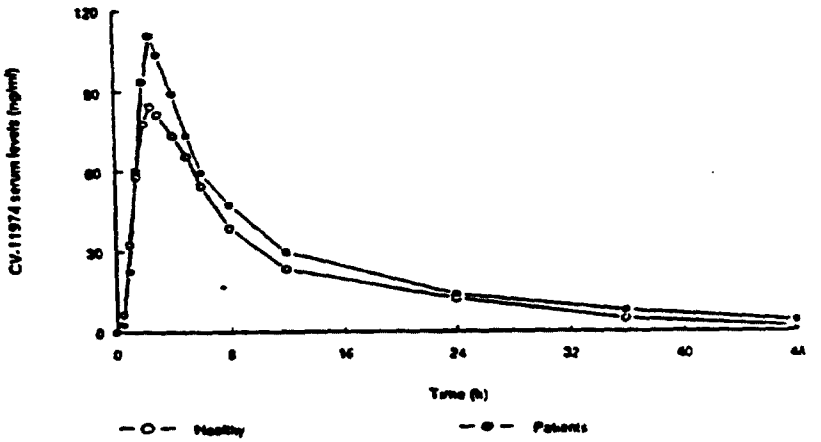


Day 7 PK results were:

LIVER IMPAIRED PATIENTS

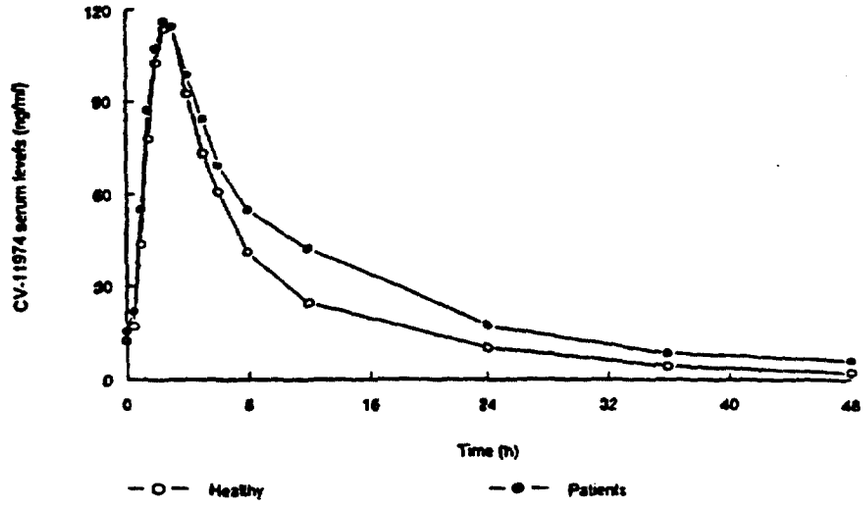
	Arithmetic					Geometric		
	Mean	SD	95% C.I. of the mean lower - upper	Median	75% percentile	Mean	SD	95% C.I. of the mean lower - upper
$T_{1/2}$(h)	12	4.2	8.5 - 15	10	15			
C_{max} (ng/ml)	15.4	13.8	6.58 - 24.1	14.1	19.4			
C_{max} (ng/ml)						112	50.2	85.3 - 147
C_{av} (ng/ml)						45.3	18.9	35.1 - 56.4
T_{max} (h)	2.8	1.1	2.2 - 3.5	2.5	3.3			
T_{pm} (actual)								
AUC_{∞}(ng.h/ml)						1080	458	834 - 1399
R_{AC}						1.0	0.31	0.80 - 1.2
PTF						2.1	1.0	1.6 - 2.8
PTS						7.7	1.2	3.7 - 16
MRT_{ext} (h)						12	2.6	10 - 14

HEALTHY VOLUNTEERS

	Arithmetic					Geometric		
	Mean	SD	95% C.I. of the mean lower - upper	Median	75% percentile	Mean	SD	95% C.I. of the mean lower - upper
$T_{1/2}$(h)	10	2.1	8.2 - 11	10	11			
C_{max} (ng/ml)	12.3	5.12	9.03 - 15.5	11.1	16.0			
C_{max} (ng/ml)						116	31.2	98.0 - 137
C_{av} (ng/ml)						36.9	8.48	32.0 - 42.6
T_{max} (h)	2.6	0.36	2.4 - 2.8	2.5	3.0			
T_{pm} (actual)								
AUC_{∞} (ng.h/ml)						880	205	760 - 1018
R_{AC}						1.0	0.38	0.8 - 1.2
PTF						2.8	0.47	2.5 - 3.1
PTS						9.2	5.0	6.7 - 13
MRT_{ext} (h)						10	1.3	9.3 - 11

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY



Numerical differences were not statistically significant.

The Candesartan free fraction results were:

UNBOUND CV-11974 IN SERUM IN % OF TOTAL AMOUNT OF CV-11974

Healthy volunteers

Subject	Day 1	Day 7
1	0.446	0.414
2	0.471	0.440
3	0.468	0.454
4	0.494	0.436
5	0.481	0.479
6	0.466	0.468
7	0.550	0.550
8	0.501	0.644
9	0.555	0.521
10	0.543	0.556
20	0.463	0.509
25	0.520	0.494
Mean	0.497	0.489
SD	0.037	0.048
Lower limit of 95% C.I.	0.473	0.458
Upper limit of 95% C.I.	0.520	0.519
Median	0.488	0.487

Liver patients

Subject	Day 1	Day 7
11	0.610	0.633
12	0.710	
13	0.469	0.436
14	0.428	0.433
15	0.438	0.392
16	0.420	0.410
17	0.510	0.527
18	0.483	0.498
19	0.540	0.520
21	0.488	0.458
22	0.545	0.520
23	0.596	0.595
24	0.563	0.549
Mean	0.523	0.498
SD	0.063	0.074
Lower limit of 95% C.I	0.473	0.450
Upper limit of 95% C.I.	0.573	0.545
Median	0.510	0.509

Safety

No deaths or serious adverse events were reported. Patient 12 withdrew consent but not for an adverse event. There were 11 adverse events reported; 7 in hepatic cases, 4 in normals. Fatigue, diarrhea, bronchitis, paresthia were reported. Liver chemistries that were abnormal remained so at the same level. 3 patients (1 normal, 2 liver cases) developed slightly elevated potassium levels, including patient #12. ECGs and vital signs remained normal.

5.6 Study EC021 - Double-blind, randomized, placebo controlled, multiple dose (2, 4 and 8 mg) crossover study of Candesartan in healthy elderly volunteers. See also EC037. Volumes 1.74, 1.75

Study Period: October 5, 1993 to May 1, 1994.
Drugs: Placebo, Candesartan cilexetil 2, 4 and 8 mg; manufactured by

Inclusion Criteria: Healthy males or females, 65-85 years of age.
Exclusion Criteria: history of relevant chronic or recurrent renal, hepatic, CV, neurological or other disease; abnormal chemistry values; smoker of more than 20 cigarettes/day; taken an OTC or prescription drug within 14 days of the study.
Randomization:

The subjects were randomly assigned to one of the seven dosing regimens described below according to their study number:

Dosing Sequence	Subject Numbers
2-4-8	6, 12, 18
2-8-4	1, 11
4-2-8	2, 10, 15, 24*
4-8-2	5, 8
8-2-4	3, 14, 19
8-4-2	4, 9, 16, 28*
0-0-0 (Placebo)	7, 13, 17

* Replacement numbers

Based on their individual number, 18 subjects were randomized to each candesartan cilexetil dose level and three subjects received placebo treatment throughout study conduct:

Treatment A: 1 x 2.0 mg tablet of candesartan cilexetil with 120 mL of water on Day 1 and again on Days 3-9.

Treatment B: 1 x 4.0 mg tablet of candesartan cilexetil with 120 mL of water on Day 1 and again on Days 3-9.

Treatment C: 1 x 8.0 mg tablet of candesartan cilexetil with 120 mL of water on Day 1 and again on Days 3-9.

Treatment D: 1 x placebo tablet with 120 mL of water on Day 1 and again on Days 3-9.

Blood samples for Candesartan and metabolite were taken on days 1, 7, 8 and 9. Blood for renin activity, aldosterans, angiotensin I and II and angiotensin converting activity were taken on days 1, 4 and 9.

Results

21 subjects enrolled; 18 completed the study. Of the 18, 10 were male and 8 female. Mean age: 68.5 years. All were Caucasian.

Pharmacokinetics

For day 1, PK results for Candesartan (CV-11974) were:

Serum CV-11974 Non-Compartmental Pharmacokinetic Parameters - Day 1

Least-Squares Mean

Dose Level	Cmax (ng/mL)	Tmax (hour)	AUC 0-24h (ng*hr/mL)	AUC-INF (ng*hr/mL)	MRT (hour)	KEL (1/hour)	t1/2 (hour)
2.0 mg	22.12 a	3.6 a	213.37 a	244.51 a	11.58 a	0.0998 a	7.29 a
4.0 mg	42.51 b	4.2 a	425.85 b	491.53 b	11.97 a	0.0903 a	7.83 a
8.0 mg	84.31 c	4.1 a	871.39 c	1017.84 c	12.41 a	0.0864 b	8.17 a

Note: In each column means marked with the same letter are not statistically significantly different. Means with different letters are statistically significantly different at the 0.05 level.

For day 9, PK results for Candesartan were:

APPEARS THIS WAY ON ORIGINAL

Serum CV-11974 Non-Compartmental Pharmacokinetic Parameters - Day 9

Least-Squares Mean

Dose Level	Cmax (ng/mL)	Tmax (hour)	Cmin (ng/mL)	AUC 0-24h (ng*hr/mL)	KEL (1/hour)	t1/2 (hour)	MRT (hour)	Cavg (ng/mL)	FLUCT	Accumulation Factor
2.0 mg	26.56 a	4.1 a	2.23 a	253.89 a	0.0916 a	7.70 a	7.68 a	10.6 a	2.241 a	1.23 a
4.0 mg	49.33 b	4.5 a	4.71 b	498.01 b	0.0943 a	7.62 a	7.79 a	20.8 b	2.151 a	1.16 a
8.0 mg	79.00 c	4.4 a	9.88 c	856.55 c	0.0746 b	9.70 b	8.62 b	35.7 c	1.926 a	1.03 a

Note: In each column means marked with the same letter are not statistically significantly different. Means with different letters are statistically significantly different at the 0.05 level.

A gender analysis of the day 9 results was:

Serum CV-11974 Non-Compartmental Pharmacokinetic Parameters by Gender - Day 9

Mean (Standard Deviation)

Dose Level	Gender	N	Cmax (ng/mL)	Tmax (hour)	Cmin (ng/mL)	AUC (ng*hr/mL)	KEL (1/hour)	t1/2 (hour)	MRT (hour)	Cavg (ng/mL)	FLUCT	Accumulation Factor
2.0 mg	Female	6	26.43 (13.29)	3.7 (1.0)	1.96 (1.54)	260.21 (90.78)	0.0842 (0.0304)	8.61 (3.01)	7.64 (0.78)	11.2 (4.1)	2.171 (0.300)	1.25 (0.46)
	Male	8	25.83 (10.81)	4.5 (1.9)	2.25 (1.36)	229.43 (61.27)	0.0904 (0.0098)	7.75 (0.89)	7.78 (1.37)	9.5 (2.5)	2.302 (0.467)	1.20 (0.43)
4.0 mg	Female	6	56.64 (27.57)	4.3 (2.2)	5.99 (1.56)	501.30 (207.50)	0.0925 (0.0256)	7.92 (1.00)	7.64 (0.91)	24.6 (12.9)	2.046 (0.204)	1.22 (0.28)
	Male	8	43.60 (12.43)	4.6 (1.7)	3.75 (0.75)	427.97 (60.64)	0.0975 (0.0166)	8.00 (1.63)	7.97 (0.99)	17.8 (3.4)	2.210 (0.537)	1.10 (0.19)
8.0 mg	Female	6	91.02 (39.09)	4.7 (2.1)	8.67 (5.12)	897.94 (306.66)	0.0752 (0.0304)	8.99 (3.21)	8.45 (0.76)	37.4 (11.1)	2.195 (0.256)	0.97 (0.23)
	Male	8	66.06 (17.60)	4.4 (1.8)	10.67 (3.07)	814.06 (177.37)	0.0720 (0.0192)	10.22 (2.62)	8.59 (0.99)	34.0 (7.4)	1.797 (0.289)	1.05 (0.14)

Gender differences were noted for C_{max} and AUC, particularly for the 4 and 8 mg Candesartan cilexetil doses.

BEST POSSIBLE COPY

Pharmacodynamics

For various PD measurements, results were summarized:

AUC of Pharmacodynamic Variables Following Candesartan Cilexetil

Least-Squares Mean

Day	Dose Level	Plasma Angiotensin I (ng•hr/mL)	Plasma Angiotensin II (pg•hr/mL)	Serum A.C.E. ((nmol/min/mL)•hr)	Plasma Renin Activity ((ng/mL/hr)•hr)	Aldosterone Concentration (pg•hr/mL)
1	2.0 mg	5.52 a	245.62 a	2388.17 a	42.48 a	474.30 a
	4.0 mg	5.13 a	215.48 a	2374.78 a	39.84 a	383.75 a
	8.0 mg	5.34 a	334.48 a	2251.06 a	52.39 a	202.14 b
9	2.0 mg	12.49 a	480.96 a	2303.86 a	92.32 a	480.50 a
	4.0 mg	13.99 a	709.94 a	2402.16 a	128.36 a	400.07 a
	8.0 mg	15.98 a	878.88 b	2372.92 a	179.83 b	392.80 a

Note: In each column for each Day, means marked with the same letter are not statistically significantly different. Means marked with different letters are statistically significantly different at the 0.05 level.

Placebo results for angiotensin II and Renin were:

APPEARS THIS WAY ON ORIGINAL

Plasma Angiotensin II Concentration Following Placebo

Mean (Standard Deviation)
(pg/mL)

Dosing Period	Day	N	Number of Hours from Dosing 0	6	12	24
1	1	2	2.75 (0.07)	9.75 (7.28)	5.30 (3.06)	5.63 (4.56)
	9	2	3.95 (0.49)	11.10 (.)	4.93 (1.25)	4.25 (2.76)
2	1	3	2.97 (0.85)	4.87 (1.60)	3.30 (0.70)	3.35 (0.92)
	9	3	2.87 (0.65)	9.33 (2.10)	5.60 (1.06)	3.03 (1.10)
3	1	3	7.63 (6.65)	14.07 (14.02)	9.20 (8.06)	6.23 (1.45)
	9	3	4.43 (1.25)	7.67 (3.77)	7.90 (2.40)	5.03 (2.83)

Individual Plasma Renin Activity
Following Placebo - Day 9

(ng/mL/hr)

Subject	Sequence	Dosing Period	Number of Hours from Dosing 0	6	12	24
7	0-0-0	1	1.0	.	1.7	1.0
7	0-0-0	2	0.5	1.4	1.2	0.4
7	0-0-0	3	0.9	1.5	1.2	0.4
13	0-0-0	1	1.5	3.5	1.7	1.6
13	0-0-0	2	0.7	3.1	1.8	0.6
13	0-0-0	3	0.9	.	1.8	1.0
17	0-0-0	1	0.4	2.6	0.7	0.4
17	0-0-0	2	0.4	2.2	1.0	0.6
17	0-0-0	3	0.0	0.6	0.5	0.0
N			9	7	9	9
MEAN			0.70	2.13	1.29	0.67
STANDARD DEVIATION			0.44	1.03	0.49	0.47

Safety

No deaths or serious adverse events were reported. Shifts in chemistries were reported for placebo and active groups from normal at baseline to above the ULN as well as from normal to low. Patients on Candesartan had significant increases in ALT, creatinine and urea and significant decreases in bilirubin lactic dehydrogenase hemoglobin and erythrocytes. Placebo patients had significant increases in creatinine. There was a significant decrease in erythrocytes, hemoglobin and hemotocrit in all ECG changes occurred in placebo and active groups. Most frequently sinus bradycardia, APCs, partial bundle branch blocks were found.

