

Baseline diastolic ABPM data shows an increased blood pressure during the day with candesartan 8 BID compared to placebo or 16 qd. (see Figure 4 below).

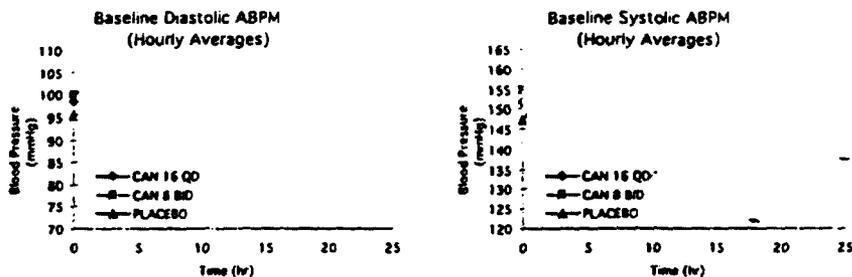


Figure 4. Baseline ABPM

Week 8 ABPM data is shown in Figure 5 below.

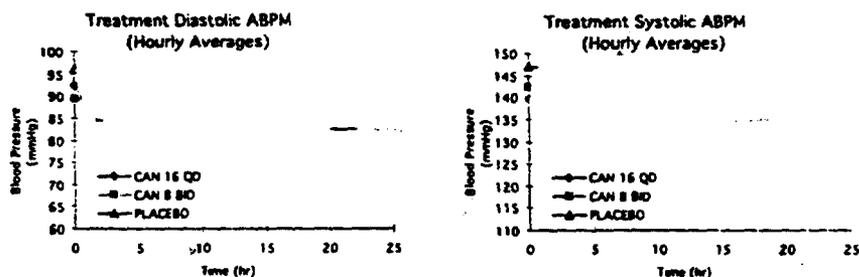


Figure 5. Week 8 ABPM

ough SeDBP mean change showed no significant difference between male and female subjects.

rough SeDBP mean change showed similar response (within 3 mm Hg) of seated diastolic blood pressures between subjects aged <65 and >65 and with respect to black and non-black subjects

A summary table of therapeutic response is shown in Table 6 below

Table 6. Therapeutic Response of Irbesartan

Variable	Placebo	Can 8 mg BID	CAN 16 mg qD
Normalized* N(%)	23(26)	47(52)	42(49)
Total Responders** N(%)			
All Subjects	24(27)	55(61)	49(58)
Baseline SeDBP >104	0(0)	8(9)	8(9)
* SeDBP < 90 mm Hg			
** SeDBP < 90 mm Hg or > 10 mm Hg drop from baseline			

There was no statistically significant difference between candesartan 8 mg BID and 16 qd at Week 8.

There was a mean exposure of the study drug of approximately 56 days with a range of 11 to 76 days. The mean exposure time of the study groups were within two days of the mean.

There were two deaths during the double-blind phase, both occurred in the placebo group. Subject 005/031 was a non-black male with a history of diabetes, hypertension and MI, who experienced severe chest pain, collapsed and died. Subject 006/001 was a 65 non black male with moderate alcohol use who died suddenly. In both cases, no autopsy was performed.

There was one death (Subject 004/010) presumably after the subject completed the trial. According the case report forms provided, the subject complained of fatigue and had experienced weight loss during the double-blind phase. The subject entered openlabel candesartan at the same

dose. The subject was hospitalized for pneumonia two months after double blind completion. The subject was found to be HIV positive and broncheolar ravage revealed Pneumocystis carinni and CMV. Despite maximal treatment, the subject expired one month after hospitalization.

Table 7 below shows a listing of discontinuations after randomization. A total of ten subjects discontinued after randomization. Five were on placebo treatment. Two died and are noted above. The three others withdrew due to blurred vision, lung cancer and congenital hydrocele.

**Table 7. Discontinuations due to Adverse Events after Randomization on Candesartan**

Site/Subject	Dose (mg)	Days on Drug	Adverse Event
003/011	8 mg	15	Vasospasm, tachycardia, HTN, fever
014/020	8 mg	18	Chest pain, dizziness, headache
016/013	8 mg	0	light headed
005/001	16 mg	13	headache, HTN
016/009	16 mg	39	Dizziness; HTN, Pre-syncope, Transient ischemic attack

There were two serious adverse events in candesartan subjects who did not withdraw from the trial. One subject (022/014) with a history of asthmatic bronchitis contracted pneumonia and was hospitalized. The other subject (003/006) complained of dizziness and was noticed to have unstable gait. Her blood pressure at that time was 182/62. The subject was admitted to the hospital for evaluation. CT scan of the brain was normal. Angiography revealed 60% occlusion of both internal carotids, with a decrease in flow of the left cerebral artery. At discharge, her gait was stable with a blood pressure of 154/90. The presumptive diagnosis at discharge vertebral-basilar insufficiency.

Treatment-emergent adverse events will be discussed as a group in the Integrated Summary of Safety. The most common treatment-emergent adverse events (> 3%) associated with either placebo or candesartan were (1) headache; (2) dizziness; (3) light-headedness; (3) upper respiratory/sinus infection; (4) sore throat; (5) coughing; (6) fatigue/tiredness; (7) peripheral edema; (8) diarrhea/nausea/vomiting; (9) rash; (10) QT prolongation. Of note, QT prolongation was 3.3% and 1.1% in the placebo and candesartan groups respectively.

There were no statistically significant mean changes from baseline for any of the clinical laboratories. All baseline and treatment means were within the normal range. A full analysis of clinical laboratories will be noted in the Integrated Summary of Safety. Mean changes in baseline laboratories which appear dose related include (1) BUN; (2) Glucose; (3) AST; (4) ALT; (5) GGT.

Three significant elevation in creatine kinase were reported in the candesartan group. The elevations were approximately 1.5 - 2 times baseline (range 135-191 IU/cc) at Week 8 (range 315-377 IU/cc). With follow-up, the creatine kinase normalized (range 107-203 IU/cc). There were a small number of subjects with similar findings who were not recorded as adverse events.

No significant changes in physical exam or ECG were noted.

### 03.1 Summary

The current study demonstrates that there is no statistical difference between 8 mg BID candesartan and 16 mg qd. This is based on the power to detect a 5 mm Hg change from baseline of trough SeDBP. The office measurements all show a <1-4 mm Hg advantage to BID dosing. The response rate is also slightly increased in the BID group. A preference to BID dosing cannot be ruled out but is probably less than 5 mm Hg at this dose. Depending on the pharmacodynamic/ pharmacokinetic relationship of dose response, it is possible that another dose could favor BID more significantly.

The protocol amendments did not affect the results of the double - blind period

The deaths reported were obviously not related to study drug.

There will be a full safety analysis in the integrated summary of safety.

Comments (Stephen Fredd, M.D.)

Two primary purposes of this study were stated:

1. Is there a difference in efficacy when CC is dosed once daily compared to twice daily?
2. Is there a difference between CC 16 mg Q.D. or 8 mg B.I.D. and placebo?

Referring back to the study design on the first page of Dr. Caras' review, I would add that randomization to Q.D. or B.I.D. dosing was done after the 4 week lead-in and before CC 8 mg Q.D. was begun. Table 5 baseline in that review is not at the time 16 mg dosing either Q.D. or in divided doses was begun. The DBP "baselines" after the 4 week lead in (randomization) and DB visit 4 when Q.D. or B.I.D. dosing was started and results from the DB4 to DB8 periods can be assessed from the following chart.

**Trough Sitting Diastolic Blood Pressure (mmHg) by Treatment and Visit  
(ITT/LOCF Population)**

Treatment		Baseline	DB 2	DB 4	DB 6	DB 8
Placebo	N	91	90	85	82	91
	Mean	99.9	96.0	95.1	95.2	96.6
	SD	3.4	7.4	7.1	7.9	9.4
CC 8 mg b.i.d.	N	93	91	89	89	93
	Mean	99.8	92.4	90.8	90.0	90.1
	SD	4.0	8.3	8.0	8.9	9.6
CC 16 mg q.d.	N	90	88	86	84	90
	Mean	100.2	93.0	90.9	90.3	90.9
	SD	3.9	7.0	7.9	7.6	8.9

The major change in all groups occurred from baseline to DB4. There is little change after this. One might conclude that 8 mg of Candesartan cilexetil was superior to placebo, but there is no evidence that forced dose doubling did any good beyond that for DBP. Also the design seems less than optimal to test the question of whether Q.D. dosing is different than B.I.D. dosing. It seems unhelpful to be on the plateau of dose response. It is not clear why an initial treatment period for both active groups was needed. Without that 8mg Q.D. phase the questions might have been more effectively been addressed, and randomization just prior to the Q.D. and B.I.D. assignments would have been feasible.

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- 01.1. Title Evaluation of the Safety and Efficacy of Candesartan Cilexetil in the Treatment of Patients with Hypertension: A Multicenter, Randomized, Double-Blind, Placebo Controlled Dose Escalation Study.
- 01.2. Source documents Study report: Volumes 1.82-1.92; (Astra Pages 08-21-261 to 08-32-37).
- 01.3. Investigators Multi-center study (11 centers).
- 01.4. Study dates April 22, 1996 - November 5, 1996
- 01.5. Study design This study description was based upon the protocol dated January 24, 1996. Revisions of the original protocol were made prior to entry of the first subject.

This is a randomized, double-blind, placebo-controlled dose escalation study in subjects with mild to moderate hypertension (95 < SeDBP < 114 mmHg and SeSBP < 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 8 mg per day of candesartan or placebo in a 2:1 ratio. Every two weeks, the subject's dose was doubled to a final dose of 64 mg per day. The intent was to randomize approximately 210 subjects.

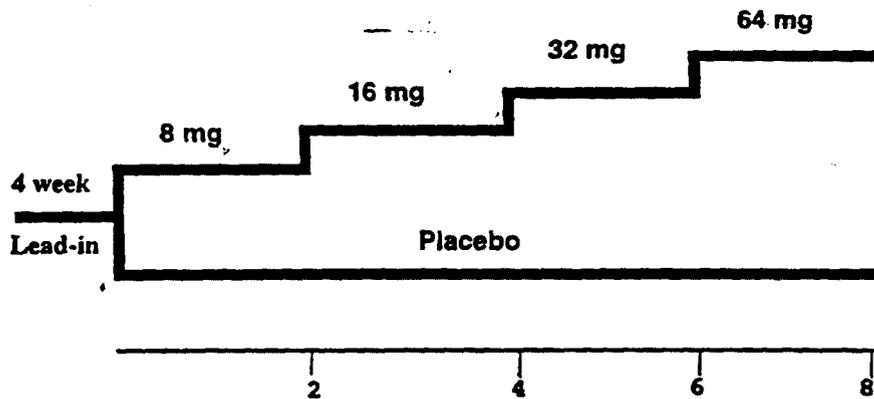


Figure 1. Study design (AM 119).

Drug supplies are shown in Table 1 below.

Table 1. Drug supplies (AM 119).

Dose	Lot
Placebo 8 mg	H1210-01-01-01
Placebo 16 mg	H1203-02-01-01 H1203-02-01-02
Candesartan 8 mg	H1156-02-01-01
Candesartan 16 mg	H1191-01-01-01

The subjects were taken from a hypertensive population aged over 18 years. Subjects must have a diagnosis of uncomplicated, mild to moderate essential or untreated hypertension. Subjects who had any condition in the opinion of the investigator may interfere with the participation of the study or potentially produce a risk to the subject were excluded. NSAIDs greater than 3 times per week (low dose ASA excepted) is allowed. Subjects must be able to wean antihypertensives and other vasoactive agents.

In addition to measurement of seated and standing blood pressures, blood for candasartan determinations at trough, trough+1+ hours and trough+ 8-20 hours were drawn at each two week visit.

The primary efficacy variable in this study was the change in trough SeDBP from baseline (last single blind placebo reading) to Week 8 of double-blind treatment. Secondary endpoints are as follows: (1) Trough SeDBP, SeSBP, StDBP and StSBP at 2, 4, 6 and 8 weeks. (2) Safety and tolerability of candasartan for 8 weeks; (3) Population pharmacokinetics and pharmacodynamics.

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.

There were 204 subjects enrolled. Disposition of enrolled subjects is shown in Table 2 below.

**Table 2. Subject Disposition**

Subject Disposition	Number
Enrolled	204
Not Randomized	71
Randomized	133
Discontinued	6
Completed Week 8	127

Reasons for not randomizing subjects was not given in the study report.

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

**Table 3. Reasons for Discontinuations**

	Candasartan	Placebo
Total Randomized	93	40
Total Discontinued	3	3
Adverse Event	1	0
Lost to Follow-up	1	1
Subject Request	1	1
Lack of Response	0	1
Subject Completed	90	37

There were nine randomized subjects who had protocol violations which would effect all efficacy measurements. 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.

**Table 4. Demographics of the Treatment Groups**

Subject		Candasartan	Placebo
Gender	Male N(%)	22(55)	46(50)
	Female N(%)	18(45)	47(50)
Race	Non-Black N(%)	67(72)	31(77)
	Black(%)	26(28)	9(23)
Elderly	< 65 years	83(89)	32(80)
	≥ 65 years	10(11)	8(20)
Age	Mean (SD)	53(10)	54(11)

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).

**Table 5. Seated Baseline Blood**

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

Measurement (mmHg or BPM)	Subjects	
	Placebo	Candasartan
SeDBP; Mean(SD)	100(4)	100(4)
SeSBP; Mean (SD)	152(14)	152(13)
SeDBP Group		
< 104 mm Hg; N(%)	32(80)	80(86)
≥ 104 mm Hg; N(%)	8(20)	13(14)
StDBP; Mean(SE)	100(4)	100(4)
StSBP; Mean (SE)	151(13)	151(13)

Trough seated and standing blood pressure using the intent to treat data set is given in Figure 2 below. DELTA is the difference between Candasartan and placebo. In this forced titration model, all blood pressures on Candasartan were statistically significant against placebo. However, the difference between Week 8 (corresponding to 2 weeks on 64 ma) and Week 2 (corresponding to 2 weeks on 8 ma) showed no statistical significance. A statistical review of the dose response relationships (if any) in this trial and AM I 13 are given in the Appendix .

