The double dummy technique was used to preserve blinding.

subjects were taken from a healthy non-obese population aged over 18 years. Subjects must have a diagnosis of .mplicated, mild to moderate essential or untreated hypertension limited to WHO Stage 1 or 2 (no evidence of end organ uamage except for mild fundoscopic changes). Subjects with renovasular, cardiovascular, diabetes, CHF or collagen-vascular, renal, renovascular or cerebrovascular disease or abnormal laboratory values prior to randomization were excluded. If seated systolic blood pressure (SeSBP) was greater than 200 mmHg, the subject was excluded. Subjects must be able to wean other antihypertensives and vasoactive agents. Other concomitant therapy considered necessary for the subject's welfare was given at the discretion of the investigator. These medications were noted on the case report forms.

The primary efficacy variable in this study was to compare the reduction in sitting trough (i.e.. 24 + 3 hours after the previous day's AM dose) office seated diastolic blood pressure after 8 weeks of double-blind therapy between the two doses of candesartan and losartan. Secondary endpoints include; (1) the reduction at Week 8 in trough office seated systolic blood pressure and standing systolic and diastolic BP; (2) the proportions of subjects whose office SeDBP is normalized (decreased to<90 mmHg) and/or responds (decreased by 10 mmHg); (3) Safety and tolerability against placebo.

Sample size calculation of 70 per group was based on 88% power to detect a difference of 4.0 mmHg (p= 0.05) with a standard deviation of 7.5 mmHg. Changes in blood pressure from baseline would be compared between treatments using analysis of covariance (ANCOVA) with the baseline and center as a covariate. If some centers do not recruit enough subjects, these centers were pooled prior to unblinding of the data.

Safety assessments were done both in the single and double blinded period. Tests included were (1) ECG; (2) Laboratory tests (CBC, SMA20, urinalysis) (3) physical examination. Clinical adverse events and its relationship to the study drug were recorded.

0.2 Efficacy results

There were 455 subjects enrolled. Disposition of enrolled subjects is shown in Table 2 below.

Table 2. Subject Disposition

Subject Disposition	Number
Enrolled	455
Not Randomized	118
Randomized	337
Discontinued	36
Completed	301

Most reasons for exclusion prior to randomization was that either the DBP < 95 mmHg or SBP >200 mmHg.

Table 3 below gives the reasons for discontinuations from study medication in the double-blind period. Also noted are the number of final ABPM records available for analysis.

Table 3. Reasons for Discontinuations

	Placebo	Candesartan 8 mg	Candesartan 16 mg	Losartan 50 mg
Total Randomized	85	82	86	84
Total Discontinued	15	5	6	10
Adverse Event	3	3	3	5
BP↑ above limit	10	2	2	5
Subject Request	2	0	0	0
Protocol Violation	0	0	1	0
Subject Completed	70	77	80	74

The actual standard deviation of the primary endpoint was 8.7 mmHg which was higher than the sponsor expected.

The treatment code was broken summary tables of the number of subjects in each center receiving each treatment was produced by the Contract Research Organization. The treatments were identified as only A, B. C and D. the statistician decided which centers should be pooled for analysis by looking at the per-protocol population and pooling centers within countries. The ITT population was pooled into the same centers as the per-protocol analysis.

There were a large number of major protocol deviations. Major protocol deviations were defined as a deviation leading to a value imputed as "missing". Protocol deviations affected the per protocol analysis, but not the intent-to-treat analysis.

Demographics of the four treatment groups are shown in Table 4 below. There was no statistical relationship between the groups in terms of race, elderly or age. The majority of subjects were male, with the exception of the placebo group. The difference was statistically significant (p= 0.03).

Table 4. Demographics of the Treatment Groups

Subject		Placebo	Candesartan 8 mg	Candesartan 16 mg	Losartan 50 mg
Gender	Male N(%)	38(45)	47(57)	56(67)	47(57)
	Female N(%)	47(55)	35(43)	28(33)	36(43)
Race	White N(%)	85(100)	82(100)	84(100)	83(100)
Elderly	< 65 N(%)	58(68)	49(60)	59(70)	57(69)
	≥ 65 N(%)	27(32)	33(40)	25(30)	26(31)
Age	Mean (SD)	60(10)	60(10)	60(10)	60(10)

Mean seated and standing baseline blood pressure is given in Table 5 below.

Mean change in trough diastolic and systolic blood pressure is given in Figure 1 below. The mean change from baseline of ·gh SeDBP using an ITT population (LOCF) was not significantly different than the subjects who finished the study. rding to the sponsor, there was a statistically significant difference between Candesartan 16 mg and losartan 50 mg at κ 8. Analysis using a linear model showed no statistical significance. There were no significant statistical differences between the treatment groups in either trough seated or standing heart rate.

Table 5. Seated and Standing Baseline Blood Pressure and Heart Rate among Treatment groups.

Measurement (mmHg or BPM)	Treatment			
	Placebo	Candesartan 8 mg	Candesartan 16 mg	Losartan 50 mg
Seated				
DBP; Mean(SD)	103(5)	102(5)	103(5)	102(5)
SBP; Mean (SD)	170(14)	169(14)	168(15)	168(16)
DBP Group				
<104 mmHg; N(%)	51(60)	58(71)	53(63)	45(54)
>104 mmHg; N(%)	34(40)	24(29)	31(37)	38(45)
Standing				
DBP; Mean(SD)	107(8)	105(6)	105(8)	106(8)
SBP; Mean (SD)	168(16)	167(14)	165(17)	168(19)

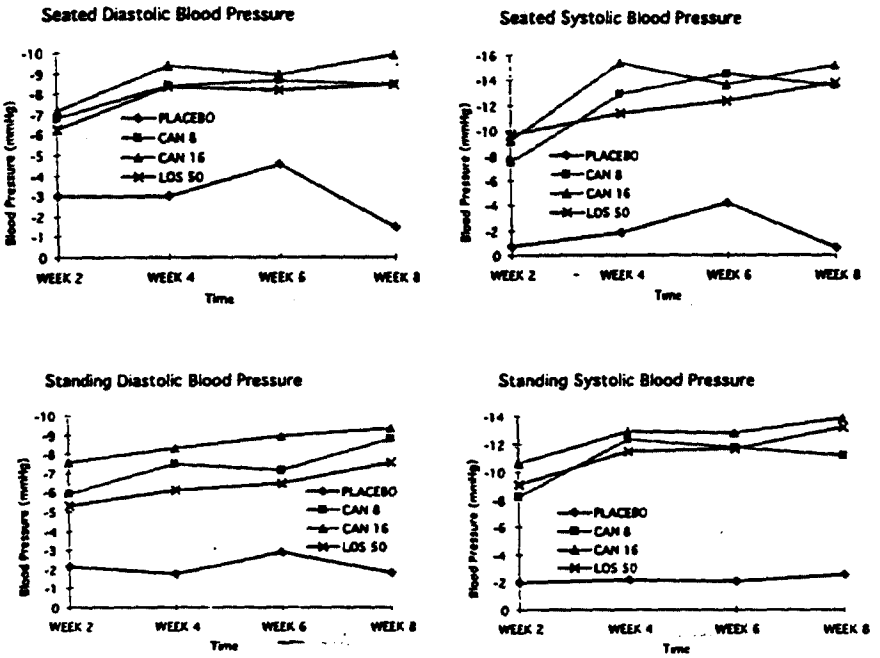


Figure 1. Trough Systolic and Diastolic Blood Pressure

Changes from baseline for peak blood pressures at Week 8 are given in

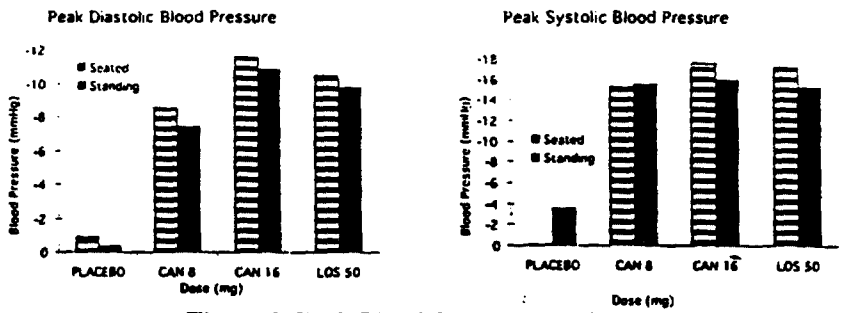


Figure 2. Peak Blood Pressure at Week 8

The summary of therapeutic response for randomized subjects who finished Week 8 is given in Table 6 below. Therapeutic response was defined as a change from baseline of -10 mmHg or SeDBP < 90 at trough. Normalized is defined as SeDBP <90 at trough.

Table 6. Therapeutic Response of Subjects at Week 8

Efficacy Variable	Placebo n=70	CAN 8 mg n=77	CAN16 mg n=79	LOS 50 mg n=74
Total Responders N(%)				
All subjects	8(11)	34(44)	43(54)	37(50)
Baseline >104 mm Hg	5(7)	13(17)	20(25)	16(21)
Normalized N(%)	2(3)	25(32)	26(33)	19(26)

Because of the statistical difference between placebo and the other drug groups in by gender, a by gender analysis was performed for the primary endpoint. There was no statistically significant difference ($p < 0.05$) as a function of gender.

There were no significant differences from baseline of SeDBP between elderly and non-elderly subjects.

The mean treatment days for all randomized subjects is between 52-55 days.

There were a total of five serious adverse events in four subjects. Of those, one subject was on candesartan 8 ma. Subject 069 ···as a 79 y.o. Caucasian male who had previous untreated primary hypertension suffered a brain stem infarction on the 39th of double-blind treatment. Seated blood pressure at the last visit (11 days prior to event) was 151/96, compared to /114 at screening. The subject was discharged 11 days after hospitalization with residual neurological findings.

There were six withdrawals on candesartan in the 8 week double-blind period. Table 7 below shows treatment duration and adverse event of the candesartan subjects..

The most common treatment emergent adverse events (>3% on 8 mg candesartan) were headache, respiratory infection, dizziness/vertigo, abdominal pain, gastroenteritis, myalgias and vasospasm. The most common treatment emergent adverse events (>3% on 16 mg candesartan) were headache, respiratory infection, dizziness/vertigo, diarrhea, viral infection, insomnia, coughing and myalgias.

Significant mean changes from baseline on candesartan versus placebo were observed for the following laboratories (1) hemoglobin; (2) Erythrocytes; (3) Creatinine; (4) uric

Table 7. Discontinuations due to Adverse Events during Double-Blind Period on Irbesartan

Subject	Duration	Dose (mg)	Adverse Event
069	39	8	Stroke
105	36	8	Muscle Aches,fever; Reduced BP; 171/93 Week 4 to 98/50 Week 6. Resolved 8 days after stopping study drug.
277	10	8	Vertigo/visual disturbance; HTN; therapy failure
164	29	16	Nausea; stomach pain Symptoms recurred on rechallenge
182	15	16	Creatinine > upper limit
211*	0	16	
* Subject randomized but did not take double-blind medication.			

acid; (4) urea. Hemoglobin and erythrocyte number increased in the placebo group but decreased in the losartan and candesartan groups to the same degree. A similar situation occurred with urea and creatinine, where urea and creatinine of the placebo group decreased and increased in all active treatment groups. None of the candesartan subjects except one(see above) had an abnormal creatinine lab value. In both cases, candesartan was not statistically different from losartan. Uric acid levels fell significantly in the losartan group compared to placebo. Uric acid reductions in the candesartan groups were numerically greater than placebo, but not statistically different.

There was one subject with significant elevations of LFTs that were observed at the last double-blind visit. Subject 378 is a 42 yo male with HTN and anxiety disorder. ALT at screening, randomization, study end and follow-up was 46, 62, 192 and 144 respectively. The subject did not complain of symptoms.

There was one case of orthostatic byotension on candesartan (Subject 237). The subject was orthostatic on the basis of heart rate for the 4th and 6th week.

No significant changes in physical exam were noted.

There were no ECG intervals(e.g. PR, QT) reported for this trial. Other descriptive abnormalities will be addressed in the Integrated Summary of Safety.

This is a randomized placebo controlled trial of 8 mg and 16 mg candesartan, 50 mg losartan versus placebo. All active treatments were statistically significant against placebo. The sponsor states that 16 mg candesartan is better than 50 mg of losartan. Based on my analysis there is no difference between 50 mg losartan and 16 mg candesartan. Whether 16 mg candesartan is statistically significant versus 50 mg losartan is currently being reviewed by our statistical division.

The issue is minimized since proposed label does not make a superiority claim with losartan. Anyway, superiority of one drug over another is based on comparing dose response relationships of active treatments. The sponsor chose not to study the 100 mg dose of losartan for the reason below.

e usually recommended dose of losartan is 50 mg once daily. In the case of ufficient blood pressure reduction with this dose, addition of hydrochlorothiazide is proposed rather than an increase is proposed rather than an increase in the dose

of losartan. Therefore, in this study, losartan 50 mg once daily was chosen for comparison with the two doses of Candesartan cilexetil."

The U.S. losartan label states that it can be given up to 100 mg total daily dose (either 100 qd or 50 BID). If blood pressure is not adequately controlled, then combination therapy of 50 losartan with HCTZ can be started. There is nothing in the instructions to physicians in either the losartan or the combination label about switching to combination therapy at 50 mg total losartan dose.

There were no deaths or serious adverse events to comment upon.

Subject 378 had significant elevations of LFTs on drug therapy. It is unclear whether the elevation is due to the study drug. The subject's LFTs were mildly elevated at randomization and increased on candesartan. No further documentation of the subject's workup (if done) is provided.

Increases in the mean changes from baseline of urea and creatinine were observed with losartan and candesartan, Interestingly, there is no change from baseline observed in any of the primary controlled studies with candesartan.

Decreases in the mean changes from baseline of hemoglobin and erythrocyte number were observed with losartan and candesartan compared to placebo. Interestingly, there is no change from baseline observed in any of the primary controlled studies with candesartan.

Decreases in uric acid were observed with losartan and to a lesser degree candesartan. The reason for this is unclear. Decreases in uric acid generally carry no clinical significance in patients. Interestingly, there is no change from baseline observed in any of the primary controlled studies with candesartan.

A full safety review will be contained in the integrated summary of safety.

Respectfully submitted,:

Steven D. Caras MD, Ph.D.

Comments

There are some differences in the results Dr. Caras presents and the sponsor's report. Additional analyses by Dr. Mahjoob are provided after the following clarifications.

The primary comparison was of Candesartan 4 and 8 mg with Losartan 50 mg Q.D. and placebo. The primary endpoint was change in sitting DBP from baseline to 8 weeks of treatment.

Table 4 re demographics in Dr. Caras' review is consistent with the sponsor's ITT population.

Subject		Placebo	Candesartan 8 mg	Candesartan 16 mg	Losartan 50 mg
Gender	Male N(%)	38(45)	47(57)	56(67)	47(57)
	Female N(%)	47(55)	35(43)	28(33)	36(43)
Race	White N(%)	85(100)	82(100)	84(100)	83(100)
Elderly	< 65 N(%)	58(68)	49(60)	59(70)	57(69)
	≥ 65 N(%)	27(32)	33(40)	25(30)	26(31)
Age	Mean (SD)	60(10)	60(10)	60(10)	60(10)

This ITT n=334, whereas 337 were randomized.

The difference in the patient numbers from the randomized group is due to three patients (2 randomized to Candesartan mg, 1 to Losartan) who had no efficacy data collected or withdrew prior to taking any drug.

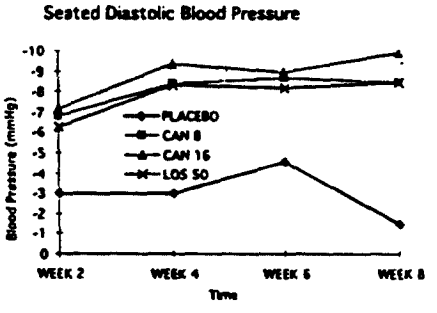
Baseline sitting DBP for Losartan differ in Dr. Caras' and the sponsor's reports.
Dr. Caras:

Measurement (mmHg or BPM)	Treatment			
	Placebo	Candesartan 8 mg	Candesartan 16 mg	Losartan 50 mg
Seated				
DBP; Mean(SD)	103(5)	102(5)	103(5)	102(5)
SBP; Mean (SD)	170(14)	169(14)	168(15)	168(16)
DBP Group				
<104 mmHg; N(%)	51(60)	58(71)	53(63)	45(54)
>104 mmHg; N(%)	34(40)	24(29)	31(37)	38(45)
Standing				
DBP; Mean(SD)	107(8)	105(6)	105(8)	106(8)
SBP; Mean (SD)	168(16)	167(14)	165(17)	168(19)

Treatment		Baseline	Week 2	Week 4	Week 6	Week 8	Week 8 (LVCF)
placebo	N	85	85	81	73	70	85
	Missing	0	0	4	12	15	0
	Mean	102.8	101.0	100.8	98.3	101.2	102.7
	SD	5.0	8.4	8.4	8.0	7.2	8.2
	Min						
	Max						
cand.cil. 8 mg	N	82	81	80	78	77	82
	Missing	0	1	2	4	5	0
	Mean	101.7	95.0	93.5	92.3	93.0	93.3
	SD	5.3	8.3	8.2	8.9	8.6	9.6
	Min						
	Max						
cand.cil. 16 mg	N	84	84	82	80	80	84
	Missing	0	0	2	4	4	0
	Mean	102.5	95.2	93.3	93.6	92.5	93.1
	SD	5.2	9.0	8.3	9.2	9.4	10.1
	Min						
	Max						
losartan	N	83	83	79	75	74	83
	Missing	0	0	4	8	9	0
	Mean	103.5	97.2	95.3	95.0	94.6	96.5
	SD	5.0	7.7	8.6	7.6	8.3	10.2
	Min						
	Max						

The change from baseline to week 8 (LOCF) in sitting DBP was N.S. according to Dr. Caras, but significant as per the sponsor for the Losartan-Candesartan 16 mg comparison.