5.7 Study EC037 - Double-blind, randomized, multiple dose (8, 12, 16 mg) crossover study of Candesartan cilexetil in healthy elderly volunteers.
NDA Volumes 1.75, 1.76, 1.77

Study Period: February 25, 1995 to June 7, 1995.
Drugs manufactured by

The protocol was the same as that for study EC021, but for the dose extension. No placebo was included. There was a 2 week washout between doses.
Randomization: 42 randomization numbers were generated, each number representing one of six dosing sequences. Assignment was:

Dosing Period 1	2	3	Subject Number
8.0	12.0	16.0 mg	3.7
12.0	16.0	8.0 mg	1.8
16.0	8.0	12.0 mg	4.10
8.0	16.0	12.0 mg	5.9
12.0	8.0	16.0 mg	2.11
16.0	12.0	8.0 mg	6.12

APPEARS THIS WAY ON ORIGINAL

Results

12 subjects, all Caucasian, 9 male, 13 female, mean age 68.6 years were enrolled and completed.

Pharmacokinetics

For day 1, results for Candesartan (CV-11974) were:

Serum CV-11974 Noncompartmental Pharmacokinetic Parameters - Day 1
Least-Squares Means

Dose Level	Cmax (ng/ml)		Tmax (hour)		AUC(0-24) (ng·hr/ml)		AUC(0-t) (ng·hr/ml)		AUC(0-INF) (ng·hr/ml)		Kel		Halflife (hour)		MRT (hour)	
8.0 mg	81.02	A	5.00	A	809.85	A	895.64	A	3013.24	A	.0646	A	12.01	A	15.10	A
12.0 mg	100.09	A	4.75	A	1120.46	A	1209.07	B	1406.92	B	.0517	A	14.10	A	17.47	A
16.0 mg	163.89	B	4.75	A	1760.62	B	1972.78	C	2268.14	C	.0570	A	13.64	A	17.40	A

Note: In each column, means marked with the same letter are not statistically different at the .05 level

For day 9,

Serum CV-11974 Noncompartmental Pharmacokinetic Parameters - Day 9
Least-Squares Means

Dose Level	Cmax (ng/ml)		Tmax (hour)		Cmin (ng/ml)		Cavg (ng/ml)		AUC(0-24) (ng·hr/ml)		Kel		Halflife (hour)		MRT (hour)		Accumulation Factor		Fluctuation Index	
8.0 mg	81.02	A	4.17	A	8.66	A	34.33	A	831.20	A	.0630	A	11.00	A	14.25	A	1.0262	A	2.066	A
12.0 mg	145.76	B	4.08	A	15.43	B	56.02	B	1361.59	B	.0627	A	11.00	A	14.00	A	1.2194	A	2.181	A
16.0 mg	179.01	B	4.42	A	16.19	B	75.04	C	1801.00	C	.0618	A	11.08	A	15.05	A	1.0937	A	2.112	A

Note: In each column, means marked with the same letter are not statistically different at the .05 level

No gender analysis was done because of the small number of females.

BEST POSSIBLE COPY

Pharmacodynamics:

For various measurements, results were:

Least-Squares Means for AUC of Pharmacodynamic Variables

Dose	Plasma Angiotensin I (ng*hr/ml)		Plasma Angiotensin II (pg*hr/ml)		Serum A.C.E. ((nmol/min/ml)*hr)		Plasma Renin Activity ((ng/ml/hr)*hr)		Aldosterone Concentration (pg*hr/ml)	
8.0 mg	7.39	A	945.95	A	2517.42	A	274.93	A	836.12	A
12.0 mg	8.20	A	1052.09	A	2523.49	A	320.04	AB	776.62	A
16.0 mg	10.33	A	1351.13	B	2533.88	A	372.73	B	770.75	A

Note: In each column, means marked with the same letter are not statistically different at the 0.05 level.

Blood Pressure

There was some effect of the drug on blood pressure, as noted below:

Variable	Dose (mg)	Day 1 (mmHg)	Day 3 (mmHg)
Supine Systolic	8.0	123.2	111.6
	12.0	121.0	113.2
	16.0	118.1	115.8
Supine Diastolic	8.0	73.6	67.0
	12.0	71.0	67.4
	16.0	70.2	67.1
Sitting Systolic	8.0	128.7	115.6
	12.0	119.9	115.4
	16.0	121.7	117.8
Sitting Diastolic	8.0	74.7	69.4
	12.0	72.1	69.6
	16.0	73.2	69.5
Standing Systolic	8.0	121.4	112.0
	12.0	120.9	115.5
	16.0	124.6	116.1
Standing Diastolic	8.0	76.2	71.3
	12.0	73.3	69.9
	16.0	74.5	72.3

APPEARS THIS WAY ON ORIGINAL

Safety

No deaths, serious adverse events or withdrawals for adverse events were reported. Headache and syncope were reported most frequently; two times each. Syncope occurred in 2 patients on the 8 mg dose, 7-8 hours post dosing.

For laboratory variables, one patient developed anemia. There was overall a significant decrease in erythrocytes, hemoglobin, and hematocrit that was similar for all doses. Platelet count was also significantly decreased in all dose groups, but not to thrombocytopenic levels. ECG changes occurred. Sinus bradycardia was the finding in most cases.

Comments

This study and EC021 were compared to PK values found in healthy young subjects (from studies EC002, and EC002A) as follows:

Combined Serum CV-11974 Nonompartmental Pharmacokinetic Parameters on Day 9

Dose	Age	Study Number	Cmax (mg/ml)	Tmax (hour)	Cmin (mg/ml)	Cavg (mg/ml)	AUC(0-24) (mg*hr/ml)	Kel	Halflife (hour)	MRT (hour)	Accumulation Factor	Fluctuation Index
2.0 mg	18-40	EC002	17.11	3.97	0.45	6.06	145.38	.1202	6.31	7.23	1.1588	2.764
	65-85	EC021	26.56	4.14	2.23	10.58	253.89	.0916	7.70	7.68	1.2308	2.241
4.0 mg	18-40	EC002	28.32	3.61	1.31	10.02	240.34	.1078	7.15	7.75	1.1146	2.661
	65-85	EC021	49.33	4.46	4.73	20.75	498.01	.0943	7.62	7.79	1.1551	2.151
8.0 mg	18-40	EC002	60.48	3.76	3.48	21.28	510.80	.0990	7.30	7.67	1.1707	2.609
	65-85	EC021	79.00	4.43	9.88	35.69	856.55	.0746	9.70	8.62	1.0185	1.926
	65-85	EC037	81.02	4.17	8.66	34.33	831.29	.0620	11.68	14.25	1.0362	2.068
12.0 mg	18-40	EC038	60.66	3.67	5.75	26.07	625.62	.0439	17.82	8.76	1.0303	2.012
	65-85	EC037	145.78	4.08	15.43	56.82	1363.59	.0627	11.80	14.90	1.2194	2.181
16.0 mg	18-40	EC002A	119.15	4.00	5.17	42.87	1028.79	.1046	6.96	7.83	1.0208	2.622
	65-85	EC037	179.01	4.42	16.19	75.04	1801.09	.0618	11.98	15.05	1.0937	2.112

The sponsor suggests that the differences in PK (C_{max}, AUC, $T_{1/2}$) between the healthy young and the healthy old are due to increased bioavailability in the elderly (? gut transit) and decreased clearance. While patients with chronic disease (kidney, liver) or clinically significant laboratory abnormalities were excluded, it is possible that diminished renal might have been present and not been detected by serum creatinine or BUN levels at entrance.

This PK effect of older age needs to be considered with other factors known to increase Candesartan blood levels e.g. renal impairment, HCTZ therapy. Whether the effect of multiple factors creates an additive, exponential or other effect on Candesartan blood levels is unknown.

APPEARS THIS WAY
ON ORIGINAL

Safety

Reported adverse events were:

subj. no.	treatment	AE as reported	AE as coded (WHO term)	severity	causal relationship	actions
4	placebo	headache	headache	mild	not related	none
4	placebo	thoracic pain	chest pain	mild	not related	none
14	placebo	headache	headache	moderate	not related	none
14	placebo	constipation	constipation	moderate	not related	none
14	placebo	epigastric discomfort	abdominal pain	moderate	possibly related	none
60	8 mg TCV-116	vomiting	vomiting	moderate	not related	none
60	8 mg TCV-116	nausea	nausea	moderate	not related	none
60	8 mg TCV-116	headache	headache	moderate	not related	one 500 mg tablet paracetamol

Laboratory

Subject 14 had a large increase in bilirubin due to Gilbert's syndrome. He was on placebo.

APPEARS THIS WAY
ON ORIGINAL

5.8 Study EC028: Double-blind, crossover, randomized, placebo-controlled, pharmacokinetic interaction study of Candesartan cilexetil (TCV-116), 12 mg capsule, and hydrochlorothiazide, 25 mg capsule, after repeated oral dose administration in 18 healthy males.
NDA Volume 1.79.
Since these drugs may well be coprescribed, this PK study was indicated.
Performed in Belgium, November 1993-June 1994.
Principal Investigator: R. Lins, M.D.
Drugs manufactured by

There was a 3 period (each 7 days) crossover study without washout. Each subject was randomly assigned to one of 6 treatment sequences as follows:

	SESSION 1	SESSION 2	SESSION 3
ARM A	HCTZ + Placebo	TCV-116 + Placebo	HCTZ + TCV-116
ARM B	HCTZ + TCV-116	HCTZ + Placebo	TCV-116 + Placebo
ARM C	TCV-116 + Placebo	HCTZ + TCV-116	HCTZ + Placebo
ARM D	HCTZ + Placebo	HCTZ + TCV-116	TCV-116 + Placebo
ARM E	TCV-116 + Placebo	HCTZ + Placebo	HCTZ + TCV-116
ARM F	HCTZ + TCV-116	TCV-116 + Placebo	HCTZ + Placebo

Doses : HCTZ : 25 mg capsule
TCV-116 : 12 mg capsule
Placebo : capsule

Blood samples were obtained on days 7, 14 and 21. Because the assessment was on the last day of each treatment period, the sponsor assumed no washout was needed.

Besides the PK interaction study, safety was to be assessed by symptoms, physical and laboratory evaluations.

Two parameters with unfamiliar identifiers were: 1) percent peak trough fluctuations (% PTE) and 2) mean residence time, calculated over one 24-hour dosing interval (MRT). One subject (#7) had no level of either Candesartan cilexetil metabolite on day 7 of session 2. The data for that subject were not included in the results that follow. As noted 18 healthy males participated. Data from 17 were presented.

HCTZ PK Interaction

The following results were provided:

Table 3 : Pharmacokinetic parameters of HCTZ at steady-state after once daily administration for 7 days of 25 mg HCTZ given with placebo or with 12 mg TCV-116 in healthy subjects.

Parameter	HCTZ + placebo	HCTZ + TCV-116	p *	90%CI for combin./alone ratio **
Cmax (ng/mL)	112	105	0.14	88 - 101 %
Tmax (h)	3	3	0.50	94 - 122 %
Cmin (ng/mL)	5.8	4.4	0.45	24 - 129 %
AUCτ (ng.h/mL)	877	752	<0.01	79 - 93 %
MRTτ (h)	7.2	6.9	0.26	90 - 102 %
%PTF (%)	291	323	0.04	102 - 120 %
Tλzel (h)	9.7	9.1	0.66	72 - 121 %

Tmax values are median (range). Cmin values are means (SD). Other values are geometric means (mean - 1 SD; mean + 1 SD) (N=18).

** : Statistical significance of the difference between formulation means.*

*** : Standard 90% confidence interval for the expected mean of the* (HCTZ+TCV)/(HCTZ alone) *ratio, derived from ANOVA for continuous parameters, and from a nonparametric method for Tmax.*

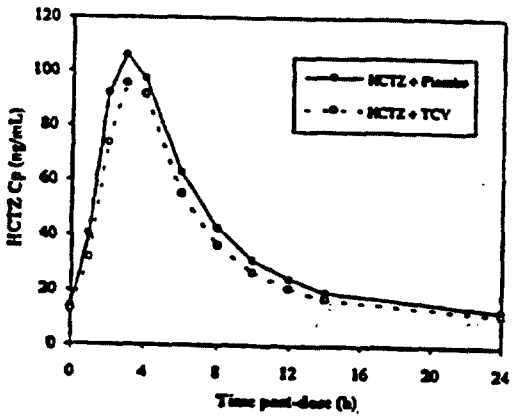


Fig. 1 : Average HCTZ serum concentration vs. time profiles (geometric means; n=18) at steady-state after once daily administration for 7 days of 25 mg HCTZ given with placebo (•) or with 12 mg TCV-116 (o) in healthy subjects.

The individual variability of the interaction was shown as follows:

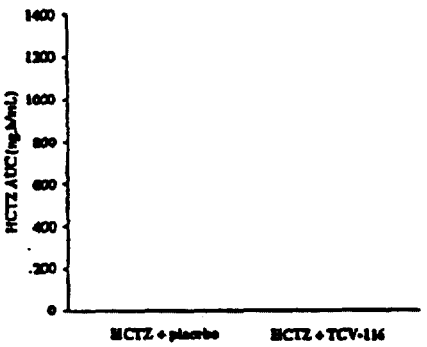


Fig. 2 : Individual HCTZ AUCτ values at steady-state after once daily administration for 7 days of 25 mg HCTZ given with placebo or with 12 mg TCV-116 in healthy subjects.

Candesartan PK Interaction

The sponsor provided the following results:

Table 4 : Pharmacokinetic parameters of TCV-116 metabolites MI (CV-11974) and MII (CV-15959) at steady-state after once daily administration for 7 days of 12 mg TCV-116 given with placebo or with 25 mg HCTZ, in healthy subjects.