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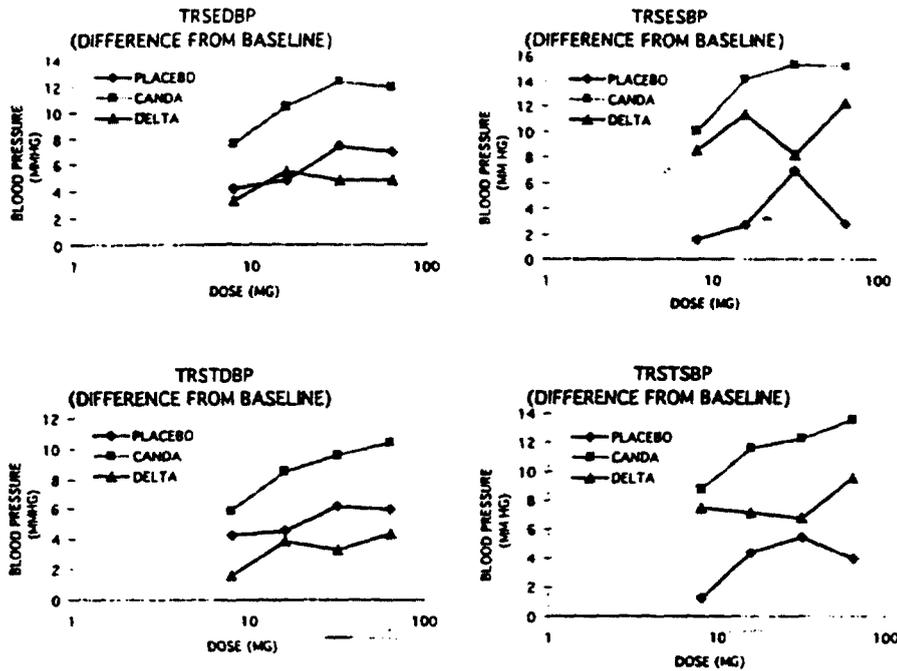


Figure 2. Dose Response of Trough Pressures

Peak blood pressure at 8 weeks are given in Figure 3 below.

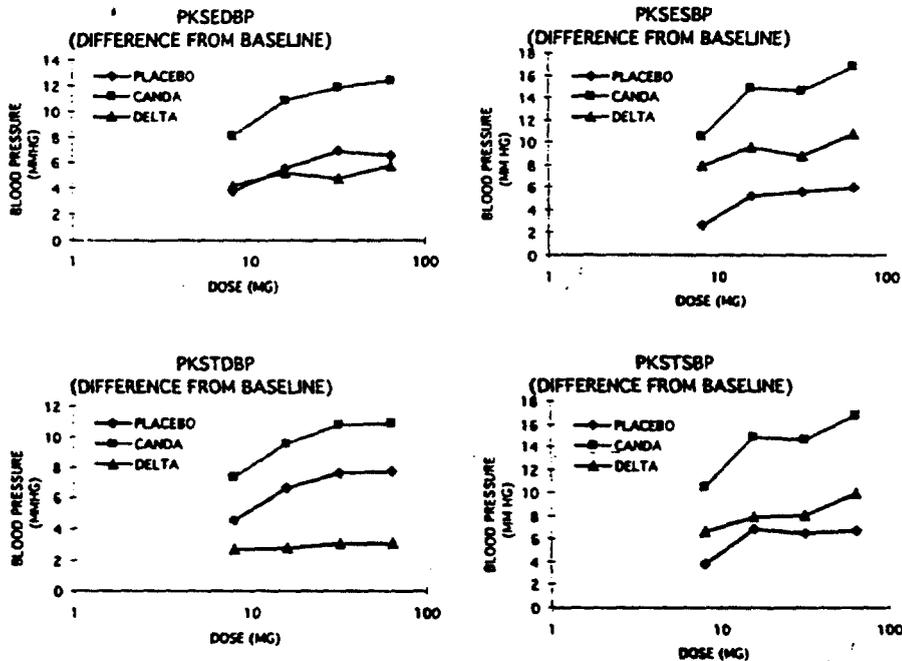


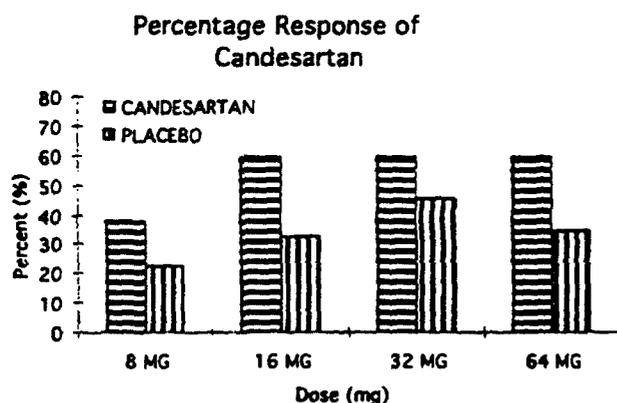
Figure 3. Dose Response of Peak Pressures

Trough SeDBP mean change on candesartan from baseline at Week 8 in non-black and black subjects was -14 and -7 mmHg (not placebo subtracted) respectively. There was near statistical significance ( $p=0.054$ ) between black and non-black subjects. Weeks 2, 4, 6 and 8 showed no statistical significance ( $p>0.1$ ) though there was a qualitative magnitude difference. There was no statistical difference between the placebo group at any week.

Trough SeDBP mean change on candesartan at Week 8 showed no significant difference (-8 and -11 mmHg respectively) between male and female subjects. No statistical effect on gender with candesartan for any week. There was a statistically significant change in mean blood pressure on the basis of sex (-12 males and -7 females) for Week 8.

Trough SeDBP mean change at Week 8 in non-elderly (<65) and elderly (>65) was - 12 and 9 mmHg respectively. There was statistically significant difference between the two groups at any Week.

A summary of therapeutic response of trough SeDBP is shown in Figure 4 below. Therapeutic response is defined as a change in baseline of -10 mmHg or SeDBP <90 mm Hg.



**Figure 4. Response of Candesartan versus Placebo**

There was a mean exposure of the study drug of approximately 56 days.

There were no deaths or serious adverse events during the double-blind period of the study.

There was only one subject (009/004) on candesartan who withdrew during the double-blind period after experiencing episodes of dizziness and headaches between 14 and 19 days of treatment.

There were five additional dropouts. Three were on placebo treatment. One candesartan subject (008/007) was lost to follow-up. No adverse events were noted. The other subject (011/14) withdrew consent. That subject had symptoms of mach ache, headache and neck pain reported at the Week 2 visit. These symptoms resolved during candesartan treatment.

Treatment-emergent adverse events will be discussed as a group in the Integrated Summary of Safety. The most common treatment-emergent adverse events (> 3%) associated were headache, dizziness, light headed, pain, inflicted injury, sore throat, back pain, diaphoresis and joint pain.

Mean changes from baseline for laboratory (clinical chemistry and hematology) for candesartan showed no significant change compared to placebo, except for creatine kinase (Mean change from baseline .8 IU/L placebo: 44 IU/L candesartan).

Significant creatine kinase elevation was reported in one candesartan subject (009/017). The baseline value was 267 IU/L and increased to 1962 IU/L at Week 8. Final follow-up value two weeks later was 287 IU/L. No symptoms were reported on the case report form.

No significant changes in physical exam or ECG were noted.

The current study shows that candesartan decreases blood pressure versus placebo.

In the forced titration scheme, the response is a function of dose and time. This is compared to a single parallel group design where time is the only variable. If the steady state response within two weeks then the trial becomes, if adequately powered a dose response curve. If not, separation of dose and time effects is crucial in determining the dose response relationship.

This trial shows no statistical difference between baseline subtracted candesartan at 8 mg visors 64 ma. This can be observed qualitatively in the Figures above. It is hard to believe any dose response relationship exists based on this trial alone.

In short, this trial was woefully underpowered to show any differences between the groups. This may be in part due to the forced titration scheme selected.

Other studies reviewed so far have shown no clear dose response. The dose response may be ascertained by combining appropriate clinical trials.

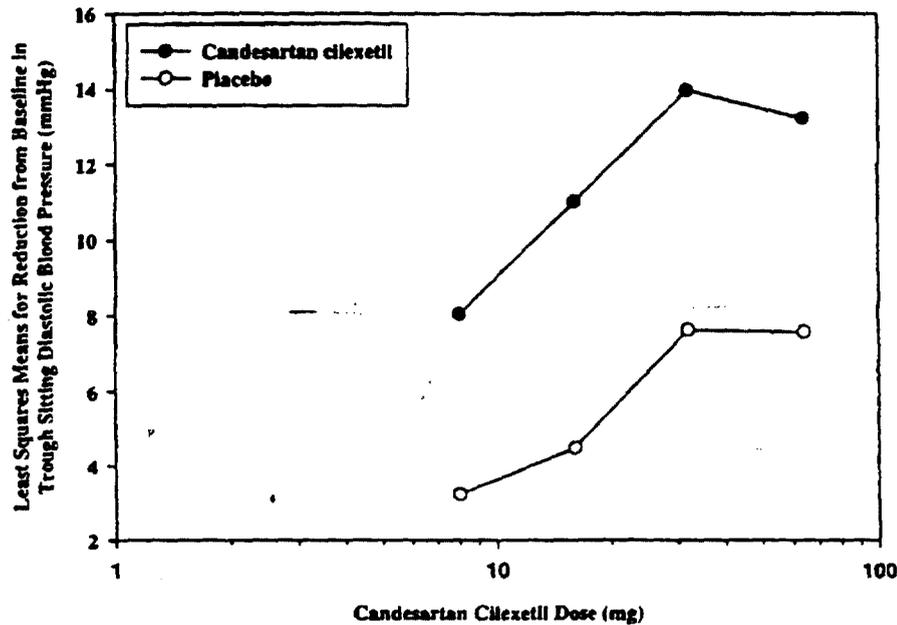
The near significance of SeDBP differences between black and non-black subjects has been observed in other antihypertensive trials with drugs affecting the angiotensin axis. This result may be tempered depending on the forced titration scheme as discussed in previous paragraphs.

There will be a full safety analysis in the integrated summary of safety.

Stephen Caras MD PhD

Comments (Stephen Fredd, M.D.)

The sponsor has claimed a dose response for CC as per the following:



As Dr. Caras states, with placebo subtraction one cannot discern a dose response on DBP. The data as per the sponsor were:

**Trough Sitting Diastolic Blood Pressure (mmHg) by Treatment and Visit (ITT/LOCF Population)**

Treatment		Baseline	DB 2	DB 4	DB 6	DB 8
Placebo	N	39	37	37	37	39
	Mean	100.1	95.4	94.7	92.1	93.0
	SD	4.3	7.1	7.3	6.9	7.5
			(CC 8 mg)	(CC 16 mg)	(CC 32 mg)	(CC 64 mg)
CC	N	92	91	90	90	92
	Mean	100.2	92.5	89.8	87.9	88.3
	SD	4.2	7.6	8.1	10.0	10.3

While one can conclude (again) that 8 mg of CC is statistically superior to placebo, it does not appear from this that increasing dose gets more response.

andomized DB study with the following arms would be of interest: placebo, 8mg, 64mg, Forced titration 8-64mg. Study might be sized to show 5 mm Hg difference on sitting DBP between 64 and 8mg, and the duration of the controlled study could be 16 weeks.

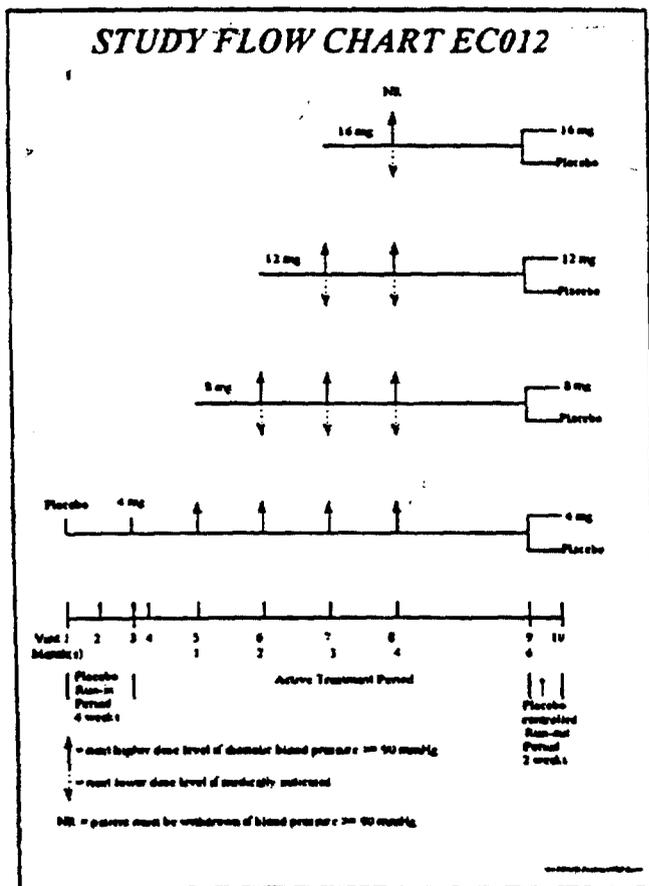
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**6.11 Study EC012 - Long term (6 months) safety and efficacy of Candesartan cilexetil in patients with mild to moderate essential hypertension (SDBP 95-109) with 2 week placebo controlled run-out phase.**

Starting Date: August 1994  
 Completion Date: September 1995  
 Multicenter (65) study in the U.K.  
 Principal Investigator: Dr. Peter Sever, London.  
 Drug and placebo manufactured

The study had 3 phases; first, a 4 week placebo run-in, then a 6 month open label uncontrolled dose titration (4-16 mg) once daily depending on results, and finally a two week double blind randomized placebo-controlled run out. A planned study population of 400 was chosen, not on a statistical basis: 489 entered the placebo phase, 388 were eligible for the dose-titration phase, and 277 completed the randomized, placebo controlled withdrawal phase.

The flow chart for the study was:



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Males and females 18 years of age and older with SDBP of 95-109 could enter, but females if of child-bearing potential had to use adequate contraception. Severe or malignant hypertension, renal, cardiac, GI, or metabolic diseases could lead to exclusion if severe.

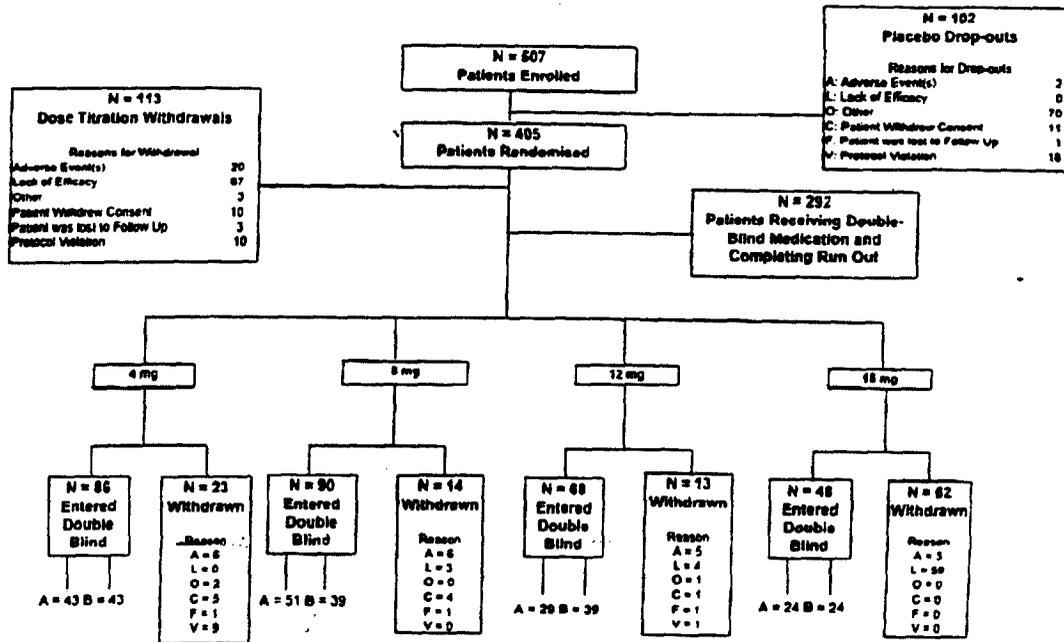
To advance the dose titration phase patients had to have had SDBP at each visit of the placebo phase between 95-109 mm Hg and SBP of no more than 179 mm Hg. During the dose titration, all started on 4 mg, but, if not normalized (DBP < 90 mm Hg) after 1 month, the dose was increased by 4 mg.

