

## Results

The primary efficacy data as given was:

Treatment group	n	Median sitting diastolic blood pressure (mmHg)		
		Baseline (BL)	Last value (LV)	Absolute difference between BL and LV
		mean* ± s.d. median min - max	mean* ± s.d. median min - max	mean* ± s.d. median min - max
0 mg/0 mg	119	102.0 ± 6.0 101 88 - 125	98.0 ± 10.5 98 71 - 133	-4.0 ± 10.4 -4 -34 - +37
2 mg/0 mg	41	100.8 ± 5.1 101 89 - 110	93.9 ± 11.9 92 67 - 120	-6.9 ± 11.7 -6 -38 - +24
4 mg/0 mg	60	100.6 ± 6.4 100 73 - 114	95.3 ± 10.1 96 70 - 120	-5.3 ± 11.2 -2.5 -32 - +28
8 mg/0 mg	131	101.4 ± 5.0 101 86 - 115	93.3 ± 10.8 94 71 - 126	-8.2 ± 10.7 -8 -37 - +28
16 mg/0 mg	36	100.8 ± 5.7 100 85 - 112	90.8 ± 11.4 87.5 68 - 114	-10.0 ± 10.8 -11 -40 - +10
0 mg/12.5 mg	60	101.0 ± 5.2 100.5 88 - 118	95.6 ± 9.8 97 75 - 118	-5.5 ± 9.1 -5 -25 - +15
2 mg/12.5 mg	45	102.5 ± 4.4 103 93 - 109	96.5 ± 13.4 94 71 - 132	-6.0 ± 12.1 -7 -35 - +24
4 mg/12.5 mg	56	101.0 ± 3.8 101 93 - 112	91.1 ± 8.2 91 72 - 111	-9.9 ± 8.3 -11 -26 - +11
8 mg/12.5 mg	61	102.3 ± 5.1 103 94 - 119	91.6 ± 9.8 91 69 - 115	-10.7 ± 10.3 -11 -39 - +19
16 mg/12.5 mg	39	102.1 ± 6.2 100 95 - 127	85.2 ± 8.0 85 70 - 106	-17.0 ± 11.0 -16 -49 - +3
0 mg/25 mg	123	101.7 ± 5.2 101 83 - 119	94.3 ± 10.1 94 66 - 123	-7.4 ± 10.4 -7 -42 - +25
2 mg/25 mg	38	101.1 ± 5.2 101 85 - 113	93.8 ± 12.1 92 66 - 130	-7.2 ± 12.3 -7 -32 - +31
4 mg/25 mg	64	101.2 ± 4.9 101 87 - 112	94.1 ± 10.5 92 77 - 128	-7.1 ± 9.9 -7 -31 - +22
8 mg/25 mg	122	100.5 ± 5.1 100 86 - 116	90.2 ± 12.1 89.5 53 - 123	-10.2 ± 12.4 -12 -48 - +33
16 mg/25 mg	43	101.0 ± 5.9 101 86 - 115	88.0 ± 9.1 87 73 - 114	-12.9 ± 9.1 -16 -31 - +6

\* mean from median values

Placebo adjusted least square means results were:

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

Both the 8 and 16 mg monotherapy arms were statistically superior to placebo.

Response surface using a quadratic and linear model were:

		Candesartan cilexetil				
		0 mg	2 mg	4 mg	8 mg	16 mg
HCTZ	0 mg	4	6.9	5.3	8.2	10
		3.9	5	6	8.1	11.8
		4.3	5.3	6.3	8.3	12.2
	12.5 mg	5.5	6	9.9	10.7	17
		6.5	7.6	8.6	10.6	14.3
		5.6	6.5	7.5	9.5	13.4
	25 mg	7.4	7.2	7.1	13.2	12.9
		6.4	7.5	8.5	10.4	14
		6.8	7.8	8.7	10.7	14.7

First line: observed values

Second line: estimates under the quadratic model

Third line: estimates under the linear model

Response and normalization results were provided:

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

Additional data re orthostatic change and systolic blood pressure were:

Treatment Group	DPB immediately upon standing mean $\pm$ s.d. (min - max)	DPB after 2 min. of standing mean $\pm$ s.d. (min - max)	Sitting SBP mean $\pm$ s.d. (min - max)	SBP immediately upon standing mean $\pm$ s.d. (min - max)	SBP after 2 min. of standing mean $\pm$ s.d. (min - max)
0 mg/0 mg	-2.5 $\pm$ 9.8 (-36 - +20)	-3.1 $\pm$ 12.3 (-56 - +33)	-4.6 $\pm$ 16.9 (-46 - +56)	-2.8 $\pm$ 18.0 (-60 - +39)	-2.9 $\pm$ 16.3 (-43 - +52)
2 mg/0 mg	-7.4 $\pm$ 12.3 (-36 - +24)	-7.4 $\pm$ 11.5 (-34 - +15)	-9.6 $\pm$ 23.6 (-57 - +43)	-2.5 $\pm$ 26.7 (-62 - +60)	-6.2 $\pm$ 25.2 (-61 - +57)
4 mg/0 mg	-8.3 $\pm$ 11.6 (-35 - +10)	-5.6 $\pm$ 11.3 (-36 - +17)	-7.9 $\pm$ 15.8 (-44 - +25)	-8.1 $\pm$ 21.6 (-62 - +39)	-8.5 $\pm$ 19.0 (-59 - +35)
8 mg/0 mg	-7.3 $\pm$ 14.3 (-66 - +35)	-7.7 $\pm$ 13.4 (-48 - +38)	-11.4 $\pm$ 19.1 (-58 - +42)	-11.9 $\pm$ 19.7 (-65 - +35)	-10.0 $\pm$ 22.0 (-67 - +84)
16 mg/0 mg	-11.6 $\pm$ 11.8 (-36 - +20)	-11.0 $\pm$ 12.9 (-35 - +18)	-12.6 $\pm$ 17.0 (-52 - +18)	-18.5 $\pm$ 23.0 (-78 - +21)	-13.8 $\pm$ 19.2 (-55 - +31)
0 mg/12.5 mg	-4.0 $\pm$ 10.8 (-29 - +31)	-2.8 $\pm$ 10.9 (-25 - +37)	-8.5 $\pm$ 13.4 (-36 - +47)	-6.8 $\pm$ 18.2 (-39 - +51)	-7.6 $\pm$ 17.2 (-38 - +71)
2 mg/12.5 mg	-5.9 $\pm$ 13.9 (-35 - +42)	-6.6 $\pm$ 11.0 (-27 - +30)	-12.1 $\pm$ 18.8 (-53 - +36)	-12.3 $\pm$ 17.8 (-42 - +43)	-9.2 $\pm$ 16.9 (-66 - +27)
4 mg/12.5 mg	-7.6 $\pm$ 10.8 (-31 - +28)	-7.1 $\pm$ 10.8 (-36 - +22)	-19.4 $\pm$ 14.6 (-58 - +20)	-17.9 $\pm$ 17.2 (-67 - +27)	-18.0 $\pm$ 17.4 (-70 - +21)
8 mg/12.5 mg	-9.4 $\pm$ 13.1 (-41 - +30)	-9.6 $\pm$ 12.1 (-34 - +29)	-20.6 $\pm$ 20.2 (-77 - +14)	-20.7 $\pm$ 20.4 (-96 - +15)	-20.6 $\pm$ 21.0 (-117 - +24)
16 mg/12.5 mg	-11.5 $\pm$ 13.4 (-37 - +19)	-12.5 $\pm$ 16.9 (-37 - +61)	-23.0 $\pm$ 17.8 (-61 - +13)	-21.5 $\pm$ 23.1 (-63 - +35)	-23.7 $\pm$ 17.9 (-69 - +24)
0 mg/25 mg	-5.7 $\pm$ 12.0 (-41 - +23)	-5.9 $\pm$ 11.8 (-44 - +22)	-10.3 $\pm$ 15.6 (-42 - +38)	-9.1 $\pm$ 20.6 (-56 - +87)	-8.4 $\pm$ 18.9 (-63 - +55)
2 mg/25 mg	-3.6 $\pm$ 14.1 (-32 - +39)	-6.0 $\pm$ 14.7 (-43 - +46)	-13.1 $\pm$ 17.8 (-50 - +21)	-10.6 $\pm$ 15.5 (-43 - +28)	-12.1 $\pm$ 19.8 (-41 - +50)
4 mg/25 mg	-6.0 $\pm$ 14.1 (-34 - +39)	-6.1 $\pm$ 11.6 (-40 - +31)	-12.9 $\pm$ 19.8 (-68 - +46)	-13.4 $\pm$ 23.3 (-102 - +50)	-11.1 $\pm$ 21.7 (-60 - +96)
8 mg/25 mg	-10.4 $\pm$ 13.8 (-59 - +27)	-9.0 $\pm$ 13.7 (-41 - +41)	-15.6 $\pm$ 19.3 (-78 - +49)	-16.2 $\pm$ 21.7 (-66 - +53)	-16.4 $\pm$ 23.4 (-95 - +82)
16 mg/25 mg	-13.8 $\pm$ 13.3 (-47 - +16)	-10.3 $\pm$ 11.4 (-28 - +29)	-21.5 $\pm$ 16.4 (-61 - +14)	-20.7 $\pm$ 17.9 (-66 - +34)	-21.9 $\pm$ 22.9 (-119 - +18)

### Safety

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

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

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

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

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

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

Not all of the patient who withdrew for adverse reactions were characterized as severe:

Group	Pat. No. (CRF No.)	Adverse Event	Relation-ship	Outcome
Serious adverse events under monitoring (includes un-blinded events)				
0 mg/0 mg	364 (S4080)	Depressive syndrome	not related	resolved without sequelae hospitalization
4 mg/0 mg	1096 (S4107)	Urinary calculus	not related	resolved without sequelae hospitalization
4 mg /12.5 mg	283 (S3595)	Perforation of aneurysm (of the right external carotid artery)	possible	symptom unchanged hospitalization
4 mg /12.5 mg	947 (S3986)	Myocardial infarction	possible	resolved without sequelae hospitalization
		Dizziness	possible	resolved without sequelae hospitalization
4 mg /12.5 mg	1282 (S4416)	Myopericarditis	unknown	resolved without sequelae hospitalization
0 mg/2.5 mg	668 (S3117)	Pneumonia	not related	resolved without sequelae hospitalization
8 mg/25 mg	430 (S3948)	Atrial flutter with rapid conduction	possible	resolved without sequelae hospitalization
8 mg/25 mg	1668 (S4189)	Massive dizziness	possible	resolved without sequelae hospitalization
		Vomiting	possible	resolved without sequelae hospitalization
8 mg/25 mg	648 (S3215)	Anal fistula	not related	resolved without sequelae hospitalization
Serious adverse events occurring after end of treatment				
8 mg/0 mg	331 (S3002)	Sudden death due to suspected pulmonary embolism	not related	death
4 mg/12.5 mg	1008 (S4046)	Holter vagus surgery	not related	resolved without sequelae hospitalization
16 mg/0 mg	891 (S3113)	Impaired withdrawal	unknown	symptom improved
		Re-adjustment of insulin	unknown	symptom improved
Pre-planned serious adverse events (i.e. scheduled surgery)				
8 mg/12.5 mg	329 (S3309)	Cataract surgery	not related	resolved without sequelae hospitalization
0 mg/25 mg	37 (S3527)	Vascular vein surgery	not related	resolved without sequelae hospitalization
16 mg/25 mg	418 (S3332)	Pneumocentesis	not related	symptom unchanged

Patient S3548 on 8 mg of Candesartan cilexetil who had a "mild non-transmural myocardial infarction" was not included on this list. Nor were cases of hypotension and dizziness, or a case of Raynands.