CV-11974

Parameter	TCV-116 + placebo	TCV-116 + HCTZ	p *	90%CI for combin./alone ratio **
Cmax (ng/mL)	78	96	0.04	106 - 143 %
Tmax (h)	4	4	0.41	82 - 115 %
Cmin (ng/mL)	6.8	7.7	0.21	89 - 136 %
AUCτ (ng.h/mL)	750	886	0.02	105 - 133 %
MRTτ (h)	8.4	8.4	0.92	94 - 105 %
%PTF (%)	227	238	0.36	97 - 115 %
T½el (h)	9.9	10.7	0.40	90 - 129 %

CV-15959

Parameter	TCV-116 + placebo	TCV-116 + HCTZ	p *	90%CI for combin./alone ratio **
Cmax (ng/mL)	11.4	14.1	0.04	107 - 148 %
Tmax (h)	6	4	0.22	82 - 105 %
Cmin (ng/mL)	4.2	5.0	0.23	100 - 149 %
AUCτ (ng.h/mL)	189	228	0.07	105 - 143 %
MRTτ (h)	10.8	10.9	0.73	97 - 104 %
%PTF (%)	89	96	0.18	98 - 117 %
T½el (h)	17.3	17.9	0.62	91 - 117 %

Tmax values are median (range). Other values are geometric means (mean - 1 SD ; mean + 1 SD) (N=17 except for Cmin : N=16).

** : Statistical significance of the difference between formulation means.*

*** : Standard 90% confidence interval for the expected mean of the* (TCV+HCTZ)/(TCV alone) *ratio, derived from ANOVA for continuous parameters, and from a nonparametric method for Tmax.*

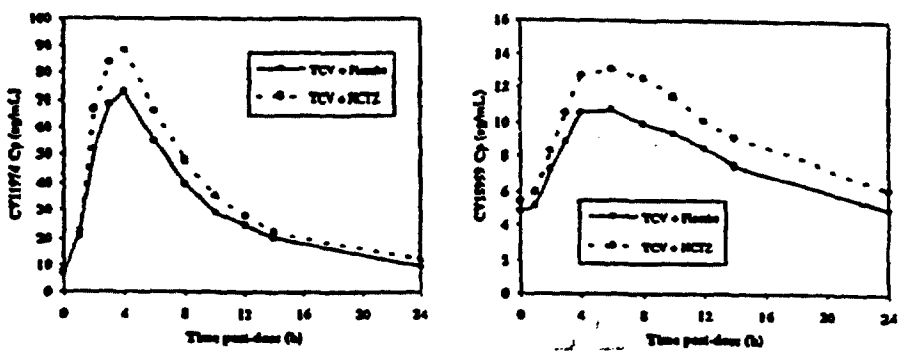


Fig. 3 : Average serum concentration vs. time profiles of TCV-116 metabolites MI (CV-11974; left) and MII (CV-15959; right) at steady-state after once daily administration for 7 days of 12 mg TCV-116 given with placebo (•) or with 25 mg HCTZ (o) in healthy subjects. Values are geometric means (n=17).

For individuals the increase in Candesartan was not universal:

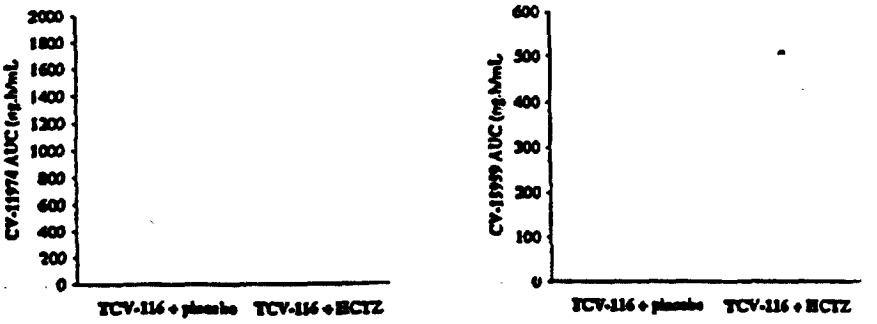


Fig. 4 : Individual AUCτ values of CV-11974 (left) and CV-15959 (right) at steady-state after once daily administration for 7 days of 12 mg TCV-116 given with placebo or with 25 mg HCTZ in healthy subjects.

Safety

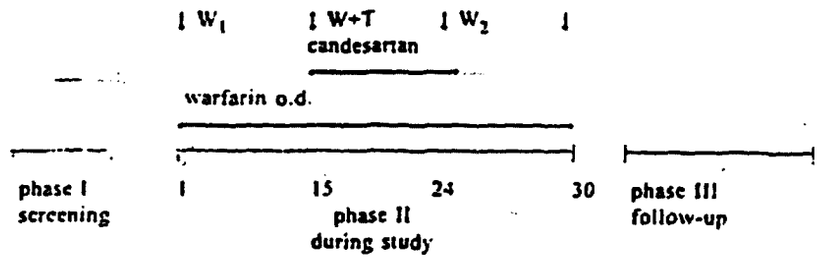
18 healthy males participated, one developed flu, dropped out, and was replaced. No subject died. There were no serious adverse events. No other patient withdrew. Fatigue, dizziness and headache were the most frequent adverse events reported, and these were numerically more frequent overall during combination therapy than monotherapy. No laboratory abnormalities were noted.

Comments

Overall there is a decrease in HCTZ and an increase in Candesartan blood levels when the two are coadministered. Results with only one dose level of the drugs were available, and given a wide safety margin and dose titration the interaction may not lead to dose reduction for either.. That, however, is a more appropriate consideration for the combination rather than for this monotherapy NDA. Labeling, even here, should make note of the interaction.

5.9 Study EC032: Open label multiple dose study to evaluate the effects of 16 mg Candesartan cilexetil on the steady state pharmacodynamics and pharmacokinetics of warfarin.
NDA Volume 1.79
Interaction with warfarin was studied because of the narrow therapeutic range of that drug, its metabolism via cytochrome P450 CYP2C9, its being extensively bound to serum proteins, and the clinical possibility of coadministration.
The study was performed in the Netherlands from October 14, 1994 to November 22, 1994.
Principal Investigator: J.J. van Lier, M.D.
Candesartan cilexetil was manufactured by , and warfarin

The plan of the study was:



Twelve (12) healthy young male caucasian volunteers participated in the study.

The target parameters were:

Pharmacodynamic Parameter:
Prothrombin time (INR)

Pharmacokinetic Parameter:
warfarin trough concentration

Safety Parameters:
adverse events, vital signs, physical examination and clinical laboratory tests.

APPEARS THIS WAY
ON ORIGINAL

The flow chart of the study was provided as follows:

day	screen-ing	1	2	3	4-10	11	12-13	14	15	16	17	18	19	20	21	22-23	24	25	26	27	28-30	31	follow-up
phase		W_1							W+T									W_2					
informed consent	X																						
medical history	X																						
physical examination	X																	X					X
ECG	X																						X
admission								X															
vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
drug screen urology	X																						
laboratory tests	X	X							X								X					X	X
adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
warfarin administration*		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
candesartan cilexetil administration									X	X	X	X	X	X	X	X	X						
blood sampling for warfarin candesartan		X X					X	X	X X**	X		X		X		X	X X**	X X			X	X	
INR		X			X		X	X	X			X		X		X	X	X			X	X	
hospitalization									X	X	X	X	X	X	X	X	X						
discharge																		X					

* warfarin run-in period may be extended by maximally five days
** series of samples

Warfarin was given once daily through the 30 day study period on the following schedule:

Day 1: 10 mg
Day 2: 1.5 mg
Day 3, 4, 5: 4 mg
Subsequently: Dose adjustment (2-10 mg daily) to maintain an INR 1.2-1.8.

Candesartan cilexetil was administered as two 8 mg tablets beginning on day 15 and ending on day 24.

Results

No effect of the coadministration was detected on the INR.

Table 1 Summary of statistics on pharmacodynamic parameters as observed during multiple dose oral administration of warfarin for 30 days and co-administration of candesartan cilexetil for 10 days

phase W_1 = warfarin o.d. on days 1-14: 10 mg on day 1, 5 mg on day 2, 4 mg on days 3-5 and individual dose adjustment on day 6 and/or 9 (if applicable)

phase W+T = individual warfarin dose o.d. and candesartan cilexetil 16 mg o.d. on days 15-24

phase W_2 = individual warfarin dose o.d. on days 25-30

parameter	treatment phase	arithmetic mean	min - max
INR_{pre}	W_1	1.55	1.21 - 1.86
	W+T	1.54	1.28 - 1.85
	W_2	1.41	1.16 - 1.90

	95% confidence interval		point estimate		p-value	
parameter	W_2/W_1	$W+T/W_1$	W_2/W_1	$W+T/W_1$	W_2/W_1	$W+T/W_1$
INR_{pre}*	-0.24 - -0.03	-0.12 - 0.09	-0.14	-0.01	0.0146	0.8039

* 95% confidence interval for the difference of means

There was a small (7%) decrease in warfarin blood levels during the coadministration period which was statistically significant.

Table 2 Summary of statistics on pharmacokinetic parameters as observed during multiple dose oral administration of warfarin for 30 days and co-administration of candesartan cilexetil for 10 days

phase W_1 = warfarin o.d. on days 1-14: 10 mg on day 1, 5 mg on day 2, 4 mg on days 3-5 and individual dose adjustment on day 6 and/or 9 (if applicable)

phase W+T = individual warfarin dose o.d. and candesartan cilexetil 16 mg o.d. on days 15-24

phase W_2 = individual warfarin dose o.d. on days 25-30

	treatment phase	geometric mean	min - max
c_{pre} ($\mu g.L^{-1}$)	W_1	672.7	383.2 - 1170.9
	W+T	629.0	369.9 - 1028.1
	W_2	704.7	469.9 - 1346.0

	95% confidence interval		point estimate		p-value	
parameter	W_2/W_1	$W+T/W_1$	W_2/W_1	$W+T/W_1$	W_2/W_1	$W+T/W_1$
c_{pre} ($\mu g.L^{-1}$)*	0.99 - 1.11	0.88 - 0.99	1.05	0.93	0.1246	0.0305

* 95% confidence interval for the ratio of geometric means (from ANOVA on log-transformed data)

subject	phase W_1 average concentration days 12-15 ($\mu g.L^{-1}$)	phase W+T average concentration days 22-25 ($\mu g.L^{-1}$)	phase W_2 average concentration days 28-31 ($\mu g.L^{-1}$)
01			
02			
04			
05			
06			
07			
08			
09			
10			
11			
13			
14			
n	12	12	12
geometric mean	672.7	629.0	704.7
mean	700.1	651.5	740.1
SD	209.5	180.5	255.6
median	678.6	629.9	688.0
min			
max			

Note: Subjects 03 and 12 were withdrawn after treatment phase W_1 and are excluded from statistical analysis

Data on the PK of Candesartan were not provided.

Safety

14 subjects entered this study. They comprise the safety database. No deaths, serious adverse events or withdrawals due to adverse events were noted. 34 adverse events were reported by 10 subjects. Headache, dizziness and fatigue were most frequently reported.

Laboratory results varied temporally and without pattern. One patient had a slight elevation of ASAT and ALAT during the coadministration period which returned to normal.

Comments

The PK interaction here is slight but should be noted in labeling. The sponsor's drafts under Drug Interactions states "no known clinically significant drug interactions." This should be replaced with a statement describing the data available for a warfarin-Candesartan interaction.

5.10 Study EC008 - A double-blind, randomized, parallel placebo controlled, multiple dose study in healthy male volunteers to investigate the inhibitory effect of Candesartan cilexetil (TCV-116) on the pressor action of exogenous angiotensin II.

Study Period: 8/10/92-11/17/92.
Drug and placebo manufacturer:
Angiotensin II obtained commercially as Clinalfa® and dissolved in 0.97% NaCl.

Study Design:

Double-blind, 4 arm (placebo; 1 mg, 2 mg, 4 mg of Candesartan cilexetil Q.D. for 8 days) parallel group comparison in healthy male volunteers given challenges of Angiotensin II (10 mg) kg Q 10-15 minutes to a systolic BP increase of 24-40 mm Hg. 24 subjects were planned to detect "trends." In a protocol amendment 4 subjects were added to receive only 8 mg of Candesartan cilexetil Q.D. on 8 days.

The study objectives were:

Primary Objectives:

- assessment of the inhibitory effect of TCV-116 on the pressor action of exogenous A II in healthy volunteers using a photoplethysmorgraph for BP-measurement
- dose-dependency of inhibitory effect
- duration of inhibitory effect
- correlation of inhibitory effect with serum levels of the active metabolite CV-11974.

Secondary Objectives:

- assessment of pharmacodymanic parameters of CV-11974 (plasma renin activity, plasma levels of aldosterone, A II, adrenalin, noradrenalin)
- assessment of pharmacokinetic parameters of CV-11974
- assessment of clinical tolerability

Randomization was by a computer generated list. This was a "hypothesis generation" study with descriptive date displays.

Blood pressure measurements were done as follows:

Blood Pressure Measurements

The pressor effect of exogenous challenges of A II was measured on the finger The measurement technique, which is a non-invasive measuring digital artery blood pressure continuously The monitor provides beat-to-beat blood pressure values (systolic, diastolic and mean) and heart rate. This device has been demonstrated to correlate well with intra-arterial pressure and to be accurate for the study of short-lasting blood pressure changes by vaso-active agents in humans. Blood pressure and heart rate were continuously recorded on graduated paper 10 minutes before and at least 15 minutes after injection of each A II challenge. Peak blood pressure changes were calculated using these tracings. The following time points were used:

Day 1: before dosing and 1, 2, 3, 4, 6, 8, 10, and 12 hours post dosing
Day 2,4: before dosing and 2, 6 and 12 hours post dosing
Day 8: before dosing and 1, 2, 3, 4, 6, 8, 10 and 12 hours post dosing
Day 9: 24, 30 and 36 hours post administration on Day 8

TREATMENT PERIOD

In each of the treatment groups (1 mg, 2 mg, 4 mg, 8 mg TCV-116 and placebo), tablets were given once daily in the morning of each of the eight trial days between 7:00 and 8:00 at the times described in section 3.7. All volunteers were required to remain in the supine position for 30-60 min prior to and for 4 hours after drug administration. They were then allowed to sit or stand but had to resume the supine position at least 30 min before the next A II challenge, blood taking or blood pressure measurement. During this time, subjects were observed for any adverse events and asked objective questions like 'How do you feel'. Blood and urine samples were collected throughout the trial period to gain information on pharmacokinetic and pharmacodynamic parameters.

Flow chart for the study was:

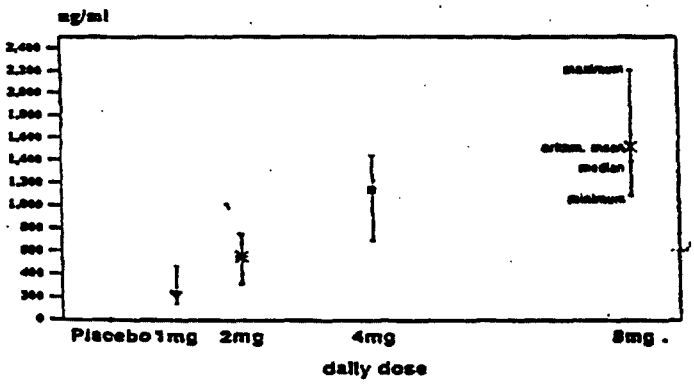
Procedure	Screening (D-14 to D0)	Administration of drug (D1 to D8)	Post Examination (up to 36 hours after last dosing)
Informed Consent	X		
Medical History	X		
Physical Examination	X		X
Clinical Laboratory tests	X		X
12 lead ECG	X		X
Test for HBSAG & HIV	X		
Dosing		X	
Exog. All administration	X	X	
B.P. measurement	X	X	
P.D. of blood param.		X	
P.K. of blood param.		X	
Adverse Events		X	X

27 male subjects were evaluated: 6-placebo, 5-1 mg., 6-2 mg, and 4-8 mg. ages were between 19 and 36 (average 26 ± 5) years. Mean body weight was 70 ± 7kg. Mean height was 179 ± 7 cm.