Dr. Caras:



onsor:

Comparison of treatments for the change from baseline to Week 8 (LVCF) in sitting DBP (mmHg). ITT population.

Treatment Comparison	Adjusted Mean	95% CI Lower	95% CI Upper	p-value
24h post dose				
cand.cil. 8 mg vs losartan	-2.3	-5.3	0.6	0.115
cand.cil. 16 mg vs losartan	-3.7	-6.7	-0.8	0.013
cand.cil. 8 mg vs placebo	-8.9	-11.8	-6.0	<0.001
cand.cil. 16 mg vs placebo	-10.3	-13.2	-7.4	<0.001
6h post dose				
cand.cil. 8 mg vs losartan	1.7	-1.3	4.7	0.265
cand.cil. 16 mg vs losartan	-1.3	-4.3	1.7	0.386
cand.cil. 8 mg vs placebo	-7.6	-10.6	-4.6	<0.001
cand.cil. 16 mg vs placebo	-10.6	-13.7	-7.6	<0.001

Dr. Caras' estimate for Candesartan cilexetil 16 mg and Losartan suggests a difference, but he states it was not significant.

Kooros Mahjoob found that the baseline sitting DBP as reported by the sponsor was correct when one used week as a second qualifying visit for entrance to the study. Utilizing that database, Dr. Mahjoob analyzed change from baseline to endpoint (LOCF) for the ITT population with only dose and baseline in the anova model.

Results were:	Si DBP Mean Square Difference	P
Losartan 50mg versus placebo	-6.5457	0.0001
Losartan 50mg versus 8mg CC	+2.0661	0.14
Losartan 50mg versus 16mg CC	+2.8389	0.04

(-) indicates a greater reduction Losartan versus comparator.

The sponsors analysis, although designated "post-hoc," claimed a p value of 0.02. After inquiry it became clear that the sponsor had put center, and dose by center interaction (neither of which were statistically significant) into the model. We believe, therefore, that, for whatever hypothesis generating purpose, the result is of marginal significance. Additionally this finding compares doses which may be moderate for Losartan and high for Candesartan. No claim can be based on these data.

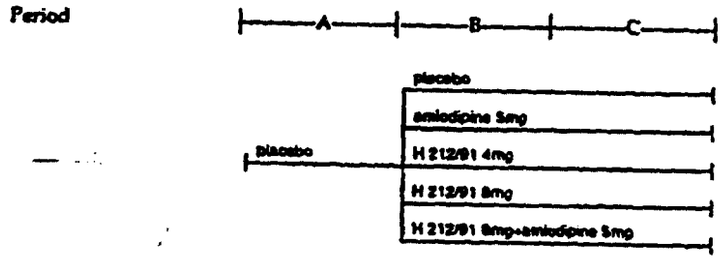
While there are numerical differences in the analyses of responders and normalization between Dr. Caras' and the sponsor's reports, there are no statistical differences to clarify.

6.5 Study AHM-0006 - Comparative double-blind, randomized, multicenter placebo controlled study of Candesartan cilexetil (H212/91) 8 or 16 mg once daily or/and amlodipine 5 mg daily in patients with mild to moderate hypertension (dbp 95-114 mm Hg).

Coordinating Investigators: Dr. Farsang (Hungary), Dr. Zannad (France), Dr. Kawecka-Jaszcz (Poland), Dr. Lanagan (UK), Dr. Burgess (South Africa).

Drugs manufactured by: Candesartan cilexetil and matching placebo, Takeda, Japan. Amlodipine, Pfizer, commercially available. Matching amlodipine placebo, FMC Corporation. Double-dummy blister strips packed by Euro-Bio Pharm.

The protocol provides a flow chart outlining the design features of the study.



Time (weeks)	-4	-2	0	2	4	6	8
Visit	1	2	3	4	5	6	7
Medical history	x						
Physical examination	(x)		x				x
Ankle circumference			x				x
BP and HR (24h post dose)	x	x	x	x	x	x	x
Body weight			x				x
Adverse events		x	x	x	x	x	x
ECG			x				x
Lab screen	(x)		x				x

(x) to check for inclusion/exclusion criteria

The study was started on July 18, 1995. On August 11, 1995 a protocol amendment changed the doses of Candesartan cilexetil alone to 8 or 16 mg. The study ended on April 29, 1996.

Randomization of eligible patients at the end of the run-in period was by a computer generated list in block size of 5.

Male or female patients, 20-80 years of age could be randomized if the diastolic pressure was between 95 and 114 mm Hg at two measurements (weeks -2 and 0) during run-in. Some exclusion criteria were:

1. secondary hypertension
2. systolic blood pressure ≥ 200 mm Hg.
3. MI, stroke, CABG or TIA within 3 months of the study.
4. cardiac failure
5. severely impaired liver function. Constant ASAT or ALAT above 2x ULN.
6. impaired renal function (5-creatinine ≥ 133 µmol/l for men; ≥106 µmol/l for women.

7. Concomitant treatment with other investigational drugs.

The primary objective of the study was to compare the antihypertensive effect and tolerability of Candesartan with amlodipine and placebo. Secondarily the pharmacodynamic interaction of the combination arm versus individual components was to be evaluated. The primary effect variable was dbp at trough (24 hours post dose).

Postulating a true mean treatment difference of 3.6 mm Hg, a sample size of 70 patients per treatment arm was calculated. It is unclear whether this true mean difference was for Candesartan-placebo or Candesartan-amlodipine. The protocol suggests the latter.

Statistical analysis for efficacy were performed for the ITT population (all randomized but for those not treated with any dose of double-blind medication or no efficacy data available) and the BP population (the ITT population minus protocol violators). Safety was evaluated for the ITT population. The protocol stated that:

> "The primary objective of the study is to estimate the true mean difference between amlodipine and each of the two doses of H 212/91, respectively. To estimate the difference, the least-squares estimate of the treatment difference will be calculated. This estimate together with its standard error and the upper 2.5% quantile of Student's t-distribution makes it possible to give a two-sided 95% confidence interval for the true mean treatment difference.
>
> The degrees of freedom in Student's t-distribution will correspond to those obtained for the mean square error in the ANOVA.
>
> Additionally, each of the H 212/91 doses will be compared to placebo. The statistical model will be the same as above and interval estimates of the mean treatment difference effects will be given as 95% confidence intervals.
>
> The results for the secondary objective, the comparisons of the H 212/91-amlodipine combination with each of the individual components, will be presented in the same way.
>
> The proportion of responders (sitting DBP ≤ 90 mmHg and/or a reduction of sitting DBP from baseline with 10 mmHg or more) and the proportion of patients with controlled DBP (sitting DBP ≤ 90 mmHg after 8 weeks will be analyzed by using the Mantel-Haenszel statistic stratified for centre."

Exclusions from the per protocol population were for the following reasons:

	placebo	cand.cil. 8 mg	cand.cil. 16 mg	amlo.	cand.cil. + amlo.	Total
Number of randomised patients	83	85	86	84	89	427
Number of patients in the ITT population	83	85	86	84	89	427
Reasons for exclusion from the PP population[1]:						
Male or Female not 20-80 (70 if Hungarian) years of age.	0	0	1	0	1	2
Sitting DBP not 95-114 mmHg inclusive at Week -2 and Week 0.	1	4	4	2	3	14
Child bearing potential.	0	0	0	1	0	1
Sitting SBP ≥ 200 mmHg at Week 0.	1	0	0	0	0	1
Severely impaired liver function (ASAT or ALAT above twice the normal range).	0	0	0	1	1	2
Impaired renal function (creatinine ≥ 133 µmol/L for men, ≥ 106 µmol/L for women).	1	0	1	1	0	3
Sodium or potassium outside the normal range.	1	0	3	3	4	11
Number of days of run-in outwith 25-35 days.	1	1	1	2	5	10
Number of days of double-blind outwith 53-63 days.	15	4	4	7	6	36
Compliance during either period of double-blind outwith 75-110%.	3	6	3	4	5	21
Concomitant anti-hypertensive on more than 4 days during run-in or any anti-hypertensive medication during double blind.	5	1	3	2	3	14
Number of patients in the PP population	62	71	69	65	67	334

[1] One patient can have more than one reason for exclusion.

Baseline demographics for the ITT population were:

Variable		placebo n=83 N(%)	cand.cil. 8 mg n=85 N(%)	cand.cil. 16 mg n=86 N(%)	amlo. n=84 N(%)	cand.cil. + amlo. n=89 N(%)	Total n=427 N (%)
Sex	Male	54 (65.1)	63 (74.1)	59 (68.6)	55 (65.5)	59 (66.3)	290 (67.9)
	Female	29 (34.9)	22 (25.9)	27 (31.4)	29 (34.5)	30 (33.7)	137 (32.1)
Race	Caucasian	79 (95.2)	81 (95.3)	79 (91.9)	80 (95.2)	83 (93.3)	402 (94.1)
	African. Negroid	3 (3.6)	1 (1.2)	3 (3.5)	1 (1.2)	1 (1.1)	9 (2.1)
	Oriental, Asian	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)	3 (3.4)	4 (0.9)
	Other	1 (1.2)	2 (2.4)	4 (4.7)	3 (3.6)	2 (2.2)	12 (2.8)
Age (years)	0 - 49	31 (37.3)	40 (47.1)	29 (33.7)	27 (32.1)	40 (44.9)	167 (39.1)
	50 - 64	44 (53.0)	37 (43.5)	44 (51.2)	42 (50.0)	38 (42.7)	205 (48.0)
	65 - 74	8 (9.6)	6 (7.1)	11 (12.8)	13 (15.5)	9 (10.1)	47 (11.0)
	≥75	0 (0.0)	2 (2.4)	2 (2.3)	2 (2.4)	2 (2.2)	8 (1.9)

Numbers and types of previous antihypertensive therapy taken before entry were provided:

Number of antihypertensive drugs	placebo n=83	cand.cil. 8 mg n=85	cand.cil. 16 mg n=86	amlo. n=84	cand.cil. + amlo. n=89	Total n=427
None	22	25	22	24	28	121
1	37	35	41	34	32	179
2	18	22	18	22	20	100
>2	6	3	5	4	9	27

	placebo n=83	cand.cil. 8 mg n=85	cand.cil. 16 mg n=86	amlo. n=84	cand.cil. + amlo. n=89	Total n=427
α-blockers	2	1	3	1	2	9
β-blockers	20	22	15	11	21	89
Diuretics	14	13	13	16	17	73
Ca-antagonists	22	16	23	24	18	103
ACE-inhibitors	24	29	25	31	27	136
AII-antagonists	0	0	0	0	1	1
Other/fixed combinations	8	7	11	5	12	43

During the double-blind period the following types of concomitant medications were taken:

	placebo n=83	cand.cil. 8 mg n=85	cand.cil. 16 mg n=86	amlo. n=84	cand.cil. + amlo. n=89	Total n=427
Diabetes medications	4	3	5	3	3	18
Lipid lowering agents	3	4	8	3	6	24
Anti-hypertensive medications	3	0	2	1	1	7
Long-acting nitrates	0	0	0	0	0	0

In randomizing double-blind medication assignments for the treatment period, some assignments were made incorrectly. There were approximately 20 such errors (out of 427) at various centers, randomly.

Compliance with the regimens (tablets and capsules) were provided:

Compliance with tablets. ITT population.

	Frequency	placebo n=83	cand.cil. 8 mg n=85	cand.cil. 16 mg n=86	amlo. n=84	cand.cil. + amlo. n=89	Total n=427
Period A	N	81	83	86	84	89	423
run-in	Missing	2	2	0	0	0	4
	<75%	0	0	1	0	0	1
	75%-90%	1	1	4	0	2	8
	90%-110%	78	80	81	82	86	407
	≥110%	2	2	0	2	1	7
Period B	N	82	84	85	82	88	421
double-blind	Missing	1	1	1	2	1	6
(Weeks 0-4)	75%-90%	2	2	1	2	1	8
	90%-110%	79	80	84	79	85	407
	≥110%	1	2	0	1	2	6
Period C	N	75	83	82	81	86	407
double-blind	Missing	8	2	4	3	3	20
(Weeks 4-8)	<75%	0	1	0	0	0	1
	75%-90%	1	4	3	4	1	13
	90%-110%	74	77	77	77	82	387
	≥110%	0	1	2	0	3	6

Note: ranges are from the first number up to but not including the second number

Compliance with capsules. ITT population.

	Frequency	placebo n=83	cand.cil. 8 mg n=85	cand.cil. 16 mg n=86	amlo. n=84	cand.cil. + amlo. n=89	Total n=427
Period A	N	81	83	86	84	89	423
run-in	Missing	2	2	0	0	0	4
	<75%	0	0	1	1	0	2
	75%-90%	1	1	4	0	2	8
	90%-110%	78	80	81	82	86	407
	≥110%	2	2	0	1	1	6
Period B	N	82	84	85	82	88	421
double-blind	Missing	1	1	1	2	1	6
(Weeks 0-4)	75%-90%	2	2	1	2	1	8
	90%-110%	79	80	84	79	85	407
	≥110%	1	2	0	1	2	6
Period C	N	75	83	82	81	86	407
double-blind	Missing	8	2	4	3	3	20
(Weeks 4-8)	<75%	0	2	0	0	0	2
	75%-90%	1	4	3	4	1	13
	90%-110%	74	76	77	77	82	386
	≥110%	0	1	2	0	3	6

Efficacy results were:

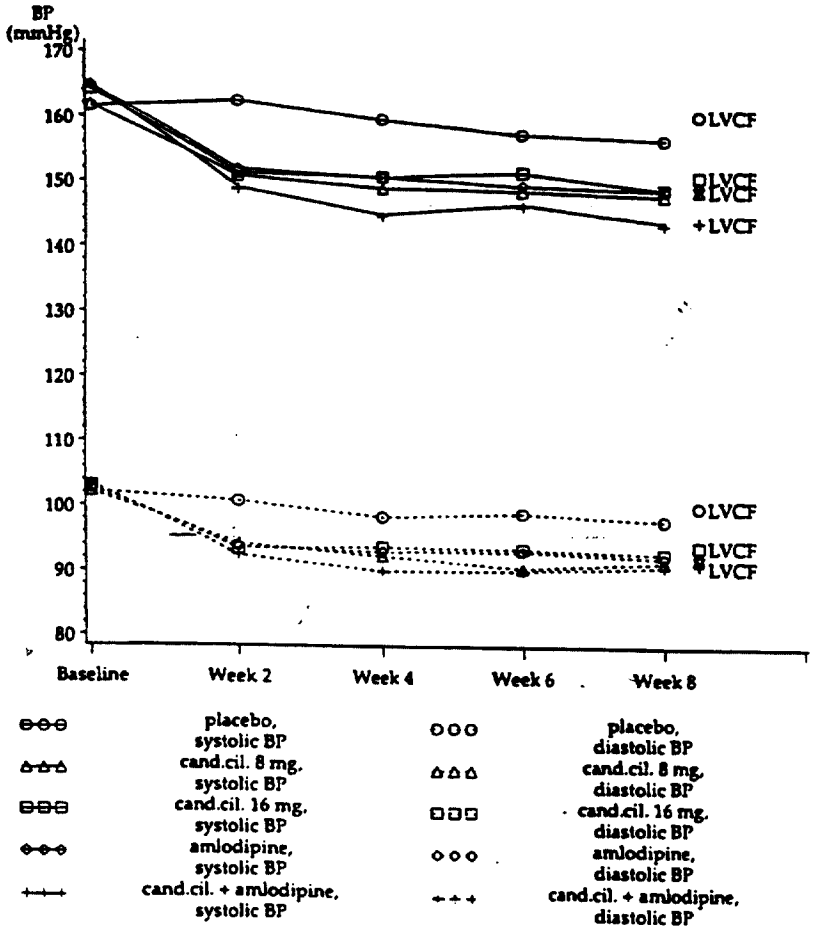
Sitting diastolic blood pressure (mmHg) summarised by visit. ITT population.

Treatment		Baseline	Week 2	Week 4	Week 6	Week 8	Week 8 (LVCF)
placebo	N	83	83	77	75	71	83
	Missing	0	0	6	8	12	0
	Mean	102.1	100.6	98.3	98.9	97.8	100.0
	SD	5.2	9.0	8.4	9.8	8.0	11.4
	Min						
	Max						
cand.cil. 8 mg	N	85	85	84	83	81	85
	Missing	0	0	1	2	4	0
	Mean	102.1	94.1	92.3	90.4	91.4	92.1
	SD	4.6	9.1	9.8	9.6	9.3	9.7
	Min						
	Max						
cand.cil. 16 mg	N	86	85	82	82	81	86
	Missing	0	1	4	4	5	0
	Mean	103.0	93.4	93.7	93.4	92.7	93.9
	SD	5.6	9.2	9.6	9.2	9.5	10.5
	Min						
	Max						
amlo.	N	84	84	82	82	81	84
	Missing	0	0	2	2	3	0
	Mean	102.5	93.6	92.9	93.0	92.1	92.4
	SD	5.1	8.6	8.5	8.3	8.2	8.5
	Min						
	Max						
cand.cil. + amlo.	N	89	89	89	86	86	89
	Missing	0	0	0	3	3	0
	Mean	103.4	92.3	90.0	90.0	90.7	91.1
	SD	5.6	7.8	9.0	10.2	8.3	9.1
	Min						
	Max						

Comparison of treatments for the change from baseline to Week 8 (LVCF) in sitting diastolic blood pressure (mmHg). ITT population.