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

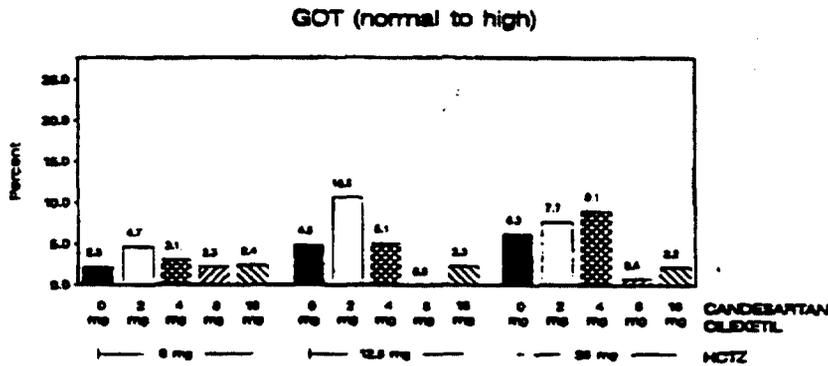
	Placebo n = 133		Candesartan Cilexetil only n = 282		HCTZ only n = 189		Combination n = 490	
	All AEs	Attrib AEs	All AEs	Attrib AEs	All AEs	Attrib AEs	All AEs	Attrib AEs
<b>Body as a whole</b>								
Influenza-like symptoms	2 (1.5%)	-	6 (2.1%)	-	9 (4.8%)	1 (0.5%)	17 (3.5%)	1 (0.2%)
Oedema peripheral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

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

### Laboratory Findings

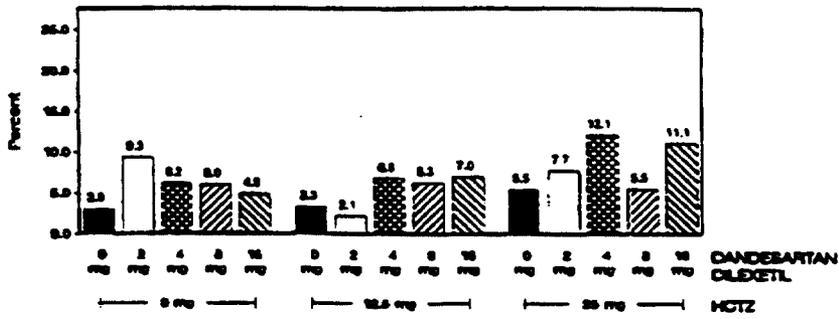
Graphic displays of shifts from normal baseline to high final value for each treatment group were provided. Selected liver and renal chemistry displays were given as follows:



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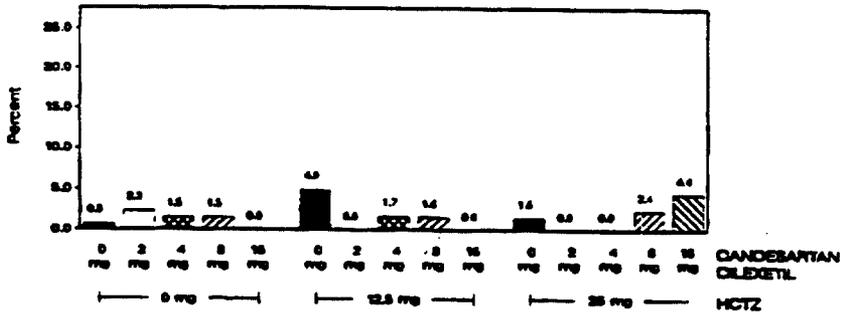
GPT (normal to high)



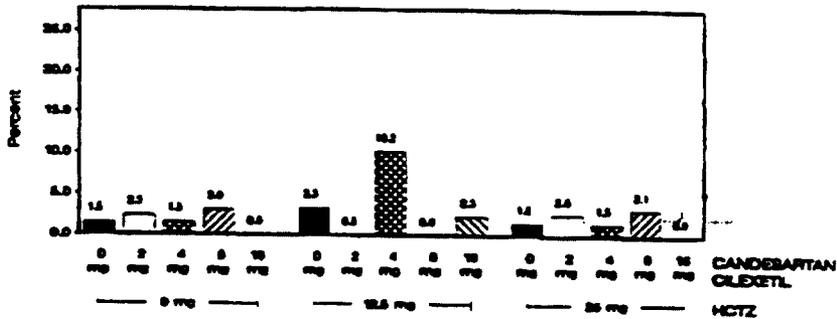
Gamma-GT (normal to high)



Total Bilirubin (normal to high)

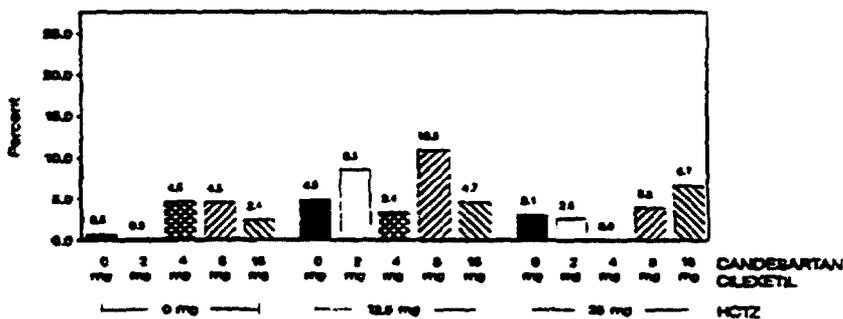


Creatinine (normal to high)



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Urea (normal to high)



The change in triglycerides was greater for the 25 mg HCTZ combinations than for the 12.5 mg HCTZ combinations.

Numerous numerical differences were present for basophilia, eosinophilia, and glucose, but without pattern.

ECG interval changes were infrequent and sporadic as well. For example, changes from baseline for placebo, 8 mg Candesartan, 16 mg Candesartan and 8 mg Candesartan with 25 mg HCTZ were:

Treatment group 0 mg / 0 mg

ECG parameter	Total No. of Patients	Visit 3 normal	Pct. of Patients	Any post-baseline low	Pct. of Patients	Last value low	Pct. of Patients	Any post-baseline high	Pct. of Patients	Last value high	Pct. of Patients
PR (sec)	133	126	94.7	1	0.8	1	0.8	1	0.8	1	0.8
QRS (sec)	133	123	92.5	1	0.8	0	0.0	2	1.5	2	1.5
QT (sec)	133	129	97.7	0	0.0	0	0.0	1	0.8	0	0.0
QT (Corrected)	133	119	89.7	0	0.0	0	0.0	4	3.0	0	0.0

Treatment group 8 mg / 0 mg

ECG parameter	Total No. of Patients	Visit 3 normal	Pct. of Patients	Any post-baseline low	Pct. of Patients	Last value low	Pct. of Patients	Any post-baseline high	Pct. of Patients	Last value high	Pct. of Patients
PR (sec)	133	121	91.0	2	1.5	0	0.0	1	0.8	1	0.8
QRS (sec)	133	123	92.5	2	1.5	0	0.0	2	1.5	0	0.0
QT (sec)	133	126	94.7	2	1.5	0	0.0	0	0.0	0	0.0
QT (Corrected)	133	112	84.3	13	9.8	4	3.0	10	7.5	3	2.3

Treatment group 16 mg / 0 mg

ECG parameter	Total No. of Patients	Visit 3 normal	Pct. of Patients	Any post-baseline low	Pct. of Patients	Last value low	Pct. of Patients	Any post-baseline high	Pct. of Patients	Last value high	Pct. of Patients
PR (sec)	41	36	87.8	1	2.4	0	0.0	0	0.0	0	0.0
QRS (sec)	41	37	90.2	1	2.4	0	0.0	1	2.4	0	0.0
QT (sec)	41	37	90.2	1	2.4	0	0.0	0	0.0	0	0.0
QT (Corrected)	41	32	78.0	6	14.6	2	4.9	0	0.0	0	0.0

Treatment group 8 mg / 25 mg

ECG parameter	Total No. of Patients	Visit 3 normal	Pct. of Patients	Any post-baseline low	Pct. of Patients	Last value low	Pct. of Patients	Any post-baseline high	Pct. of Patients	Last value high	Pct. of Patients
PR (sec)	127	115	90.6	2	1.6	0	0.0	5	3.9	3	2.4
QRS (sec)	127	114	90.5	0	0.0	0	0.0	4	3.1	0	0.0
QT (sec)	127	120	94.5	4	3.1	0	0.0	0	0.0	0	0.0
QT (Corrected)	127	107	84.3	10	12.6	7	5.5	12	9.4	3	2.4

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### Comments

This study with many cells provides evidence that 8 and 16 mg of CC are statistically superior to placebo to lower DBP in patients with mild to moderate essential hypertension. At CC doses of 8 mg to 16 mg, HCTZ adds to this effect. 4 mg CC plus HCTZ gave a variable result; an additive result when 12.5 mg of HCTZ was used, but not additive for the 25 mg HCTZ/4 mg CC combination. CC 16 mg/12.5 mg HCTZ appeared best. Whether the drug interactions noted in study EC028 plays a part in these results is not established, but possible.

Although same orthostatic reactions occurred, mean DBP and SBP changes from sitting to standing were not found. Adverse events, a few of concern, appeared randomly distributed across all cells. The same seemed true for laboratory findings. The combinations appeared to be as well tolerated as monotherapy.