Results

PK

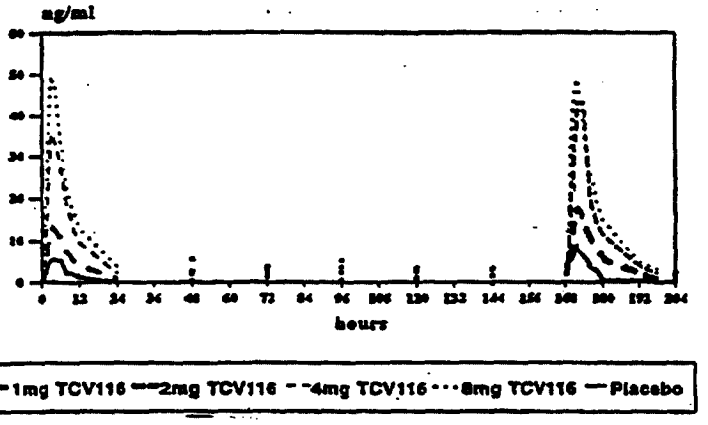
Plasma AUC (0-204) Concentrations of Candesartan after multiple dosing were depicted as follows:



APPEARS THIS WAY ON ORIGINAL

BEST POSSIBLE COPY

Day 1 and day 8 pharmacokinetic profiles of Candesartan were:



APPEARS THIS WAY ON ORIGINAL

BP

Systolic BP change on day 1 was:

Systolic Blood Pressure Changes after A II Challenge (expressed as percentage of baseline response)

Day 1	1 mg TCV-116	2 mg TCV-116	4 mg TCV-116	8 mg TCV-116	placebo
before admin.	100	100	100	100	100
after 1 hour	102	102	108	81	87
after 2 hours	93	85	87	62	104
after 3 hours	86	84	74	33	104
after 4 hours	89	82	41	22	97
after 6 hours	82	67	40	19	99
after 8 hours	84	58	36	35	87
after 10 hours	80	64	48	44	96
after 12 hours	93	67	64	38	86
after 24 hours	94	75	58	49	101
Day 2					
before admin.	94	75	58	49	101
after 2 hours	87	73	62	42	99
after 6 hours	84	46	29	25	97
after 12 hours	70	61	44	34	97
Day 4					
before admin.	91	74	64	76	99
after 2 hours	81	83	81	80	100
after 6 hours	63	41	26	16	96
after 12 hours	74	84	33	27	97
Day 8					
before admin.	83	82	66	44	100
after 1 hour	77	83	88	46	106
after 2 hours	71	74	61	36	104
after 3 hours	60	62	35	17	98
after 4 hours	64	58	21	16	100
after 6 hours	51	57	35	15	106
after 8 hours	48	46	30	6	97
after 10 hours	55	52	38	17	102
after 12 hours	65	66	64	25	102
after 24 hours	84	70	53	53	99
after 30 hours	80	72	78	55	92
after 36 hours	89	89	98	70	96

BEST POSSIBLE COPY

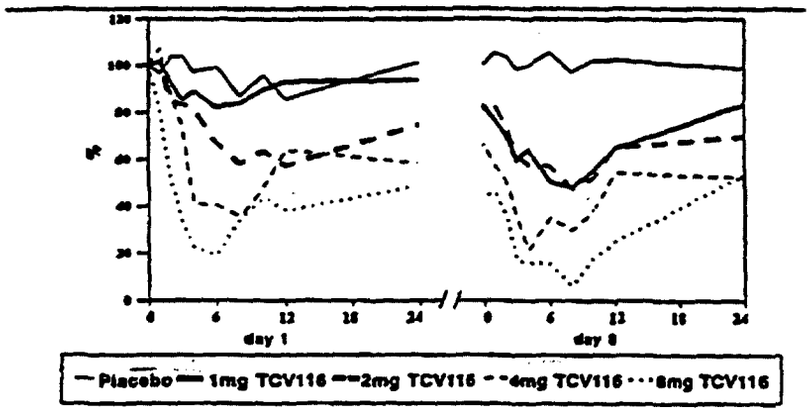
Diastolic BP change on day 1 was:

Diastolic Blood Pressure Changes after A II Challenge (expressed as percentage of baseline response)

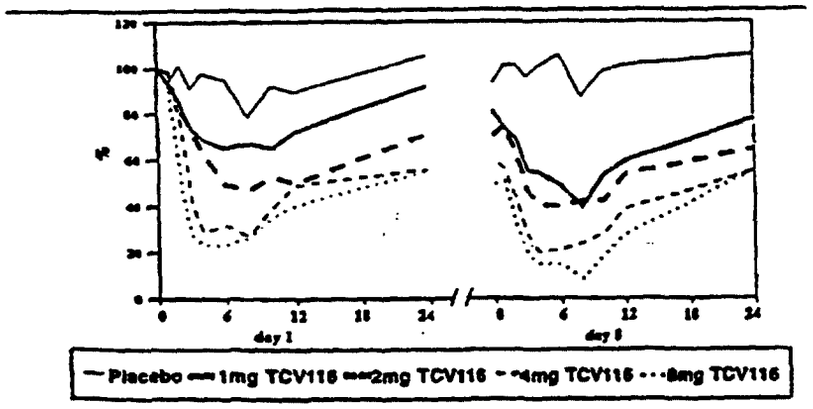
Day 1	1 mg TCV-116	2 mg TCV-116	4 mg TCV-116	8 mg TCV-116	placebo
before admin.	100	100	100	100	100
after 1 hour	94	98	89	96	93
after 2 hours	85	83	78	52	101
after 3 hours	74	73	42	27	91
after 4 hours	69	63	29	23	98
after 6 hours	65	49	32	23	95
after 8 hours	67	47	27	26	79
after 10 hours	65	53	39	35	92
after 12 hours	72	50	49	40	89
after 24 hours	92	71	56	55	105
Day 2					
before admin.	92	71	56	55	105
after 2 hours	77	66	50	41	90
after 6 hours	63	41	23	22	92
after 12 hours	51	47	31	29	92
Day 4					
before admin.	80	70	55	63	101
after 2 hours	74	53	50	32	94
after 6 hours	50	35	22	13	94
after 12 hours	59	45	27	22	93
Day 8					
before admin.	81	71	59	49	93
after 1 hour	74	75	56	51	101
after 2 hours	69	62	43	32	101
after 3 hours	55	47	27	19	96
after 4 hours	54	41	20	15	100
after 6 hours	49	40	21	15	105
after 8 hours	39	42	24	8	87
after 10 hours	53	42	28	18	98
after 12 hours	59	63	39	27	101
after 24 hours	77	64	55	55	105
after 30 hours	64	61	60	54	91
after 36 hours	75	74	81	72	98

Graphs of changes on days 1 and 8 were:

Change of Systolic Blood Pressure after AII Challenge
Expressed as Percentage of Baseline Response
arithmetic means



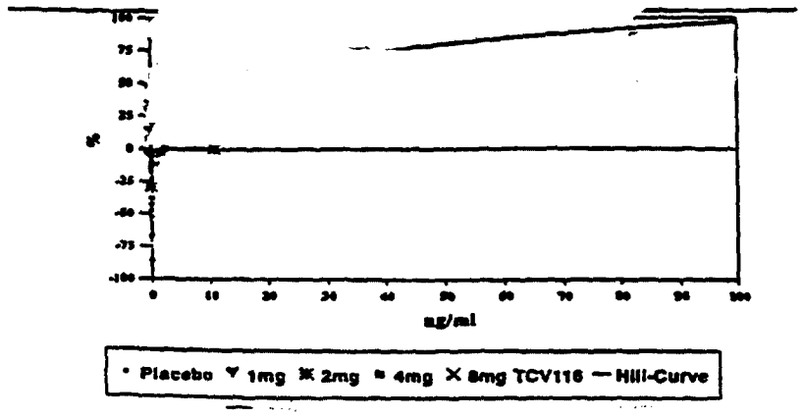
Change of Diastolic Blood Pressure after AII Challenge
Expressed as Percentage of Baseline Response
arithmetic means



APPEARS THIS WAY
ON ORIGINAL

The relationship of change in systolic BP and Candesartan plasma concentration on day 8 was:

Inhibition of Systolic Blood Pressure after AII Challenge vs Concentration of CV11974 (Day 8)

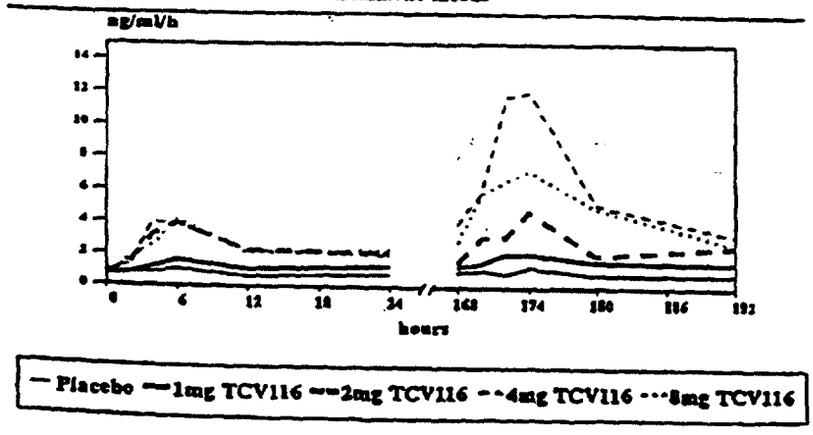


Hormone Effects

Renin

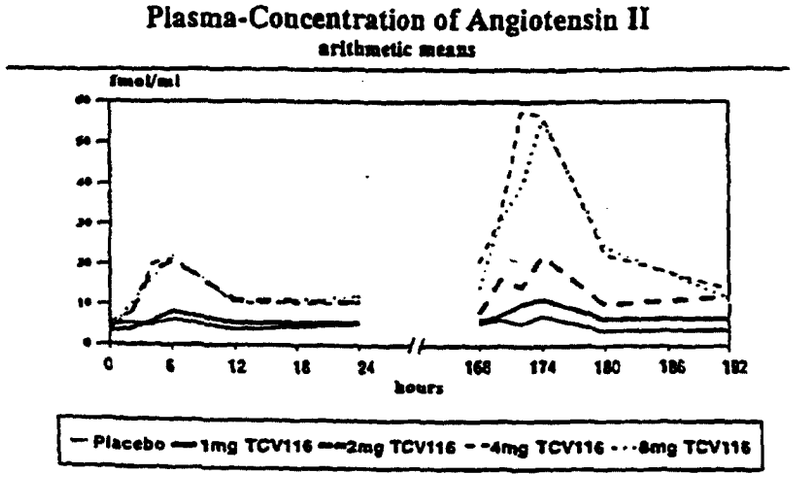
For days 1 and 8 the change in plasma renin was depicted as follows:

Plasma Renin Activity
arithmetic means



For unexplained reasons on day 8 the renin rise was greatest for the 4 mg dose.

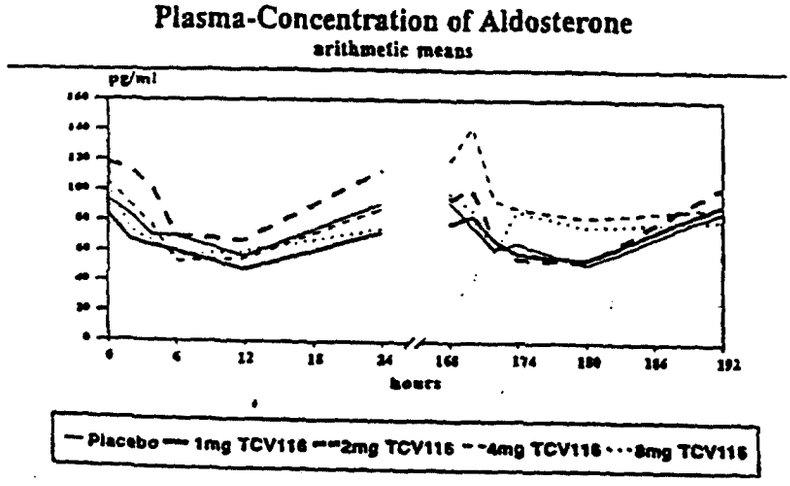
Angiotensisn II



Here 4 and 8 mg gave similar increases.

Aldosterone

APPEARS THIS WAY
ON ORIGINAL



The day 8 variability for the 8 mg dose was again present. High intersubject variability and only 4 subjects in the 8 mg group may be factors in these results.

Safety

Reported adverse events were:

subj. no.	treatment	AE as reported	AE as coded (WHO term)	severity	causal relationship	actions
4	placebo	headache	headache	mild	not related	none
4	placebo	thoracic pain	chest pain	mild	not related	none
14	placebo	headache	headache	moderate	not related	none
14	placebo	constipation	constipation	moderate	not related	none
14	placebo	epigastric discomfort	abdominal pain	moderate	possibly related	none
60	8 mg TCV-116	vomiting	vomiting	moderate	not related	none
60	8 mg TCV-116	nausea	nausea	moderate	not related	none
60	8 mg TCV-116	headache	headache	moderate	not related	one 500 mg tablet paracetamol

Laboratory

Subject 14 had a large increase in bilirubin due to Gilbert's syndrome. He was on placebo.

5.11 Summary

Candesartan cilexetil is a prodrug with less than 50% bioavailability and dependent on gut wall metabolism for Candesartan, the active molecule, to be delivered systematically. The cilexetil moiety is absorbed, metabolized, and, like Candesartan, renally eliminated. Additionally Candesartan is eliminated by the liver. An inactive metabolite of Candesartan is also eliminated in urine and feces. Candesartan is non-lipophilic with an octanol/water partition coefficient of 0.05% at 37° C. It is 99.8% protein bound.

In healthy male volunteers there was dose proportionality over a dose range of 2-16 mg. The terminal half-life was approximately 9 hours.

In the healthy elderly (65-78 years) C_{max} and AUC were about 50% and 80% greater than for younger healthy subjects at the same dose. After adjustment for body mass index, no gender differences were found.

In patients with mild to moderately impaired hepatic function, the sponsor states that no differences in PK were noted compared to normals, but C_{max} and AUC were numerically greater in the hepatic cases and more severely affected patients have not as yet been studied.

With renal dysfunction there is no disagreement that AUC and $T_{1/2}$ were prolonged. Serum protein binding was also reduced in patients with severe renal dysfunction compared to normals. The sponsor suggests in the labeling that no initial dose adjustment is recommended in patients with renal impairment.

With HCTZ, Candesartan's AUC was increased by about 20%, while HCTZ's AUC decreased 10-15%. With warfarin there was a decrease in trough warfarin concentrations, not associated with a change in prothrombin time. However, there was considerable individual variation, and pro times were kept low in these normal volunteers.