Treatment Comparison	Adjusted Mean	95% CI Lower	95% CI Upper	p-value
cand.cil. 8 mg vs amlo.	-1.2	-4.4	1.9	0.436
cand.cil. 16 mg vs amlo.	0.9	-2.3	4.0	0.593
cand.cil. 8 mg vs placebo	-9.2	-12.3	-6.1	<0.001
cand.cil. 16 mg vs placebo	-7.1	-10.2	-4.0	<0.001
cand.cil. 8 mg vs cand.cil. + amlo.	0.8	-2.3	3.8	0.609
amlo. vs cand.cil. + amlo.	2.0	-1.0	5.1	0.194

Many graphical displays of data were provided. One such for systolic and diastolic change over the treatment period was:



Responder (diastolic pressure ≤ 90 mm Hg or 10 mm Hg reduction at week 8) results were:

Comparison of treatments for the proportion of responders from baseline to Week 8 (LVCF). Results of the Mantel-Haenszel test (adjusted for centres) as well as results of Fisher's exact test (not adjusted for centres) are presented. ITT population.

	Results of the Mantel-Haenszel test (adjusted for centres)				Results of Fisher's exact test (not adjusted for centres)			
		95% CI				95% CI		
Comparison	Estimated odds ratio	lower	upper	p-value	Estimated difference	lower	upper	p-value
cand.cil. 8 mg vs amlo.	0.732	0.410	1.306	0.291	-0.078	-0.226	0.070	0.349
cand.cil. 16 mg vs amlo.	0.740	0.412	1.329	0.313	-0.073	-0.220	0.074	0.353
cand.cil. 8 mg vs placebo	3.433	1.844	6.391	<0.001	0.300	0.159	0.441	<0.001
cand.cil. 16 mg vs placebo	3.376	1.802	6.323	<0.001	0.305	0.165	0.446	<0.001
cand.cil. 8 mg vs cand.cil. + amlo.	0.629	0.345	1.147	0.130	-0.121	-0.265	0.023	0.120
amlo. vs cand.cil. + amlo.	0.829	0.448	1.534	0.549	-0.043	-0.185	0.099	0.632

The active drugs gave 55.3% to 67.4% response rates compared to 25.3% for placebo. Controlled (diastolic pressure ≤ 90 mm Hg at the end of 8 weeks of treatment) results were:

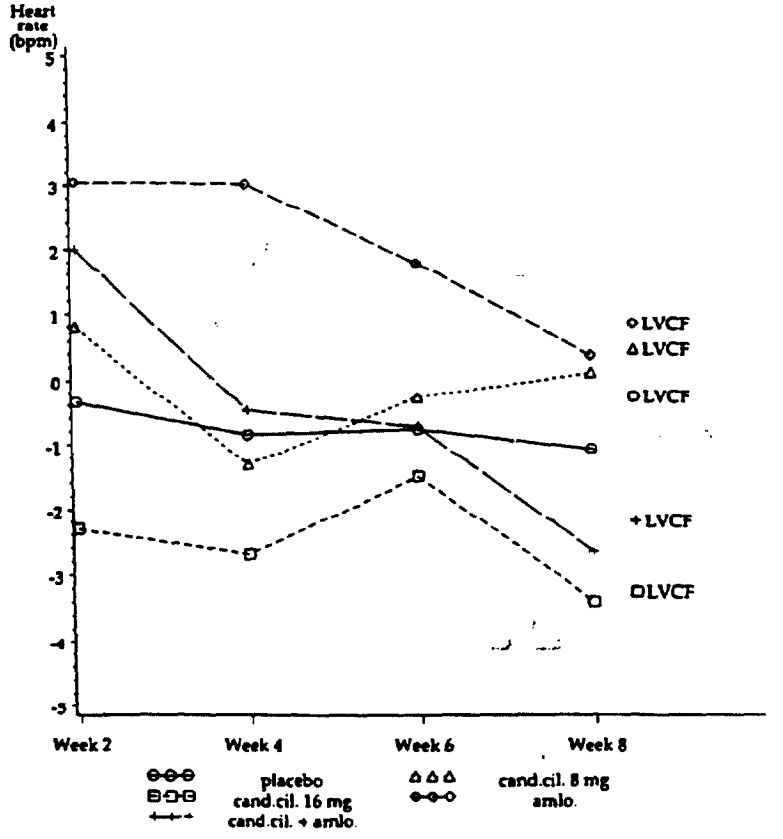
Table 5.2.2.9.2. Comparison of treatments for the proportion of controlled patient at Week 8 (LVCF). Results of the Mantel-Haenszel test (adjusted for centres) as well as results of Fisher's exact test (not adjusted for centres) are presented. ITT Population.

	Results of the Mantel-Haenszel test (adjusted for centres)				Results of Fisher's exact test (not adjusted for centres)			
		95% CI				95% CI		
Comparison	Estimated odds ratio	lower	upper	p-value	Estimated difference	lower	upper	p-value
cand.cil. 8 mg vs amlo.	0.968	0.516	1.813	0.918	-0.005	-0.155	0.144	1.000
cand.cil. 16 mg vs amlo.	1.003	0.559	1.798	0.992	0.001	-0.148	0.151	1.000
cand.cil. 8 mg vs placebo	4.033	2.011	8.091	<0.001	0.279	0.147	0.410	<0.001
cand.cil. 16 mg vs placebo	3.638	1.875	7.057	<0.001	0.285	0.154	0.416	<0.001
cand.cil. 8 mg vs cand.cil. + amlo.	0.785	0.432	1.428	0.428	-0.070	-0.218	0.078	0.366
amlo. vs cand.cil. + amlo.	0.787	0.436	1.419	0.426	-0.065	-0.214	0.083	0.447

The active drugs controlled between 43.5 and 50.6% of patients compared to 15.7% for placebo.

Sitting heart rate changed slightly, within and between groups but did not increase as blood pressure fell.

Graph of mean change from baseline for sitting heart rate (bpm) by treatment. ITT population. Not adjusted for centres.



Orthostatic change in systolic and diastolic pressure was greatest for the combination drug arm:

Adjusted mean and 95% confidence interval for each treatment for the change from baseline to Week 8 (LVCF) in standing diastolic BP (mmHg). ITT population.

			95% CI	
Treatment	N	Adjusted Mean	Lower	Upper
placebo	82	0.3	-2.1	2.8
cand.cil. 8 mg	85	-7.1	-9.5	-4.7
cand.cil. 16 mg	86	-6.9	-9.4	-4.5
amlo.	84	-7.6	-10.0	-5.1
cand.cil. + amlo.	89	-11.0	-13.3	-8.7

Comparison of treatments for the change from baseline to Week 8 (LVCF) in standing diastolic BP (mmHg). ITT population.

		95% CI		
Treatment Comparison	Adjusted Mean	Lower	Upper	p-value
cand.cil. 8 mg vs amlo.	0.5	-2.9	3.9	0.777
cand.cil. 16 mg vs amlo.	0.6	-2.8	4.1	0.723
cand.cil. 8 mg vs placebo	-7.4	-10.8	-4.0	<0.001
cand.cil. 16 mg vs placebo	-7.3	-10.7	-3.8	<0.001
cand.cil. 8 mg vs cand.cil. + amlo.	3.9	0.5	7.3	0.023
amlo. vs cand.cil. + amlo.	3.4	0.0	6.8	0.048

Adjusted mean and 95% confidence interval for each treatment for the change from baseline to Week 8 (LVCF) in standing systolic BP (mmHg). ITT population.

			95% CI	
Treatment	N	Adjusted Mean	Lower	Upper
placebo	82	-0.1	-4.1	4.0
cand.cil. 8 mg	85	-11.7	-15.7	-7.7
cand.cil. 16 mg	86	-10.0	-13.9	-6.0
amlo.	84	-11.8	-15.8	-7.8
cand.cil. + amlo.	89	-18.6	-22.4	-14.7

Comparison of treatments for the change from baseline to Week 8 (LVCF) in standing systolic BP (mmHg). ITT population.

		95% CI		
Treatment Comparison	Adjusted Mean	Lower	Upper	p-value
cand.cil. 8 mg vs amlo.	0.1	-5.6	5.8	0.975
cand.cil. 16 mg vs amlo.	1.9	-3.8	7.5	0.519
cand.cil. 8 mg vs placebo	-11.7	-17.3	-6.0	<0.001
cand.cil. 16 mg vs placebo	-9.9	-15.6	-4.2	<0.001
cand.cil. 8 mg vs cand.cil. + amlo.	6.8	1.3	12.4	0.016
amlo. vs cand.cil. + amlo.	6.7	1.2	12.3	0.018

Safety

No deaths were reported. A summary of adverse events for the safety (ITT) population was provided:

Summary of patients with adverse events, number (%) of patients. Double-blind treatment period. Safety population.

Type of event	placebo n=83	cand.cil. 8 mg n=85	cand.cil. 16 mg n=86	amlo. n=84	cand.cil. + amlo. n=89	Total n=427
Any AE	32 (38.6%)	36 (42.4%)	25 (29.1%)	30 (35.7%)	31 (34.8%)	154 (36.1%)
New onset AE	27 (32.5%)	35 (41.2%)	21 (24.4%)	25 (29.8%)	26 (29.2%)	134 (31.4%)
Serious AE	1 (1.2%)	0	1 (1.2%)	1 (1.2%)	0	3 (0.7%)
Drug stopped due to AE	1 (1.2%)	0	2 (2.3%)	1 (1.2%)	1 (1.1%)	5 (1.2%)
Severe AE	4 (4.8%)	3 (3.5%)	3 (3.5%)	4 (4.8%)	3 (3.4%)	17 (4.0%)
Attributable AE	11 (13.3%)	24 (28.2%)	10 (11.6%)	13 (15.5%)	15 (16.9%)	73 (17.1%)

Note: Attributable AEs are those for which there was a physician's causality rating of possible or probable relationship to study treatment.

The serious events in the double-blind report were:

Patient No.	Sex	Age (yrs)	Treatment	Serious Adverse Event	Exposure before onset (days)	Outcome
351	M	61	placebo	Asthma aggravated	38	AE still present
436	M	68	cand.cil. 16 mg	Duodenal ulcer haemorrhagic	20	AE no longer present
342	M	32	amlo.	Sinusitis	54	AE no longer present

Five patients discontinued treatment during the double-blind period as follows:

Patient No.	Sex	Age (yrs)	Treatment	Adverse event	Exposure before onset (days)	Outcome
318	F	61	placebo	Stomatitis	0"	AE no longer present
				Taste alteration	22	AE still present
				Herpes simplex labial	27	AE no longer present
436	M	68	cand.cil. 16 mg	Duodenal ulcer haemorrhagic	20	AE no longer present
452	M	56	cand.cil. 16 mg	Rigors (chills)	48	AE no longer present
471	F	58	cand.cil. + amlo.	Ankle oedema	2	AE no longer present
				Flushing, face	19	AE no longer present
310	M	46	amlo.	Chest pain	1	AE no longer present
				Flushing, face	1	AE no longer present

" AE started on the last day of the run-in and continued into the double-blind period

The most commonly reported adverse events reported were:

Number (%) of patients by the most common adverse events. Double-blind treatment period. Safety population.

placebo n=83		cand.cil. 8 mg n=85		cand.cil. 16 mg n=86	
Headache	7 (8.4%)	Headache	8 (9.4%)	Headache	4 (4.7%)
Respiratory infection	3 (3.6%)	Respiratory infection	5 (5.9%)	Respiratory infection	3 (3.5%)
Abdominal pain	2 (2.4%)	Diarrhoea	3 (3.5%)	Coughing	2 (2.3%)
Bronchitis	2 (2.4%)	Dizziness/vertigo	3 (3.5%)	Rhinitis	2 (2.3%)
Coughing	2 (2.4%)	Oedema dependent/legs/peripheral	3 (3.5%)		
Diarrhoea	2 (2.4%)	Abdominal pain	2 (2.4%)		
Somnolence	2 (2.4%)	Albuminuria	2 (2.4%)		
		Feeling of warmth/flushing	2 (2.4%)		
		Hyperuricaemia	2 (2.4%)		
		Insomnia	2 (2.4%)		
		Nausea	2 (2.4%)		
		Rhinitis	2 (2.4%)		
		SGPT increased	2 (2.4%)		
		Tachycardia	2 (2.4%)		

amlo. n=84		cand.cil. + amlo. n=89	
Headache	7 (8.3%)	Headache	3 (3.4%)
Oedema dependent/legs/peripheral	4 (4.8%)	Oedema dependent/legs/peripheral	3 (3.4%)
Back pain	2 (2.4%)	Pain	3 (3.4%)
Bronchitis	2 (2.4%)	Pruritus	3 (3.4%)
Diarrhoea	2 (2.4%)	Albuminuria	2 (2.2%)
Dizziness/vertigo	2 (2.4%)	Arthralgia	2 (2.2%)
Infection viral	2 (2.4%)	Dizziness/vertigo	2 (2.2%)
Respiratory infection	2 (2.4%)	Pharyngitis	2 (2.2%)
Weight increase	2 (2.4%)	Respiratory infection	2 (2.2%)
		SGPT increased	2 (2.2%)

Laboratory abnormalities occurred sporadically in all treatment groups. None were serious. None required discontinuation of treatment. An example of these findings might be ALAT (SGPT) elevations. Elevations slightly above the ULN were found in 4 placebo

patients, 3 Candesartan cilexetil 8 mg patients, 1 Candesartan cilexetil 16 mg patient, 6 amlodipine patients, and 6 combination therapy patients. None of these cases were associated with hyperbilirubinemia or elevated alpoline phosphate.

A listing of the numbers of patients with chemistry or ECG adverse events in the double-blind period were provided. A single patient could have had more than one adverse event under the same system organ class.

Body System/Event	placebo n=83	cand.cil. 8 mg n=85	cand.cil. 16 mg n=86	amlo. n=84	cand.cil. + amlo. n=89
LIVER AND BILIARY SYSTEM DISORDERS	1(1.2%)	2(2.4%)	0	0	2(2.2%)
ALAT increased	1(1.2%)	2(2.4%)	0	0	2(2.2%)
ASAT increased	0	1(1.2%)	0	0	1(1.1%)
METABOLIC AND NUTRITIONAL DISORDERS	2(2.4%)	4(4.7%)	3(3.5%)	3(3.6%)	2(2.2%)
Blood urea increased	0	1(1.2%)	0	1(1.2%)	0
Creatinine serum increased	0	1(1.2%)	0	1(1.2%)	0
Hyperuricaemia	1(1.2%)	0	0	0	0
Hypopotassaemia	0	0	1(1.2%)	0	0
Potassium serum decreased	0	0	0	0	1(1.1%)
Potassium serum increased	1(1.2%)	0	0	1(1.2%)	0
Urates blood increased	0	2(2.4%)	0	0	0
Uric acid blood increased	0	0	1(1.2%)	0	0
Weight decrease	0	1(1.2%)	0	0	0
Weight increase	0	0	1(1.2%)	2(2.4%)	1(1.1%)
CARDIOVASCULAR DISORDERS. GENERAL	1(1.2%)	1(1.2%)	0	0	0
Hypertension	1(1.2%)	1(1.2%)	0	0	0
HEART RATE AND RHYTHM DISORDERS	1(1.2%)	5(5.9%)	1(1.2%)	2(2.4%)	0
AV block first degree	0	0	0	1(1.2%)	0
Extrasystoles	0	0	1(1.2%)	0	0
Fibrillation atrial	1(1.2%)	0	0	0	0
Left bundle branch block	1(1.2%)	0	0	0	0
PR interval prolonged	0	1(1.2%)	0	0	0
Palpitation	0	1(1.2%)	0	1(1.2%)	0
Pulse rate increased	0	1(1.2%)	0	0	0
QT prolonged	0	1(1.2%)	0	0	0
Sinus tachycardia	0	1(1.2%)	0	0	0
Ventricular conduction disturb.	0	1(1.2%)	0	0	0
Ventricular extrasystoles	0	1(1.2%)	0	0	0
RED BLOOD CELL DISORDERS	0	1(1.2%)	1(1.2%)	0	0
Haematocrit increased	0	1(1.2%)	0	0	0
Haemoglobin decreased	0	0	1(1.2%)	0	0
Hyperhaemoglobinaemia	0	1(1.2%)	0	0	0
WHITE CELL AND RES DISORDERS	2(2.4%)	1(1.2%)	0	0	1(1.1%)
Eosinophilia	1(1.2%)	0	0	0	0
Lymph nodes enlarged	0	0	0	0	1(1.1%)
WBC decreased	1(1.2%)	0	0	0	0
WBC diff count changed	0	1(1.2%)	0	0	0
WBC increased	0	1(1.2%)	0	0	0
PLATELET, BLEEDING & CLOTTING DISORDERS	0	1(1.2%)	0	0	0
Epistaxis	0	1(1.2%)	0	0	0
URINARY SYSTEM DISORDERS	2(2.4%)	2(2.4%)	1(1.2%)	2(2.4%)	3(3.4%)
Albuminuria	0	0	0	0	1(1.1%)
Dysuria	1(1.2%)	0	0	0	0
Haematuria	0	0	1(1.2%)	1(1.2%)	0
Micturition frequency	0	0	0	0	1(1.1%)
Proteinuria	0	2(2.4%)	0	1(1.2%)	1(1.1%)
Urinary tract infection	1(1.2%)	0	0	0	0

Comments:

8 or 16 mg of Candesartan cilexetil were superior to placebo. No statistical differences were noted for Candesartan versus amlodipine, or the combination of Candesartan plus amlodipine versus amlodipine alone for sitting DBP. The change of 8.3 mm Hg for amlodipine versus placebo was also significant ($p<0.001$). While no additive significant benefit of CC plus amlodipine versus each single active was demonstrated on sitting DBP, there were suggestions of increased orthostatic change for the combination compared to each single active. Safety was not worse for the combination versus single active or placebo.