For those finishing the dose titration period, a computer generated sequence was used. "Each of the participating centres were asked to include at least 6 and no more than 18 patients in the active treatment period." Randomization for the withdrawal phase was done prior to the dose titration phase. The following populations were to be analyzed.

- |                            |   |
|----------------------------|---|
| Placebo run-in period:     | Safety: All patients enrolled   |
| Longterm treatment period: | Safety: All patients with intake of at least one dose of candesartan cilexetil  |
|                            | Efficacy (ITT): As for safety <u>and</u> availability of baseline (Visit 3) and at least one post-baseline diastolic blood pressure value |
|                            | Efficacy (PP): As for ITT <u>and</u> absence of major protocol violations   |
| Final double-blind period: | Safety: All patients with intake of at least one dose of candesartan cilexetil or placebo after randomization                             |
|                            | Efficacy (ITT): As for safety <u>and</u> availability of diastolic blood pressure values at Visits 9 and 10                               |
|                            | Efficacy (PP): As for ITT <u>and</u> absence of major protocol violations   |

For the double-blind withdrawal phase it was estimated that 151 patients per treatment group was need to demonstrate a 3 mm Hg difference between the CC group and placebo with a 90% probability. Dispostion of patients throughout the study was:

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NOTE: This figure includes 18 patients who were enrolled at the centre which was excluded from the analysis. One patient of the 405 randomised, (patient 33/0072) received 20 mg TCY-116. He was withdrawn at visit 8, due to lack of efficacy. A = Placebo, B = TCY-116

The text clarifies this somewhat confusing chart. 18 patients from one center with questionable data were excluded. 489 patients were enrolled into the dose titration period. The smaller number (405) for patients randomized may have been due to the limitation on number of patients per center. Of the 489 enrolled at the placebo phase, 101 were withdrawn. 388 continued into the dose titration phase. These 389 were called the safety population. Of these, 111 were withdrawn, leaving 277 for the withdrawal phase.

The demographics of those entering the dose titration phase were:

	Treatment Group*	N					
		4mg	8mg	12mg	18mg	LOE	Placebo
Age (years)	18-29	0	0	0	0	0	0
	30-39	15	22	12	0	11	89
	40-49	12	22	12	0	9	66
	50-59	23	12	12	13	10	71
	60-64	20	13	11	10	10	64
	65-69	22	5	11	7	11	64
	70-79	10	13	8	3	7	63
	>= 80	-	2	-	-	-	1
	n	104	96	71	47	67	385
	Mean	66	64.9	67.1	66	67.6	64.8
	Median	67	64	67	66	67	66
St. Dev.	10.9	11.7	9.8	8.6	11.6	10.8	
Min							
Max							
Sex	Male	60	52	41	28	30	237
	Female	44	44	30	19	37	148
Race	Caucasian	103	93	71	44	55	378
	Hispanic	-	-	-	-	1	1
	Oriental	1	3	-	1	1	6
Weight (kg)**	n	104	96	71	47	67	385
	Mean	70.7	68.3	70.5	63.2	64	68.6
	Median	72	70.5	70	62	65.4	70.9
	St. Dev.	14.9	14.7	15.3	11.0	10.7	14.0
	Min						
	Max						
Weight (cm)	n	104	96	71	47	67	385
	Mean	165.8	168.4	168.2	169.5	168.4	168
	Median	167.0	169.5	166.4	167	170	169
	St. Dev.	6.8	10.3	9.3	9.4	9.6	9.4
	Min						
	Max						

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LOE meant lack of efficacy prior to or at the end of the dose titration phase.

For the withdrawal phase, demographics were:

		Treatment Group*			
		Placebo	TCV-116	Total	
Age (years)	18-29	2	1	3	
	30-39	9	25	34	
	40-49	30	24	54	
	50-54	27	23	50	
	55-59	26	28	54	
	60-64	24	24	48	
	65-69	8	13	21	
	70-79	18	10	28	
	≥ 80	-	2	2	
	N		140	137	277
	Mean		55.7	55	55.4
Median		55.5	56	56	
St.Dev.		10.4	10.6	10.5	
Min					
Max					
Sex	Male	85	77	162	
	Female	55	60	115	
Race	Caucasian	139	135	274	
	Oriental	2	2	4	
Weight (kg)**	N	140	137	277	
	Mean	80.1	80.3	80.2	
	Median	79.4	79	79	
	St.Dev.	14.1	15	14.6	
	Min				
	Max				
Height (cm)	N	140	137	277	
	Mean	168.8	167.7	168.1	
	Median	169.6	167.6	168	
	St.Dev.	9.6	9.4	9.5	
	Min				
	Max				

During the dose titration the following doses of CC were given:

Regimen (V4, V5, V6, V7, V8, V9)	N
4. . . . .	3
4. 4. . . .	6
4. 4. 4. . .	1
4. 4. 4. 4. .	1
4. 4. 4. 4. 4. .	5
4. 4. 4. 4. 4. 4.	83
4. 4. 4. 4. 8. 8	6
4. 4. 4. 8. 8. .	1
4. 4. 4. 8. 8. 8	4
4. 4. 4. 8. 12. .	1
4. 4. 4. 8. 12. 12	3
4. 4. 8. 4. 4. 4	2
4. 4. 8. 8. 8. .	1
4. 4. 8. 8. 8. 8	19
4. 4. 8. 8. 12. 12	5
4. 4. 8. 12. . . .	1
4. 4. 8. 12. 12. 12	12
4. 4. 8. 12. 16. 16	4
4. 8. . . . .	4
4. 8. 4. 4. . . .	1
4. 8. 4. 4. 4. 4	1
4. 8. 8. . . . .	5
4. 8. 8. 8. 8. 8	57
4. 8. 8. 8. 12. 12	8
4. 8. 8. 12. 12. 12	7
4. 8. 8. 12. 16. .	1
4. 8. 8. 12. 16. 16	1
4. 8. 12. . . . .	2
4. 8. 12. 8. 8. 8	1
4. 8. 12. 12. . . .	5
4. 8. 12. 12. 12. 12	29
4. 8. 12. 12. 16. 16	12
4. 8. 12. 16. . . .	2
4. 8. 12. 16. 12. 12	1
4. 8. 12. 16. 16. .	52
4. 8. 12. 16. 16. 16	33
4. 8. 12. 16. 20. .	1
4. 12. 12. 12. 16. 16	1
8. 8. 8. 8. 8. 8	1
<b>Total</b>	<b>384</b>

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The 384 patients noted here are less than the 388 who were said to have completed the dose titration phase.

Other antihypertensive medications given during dose titration were:

ANTIHYPERTENSIVE MEDICATION CLASS	Treatment Group*										TOTAL	
	Long		Long		Short		Long		LOC		Number of patients	Number of reports
	Number of patients	Number of reports										
Total number of Patients	107	--	96	--	71	--	67	--	67	--	388	--
Antihypertensive Medication Yes	36	--	40	--	30	--	34	--	32	--	202	--
Antihypertensive Medication No	57	--	46	--	37	--	33	--	35	--	186	--
ANTIADRENERGIC AGENTS, CENTRALLY AC	2	--	1	1	--	--	2	2	1	1	1	3
ANTIADRENERGIC AGENTS, PERIPHERALLY	--	--	1	1	--	--	--	--	1	1	6	6
ANTIHYPERTENSIVES AND DRUGS IN	--	--	1	1	--	--	4	4	--	--	1	2
ARTERIAL SMOOTH MUSCLE AGENTS AC	17	17	9	9	10	11	17	18	8	8	67	68
BETA BLOCKING AGENTS AND OTHER DIUR	--	--	1	1	1	1	1	4	4	4	7	7
BETA BLOCKING AGENTS AND THIAZIDES	1	1	2	2	--	--	--	--	--	--	3	3
BETA BLOCKING AGENTS, BETA1	13	13	10	10	15	15	7	7	11	11	51	51
BETA BLOCKING AGENTS, THIAZIDES AND	1	1	--	--	1	1	--	--	--	--	2	2
DIURETIC AND POTASSIUM-SPARING AG	4	4	4	4	4	6	2	2	2	2	16	18
HIGH-CEILING DIURETICS	1	1	--	--	--	--	--	--	1	1	2	2
LOW-CEILING DIURETICS, EXCL THIASID	--	--	--	--	--	--	--	--	--	--	--	1
LOW-CEILING DIURETICS, THIAZIDES	9	9	9	9	11	11	9	9	6	6	44	44
RENIN-ANGIOTENSIN SYSTEM AGENTS AC	9	10	16	16	6	8	10	13	8	8	40	40
UNCODED	--	--	--	--	--	--	--	--	1	1	1	1

Number of patients : Number of patients reporting at least one antihypertensive medication in a particular class  
 Number of reports : Number of different antihypertensive medications (WHO classes) reported.

\* Treatment refers to the dose of TCV-116 that the patient was taking at the end of the dose-titration phase or at withdrawal for reasons other than lack of efficacy. LOC indicates Lack of Efficacy withdrawal prior to or at visit 9.

## Results

### Efficacy

For the double-blind withdrawal phase, CC was found to be statistically superior to placebo.

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	Treatment Group			
	Placebo	TCV-116	Total	
Visit 9	< 80	15	13	28
	80-89	102	103	205
	90-95	18	15	33
	96-99	3	5	8
	100-103	2	1	3
	N	140	137	277
	Mean	85.8	85.6	85.7
	Median	86.7	86.7	86.7
	St.Dev.	5.7	5.8	5.7
	Min			
	Max			
Visit 10	< 80	12	14	26
	80-89	58	76	134
	90-95	24	29	53
	96-99	23	10	33
	100-103	10	6	16
	104-108	9	2	11
	109-114	4	0	4
	N	140	137	277
	Mean	81.2	87.3	89.3
	Median	89.7	87.3	88.7
	St.Dev.	8.7	7.6	8.4
Min				
Max				
Change *	Less than -20	5	1	6
	-20 to < -10	30	14	44
	-10 to < 0	66	58	124
	0 to < 10	35	55	90
	10 to < 20	4	5	13
	N	140	137	277
	Mean	-5.4	-1.7	-3.6
	Median	-4	-0.7	-2.7
	St.Dev.	7.3	7.2	7.5
	Min			
	Max			

Analysis of Covariance Results

Source	Degrees of Freedom	F	P-value
Treatment	1, 243	23.33	<0.0001
Centre	31, 243	2.28	0.0003
Visit 9 DBP	1, 243	21.29	<0.0001

\* Change = Visit 9 - Visit 10, ie. a negative change indicates that BP has increased between Visits 9 and 10.

For each CC dose compared to placebo, results were:

DOSE AT VISIT 9	PLACEBO	CANDESARTAN CILEXETIL	DIFFERENCE**	P-VALUE***
Double-Blind Completers (n=277)	5.4	1.7	3.7	<0.0001
candesartan cilexetil 4mg od (n=86)	2.8	0.3	2.5	0.1269
candesartan cilexetil 8mg od (n=85)	5.8	0.7	5.1	0.0004
candesartan cilexetil 12mg od (n=62)	5.8	3.0	2.9	0.0246
candesartan cilexetil 16mg od (n=44)	8.8	3.9	4.9	0.5091

\* Positive figures indicate increase in DBP at visit 10 compared to visit 9  
 \*\* Difference is placebo - candesartan cilexetil  
 \*\*\* P-value taken from the treatment effect in the Analysis of Covariance results

While there is considerable confusion in the writeup of this study, there appears to be a continued real treatment effect of CC compared to placebo.

### Safety

One death was reported in a 68 year old male on 12 mg of CC due to esophageal carcinoma. 111 patients withdrew from the study, 21 of these withdrew for adverse reactions as follows:

Patients withdrawn due to an adverse event or clinically significant laboratory abnormality

PATIENT NUMBER	DOSE AT ONSET OF EVENT	EVENT DESCRIPTION	SEVERITY	CAUSAL RELATIONSHIP TO CANDESARTAN CILEXETIL
05/0504	8mg	Abdominal pain	Moderate	Unknown
06/0434	4mg	Stroke	Serious	Not related
06/0437	16mg	Stroke	Serious	Not related
08/0345	4mg	Hepatic enzymes increased	Moderate	Possible
18/0090	12mg	Carcinoma of oesophagus	Serious	Not related
	12mg	Blepharitis	Mild	Not related
20/0397	8mg	Pleural effusion	Moderate	Unknown
26/0163	4mg	Arrhythmia ventricular	Severe	Unknown
28/0233	4mg	Appetite lost	Severe	Possible
	4mg	Abdominal pain	Severe	Possible
	4mg	Chest pain	Moderate	Possible
	4mg	Hepatic enzymes increased	Severe	Possible
29/0153	Placebo	Headache	Moderate	Definite
31/0408	8mg	Rash	Moderate	Probable
33/0043	12mg	Head discomfort	Mild	Probable
33/0200	8mg	Back pain	Moderate	Not related
	12mg	Bronchial carcinoma	Moderate	Not related
35/0116	Placebo	Myocardial infarction	Serious	Not related
40/1092	Placebo	Hyperthyroidism	Moderate	Not related
45/0441	8mg	Burning sensation	Moderate	Unknown
51/1244	Placebo	Indigestion	Moderate	Not related
57/0320	8mg	Dizziness	Severe	Definite
	8mg	Headache	Severe	Definite
	8mg	Nausea	Severe	Definite
59/0253	4mg	Leucopenia	Mild	Probable
60/0333	8mg	Numbness of fingers	Mild	Possible
63/0317	8mg	Faintness	Moderate	Probable
	8mg	Lower extremities weakness	Moderate	Probable
72/0302	12mg	Gastroenteritis	Moderate	Possible
	12mg	Tiredness	Moderate	Possible

Patient 434, one of the stroke patients, was a 62 year old male whose BP was controlled (sitting mean 127/84 on 4/5/95, standing mean 128/80) prior to stroke on 4/6/95. Has been on CC since 8/94.

The other stroke case, patient 437, was a 64 year old male who was withdrawn on 12/5/95. Had been titrated up to 16 mg of CC in spite of which is last BP prior to event was 169/101 (prior to entry to dose escalation phase it was 179/107).

Patient 345, a 67 year old female, had mildly abnormal LFTs on entrance (AST, ALT, GGT) which rose during the study. LDH and uric acid also became elevated. Follow up did not indicate resolution or worsening of LFTs.

Patient 233, a 57 year old female, developed chest and abdominal pains with elevated AST, ALT and GGT (all around 200 IU/L) 10 days after beginning CC therapy. Last follow up indicated a return of LFTs toward normal.

20 events were classified as serious. Some led to withdrawal, but 6 other patients completed the study. Of the 6 others, patient 344, a 55 year old male, was notable because of persistent muscle aches and weakness with elevated creatinine kinase. Rash also developed. Patient was thought to have a chronic Guillan-Barre Syndrome. Remained on the constant 4 mg dose of CC throughout the study.