For pharmacodynamics, a study in normals given Angiotensin II and placebo or varying doses of Candesartan cilexetil demonstrated that the drug could lower blood pressure elevation induced by Angiotensin II. Angiotensin II and plasma renin were increased for subjects on drug compared to placebo. Serum A.C.E. was not increased; aldosterone concentrations were variable.

While descriptive, the clinical relevance of these findings need to be considered in light of the clinical studies and dose related effects on safety and efficacy. In some of these clinical studies to be described in the next section, sparse plasma sampling was done and correlations to blood pressure change made. However, these evaluations were not completed at the time of NDA submission.

6.0 Clinical Safety and Efficacy Studies

The pertinent clinical studies will be presented in the following order.

I. Randomized Placebo Controlled Monotherapy Studies
   a) Fixed Dose
      AM113
      EC009
      EC047
   b) Fixed Dose and Active Comparator
      AHM0001 (Losartan)
      AHM0006 (Amlodipine)
      EC011 (Enalapril)
      EC033 (long term follow-up of EC 011)
      EC018 (Enalapril)
   c) Dose Escalation
      AM116
      AM119
   d) Withdrawal
      EC012
      EC015
      EC040

II. Randomized Placebo Controlled Drug Combination Studies
   EC016 (CC + HCTZ)
   EC403 (CC + HCTZ)
   AM117 (CC + HCTZ)

III. Special Populations
   AHM0002 (Diabetics)
   AHM0004 (Elderly)
   RESOLVD (CHF)

As previously noted, Dr. Caras did the primary reviews for studies AM113, AM116, AM119, AHM0001 which were designated as primary by the sponsor. Dr.Caras' reviews are placed in the above order followed by additional comments, if any.

6.1 Study AM 113 (Dr. Caras)

01. Study AM113

01.1. Title	Evaluation of the Efficacy and Safety of Candesartan Cilexetil in the Treatment of Patients with Hypertension: A Multicenter, Randomized, Double-Blind, Placebo Controlled, Dose Response Study
01.2. Source documents	Study report: 1.93-1.108; CANDA
01.3. Investigators	This study was conducted at 29 sites.
01.4. Study dates	11 December 1995 to 29 October 1996.
01.5. Study design	This study description was based upon the protocol dated November 30, 1995. There were three prior protocols published. There were no protocol amendments after the start of enrollment.

This is a randomized, double-blind, placebo-controlled parallel study in subjects with mild to moderate hypertension (95< SeDBP <114 mmHg). Figure 1 below shows a schematic of this trial. After a 4-5 week lead-in period, an ambulatory blood pressure monitor (APBM) was placed if the subject's seated diastolic blood pressure (SeDBP)was between 95-110 mmHg on the last two successive visits . An ambulatory blood pressure monitor was placed on 50% of the subject population for at least 24 hours for a baseline. Readings were taken every 20 minutes from 4AM to 10 PM and every 30 minutes from 10PM to 4AM. The patient was randomized either to placebo, 2,4,8, 16 or 32 mg of candesartan per day. There were routine visits at 2, 4, 6 and 8 weeks with trough seated and standing blood pressures measured. Peak blood pressure measurements will be performed on Weeks 2 and 8. Pharmacokinetic sampling will be performed on Weeks 2 and 8. On Week 8, an on-treatment APBM was placed after ingestion of study drug.

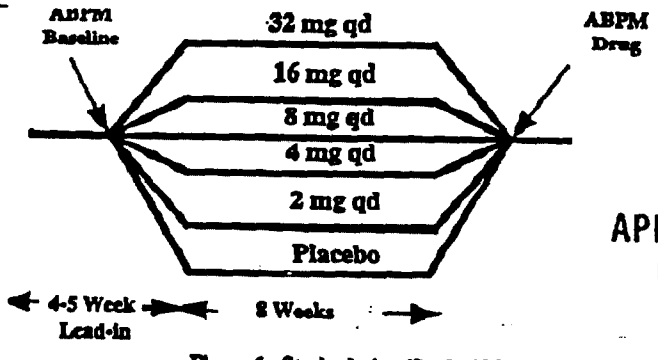


Figure 1. Study design (Study AM113).

APPEARS THIS WAY ON ORIGINAL

BEST POSSIBLE COPY

Drug supplies are shown in Table 1 below.

The subjects were taken from a healthy population aged over 18 years. Subjects must have a diagnosis of uncomplicated, mild to moderate essential or untreated hypertension limited to WHO Stage 1 or 2 (no evidence of end organ damage except for mild fundoscopic changes). Subjects with renovasular, cardiovascular, diabetes, CHF or collagen-vascular, renal, renovascular or cerebrovascular disease or abnormal laboratory values prior to randomization were excluded. If seated systolic blood pressure (SeSBP) was greater than 210 mmHg, the subject was excluded. Subjects who were taking the following agents were excluded; (1) Steroids with exception of low dose estrogen replacement therapy; (2) NSAIDs; (3) ASA exceeding lg / day; (4)

Table 1. Drug supplies (Study AM113).

Dose	Lot
Placebo	H157-01-01-03 H157-01-01-04
2 mg	H1181-01-01-01 H1181-01-01-02
4 mg	H1155-01-01-02 H1155-01-01-04
8 mg	H1156-01-01-02 H1156-01-01-07

Lithium; (5) tricyclic antidepressants. Subjects must be able to wean other antihypertensives and vasoactive agents.

The primary efficacy variable in this study was the change in trough seated diastolic pressure at Week 8 of the double-blind period. Secondary endpoints are as follows: (1) the reduction in trough of fice seated systolic blood pressure and standing systolic and diastolic BP at Weeks 2-8 compared to baseline; (2) the change in hour averaged APBM data over a 24 hour period after the ingestion of study drug from baseline. (3) the reduction in the mean daytime (i.e. the first 12 hours after the AM dose); (4) the reduction in the mean 24-hour and daytime ambulatory systolic BP; (5) the proportions of subjects whose of fice SeDBP is normalized (decreased to<90 mmHg) and/or responds (decreased by 10 mmHg); (6) Safety and tolerability against placebo.

The primary and secondary efficacy endpoints were evaluated for significance by analysis of covariance using center and baseline as covariates. Sixty subjects per treatment arm was estimated based on providing 95% power to detect a mean difference from baseline of 5 mm Hg between any two treatments.

Subjects who discontinued early would go through the schedule of events at Week 8 including ABPM.

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

02. Efficacy results

There were 569 subjects enrolled. Disposition of enrolled subjects is shown in Table 2 below.

Table 2. Subject Disposition

Subject Disposition	Number
Enrolled	569
Not Randomized	204
Randomized	365
Discontinued	33
Completed	232

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

Table 3. Reasons for Discontinuations

	Placebo	2 mg	4 mg	8 mg	16 mg	32 mg
Total Randomized	64	59	63	60	60	59
Total Discontinued	9	3	4	4	6	7
Adverse Event	3	0	2	1	1	2
Sponsor/Inv Decis.	1	2	0	0	1	1
Subject Request	1	0	1	2	1	3
Lost to Follow-up	0	0	0	0	1	1
Lack of Response	4	1	1	1	2	0
Subject Completed	55	56	59	56	54	52

There were a total of 22 protocol violations. Most of the protocol violations were (1) DBP missing at baseline visits; (2) Non-compliance. One center (007) had a number of subjects who had missing baseline values. Protocol violations were ignored in the intent to treat analysis.

Demographics of the four treatment groups are shown in Table 4 below. A reduction in the proportion of male subjects in the 4 mg group is noted.

Table 4. Demographics of the Treatment Groups

	Subject	Placebo	2 mg	4 mg	8 mg	16 mg	32 mg
Gender	Male N(%)	46(72)	29(49)	44(70)	34(57)	38(63)	41(70)
	Female N(%)	18(28)	30(50)	19(30)	26(43)	22(37)	18(30)
Race	Non-Black N(%)	51(80)	45(76)	51(81)	43(72)	48(80)	45(76)
	Black N(%)	13(20)	14(24)	12(19)	17(28)	12(20)	14(23)
Elderly	< 65 N(%)	47(80)	50(86)	47(77)	47(80)	44(75)	39(71)
	≥ 65 N(%)	12(20)	8(14)	14(23)	12(20)	15(25)	16(29)
Age	Mean (SD)	55(12)	59(10)	63(11)	60(11)	60(11)	55(12)

There was no statistical relationship between ABPM diastolic or systolic blood pressure (at last visit before randomization) for any of the treatment groups (Figure 2 below).

There was no statistical relationship between ABPM diastolic or systolic blood pressure (at last visit before randomization) for any of the treatment groups (Figure 2 below).

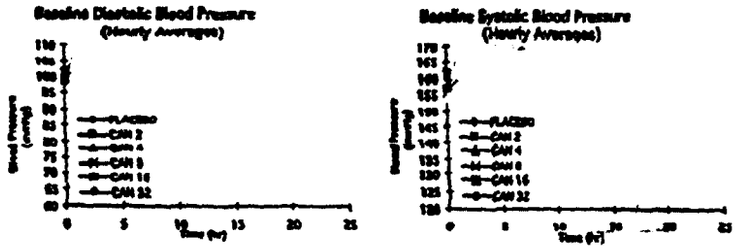


Figure 2. Baseline ABPM

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

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

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

Measurement (mmHg or BPM)	Treatment					
	Placebo	2 mg	4 mg	8 mg	16 mg	32 mg
Seated						
DBP; Mean(SD)	100(7)	100(4)	100(5)	101(6)	100(6)	101(5)
SBP; Mean (SD)	152(13)	154(13)	153(17)	154(15)	153(19)	152(17)
DBP Group						
<104 mmHg; N(%)	44(70)	45(78)	47(75)	37(62)	46(77)	44(75)
>104 mmHg; N(%)	19(30)	13(22)	16(25)	23(38)	14(23)	15(25)
Standing						
DBP; Mean(SD)	102(8)	101(6)	101(7)	102(7)	101(7)	101(7)
SBP; Mean (SD)	152(14)	153(13)	151(16)	152(16)	152(18)	151(19)

24-hour ambulatory disastolic and systolic pressures at Week 8 are given in Figure 3 below.

24-hour ambulatory disastolic and systolic pressures at Week 8 are given in Figure 3 below.

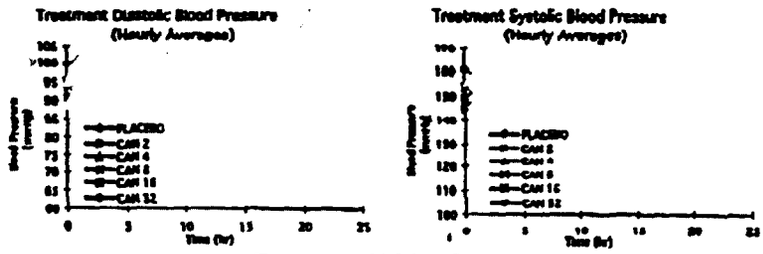


Figure 3. ABPM on Treatment

For the of lice based blood pressures, there was a discrepancy between the number of observations and the number of patients randomized because those patients had baseline measurements but no post dose measurements. The linear model underlying ANOVA was violated. The sponsor analyzed of lice data by both linear and non-linear techniques.

Mean change in trough seated diastolic and systolic blood pressure (summary statistics) is given in Figure 4 below. All blood pressures for the candesartan subjects were statistically significant against placebo for both linear and non-linear analysis. A regression model was fit using indicator variables for the investigative sites, baseline blood pressure and dose. The regression showed a trend in the mean change in blood pressure with the log of increasing candesartan dose..

APPEARS THIS WAY
ON ORIGINAL

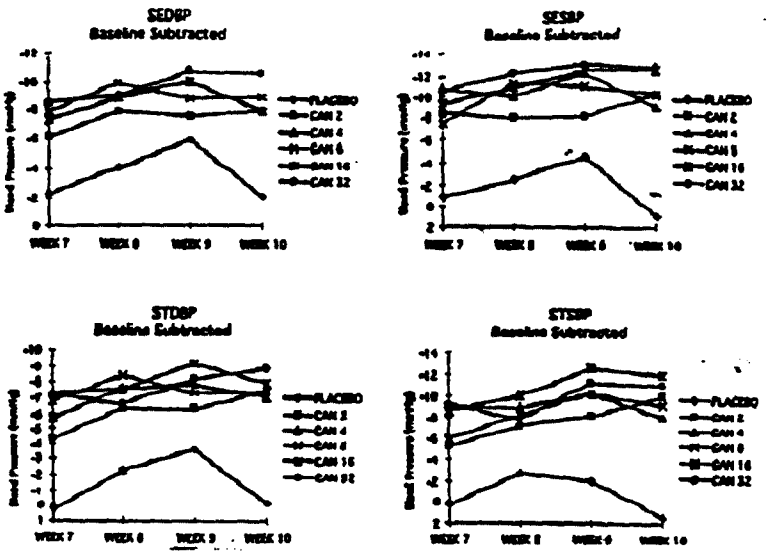


Figure 4. Seated and Standing Blood Pressure on Treatment

Table 6 below shows the change from baseline of peak blood pressures at Week 8.

Table 6. Peak Mean Change from Baseline Seated and Standing Blood Pressure among Treatment Groups. (Week 8)

Measurement (mmHg)	Treatment					
	Placebo	2 mg	4 mg	8 mg	16 mg	32 mg
Seated						
DBP; Mean(SE)	-5(1)	-6(1)	-7(1)*	-8(1)*	-10(1)*	-12(1)*
SBP; Mean (SE)	-5(2)	-9(2)*	-8(2)*	-11(2)*	-15(2)*	-18(2)*
Standing						
DBP; Mean(SE)	-3(1)	-7(1)*	-5(1)	-6(1)*	-9(1)*	-11(1)*
SBP; Mean (SE)	-3(2)	-8(2)*	-8(2)*	-11(2)*	-13(2)*	-16(2)*
* statistically significant ($p<0.01$) versus placebo.						

For all subsequent subgroup analysis the linear model was assumed.

For all subsequent subgroup analysis the linear model was assumed.

There was a statistical difference in the mean change of SeDBP by black and non-black subjects, but none when separated by treatment. There was no placebo effect in the black subjects (+1 mm Hg). Differences in the mean change in black subjects were within 3 mm Hg of the non-black means.

There was no statistical difference in the mean change of blood pressure or mean change by treatment with respect to gender or elderly (>65 years). Differences between females/elderly were within 3 mm Hg of the male/non-elderly means.

03. Safety

The summary of therapeutic response for randomized subjects at Week 8 is given in Table 7 below.

Table 7. Therapeutic Response of Subjects at Week 8

Efficacy Variable	Placebo n=59	2 mg n=58	4 mg n=61	8mg n=59	16 mg n=59	32 mg n=55
Normalized[1] N(%)	12(20)	20(34)	27(44)	21(35)	27(45)	26(47)
Total Responders[2] N(%)						
All subjects	13(22)	24(41)	32(52)	28(47)	30(50)	32(56)
Baseline SeDBP>104	0(0)	4(7)	5(8)	9(15)	4(7)	5(9)

1- SeDBP <90 mmHg
2 -SeDBP <90 mm Hg or Δ SeDBP > 10mmHg

There was a mean exposure of the study drug of approximately 57 days (min 56 d, max 58 d). The database includes 360 subjects. Five subjects who were randomized were missing.