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**6.16 AM 117 - Evaluation of Safety and Efficacy of adding Candesartan Cilexetil (8 to 16 mg) to HCTZ in Patients with Severe (JNC-V) Hypertension.**

Multicenter, randomized, double-blind, placebo controlled, parallel design; four week controlled period followed by open label long term extension.

Study initiated April 19, 1996.

DB Study completed December 12, 1996.

Protocol approved August 30, 1996; amended January 19, 1996 and June 3, 1996.

The last protocol amendment for the DB study moved the time of fasting laboratory assessment from week 1 of the DB period to week 1 of the open label HCTZ period. Other changes were similarly minor and reasonable.

This was a U.S. study, conducted at 37 sites, supervised by Astra Merck. Drug and placebo were manufactured by Takeda Chemical Industries, Japan and packaged by Astra in Sweden. HCTZ was manufactured by Merck & Co.

Study objectives were:

- A. To determine the efficacy of candesartan cilexetil 8 mg once daily titrated, if necessary, to 16 mg once daily added to hydrochlorothiazide 12.5 mg in patients with severe hypertension.
- B. To determine the tolerability and safety of candesartan cilexetil added to hydrochlorothiazide in patients with severe hypertension.

Inclusion criteria:

Male or female (without child-bearing potential) patients with severe hypertension (sitting DBP  $\geq$  110 mm Hg at entrance) on antihypertensive Rx, 18-80 years of age.

Exclusion criteria:

Systolic BP  $\geq$  210 mm Hg, organic cardiovascular, renal, hepatic, pulmonary or hemotologic disease. Taking steroids, NSAIDS or ASA exceeding 1 gm daily.

Randomization (2:1, active: placebo) via computer generated list by investigative site. Race (black, non-black) was also considered in the randomization program. A sample size of 210 entering the double blind phase (180 completers) was considered adequate to provide 95% power to detect a mean difference of 5 mm Hg in sitting DBP between HCTZ and placebo versus HCTZ and Candesartan. This assumed a standard deviation of 7.5 mm Hg and a two tailed test at an  $\alpha$  of 0.05. Primary analysis was to be (for the ITT population using LOCF) the change in trough sitting DBP from randomization to the end of the DB phase. Secondly, standing trough DBP, sitting and standing trough SBP, and proportion of responders ( $<$  90 mm Hg or  $\geq$  10 mm Hg drop in sitting trough DBP) by Mantel - Haenszel stratified by site.

Safety would also be evaluated. Compliance was to be assessed by pill count. A chart of the study was:

Procedures	Screening	Placebo Run-In		Open-Label HCTZ	Double-Blind				Open-Label Extension								Off-Drug Follow-Up	
	Week 0	Weeks 1 2	Week 1	Weeks 1 2 3 4 6 8 12 16 24 32 40 48 52	Weeks 2													
Informed Consent	X																	
Medical History	X																	
Chest X-ray	X																	
12-lead ECG	X			X				X										X
Complete Physical Exam	X							X										X
Brief Physical Exam		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Trough BP Measurement	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fasting Laboratory Assessment*	X			X				X						X				X
Drug Accountability		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE Assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Final Report																		X

\* In any phase of the study, patients with clinically significant symptoms of myalgia not completely explained by a concurrent illness (e.g., viral syndrome), trauma or severe exertion, that persist for more than 1 (one) week should have a CPK determination, with isozyme fractionation of the CPK, if the abnormality is greater than twice the upper limit of normal range.

To be randomized patients had to have a sitting trough DBP of  $\geq 110$  mm Hg on or without antihypertensive therapy prior to the open label HCTZ 12.5 mg 1 week treatment period, but a SDBP of  $> 95$  mm Hg after the HCTZ treatment was acceptable for randomization. Randomization was done at entrance to the double blind period. During the DB phase (after at least 1 week) the 8 mg dose of Candesartan cilexetil or placebo could be doubled if the sitting DBP was  $\geq 90$  mm Hg.

289 patients were screened, and of these 217 patients were randomized into the double blind period. The demographics were provided in the following chart.

			Placebo + HCTZ	CC + HCTZ	Total
Age (yrs)	Overall	N	76	141	217
		Mean	30.5	31.5	31.1
		SD	10.2	9.1	9.2
Weight (lbs)	Overall	N	76	140	216
		Mean	202.2	215.0	212.9
		SD	47.6	51.5	50.1
Sex	Overall	N	33	94	127
		Mean	219.2	222.5	221.3
		SD	47.4	51.5	49.9
Race	Overall	N	33	66	99
		Mean	186.1	199.5	192.1
		SD	49.4	46.4	46.0
Duration of Hypertension (years)	Overall	N	76	141	217
		Mean	9.1	12.8	11.2
		SD	5.2	10.4	9.8
Ethnicity	Overall	N(%)	52(67.7%)	92(67.4%)	148(68.2%)
		Female	25(32.3%)	46(32.6%)	69(31.8%)
		Male	46(60.3%)	52(37.5%)	130(59.4%)
Pre-HCTZ Trough Sitting DBP (mmHg)	Overall	Mean	111.4	112.6	112.2
		Mean	105.6	105.0	105.3
		Mean	104.1	106.2	105.3
Baseline Trough Sitting DBP (mmHg)	Overall	Mean	136.5	136.2	136.3
		Mean	136.5	136.2	136.3
		Mean	136.5	136.2	136.3

Complete tables for baseline characteristics can be found in the 10.1.3 series of tables. Baseline trough sitting diastolic blood pressure data can be found in Tables 10.2.1.01, 10.2.1.04, and 10.2.1.32. Lengthy by rows are presented in the Appendix 12.1.1.1 series and complete lengths in the Appendix 12.2.1.2 and 12.2.1.3 series.

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Disposition was noted as follows:

	Placebo/HCTZ	CC 8-16 mg/HCTZ	Total
Patients Entered			289
Randomized to Double Blind	76(100%)	141(100%)	217(100%)
Discontinued	20(26.3%)	21(14.9%)	41(18.9%)
Lost to Follow Up	0(0.0%)	2(1.4%)	2(0.9%)
Lack of Response	13(17.1%)	8(5.7%)	21(9.7%)
Adverse Event	4(5.3%)	3(2.1%)	7(3.2%)
Consent Withdrawn	1(1.3%)	3(2.1%)	4(1.8%)
Sponsor/Investigator Decision	2(2.6%)	5(3.5%)	7(3.2%)
Completed Study	56(73.7%)	120(85.1%)	176(81.1%)

Dose doubling was done for the majority in both groups.

Patient Status	Placebo + HCTZ		CC + HCTZ		Overall	
	N	%	N	%	N	%
Not Uptitrated	11	14.5	24	17.0	35	16.1
Uptitrated	65	85.5	117	83.0	182	83.9

Compliance was not calculated because of inconsistencies and inaccuracies in the data.

### Double Blind Results

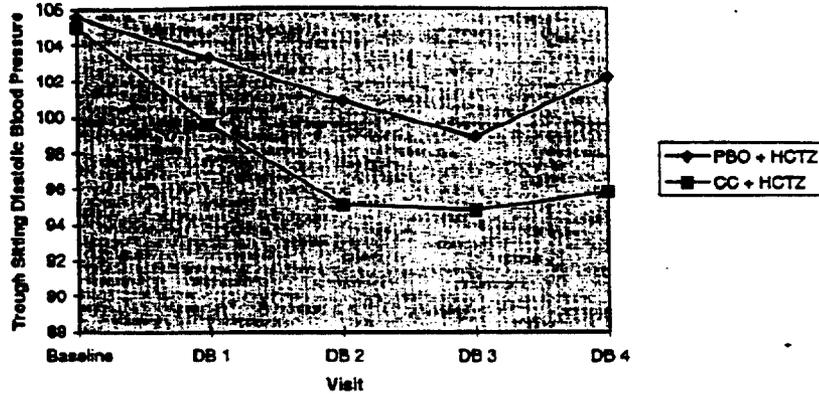
#### Efficacy:

##### Primary

Treatment		Baseline	DB 1	DB 2	DB 3	DB 4
Placebo + HCTZ	N	74	70	58	55	74
	Mean	105.6	103.3	100.9	98.9	102.2
	SD	6.2	7.4	9.0	8.1	10.7
CC + HCTZ	N	135	129	126	121	135
	Mean	105.0	99.6	95.1	94.8	95.8
	SD	6.6	8.2	8.8	9.2	10.1

- 3.4

- 9.2



Treatment Comparison	LSM	95% CI		p-value
		Lower	Upper	
CC + HCTZ vs. Placebo + HCTZ	-6.0	-8.5	-3.4	0.0001

Secondary

Standing DBP (n=209)

ANALYSIS OF COVARIANCE  
 Change from Baseline in Trough Standing Diastolic Blood Pressure (mmHg) at Week 4  
 Population: Efficacy Evaluable with Last Observation Carried Forward

Model: Baseline Trough Standing DBP, Treatment, Pooled Center, Treatment\*Pooled Center

Pairwise Comparisons of Active Treatment Groups with Placebo Group

Treatment	N	Least Squares Mean (LSM) Change from Baseline	LSM Standard Error	Difference from Placebo in LSM Change from Baseline	95% Confidence Interval for Difference from Placebo in LSM Change from Baseline	Treatment LSM Change from Baseline Different than Placebo (p value)
Candesartan+HCTZ	125	-8.3118	0.7903	-6.8685	(-8.6211, -5.1160)	0.0001
Placebo+HCTZ	74	-2.2425	1.0235			

Tests for Significance of Main Effects and Interaction Term (Type III Tests; Each Effect Adjusted for All Other Effects)

Factor	F value	p value
Treatment	32.84	0.0001
Pooled Center	2.21	0.0026
Treatment*Pooled Center Interaction	0.93	0.5531