6.6 Study EC011 - Comparative, double-blind randomized, multicenter (FRG), placebo controlled study of Candesartan cilextetil (TCV-116) at a dose of 4 mg or 8 mg or 12 mg once daily, or enalapril 10 mg once daily in patients with mild to moderate hypertension (dbp 95-114 mm Hg).

Principal Investigator: Prof. Dr. Werner M. Herrmann.

Drugs and Placebo manufactured by

The protocol provided the following description and flow chart for the study:

The trial consists of 3 periods:

1. A wash-out period of 4 (2) weeks for patients with (without) previous antihypertensive medication;
2. a placebo run-in period of 2 weeks (single-blind);
3. a 12-week double-blind treatment period with 5 parallel groups: TCV-116 4, 8, 12 mg, placebo, enalapril 10 mg.

Study EC011 will be continued by a further 40-week double-blind follow-up study (EC033) consisting of 5 parallel groups. This study will be performed in responders to previous (EC011) treatment (see section 8.1.2).

Flow Chart of Study EC 011

Total study week #	0	1	2 - 4	5	6	7	8	10	14	18
Study period	Screening[1]	Wash-out		Placebo run-in		Double-blind treatment				
Week # of study period	0	1	2 (3,4)[2]	1	2	1	2	4	8	12
Visit #	SCR/0[1]	1	2 (3, 4)	5	6*	7	8	9	10	11
Informed consent	•									
Inclusion, exclusion criteria	•				•					
Medical history	•									
Concomitant medication	•	•	• (• •)	•	•	•	•	•	•	•
Extensive physical exam	•									•
Brief physical exam[3]		•	• (• •)	•	•	•	•	•	•	
Blood pressure/Pulse rate	•	•	• (• •)	•	•	•	•	•	•	•
Randomization					•					
Adverse events		•	•	•	•	•	•	•	•	•
Laboratory[4]	•			•				•		•
ECG					•					•
Dispensing medication			• (•)		•			•	•	(•)[5]
Check of compliance					•			•	•	•

AFB-PAREXEL Study No. 301728-93

*: Baseline visit

1: First trial day; visit 1 is the 7th day after screening day; except for the screening day all visits are scheduled for the last day of the respective study week

2: 2 weeks for untreated patients
4 weeks in case of antihypertensive pre-medication: e.g. Ca-channel blockers, diuretics, β-blockers, peripheral vasodilating agents, ACE inhibitor, centrally acting antihypertensive agents

3: Weight, heart (auscultation), lung, skin

4: Hematology, biochemistry, urinalysis

5: For follow-up study (EC033)

Randomization followed a computer-generated list with an equal probability of receiving any one of the five treatments.

Patients, male or female, between the ages of 18 and 70 years could enter with a sitting diastolic blood pressure between 95 and 114 mm Hg.

Some exclusion criteria were:

1. secondary hypertension
2. severe cardiac disease, e.g. CHF (NYHA III and IV)
3. hypertension difficult to stabilize
4. suspected impairment of renal function (males; creatinine ≥ 1.3 mg/dl, females; creatinine ≥ 1.2 mg/dl).

5. transaminases above normal levels, γ-GT > 1.5 times the ULN, chronic liver disease, and GI surgery that might affect absorption.

Concomitant medications not allowed were handled as follows:

If a patient needs one of the drugs mentioned under this point, these should be administered; this patient then has to be regarded as a drop-out.

Concomitant antihypertensive treatments (such as ACE inhibitors, Ca-channel blockers, diuretics, beta-blocking agents, alph-methylodopa, prazosine, reserpine, and other centrally active antihypertensive drugs);

oral hypoglycemic agents, insulin;

medication causing systemic vasodilation or vasoconstriction such as theophylline, papvarine, tricyclic antidepressants, neuroleptics, long-acting nitrates, sympathicomimetic nasal agents;

non-steroid anti-inflammatory agents, aspirin in chronic use (occasional aspirin or paracetamol for headaches etc. are permitted);

immunosupressive or cytotoxic agents;

any drug known to affect the gastro-intestinal absorption of drugs (e.g. chronic laxatives or antacids);

all H2 antagonists;

potassium supplements.

The primary objective of the study was to compare the antihypertensive efficacy of each dose of Candesartan cilexetil with placebo after 12 weeks of double-blind treatment. Secondarily they proposed to evaluate the optimum dose of Candesartan cilexetil "to confirm a dose finding study by **TAKEDA**," to compare the efficacy of three doses with enalapril 10 mg daily, and to assess safety.

The study was sized based on a 5 mm Hg difference of active drug from placebo as measured by the change from baseline in diastolic blood pressure after 12 weeks of treatment. The type I error level α was fixed at 5%. Following the sequentially rejecting

testing procedure according to Holm/Bonferroni, the smallest of the three p-values must not exceed $\alpha/3$ in order to get a significant result. From this they determined that 56 patients per treatment group would be needed.

Statistical analysis was to be performed as follows:

> 1. The "intention-to-treat group", which includes all patients who were randomized to the controlled treatment phase and received their study medication, and
>
> 2. the "per protocol group", which is a subgroup of the intention-to-treat group and includes all patients who performed the trial without major deviations from the protocol. Patients who terminated the trial prematurely due to lack of efficacy must be included in the "per protocol group" in order to avoid a substantial bias. (A few placebo responders might show a similar mean effect compared to a large group of verum responders.) Before the random code will be broken, the principal investigator and the sponsor will sign a list of those patients who will be included in the "per protocol group."

For patients who terminated the trial prematurely the blood pressure values of the last performed trial day will be carried forward and used for all analyses in order to avoid an over-estimation of the treatment effects.

For analysis of safety and tolerability all randomized patients with at least one intake of study medication after randomization will be considered (safety group).

Primary analysis was to be the decrease in diastolic blood pressure in the ITT group from baseline to 12 weeks for each active treatment compared to placebo. Change in systolic blood pressure and pulse was also to be analyzed. The four actives would be descriptively analyzed comparing one to the other on change in diastolic blood pressure without α adjustment by the Tukey-Kramer test. In addition clinical response rates will be determined. A response was defined as a diastolic blood pressure decrease of at least 5 mm Hg. The Cochran-Mantel-Haensel test was to be used to analyze response rates.

Results

Enrollment began December 17, 1993. Last patient was completed on January 13, 1993. Flow chart of patient enrollment and disposition was given as:

Patients per analysis group and per treatment group including reasons for exclusion from one analysis group

	enrolled n = 472					
non-rand. n = 108	randomised n = 364					
	Placebo	Candesartan cilexetil 4 mg	8 mg	12 mg	Enalapril	excluded
	n = 65	n = 67	n = 68	n = 65	n = 71	
	SAFETY POPULATION n = 336 = randomised patients - drug intake for at least one day					centre 2 (n = 20) and centre 37 (n = 8) [a]
	n = 65	n = 66	n = 68	n = 65	n = 71	
	ITT POPULATION n = 335					n = 1 (pat. no. 184 - ctr.19)
	n = 57	n = 55	n = 59	n = 59	n = 61	
	PER-PROTOCOL POPULATION n = 291					n = 44 [b]

[a] reason for exclusion: sufficient evidence of fraud.
[b] reason for exclusion: deviations from study protocol.

The sponsor states that centers 2 and 37 were closed on October 17, 1994 and September 5, 1994 respectively because of protocol violations and "strong evidence of fraud." All data from these patients were excluded from all analyses. Patient 184 from center 19 was a dropout before entering the treatment phase. Also center 14 was closed on July 28, 1994 because of study protocol violations and interchange of medication in 4 patients. Data were included in ITT analyses. Study center 32 was closed on September 5, 1994 due to suspicious lab values. Lab data were not included in ITT dataset, Center 32 randomized 10 patients. Study center 35 was closed on July 4, 1994 due to study protocol violations. Data from patient 341 was included in ITT analyses, but the one other randomized patient was not included.

Baseline demographics of age, and weight were comparable between groups with mean age varying from 51.4 years in the enalapril group to 54.2 years in the 8 mg Candesartan group. Mean weight varied from 76.77 Kg in the 4 mg Candesartan group to 81.07 Kg in the placebo group. Proportion of females randomized varied from 40% in the placebo group to 48% in the enalapril group.

APPEARS THIS WAY
ON ORIGINAL

There was variability in duration of hypertension between study arms as noted below:

Duration of hypertension (safety population). Figures denote number (percentage) of patients.

Duration of hypertension	Placebo	Candesartan cilexetil 4 mg	Candesartan cilexetil 8 mg	Candesartan cilexetil 12 mg	Enalapril	Total
	n = 65	n = 67	n = 68	n = 65	n = 71	n = 336
Newly diagnosed	11 16.9 %	17 25.4 %	20 29.4 %	17 26.2 %	18 25.4 %	83 24.7 %
< 1 year	14 21.5 %	9 13.4 %	16 23.5 %	10 15.4 %	9 12.7 %	58 17.3 %
1 to 3 years	17 26.2 %	14 20.9 %	14 20.6 %	15 23.1 %	15 21.1 %	75 22.3 %
> 3 years	23 35.4 %	27 40.3 %	18 26.5 %	23 35.4 %	29 40.8 %	120 35.7 %

APPEARS THIS WAY
ON ORIGINAL

Previous antihypertensive therapy was:

Class of previous antihypertensive medication. Figures denote number of patients.
(Results identical for all randomised patients and for the ITT population)

Class of drug	Placebo	Candesartan cilexetil 4 mg	Candesartan cilexetil 8 mg	Candesartan cilexetil 12 mg	Enalapril	Total
	n = 65	n = 66	n = 68	n = 65	n = 71	n = 335
ß blocker	18	13	12	22	11	76
Ca-channel blocker	12	8	5	15	17	57
ACE inhibitor	5	6	5	5	6	27
Diuretic	3	6	-	4	9	22
ACE inhibitor + diuretic	2	7	2	3	2	16
other	2	2	4	3	4	15
Diuretic + other	5	4	1	1	3	14
ß blocker + diuretic	3	1	4	2	3	13
Ca-channel blocker + ß blocker	-	-	4	-	2	6
Total number of patients with any previous antihypertensive medication	35 53.8%	31 47.0%	26 38.2%	32 49.2%	32 45.1%	156 46.6%

APPEARS THIS WAY
ON ORIGINAL

During the course of the study the following types of concomitant medications were taken:

Concomitant medication: distribution of the most frequent comedication across treatment.
Same medication counted once per patient. Figures denote number of patients (Safety Population).

ATC code total number of patients	Placebo n=65	Candesartan cilexetil 4mg n=67	8mg n=68	12mg n=65	Enalapril n=71	Total n=336
Other analgesics and antipyretics	4	7	7	3	6	27
Antiinflammatory/antirheumatic prod., non-steroids	1	6	8	5	5	25
Thyroid preparations	3	2	6	4	3	18
Expectorants, excl combinations with cough suppr.	4	3	2	1	5	15
All other therapeutic products	2	2	3	5	-	12
Propulsives	1	1	3	4	2	11
Anesthetics, local	2	1	4	2	1	10
Cholesterol- and triglyceride reducers	2	3	1	1	1	8
Antigout preparations	3	3	1	-	1	8
Tetracyclines	3	1	1	2	1	8
Antithrombotic agents	-	2	2	3	-	7
Antipropulsives	-	1	1	2	2	6
Beta-lactam antibacterials, penicillins	1	-	2	1	2	6
Other chemotherapeutics	-	2	1	2	-	5
Topical products for joint and muscular pain	-	1	2	2	-	5
Other cold combination preparations	-	-	2	1	2	5
Antifungals for topical use	2	-	2	-	1	5
Sulfonamides and antiinfectives in combination	2	1	-	1	1	5
Urinary antiseptics and antiinfectives	-	1	1	-	3	5
Estrogens	-	1	3	-	-	4
Stomatological preparations	-	-	2	2	-	4
Other urologicals, incl antispasmodics	-	2	1		1	4
Antihistamines for systemic use	-	1	-	1	2	4
Anxiolytics	1	-	1	-	2	4
Other beta-lactam antibacterials	3	1	-	-	-	4
Vasoprotectives	3	-	-	1	-	4
Vitamin B1, plain and in comb with vit B6 and B12	-	-	-	-	4	4
Antipruritics, incl antihist, anesthet, etc.	-	3	-	-	-	3
Decongestants and other nasal prep. for topical use	-	1	1	1	-	3
Iron preparations	-	2	-	-	1	3
Viral vaccines	-	-	1	1	1	3
Corticosteroids, plain	-	-	1	-	2	3
Opioids	-	-	-	-	3	3
Total number (percentage) of patients with any concomitant medication	22 33.8%	25 37.3%	27 39.7%	26 40.0%	27 38.0%	127 37.8%

Efficacy results for change in diastolic from baseline were:

Sitting diastolic blood pressure values (mmHg) at baseline and for LOCF, and differences baseline to LOCF - ITT population (data presented as mean ± SD)

	Placebo		Candesartan cilexetil						Enalapril	
			4 mg		8 mg		12 mg		10 mg	
	n=65		n=66		n=68		n=65		n=71	
	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD
Baseline (visit 6)	103.6	5.5	103.5	6.2	102.4	6.3	103.3	5.6	103.4	5.2
LOCF	98.3	10.7	95.1	9.5	91.9	9.0	93.3	9.3	92.8	9.8
Difference baseline to LOCF	-5.3	11.1	-8.4	10.5	-10.5	9.9	-10.0	10.0	-10.6	9.8

The p values for 4 mg, 8 mg, and 12 mg Candesartan cilexetil were 0.07, 0.0024, and 0.0085 for the ITT analyses. The magnitude of change was similar for 8 and 12 mg of Candesartan cilexetil and enalapril 10 mg. Results for the per protocol population were similar. Results for two response criteria (1. ≥ 5 mm Hg decrease in diastolic from baseline; 2. ≥ 10 mm Hg decrease and/or sitting diastolic ≤ 90 mm Hg) were provided:

Response rate to study drug (decrease in sitting diastolic blood pressure from baseline ≥ 5 mmHg) for visit 11 and for LOCF (ITT population)

	Placebo		Candesartan cilexetil						Enalapril	
			4 mg		8 mg		12 mg		10 mg	
	n=65		n=66		n=68		n=65		n=71	
	n	%	n	%	n	%	n	%	n	%
Visit 11	30/59	50.85	41/58	70.69	50/58	86.21	41/61	67.21	49/64	76.56
Last Individual Value	31/65	47.69	44/66	66.67	54/68	79.41	42/65	64.62	55/71	77.46

Response rate to study drug (decrease in sitting diastolic blood pressure from baseline ≥ 10 mmHg and/or a sitting diastolic blood pressure ≤ 90 mmHg) for visit 11 and for LOCF (ITT population)

	Placebo		Candesartan cilexetil						Enalapril	
			4 mg		8 mg		12 mg		10 mg	
	n=65		n=66		n=68		n=65		n=71	
	n	%	n	%	n	%	n	%	n	%
Visit 11	27/59	45.76	32/58	55.17	43/58	74.14	37/61	60.66	43/64	67.19
Last Individual Value	27/65	41.54	35/66	53.03	47/68	69.12	38/65	58.46	49/71	69.01

Visit 11 was the end of the double-blind period.
Effects on systolic and diastolic pressures and pulse were presented graphically:

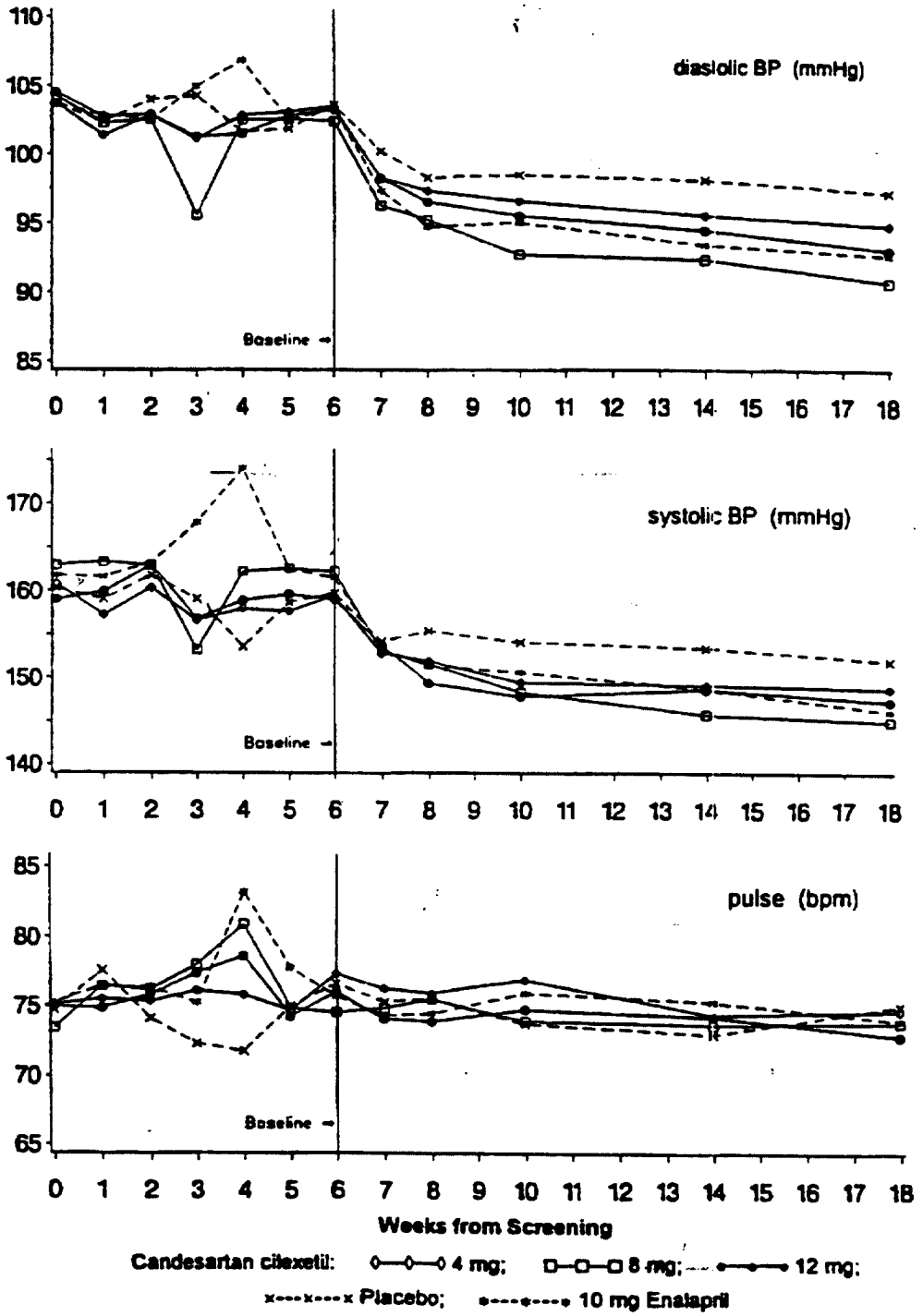


Figure R1
Time courses of sitting diastolic (upper panel), systolic blood pressure (middle panel) and pulse rate (lower panel) for the ITT population. Data presented as means (n = 65 to 71).

In sitting versus standing blood pressure analyses no orthostatic hypotensive effect was found for any group.

Safety

There was one death among the eight patients listed with serious adverse events. Patient 368 from center 37 was an 82 year old male on 4 mg of Candesartan cilexetil who developed an arterial occlusion in the left leg during the double-blind period of the study. He died during the hospitalization for this.

The other SAE of note is patient 108 from Center 11 who developed syncope on enalapril associated with a low systolic pressure.

Other events seemed unrelated to drug therapy, car accident, persistent gonocoecal arthritis, chondropathy, "apoplexy" after the study terminated, gastric ulcer, and urinary retention. Five additional patients withdrew for adverse events; one on endapril, four on Candesartan. Of the four additional Candesartan withdrawals, one was for cough and dizziness, one had leg edema, one had biliary colic, and one had "purulent angina and asthenia."

Overall adverse event rates were:

Frequency of adverse events (AE) within the double-blind treatment period (safety population)

	Treatment group					Total
	Placebo	Candesartan cilexetil			Enalapril	
		4mg	8mg	12mg	10mg	
total number of patients	n = 65	n = 67	n = 68	n = 65	n = 71	n = 336
Number of adverse events [1]	28	42	38	39	39	186
Number and percentage of patients affected by at least one AE	15	22	19	21	25	102
	23.1 %	32.8 %	27.9 %	32.3 %	35.2 %	30.4 %

[1] multiple occurrence of one symptom within one patient counted once

APPEARS THIS WAY
ON ORIGINAL

Adverse events reported by more than one patient were:

Adverse events after the start of randomised double-blind treatment reported in total by more than one patient. Figures denote number and percentages (*small italics*) of patients (safety population). Multiple symptoms within one patient are counted once.

	Treatment group								Total	
	Placebo		Candesartan cilexetil				Enalapril			
			4mg		8mg		12mg		10mg		
Symptom (WHO-ART code)	n = 65		n = 67		n = 68		n = 65		n = 71		n = 336	
Gastroenteritis	2	*3.1*	1	*1.5*	1	*1.5*	3	*4.6*	2	*2.8*	9	*2.7*
Lumbar pain			1	*1.5*	3	*4.4*	2	*3.1*	3	*4.2*	9	*2.7*
Bronchitis	3	*4.6*			2	*2.9*	2	*3.1*	1	*1.4*	8	*2.4*
Cervical pain			3	*4.5*	3	*4.4*	1	*1.5*	1	*1.4*	8	*2.4*
Accidental injury	1	*1.5*	2	*3.0*	1	*1.5*	2	*3.1*			6	*1.8*
Coughing			2	*3.0*	1	*1.5*	1	*1.5*	2	*2.8*	6	*1.8*
Headache	1	*1.5*	1	*1.5*	1	*1.5*			3	*4.2*	6	*1.8*
Influenza-like symptoms	3	*4.6*	2	*3.0*	1	*1.5*					6	*1.8*
Urinary tract infection	1	*1.5*	3	*4.5*					1	*1.4*	5	*1.5*
Dizziness	1	*1.5*	1	*1.5*	1	*1.5*	1	*1.5*			4	*1.2*
Eczema			1	*1.5*					3	*4.2*	4	*1.2*
Hypertriglyceridaemia	2	*3.1*	2	*3.0*							4	*1.2*
Oedema legs			1	*1.5*			3	*4.6*			4	*1.2*
Rhinitis					1	*1.5*	3	*4.6*			4	*1.2*
Back pain			1	*1.5*					2	*2.8*	3	*0.9*
Cephalgia	1	*1.5*	1	*1.5*			1	*1.5*			3	*0.9*
Skin disorder			2	*3.0*			1	*1.5*			3	*0.9*
Tonsillitis	1	*1.5*	1	*1.5*	1	*1.5*					3	*0.9*
Cystitis							2	*3.1*			2	*0.6*
Diarrhoea			1	*1.5*	1	*1.5*					2	*0.6*
Infection					1	*1.5*	1	*1.5*			2	*0.6*
Infection viral			2	*3.0*							2	*0.6*
Laryngitis	1	*1.5*			1	*1.5*					2	*0.6*
Muscle rigidity			2	*3.0*							2	*0.6*
Pharyngitis			1	*1.5*			1	*1.5*			2	*0.6*
Stomach pain							1	*1.5*	1	*1.4*	2	*0.6*
Throat sore							1	*1.5*	1	*1.4*	2	*0.6*
Tracheitis	1	*1.5*			1	*1.5*					2	*0.6*
Vein disorder	1	*1.5*			1	*1.5*					2	*0.6*
Total number of patients affected by at least one AE (incl. those not given above)	15	*23.1*	22	*32.8*	19	*27.9*	21	*32.3*	25	*35.2*	102	*30.4*

Laboratory Values

1. Liver Enzyme Changes.

While most changes were variations within the normal range or slightly above, three patients (2 placebo, 1 Candesartan) had elevations of SGOT or SGPT slightly more than 2X ULN which returned to normal on continued therapy. Creatinine values rose in eight patients during the double-blind period (6 Candesartan, 2 enalapril). The highest value was 1.49 mg/dl (enalapril case).

Some elevated potassiums were noted in all groups as below:

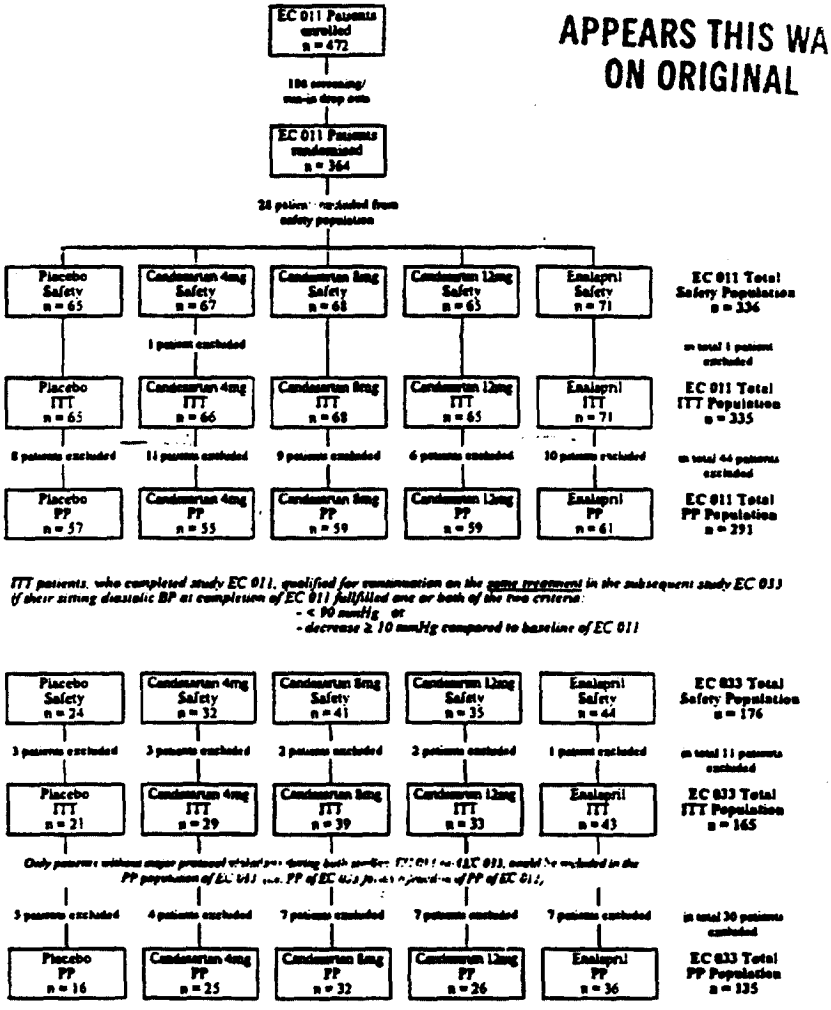
		N	MEAN	SD	MINIMUM	MEDIAN	MAXIMUM
Treatment	Trial Visit						
Placebo	visit 5	62	4.472	0.588	3.67	4.385	7.15
	visit 9	59	4.582	1.018	3.63	4.280	8.00
	visit 11	57	4.532	0.698	3.28	4.440	8.00
	visit 9 - visit 5	59	0.131	1.137	-2.46	-0.050	4.09
	visit 11 - visit 5	57	0.048	0.979	-3.55	-0.010	3.90
4 mg TCV-116	visit 5	64	4.369	0.491	3.37	4.340	7.21
	visit 9	59	4.551	0.978	3.51	4.300	8.00
	visit 11	56	4.545	0.731	3.67	4.410	7.90
	visit 9 - visit 5	58	0.198	0.906	-0.81	0.010	3.64
	visit 11 - visit 5	56	0.182	0.811	-1.71	0.115	3.76
8 mg TCV-116	visit 5	65	4.511	0.587	3.53	4.360	6.85
	visit 9	58	4.723	1.112	3.12	4.355	8.00
	visit 11	57	4.497	0.733	3.68	4.300	8.00
	visit 9 - visit 5	57	0.181	1.243	-2.51	-0.050	3.96
	visit 11 - visit 5	56	-0.052	0.833	-2.41	-0.105	2.40
12 mg TCV-116	visit 5	63	4.303	0.404	3.21	4.290	5.65
	visit 9	61	4.644	1.002	3.62	4.350	8.00
	visit 11	59	4.452	0.665	3.50	4.350	7.67
	visit 9 - visit 5	61	0.346	1.060	-1.62	0.190	4.00
	visit 11 - visit 5	59	0.166	0.701	-1.98	0.080	2.91
10 mg Enalapril	visit 5	69	4.274	0.463	3.21	4.310	6.25
	visit 9	68	4.667	0.977	3.57	4.435	8.00
	visit 11	62	4.460	0.533	3.62	4.400	6.93
	visit 9 - visit 5	68	0.400	1.081	-1.84	0.225	4.18
	visit 11 - visit 5	62	0.178	0.671	-1.95	0.045	2.65

Comments:

The efficacy data demonstrate effectiveness of 8, 16 mg CC and enalapril versus placebo. No significant differences among these actives could be demonstrated at this sample size.

6.7 Study EC033 - Follow-up safety study of study EC011.

A flow chart of patients entering this follow-up study from EC011 was provided:



APPEARS THIS WAY ON ORIGINAL

BEST POSSIBLE COPY

The first patient was enrolled in EC011 on December 17, 1993, and the last patient completed EC033 on October 20, 1995.

Although unblinding occurred after EC011 was concluded for purposes of analysis, the assignment was not disclosed to the investigators.

The study objectives were:

Primary objective:

- To assess the long-term safety of Candesartan cilexetil by clinical laboratory tests, ECG and the frequency and intensity of adverse events.

Secondary objective:

- To compare the long-term efficacy of three doses (4,8 and 12 mg Qd) of Candesartan cilexetil with each other as well as with placebo and the standard drug enalapril (10 mg od).

The study schedule and procedures were:

	Study EC 011								Study EC 033										
	2 to 4 week Wash-out [a]	2 week Placebo run-in	12 week double-blind, randomised treatment						40 week double-blind [b], randomised treatment (same treatment as for EC 011)										
Visit	0	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
weeks of random. treatment					1	2	4	8	12	16	20	24	28	32	36	40	44	48	52

[a] Length of wash-out period depended on previous antihypertensive medication.

[b] The random code had to be released to the trial management for analysis of EC 011. It was not disclosed to the investigators.

Flow Chart of Study EC 033											
Study week no.	0	4	8	12	16	20	24	28	32	36	40
Visit no.	11	12	13	14	15	16	17	18	19	20	21
Informed consent	•*										
Inclusion, exclusion criteria	•*										
Concomitant medication	•	•	•	•	•	•	•	•	•	•	•
Extensive physical exam.	•										•
Brief physical exam.[1]		•	•	•	•	•	•	•	•	•	
Blood pressure/Pulse	•	•	•	•	•	•	•	•	•	•	•
Adverse events	•	•	•	•	•	•	•	•	•	•	•
Laboratory[2]	•			•			•				•
ECG	•										•
Dispensing medication	•*	•	•	•	•	•	•	•	•	•	
Check of compliance	•	•	•	•	•	•	•	•	•	•	•

*: As most procedures of Visit 11 were performed on the last study day of the preceding study EC 011 (visit 11 of that study) only these additional items were to be recorded in the CRF.

1: Weight, heart (auscultation), lung, skin

2: Hematology, biochemistry, urinalysis

Safety evaluation was primary with adverse events, laboratory assessments to be analyzed for the safety patients (n=176).

For efficacy, 11 patients with no efficacy assessment were excluded from the safety population. Therefore the ITT population consisted of 165 patients.

While noted to be exploratory analyses only, the following efficacy measures were proposed.

1. Maximal decrease of diastolic and maximal decrease of systolic BP measured during this long-term continuation compared to baseline of study EC011.

2. Minimal decrease of diastolic and minimal decrease of systolic BP measured during this long-term continuation compared to baseline of study EC011.

3. Median decrease of diastolic and median decrease of systolic BP measured during this long-term continuation compared to baseline of study EC011.

4. Area under the curve (AUC) using baseline (visit 6) BP and the BP measurements of EC033, calculated according to the linear trapezoidal rule.

Since HCTZ was permitted to be added where necessary, the efficacy analyses were stratified for HCTZ use and no HCTZ use.

Safety

No deaths were reported. Two patients had serious adverse events. The first on placebo for 5 months had an intracranial hemorrhage. Blood pressure was not controlled. The second patient on 8 mg of Candesartan cilexetil had preexisting joint problems which during the course of the study needed arthroscopy and surgery.

The overall frequency of adverse events was:

Frequency of adverse events: Summary of all events within the double-blind treatment period of study EC 011 and EC 033 (52 weeks; Safety population)

		Placebo	Candesartan cilexetil 4mg	Candesartan cilexetil 8mg	Candesartan cilexetil 12mg	Enalapril	Total
total number of patients		n = 24	n = 32	n = 41	n = 35	n = 44	n = 176
Number of adverse events		40	47	80	49	63	279
Patients affected by at least one AE	Number	12	15	21	19	26	93
	Percentage	50.0 %	46.9 %	51.2 %	54.3 %	59.1 %	52.8 %

Adverse events reported by at least 3 patients were:

Frequency of adverse events overall: AEs in studies EC 011 and EC 033 after the start of randomised double-blind treatment (52 weeks) reported in total by at least three patients. Figures denote number and percentages (*small italics*) of patients (Safety population).