Adverse events noted for more than 2% of patients during the dose titration phase were:

WHO DECODE CLASSIFICATION	DOSE OF CANDESARTAN CILEXETIL				
	4mg	8mg	12mg	16mg	All
Upper Respiratory Tract Infection	21	9	8	6	44
Headache	9	10	5	2	26
Nausea	11	3	1	-	15
Coryza	10	3	1	1	15
Back Pain	6	4	3	2	15
Bronchitis	6	5	2	1	14
Coughing	6	4	-	2	12
Influenza-like Symptoms	7	1	4	-	12
Tiredness	7	-	3	2	12
Dizziness	5	4	2	-	11
<b>TOTAL</b>	<b>88</b>	<b>43</b>	<b>29</b>	<b>16</b>	<b>176</b>

In the double-blind withdrawal phase the following adverse events were noted:

BODY SYSTEM CLASSIFICATION	NUMBER OF PATIENTS	NUMBER OF REPORTS
Body as a Whole - General Disorder	36/73 (49.3%)	43/88 (48.9%)
Resistance Mechanism Disorder	38/78 (48.7%)	43/84 (51.2%)
Gastrointestinal System Disorder	35/66 (53.0%)	47/87 (54.0%)
Central & Peripheral Nervous System	22/61 (36.1%)	26/70 (37.1%)
Respiratory System	29/63 (46.0%)	32/67 (47.8%)

### Laboratory Abnormalities

Changes triggering a phone call were noted as follows:

PARAMETER	PHONING REFERENCE	# RESULTS	# PATIENTS	# ISOLATED INCIDENTS
<b>HAEMATOLOGY</b>				
Haemoglobin	<LPR	2	1	0
WBC	<LPR	66	27	15
Platelets	<LPR	8	1	0
<b>BIOCHEMISTRY</b>				
Potassium	>UPR	25	16	10
Alkaline Phosphatase	>UPR	1	1	1
Total Bilirubin	>UPR	5	3	2
CPK	>UPR	90	40	24
Glucose	>UPR	91	35	16
Creatinine	>UPR	21	8	6
SGOT	>UPR	14	9	6
SGPT	>UPR	20	13	8

Patients withdrawn for LFTs, leucopenia were previously noted.

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Sample size for the dose titration phase was not based on statistical considerations, but at least 80 patients per group were estimated to be needed to detect a 4.1 mm Hg difference in the change of DBP from the end of the dose titration to the end of the withdrawal phase. A standard deviation of 8 mm Hg was postulated to achieve a 5% significance level with 90% power. In one protocol amendment sample size was increased from 200 to 216 patients enrolled to obtain 159 patients for the withdrawal phase.

Other protocol amendments included identification of an S (for special) group of patients who deviated from the dose titration schedule and inclusion of these patients in the data analyses.

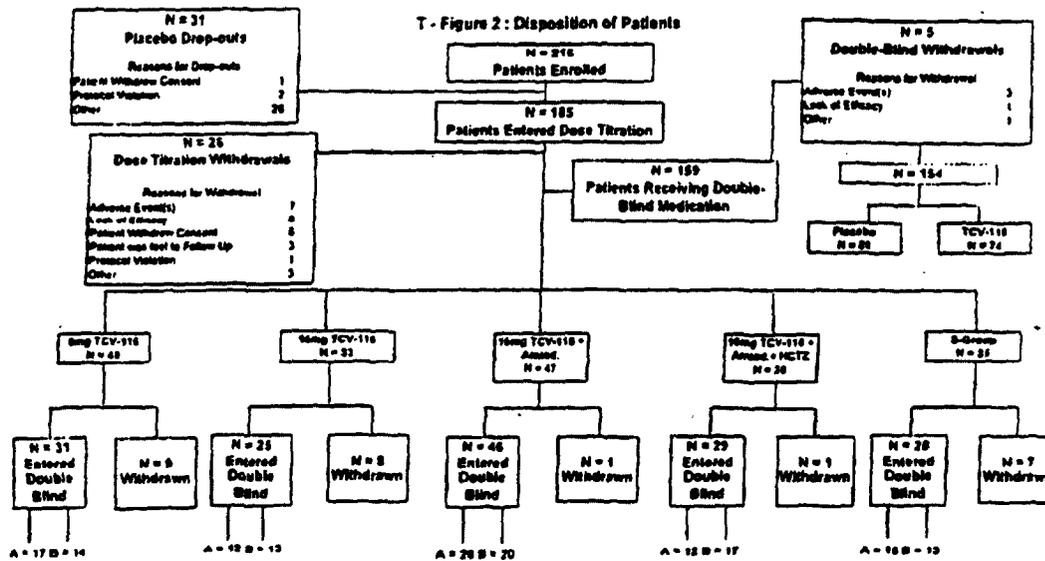
Randomization was done by a computer generated list, "using appropriate blocks," for a 1:1 assignment in the placebo controlled withdrawal phase. The randomization number was assigned to the patient at the beginning of the dose escalation phase. Each center was asked to include 20 patients in the dose escalation phase. The primary objective of the study was to assess the response rate (SDBP <95 mm Hg) in the dose escalation phase.

Secondary objectives were to assess the change in DBP and SBP between groups during the placebo controlled withdrawal phase, as well as safety throughout all phases of the study.

Populations to be analyzed were:

Placebo run-in period:	Safety:	All patients enrolled
Open treatment period:	Safety:	All patients with intake of at least one dose of candesartan cilexetil
	Efficacy (ITT):	As for safety and availability of baseline (Visit 2) and at least one post-baseline diastolic blood pressure value
Final double-blind period:	Safety:	All patients with intake of at least one dose of candesartan cilexetil or placebo after randomisation at Visit 8
	Efficacy (ITT):	As for safety and availability of diastolic blood pressure values at Visits 8 and at least one post-Visit 8 DBP value
	Efficacy (PP):	As for ITT and absence of major protocol violations
S-group:	Patients with certain diastolic blood pressure criteria at Visit 6 and/or Visit 7 could be treated at the discretion of the investigator as a special S-group rather than being excluded from the study.	
S-group Criteria:	DBP still $\geq 95$ mmHg at Visit 6. DBP $\geq 100$ mmHg at Visit 6 but DBP $< 95$ mmHg at previous visit(s). DBP $\geq 100$ mmHg at Visit 7 but DBP $< 95$ mmHg at previous visit(s).	

Subjects enrolled and their disposition was noted as follows:



Of the 159 patients who entered the double-blind phase, 82 patients were given placebo, 77 CC with additional therapy in the dose escalation phase, if needed. 5 patients withdrew for adverse events during the withdrawal phase (2 placebo, 3 CC).

The demographic data for the overall study showed that over 90% were Caucasian and 40 years of age or older (mean age 54.7). There were 130 males and 55 females in the dose titration phase. Demography for the withdrawal phase was:

		Treatment Group*		
		Placebo	TCV-116	Total
Age (years)	30-39	5	4	9
	40-49	16	18	34
	50-54	21	15	36
	55-59	21	11	32
	60-64	18	13	31
	65-69	8	9	17
	70-79	4	4	8
		N	80	74
	Mean	55.5	55.1	55.3
	Median	57	54	56
	St.Dev.	9.1	9.3	9.2
	Min			
	Max			
Sex	Male	54	54	108
	Female	26	20	46
Race	Caucasian	76	67	143
	Negroid	3	6	9
	Oriental	-	1	1
	Other	1	-	1
Weight (kg)	N	80	74	154
	Mean	83.1	80.3	81.7
	Median	80.5	78	80
	St.Dev.	15.3	14.4	14.9
	Min			
	Max			
Height (cm)	N	80	74	154
	Mean	168.9	168.1	168.5
	Median	170	168	169
	St.Dev.	10	8.3	9.2
	Min			
	Max			

\*medication allocated in withdrawal phase

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	Study Population		
	Enrolled	Dose-Titration Safety	Double-Blind Completers
<b>Total number of Patients</b>	<b>216</b>	<b>185</b>	<b>154</b>
Date of Diagnosis unknown	2	1	1
Less than 1 year	25	19	14
Approx. 1 year	12	8	7
Approx. 2 years	16	11	7
Approx. 3 years	10	9	9
Approx. 4 years	9	8	8
Approx. 5 years	14	13	12
5-10 years	50	45	38
More than 10 years	78	71	58
Mean (years)	9.3	9.7	9.6
Median (years)	6.7	7.5	6.8
St. Dev (years)	8.3	8.2	8
Min (years)			
Max (years)			

Double-blind completers were those randomized with mean SDBP values available at entrance to withdrawal phase and last scheduled visit who also did not withdraw at the last visit.

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## Results

### Withdrawal Phase

#### Change in sitting DBP (ITT excluding S group)

Visit #		Treatment Group		
		Placebo	TCV-116	All
	< 80	8	6	14
	80-89	28	34	62
	90-94	20	16	36
	95-99	10	6	16
	100-103	1	2	3
	N	67	64	131
	Mean	87.5	87.6	87.6
	Median	89	87.8	88
	St.Dev.	7.3	6.5	6.9
	Min			
	Max			
Endpoint	< 80	4	8	12
	80-89	12	28	40
	90-94	19	15	34
	95-99	11	9	20
	100-103	6	4	10
	104-108	10	0	10
	109-114	4	0	4
	>= 115	1	0	1
	N	67	64	131
	Mean	94.6	88.2	91.5
	Median	93	87.5	91.5
	St.Dev.	10	7.1	9.2
	Min			
	Max			
Change*	-20 to < -10	0	5	5
	-10 to < 0	12	23	35
	0 to < 10	31	28	59
	10 to < 20	18	8	26
	20 to < 30	5	0	5
	>= 30	1	0	1
	N	67	64	131
	Mean	7.1	0.6	3.9
	Median	6.5	0.8	3.5
	St.Dev.	8.5	7.7	8.7
	Min			
	Max			

#### Analysis of Covariance Results\*\*

Source	Degrees of Freedom	F-Value	P-Value
Treatment	1, 118	24.00	<0.0001
Centre	10, 118	1.21	0.2912
Visit # DBP	1, 118	20.51	<0.0001

Endpoint is the last available BP data after visit 8.

\* Change = Endpoint - Visit 8, i.e. a positive change indicates that BP has increased.

\*\* The ANCOVA results are based on type II SS.

With the S group results are similar.

		Treatment Group		
		Placebo	TCV-116	All
Visit 8	< 80	9	9	18
	80-89	38	37	75
	90-94	21	18	39
	95-99	13	11	24
	100-103	1	2	3
	N	82	77	159
	Mean	87.6	87.6	87.6
	Median	88.6	88	88
	St. Dev.	7	7.2	7.1
	Min			
	Max			
Endpoint	< 80	5	9	14
	80-89	12	32	44
	90-94	27	18	45
	95-99	14	14	28
	100-103	7	6	13
	104-108	11	0	11
	109-114	4	0	4
	>= 115	2	0	2
	N	82	77	159
	Mean	94.8	88.7	91.8
	Median	93.3	88	92
St. Dev.	10	7.3	9.3	
Min				
Max				
Change*	-20 to < -10	0	5	5
	-10 to < 0	13	27	40
	0 to < 10	41	36	77
	10 to < 20	21	3	24
	20 to < 30	6	0	6
	>= 30	1	0	1
	N	82	77	159
	Mean	7.2	1	4.2
	Median	6.8	1	4
	St. Dev.	8.4	7.3	8.4
	Min			
Max				

Analysis of Covariance results\*\*

Source	Degrees of Freedom	F Value	P-Value
Treatment	1, 146	26.64	<0.0001
Centre	10, 146	0.94	0.5017
Visit 8 DBP	1, 146	20.69	<0.0001

Endpoint is the last available BP data after visit 8.  
 \* Change = Endpoint - Visit 8, i.e. a positive change indicates that BP has increased.  
 \*\* The ANCOVA results are based on type III SS.

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The difference in change for SBP was also significant. For the ITT with the S group results given were:

		Treatment Group		
		Placebo	TCV-116	All
Visit 8	< 130	17	21	38
	130-139	21	25	46
	140-149	22	17	39
	150-159	17	13	30
	160-169	3	6	9
	>= 170	2	5	7
	N	82	77	159
	Mean	140.2	141.5	140.8
	Median	140	142	140
	St.Dev.	13.5	16.4	15
	Min Max			
Endpoint	< 130	2	18	20
	130-139	12	18	30
	140-149	19	22	41
	150-159	21	10	31
	160-169	14	4	18
	>= 170	14	5	19
	N	82	77	159
	Mean	153.2	141.7	147.6
	Median	150.8	140.5	146.5
	St.Dev.	16.1	16.5	17.2
	Min Max			
Change*	< -20	0	2	2
	-20 to < -10	1	8	9
	-10 to < 0	13	30	43
	0 to < 10	29	24	53
	10 to < 20	18	9	27
	20 to < 30	11	3	14
	>= 30	10	1	11
	N	82	77	159
	Mean	13	0.1	6.8
	Median	0.5	-0.5	4.5
	St.Dev.	14.2	12.3	14.7
Min Max				

Analysis of Covariance Results\*\*

Source	Degrees of Freedom	F-Value	P-Value
Treatment	1, 146	37.41	<0.0001
Centre	10, 146	0.34	0.9692
Visit 8 SBP	1, 146	17.44	0.0001

Endpoint is the last available BP data after visit 8.  
 \* Change = Endpoint - Visit 8, ie. a positive change indicates that BP has increased.  
 \*\* The ANCOVA results are based on type II SS.

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The mean change for the various treatment regimens were:

**T-Table 11 DESCRIPTION OF CHANGE\* IN MEAN SITTING DBP (mmHg) (VISIT 8 TO VISIT 10)**  
Double-blind placebo controlled withdrawal period

DOSE	PLACEBO	CANDESARTAN CILEXETIL	DIFFERENCE*	P-VALUE*
candesartan cilexetil 8mg (n=31)	12.5	1.1	11.4	0.0003
candesartan cilexetil 16mg (n=25)	5.4	1.5	3.9	0.6288
candesartan cilexetil 16mg + amlodipine (n=46)	4.8	-3.0	7.8	0.0033
candesartan cilexetil 16mg + amlodipine/HCTZ (n=29)	6.1	3.8	2.3	0.3801
S-group (n=26)	7.9	3.0	4.9	0.1414

\* Negative figures indicate decrease in DBP at endpoint compared to Visit 8  
\* Difference is placebo-candesartan cilexetil  
\* P-value taken from the treatment effect in the Analysis of Covariance results

**T-Table 13 DESCRIPTION OF CHANGE\* IN MEAN SBP (mmHg)**  
Double-blind placebo controlled withdrawal period

DOSE	PLACEBO	CANDESARTAN CILEXETIL	DIFFERENCE*	P-VALUE*
candesartan cilexetil 8mg od (n=31)	20.1	2.5	17.6	0.0105
candesartan cilexetil 16mg bd (n=25)	6.0	2.3	3.7	0.5523
candesartan cilexetil 16mg od + amlodipine (n=46)	11.5	-4.0	15.5	0.0011
candesartan cilexetil 16mg od + amlodipine + HCTZ (n=29)	10.3	-3.1	13.4	0.0098
S-group (n=28)	15.2	6.1	9.2	0.1573

\* Negative figures indicate decrease in SBP at endpoint compared to Visit 8  
\* Difference is placebo-candesartan cilexetil  
\* P-value taken from the treatment effect in the Analysis of Covariance results

Since results given by the sponsor for responder rates during dose titration are uncontrolled, they will not be repeated here.