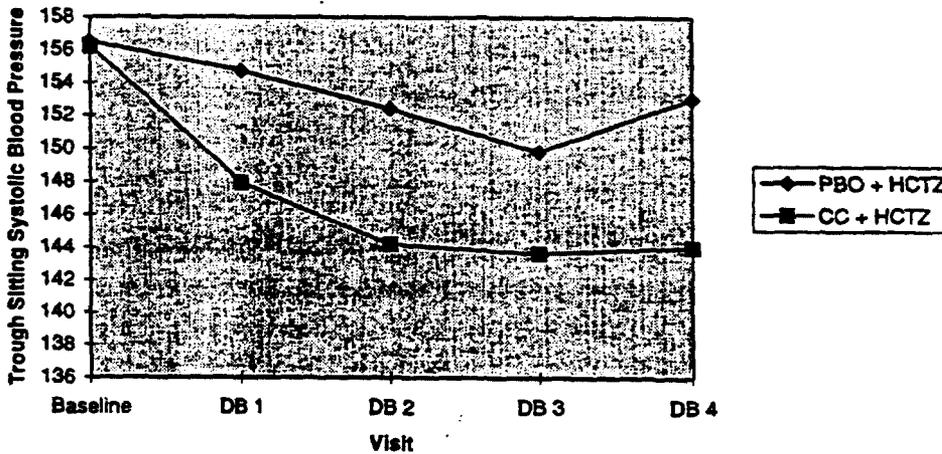
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Sitting SBP (ITT/LOCF)

Treatment		Baseline	DB 1	DB 2	DB 3	DB 4
Placebo + HCTZ	N	74	70	58	55	74
	Mean	156.5	154.7	152.4	149.8	153.0
	SD	18.0	17.4	17.7	16.4	18.4
CC + HCTZ	N	135	129	126	121	135
	Mean	156.2	147.9	144.2	143.6	144.0
	SD	18.7	18.1	18.1	18.0	19.7

-3.5

-12.9



Treatment Comparison	LSM	95% CI		p-value
		Lower	Upper	
CC + HCTZ vs. Placebo + HCTZ	-7.1	-11.3	-3.0	0.0009

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Standing SBP

**Analysis of Covariance**  
**Change from Baseline in Trough Standing Systolic Blood Pressure (mmHg) at Week 4**  
**Population: Efficacy Evaluable with Last Observation Carried Forward**

Model: Baseline Trough Standing SBP, Treatment, Pooled Center, Treatment\*Pooled Center

**Pairwise Comparisons of Active Treatment Groups with Placebo Group**

Treatment	N	Least Squares Mean (LSM) Change from Baseline	LSM Standard Error	Difference from Placebo in LSM Change from Baseline	95% Confidence Interval for Difference from Placebo in LSM Change from Baseline	Treatment LSM Change from Baseline Different than Placebo (p value)
Candesartan+HCTZ	125	-10.2538	1.3955	-6.8333	(-11.3333, -2.3333)	0.0031
Placebo+HCTZ	74	-3.4205	1.7847			

Tests for Significance of Main Effects and Interaction Term (Type III Tests: Each Effect Adjusted for All Other Effects):

Factor	F Value	p value
Treatment	8.99	0.0031
Pooled Center	0.93	0.5548
Treatment*Pooled Center Interaction	0.79	0.7305

Responders

	Placebo + HCTZ	CC + HCTZ
N	56	123
Number Responders	16	65
% Responders	28.6	52.8

While this is said to be ITT, only 179 patients are represented. If the other randomized patients are considered non-responders, the proportions are:

HCTZ and Placebo

21%

CC and HCTZ

46%

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Controlled

	Placebo + HCTZ	CC + HCTZ
N	56	123
Number Controlled	9	39
% Controlled	16.1	31.7

Again this is for completers. For all randomized the percentages are:

HCTZ and PL

12%

CC and HCTZ

28%

Subgroup Analyses

Sitting DBP (LSM mm Hg) Change

	HCTZ and Placebo	HCTZ and CC
Black n = 85	-1.9	-8.6
Non Black n = 124	-4.1	-9.5
≥ 65 years n = 13	-1.8	-2.1
< 65 years n = 196	-2.8	-9.2
male n = 142	-3.6	-7.0
female n = 67	-3.5	-12.2

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By baseline sitting DBP results were:

Baseline DBP (n)	Placebo + HCTZ		CC + HCTZ	
	SBP LSM (n)	DBP LSM (n)	SBP LSM (n)	DBP LSM (n)
90-99 mmHg (n=47)	-4.2 (n=17)	-5.0 (n=17)	-9.4 (n=30)	-6.8 (n=30)
100-109 mmHg (n=109)	-2.6 (n=36)	-3.3 (n=36)	-10.7 (n=73)	-8.8 (n=73)
≥110 mmHg (n=53)	-4.6 (n=21)	-1.9 (n=21)	-18.2 (n=32)	-12.6 (n=32)

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### Safety

Heart rate was assessed in both groups as follows:

Treatment		Baseline	DB 1	DB 2	DB 3	DB 4
Placebo + HCTZ	N	74	70	58	55	74
	Mean	74.1	76.4	76.5	75.7	75.7
	SD	9.5	9.0	9.8	8.8	9.9
CC + HCTZ	N	135	129	126	121	135
	Mean	75.2	77.0	77.3	76.5	75.3
	SD	9.6	9.2	9.2	9.1	9.5

Tachycardia associated with decreases in blood pressure was not found, and no orthostatic hypotension was noted. No deaths occurred. There were two patients with a serious adverse reaction, both in the placebo + HCTZ group. These two cases were treatment failures; one also having chest pain and lightheadedness, the other stroke. These cases are included in the following chart of patients who withdrew for adverse events.

Patient	Treatment	Adverse Event (Included Term)	Days on Treatment
001/004	Placebo+HCTZ	Influenza-like Symptoms	4
		Liver Function Tests Abnormal	7
009/003	Placebo+HCTZ	Indigestion	5
		Anxiety	6
		Blood Pressure Increased	6
		Chest Pain	6
		Light-headed Feeling	6
		Headache	7
		Insomnia	7
022/009	Placebo+HCTZ	Stroke	6
034/014	Placebo+HCTZ	Dizziness	8
		Numbness Localized	8
		Vascular Disorder	8
0017/003	CC+HCTZ	Hypokalemia	1
018/008	CC+HCTZ	Liver Function Tests Abnormal	1
025/002	CC+HCTZ	Dizziness	1
		Allergy	5
		Dizziness	7
		Heartburn	13
		Heartburn	19

While CRFs have not as yet been provided for these cases, the line listings show that the patient withdrawn for LFT abnormalities had 0 days on study drug in the DB period. In this case, ALT and AST were only slightly elevated, but alkaline phosphatase was more than 2X ULN with normal bilirubin.

The patient with hypokalemia also had 0 days of exposure to the study drug.

For multiple chemistry and hematology parameters, mean changes from baseline were provided, and no significant differences or shifts were found. In the placebo + HCTZ group, CPK increased 21.4 IU/L while the CC + HCTZ decreased 9.3 IU/L. Triglycerides and LDH had similar but less marked numerical shifts. ECG findings at baseline and to week 4 were:

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VISIT: Double Blind Week 0

	TREATMENT					
	PBO+HCTZ		CC+HCTZ		Overall	
	N	%	N	%	N	%
<b>RANDOMIZED PATIENTS</b>	76	100.0	141	100.0	217	100.0
<b>Sinus Rhythm</b>						
--- Unknown	3	3.9	5	3.5	8	3.7
--- No	4	5.3	3	2.1	7	3.2
--- Yes	69	90.8	133	94.3	202	93.1
<b>Extra Systoles</b>						
--- Unknown	3	3.9	5	3.5	8	3.7
--- No	72	94.7	132	93.6	204	94.0
--- Yes	1	1.3	4	2.8	5	2.3
<b>Conduction</b>						
--- Unknown	3	3.9	5	3.5	8	3.7
--- Normal	64	84.2	120	85.1	184	84.8
--- Abnormal	9	11.8	16	11.3	25	11.5
<b>ST-T Changes</b>						
--- Unknown	3	3.9	5	3.5	8	3.7
--- No	50	65.8	88	62.4	138	63.6
--- Yes	23	30.3	48	34.0	71	32.7
<b>AV-Block</b>						
--- Unknown	3	3.9	5	3.5	8	3.7
--- No	71	93.4	132	93.6	203	93.5
--- Yes	2	2.6	4	2.8	6	2.8
<b>Chamber Hypertrophy</b>						
--- Unknown	3	3.9	5	3.5	8	3.7
--- No	63	82.9	110	78.0	173	79.7
--- Yes	10	13.2	26	18.4	36	16.6
<b>Evidence of MI</b>						
--- Unknown	3	3.9	5	3.5	8	3.7
--- None	68	89.5	130	92.2	198	91.2
--- Previous	5	6.6	6	4.3	11	5.1

VISIT: Double Blind Week 4

	TREATMENT					
	PBO+HCTZ		CC+HCTZ		Overall	
	N	%	N	%	N	%
<b>RANDOMIZED PATIENTS</b>	76	100.0	141	100.0	217	100.0
<b>Sinus Rhythm</b>						
--- Unknown	3	3.9	8	5.7	11	5.1
--- No	0	0	1	0.7	1	0.5
--- Yes	73	96.1	132	93.6	205	94.5
<b>Extra Systoles</b>						
--- Unknown	3	3.9	8	5.7	11	5.1
--- No	71	93.4	130	92.2	201	92.6
--- Yes	2	2.6	3	2.1	5	2.3
<b>Conduction</b>						
--- Unknown	3	3.9	8	5.7	11	5.1
--- Normal	58	76.3	122	86.5	180	82.9
--- Abnormal	15	19.7	11	7.8	26	12.0
<b>ST-T Changes</b>						
--- Unknown	3	3.9	8	5.7	11	5.1
--- No	46	60.5	97	68.8	143	65.9
--- Yes	27	35.5	36	25.5	63	29.0
<b>AV-Block</b>						
--- Unknown	3	3.9	8	5.7	11	5.1
--- No	71	93.4	127	90.1	198	91.2
--- Yes	2	2.6	6	4.3	8	3.7
<b>Chamber Hypertrophy</b>						
--- Unknown	3	3.9	8	5.7	11	5.1
--- No	65	85.5	108	76.6	173	79.7
--- Yes	8	10.5	25	17.7	33	15.2
<b>Evidence of MI</b>						
--- Unknown	3	3.9	8	5.7	11	5.1
--- None	69	90.8	126	89.4	195	89.9
--- Previous	4	5.3	7	5.0	11	5.1

### Comments

This study demonstrates effectiveness of CC in a hypertensive population pretreated briefly with HCTZ and then continued. Since there is no CC alone arm, one cannot tell whether there is a contribution of each component to the effect seen. While effects on diastolic and systolic BPs in mm Hg are significant (6 mm and 7.1 mm LSM respectively), the proportion of those who normalized the BP is small (28% for CC compared to 12% ITT). Safety analysis however, showed few problems with the combination.