	Placebo		Candesartan cilexetil 4mg		Candesartan cilexetil 8mg		Candesartan cilexetil 12mg		Enalapril		Total	
Symptom (WHO-ART code)	n = 24		n = 32		n = 41		n = 35		n = 44		n = 176	
Bronchitis	4	*16.67*	5	*15.63*	5	*12.20*	3	*8.57*	7	*15.91*	24	*13.64*
Lumbar pain					6	*14.63*	4	*11.43*	3	*6.82*	13	*7.39*
Accidental injury			1	*3.13*	6	*14.63*	2	*5.71*	2	*4.55*	11	*6.25*
Gastroenteritis	2	*8.33*	1	*3.13*	2	*4.88*	2	*5.71*	3	*6.82*	10	*5.68*
Eczema	1	*4.17*	2	*6.25*	1	*2.44*	2	*5.71*	3	*6.82*	9	*5.11*
Tonsillitis	2	*8.33*	1	*3.13*	1	*2.44*	3	*8.57*	2	*4.55*	9	*5.11*
Back pain	1	*4.17*	3	*9.38*			2	*5.71*	2	*4.55*	8	*4.55*
Coughing			1	*3.13*	3	*7.32*	1	*2.86*	3	*6.82*	8	*4.55*
Cervical pain			2	*6.25*	4	*9.76*			1	*2.27*	7	*3.98*
Joint dysfunction	1	*4.17*			2	*4.88*	2	*5.71*	2	*4.55*	7	*3.98*
Skin disorder	1	*4.17*	2	*6.25*	1	*2.44*	1	*2.86*	2	*4.55*	7	*3.98*
Dizziness	2	*8.33*	1	*3.13*	2	*4.88*	1	*2.86*			6	*3.41*
Headache	2	*8.33*			2	*4.88*			2	*4.55*	6	*3.41*
Pharyngitis			1	*3.13*	3	*7.32*	1	*2.86*	1	*2.27*	6	*3.41*
Common cold syndrome	1	*4.17*	1	*3.13*	1	*2.44*			2	*4.55*	5	*2.84*
Influenza-like symptoms			1	*3.13*	1	*2.44*			2	*4.55*	4	*2.27*
Conjunctivitis			1	*3.13*	1	*2.44*			1	*2.27*	3	*1.70*
Diarrhoea	2	*8.33*			1	*2.44*					3	*1.70*
Infection					1	*2.44*	2	*5.71*			3	*1.70*
Lipids serum increased			1	*3.13*	2	*4.88*					3	*1.70*
Nausea			1	*3.13*	1	*2.44*			1	*2.27*	3	*1.70*
Otitis media	1	*4.17*					1	*2.86*	1	*2.27*	3	*1.70*
Rhinitis					1	*2.44*	2	*5.71*			3	*1.70*
Urinary tract infection	1	*4.17*	1	*3.13*	1	*2.44*					3	*1.70*
Verruca	1	*4.17*	1	*3.13*			1	*2.86*			3	*1.70*
Total number of patients affected by at least one AE (incl. those not given above)	12	*50.0*	15	*46.9*	21	*51.2*	19	*54.3*	26	*59.1*	93	*52.8*

There were two withdrawals for adverse experiences, both on placebo. The first was the patient with the intracranial hemorrhage, already cited. The second was a patient with hypertensive crisis and pulmonary edema.

APPEARS THIS WAY
ON ORIGINAL

Orthostatic data was provided:

Orthostatic reaction:
Differences "standing" minus "sitting" for systolic/diastolic blood pressure and pulse.
"Baseline" is start of randomised treatment in EC 011. (Safety population)

	Placebo				4 mg				8 mg				12 mg				Enalapril			
	n	mean	min	max	n	mean	min	max	n	mean	min	max	n	mean	min	max	n	mean	min	max
Diastolic Blood Pressure (mmHg)																				
Baseline	24	-0.1	-16	13	32	3.3	-10	24	41	1.5	-9	22	33	5			50			
Week 16	21	4.1	-12	40	29	2.0	-24	16	39	3.2	-7	27	33	3.9	-4	31	43	2.0	-12	28
Week 20	19	4.4	-4	22	28	2.3	-10	16	38	5.8	-7	21	32	4.2	-9	18	42	3.1	-8	18
Week 24	19	1.6	-11	18	28	3.8	-12	26	38	5.1	-6	28	30	5.2	-10	39	41	2.5	-17	41
Week 28	19	3.9	-8	35	28	1.1	-15	20	38	2.5	-25	18	30	2.5	-15	18	41	1.3	-9	11
Week 32	18	2.1	-8	13	27	2.8	-7	19	37	4.6	-24	30	29	2.5	-10	13	39	2.7	-11	23
Week 36	17	2.5	-2	17	25	3.0	-9	15	36	2.5	-31	23	28	2.7	-11	19	37	2.4	-6	22
Week 40	17	3.1	-5	12	25	4.8	-19	30	34	3.6	-9	20	28	-0.1	-19	8	37	4.0	-20	30
Week 44	17	1.7	-14	16	25	2.4	-8	28	33	2.9	-13	20	27	3.2	-4	20	37	1.8	-12	17
Week 48	16	2.4	-12	21	25	1.4	-26	30	33	3.5	-9	21	27	4.1	-11	27	37	1.3	-15	12
Week 52	16	3.6	-13	18	25	2.2	-13	16	33	1.4	-11	17	27	1.5	-18	18	37	2.9	-16	21
Systolic Blood Pressure (mmHg)																				
Baseline	24	-3.1	-29	23	32	0.5	-36	28	41	-0.4	-50	30	35	1.4	-14	57	44	-2.7	-48	40
Week 16	21	-3.9	-27	16	29	0.5	-49	31	39	-0.2	-21	30	33	1.2	-17	22	43	1.3	-21	22
Week 20	19	0.2	-18	26	28	-1.4	-24	11	38	0.8	-20	14	32	2.0	-21	24	42	-0.7	-31	16
Week 24	19	-6.1	-40	13	28	-1.8	-23	24	38	-0.3	-29	44	30	-2.6	-23	17	41	1.8	-24	32
Week 28	19	-1.9	-16	15	28	-0.5	-32	22	38	2.3	-25	31	30	0.9	-35	34	41	-1.6	-28	23
Week 32	18	0.3	-20	23	27	-3.4	-36	17	37	-1.1	-27	16	29	-1.0	-12	17	39	-0.5	-28	26
Week 36	17	-5.3	-26	24	25	-2.3	-22	20	36	-1.5	-43	38	28	-0.4	-33	28	37	-1.0	-31	23
Week 40	17	-3.1	-31	23	25	-2.8	-30	15	34	0.2	-29	43	28	-2.1	-20	19	37	3.9	-40	29
Week 44	17	-1.8	-24	13	25	-3.2	-23	13	33	-0.9	-38	33	27	0.6	-23	20	37	-3.0	-60	68
Week 48	16	-1.7	-23	19	25	-4.2	-66	36	33	2.1	-16	28	27	-2.3	-32	33	37	-4.0	-40	11
Week 52	16	-2.9	-34	13	25	-2.0	-17	23	33	-1.4	-29	17	27	-5.0	-33	15	37	-3.0	-48	18
Pulse Rate (bpm)																				
Baseline	24	3.2	-8	11	32	2.2	-22	23	41	1.7	-12	16	35	0.0	-15	12	43	4.6	-7	22
Week 16	21	3.1	-13	14	29	3.1	-7	24	39	3.3	-18	22	33	5.2	-4	43	43	1.6	-16	18
Week 20	19	0.5	-29	13	28	1.0	-23	16	38	4.8	-3	23	32	2.8	-17	16	42	3.1	-21	16
Week 24	19	4.0	-3	12	28	4.1	-29	19	38	4.4	-11	13	30	4.7	-13	32	41	4.8	-9	32
Week 28	19	4.1	-20	20	28	5.2	-19	27	38	5.5	-33	21	30	0.1	-33	13	41	4.2	-72	51
Week 32	18	3.4	-7	19	27	5.0	-5	32	37	0.1	-26	38	29	2.8	-11	17	39	3.4	-13	17
Week 36	17	2.5	-6	12	25	3.9	-12	33	36	4.1	-17	32	28	4.1	-9	45	36	3.0	-16	33
Week 40	17	2.5	-8	12	25	4.1	-56	32	34	3.5	-6	31	28	1.2	-16	9	37	4.2	-16	18
Week 44	17	1.2	-27	20	25	1.2	-10	12	33	4.0	-17	21	27	1.5	-33	11	37	4.2	-13	49
Week 48	15	2.2	-5	12	25	8.7	-8	64	33	4.1	-20	23	26	3.2	-4	16	37	5.4	-9	34
Week 52	16	3.6	-8	22	25	5.1	-10	61	33	3.3	-28	21	27	1.7	-32	26	37	1.9	-38	17

Negative values indicate that the sitting value was higher than the standing value.

The greatest pressure changes were:

Systolic	66 mm Hg decrease	Candesartan 4 mg
Diastolic	31 mm Hg decrease	Candesartan 8 mg
Diastolic	41 mm Hg increase	Enalapril

Other laboratory findings noted as adverse events were:

Laboratory findings judged as adverse event. Figures denote number of patients (safety population).

adverse event total no. of patients	Candesartan cilexetil Placebo n = 24	4 mg n = 32	8 mg n = 41	12 mg n = 35	Enalapril n = 44	Total n = 176
lipids serum increased		1	2	-	-	3
anaemia iron deficiency		1	-	-	1	2
hypertriglyceridaemia	1	1	-	-	-	2
hyperuricaemia	-	1	-	-	1	2
leukocytopenia	-	1	-	-	1	2
hepatic enzymes increased	-	-	1	-	-	1
hypercholesterolaemia	-	-	1	-	-	1

Efficacy

For the ITT population, the number of patients on HCTZ and not requiring HCTZ was:

Antihypertensive comedication: Number and percentage of patients with additional HCTZ treatment during the course of randomised treatment.

	Patients	Placebo		4 mg		8 mg		12 mg		Enalapril		Total	
ITT	with HCTZ	3	14.3%	9	31.0%	7	17.9%	7	21.2%	9	20.9%	35	21.2%
	without HCTZ	18	85.7%	20	69.0%	32	82.1%	26	78.8%	34	79.1%	130	78.8%
	total	21	100%	29	100%	39	100%	33	100%	43	100%	165	100%
PP	with HCTZ	3	18.8%	9	36.0%	7	21.9%	5	19.2%	9	25.0%	33	24.4%
	without HCTZ	13	81.3%	16	64.0%	25	78.1%	21	80.8%	27	75.0%	102	75.6%
	total	16	100%	25	100%	32	100%	26	100%	36	100%	135	100%

APPEARS THIS WAY
ON ORIGINAL

Results of the exploratory analyses performed were:

Sitting systolic/diastolic blood pressure:
Decreases during the 40 week course of study EC 033 (ITT population)

		Candesartan cilexetil											
		4 mg			8 mg			12 mg			Enalapril		
Decrease [1]	Subgroup [2]	n	mean	SD	n	mean	SD	n	mean	SD	n	mean	SD
		Diastolic Blood Pressure (mmHg)											
Maximum	total												
	HCTZ												
	non-HCTZ												
Median	total	29	-14.00	6.89	39	-14.58	6.97	33	-14.15	9.80	43	-13.40	7.30
	HCTZ	9	-9.06	6.92	7	-6.79	5.07	7	-6.64	10.05	9	-10.39	9.34
	non-HCTZ	20	-16.23	5.74	32	-16.28	6.15	26	-16.17	8.86	34	-14.19	6.60
Minimum	total												
	HCTZ												
	non-HCTZ												
		Systolic Blood Pressure (mmHg)											
Maximum	total												
	HCTZ												
	non-HCTZ												
Median	total	29	-19.19	14.45	39	-20.24	13.30	33	-21.08	21.54	43	-18.06	14.13
	HCTZ	9	-15.17	10.27	7	-14.00	9.59	7	-10.57	26.86	9	-13.17	17.56
	non-HCTZ	20	-21.00	15.88	32	-21.61	13.72	26	-23.90	19.53	34	-19.35	13.08
Minimum	total												
	HCTZ												
	non-HCTZ												

[1] For each patient the minimum, median and maximum decrease during the course of the study relative to baseline of EC 0111 was taken.

[2] The investigators could prescribe additional HCTZ (12.5 mg od) if during repeated visits the sitting diastolic BP was ≥ 95 mmHg. If at the next visit this threshold value was still exceeded, the HCTZ dose could be doubled.

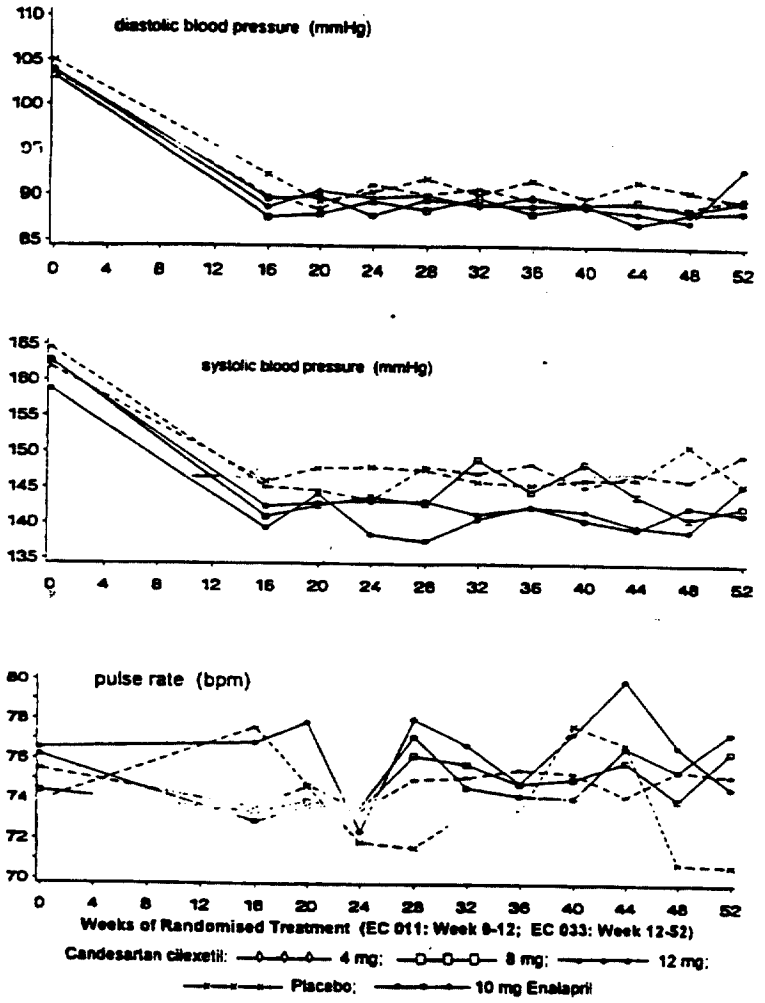
Area under the time versus sitting blood pressure curve (AUC [mmHg × weeks]; ITT population)

		Candesartan cilexetil											
		4 mg			8 mg			12 mg			Enalapril		
		n	mean	SD	n	mean	SD	n	mean	SD	n	mean	SD
diastolic BP	total	29	-637.0	281.0	39	-640.4	282.7	33	-642.2	424.9	43	-594.5	292.9
	HCTZ	9	-471.1	323.7	7	-347.1	210.3	7	-295.7	437.6	9	-442.9	377.1
	non-HCTZ	20	-711.7	229.8	32	-704.5	256.4	26	-735.5	377.4	34	-634.6	258.5
systolic BP	total	29	-804.3	632.7	39	-871.9	592.6	33	-921.9	940.1	43	-818.5	622.0
	HCTZ	9	-644.9	530.7	7	-566.3	499.9	7	-380.9	1097.0	9	-619.8	793.6
	non-HCTZ	20	-876.0	673.8	32	-938.8	596.9	26	-1067.6	859.3	34	-871.1	571.0

AUC from baseline (Visit 6 of study EC 011) to LOCF for final visit of EC 033. The BP value at baseline was set as 0.
I.e., the lower the nominal value of AUC, the more overall BP reduction occurred during the course of the study.

Most patients could be maintained on drug or placebo without the need for HCTZ.

The time response curves for the total groups were:



T-Figure 2
Time courses of sitting diastolic (upper panel), systolic blood pressure (middle panel) and pulse rate (lower panel) for the ITT population. Data presented as means (n = 21 to 43).

Comments:

Observationally long term safety was similar for placebo and actives. There will be randomized placebo controlled withdrawal studies reported to evaluate whether long term maintenance of BP efficacy is really due to continued activity of CC.

