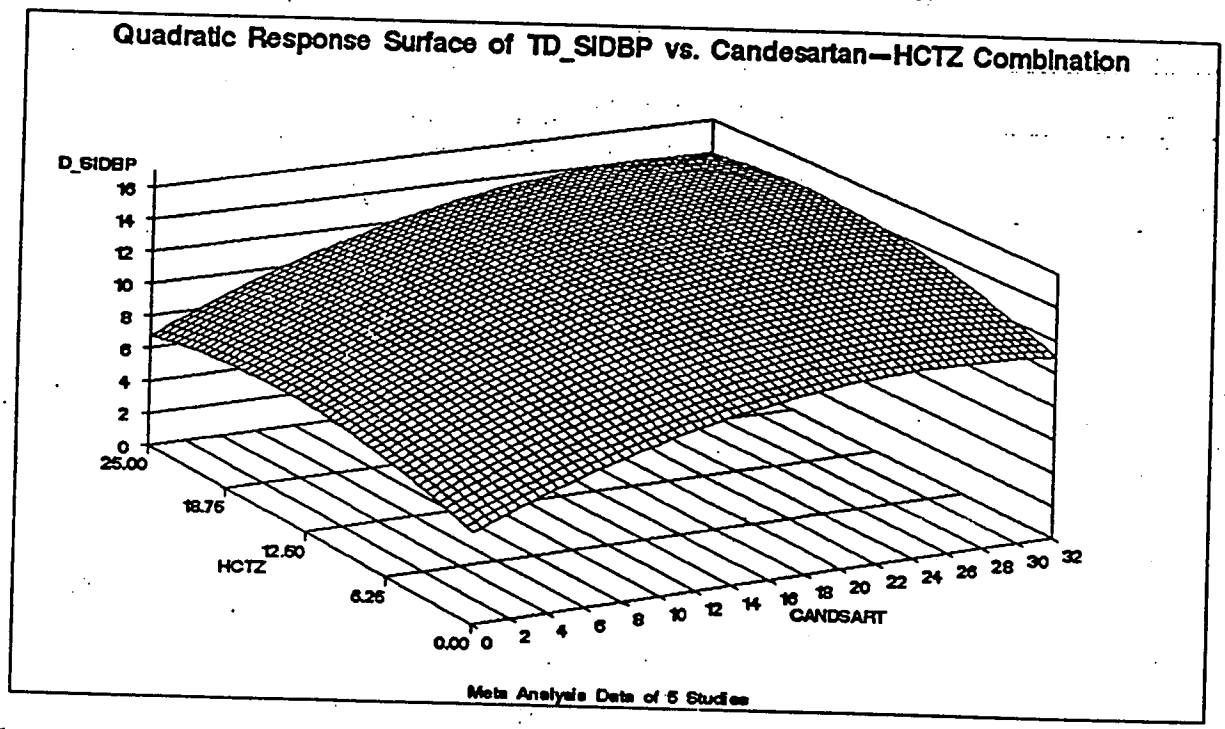
Therefore, the fitted model will be:

(2) $D\_SiDBP_i = 5.3764 + 0.4601CC + 0.30488HCTZ - 0.0089CC^2 - 0.0099HCTZ^2 + 0.0018CC*HCTZ.$

Note: We left the interaction term in the estimated model, although its effect is statistically non-significant.

The graph of the response surface is presented in **Figure 1.**

Figure 1: Quadratic Response Surface for Reduction from Baseline in SiDBP As a Function of Candesartan/HCTZ Combination Therapy



The response surface presents the predicted values of the mean response of D_SiDBP for the CC/HCTZ combination treatment, rather than the observed means. Therefore, it is useful to assess how the predicted and the raw means for D_SiDBP are close to each other. Table 12, on the next page, presents the predicted means, raw means and the difference between the predicted and raw means ($D_{(P-R)}$ = Predicted - Raw) for the CC/HCTZ combination therapy. Comparisons of the predicted and the raw means of D_SiDBP indicate that, except for the CC 4/HCTZ 6.25 mg ($D_{(P-R)}$ = -4.21 mmHg) and CC 2/HCTZ 12.5 mg ($D_{(P-R)}$ = 4.53 mmHg), the differences between the predicted and raw means are minimal.