No deaths were reported

There were six subjects who experienced a serious adverse event.

Table 8. Serious Adverse Event during the Double-Blind Period

Site/Subject	Drug	Complication
004/006	Placebo	Breast Cancer
002/001	CAN 2 mg	Back Pain
006/020	CAN 2 mg	Prostatic Cancer
011/013	CAN 4 mg	Spinal Cord Neoplasm
020/015	CAN 4 mg	Diverticular (GI) Bleeding
022/014	CAN 32 mg	Myocardial Infarction

Subject 022/014 was a 55 year old obese male with hypertension who was randomized to candasartan 32 ma. Eleven days after beginning double-blind therapy, the subject experienced an abrupt onset of chest pain following yard work. ECG showed evidence of an anterior wall myocardial infarction. The subject did not respond to thrombolytic therapy. Angiography showed a completely occluded LAD.

There were nine dropouts in the 8 week double-blind period. Table 9 below showb treatment duration and adverse event of the irbesartan subjects.

APPEARS THIS WAY
ON ORIGINAL

Table 9. Discontinuations due to Adverse Events during Double-Blind Period on Candesartan

Site/Subject	Dose (mg)	Days on Drug	Adverse Event
011/013	CAN 4 mg	44	Spinal Cord Neoplasm

Table 9. Discontinuations due to Adverse Events during Double-Blind Period on Candesartan

Site/Subject	Dose (mg)	Days on Drug	Adverse Event
022/019	CAN 4 mg	49	rash, urticaria, fever
010/001	CAN 8 mg	4	anxiety
008/011	CAN 16 mg	0	multiple complaints
018/010	CAN 32 mg	42	chest pain, headache, hypertension
022/014	CAN 32 mg	11	myocardial infarction

Treatment-emergent adverse events across studies will be discussed as a group in the Integrated Summary of Safety. The most common treatment emergent adverse events (>5%) were headache, light-headedness/dizziness, upper respiratory infections, coughing, nausea, diarrhea, edema, chest pain, back pain, fluid retention and depression.

According to the sponsor, only two subjects met the blood pressure criteria for orthostatic hypotension (ASBP>30mmHg). Neither subject had symptoms associated with hypotension.

There was no statistically significant mean changes in baseline as a function of dose for all clinical chemistries and hemotological parameters. However, increasing trends at 16mg and 32mg were observed with BUN and GGT. Both treatment and baseline means were well within the normal range.

A mild elevation of AST and ALT (<1.5 ULN) were reported in one patient (20/18) on candesartan 32 mg during the double-blind period.

There were two subjects who had abnormal creatine kineses on treatment. One subject on candesartan 32 mg had an elevated baseline value (CK=584 to 680 IU/L). The other was on 4 mg (CK=177 to 499 IU/L). Neither subject had any clinical symptoms.

No significant changes in physical exam and ECG were noted.

The study is a randomized placebo controlled trial of candesartan from 2 - 32 mg. Statistically significant changes in trough SeDBP at 8 weeks were observed for the 4, 8, 16 and 32 mg dose. The percent of subjects normalized or responded were not significantly different between the candesartan doses, even though better than placebo. Based on this data, it is hard discern a dose response relationship with this study, since there was not an adequate number of subjects to differentiate between groups. Interestingly, the peak blood pressure data shows more separation.

There was no significant difference in response between males and females. Because of the small number of subjects who were >65 years and were non-white, inferences about the differences of response between groups cannot be made.

There were no deaths during this study. Serious adverse events were most likely not related to study drug. A mild increase in BUN would be expected at the higher doses based on the drug's mechanism of action. Mild elevations of GGT without elevations of traditional LFTs are of limited value. A full analysis of SAEs, treatment emergent symptoms, clinical labs and ECGs will be performed and discussed in the Integrated Summary of Safety.

Respectively submitted,

Steven D. Caras, MD, PhD

Comments (Stephen Fredd, M.D.)

Dr. Caras' review contains information which conveys many of the important results of this well conceived study. While these data (minus Dr. Fides' patients) will be included in a meta-analysis, some additional clarifications might be useful.

In Table 2, the number of patients who completed the study was 332. The ITT population was all randomized patients who had both baseline and at least one post-baseline measurement. Following this procedure, 5 patients were not included in the sponsor's ITT analysis.

	Placebo	2mg	4mg	8mg	16mg	32mg
Randomized	64	59	63	60	60	59
ITT	63	59	62	60	59	57

The primary efficacy variable was the mean change from baseline in trough (24 ± 3 hours post-dose) sitting DBP. Those results were reported as:

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

Treatment		Baseline	DB 2	DB 4	DB 6	DB 8
Placebo	N	63	60	57	55	63
	Mean	101.1	98.3	95.6	93.7	98.7
	SD	5.4	9.8	9.7	9.5	11.4
CC 2 mg	N	59	58	56	56	59
	Mean	99.0	94.4	91.8	92.5	92.1
	SD	4.2	8.6	8.5	8.4	8.9
CC 4 mg	N	62	62	62	60	62
	Mean	100.1	92.4	91.1	90.6	92.5
	SD	4.8	8.0	9.2	8.7	8.7
CC 8 mg	N	60	59	57	56	60
	Mean	101.1	93.4	91.2	92.4	92.4
	SD	5.9	8.5	8.0	7.6	9.7
CC 16 mg	N	59	58	57	55	59
	Mean	100.1	93.1	91.5	89.8	92.2
	SD	5.4	9.2	10.3	9.8	9.7
CC 32 mg	N	57	54	53	53	57
	Mean	100.1	92.2	90.8	89.3	89.8
	SD	4.5	8.9	9.0	8.6	10.3

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

Treatment Comparison	LSM	95% CI		p-value
		Lower	Upper	
CC 2 mg vs. Placebo	-4.4	-7.5	-1.4	0.0043
CC 4 mg vs. Placebo	-5.7	-8.6	-2.8	0.0001
CC 8 mg vs. Placebo	-6.1	-9.0	-3.2	0.0001
CC 16 mg vs. Placebo	-5.2	-8.2	-2.2	0.0009
CC 32 mg vs. Placebo	-7.5	-10.5	-4.5	0.0001

The baseline means are not entirely in agreement with Table 5 in Dr. Caras' review, which may reflect the slightly different n.

In presenting therapeutic response neither Dr. Caras nor the sponsor use the ITT population as the denominator. Table 7 in Dr. Caras' review shows:

Table 7. Therapeutic Response of Subjects at Week 8

Efficacy Variable	Placebo n=59	2 mg n=58	4 mg n=61	8mg n=59	16 mg n=59	32 mg n=55
Normalized[1] N(%)	12(20)	20(34)	27(44)	21(35)	27(45)	26(47)
Total Responders[2] N(%)						
All subjects	13(22)	24(41)	32(52)	28(47)	30(50)	32(56)
Baseline SeDBP>104	0(0)	4(7)	5(8)	9(15)	4(7)	5(9)

1- SeDBP <90 mmHg
2 -SeDBP <90 mm Hg or Δ SeDBP > 10mmHg

The sponsor's results were:

Frequency Distribution of Responders Based on Change from Baseline to Double Blind Week 8 in Trough Sitting Diastolic Blood Pressure (ITT Population)

	Placebo	CC 2 mg	CC 4 mg	CC 8 mg	CC 16 mg	CC 32 mg
N	55	56	60	56	56	53
Number Responders	11	22	31	24	30	34
% Responders	20.0%	39.3%	51.7%	42.9%	53.6%	64.2%

Using the ITT numbers as denominator, the sponsor's results for responders would be:

Placebo	2mg	4mg	8mg	16mg	32mg
17.5%	37%	52%	40%	51%	60%

Table 6 in Dr. Caras' review as well as the presentations by the sponsor of peak blood pressure analyses more clearly indicate the presence of a dose response not leveling off at 32 mg.

The efficacy analyses for blacks and non-blacks are not provided in Dr. Caras' review, but to clarify those statements the sponsor found:

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

Treatment	Subgroup	N	LSM	95% CI	
	Nonblack			Lower	Upper
Placebo		51	-3.1	-5.5	-0.7
CC 2 mg		45	-6.9	-9.4	-4.5
CC 4 mg		50	-8.0	-10.3	-5.7
CC 8 mg		43	-9.4	-11.9	-6.7
CC 16 mg		47	-8.0	-10.4	-5.5
CC 32 mg		43	-10.7	-13.2	-8.1
	Black				
Placebo		12	+3.0	-2.3	+8.2
CC 2 mg		14	-7.0	-12.3	-1.8
CC 4 mg		12	-8.2	-12.8	-3.7
CC 8 mg		17	-7.0	-10.9	-3.0
CC 16 mg		12	-6.2	-10.8	-1.6
CC 32 mg		14	-7.8	-12.0	-3.6

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

Treatment Comparison	LSM	95% CI		p-value
		Lower	Upper	
Nonblack				
CC 2mg vs. Placebo	-3.8	-7.2	-0.3	0.0330
CC 4 mg vs. Placebo	-4.8	-8.2	-1.5	0.0051
CC 8 mg vs. Placebo	-6.2	-9.7	-2.7	0.0005
CC 16 mg vs. Placebo	-4.8	-8.3	-1.3	0.0068
CC 32 mg vs. Placebo	-7.5	-11.0	-4.0	0.0001
Black				
CC 2 mg vs. Placebo	-10.0	-17.7	-2.3	0.0117
CC 4 mg vs. Placebo	-11.2	-18.3	-4.1	0.0025
CC 8 mg vs. Placebo	-9.9	-16.6	-3.2	0.0044
CC 16 mg vs. Placebo	-9.1	-16.2	-2.1	0.0121
CC 32 mg vs. Placebo	-10.7	-17.6	-3.8	0.0027

APPEARS THIS WAY
ON ORIGINAL

6.2 Study EC009 - Randomized, double-blind, placebo controlled phase II study of 2, 4, 8, 12 or 16 mg of Candesartan cilexetil in patients with mild to moderate essential hypertension (DBP 95-114 mm Hg).

L.A.B. performed the study at 3 sites in Germany for Takeda. The first patient was enrolled April 8, 1993 and the last patient finished the study on May 2, 1994. Unblinding of the database occurred on June 1, 1994. The database was "reopened for additional data entry and data corrections between June 15, 1995 and November 20, 1995." Date of report is February 1996. An unplanned interim safety analysis was done on the first 130 patients in February 1994. Since the study did not demonstrate a significant difference for any dose of active compared to placebo as per the primary blood pressure efficacy comparison (baseline week 3 to end of treatment period, visit 9), the study will be briefly discussed here for efficacy, though later it will be included in our metaanalysis. Safety findings will be included here and in the overall safety evaluation.

The flow chart for the study was:

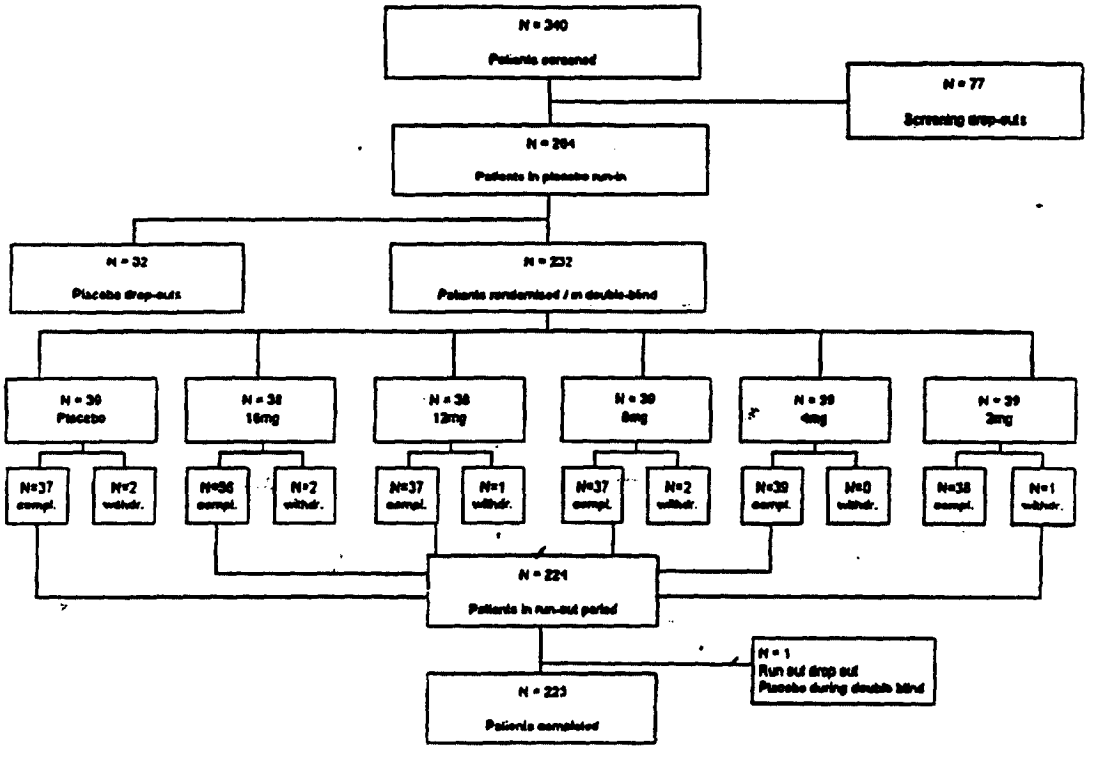
	Wash-out Period(*)		Placebo Period			Treatment Period						Run-out P.		
Week	Wo1	Wo2 (...5)	W1		W2	W3			W4	W5	W6	W7		
Visit	Scr	C1 (...4)	V1	V2	V3	V4	V5	V6	V7	–	V8	V9	V10	V11
Day			-14	-7	-1	0	1	7	14	–	28	29	32	35
Medical History	x													
Incl.& Excl. Crit.	x				x									
Physical Exam.	x										x			
Labor Param.	x				x				x[1]		x			
Inf. Consent	x													
Adverse Events		x	x	x	x	x	x	x	x		x	x	x	x
BP/PR	R_0	R_0	R_0	R_0	R_4	R_4	R_0	R_0	R_0		R_4	R_0	R_2	R_1
12-lead ECG	x				x				x		x			
Med. Dispensing			x				x		x			x		
Med. Counting				x	x			x	x		x		x	x
Serum conc. M-I						x	x	x	x		x	x		

(*) up to 5 weeks respective to pre-medication
[1] no pregnancy test
The grids R_j j=0,1,2,3,4 for BP/PR measurements are defined as follows: R_0 = {0} R_1 = {0,1} R_2 = {0,1,2,3,4} R_3 = {0,2,4,6} R_4 = {0,1,2,3,4,6,8,10} [h]

To blind the study placebo and each dose of active drug were put in identical capsules.

APPEARS THIS WAY
ON ORIGINAL

Patient disposition was as follows:



Efficacy

Primary endpoint was trough diastolic blood pressure. Pairwise comparison of each active dose versus placebo was done for the difference from end of baseline to end of treatment period.