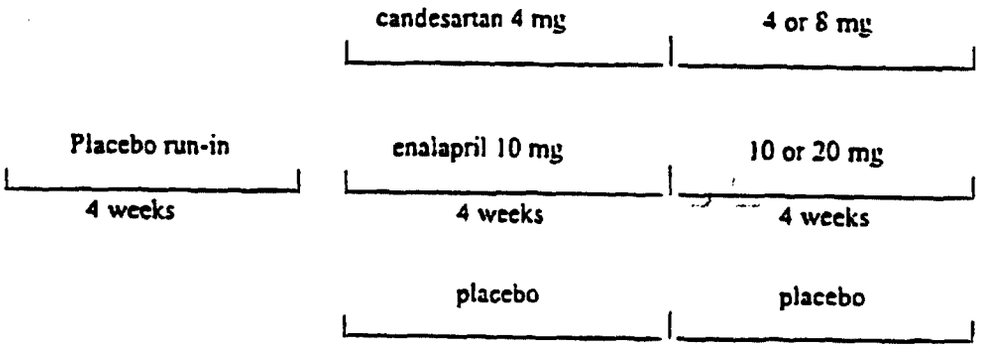
6.8 Study EC018 - Comparative, double-blind, randomized, multicenter, placebo controlled study of Candesartan cilexetil and enalapril in patients with mild to moderate hypertension (dbp 95-109 mm Hg).

Principal Investigator: Prof. A. Zanchette, Milan, Italy.

Drugs and Placebo manufactured by

The protocol provides the following flow chart for the study which summarizes design features for this study.

Study Period	Placebo Run-In Period			Treatment Period		
WEEK	0	2	4	2	4	8
VISIT	1	2	3	4	5	6
Medical History	X					
Incl./Excl. criteria	X		X			
Concomitant medication	X	X	X	X	X	X
Extensive physical examination	X					X
Brief physical examination		X	X	X	X	
Blood Pressure/Heart rate	X	X	X	X	X	X
24h blood pressure monitoring			X			X
Adverse events		X	X	X	X	X
Laboratory tests	X	(X)		X	X	X
ECG	X		X	X	X	X
Distribution of medication	X		X		X	
Drug accountability			X		X	X
Global assessment of efficacy and safety						X



Randomization was done at the end of the run-in period for those qualifying with a 1 in 5 chance of receiving placebo and a 2 in 5 chance for active drug.

Patients 18 years of age or older, males or females entered with untreated or unsatisfactorily treated hypertension with a diastolic of ≥ 95 mm Hg and ≤ 109 mm Hg. Some exclusion criteria were:

1. secondary hypertension;
2. severe cardiac disease, e.g. CHF (NYHA III and IV);
3. suspected impairment of renal function, defined serum creatinine;
4. elevated potassium, liver transaminases, and GI surgery that might affect absorption.

Concomitant medications not allowed during the study were:

Concomitant antihypertensive treatments (such as other ACE inhibitors, Ca-channel blockers, beta-blocking agents, alpha-methylDOPA, prazosin, reserpine, and other centrally acting antihypertensive drugs), diuretics

medication causing systemic vasodilation or vasoconsrriction such as theophylline, papaverine, tricyclic antidepressants, neuroleptics, sympathicomimeric nasal agents

anti-arrhythmic agents

non-steroidal anti-inflammatory agents with the exception of aspirin

chronic use of oral corticosteroids

immunosuppressive or cytotoxic agents

any drug known to affect the gastrointestinal absorption of drugs (e.g. chronic laxatives or
antacids)

appetite depressant

potassium supplements

The primary objective of the study was to evaluate the efficacy of each active compared to placebo in treating mild to moderate hypertension as measured by the diastolic blood pressure after 8 weeks of treatment. Secondarily the effect of each active compared to placebo on systolic blood pressure, the effect of one active versus the other on systolic and diastolic pressure, and safety were to be evaluated. The study sized based on a postulated delta of active minus placebo on diastolic blood pressure 5 mm Hg at an α of 0.05 and a β of 0.2. It was calculated that 33 placebo patients and 66 in each active group would be needed for analysis. Since it was assumed that 30% of run-in patients would drop out, they decided to enter 240 patients in that phase so that 165 could be available for the treatment phase.

Statistical analysis was to be performed as follows:

- The "intention-to-treat group", which includes all patients who were randomized to the controlled treatment period and received their study medication and had at least one post baseline assessment of diastolic blood pressure.

- The "per-protocol group", which is a subgroup of the intention-to-treat group and includes all patients who participated in the trial without major deviations from the protocol. Patients who terminated the trial prematurely due to lack of efficacy are included in the "per protocol group" in order to avoid a substantial bias. (A few placebo responders might show a similar mean effect compared to a large group of verum responders). Before the randomization code will be broken, the study coordinator and the sponsor will sign-off a list of those patients who will be included in the "per protocol group".

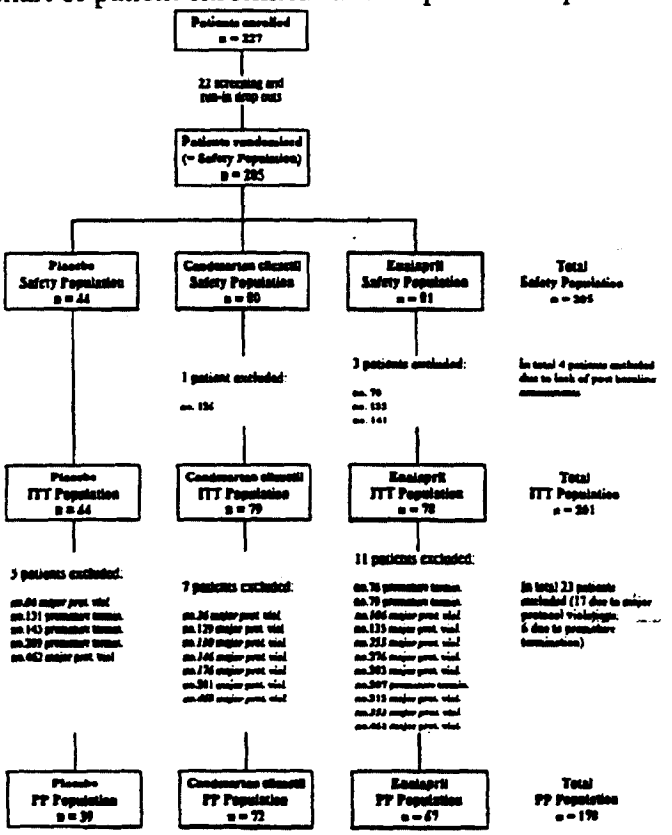
For patients who terminated the trial prematurely, the blood pressure values of the last performed trial day was carried forward and used for all analyses.

For analysis of safety and tolerability, all enrolled patients with at least one dose of study medication after randomization would be considered (safety group).

Results

Enrollment began March 27, 1995 and last patient completed January 8, 1996.

A flow chart of patient enrollment and disposition is provided as follows:



Specifications for major protocol violations were determined prior to unblinding and were as follows:

1. **Timing of Sphygmomanometric Blood Pressure Measurements**
   All sphygmomanometric BP measurements carried out beyond 12h00 a.m. at Visit 6.

2. **Between-arm differences in BP**
   A between-arm difference in sitting diastolic BP > 3 mmHg at Visit 1.

3. **Compliance**
   According to the protocol, compliance below 75% or above 125% are to be considered as major protocol violations. It was agreed to consider this violation as major when it occurred at Visit 6, or when it occurred at Visit 5 if the investigator doubled the dose.

4. **Duration of placebo period**
   A placebo period of two weeks or less.

5. **Final assessment too late**
   Return for Visit 6 after more than 35 days post Visit 5.

6. **Unjustified dose doubling**
   Dose doubling at Visit 5, if Visit 5 occurred more than 35 days post Visit 3.

This resulted in the following exclusions from the per protocol population:

	Screening No.	Category of major violation
Identification prior to unblinding	106	3
	129	3, 4, 6
	130	3
	135	3, 6
	201	2
	276	5
	303	1, 5
	313	5
	461	5
	462	5
Identification after unblinding	026	6
	086	6
	146	6
	176	6
	255	6
	353	6
	469	6

For baseline demographic variables of age, sex and weight, while the mean age varied from 48.6 in the Candesartan cilexetil group to 49.8 in the enalapril group, there was a preponderance of males in the Candesartan group versus a preponderance of females in the enalapril group with an associated weight difference. No race distribution is provided.

For duration of hypertension the following table was provided.

T-Table 2
Duration of hypertension (ITT population).
Figures denote number (percentage) of patients.

Duration of hypertension	Placebo n = 44		Candesartan cilexetil n = 79		Enalapril n = 78		Total n = 201	
< 1 year	10	22.7%	24	30.4%	18	23.1%	52	25.9%
1 to 3 years	12	27.3%	12	15.2%	21	26.9%	45	22.4%
> 3 years	22	50.0%	43	54.4%	39	50.0%	104	51.7%

Previous antihypertensive therapy was:

T-Table 3
Class of previous antihypertensive medication.
Figures denote percentage (proportion) of patients (ITT population).

Class of drug	Placebo		Candesartan cilexetil		Enalapril		Total	
Monotherapy								
ACE Inhibitor	18.2%	8/44	19.0%	15/79	15.4%	12/78	17.4%	35/201
Calcium blocker	15.9%	7/44	11.4%	9/79	12.8%	10/78	12.9%	26/201
Betablocker	4.5%	2/44	5.1%	4/79	5.1%	4/78	5.0%	10/201
Diuretic	2.3%	1/44	2.5%	2/79	9.0%	7/78	5.0%	10/201
Other	-	-	2.5%	2/79	-	-	1.0%	2/201
Combination of 2 classes								
(ACE Inhibitor + diuretic)	9.1%	4/44	3.8%	3/79	5.1%	4/78	5.5%	11/201
ACE Inhibitor and Diuretic	2.3%	1/44	-	-	5.1%	4/78	2.5%	5/201
ACE Inhibitor and Calcium blocker	2.3%	1/44	2.5%	2/79	1.3%	1/78	2.0%	4/201
ACE Inhibitor and Betablocker	-	-	1.3%	1/79	1.3%	1/78	1.0%	2/201
Calcium blocker and Other	2.3%	1/44	1.3%	1/79	-	-	1.0%	2/201
Betablocker and Calcium blocker	-	-	2.5%	2/79	-	-	1.0%	2/201
Calcium blocker and Diuretic	-	-	2.5%	2/79	-	-	1.0%	2/201
(Betablocker + diuretic)	2.3%	1/44	-	-	-	-	0.5%	1/201
Betablocker and Diuretic	-	-	-	-	1.3%	1/78	0.5%	1/201
Betablocker and Other	-	-	-	-	1.3%	1/78	0.5%	1/201
Combination of 3 classes								
ACE Inhibitor and Calcium blocker and Diuretic	2.3%	1/44	2.5%	2/79	-	-	1.5%	3/201
(ACE Inhibitor + diuretic) and Calcium blocker	-	-	2.5%	2/79	-	-	1.0%	2/201
ACE Inhibitor and (ACE Inhibitor + diuretic) and Calcium blocker	-	-	1.3%	1/79	-	-	0.5%	1/201
ACE Inhibitor and (Betablocker + diuretic)	-	-	1.3%	1/79	-	-	0.5%	1/201
ACE Inhibitor and Calcium blocker and Other	-	-	1.3%	1/79	-	-	0.5%	1/201
(ACE Inhibitor + diuretic) and Calcium blocker and Diuretic	-	-	1.3%	1/79	-	-	0.5%	1/201
Combination of 4 classes								
(ACE Inhibitor + diuretic) and Calcium blocker and Other	-	-	1.3%	1/79	-	-	0.5%	1/201
TOTAL[a]	61.4%	27/44	65.8%	52/79	57.7%	45/78	61.7%	124/201

[a] Brackets denote combinational drugs.

During the course of the study, the following types of concomitant medications were taken:

T-Table 5
Concomitant medication: Distribution across treatment groups. Same medication counted once per patient. Figures denote number (percentage) of patients, except line "total medications" (ITT Population).

ATC code / total number of patients	Placebo n=44		Candesartan cilexetil n=79		Enalapril n=78		Total n=201	
Patients with concomitant medication	3	7%	9	11%	7	9%	19	9%
Total medications	6		18		17		41	
Other analgesics and antipyretics	3	7%	5	6%	11	14%	19	9%
Anxiolytics	-		4	5%	-		4	2%
Beta-lactam antibacterials, penicillins	2	5%	2	3%	-		4	2%
Antigout preparations	1	2%	2	3%	-		3	1%
Antihistamines for systemic use	-		2	3%	-		2	1%
Antiinflammatory/antirheumatic prod.	-		1	1%	1	1%	2	1%
Antipruritics, incl. antihist. ,anesthet.	-		2	3%	-		2	1%
Cholesterol- and triglyceride reducers	-		-		2	3%	2	1%
Other beta-lactam antibacterials	-		-		2	3%	2	1%
Anticholinergic agents	-		-		1	1%	1	0.5%

Dose doubling after 4 weeks in the treatment phase was:

T-Table 6
Percentage and proportion of patients with dose adjustment due to insufficient blood pressure reduction after four weeks of randomised treatment.

		Placebo		Candesartan cilexetil		Enalapril	
ITT	dose doubled	43.2 %	19/44	36.7 %	29/79	28.2 %	22/78
	dose unchanged	50.0 %	22/44	62.0 %	49/79	66.7 %	52/78
	no entry	6.8 %	3/44	1.3 %	1/79	5.1 %	4/78
PP	dose doubled	43.6 %	17/39	31.9 %	23/72	28.4 %	19/67
	dose unchanged	56.4 %	22/39	66.7 %	48/72	70.1 %	47/67
	no entry	-		1.4 %	1/72	1.5 %	1/67

"insufficient reduction" = sitting diastolic BP > 90 mmHg

The efficacy results demonstrated that each active drug was statistically superior to placebo in change from baseline to last diastolic value (mean reduction for actives minus placebo approximately 4 mm Hg).

APPEARS THIS WAY
ON ORIGINAL

T-Table 7

Primary efficacy evaluation: Mean (± SD) reduction in sitting diastolic blood pressure (mmHg) at the individual endpoint of eight scheduled weeks of randomised treatment.

	Placebo	Candesartan cilexetil	Enalapril
ITT	-6.3 ± 7.3 n = 44	-10.1 ± 6.6 n = 79	-10.5 ± 6.6 n=78
PP	-6.6 ± 7.5 n=39	-10.2 ± 6.7 n=72	-10.4 ± 6.9 n=67

The individual endpoint for Patient 211 (enalapril) was an unscheduled visit (post Visit 5).

T-Table 8

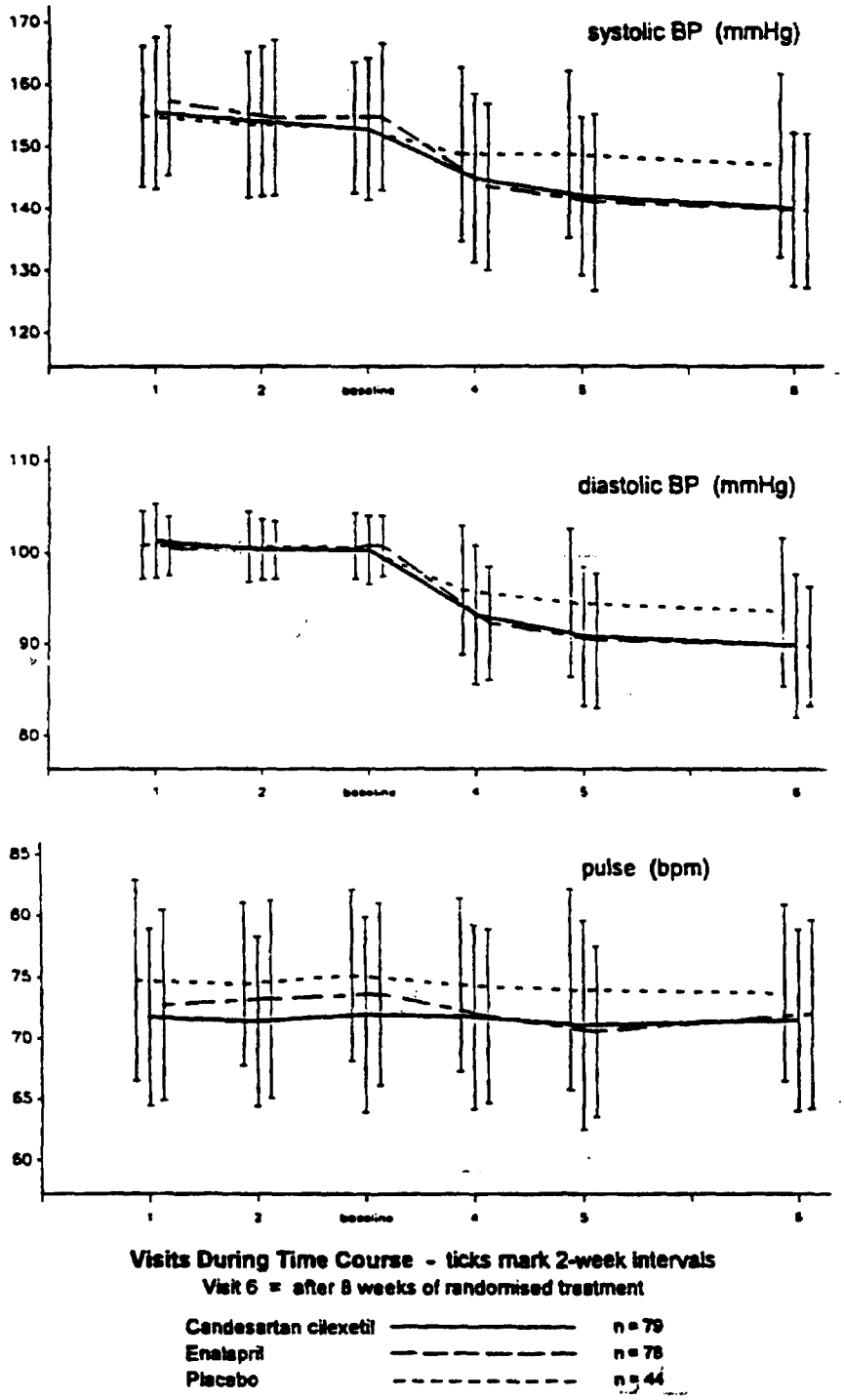
Primary efficacy evaluation: ANCOVA on reduction in sitting diastolic blood pressure (individual last value versus baseline). The primary confirmatory analysis according to protocol is set in bold (first line).