Although in the pooled data there were no actual treatment arms, hence the observations, for the treatment combinations CC 2/HCTZ 6.25, CC 8/HCTZ 6.25, CC 16/HCTZ 6.25, CC 32/HCTZ 6.25, however, the response surface provided the predicted means by the interpolation. Also, the response surface provided an extrapolated predicted mean for treatment combination CC 32/HCTZ 25 that was not an arm of the pooled data.

Table 12: Predicted, Raw and their difference of Reduction from Baseline in SiDBP in mmHg✣

		Candesartan (mg)					
		0	2	4	8	16	32
HCTZ (mg)	0	5.38, (5.40) -0.02	6.26, (6.81) -0.55	7.07, (7.36) -0.29	8.49, (7.95) 0.54	10.46, (10.41) 0.05	10.99, (10.85) 0.14
	6.25	6.89, (5.25) 1.64	7.80, (—) —	8.64, (12.85) -4.21	10.10, (—) —	12.16, (—) —	12.86, (—) —
	12.5	7.64, (7.43) 0.21	8.57, 4.04 4.53	9.43, (9.55) -0.12	10.93, (11.42) -0.49	13.08, (12.95) 0.13	13.97, (14.32) -0.35
	25	6.81, (7.72) -0.91	7.78, (7.70) 0.08	8.69, (6.59) 2.10	10.28, (10.11) 0.17	12.61, (12.54) 0.07	13.86, (—) —

✣: In each cell, the first top value is the predicted mean D_SiDBP and second top value in ( ) is the raw mean of D_SiDBP and the bottom value is the difference of the Raw and Predicted mean ($D_{(P-R)}$ = Predicted - Raw).

For the fitted quadratic response surface there will be a CC/HCTZ combination therapy at which the D_SiDBP response will reach its maximum. This CC/HCTZ is the combination with the maximum effect. Although, one can use the estimated equation (2) to mathematically compute the CC and HCTZ values corresponding to maximum response, however, we have selected to do this investigation graphically by the visual inspection. The approximate values by the visual inspection are close enough for our purposes. Also, since the visual inspection to detect the maximum (peak) from the three dimensional surface (Figure 1) is difficult we preferred to do this investigation using the profiles of the response surface for the fixed CC and Fixed HCTZ doses, as will be discussed in the following paragraphs.

Figure 2 shows the profiles of D_SiDBP response surface as function of CC doses for fixed 0, 12.5 and 25 mg HCTZ. Visual inspection shows that, for the three HCTZ curves, the maximum of D_SiDBP, approximately, occurred within the range of 26 to 28.5 mg of CC doses (also confirmed by mathematical calculation).

Figure 2: Profiles of D_SiDBP Response Surface for Given HCTZs as Functions of CC Doses