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**6.17 AHM-0002 - Metabolic control and lipid profile during treatment for 12 weeks with Candesartan cilexetil (8/16 mg) or placebo in Diabetic (type II) patients with hypertension.**

Multicenter study in Finland, Germany, The Netherlands, and Norway. Study period: August 22, 1995 to April 19, 1996.

Randomized, double-blind, placebo controlled study in patients with primary hypertension (sitting diastolic 90-100 mm Hg), stable type II diabetes (HbA1c 5.5 - 9.0%), male or female, ages 30-75 years.

Primary variable: change in HbA1c for ITT population from baseline to week 12. The study was sized to estimate a  $\pm 3.5$  unit difference with 80% power.

Secondary variables; blood glucose, serum lipids, GFR, albuminuria, blood pressure/pulse, and safety.

Patients were excluded for type I diabetes, treatment with biguanides, women of child-bearing potential, vascular disease such as MI or stroke, cardiac failure, liver or kidney disease, abnormal sodium or potassium.

The study plan was:

Period	A	B	C	D	E	F	G		
		8 mg	16 mg						
	wash-out*	placebo	candesartan cilexetil						
			placebo						
Time (Weeks)	-4	-2	0	2	4 <sup>(1)</sup>	6 <sup>(1)</sup>	8 <sup>(1)</sup>	10 <sup>(1)</sup>	12
Visit	1	2	3	4	5	6	7	8	9
Medical history	x								
Physical examination	x <sup>(2)</sup>		x						x
BP & HR	x	x	x	x	x	x	x	x	x
Body weight	x <sup>(2)</sup>		x						x
Height	x <sup>(2)</sup>								
AEs		x	x	x	x	x	x	x	x
ECC			x						x
Lab screen	x <sup>(2)</sup>		x						x
HbA1c	x <sup>(2)</sup>		x						x
Blood glucose			x						x
Lipids <sup>(1)</sup>			x						x
GFR			x						x
UAE			x						x

\* wash-out visit for patients treated with more than one antihypertensive drug or a  $\beta$ -blocker. Patients were asked to give written informed consent before any antihypertensive medication was withdrawn.

<sup>(1)</sup> total cholesterol, HDL and LDL cholesterol, triglycerides, apolipoproteins A1 and B.

(1) if the patient was on the high dose and sitting DBP > 100 mmHg or sitting SBP > 180 mmHg an extra visit had to be performed within one week.

(2) to check for inclusion/exclusion criteria.

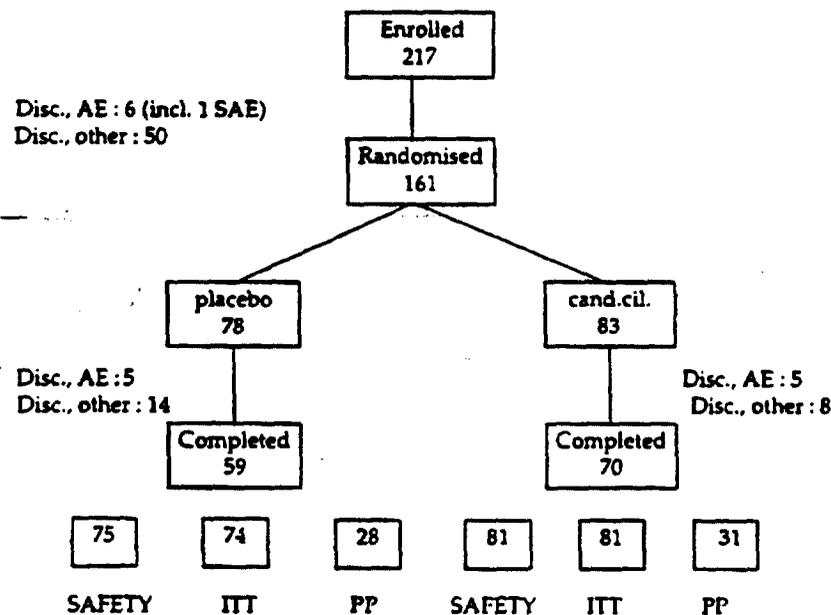
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If a patient's sitting diastolic was not  $\leq 90$  mm Hg at the end of an assessment period, the dose of whichever initial drug and dose was to be doubled. If the doubled dose was not tolerated, the dose could be reduced to the initial level.

During the study (October 9, 1995) the method of analyzing HbA1c was changed from a 1MX method to a Roche method. The earlier results (approximately 2 months into the study) were converted by a Quintiles formula as follows:

$$\text{HbA1c}_{\text{1MX}} = (\text{HbA1c}_{\text{ROCHE}} + 1.892) \div 1.242$$

Flow chart of patients was:



All randomized patients who took one dose or more of the assigned medication and had some metabolic or efficacy data were included in the ITT population. The per protocol population also excluded patients who violated the protocol. Randomization was by a computer generated blocked list with a block size of two. At baseline the groups were comparable for age, sex, race, height, body mass index, and HbA1c.

### Results

For the primary variable, there was no significance in HbA1c change comparing active drug to placebo.

HbA1c (%) summarised by visit. ITT population.

Treatment		baseline	Week 12	Week 12 (LVCF)
placebo	N	73	58	63
	Missing	1	16	11
	Mean	7.129	7.169	7.236
	SD	0.995	1.082	1.146
	Min			
	Median	7.160	7.040	7.080
	Max			
cand.cil.	N	81	68	72
	Missing	0	13	9
	Mean	7.280	7.189	7.179
	SD	1.133	1.242	1.225
	Min			
	Median	7.080	7.120	7.080
	Max			

For secondary variable, glucose, lipids including HDL and LDL did not increase over time for the Candesartan ITT cohort and there were no significant differences for these and other variables such as GFR and microalbuminuria when placebo and Candesartan results were compared.

Considering hemodynamic variables, doubling of the dose was as follows:

Number and proportion of patients receiving each dose prior to the visit. ITT population.

Visit	placebo				cand.cil.			
	8 mg		16 mg		8 mg		16 mg	
	N	%	N	%	N	%	N	%
Week 2	74	100.0	0	0.0	81	100.0	0	0.0
Week 4	25	33.8	46	62.2	41	50.6	37	45.7
Week 6	19	25.7	51	68.9	29	35.8	45	55.6
Week 8	20	27.0	46	62.2	33	40.7	40	49.4
Week 10	17	23.0	45	60.8	28	34.6	42	51.9
Week 12	20	27.0	41	55.4	29	35.8	41	50.6

Note: After Week 2 the percentages of patients do not add up to 100 % due to withdrawn patients.

Sitting diastolic for these mild hypertensive patients was reduced in both groups at endpoint, but was not significantly different when placebo and Candesartan results were compared.

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

Week	baseline	2	4	6	8	10	12	12 (LVCF)
placebo								
N	74	74	70	68	64	61	58	74
Missing	0	0	4	6	10	13	16	0
Mean	95.8	92.5	92.4	90.8	89.8	90.1	88.9	90.3
SD	3.1	6.7	5.9	7.5	7.3	7.2	7.0	8.6
Min								
Max								
cand.cil.								
N	81	80	75	73	72	70	70	81
Missing	0	1	6	8	9	11	11	0
Mean	95.3	90.7	90.1	88.5	88.3	86.6	88.5	89.4
SD	3.4	7.0	5.9	5.7	6.2	6.4	7.0	7.9
Min								
Max								

-5.8

-5.9

Similar conclusions were reached for systolic blood pressure and pulse.

Sitting systolic blood pressure (mmHg) by visit. ITT population.

Week	baseline	2	4	6	8	10	12	12 (LVCF)
placebo								
N	74	74	70	68	64	61	58	74
Missing	0	0	4	6	10	13	16	0
Mean	156.6	154.5	154.3	153.0	151.0	149.8	148.2	150.6
SD	13.8	13.5	11.9	12.2	11.3	8.6	10.4	14.4
Min								
Max								
cand.cil.								
N	81	80	75	73	72	70	70	81
Missing	0	1	6	8	9	11	11	0
Mean	155.2	150.3	149.5	146.1	147.4	145.8	146.6	148.8
SD	13.2	13.2	13.5	13.6	15.5	14.2	15.9	16.6
Min								
Max								

6.0

-6.4

Sitting heart rate (bpm) by visit. ITT population.

Week	baseline	2	4	6	8	10	12	12 (LVCF)
placebo								
N	74	73	70	68	64	61	58	74
Missing	0	1	4	6	10	13	16	0
Mean	75.9	76.3	75.0	75.3	75.1	75.8	76.2	75.9
SD	8.4	8.3	8.5	9.1	7.5	8.3	8.5	8.8
Min								
Max								
cand.cil.								
N	81	80	75	73	72	70	70	81
Missing	0	1	6	8	9	11	11	0
Mean	74.7	76.2	75.4	74.4	74.4	74.3	73.9	75.0
SD	9.1	9.4	8.7	7.7	8.6	8.6	8.6	8.8
Min								
Max								

Safety

No deaths were reported.

In the double-blind period the following overview of adverse reactions was provided:

Type of event	placebo n=75	cand.cil. n=81	Total n=156
Any AE	40 (53.3 %)	44 (54.3 %)	84 (53.8 %)
New onset AE	40 (53.3 %)	42 (51.9 %)	82 (52.6 %)
Serious AE	2 (2.7 %)	2 (2.5 %)	4 (2.6 %)
Drug stopped due to AE	5 (6.7 %)	5 (6.2 %)	10 (6.4 %)
Severe AE	5 (6.7 %)	4 (4.9 %)	9 (5.8 %)
Attributable AE	22 (29.3 %)	19 (23.5 %)	41 (26.3 %)

Note: Attributable AEs are the investigator's causality rating of possible or probable relationship to study treatment.

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6 serious adverse events in 4 patients were detailed:

Patient No.	Sex	Age (yrs)	Treatment	Serious adverse event	Exposure before onset (days)	Outcome
178	F	53	placebo	Tremor	83	AE no longer present
				Sinusitis	83	AE no longer present
				Fatigue	83	AE no longer present
242	F	72	placebo	Hypertension aggravated	5	AE no longer present
057	M	63	cand.cil. 8 mg <sup>11</sup>	Epistaxis	65	AE no longer present
274	M	53	cand.cil. 8 mg	Pulmonary carcinoma	7	AE still present

<sup>11</sup> Although not recorded in the CRF, the dose was increased to 16 mg at Week 2

Drug was stopped for patients 242 and 274.