Reduction of diastolic b.p. in mmHg after 4 weeks of treatment (ITT, LOCF)

	Placebo	2 mg	4 mg	8 mg	12 mg	16 mg
Abs. reduct. (mean)	- 3.4	- 5.9	- 6.5	- 6.9	- 8.7	- 8.9
SD	7.9	6.9	7.3	7.1	7.4	8.0
Difference betw. means	-	2.5	3.1	3.6	5.3	5.5
Conf. interv.	-	- 2.4 - + 7.5	- 1.9 - + 8.1	- 1.4 - + 8.6	+ 0.3 - + 10.3	+ 0.5 - + 10.6

The statistical report noted that because of the large number of single comparisons the null hypothesis could not be rejected, though the 12 and 16 mg doses results were close to significance.

Diastolic normalization rates (≤ 90 mm Hg) were also not significant.

Normalization rates in the different dosage groups

	Placebo	2 mg	4 mg	8 mg	12 mg	16 mg
No. of patients	6	9	8	8	13	13
%	15.4	23.1	20.5	20.5	34.2	34.2
Conf. Int.	5.9-30.5	11.1-39.3	9.3-36.5	9.3-36.5	19.6-51.4	19.6-51.4

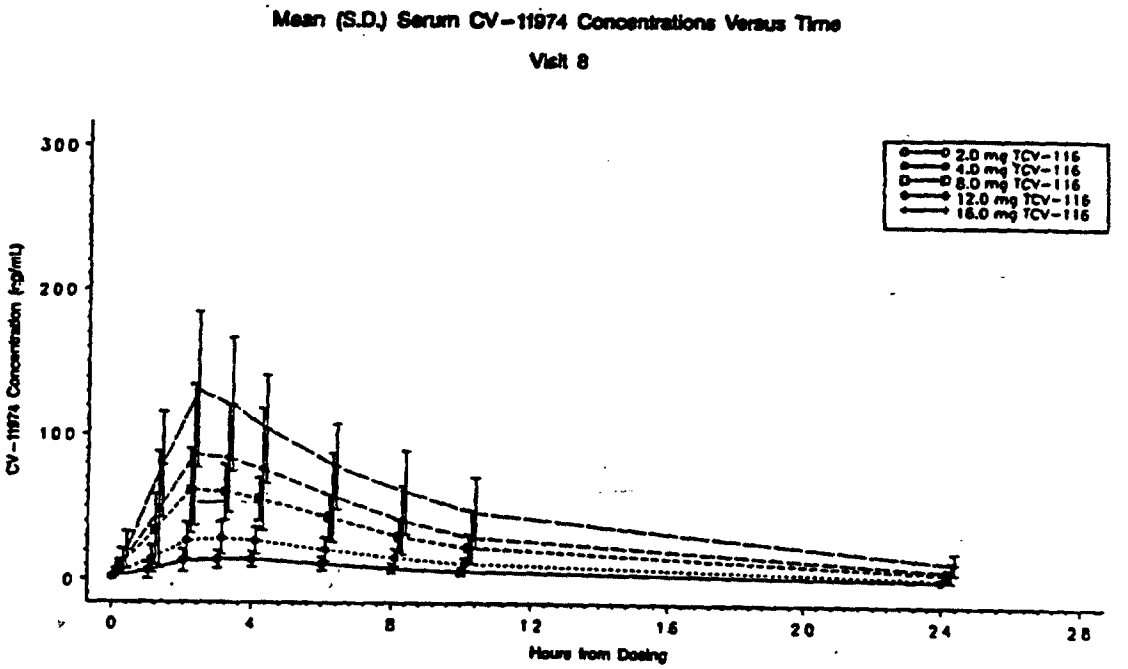
It was claimed that the response rate (diastolic normalization or reduction by 10 mm Hg or more) was significant for each dose compared to placebo.

	Placebo	2 mg	4 mg	8 mg	12 mg	16 mg
No. of patients	9	17	13	16	24	20
%	23.1	43.6	33.3	41.0	63.2	52.6
Conf. Int.	11.1-39.3	27.8-60.4	19.1-50.2	25.6-57.9	46.0-78.2	35.8-69.0

Systolic blood pressure was reduced in a dose dependent manner, similar to the diastolic reduction. Pulse rate did not change. No orthostatic data were provided.

APPEARS THIS WAY
ON ORIGINAL

The study included an evaluation of dose and the pharmacokinectics of the active metabolite which was graphically presented:



Safety

No deaths or serious adverse reactions occurred.

Patients reporting at least one adverse reaction in the double-blind treatment and run-out periods were:

	new adverse events		all adverse events	
Dose	number	%	number	%
Placebo	19/39	48.7	22/39	56.4
2 mg	21/39	53.8	28/39	71.8
4 mg	25/39	64.1	32/39	82.1
8 mg	31/39	79.5	33/39	84.6
12 mg	24/38	63.1	29/38	76.3
16 mg	21/38	55.3	27/38	71.1

Five such events (4 in one patient) were rated as severe. The most frequently observed adverse reactions were:

	Placebo	2mg	4mg	8mg	12mg	16mg	total
Headache	11	19	18	25	21	18	104
Influenza/Coryza	5	2	6	6	4	0	23
Nausea	0	0	1	5	2	4	12
T Wave inversion of	6	2	0	0	2	0	10
Dizziness	1	2	0	3	1	3	10
Migraine	3	0	4	0	3	0	10
AV Block 1st *	1	0	0	0	4	2	7
Throat sore	0	2	2	1	0	1	6
Vomiting	1	0	1	2	0	2	6
Back pain/back ache	0	3	1	1	0	1	6
Abdominal pain	1	0	0	3	0	2	6
Tiredness	1	0	0	3	0	1	5
Palpitation	2	0	0	1	2	0	5
Rhinitis	2	0	0	0	2	0	4
Tinnitus	0	0	0	4	0	0	4
Bronchitis	0	0	1	2	1	0	4
Tooth ache	1	0	0	1	2	0	4
Stomach upset	0	1	0	3	0	0	4
Cramp abdominal	0	0	0	3	0	0	3
Heartburn	0	0	0	3	0	0	3

One of the two severe patients had a vasovagal reaction on standing for that blood pressure measurement. This was after one day on 12 mg Candesartan cilexetil, but before the second day's dose.

Of the laboratory evaluations some ECG changes were noted in 3 patients on 12 mg Candesartan cilexetil. Three patients developed first degree A-V block. However, one patient on placebo developed first degree A-V block.

No clinically significant changes were noted for creatinine, potassium, leukocytes or liver enzymes.

The reopening of the database was to correct safety data for 4 patients (#106, 128, 130 and 131). All were on Candesartan.

For patient 106 the adverse experience initially termed "paresis" was changed to "weakness." In the other three cases withdrawal for increased blood pressure was changed to adverse experiences, i.e. headache, headache and vomiting, tinitus respectively.

Comments

This was an underpowered and too short a study to demonstrate pairwise (drug to placebo) significance, much less dose response. One might best consider it as a warmup for EC047 which follows.

6.3 Study EC047 - Double-blind, placebo controlled, randomized, multicenter phase II study of Candesartan cilexetil (4, 8, 12 or 16 mg) for 12 weeks in patients with mild to moderate essential hypertension (diastolic blood pressure 95-114 mm Hg).

L.A.B. performed the study at 3 sites in Germany for Takeda. The first patient was enrolled January 16, 1995 and the last patient was completed on February 20, 1996.

Principal Investigators: Dr. Heike Rosendahl (L.A.B. Stutgart) and Dr. Georg Schondorfer (L.A.B. Munich).

Placebo and active drugs were manufactured by
For blinding they were put into capsules. The overview of the study design and schedule was:

Study Design

	Screening	Wash-out for pre-treated patients	Placebo Run-in			Treatment								
Day			0	14	28	29	42	56	70	71	84	98	112	113
Visit			1	2	3	4	5	6	7	8	9	10	11	12

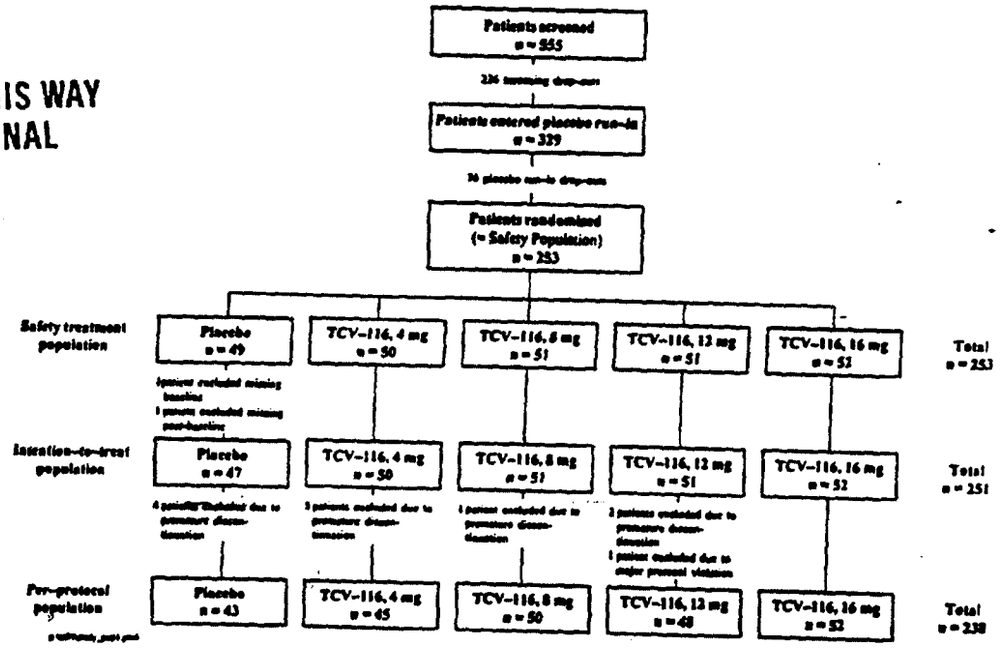
Schedule of examinations and assessments

Activity	Screening	V1 Day 0	V2 Day 14	V3 Day 28	V4 Day 29	V5 Day 42	V6 Day 56	V7 Day 70	V8 Day 71	V9 Day 84	V10 Day 98	V11 Day 112	V12 Day 113
Medical history	x												
Physical examination	x			x				x					x
Incl./excl. criteria	x			x									
Laboratory parameters	x			x				x				x	
BP/HR	x	x	x	x		x	x	x		x	x		x
ECG	x			x				x					x
ABPM				x	x			x	x			x	x
Blood sampling Pk				x		x	x	x		x	x	x	x
Adverse events			x	x	x	x	x	x	x	x	x	x	x
Compliance			x	x		x	x	x		x	x	x	
Dispensing of drugs		x			x		x			x			

Compliance was assessed by a device as well as by count of capsules returned.

The disposition of patients from screening through the double-blind study was:

APPEARS THIS WAY ON ORIGINAL



BEST POSSIBLE COPY

From the ITT population of 251 patients, 13 patients were not included in the per protocol population as follows:

Reasons for discontinuation	Placebo	Candesartan Cilexetil			
		4 mg	8 mg	12 mg	16 mg
	n=49	n=50	n=51	n=51	n=52
Adverse event	3 (19464, 21327, 21406)	1 (09904)	1 (21282)	1 (19387)	-
Patient request	-	1 (21463)	-	-	-
Investigator's discretion	-	1 (21283)	-	-	-
Non-adherence to protocol	1 (16385)	-	-	-	-
Non-compliance	-	-	-	1 (21468)	-
Other	1 (16324, 16385)	2 (18957, 25198)	-	-	-

Male or female patients who entered had to have had essential hypertension (mean sitting DBP 95-114 mm Hg). They could not

1. have been in earlier trials;
2. have severe cardiac disease (NYHA III or IV), history of MI within the last 6 months;
3. have renal impairment, potassium outside the normal range, liver disease or SGOT, SGPT, γGT elevations above 2X ULN.
4. surgery of the GI tract;
5. organic factors that might interfere with absorption and pharmacokinetics of the drug;
6. body weight exceeding 30% of the upper range in Metropolitan Life Tables.

The demographic characteristics of those who entered were:

	Placebo	Candesartan Cilexetil			
		4 mg	8 mg	12 mg	16 mg
	n=49	n=50	n=51	n=51	n=52
Male patients (%)	31 (63.3)	35 (70.0)	42 (82.4)	29 (56.9)	41 (78.8)
Female patients (%)	18 (36.7)	15 (30.0)	9 (17.6)	22 (43.1)	11 (21.2)
Age [years] (mean ± sd)	51.3 ± 11.1	50.8 ± 10.0	49.4 ± 10.3	51.9 ± 12.3	50.6 ± 11.4
Height [cm] (mean ± sd)	172.4 ± 9.5	170.8 ± 6.8	173.8 ± 7.5	170.1 ± 9.6	172.9 ± 9.5
Weight [kg] (mean ± sd)	81.3 ± 12.5	81.3 ± 11.1	85.9 ± 12.2	76.7 ± 12.5	83.8 ± 12.6

The primary efficacy parameter was the change in mean sitting DBP at trough from baseline (Visit 4) to the end of the treatment period (Visit 12).

Secondary parameters studied were:

1. 24 hour ABPM
2. systolic pressure and pulse rate
3. response rate (DBP ≤ 90 mm Hg or 10 mm Hg or more decrease)
4. trough/peak ratio for DBP and SBP.

APPEARS THIS WAY
ON ORIGINAL

Results

For the ITT population results for primary and secondary endpoints as per the sponsor were:

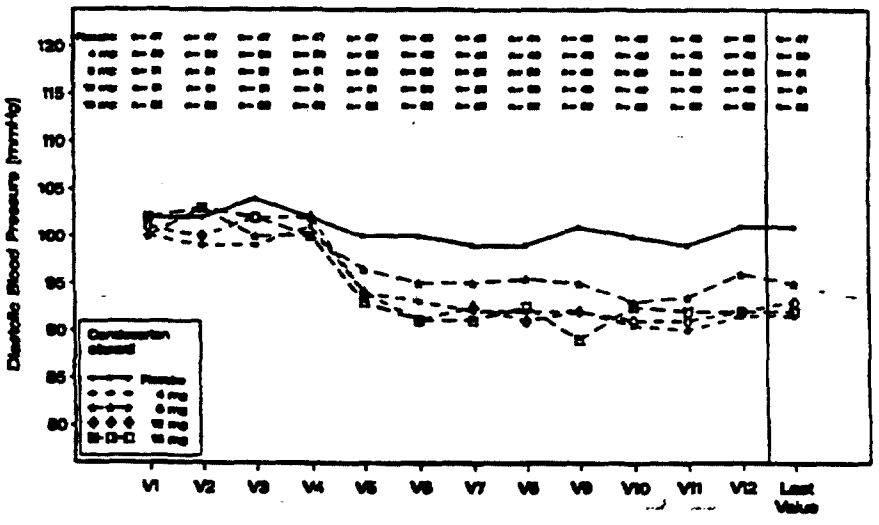
1. Change in DBP

Sitting diastolic blood pressure - baseline values and reduction estimates from analysis of covariance - Intention-to-treat Population (n=251)

	Placebo	Candesartan Cilexetil			
		4 mg	8 mg	12 mg	16 mg
	n=47	n=50	n=51	n=51	n=52
Mean baseline sitting diastolic blood pressure [mmHg]	102.9	101.8	102.2	102.0	101.9
Reduction in sitting diastolic blood pressure [mmHg]	2.03	8.72	7.77	10.02	10.26
p-values for comparison with placebo	-	< 0.0001	0.0001	< 0.0001	< 0.0001

The covariates 'baseline value' and 'sex' were both significant ($p < 0.05$), which meant that their inclusion in the ANCOVA model was justified. The testing procedure involved the comparison of all doses of Candesartan Cilexetil with placebo starting at the highest dose level 16 mg. As this was statistically significant at the 5% level, the next lower dose could be tested, and so on. All doses of Candesartan Cilexetil showed statistically significant larger reductions in sitting diastolic blood pressure than placebo.