### Ambulatory BP Monitoring

For 106 evaluable patients having ABPM, the 24 hour DBP means at baseline for the withdrawal period were 78.8 mm Hg and 81.7 mm Hg for placebo and CC respectively. The difference between groups in change at endpoint was 6.4 mm Hg for a p=0.0001.

Absolute change from placebo in the various dose and drug groups was:

**T-Table 14 ABSOLUTE CHANGE\* OF MEAN 24H DIASTOLIC BLOOD PRESSURE (mmHg)**  
BETWEEN VISIT 8 AND VISIT 10

	CANDESARTAN CILEXETIL 8MG	CANDESARTAN CILEXETIL 16MG	CANDESARTAN CILEXETIL PLUS AMLODIPINE	CANDESARTAN CILEXETIL PLUS AMLODIPINE PLUS HCTZ
Absolute change between placebo and active treatment p-value*	10.1 0.0085	7.8 0.0063	1.9 0.6807	7.2 0.0205

\* Negative figures indicate decrease at endpoint compared to Visit 8  
\* P-value taken from the treatment group term in the Analysis of Variance results

Safety

A 46 year old male was stabbed to death while pursuing a burglar. He had been on 8 mg CC for 5 weeks. 15 patients were withdrawn for an adverse event or laboratory abnormality as follows:

PATIENT JOINT ID	DOSE AT ONSET OF EVENT	EVENT DESCRIPTION	SEVERITY	CAUSAL RELATIONSHIP TO CANDESARTAN CILEXETIL
01/0229	8mg	Bradycardia	Mild	Probable
		Fatigue	Mild	Probable
		Polyuria	Mild	Probable
02/0085	Placebo	CK increased	Severe	Probable
04/0089	16mg	Lethargy	Moderate	Possible
04/0090	16mg	Myalgia	Moderate	Possible
05/0072	16mg + amlodipine 5mg	CK increased	Moderate	Possible
	+ HCTZ 25mg			
05/0146	16mg + amlodipine 5mg	Blood sugar increased	Moderate	Possible
	+ HCTZ 25mg			
05/1422*	Placebo	Throbbing in neck	Moderate	Not related
13/0010	16mg	Heartburn	Moderate	Possible
	16mg	Impotence	Mild	Possible
17/1197*	Placebo	Headache	Mild	Not related
18/0114*	8mg	Coughing	Moderate	Probable
18/0156*	8mg	Headache	Moderate	Probable
20/0101**	8mg	Myocardial Infarction	Severe	Unknown
20/0131	8mg	Headache	Severe	Possible
20/0422*	8mg	Rash	Mild	Possible
02/0062	16mg	Feeling Unwell	Mild	Unknown

\* Patients in whom the adverse event was the secondary reason for withdrawal. The primary reason being withdrawal of consent in 4 cases and failure to meet the blood pressure criteria for entry into the treatment period in one case.  
 \*\* SAE described in 6.3.5.2.

Of 10 patients whose primary reason for withdrawal was an adverse reaction, 7 withdrew during dose escalation, 3 in the withdrawal phase.

One other serious case of note. A 46 year old male with hypotension was found to have had a recent myocardial infarction on pyrophosphate scan. He had been treated for 3.5 months, the event being in the withdrawal phase during which he was on 16 mg of CC plus amlodipine 5 mg. Mean BP at the time of the event was 117/78 mm Hg (it was 184/114 mm Hg prior to entrance). He completed the study on treatment medication with a final mean BP of 117/78 mm Hg being recorded.

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Adverse events most frequently reported were:

**T-Table 25: ADVERSE EVENTS (DOSE-TITRATION PERIOD)**  
 Number of reports of most common AEs (incidence >2%) by WHO decode

ADVERSE EVENT	TOTAL	8MG	16MG	16MG + AMLODIPINE	16MG + AMLODIPINE + HCTZ	S-GROUP
Headache	24	11	8	2	3	0
URTI	10	2	5	1	2	0
Tiredness	6	1	2	3	0	0
CK increased	6	1	0	2	1	0
Dizziness	5	0	4	1	0	2
Lethargy	5	0	3	2	0	0
Coughing	5	2	1	1	1	0
Nausea	4	1	2	0	0	0
Common cold syndrome	4	1	1	1	1	1
Rash	4	2	1	1	0	0
Flushing	4	1	0	0	1	2

**T-Table 27: ADVERSE EVENTS (DOUBLE-BLIND, WITHDRAWAL PERIOD)**  
 Number of reports of most common AEs (incidence >2%) by WHO decode

WHO DECODE CLASSIFICATION	NUMBER OF REPORTS
Headache	10
Blood sugar increased	3
Upper Respiratory Tract Infection	3
Contact dermatitis	3

During the withdrawal phase 17 adverse events were reported on placebo, and 24 on CC (p=NS).

It should be noted that diabetics requiring insulin were not to be entered, but those not requiring insulin could.

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## Laboratory Findings

Lab results that triggered phone contacts were:

1-Table 30 RESULTS OUTSIDE PHONING RANGE

PARAMETER	PHONING REFERENCE	# RESULTS	# PATIENTS	# ISOLATED CASES
<b>HAEMATOLOGY</b>				
Haemoglobin	<LPR	1	1	1
WBC	<LPR	8	5	3
Lymphocytes	<LPR	2	2	2
<b>BIOCHEMISTRY</b>				
Potassium	>UPR	1	1	1
Total Bilirubin	>UPR	1	1	1
CK	>UPR	22	16	9
Glucose	>UPR	22	16	12
Creatinine	>UPR	3	2	1
SGOT	>UPR	3	2	1
SGPT	>UPR	4	3	1
Gamma GT	>UPR	4	2	1
Triglycerides	>UPR	5	4	3
Calcium	>UPR	3	2	1
Uric Acid	>UPR	12	8	5
Cholesterol	>UPR	1	1	1

Comparison of the shift in CK and glucose during the withdrawal phase were presented as:

Table 4.28.2 : Changes in Creatinine Kinase (Biochemistry) Assessments Between Visits 8 & 10 Safety Population

	Treatment Group											
	Placebo				TCV116				All			
	Visit 8				Visit 8				Visit 8			
	L	N	H	All	L	N	H	All	L	N	H	All
Visit 10 Low												
Normal	3	48	4	55	4	46	4	54	6	104	9	119
High												
All	3	52	7	72	10	52	11	73	12	118	18	137

Table 4.29.2 : Changes in Glucose (Biochemistry) Assessments Between Visits 8 & 10 safety population

	Treatment Group								
	Placebo			TCV116			All		
	Visit 8			Visit 8			Visit 8		
	N	H	All	N	H	All	N	H	All
Visit 10 normal	66	1	67	41	1	42	124	2	126
High	2	9	11	4	7	11	6	16	22
All	68	10	78	45	10	75	130	18	151

**6.13 EC040 - Long-term Safety and Efficacy of Candesartan cilexetil (4, 8, 12, and 16 mg once daily) in patients with mild to moderate essential hypertension (SiDBP 95-109 mm Hg).**

Open, prospective, multicenter (37 in Germany), response-dependent dose titration (12 months) period, preceded by a 4 week placebo run-in, and followed with a double-blind, placebo controlled run-out period (2 weeks).

Study began: September 5, 1994.

Study completed: January 24, 1996.

Principal Investigator: Heinrich Holzgrove, M.D., Munich, Germany.

Drug and placebo manufactured by

The plan for this study was:

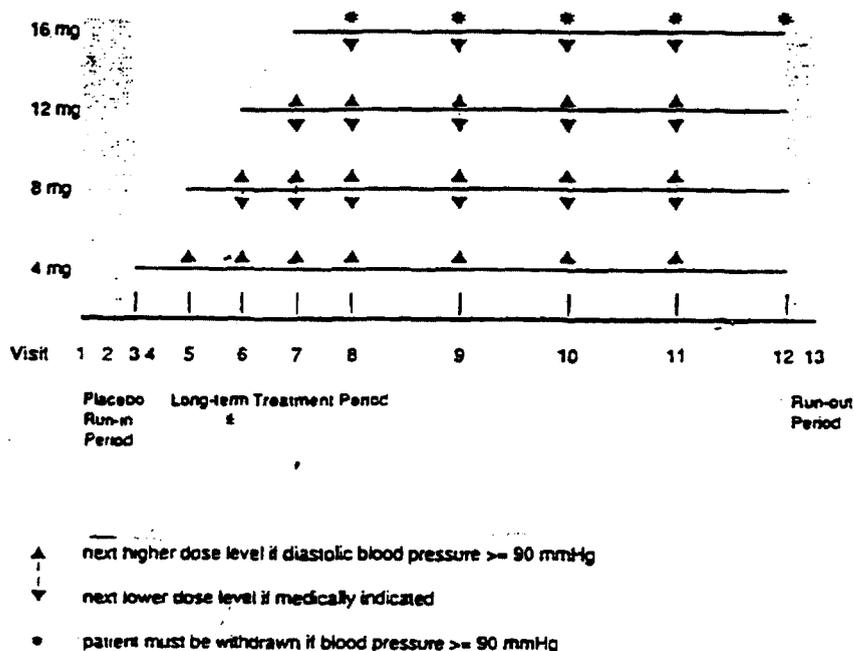
Study period	Placebo run-in period		Long-term treatment period											Double-blind run-out period		
	0	2	1	2												2
Week																
Month			1			1	2	3	4	6	8	10	12			
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14		
Medical history	x															
Inclusion/exclusion criteria	x		x													
Concomitant medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Extensive physical examination	x														x	x
Brief physical examination		x	x	x	x	x	x	x	x	x	x	x	x			
Blood pressure/ pulse	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Laboratory tests	x	(x)		x		x	x	x	x	x	x	x	x	x	x	x
ECG	x		x	x		x	x	x	x	(x)	(x)	(x)	x	x		
Discontinuation of medication	x		x			x	x	x	x	x	x	x	x			
Drug accountability			x			x	x	x	x	x	x	x	x	x	x	x
Serum sample for determination of CV-11974															x	
Assessment of efficacy/safety															x	x

(x) optional  
 (x) to be collected at premature discontinuation between Visit 3 and Visit 13

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**Flow-Chart of Dose Titration**



Patients with untreated or unsatisfactorily treated mild to moderate primary hypertension (mean sitting DBP 95-109 mm Hg), male or female 18-75 years of age were eligible. Women who were pregnant or who were not using acceptable contraception, as well as any patient with severe cardiac, cerebrovascular, renal, hepatic or metabolic disease were not eligible.

Randomization for the double-blind placebo controlled phase of the study was based on a computer generated list in blocks of 6. Patients entered into the long-term treatment period were assigned a number then which determined assignment if they got to and were eligible for the controlled phase. Each center was to include at least 16 and no more than 18 patients. Compliance was assessed by pill count.

The primary efficacy parameter was a safety evaluation of the drug.

Secondary objectives were:

- 1) individual dose response (SBP and DBP) after long term treatment.
- 2) change in DBP from baseline for placebo and drug in double-blind controlled phase.

Sample size was set at 200 patients for the long term period to detect adverse events with an incidence of 1.5% or more with 95% power assuming a 30 dropout rate, it was estimated that 40 patients would be available for the controlled phase. 70 patients per group was believed adequate to detect a 4 mm Hg difference in change of DBP with an 8 mm-Hg S.D.

Populations to be analyzed were:

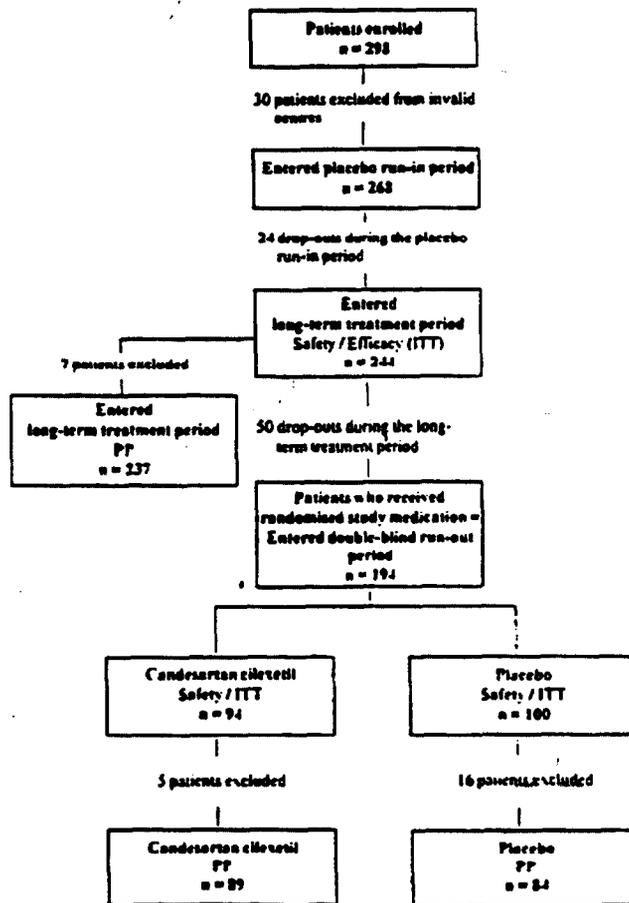
Placebo run-in period:  
Long-term treatment period:

Safety - All patients enrolled  
Safety - All patients with intake of at least one dose of Candesartan cilexetil  
Efficacy (ITT) - As for safety and availability of baseline (Visit 3) and at least one post-baseline diastolic blood pressure value  
Efficacy (PP) - As for ITT and absence of major protocol violations

Double-blind run-out period:

Safety - All patients with intake of at least one dose of Candesartan cilexetil or placebo after randomisation  
Efficacy (ITT) - As for safety and availability of diastolic blood pressure values at Visits 13 and 14  
Efficacy (PP) - As for ITT and absence of major protocol violations

Patient enrollment and disposition was:



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Specifics as to the reasons ("major irregularities") 3 centers were considered invalid, and results for the 30 patients were provided in appendix 9. These patients went through the entire trial, presumably were assigned a randomization number, but not considered in the controlled portion of the study. It is not clear when the decision to exclude these centers was made.

Another problem with "implausibly high potassium values" surfaced, were investigated, and found related to potassium fluoride contamination in the collection tubes.

Reasons for discontinuation were:

Reason for premature discontinuation	Patients who discontinued during the placebo run-in period* (n=24)		Patients who entered the long-term treatment period* (n=244)	
	n	%	n	%
Insufficient blood pressure reduction	-	-	26	10.7
Adverse event	1	4.2	15	6.1
Patient request	6	25.0	8	3.3
Protocol violation	20	83.3	4	1.6
Other reasons	-	-	7	2.9

\* Analysis populations, percentages based on the respective population

For the 244 patients who entered the long-term phase, 122 were male, 122 female. Males had a mean age of  $54.5 \pm 11.7$  years; females  $57.6 \pm 10.5$  years. Males weighed  $83.8 \pm 13.0$  kg; females  $72 \pm 12.8$  kg.