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While not termed serious, other adverse events which led to drug discontinuation were:

Patient No.	Sex	Age (yrs)	Treatment	Adverse event	Exposure before onset (days)	Outcome
058	M	64	placebo	Flushing	4	AE no longer present
				Rash	4	AE no longer present
				Skin dry	4	AE no longer present
103	M	68	placebo	Angina pectoris	24	AE still present
				Arrhythmia	24	AE still present
167	M	52	placebo	Hypertension	84	AE no longer present
203	M	66	placebo	Headache	21	AE no longer present
				Blood pressure high	33	AE no longer present
242	F	72	placebo	Hypertension aggravated	5	AE no longer present
102	M	59	cand.cil. 8 mg	Nausea	12	AE no longer present
				Vertigo	12	AE no longer present
170	F	53	cand.cil. 8 mg	Headache	1	AE no longer present
193	F	55	cand.cil. 8 mg	Fatigue	5	AE no longer present
				Headache	5	AE no longer present
				Dizziness	17 <sup>11</sup>	AE no longer present
238	M	48	cand.cil. 8 mg	Dizziness	8	AE still present
				Headache	29 <sup>12</sup>	AE still present
274	M	53	cand.cil. 8 mg	Pulmonary carcinoma	7	AE still present

<sup>11</sup> Five days after dose increase to 16 mg

<sup>12</sup> Three days after dose increase to 16 mg

The most common, new onset adverse events reported were:

	placebo n=75		cand.cil. n=81
Headache	9 (12.0%)	Headache	10 (12.3%)
Insomnia	4 (5.3%)	Respiratory infection	10 (12.3%)
Sinusitis	4 (5.3%)	Dizziness/vertigo	8 (9.9%)
Coughing	3 (4.0%)	Chest pain	4 (4.9%)
Diarrhoea	3 (4.0%)	Coughing	4 (4.9%)
Infection viral	3 (4.0%)	Diarrhoea	4 (4.9%)
Nausea	3 (4.0%)	Nausea	4 (4.9%)
Urinary tract infection	3 (4.0%)	Bronchitis	3 (3.7%)
Albuminuria	2 (2.7%)	Fatigue	3 (3.7%)
Back pain	2 (2.7%)	Albuminuria	2 (2.5%)
Fever	2 (2.7%)	Epistaxis	2 (2.5%)
Gastroenteritis	2 (2.7%)	Fever	2 (2.5%)
Hypertension	2 (2.7%)	Glycosuria	2 (2.5%)
Respiratory infection	2 (2.7%)	Insomnia	2 (2.5%)
		Rhinitis	2 (2.5%)
		Sinusitis	2 (2.5%)
		Sweating increased	2 (2.5%)

Respiratory infection was more frequent in the Candesartan group than placebo, as was dizziness/vertigo and chest pain.

Comments:

While efficacy in these mild diabetic patients was not demonstrated, Candesartan had no discernible adverse effect on HbA1c.

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**6.18 Study AHM0004 - Effect and Safety of Candesartan cilexetil (8/16 mg) in the treatment of the elderly (> 65 years) hypertensive patient. A randomized, double-blind, placebo controlled parallel group study.**

Multicenter (41): Netherlands and U.K.  
 Coordinating Investigators: Dr. Jonker, Netherlands; Dr. McInnes, U.K.  
 Study Period: 8/95-10/96.  
 Drug and placebo manufactured by Takeda, Japan.

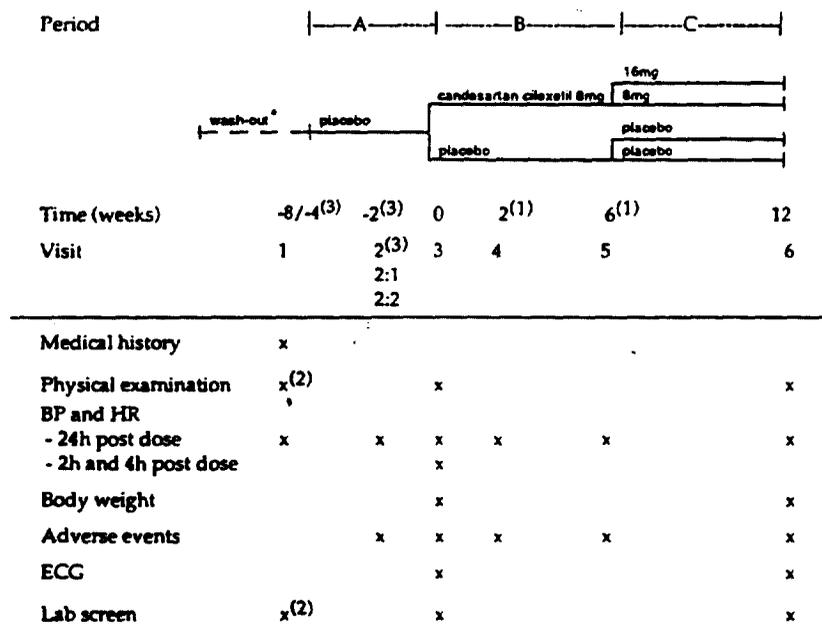
**Inclusion criteria:** Male or female. Primary hypertension. 65 or older, (at least 50% of population older than 75). Supine DBP 95-114 prior to double-blind.

**Exclusion criteria:** MI, stroke, TIA, CABG 3 months prior to study. Angina requiring more than short acting nitrates. Impaired liver function e.g. enzymes > 2x ULN. Cardiac failure requiring treatment.

**Randomization**

Computer generated, blocked, stratified for 65-75 years and above 75 years. Assignment made at the end of run-in period.

**Study outline**



- (1) If supine DBP >110 mmHg and/or supine SBP ≥ 200 mmHg, an extra visit must be performed within one week.
  - (2) To check for inclusion/exclusion criteria.
  - (3) The time between visit 1 and 3 are flexible and is depending on the BP value. If inclusion criterion is not met at visit 2, then a visit 2:1 will take place in 2 weeks time. If inclusion criterion is still not met at visit 2:1, then a visit 2:2 will take place in 2 weeks time. There should be 2 weeks between last visit 2 and 3. The total run-in period must not exceed 56 days.
- Wash-out visit for patients treated with more than one antihypertensive drug or a β-blocker. Patients will be asked to give written informed consent to participate before any antihypertensive medication is withdrawn.

Primary endpoint

Change in supine DBP from baseline to end of treatment (12 weeks). ITT analyses primary.

Secondary endpoints

Other hemodynamic variables, responders ( $\leq 90$  mm supine DBP or  $\leq 10$  mm Hg drop), controlled ( $\leq 90$  mm Hg).

Covariate

Influence of age on DBP.

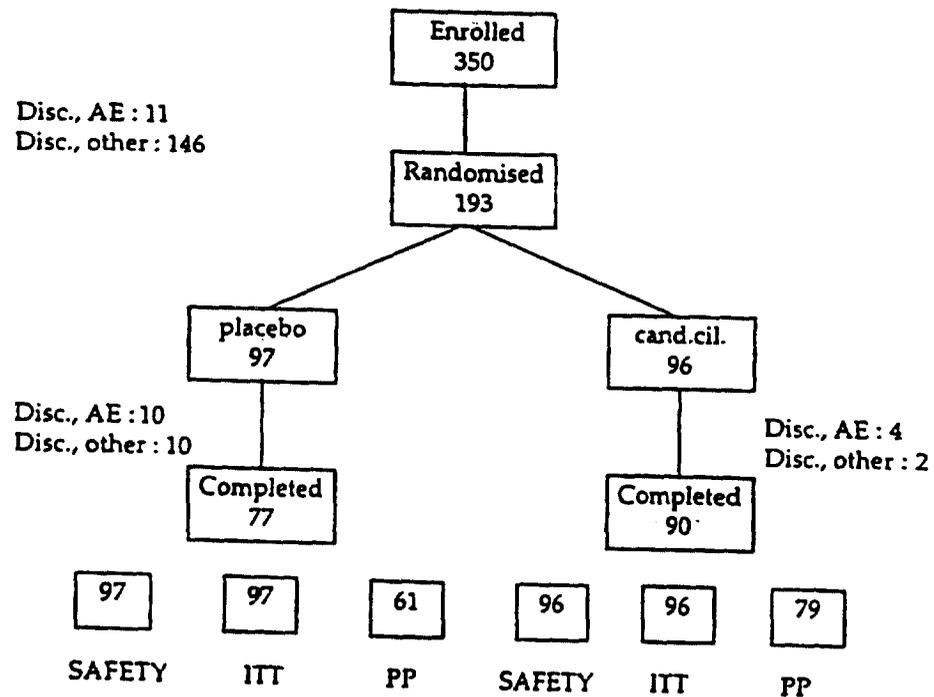
Dose

Candesartan cilexetil 8 mg (given two 4 mg tablets) or placebo given for first 6 wks of double-blind period. If BP not controlled by end of week 6, dose doubled (two 8 mg Candesartan cilexetil tablets or placebo).

Sizing of Study

A treatment difference between treatments of 3.6 Hg could be discerned with 80% power given a sample size of 70 per group.

Enrollment and Disposition of Patients



Demographics

95 males and 98 females were randomized. Age range was 65 to 87 years, but only 34 patients were 75 years or older.

Treatment groups were similar in age, gender, race, body weight and height.

## Compliance

By tablet count, compliance was estimated as:

	Frequency	placebo n=97	cand.cil. n=96	Total n=193
<b>Period A run-in</b>	<b>N</b>	<b>97</b>	<b>96</b>	<b>193</b>
	75%-90%	11	4	15
	90%-110%	86	92	178
<b>Period B-C double-blind</b>	<b>N</b>	<b>93</b>	<b>95</b>	<b>188</b>
	Missing	4	1	5
	<75%	2	2	4
	75%-90%	6	4	10
	90%-110%	83	89	172
	>=110%	2	0	2

## Conduct of Trial

96 patients from the Netherlands were randomized; 97 patients from the U.K.

Some assignment errors occurred within centers, and numbers 102, 177, 363, 461 and 462 were skipped. Patients 460 and 161 received incorrect doses of the correctly randomized study medication.

The various populations analyzed were defined as:

- Safety population:** all patients who took at least one dose of double-blind study medication and who provided post-dose data.
- ITT population:** all patients who took at least one dose of double-blind study medication and who had efficacy data available after randomization.
- PP population:** all patients in the ITT population who met all of the inclusion criteria, did not meet any of the exclusion criteria and did not meet any of the following pre-defined design violation criteria:
- placebo run-in period outside the range 25-56 days
  - double-blind treatment period outside the range 78-98 days
  - compliance in either of the double-blind treatment periods less than 75% or greater than or equal to 110%
  - antihypertensive medication taken after the fourth day of the run-in period
  - any concomitant antihypertensive medication taken during the double-blind treatment period
  - Supine DBP > 110 mmHg or supine SBP ≥ 200 mmHg at 2 or 6 Weeks and an extra visit not performed within one week.
  - Supine DBP > 110 mgHg or supine SBP ≥ 200 mmHg at the extra visit after 2 or 6 Weeks but patient not withdrawn.