The time course of the reduction was depicted:



2. ABPM Results

Diastolic blood pressure measurements from 24-hour ABPM - Per-protocol Population (n=238)

	Placebo	Candesartan Cilexetil			
		4 mg	8 mg	12 mg	16 mg
	n=43	n=45	n=50	n=48	n=52
24-hour means [mmHg]					
Baseline (Visit 3/4)	92.7	92.5	92.8	90.9	92.6
Visit 7/8	91.2	85.7	86.3	82.8	84.1
Reduction Baseline - Visit 7/8	1.5	6.8	6.6	8.2	8.4
Visit 11/12	93.2	85.1	85.7	82.7	84.4
Reduction Baseline - Visit 11/12	- 0.4	7.5	7.2	8.3	8.2
Daytime (7 a.m. - 11 p.m.) means [mmHg]					
Baseline (Visit 3/4)	97.3	96.9	97.2	95.6	97.5
Visit 7/8	96.2	89.6	90.1	86.8	88.6
Reduction Baseline - Visit 7/8	1.2	7.4	7.2	8.8	9.0
Visit 11/12	98.0	89.5	89.8	86.8	89.0
Reduction Baseline - Visit 11/12	-0.6	7.5	7.5	8.8	8.6
Night-time (11 p.m. - 7 a.m.) means [mmHg]					
Baseline (Visit 3/4)	83.6	83.7	84.2	81.6	82.7
Visit 7/8	81.4	78.0	78.7	74.7	75.3
Reduction Baseline - Visit 7/8	2.1	5.6	5.5	7.0	7.4
Visit 11/12	83.6	76.3	77.5	74.4	75.4
Reduction Baseline - Visit 11/12	-0.3	7.4	6.7	7.2	7.3

With respect to baseline values, there were no relevant differences between the treatment groups for the 24-hour means as well for the means of daytime and night-time segments. Baseline daytime means were all above 95 mmHg and thus compatible with the diagnosis of hypertension and about 13 mmHg higher than the night-time means. After six weeks (Visit 7/8), there was no relevant change in the placebo group with respect to 24-hour means as well as daytime and night-time means while a clear treatment effect was seen in the groups treated with Candesartan Cilexetil. Except for the 16 mg group, the mean reductions after 12 weeks (Visit 11/12) were slightly larger than the reductions after six weeks. A pattern of dose-dependence was not discernible as the magnitude of the treatment effect in all Candesartan Cilexetil group was very similar. In the Candesartan Cilexetil groups, the reductions during daytime were slightly larger than during night-time.

3. Systolic pressure and pulse (per protocol population).

Sitting systolic blood pressure - baseline values and reduction estimates from analysis of covariance (ANCOVA) - Per-protocol Population (n=238)

	Placebo	Candesartan Cilexetil			
		4 mg	8 mg	12 mg	16 mg
	n=43	n=45	n=50	n=48	n=52
Mean baseline sitting systolic blood pressure [mmHg]	154.2	149.1	152.5	154.2	150.2
Reduction in sitting systolic blood pressure [mmHg]	1.3	14.5	12.2	16.0	15.3
p-values for comparison with placebo	-	<0.0001	<0.0001	<0.0001	<0.0001

There was little change in pulse rate from baseline to test value.

Mean sitting pulse rates (bpm)

	Placebo	Candesartan Cilexetil			
		4 mg	8 mg	12 mg	16 mg
	n=49	n=50	n=51	n=51	n=52
Baseline (Mean ± sd)	75.7 ± 9.6	76.0 ± 10.0	73.6 ±7.7	73.5 ± 9.0	72.3 ± 8.6
Last value (Mean ±sd)	76.4 ± 10.2	74.5 ± 9.2	75.8 ± 8.7	75.3 ± 9.4	73.2 ± 7.6

4. Response rate (per protocol population).

Per-protocol population (n=238)

		Candesartan Cilexetil			
	Placebo n=43	4 mg n=45	8 mg n=50	12 mg n=48	16 mg n=52
Response rate [%]	16.3	51.1	36.0	56.3	53.9
95 % Confidence Intervals	6.83 - 30.71	35.78 - 66.29	22.98 - 50.81	41.18 - 70.61	39.47 - 67.77

APPEARS THIS WAY
ON ORIGINAL

5. Trough/Peak Ratio.

Reductions of diastolic blood pressure from 24-hour ambulatory blood pressure measurements (estimates from ANCOVA, absolute and placebo-corrected) at trough and at peak and trough/peak ratios with 95% confidence intervals on placebo-corrected values - Per-protocol Population (n=238)

Group		Treatment effect estimates at trough [mmHg]	Treatment effect estimates at peak [mmHg]	Trough/peak ratio	95% Confidence Interval
Placebo		- 0.59	1.19		
4 mg		6.77	6.31		
	placebo-corrected	7.36	5.11	1.44	0.48 - 6.04
8 mg		5.11	10.29		
	placebo-corrected	5.70	9.10	0.63	0.18 - 1.24
12 mg		6.28	11.47		
	placebo-corrected	6.87	10.28	0.67	0.21 - 1.13
16 mg		5.87	9.41		
	placebo-corrected	6.46	8.22	0.79	0.29 - 1.57

Trough and peak reductions of systolic blood pressure from 24-hour ambulatory blood pressure measurements (ANCOVA, absolute and placebo-corrected) and trough/peak ratios with 95% confidence intervals on placebo-corrected values - Per-protocol Population (n=238)

Group		Treatment effect estimates at trough [mmHg]	Treatment effect estimates at peak [mmHg]	Trough/peak ratio	95% Confidence Interval
Placebo		- 1.52	- 1.29		
4 mg		9.53	7.92		
	placebo-corrected	11.04*	9.21	1.20	0.52 - 2.75
8 mg		5.23	14.95		
	placebo-corrected	6.74*	16.24	0.42	0.06 - 0.79
12 mg		7.54	14.90		
	placebo-corrected	9.06	16.19	0.56	0.20 - 0.95
16 mg		9.43	12.41		
	placebo-corrected	10.94*	13.70	0.80	0.40 - 1.37

* values contain rounding errors

In addition, compliance measured either by MEMS or pill count and was above 98%.

The results of a pharmacokinetic study were to be provided separately.

Safety

No deaths but two serious adverse experiences were reported, both in patients on Candesartan.

One of the serious cases developed thrombophlebitis. The other (case #19387) was a myocardial infarction. This latter patient, a 53 year old male, had the infarct after 6 weeks on 12 mg of Candesartan cilexetil. This patient's blood pressure was 151/89 without orthostatic change at the time of the infarct. These and other severe cases are listed below.

Patients with severe adverse events

Group	LAB Vol ID	Adverse event (Preferred term)	Relationship to study medication
Placebo	02589	Accidental injury	not related
	02932	Headache	possible
	18878	Menstrual disorder	not related
	19418	Nausea	possible
		Vomiting	possible
	19435	Sinusitis	possible
	21327	Arrhythmia	unknown
4 mg	09904	Thrombophlebitis	not related
	25571	PTT prolonged	possible
	25661	Headache	possible
8 mg	18829	Toothache	not related
	19072	Pyuria	possible
	19465	Back pain	possible
	21282	Rash	possible
	25639	Nausea	possible
12 mg	02275	Accidental injury	not related
	17356	Abdominal pain	possible
	19387	Myocardial infarction	possible
	19458	Headache	possible
		Nausea	possible
	19463	Influenza-like symptoms	possible
	25660	Diarrhoea	possible
16 mg	16530	Hypercholesterolaemia	not related
		Hypertriglyceridaemia	not related
	18810	Back pain	not related
	19152	Rash pustular	not related
	19154	Earache	possible
	19395	Headache	not related
		Hypercholesterolaemia	not related
	19481	Toothache	not Related

Any adverse experience reported was presented as follows:

Total number of patients with adverse events by study population and study period

Study population	Onset during the placebo run-in period		Onset during the randomised treatment period	
	Events	Patients	Events	Patients
Patients who entered the randomised treatment period (n=253)	168	99 (39.3%)	465	195 (77.1%)
Patients who discontinued during the placebo run-in period (n=76)	54	30 (39.5%)	-	-

Patients with AEs during the treatment period

System Organ Class	Placebo n=49	Candesartan Cilexetil				
		4 mg n=50	8 mg n=51	12 mg n=51	16 mg n=52	Total n=204
Body as a whole - general disorders	20 (40.8%)	20 (40.0%)	23 (45.1%)	22 (43.1%)	19 (36.5%)	84 (41.2%)
Central and peripheral nervous system	13 (26.5%)	15 (30.0%)	13 (25.5%)	18 (35.3%)	11 (21.2%)	57 (27.9%)
Gastrointestinal system	8 (16.3%)	5 (10.0%)	7 (13.7%)	7 (13.7%)	9 (17.3%)	28 (13.7%)
Liver and biliary system	5 (10.2%)	4 (8.0%)	5 (9.8%)	7 (13.7%)	10 (19.2%)	26 (12.7%)
Respiratory system disorders	4 (8.2%)	7 (14.0%)	3 (5.9%)	5 (9.8%)	4 (7.7%)	19 (9.3%)
Metabolic and nutritional disorders	5 (10.2%)	5 (10.0%)	4 (7.8%)	-	6 (11.5%)	15 (7.4%)
Urinary system disorders	3 (6.1%)	2 (4.0%)	7 (13.7%)	4 (7.8%)	1 (1.9%)	14 (6.9%)
Skin and appendages disorders	2 (4.1%)	5 (10.0%)	2 (3.9%)	6 (11.8%)	1 (1.9%)	14 (6.9%)
Platelet, bleeding and clotting disorders	3 (6.1%)	4 (8.0%)	2 (3.9%)	3 (5.9%)	1 (1.9%)	10 (4.9%)
White cell and RES	1 (2.0%)	2 (4.0%)	3 (5.9%)	3 (5.9%)	2 (3.8%)	10 (4.9%)
Musculoskeletal system disorders	2 (4.1%)	3 (6.0%)	-	4 (7.8%)	1 (1.9%)	8 (3.9%)
Heart rate and rhythm disorders	1 (2.0%)	2 (4.0%)	2 (3.9%)	-	-	4 (2.0%)
Psychiatric disorders	2 (4.1%)	-	-	1 (2.0%)	2 (3.8%)	3 (1.5%)
Cardiovascular disorders, general	1 (2.0%)	2 (4.0%)	-	1 (2.0%)	-	3 (1.5%)
Vision disorders	2 (4.1%)	1 (2.0%)	-	1 (2.0%)	-	2 (1.0%)
Reproductive disorders, female	2 (4.1%)	-	-	-	1 (1.9%)	1 (0.5%)
Hearing and vestibular disorders	-	-	-	-	1 (1.9%)	1 (0.5%)
Myo-, endo-, pericardial and valve disorders	-	-	-	1 (2.0%)	-	1 (0.5%)
Red blood cell disorders	-	-	1 (2.0%)	-	-	1 (0.5%)
Resistance mechanism disorders	-	-	-	-	1 (1.9%)	1 (0.5%)
Vascular (extracardiac) disorders	-	1(2.0%)	-	-	2 (3.8%)	3 (1.5%)

Hematology and chemistry values did not change significantly in any group or between groups from baseline to end. One prothrombin time was reported as decreased in a patient on Candesartan, but no lab value led to withdrawal of the patient.

Comments

From 4-16 mg once daily for 12 weeks, Candesartan was statistically superior to placebo. Numerically 12 and 16 mg were better than 4 or 8 mg, but with around 50 per group the power to discern dose response is inadequate. Candesartan's effect appears to plateau at 4 weeks. The BP reduction was accomplished without an increase in heart rate. The trough/peak ratios suggest that 16mg could be given once daily.

6.4 Study AHM-0001 (Dr. Caras)

. Title	The Antihypertensive Effect of Candesartan Cilexetil (8. 16 mg) once daily. in comparison with Losartan (50 m=) once daily, and Placebo.
01.2. Source documents	Study report: vol 1.120-1.127, CANDA
01.3. Investigators	Multiple Centers in Denmark and Sweden
01.4. Study dates	11 August 1995 - 15 May 1996
01.5. Study design	This study description was based upon the protocol dated April 6, 1995. There were a total of four protocol amendments. The first two protocol amendments were prior to the start of the trial. Notable changes in the first two protocols included (1) Change the Candesartan dose from 4 and 8 mg to 8 and 16 ma. This change required new packaging. (2) Change to another automated blood pressure measuring device. The other protocol amendments were made after the start of enrollment. This allowed the use of manual blood pressure measurements in cases when the automated device is not working well.

This is a randomized, double-blind, placebo-controlled parallel study in subjects with mild to moderate hypertension (95< SeDBP <114 mmHg). Figure I below shows a schematic of this trial. After a 4-5 week lead-in period, the patient was randomized either to placebo, Candesartan 8mg qd, 16 mg qd or losartan 50mg qd. There were routine visits at 2 4 6 and 8 weeks.

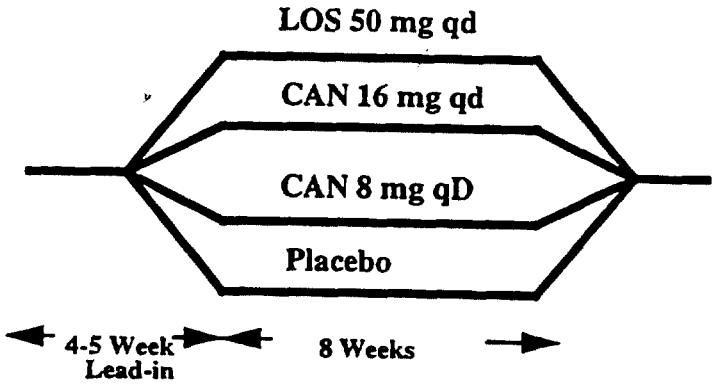


Figure 1. Study design (Study AHM-0001).

The blood pressure was measured by an automated device (Omron HEM-705P). Both hand- written and printouts from the device were entered on the case report form.

Drug supplies are shown in Table I below.

Table 1. Drug supplies (Study AHM-0001).

Dose	Batch
Candesartan Placebo	H 1157-01-01-02
Losartan Placebo	H 1164-01-01-01
Candesartan 4 mg	H 1155-01-01-02
Candesartan 8 mg	H 1156-01-01-02
Losartan 50 mg	H 1164-01-01-01

ımercially available losartan was obtained and encapsulated into gelatin capsules. According to the sponsor, in-vitro olution testing were performed to insure that the characteristics of tile losartan tablets \were not altered by the ɛncapsulation".