Comparison A *versus* B			Estimate [a] (mmHg)	95% Confidence interval (mmHg)	p-value (2-sided)
Candesartan cilexetil	placebo	ITT	-3.53	-6.049 / -1.015	0.0062 *
		PP	-3.04	-5.749 / -0.323	0.0285 *
Candesartan cilexetil	enalapril	ITT	0.70	-1.444 / 2.846	0.5200
		PP	0.72	-1.594 / 3.036	0.5395
Enalapril	placebo	ITT	-4.23	-6.750 / -1.715	0.0011 *
		PP	-3.76	-6.506 / -1.008	0.0077 *

[a] A minus B; i.e. a negative estimate indicates greater reduction for A.

* p-value < 5%

Effects on systolic and diastolic pressure and pulse were presented graphically:



T-Figure 2
Time courses of sitting systolic (upper panel), diastolic blood pressure (middle panel) and pulse rate (lower panel) for the ITT population. Data presented as means ± SD.

On standing there was some numerical decrease in the deltas comparing actives to placebo, but not any decrease suggesting postural hypotension.

Clinical "success: of therapy was assured if one or both of the following criteria were met: decrease of diastolic BP from baseline ≥ 10 mm Hg, diastolic BP ≤ 90 mm Hg.

Overall results were:

T-Table 13
Response rates (percentage and proportions of patients) taken at the individual endpoint across treatment groups.

		Placebo		Candesartan cilexetil		Enalapril	
Response (either of the criteria below)	ITT	38.6%	17/44	65.8%	52/79	73.1%	57/78
	PP	41.0%	16/39	68.1%	49/72	70.1%	47/67
diastolic BP ≤ 90 mmHg ("normalised")	ITT	36.4%	16/44	58.2%	46/79	65.4%	51/78
	PP	38.5%	15/39	61.1%	44/72	62.7%	42/67
decrease of diastolic BP from baseline ≥ 10 mmHg	ITT	31.8%	14/44	58.2%	46/79	64.1%	50/78
	PP	35.9%	14/39	59.7%	43/72	62.7%	42/67

For those needing a doubling of dose in any arm, therapeutic results were numerically inferior to those remaining on the initial dose.

T-Table 12
Sitting systolic/diastolic blood pressure and pulse
Changes from baseline to individual last value stratified by dose level (PP population).

	dose adjustment at Visit 5	Placebo			Candesartan cilexetil			Enalapril		
		n	mean	SD	n	mean	SD	n	mean	SD
Systolic BP (mmHg)	dose unchanged	22	-10.3	10.3	49	-15.7	11.0	48	-16.8	12.2
	dose doubled	17	-0.2	10.0	23	-6.0	10.9	19	-6.9	9.2
Diastolic BP (mmHg)	dose unchanged	22	-9.7	8.1	49	-12.6	5.6	48	-12.9	6.0
	dose doubled	17	-2.6	4.3	23	-5.0	5.8	19	-4.1	4.6
Pulse rate (bpm)	dose unchanged	22	-1.9	6.8	49	-0.5	6.5	48	-2.3	9.1
	dose doubled	17	-0.1	5.0	23	0.7	8.8	19	1.0	4.9

Patients with insufficient BP reduction (sitting diastolic BP > 90 mmHg) at Visit 5 after four weeks of randomised treatment were put on the double dose (maintaining double blind conditions) for the remaining four weeks of treatment.

T-Table 15
Response rates (percentage and proportions of patients) stratified by dose level (PP population).

	Placebo				Candesartan cilexetil				Enalapril			
dose level	unchanged		doubled		unchanged		doubled		unchanged		doubled	
Visit 4	50.0%	11/22	-	0/17	63.3%	31/49	17.4%	4/23	77.1%	37/48	5.3%	1/19
Visit 5	81.8%	18/22	-	0/17	91.7%	44/48	-	0/23	97.9%	46/47	-	0/19
Visit 6	66.7%	14/21	12.5%	2/16	89.6%	43/48	27.3%	6/22	91.5%	43/47	22.2%	4/18
Indiv. last value	63.6%	14/22	11.8%	2/17	87.8%	43/49	26.1%	6/23	89.6%	43/48	21.1%	4/19

Patients with insufficiently reduced BP (sitting diastolic BP > 90 mmHg) at Visit 5 after four weeks of randomised treatment were put on the double dose (maintaining double blind conditions) for the remaining four weeks of treatment.

Safety

No deaths or serious adverse events were reported in this study.

3 adverse events leading to withdrawal (rash, cough, thyroiditis) all occurred in the enalapril group.

Overall adverse event rates were:

T-Table 17
Frequency of adverse events (AE) during randomised treatment (safety population)

		Placebo	Candesartan cilexetil	Enalapril	Total
Patients affected	Percentage	15.9 %	11.3 %	23.5 %	17.1 %
by at least one AE	Proportion	7/44	9/80	19/81	35/205
Total number of adverse events [1]		8	15	26	49

[1] multiple occurrence of one symptom within one patient counted once

APPEARS THIS WAY
ON ORIGINAL

Adverse events reported by more than one patient were:

T-Table 19
Adverse events during randomised treatment reported in total by more than one patient. Figures denote percentages and proportions of patients (safety population). Multiple AEs within one patient are counted once.

Symptom (WHO-ART code)	Placebo		Candesartan cilexetil		Enalapril		Total	
Headache	2.3%	1/44	2.5%	2/80	4.9%	4/81	3.4%	7/205
Epigastric pain epigastralgias	2.3%	1/44	1.3%	1/80	2.5%	2/81	2.0%	4/205
Influenza-like symptoms	2.3%	1/44	1.3%	1/80	1.2%	1/81	1.5%	3/205
Anxiety			3.8%	3/80			1.5%	3/205
Coughing					3.7%	3/81	1.5%	3/205
Dizziness					2.5%	2/81	1.0%	2/205
Forehead headache	2.3%	1/44			1.2%	1/81	1.0%	2/205
γ-GTP increased					2.5%	2/81	1.0%	2/205
Rhinitis			1.3%	1/80	1.2%	1/81	1.0%	2/205
Thrombocytopenia			1.3%	1/80	1.2%	1/81	1.0%	2/205
Total of patients affected by at least one AE (incl. those not given above)	15.9%	7/44	11.3%	9/80	23.5%	19/81	17.1%	35/205

Comments:

Again the efficacy of the actives versus placebo and no difference between actives were demonstrated. However, dose doubling did not seem to add to benefit, though the design is not adequate to assess this definitively.

APPEARS THIS WAY
ON ORIGINAL

6.9 Study AM116 (Dr. Caras)

01. Study AM116

01.1. Title	Evaluation of the Safety and Comparative Efficacy of Candesartan Cilexetil. Force Titrated from 8 mg Once Daily to 16 mg Once Daily or 8 mg BID. in the Treatment of Patients with Hypertension: A Multicenter, Randomized, Double-Blind, Placebo Controlled, Parallel-Design Study with an Open-Label Extension
..2. Source documents	Study report: 1.108 - 1.120; CANDA
01.3. Investigators	Multi-center study (22 sites initiated; 21 sites recruited subjects)
01.4. Study dates	21 February 1996 - 20 September 1996
01.5. Study design	This study description was based upon the protocol dated November 21, 1995. The original protocol was revised March 29, 1996 one month after enrollment of the first subject. Notable changes include (1) an increase in the number of subjects from 300 - 375; (2) Exclusion of subjects with sitting SBP > 210 mmHg.

This is a randomized, double-blind, parallel group study in subjects with mild to moderate hypertension (95< SeDBP <109 mmHg and SeSBP s 210 mm Hg) Figure 1 below shows a schematic of this trial. After a single blind four week lead-in period, eligible subjects were randomized to either 8 mg Candesartan qd or placebo. After four weeks, all Candesartan subjects had their dose increased to either 8 mg BID or 16 mg per day. The intent was to randomize approximately 125 subjects equally among the treatment groups for a total of 375 subjects. Subjects completing the double-blind period were offered to participate in an open-label study with hydrochlorothiazide.

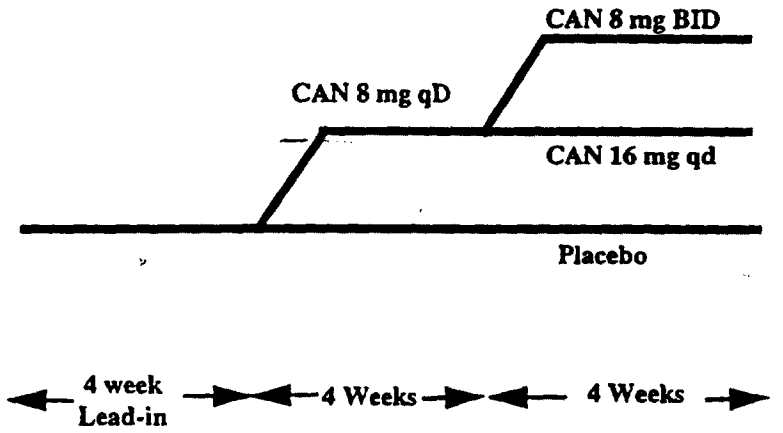


Figure 1.Study Design

Drug supplies are shown in Table 1 below.

Table 1. Drug supplies (Study AM116).

Dose	Lot
Placebo	H1156-01-01-07
Candesartan 8 mg	H1157-01-01-03

The subjects were taken from a healthy non-obese population aged over 18 years. Subjects must have a diagnosis of uncomplicated, mild to moderate essential or untreated hypertension limited to WHO Stage 1 or 2 (no evidence of end organ damage except for mild fundoscopic changes). Subject with significant renovasular, cardiovascular, diabetes, CHF or collagen-vascular, renal or cerebrovascular disease or abnormal laboratory values (with exception of mild increases in serum creatinine and urine protein) prior to randomization were excluded. Subjects must be able to wean antihypertensives and other vasoactive agents.

The subjects will be examined biweekly during the double-blind phase. Office based seated and standing blood pressure measurements will be made at that time. Peak measurements (approximately 6 hours after ingestion) will be performed at Weeks 2 and 8.

In addition, ABPM will be performed on selected subjects at Week 3 of the run-in, Week 8 of the double-blind and Week 52 of the open-label periods.

The primary efficacy variable in this study was the change in trough SeDBP from baseline (last single-blind placebo visit) to week 12 of ·ible-blind treatment. Secondary endpoints are as follows: (1) comparison of seated and sitting blood pressure at all double-blind visits; comparison of ABPM measurements for each treatment group; (3) Safety and tolerability of candesartan.

The data sets used for the primary and secondary analysis were intent-to-treat(primary data set) and one which excludes protocol violations (secondary data set). Statistical significance was determined by analysis of covariance using baseline and center as covariates.

Safety assessments were done both in the single and double blinded period. Tests included were (1) ECG; (2) Laboratory tests (CBC, SMA20, urinalysis). Clinical adverse events and its relationship to the study drug were recorded.

e were 232 subjects enrolled. Disposition of enrolled subjects is shown in Table 2 below.

Table 2. Subject Disposition

Subject Disposition	Number
Enrolled	391
Not Randomized	113
Randomized	278
Discontinued	22*
Completed Week 12	256

Table 3 below gives the reasons for discontinuations from study medication in the double-blind period.

There were eighteen randomized subjects who had protocol violations which would effect all efficacy measurements and six subjects that would affect efficacy measurements at Week 12. These were excluded from the secondary data set but were included in the primary (ITT) data set.

Demographics of the two treatment groups are shown in Table 4 below.

There was no statistical relationship between baseline seated blood pressure (at last visit before randomization) or heart rate for any of the treatment groups (see Table 5 below).

Compliance was >95% for candesartan 16mg qd and 8 mg BID.

Table 3. Reasons for Discontinuations

	Placebo	CAN 8 mg BID	CAN 16 mg qd
Total Randomized	92	94	91
Total Discontinued	11	5	5
Adverse Event	5	3	2
Lost to Follow-up	0	1	1
Subject Request	2	1	1
Sponsor/Investigator Decision	1	0	1
Lack of Response	3	0	0
Subject Completed	81	89	86

Table 4. Demographics of the Treatment Groups

Subject		Placebo	8 mg BID	16 mg qd
Gender	Male N(%)	55(60)	57(60)	56(61)
	Female N(%)	37(40)	37(40)	35(39)
Race	Non-Black N(%)	72(78)	71(75)	72(79)
	Black(%)	20(22)	23(25)	19(21)
Elderly	< 65 years N(%)	75(82)	77(82)	71(78)
	≥ 65 years N(%)	17(18)	17(18)	20(22)
Age	Mean (SD)	53(11)	53(12)	54(11)

Table 5. Seated and Standing Baseline Blood Pressure among Treatment groups.

Blood Pressure (mmHg)	Subjects		
	Placebo	8 mg BID	16 mg qd
SeDBP; Mean(SD)	100(3)	100(4)	100(4)
SeSBP; Mean (SD)	153(15)	152(14)	151(14)
SeDBP Group			
< 104 mm Hg; N(%)	78(84)	76(80)	71(78)
≥ 104 mm Hg; N(%)	14(16)	18(20)	20(22)
StDBP; Mean(SD)	101(5)	101(5)	101(5)
StSBP; Mean (SD)	152(15)	152(15)	150(15)
Peak Blood Pressure			
SeDBP; Mean (SD)	97(6)	98(6)	97(6)
SeSBP; Mean (SD)	151(16)	151(14)	148(13)
StDBP; Mean(SD)	99(7)	99(6)	98(6)
StSBP; Mean (SD)	151(16)	150(16)	148(14)

Trough seated and standing blood pressure during the double-blind phase using the intent to treat data set is shown in Figure 2 below.

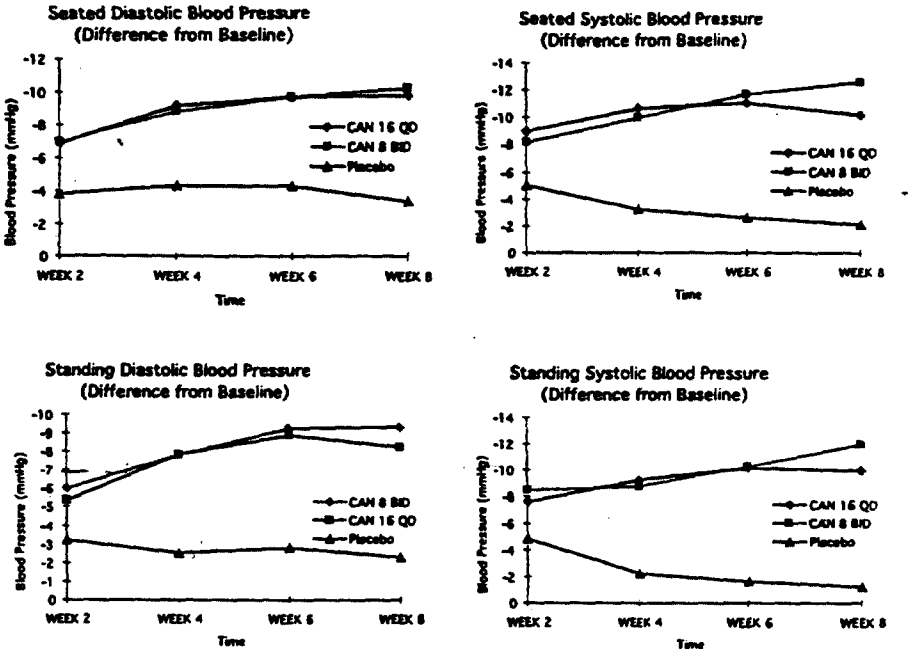


Figure 2.Seated and Diastolic Blood Pressure versus Time

Changes from baseline for peak pressures is given in Figure 3 below.

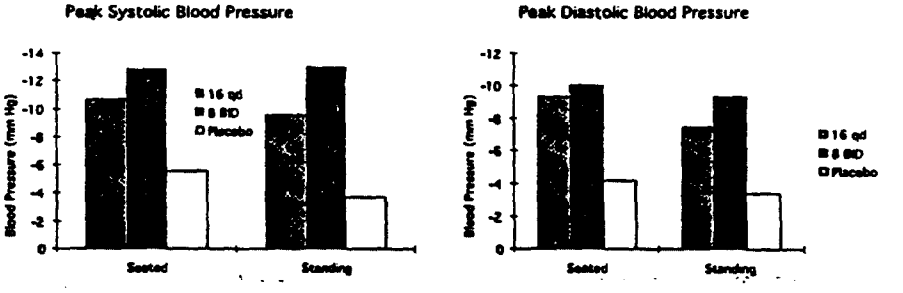


Figure 3.Peak Pressure Change from Baseline (Week 8)

APPEARS THIS WAY
ON ORIGINAL