There were no exclusions from the randomized population for the safety and ITT populations which were the analyses provided.

Results

Primary: Change in Supine DBP

Supine diastolic BP (mmHg) summarised by visit. ITT population.

Treatment		Baseline	Week 2	Week 6	Week 12	Week 12 (LVCF)
placebo	N	97	93	87	77	95
	Missing	0	4	10	20	2
	Mean	102.3	99.3	97.3	98.8	99.8
	SD	5.0	9.2	10.1	9.0	10.3
	Min					
	Median	102.0	99.0	97.0	98.0	99.0
	Max					
cand.cil.	N	96	95	91	90	96
	Missing	0	1	5	6	0
	Mean	101.0	93.4	90.8	91.7	92.3
	SD	4.1	8.0	7.3	7.6	8.3
	Min					
	Median	100.0	93.0	90.0	92.0	92.0
	Max					

-2.5  
-87  
6.2

Comparison of treatments for the change from baseline to Week 12 (LVCF) in supine diastolic BP (mmHg). ITT population.

Treatment Comparison	Adjusted Mean	95% CI		p-value
		Lower	Upper	
cand.cil. vs placebo	-7.5	-11.4	-3.6	<0.001

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Secondary variables

SBP

Supine systolic BP (mmHg) summarised by visit. All centres. ITT population.

Treatment		Baseline	Week 2	Week 6	Week 12	Week 12 (LVCF)	
placebo	N	97	93	87	77	95	
	Missing	0	4	10	20	2	
	Mean	175.2	171.7	170.0	170.7	173.1	-2.1
	SD	13.4	17.8	18.4	18.1	20.0	
	Min						
	Median	175.0	173.0	*173.0	170.0	174.0	
	Max						
cand.cil.	N	96	95	91	90	96	
	Missing	0	1	5	6	0	
	Mean	172.8	160.1	156.4	157.2	158.5	-14.3
	SD	13.4	17.2	15.6	16.6	18.1	
	Min						
	Median	174.0	160.0	155.0	155.0	156.5	
	Max						

} 12.2

Comparison of treatments for the change from baseline to Week 12 (LVCF) in supine systolic BP (mmHg). ITT population.

Treatment Comparison	Adjusted Mean	95% CI		p-value
		Lower	Upper	
cand.cil. vs placebo	-13.6	-20.2	-6.9	<0.001

**Responders**

Dose doubling occurred as follows:

Number and proportion of patients receiving each dose. ITT population.

Visit	Missing	placebo n=97					cand.cil. n=96				
		8 mg		16 mg		Missing	8 mg		16 mg		
		N	%	N	%		N	%	N	%	
Week 0	0	97	100.0	0	0.0	0	96	100.0	0	0.0	
Week 6	12	18	21.2	67	78.8	5	45	49.5	46	50.5	

Proportion of responders after 12 weeks of treatment. ITT population.

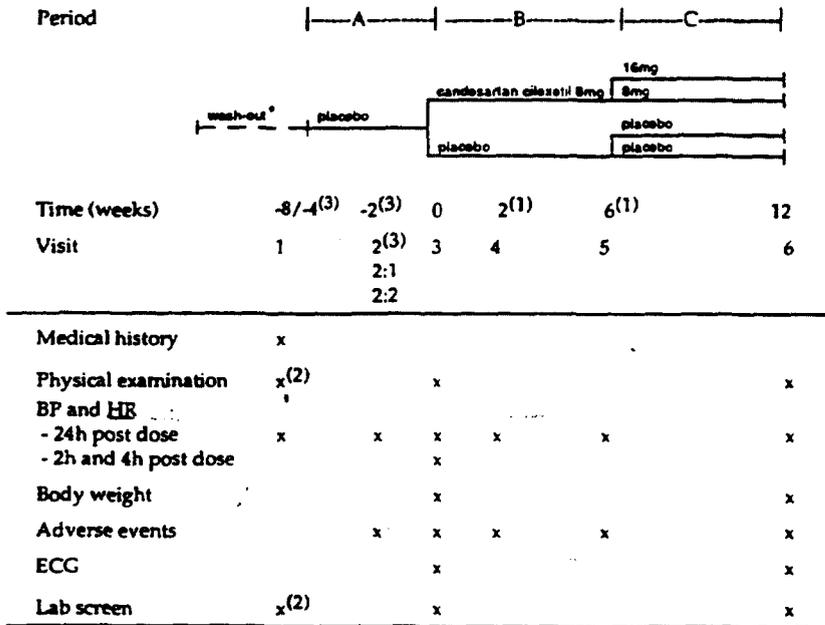
	placebo n=97	cand.cil. n=96
%	21.1	46.9
N	95	96
Missing	2	0

Comparison of treatments for the proportion of responders at Week 12 (LVCF). Results of Fisher's exact test (not adjusted for centres) are presented. ITT population.

Comparison	Estimated difference	95% CI		p-value
		lower	upper	
cand.cil. vs placebo	0.258	0.129	0.387	<0.001

While the number of responders at week 12 was significantly greater for drug versus placebo, increasing the dose did not increase the number of responders.

Controlled



- (1) If supine DBP >110 mmHg and/or supine SBP ≥ 200 mmHg, an extra visit must be performed within one week.
- (2) To check for inclusion/exclusion criteria.
- (3) The time between visit 1 and 3 are flexible and is depending on the BP value. If inclusion criterion is not met at visit 2, then a visit 2:1 will take place in 2 weeks time. If inclusion criterion is still not met at visit 2:1, then a visit 2:2 will take place in 2 weeks time. There should be 2 weeks between last visit 2 and 3. The total run-in period must not exceed 56 days.
- Wash-out visit for patients treated with more than one antihypertensive drug or a β-blocker. Patients will be asked to give written informed consent to participate before any antihypertensive medication is withdrawn.

Comparison of treatments for the proportion of controlled patients at Week 12 (LVCF). Results of Fisher's exact test (not adjusted for centres) are presented. ITT population.

Comparison	Estimated difference	95% CI		p-value
		lower	upper	
cand.cil. vs placebo	0.248	0.124	0.372	<0.001

## Influence of Age

Without elaboration, the sponsor states that age "did not seem to influence the effect of Candesartan cilexetil on BP." They note that the effect on supine SBP was smaller in patients over 75 with an interaction p-value for test age group by treatment of 0.074.

## Safety

An overview of adverse events was provided:

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

Type of event	Placebo (n=97)	Cand.cil. (n=96)	Total (n=193)
Any AE	63 (64.9)	63 (65.6)	126 (65.3)
New onset AE	56 (57.7)	54 (56.3)	110 (57.0)
Serious AE	2 (2.1)	3 (3.1)	5 (2.6)
Drug stopped due to AE	10 (10.3)	4 (4.2)	14 (7.3)
Severe AE	5 (5.2)	9 (9.4)	14 (7.3)
Attributable AE	26 (26.8)	22 (22.9)	48 (24.9)

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

	Placebo (n=97)		Cand.cil. (n=96)
Headache	15 (15.5)	Headache	11 (11.5)
Dizziness/vertigo	12 (12.4)	Accident and/or injury	6 (6.3)
Respiratory infection	8 (8.2)	Dizziness/vertigo	5 (5.2)
Back pain	6 (6.2)	Respiratory infection	5 (5.2)
Dyspnoea/dyspnoea (aggravated)	5 (5.2)	Abdominal pain	4 (4.2)
Albuminuria	4 (4.1)	Diarrhoea	4 (4.2)
Arthralgia	4 (4.1)	Infection viral	4 (4.2)
Chest pain	4 (4.1)	Arthralgia	3 (3.1)
Feeling of warmth/flush	4 (4.1)	Fatigue	3 (3.1)
Accident and/or injury	3 (3.1)	Haematuria	3 (3.1)
Antinuclear factor test positive	3 (3.1)	Heart murmur	3 (3.1)
Diarrhoea	3 (3.1)	Pain	3 (3.1)
Nervousness	3 (3.1)	Pharyngitis	3 (3.1)
Urinary tract infection	3 (3.1)	Rhinitis	3 (3.1)

Withdrawals for adverse events were more frequent with placebo as noted below:

Patients with adverse events causing discontinuation of study drug in the double-blind treatment period. Safety population.

Patient No.	Sex	Age (yrs)	Treatment	Adverse Event	Exposure before onset (days)	Outcome code
137	F	65	Placebo	Headache	1	AE no longer present
152	F	73	Placebo	Lupus erythematosus systemic	17	AE still present
164	F	68	Placebo	Collapse nos	1	AE no longer present
188	M	68	Placebo	Tachycardia	48	AE no longer present
227	F	68	Placebo	Dizziness	56	AE no longer present
291	M	77	Placebo	Ankle oedema	--	AE no longer present
316	F	70	Placebo	Dyspnoea on exertion Ankle oedema	3	AE still present AE no longer present
329	M	71	Placebo	Ear ringing Heart pounding Tingling sensation fingers Flushing Hypertension	-- -- -- 44 51	AE still present AE no longer present AE no longer present AE no longer present AE still present
409	F	72	Placebo	Headache	56	AE no longer present
497	F	67	Placebo	Antinuclear factor test positive	10	AE no longer present
145	M	71	Cand.cil. 8 mg	Dizziness	--	AE still present
189	M	66	Cand.cil. 8 mg	Headache	12	AE no longer present
374	F	77	Cand.cil. 8 mg	Breast enlargement female Ankle oedema	17 17	AE still present AE no longer present
494	F	68	Cand.cil. 8 mg	Atrial fibrillation paroxysmal	24	AE no longer present

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Headache, dizziness, respiratory infection were among the most frequently reported adverse events, with more events in placebo compared to active drug.

### Laboratory

Hemoglobin, hematocrit, and erythrocytes decreased in the Candesartan group but did not in the placebo group. The sponsor notes that this has been seen in other studies, and with ACE inhibitors. BUN, creatinine, LFTs did not increase.