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Median duration of hypertension was 2.8 years, and 63.5% of patients were on antihypertensive medication 3 months before inclusion into the study. Concomitant diseases 72% at study start (n=244) were:

Concomitant diseases (ICD-9 3-digit categories)	n	%
Disorder of lipid metabolism	143	58.6
Unspecified disorders of heart	40	16.4
Nonspecific findings on examination of blood	33	13.5
Diabetes mellitus	31	12.7
Surgery	28	11.5
Concomitant and allied disorders	20	8.2
Chronic liver disease and cirrhosis	20	8.2
Vascular waves of lower extremities	17	7.0
Cancerous and doubtful	14	5.7
Hypertrophy of prostate	14	5.7
Other disorders of cervical region	13	5.3
Septic and unspecified poore	12	4.9
Chronic bronchitis	12	4.9
Obesity and other hyperalimentation	12	4.9
Other forms of chronic carbonic acid disease	11	4.5
Other and unspecified disorders of metabolism	9	3.7
Curvature of spine	9	3.7
Other disorders of liver	8	3.3
Old myocardial infarction	8	3.3
Spondylitis and allied disorders	7	2.9
Other disorders of bone and cartilage	7	2.9
Menopausal and postmenopausal disorders	7	2.9
Contact dermatitis and other eczema	4	1.6
Osteoarthritis	4	1.6

For the controlled portion of the study (n=173) there were more males (57.4% versus 43%) in the Candesartan and placebo groups respectively (p=0.044). Baseline DBP for this phase was  $84.6 \pm 4.8$  mm Hg for the Candesartan group and  $84.8 \pm 4.8$  mm Hg for placebo patients.

Data sets analyzed were:

	Total	Candesartan cilexetil			
		4 mg	8 mg	12 mg	16 mg
	n	n	n	n	n
Entered long-term treatment period	244				
Eligible for per-protocol population (Long-term treatment period)	237				
Entered double-blind run-out period	194				
Candesartan cilexetil group	94	31	27	23	13
Placebo group	100	35	24	23	18
Eligible for per-protocol population (Double-blind run-out period)	173				
Candesartan cilexetil group	89	30	26	22	11
Placebo group	84	34	20	22	8

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Dose distribution at the end of the long-term period was:

	Candesartan cilexetil			
	4 mg n=79	8 mg n=55	12 mg n=51	16 mg n=59
Baseline (Visit 3) (mmHg)	99.7 ± 2.7	100.1 ± 3.2	101.5 ± 3.3	102.2 ± 4.2
Last value* (mmHg)	84.3 ± 6.7	84.5 ± 5.7	86.6 ± 6.3	94.3 ± 9.3
Decrease between baseline and last value (mmHg)	15.3 ± 6.5	15.5 ± 5.7	14.9 ± 6.1	8.0 ± 9.2
Response (last value)	89.9%	94.5%	90.2%	49.2%
Normalisation (last value)	86.1%	85.5%	80.4%	40.7%

\* Blood pressure at Visit 13 or at the time of premature discontinuation (only values under medication)

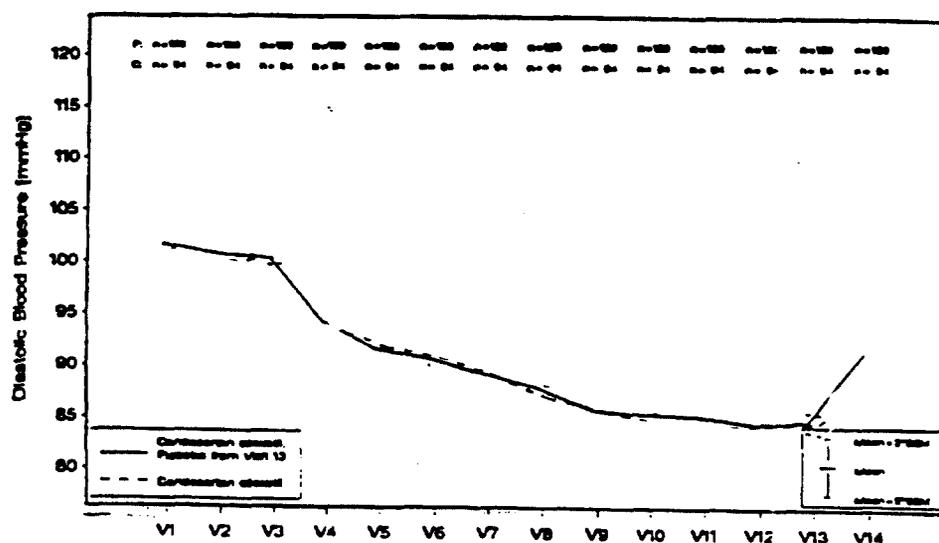
Patients who were randomized but did not enter the controlled phase were designated "yes" on the following accounting:

Candesartan cilexetil	No. of patients	Pct. of patients
yes	25	21.0
no	94	79.0
Total no. of patients	119	100.0

Placebo	No. of patients	Pct. of patients
yes	25	20.0
no	100	80.0
Total no. of patients	125	100.0

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Efficacy for those who entered the controlled phase was graphed as follows:



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During the 2 week controlled phase, DBP increased from baseline in both groups. For the Candesartan group the increase was  $3.9 \pm 6.6$  mm Hg; for placebo it was  $6.7 \pm 7.2$  mm Hg. The difference was not statistically significant.

Change in SBP showed similar numerical but not statistically significant differences in change from baseline when Candesartan and placebo were compared. The numerical changes were a mean increase of  $4.4 \pm 11$  mm Hg for Candesartan;  $8.5 \pm 12$  mm Hg for placebo.

#### Safety

No deaths were reported. Adverse events throughout the study were numerically:

Study population	Patients experiencing adverse events with onset during		
	Placebo run-in period	Long-term treatment period	Double-blind run-out period
Premature discontinuations during the placebo run-in period (n=24)	6 (25.0%)	-	-
Safety - Long-term treatment period (n=244)	35 (14.3%)	155 (63.5%)	-
Safety - Double-blind run-out period (n=194)			
- Candesartan cilexetil (n=94)	8 (8.5%)	58 (61.7%)	7 (7.4%)
- Placebo (n=100)	16 (16.0%)	62 (62%)	3(3.0%)

Adverse events leading to premature withdrawal were:

Age at onset (years)	Sex	Adverse event (Verbatim translated into English)	Adverse event (Preferred term)		
<b>Placebo run-in period</b>					
<b>CRF No.</b>					
G1382	65	f	Hypertensive crisis	Hypertension aggravated	
<b>Long-term treatment period</b>					
<b>Pat. Date</b>					
003	6 mg	70	m	Fracture of 7th and 8th left lateral ribs after fall (sensory syncope due to induction)**	Accidental injury
004	16 mg	69	f	Gastritis with stomach ache and heartburn	Gastritis
025	4 mg	55	m	Hypertension (worsening)	Hypertension aggravated
068	4 mg	63	m	Acute posterior myocardial infarction with angina pectoris**	Myocardial infarction
108	16 mg	54	m	Multiple fractures (spine, ribs, scapula), fall from approx. 2½ m height**	Accidental injury
109	4 mg	44	f	Dizziness	Dizziness
				Reddening (face)	Flushing
186	16 mg	54	f	Anxieties related to heart and circulation**	Anxiety
187	4 mg	73	f	Restriction of movement due to pain in active bilateral gonarthrosis (hospitalization)**	Arthritis
				Hypertensive crises	Hypertension aggravated
188	8 mg	64	f	Hepatitis (chronic persisting) with elevation of transaminases	Hepatitis
192	4 mg	58	f	Elevation of liver values (status post hepatitis)	Hepatic function abnormal
199	4 mg	51	f	Pulmonary embolism with hospitalization**	Embolism pulmonary
210	12 mg	55	m	Thrombocytopenia of unknown origin	Thrombocytopenia
213	4 mg	60	f	Facial rosacea	Rosacea
221	16 mg	57	f	Acute febrile bronchitis**	Bronchitis
				Recurrent gastroenteritis	Gastroenteritis
249	4 mg	60	f	Worsening of laboratory findings: transaminases (Gamma-GT, GPT, GOT)	Hepatic function abnormal
				Worsening of laboratory findings: uric acid	Hypertension

m = male, f = female  
 \*\* reported as serious adverse event

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No patients withdrew for serious adverse events during the controlled portion of the study.

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Age at onset (years)	Sex	Adverse event (Verbatim translated into English)	Adverse event (Preferred term)
----------------------	-----	--	--------------------------------

Placebo run-in period

CRF No.

G1134	49	m	Renal calculus (left ureteric grain stones)	Renal calculus
G1391	64	f	Car accident with concussion of the abdominal wall and thorax	Accidental injury

Long-term treatment period

Pts Dose

003	8 mg	70	m	Fracture of 7th and 8th left lateral ribs after fall (luxure syncope due to infection)	Accidental injury
010	4 mg	73	m	Small bladder tumour (papillary with increasing prostatic complaints)	Bladder carcinoma
083	4 mg	63	m	Acute posterior myocardial infarction with angina pectoris	Myocardial infarction
108	16 mg	54	m	Multiple fractures (spine, ribs, scapula), fell from approximately 2m height	Accidental injury
141	4 mg	62	m	Growth of prostate adenoma, increased micturition difficulties	Neoptam NOS
186	16 mg	54	f	Anxieties related to heart and circulation	Anxiety
187	4 mg	73	f	Restriction of movement due to pain in active bilateral gonarthrosis (hospitalisation)	Arthrosis
199	4 mg	51	f	Pulmonary embolism with hospitalization	Embolism pulmonary
221	16 mg	57	f	Acute febrile bronchitis	Bronchitis
283	16 mg	60	m	Inguinal hernia and subcutaneous tumour of the right cheek	Hernia inguinal

Adverse events, stratified by sex, incidence > 2% were:

Adverse event (Preferred term)	Male patients (n=122)		Female patients (n=122)	
	n	%	n	%
Bronchitis	9	7.4	15	12.3
Back pain	9	7.4	10	8.2
Influenza-like symptoms	6	4.9	8	6.6
Upper respiratory tract infection	5	4.1	9	7.4
Accidental injury*	8	6.6	4	3.3
Dizziness	5	4.1	6	4.9
Headache	3	2.5	8	6.6
Gastroenteritis	5	4.1	6	4.9
Pharyngitis	7	5.7	3	2.5
Hypertunglycaemia	7	5.7	2	1.6
Urinary tract infection	3	2.5	6	4.9
Hyperuricaemia	7	5.7	1	0.8
Sinusitis	4	3.3	3	2.5
Dyspepsia	2	1.6	4	3.3
Hypercholesterolaemia	3	2.5	3	2.5
Ischaem	3	2.5	3	2.5

\* Musculo-skeletal system disorders

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By age:

Adverse event (Preferred term)	Patients with age < 65 years (n=181)		Patients with age ≥ 65 years (n=63)	
	n	%	n	%
Bronchitis	19	10.5	5	7.9
Back pain	17	9.4	2	3.2
Influenza-like symptoms	12	6.6	2	3.2
Upper respiratory tract infection	13	7.2	1	1.6
Accidental injury*	8	4.4	4	6.3
Dizziness	8	4.4	3	4.8
Headache	9	5.0	2	3.2
Gastroenteritis	6	3.3	5	7.9
Pharyngitis	8	4.4	2	3.2
Hyperglycaemia	7	3.9	2	3.2
Urinary tract infection	6	3.3	3	4.8
Hyperuricaemia	7	3.9	1	1.6
Sinusitis	7	3.9	-	-
Dyspnoea	4	2.2	2	3.2
Hypercholesterolaemia	2	1.1	4	6.3
Ischias	5	2.8	1	1.6

\* Musculo-skeletal system disorders

By dose:

Adverse event (Preferred term)	Candesartan cilexetil dose at onset of event							
	4 mg (n=244)		8 mg (n=166)		12 mg (n=116)		16 mg (n=62)	
	n	%	n	%	n	%	n	%
Bronchitis	10	4.1	8	4.8	6	5.2	-	-
Back pain	10	4.1	4	2.4	3	2.6	3	4.8
Influenza-like symptoms	7	2.9	5	3.0	1	0.9	1	1.6
Upper respiratory tract infection	7	2.9	5	3.0	3	2.6	-	-
Accidental injury*	5	2.0	1	0.6	3	2.6	3	4.8
Dizziness	5	2.0	2	1.2	4	3.4	-	-
Headache	6	2.5	4	2.4	-	-	1	1.6
Gastroenteritis	3	1.2	5	3.0	1	0.9	1	1.6
Pharyngitis	6	2.5	2	1.2	2	1.7	-	-
Hyperglycaemia	5	2.0	1	0.6	-	-	2	3.2
Urinary tract infection	7	2.9	2	1.2	-	-	2	3.2
Hyperuricaemia	3	1.2	3	1.8	1	0.9	1	1.6
Sinusitis	1	0.4	1	0.6	5	4.3	-	-
Dyspnoea	2	0.8	1	0.6	2	1.7	1	1.6
Hypercholesterolaemia	3	1.2	3	1.8	-	-	-	-
Ischias	3	1.2	2	1.2	1	0.9	-	-

\* Musculo-skeletal system disorders

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Combined and attributable:

Preferred term	All patients with respective adverse events		Patients with attributable* adverse events	
	n	%	n	%
Bronchitis	24	9.8	-	-
Back pain	19	7.8	-	-
Influenza-like symptoms	14	5.7	-	-
Upper respiratory tract infection	14	5.7	-	-
Accidental injury**	12	4.9	-	-
Dizziness	11	4.5	8	3.3
Headache	11	4.5	3	1.2
Gastroenteritis	11	4.5	1	0.4
Pharyngitis	10	4.1	-	-
Hypertglycaemia	9	3.7	-	-
Urinary tract infection	9	3.7	-	-
Hyperuricaemia	8	3.3	1	0.4
Sinusitis	7	2.9	-	-
Dyspepsia	6	2.5	2	0.8
Hypercholesterolaemia	6	2.5	1	0.4
Ischias	6	2.5	-	-

\* Relationship: definite, probable, possible (as assessed by the investigator)  
 \*\* Musculo-skeletal system disorders

Biochemical laboratory changes from baseline numerically were:

	normal (Visit 1)		low (post-baseline*)		low (last value)		high (post-baseline*)		high (last value)	
	n	%	n	%	n	%	n	%	n	%
SGOT	215	88.1	n.a.**	n.a.	n.a.	n.a.	59	24.2	20	8.2
SGPT	197	80.7	n.a.	n.a.	n.a.	n.a.	64	26.2	17	7.0
Gamma-GT	161	66.0	2	0.8	-	-	57	23.4	27	11.1
Total bilirubin	234	95.9	n.a.	n.a.	n.a.	n.a.	34	13.9	9	3.7
LDH	231	94.7	n.a.	n.a.	n.a.	n.a.	36	14.8	8	3.3
Creatine Kinase (activated)	199	81.6	n.a.	n.a.	n.a.	n.a.	64	26.2	18	7.4
Alkaline phosphatase	226	92.6	5	2.0	1	0.4	31	12.7	9	3.7
Total cholesterol	24	9.8	n.a.	n.a.	n.a.	n.a.	17	7.0	10	4.1
Triglycerides	187	76.6	n.a.	n.a.	n.a.	n.a.	62	25.4	22	9.0
Potassium***	212	86.9	n.a.	n.a.	n.a.	n.a.	11	4.5	2	0.8
Sodium	210	86.1	7	2.9	2	0.8	-	-	-	-
Chloride	231	94.7	16	6.6	3	1.2	23	9.4	2	0.8
Calcium	232	95.1	30	12.3	6	2.5	19	7.8	4	1.6
Urea	230	94.3	-	-	-	-	48	19.7	11	4.5
Glucose	167	68.4	13	5.3	5	2.0	94	38.5	44	18.0
Uric acid	212	86.9	2	0.8	-	-	67	27.5	22	9.0
Creatinine	238	97.5	1	0.4	-	-	26	10.7	6	2.5