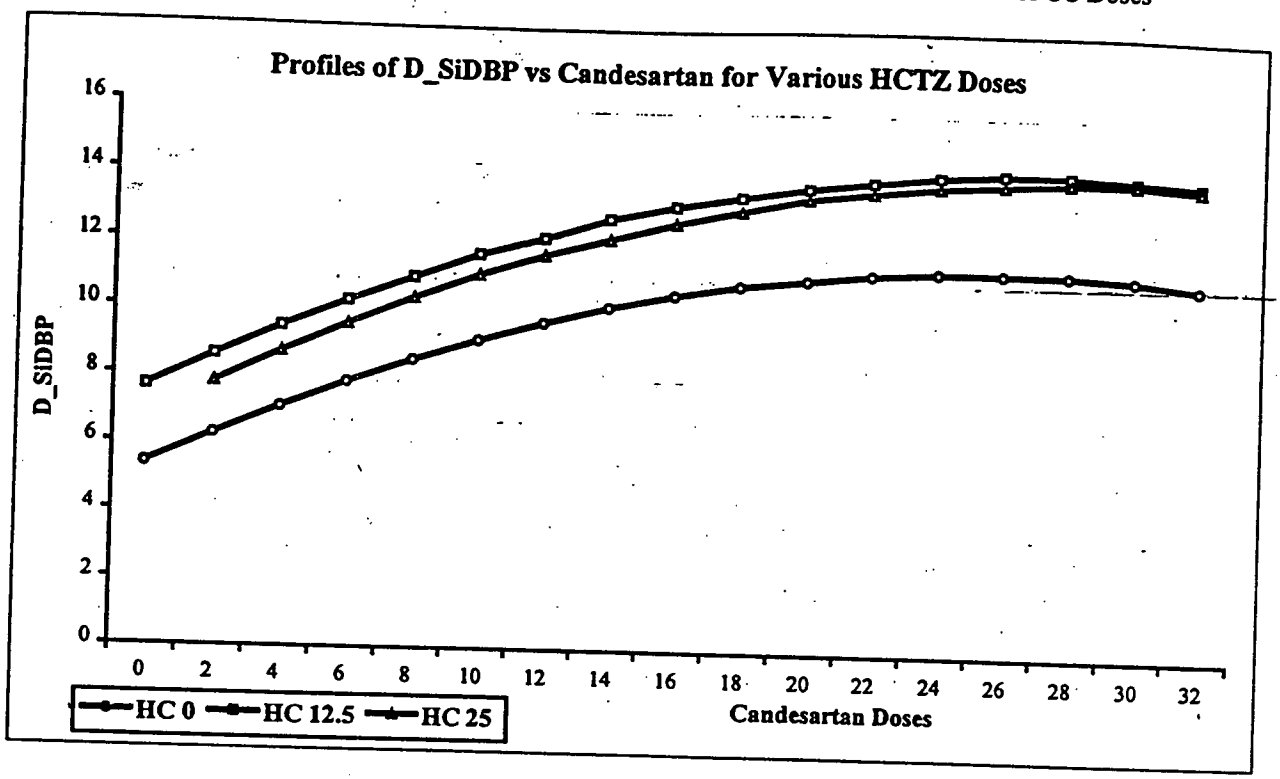
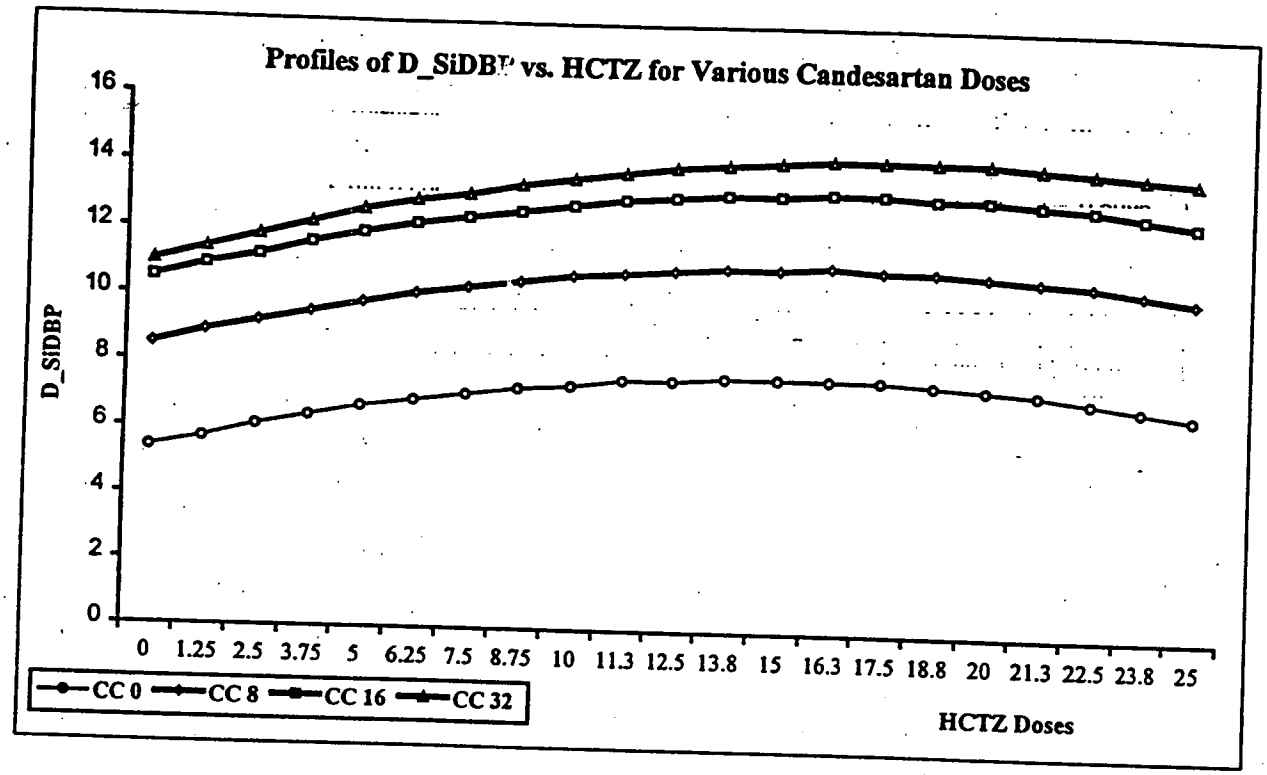


Figure 3 shows the profiles of D_SiDBP response surface as function of HCTZ doses for fixed 0, 8, 16, 32 mg CC. Visual inspection shows that, for the three HCTZ curves, the maximum of D_SiDBP, approximately, occurred within the range of 15 to 18.5 mg of HCTZ doses (also confirmed by mathematical calculation).

Figure 3: Profiles of D_SiDBP Response Surface for Given CCs as Functions of HCTZ Doses



In conclusion, the maximum of D_SiDBP occurred within the range of 26 to 28.5 for CC and within 15 to 18.5 mg for HCTZ on the surface.

Results on D_SiSBP:
The following table gives the analysis results with respect to parameter estimates:

Table 13: Summary of Quadratic Response Surface Analysis on D_SiSBP

Variable	Parameter (Coefficient)	Parameter Estimate	Standard Error	P-Value for Testing Ho: Para. = 0 vs. Ha: Para. ≠ 0
Intercept	α	5.3730	0.6096	< 0.0001
Candesartan	β	0.8846	0.1042	< 0.0001
HCTZ	δ	0.6103	0.1123	< 0.0001
Candesartan*Candesartan	θ	-0.0218	0.0034	< 0.0001
HCTZ*HCTZ	λ	-0.0170	0.0043	0.0001
Candesartan*HCTZ	ρ	0.0056	0.0050	0.2644
Lack of Fit P-Value = 0.0718 The null hypothesis of quadratic fit (Test a) is rejected, at $\alpha = 0.05$ but cannot be rejected at $\alpha = 0.10$. In this case the Lack of Fit is marginally significant				

Table 13 shows that:

- The statistical test for testing "Lack of Fit" (Test a) produced a P-Value = 0.0718, indicating that the null hypothesis of quadratic fit (Test a) is rejected, at $\alpha = 0.10$ but cannot be rejected at $\alpha = 0.05$. For this case there is goodness of the quadratic fit is not as strongly supported as the case of DS-DBP.

- Except for the coefficient of the interaction term (ρ), the P-values of the statistical tests (Test b) on the other parameters (α, β, δ, θ, and λ) indicate that the parameter estimates are statistically significantly different from zero (P-Values ≤ 0.0001, for all parameters). With respect to the interaction, the P-Value = 0.2644 is indicating that the interaction is not statistically significant and hence the effect of Candesartan and HCTZ are, quadratically, additive.