\* Visit 4 or later (including last value)  
 \*\* n.a. = not applicable (category not defined by reference range, e.g. 'low' for SGPT, as lower limit of reference range for SGPT is 0 U/l)  
 \*\*\* 'normal' includes both 'low' and 'normal' (see Section 8.2.1)

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Hematologic laboratory changes were:

	normal (Visit 1)		low (post- baseline <sup>a</sup> )		low (last value)		high (post- baseline <sup>a</sup> )		high (last value)	
	n	%	n	%	n	%	n	%	n	%
Red blood count	211	86.5	62	25.4	15	6.1	3	1.2	-	-
Haemoglobin	214	87.7	31	12.7	7	2.9	19	7.8	5	2.0
Haematocrit	219	89.8	36	14.8	9	3.7	20	8.2	2	0.8
MCV	230	94.3	9	3.7	2	0.8	15	6.1	2	0.8
White blood count	223	91.4	18	7.4	2	0.8	43	17.6	9	3.7
Basophils	192	78.7	n.a.	n.a.	n.a.	n.a.	120	49.2	41	16.8
Eosinophils	191	78.3	n.a.	n.a.	n.a.	n.a.	87	35.7	25	10.2
Banded neutrophils	240	98.4	n.a.	n.a.	n.a.	n.a.	16	6.6	-	-
Segmented neutrophils	175	71.7	93	38.1	34	13.9	23	9.4	5	2.0
Lymphocytes	166	68.0	65	26.6	13	5.3	78	32.0	28	11.5
Monocytes	241	98.3	n.a.	n.a.	n.a.	n.a.	6	2.5	-	-
Platelets	227	91.0	26	10.7	8	3.3	5	2.0	1	0.4

<sup>a</sup> Visit 4 or later (including last value)

n.a. = not applicable (category not defined by reference range, e.g. 'low' for basophils, as lower limit of reference range for basophils is 0%)

The three patients who withdrew for LFT elevations were:

Patient 192, a 58 year old Caucasian female, was noted to have "fatty infiltration of the liver on entrance, beginning 7/93. SGPT, GGT, bilirubin just over ULN on entrance. Patients could enter with LFTs < 2 ULN. After 11 days on 4 mg of Candesartan cilexetil SGPT, GGT, bilirubin were somewhat more elevated, and in spite of discontinuation of drug remained elevated to 1.5 - 2 x ULN.

Patient 249, a 60 year old Caucasian female, withdrew for inadequate compliance, and had very slight elevations of SGPT and GGT, just above ULN. Was on 4 mg of Candesartan cilexetil for 8.5 months prior to incident.

Patient 188, a 64 year old Caucasian female, entered with very slightly elevated SGPT, GGT, said to have chronic hepatitis. After 4 months on Candesartan cilexetil, SGPT and GGT increased, patient withdrew, but in spite of discontinuing medication, LFT elevations persisted.

Randomization assigned 2 to placebo, 1 to CC for the controlled period had they not withdrawn.

One case of thrombocytopenia occurred in a 55 year old male who entered with a platelet count of 127/nl. At 8 months on 12 mg CC platelet count was 61/nl and he was withdrawn. Platelet count remains low 4 months after drug discontinuation. This patient (#210) was assigned placebo for the controlled study had he made it to that point.

**6.14 Study EC016 - Efficacy and Safety of Candesartan cilexetil (TCV-116) in combination with HCTZ in the treatment of patients with mild to moderate hypertension, not responding to low dose monotherapy with HCTZ.**

Randomized, double-blind, placebo controlled, multi-center, parallel study.

Study began January 17, 1995.

Study completed January 28, 1996.

Principal Investigator: Dr. P-F Plouin, Paris, France.

French multicenter study.

Drugs: Encapsulated tablets for blinding purposed; manufactured by

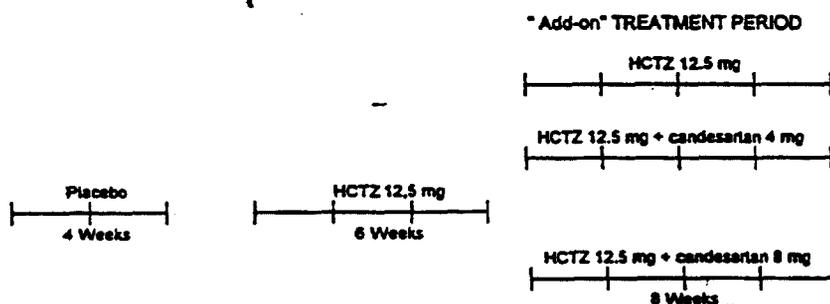
The flow chart and design of the study was:

Study period	Placebo Run-in Period			HCTZ Monotherapy		"Add-On" Treatment Period	
	0	2	4	7	10	14	18
WEEK							
VISIT	1	2	3	4	5	6	7
Medical History	x						
Incl./Excl. criteria	x		x		x		
Concomitant medication	x	x	x	x	x	x	x
Extensive physical examination	x				(x)		x
Brief physical examination		x	x	x	x	x	
Blood pressure/Heart rate	x	x	x	x	x	x	x
Adverse events		x	x	x	x	x	x
Laboratory tests (blood) <sup>1</sup>	x			x <sup>2</sup>		x <sup>3</sup>	
Urinalysis (dipstick)	x		x		x		x
ECG	x		x		x		x
Distribution of medication	x		x	x	x	x	
Drug accountability			x	x	x	x	x
Global assessment of efficacy and safety					x		x

<sup>1</sup> to be taken at patients' home

<sup>2</sup> results have to be available at visit 5

<sup>3</sup> results have to be available at visit 7



To be eligible for the placebo run-in, patients had to be  $\geq 18$  years, male or female and have unsatisfactorily treated mild to moderate essential hypertension (sitting DBP 95-109 mm

Hg). For the HCTZ monotherapy period SDBP 95-109 mm Hg and sitting SBP < 200 mm Hg had to be present.

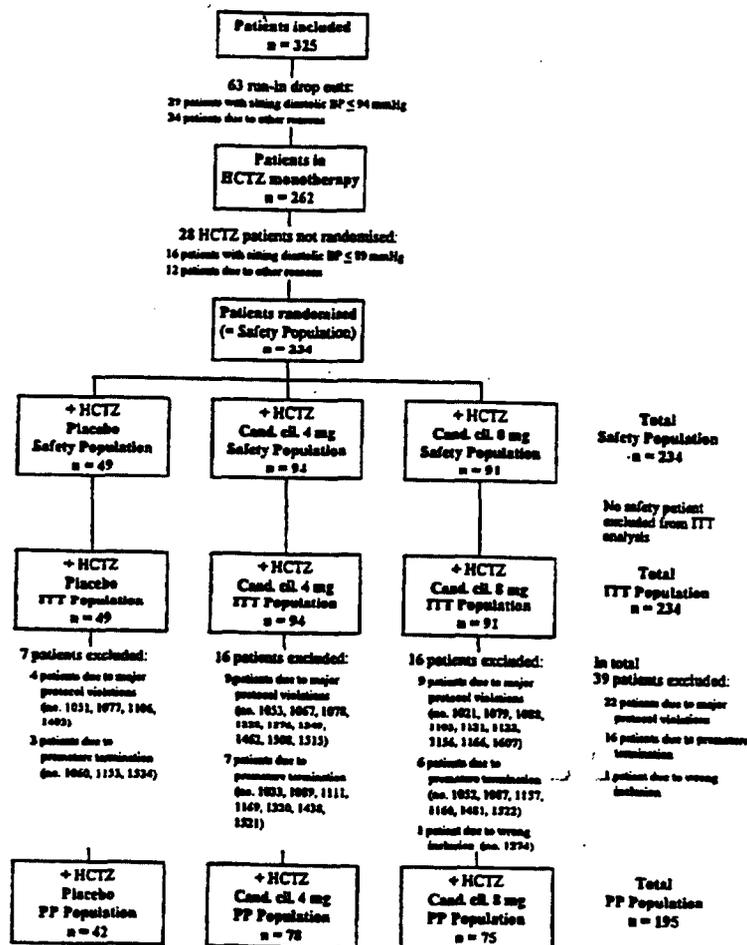
For inclusion into the DB treatment study, SDBP 90 mm Hg or more had to be present, as well as no malignant hypertensive findings, no child-bearing potential for women, no cardiac, hepatic, GI, renal, autoimmune, or metabolic disease.

At visit 5 (DB period) if eligible, the patient was randomized by computer generated list to HCTZ & Placebo, HCTZ & CC 4 mg, or HCTZ & CC mg in a 1:2:2 manner. The primary efficacy parameter was comparison of SDBP between CC and Placebo groups from DB entrance to end of DB period.

Secondarily, SBP and response rates were to be evaluated. Safety was also to be determined. Compliance was measured by returned pill count versus dispenses, and less than 75% or more than 125% was considered a major protocol violation.

A sample size of 125 randomized to one of the 3 treatments in the DB phase was thought adequate to demonstrate a 4.5 mm difference of HCTZ & Placebo versus CC & Placebo with a standard deviation of 7 mm Hg.

The disposition of patients was:



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Demography for the DB period was:

		ITT population				PP population			
		n	mean	min.	max.	n	mean	min.	max.
<b>Age (years)</b>									
Placebo	male	26	57.8	32.0	80.0	24	57.5	32.0	73.0
+ HCTZ	female	23	56.2	34.0	77.0	18	56.7	34.0	77.0
	total	49	57.0	32.0	80.0	42	57.2	32.0	77.0
Candesartan	male	51	51.1	32.0	71.0	45	51.3	32.0	71.0
cilixetil 4 mg	female	43	60.3	26.0	87.0	33	60.8	26.0	87.0
+ HCTZ	total	94	55.4	26.0	87.0	78	55.3	26.0	87.0
Candesartan	male	46	54.6	29.0	81.0	37	54.5	35.0	81.0
cilixetil 8 mg	female	45	58.8	26.0	88.0	38	58.9	28.0	88.0
+ HCTZ	total	91	56.6	26.0	88.0	75	56.7	28.0	88.0
<b>Height (cm)</b>									
Placebo	male	26	170.6	150.0	190.0	24	170.8	150.0	190.0
+ HCTZ	female	23	160.8	153.0	173.0	18	160.7	153.0	168.0
	total	49	166.0	150.0	190.0	42	166.5	150.0	190.0
Candesartan	male	51	171.4	157.0	188.0	45	171.4	157.0	188.0
cilixetil 4 mg	female	43	158.8	144.0	170.0	33	158.6	144.0	170.0
+ HCTZ	total	94	165.6	144.0	188.0	78	166.0	144.0	188.0
Candesartan	male	46	172.0	155.0	188.0	37	173.1	159.0	188.0
cilixetil 8 mg	female	45	159.3	143.0	173.0	38	159.8	148.0	173.0
+ HCTZ	total	91	165.7	143.0	188.0	75	166.3	148.0	188.0
<b>Weight (kg)</b>									
Placebo	male	26	81.25	54.00	110.00	24	82.40	54.00	110.00
+ HCTZ	female	23	67.81	49.00	88.00	18	66.18	49.00	88.00
	total	49	74.94	49.00	110.00	42	75.45	49.00	110.00
Candesartan	male	51	80.74	53.00	122.00	45	80.55	53.00	122.00
cilixetil 4 mg	female	43	66.91	42.00	108.00	33	66.25	42.00	108.00
+ HCTZ	total	94	74.41	42.00	122.00	78	74.50	42.00	122.00
Candesartan	male	46	79.10	60.00	100.00	37	79.54	65.00	100.00
cilixetil 8 mg	female	45	64.15	36.50	94.00	38	64.89	50.00	94.00
+ HCTZ	total	91	71.71	36.50	100.00	75	72.12	50.00	100.00

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

Duration of hypertension	HCTZ + Placebo n = 49	HCTZ + Cand. cil. 4 mg n = 94	HCTZ + Cand. cil. 8 mg n = 91	Total n = 234
< 1 year	15 30.6%	22 23.4%	23 25.3%	60 25.6%
1 to 3 years	11 22.4%	19 20.2%	22 24.2%	52 22.2%
> 3 years	23 46.9%	53 56.4%	46 50.5%	122 52.1%

Major protocol violations were noted as follows:

**Major protocol violations.**

Patients are identified by screening numbers (ITT population).

Type of major protocol violation	HCTZ + Placebo n = 49	HCTZ + Cand. cil. 4 mg n = 94	HCTZ + Cand. cil. 8 mg n = 91	Total n = 234
Timing of BP measurement	2 patients (1051, 1077)	4 patients (1053, 1067, 1078, 1228)	5 patients (1021, 1082, 1121, 1122, 1607)	11 patients
Compliance	2 patients (1106, 1493)	5 patients (1276, 1349, 1462, 1508, 1515)	4 patients (1079, 1103, 1156, 1166)	11 patients
<b>Total</b>	<b>4 patients (8.2%)</b>	<b>9 patients (9.6%)</b>	<b>9 patients (9.9%)</b>	<b>22 patients (9.4%)</b>

All patients with major protocol violations were not included into the PP population.

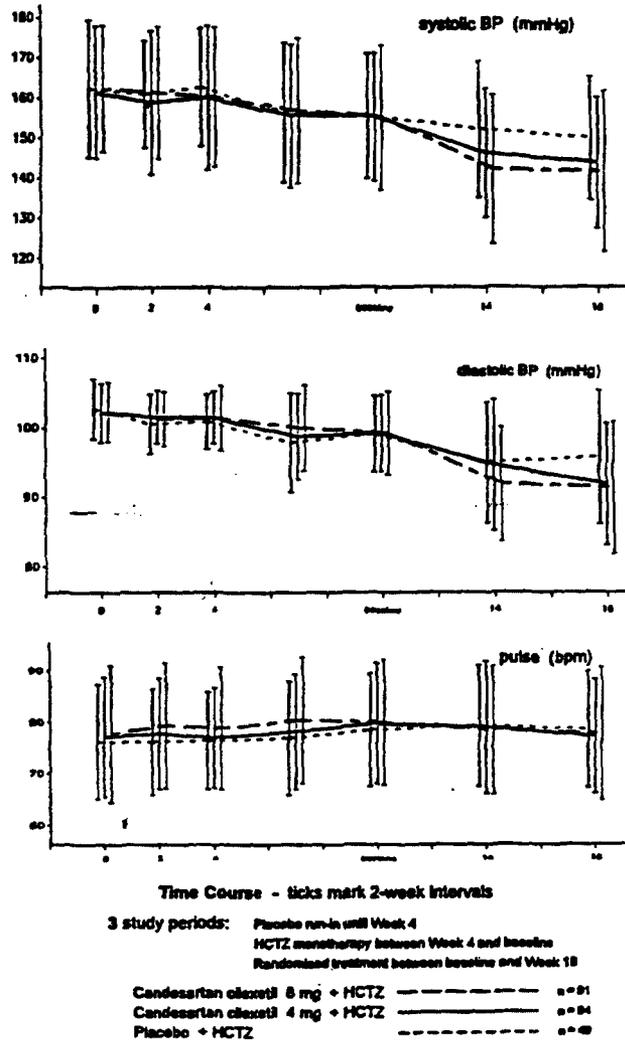
**Results**

Comprehensive SBP, DBP, pulse results from screening to the end of the DB phase were presented.

**Sitting systolic/diastolic blood pressure and pulse (ITT population)**

	HCTZ + Placebo		HCTZ + Cand. cil. 4 mg		HCTZ + Cand. cil. 8 mg				
	n	mean	SD	n	mean	SD	n	mean	SD
<b>Systolic Blood Pressure (mmHg)</b>									
Visit 1 Screening	49	162.2	17.1	94	161.2	16.5	91	162.2	15.7
Visit 2	49	160.6	13.3	94	158.6	17.9	91	161.0	16.5
Visit 3 start HCTZ monotherapy	49	162.4	14.7	94	159.7	17.9	91	160.0	17.4
Visit 4	49	156.1	17.4	94	155.3	17.8	91	156.5	18.1
Visit 5, baseline	49	155.1	18.4	94	155.0	18.8	91	154.9	18.0
Visit 6, 4 weeks post baseline	49	151.8	16.9	93	145.8	16.1	90	141.8	18.6
Visit 7, 8 weeks post baseline	49	149.7	15.3	93	143.6	16.3	91	141.5	19.9
individual last value	49	149.7	15.3	94	144.0	16.8	91	141.5	19.9
<b>Diastolic Blood Pressure (mmHg)</b>									
Visit 1 Screening	49	102.6	4.3	94	102.1	4.2	91	102.3	4.2
Visit 2	49	100.5	4.3	94	101.5	3.8	91	101.2	3.9
Visit 3 start HCTZ monotherapy	49	100.8	3.9	94	101.4	3.7	91	101.3	4.6
Visit 4	49	97.8	7.1	94	98.7	6.1	91	99.9	6.1
Visit 5, baseline	49	99.0	8.5	94	99.1	8.5	91	99.2	8.9
Visit 6, 4 weeks post baseline	49	94.9	8.7	93	94.5	8.8	90	91.8	8.2
Visit 7, 8 weeks post baseline	49	95.6	9.6	93	91.8	8.7	91	91.2	9.5
individual last value	49	95.6	9.6	94	92.1	9.4	91	91.2	9.5
<b>Pulse (bpm)</b>									
Visit 1 Screening	49	76.2	11.1	94	77.1	11.6	91	77.7	13.3
Visit 2	49	76.1	10.3	94	77.7	10.7	91	79.3	12.2
Visit 3 start HCTZ monotherapy	49	76.4	9.4	94	76.9	9.6	91	78.7	11.8
Visit 4	49	76.8	11.0	93	78.1	11.1	91	80.4	12.3
Visit 5, baseline	49	78.4	10.9	94	79.7	11.7	91	79.9	12.1
Visit 6, 4 weeks post baseline	49	79.3	11.7	93	78.9	12.8	90	78.4	12.4
Visit 7, 8 weeks post baseline	49	78.5	11.3	93	77.1	11.0	91	77.7	12.9

Mean time courses with  $\pm$  SD were:



As per the sponsor, the change from baseline to the last individual value was:

	HCTZ + Placebo			HCTZ + Candesartan cilexetil 4mg			HCTZ + Candesartan cilexetil 8mg		
	n	mean	SD	n	mean	SD	n	mean	SD
<b>ITT</b>									
Systolic BP	49	-5.4	13.1	94	-11.0	13.5	91	-13.4	20.0
Diastolic BP	49	-3.3	10.1	94	-7.0	8.0	91	-7.9	9.6
<b>FP</b>									
Systolic BP	42	-5.1	13.7	78	-12.4	13.4	75	-14.8	19.8
Diastolic BP	42	-3.4	10.5	78	-7.6	8.2	75	-8.5	9.6

For DBP, these differences are not entirely consistent with the comprehensive table presented above, also from the sponsor, but reflect general magnitudes of change from visit 5 baseline to last observation.

The comparisons of active to placebo was significant for DBP (p=0.017, 0.009 by T test for 4 and 8 mg compared to placebo respectively by Dr. K. Mahjoob), as they were for SBP differences.

Comparison A versus B			p-value (2-sided)
Candesartan cilixetil 4 mg	placebo	ITT	0.0454*
		PP	0.0126*
Candesartan cilixetil 8 mg	placebo	ITT	0.0028*
		PP	0.0005*
Candesartan cilixetil 4 mg	Candesartan cilixetil 8 mg	ITT	0.2167
		PP	0.2164

ANOVA with "treatment" and "centre" as factors.

Centres with less than 4 patients were pooled.

\* p-value < 5%.

For response to treatment (i.e. SDBP < 90 mm Hg decrease of ≥ 10 mm Hg from baseline),

Response rates taken at the individual endpoint across treatment groups.

	HCTZ + Placebo		HCTZ + Cand. cil. 4mg		HCTZ + Cand. cil. 8mg	
ITT	32.7%	16/49	46.8%	44/94	53.8%	49/91
PP	33.3%	14/42	52.6%	41/78	56.0%	42/75

These findings were significant at p < 0.05.

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Safety

The overall frequency of adverse events was:

**T-Table 16**  
**Frequency of adverse events (AE) (all patients included, n = 325)**

Population	Study period of AE occurrence	Patients affected by at least 1 AE		
		Percentage	Number	
Run-in n = 63	4 weeks	15.9%	10	
HCTZ n = 28	run-in 4 weeks	14.3%	4	
	HCTZ 6 weeks	21.4%	6	
	Total 10 weeks	35.7%	10	
HCTZ / Elacebo n = 49	run-in 4 weeks	8.2%	4	
	HCTZ 6 weeks	14.3%	7	
	Add-on 8 weeks	28.6%	14	
	Total 18 weeks	40.8%	20	
Safety Population n = 234	HCTZ / Cand. cil. 4mg n = 94	run-in 4 weeks	11.7%	11
		HCTZ 6 weeks	13.8%	13
		Add-on 8 weeks	31.9%	30
		Total 18 weeks	43.6%	41
Safety Population n = 234	HCTZ / Cand. cil. 8mg n = 91	run-in 4 weeks	9.9%	9
		HCTZ 6 weeks	20.9%	19
		Add-on 8 weeks	25.3%	23
		Total 18 weeks	39.6%	36
<b>Overall total</b>		<b>36.0%</b>	<b>117</b>	

No deaths occurred.

Serious adverse events were:

**Serious adverse events (SAE) (all patients included, n = 325)**

Population	Treatment group	patient scr. no.	Study period of SAE occurrence	Event
Run-in n = 63	-	-	-	no SAE
HCTZ n = 28	-	1442	HCTZ	Ischias
		1572	run-in	Endometrial hyperplasia
Safety Population n = 234	HCTZ / Placebo n = 49	-	-	no SAE
Safety Population n = 234	HCTZ / Cand. cil. 4mg n = 94	1234	Add-on	Removal of nasal polypus
		1571	Add-on	Epistaxis

Adverse events leading to withdrawal during the DB period were:

Patient 1270 (centre 18, 4 mg): headache (unknown relationship), dizziness (unknown relationship); withdrawn at Visit 6.

Patient 1320 (centre 22, 4 mg): muscle cramp (definitely related); withdrawn at Visit 7.

Patient 1052 (centre 4, 8 mg): vertigo (probably related), arrhythmia (possibly related), withdrawn at Visit 7.

Patient 1607 (centre 21, 8 mg): anxiety (definitely related), withdrawn at Visit 7.

The most common adverse events were:

HCTZ + Placebo n = 49	HCTZ + Candesartan cilexetil 4 mg n = 94	HCTZ + Candesartan cilexetil 8 mg n = 91
hypertriglyceridaemia 2 patients (4.1%)	headache 4 patients (4.3%)	vertigo 3 patients (3.3%)
upper respiratory tract infection 2 patients (4.1%)	diarrhoea 3 patients (3.2%)	coughing 2 patients (2.2%)
	arthralgia 2 patients (2.1%)	headache 2 patients (2.2%)
	muscle cramp 2 patients (2.1%)	
	throat sore 2 patients (2.1%)	

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Changes in laboratory values were:

Change from Visit 1 to Visit 7	HCTZ + Placebo total n = 49 within		HCTZ + Cand. cil. 4 mg total n = 94 within		HCTZ + Cand. cil. 8 mg total n = 91 within	
	below	above	below	above	below	above
<i>Haematology</i>						
Red cell count	-	-	3	-	3	-
Haematocrit	2	1	3	1	3	1
Haemoglobin	1	-	1	-	1	-
Platelet count	-	1	-	-	2	-
White cell count	-	1	-	1	1	2
<i>Metabolites</i>						
Glucose	1	-	5	3	5	6
Triglycerides	-	4	-	8	-	3
Cholesterol, total	-	9	-	7	-	12
Uric acid	2	1	1	7	1	4
Creatinine	2	-	2	1	1	1
Bilirubin, total	-	1	3	-	2	1
Urea nitrogen	-	2	-	2	1	3
<i>Electrolytes</i>						
Sodium	5	-	5	-	5	-
Potassium	-	1	-	-	1	1
<i>Liver enzymes</i>						
Alkaline phos	-	-	-	-	-	-
AST (SGOT)	-	2	-	-	-	4
ALT (SGPT)	-	1	-	3	-	5
γ-GT	-	2	-	4	-	8

- = 0

Reading example: For triglycerides, 4 patients in the placebo group shifted from "within normal range" at Visit 1 to "above normal range" at Visit 7.

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Mean potassium and increased uric acid values did not differ between groups or from baseline to end of DB period. Cardiovascular abnormalities found during the entire study were summarized as:

- Patient 1032 (HCTZ + Candesartan cilexetil 8 mg) lower limbs varices (Visit 1 and 7)
- Patient 1052 (HCTZ + Candesartan cilexetil 8 mg) slowing down of the rhythm (Visit 7)
- Patient 1181 (HCTZ + Candesartan cilexetil 4 mg) functional venous insufficiency (Visit 1 and 7)
- Patient 1185 (HCTZ + Candesartan cilexetil 8 mg) murmur aortic insufficiency (Visit 1 and 7)
- Patient 1237 (HCTZ + Candesartan cilexetil 8 mg) small varices (Visit 1 and 7)
- Patient 1239 (HCTZ + Candesartan cilexetil 8 mg) varices (Visit 1 and 7)
- Patient 1240 (HCTZ + placebo) venous insufficiency (Visit 1 and 7)
- Patient 1245 (HCTZ + Candesartan cilexetil 4 mg) venous insufficiency (Visit 1, 6 and 7)
- Patient 1272 (HCTZ + placebo) venous insufficiency (Visit 1 and 7)
- Patient 1273 (HCTZ + Candesartan cilexetil 4 mg) venous insufficiency (Visit 1 and 7)
- Patient 1274 (HCTZ + Candesartan cilexetil 8 mg) venous insufficiency (Visit 1 and 7)
- Patient 1306 (HCTZ + placebo) venous insufficiency (Visit 1 and 7)
- Patient 1308 (HCTZ + Candesartan cilexetil 8 mg) venous insufficiency (Visit 1 and 7)
- Patient 1314 (HCTZ + Candesartan cilexetil 4 mg) venous insufficiency (Visit 1 and 7)
- Patient 1609 (HCTZ + Candesartan cilexetil 4 mg) venous insufficiency (Visit 1 and 7)
- Patient 1362 (HCTZ + Candesartan cilexetil 8 mg) venous insufficiency (Visit 7)
- Patient 1363 (HCTZ + placebo) left bundle branch block (Visit 1 and 7)
- Patient 1364 (HCTZ + Candesartan cilexetil 4 mg) ventricular hypertrophy (Visit 1 and 7)
- Patient 1501 (HCTZ + Candesartan cilexetil 4 mg) varices (Visit 1 and 7)

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6.15 Study EC403 - Dose-finding study of Candesartan cilexetil (TCV-116)/HCTZ combination (2, 4, 8, 16 mg for Candesartan; 12.5, 25 mg for HCTZ) in patients with mild to moderate essential hypertension (95-110 mm Hg DBP).

Double-blind, randomized, multicenter (120 in Germany) parallel group factorial design study.

First enrollment: February 1, 1995

Last completed: January 22, 1996

Principal Investigator: Dr. Thomas Philipp.

Drugs and placebo manufactured by \_\_\_\_\_ The study drugs or combinations were to be provided as tablets, identical in appearance, taste and smell.

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

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

Primary objectives:

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

Secondary objectives:

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

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

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Sample size assumptions in the different cells were:

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

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

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

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

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

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

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One sided tests were used for planning and analysis.

On a priori specification of the order of a family group of testing was noted. If one family was non-significant, no other family groups would be tested.

For a combination to be judged effective, it would have to be significantly superior to each monotherapy component.

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

combinations, pooled placebo means to HCTZ pooled means, pooled placebo means to pooled Candesartan means.

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

Next one combination would be compared to placebo and each other. A series of these at each combination would be done.

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

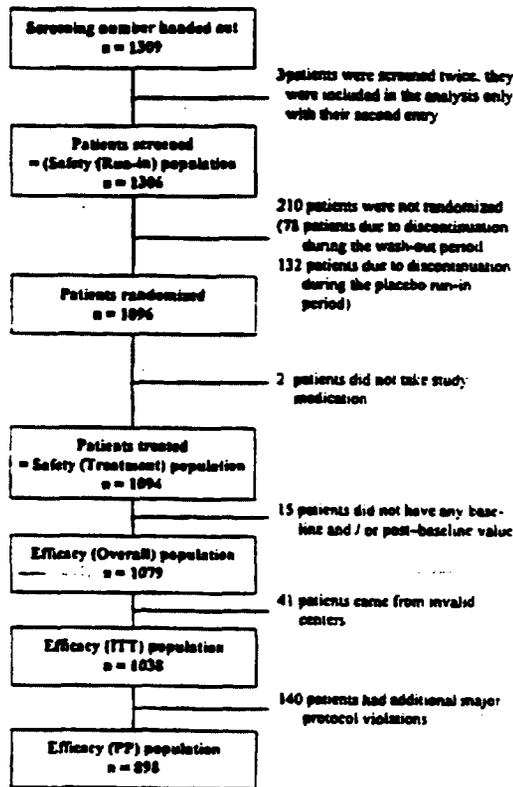
A computer generated randomization list was used as prepared by TAKEDA. There was unequal randomization and a block size of "51."

The study flow chart was:

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

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The disposition of those who entered the study was:



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

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

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

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Baseline characteristics were:

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

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