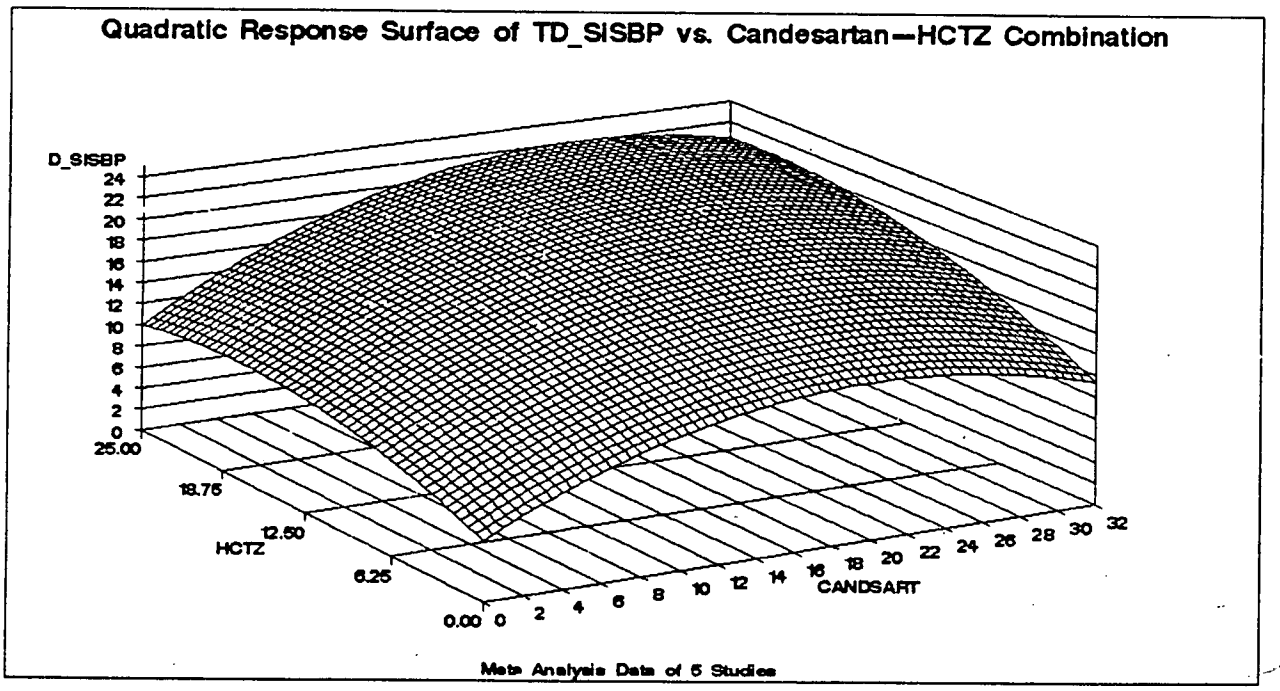
Therefore, the fitted model will be:

(3) $D\_SiDBP_i = 5.3730 + 0.8846CC + 0.6103HCTZ - 0.0218CC^2 - 0.0170HCTZ^2 + 0.0056CC*HCTZ.$

Note: We left the interaction term in the estimated model, although its effect is statistically non-significant.

The graph of the response surface is presented in Figure 4.

Figure 4: Quadratic Response Surface for Reduction from Baseline in SiSBP
As a Function of Candesartan/HCTZ Combination Therapy



As was discussed for the case of D_SiDBP, the response surface presents the predicted values of the mean response of D_SiDBP for the CC/HCTZ combination treatment, rather than the observed means. Here also, it is useful to assess how the predicted and the raw means for D_SiDBP are close to each other. Table 14, on the next page, presents the predicted means, raw means and the difference between the predicted and raw means ($D_{(P-R)}$ = Predicted - Raw) for the CC/HCTZ combination therapy.