One patient developed paroxysmal atrial fibrillation. This 68 year old female was hospitalized due to chest pain after 24 days on 8 mg Candesartan cilexetil. Past history of palpitations and taking propranolol prn. BP 164/104 on admission. Visit 4 BP had been 141/85. No CHF. Given IV heparin, converted to sinus rhythm spontaneously. Cardiac enzymes were negative. Some mitral disease noted on echo. Discontinued from Candesartan, and discharged on sotalol, warfarin and betahistine.

### Comments:

Pharmacokinetic studies (EC021, EC037) provided data in the healthy elderly patient compared to younger normals which indicated an increase in  $C_{max}$  and AUC as well as a prolonged  $T_{1/2}$  in the elderly. In spite of this, half of the patients on CC were uptitrated to 16 mg. CC was effective in the elderly but the effect on RBC indices should also be noted.

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**THIS SECTION  
WAS  
DETERMINED  
NOT  
TO BE  
RELEASABLE**

*7 pages*

## 6.20 Discussion

The design of the clinical studies permits one to conclude that CC doses of 2-32 mg are effective to treat mild to moderate hypertension. The studies were not powered to demonstrate a dose response. A meta analysis to examine this question follows.

The forced titration and dose doubling studies provided no evidence that dose escalation would be as effective as starting with a dose such as 16 mg.

The drug appears to be safe over a 2-16 mg range; few patients were exposed to 32 mg and 64 mg. However, patients who entered these studies did not have serious concomitant diseases, so the safety conclusions must be preliminary.

From the combination studies, CC can be given with other antihypertensives and HCTZ can add to the CC effect. Superiority or equivalence to other antihypertensives over their dose ranges have not been demonstrated.

In special populations - the elderly, diabetics - the drug appears to be safe, but in patients with CHF a safety question has been raised.

**APPEARS THIS WAY  
ON ORIGINAL**

## 6.21 Meta analysis

Since individual studies were not sized to evaluate dose response to assess this, a meta-analysis was performed utilizing data in the original submission from all randomized controlled studies where fixed doses and placebo could be compared in patients with mild to moderate hypertension. These studies were:

Study Name	Number of Patients	Percentage
AM 113	333	14.1
AM 116	274	11.6
EC009	231	9.8
EC011	264	11.2
EC018	123	5.2
EC047	251	10.6
EC403	386	16.3
SH-AHM-0001	251	10.6
SH-AHM-0006	254	10.7
<b>Total</b>	<b>2367</b>	<b>100.0</b>

The mean age of these patients was 54 (SD11, minimum 20, maximum 80). 922 females and 1445 males were included. There were 2167 Caucasians, 152 blacks, and 48 other in this database.

Three endpoints as predefined in the individual studies were analyzed.

1. Change from baseline to endpoint for trough sitting DBP and SBP.
2. Response rates (sitting DBP  $\leq$  90mm Hg or 10mm Hg fall baseline to endpoint).
3. Normalization rates (sitting DBP  $\leq$  90 mm Hg at endpoint).

1. For change from baseline to endpoint for trough sitting DBP and SBP, overall results are displayed in the following chart from Dr. Mahjoob:

Additionally, an analysis of no benefit was done.

Crosstabs: Sample Size, Raw Mean, SD, Min., Max., Least Square means, and Median by Dose  
All Studies in Meta Analysis Data Combined

Dose	D-SiDBP (mmHg)						D-SISBP (mmHg)							
	n	Mean	SD	Max *	Min *	LSMean †	Med	n	Mean	SD	Max *	Min *	LSMean ‡	Med
0	630	-2.9	9.20			-2.2	-2.7	630	-2.5	14.87			0.0	-2.8
2	133	-6.6	9.02			-6.8	-6.0	133	-10.2	17.04			-8.3	-10.0
4	352	-7.6	8.83			-6.4	-8.0	352	-10.1	13.83			-7.2	-9.3
8	695	-8.1	8.75			-6.0	-8.0	695	-11.3	13.04			-9.6	-10.7
12	154	-9.3	8.58			-8.3	-9.0	154	-14.6	13.53			-10.6	-14.8
16	347	-9.3	9.37			-9.4	-10.0	347	-14.1	14.17			-12.3	-14.0
32	54	-10.4	8.15			-10.2	-9.7	54	-12.1	15.63			-12.4	-10.3

\*: The magnitude of Minimum reduction from baseline in SiDBP observed for a patient in the data set.

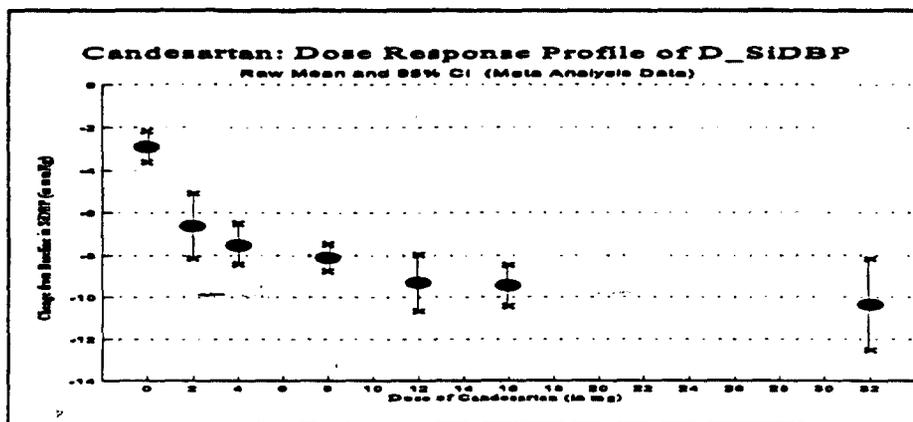
†: The magnitude of Minimum reduction from baseline in SiDBP observed for a patient in the data set.

‡: For SiDBP, the ANCOVA model used to calculate the Least Square Means contained the class variables and covariates (which were statistically significant in the model): Study, Dose, Sex and Race as class variables and the baseline SiDBP as the covariate.

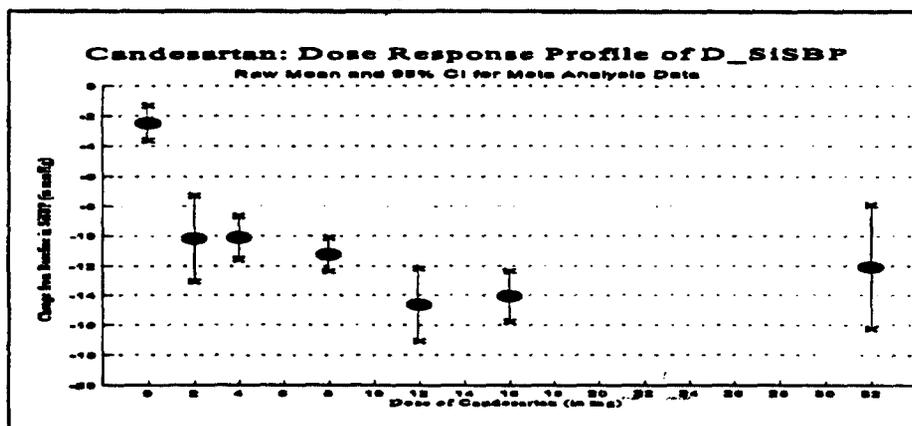
§: For SISBP, the ANCOVA model used to calculate the Least Square Means contained the class variables and covariates (which were statistically significant in the model): Study, Dose, Sex, Race and age ( $\leq$  65 or  $>$  65) as class variables and the baseline SISBP as the covariate.

Graphic displays of results with 95% confidence intervals by dose for DBP and SBP using the raw means were:

**Candesartan: Raw Means Dose Response Profile of Change From Baseline in SiDBP  
All Studies in the Meta Analysis Data**

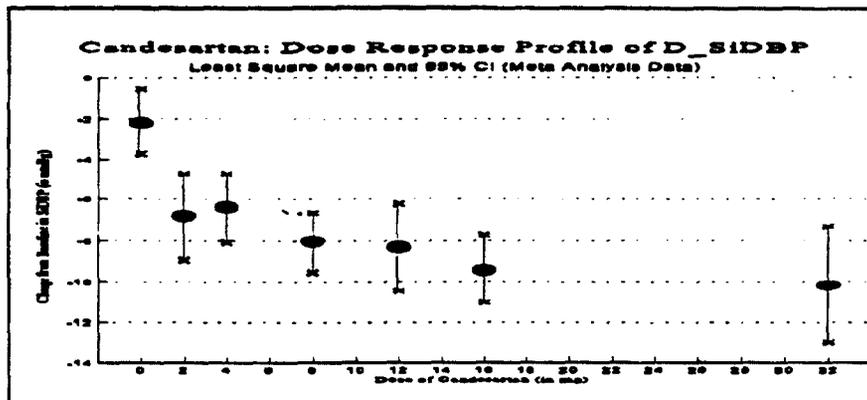


**Candesartan: Raw Means Dose Response Profile of Change From Baseline in SiSBP  
All Studies in the Meta Analysis Data**



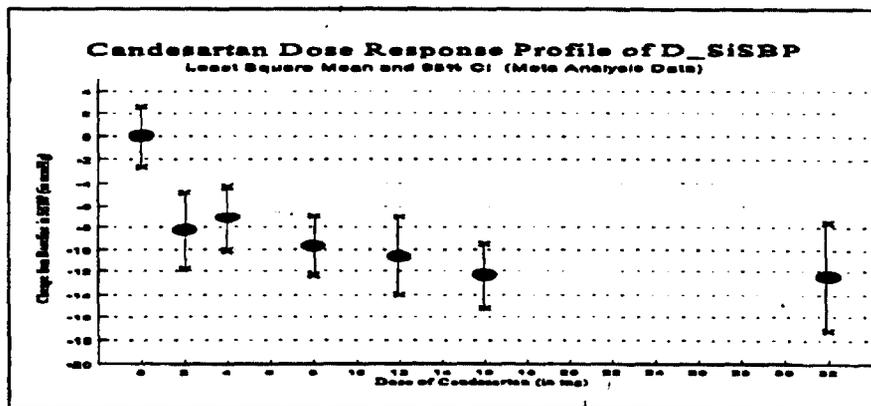
Using the least square means, these displays were:

**Candesartan: Least Square Means Profile of Change From Baseline in SiDBP  
All Studies in the Meta Analysis Data**



The circles are the Least Square means of the meta analysis data (all studies combined). The ANCOVA model used to calculate the Least Square Means contained the class variables and covariates (which were statistically significant in the model): Study, Dose, Sex and Race as class variables and the baseline SiDBP as the covariate.

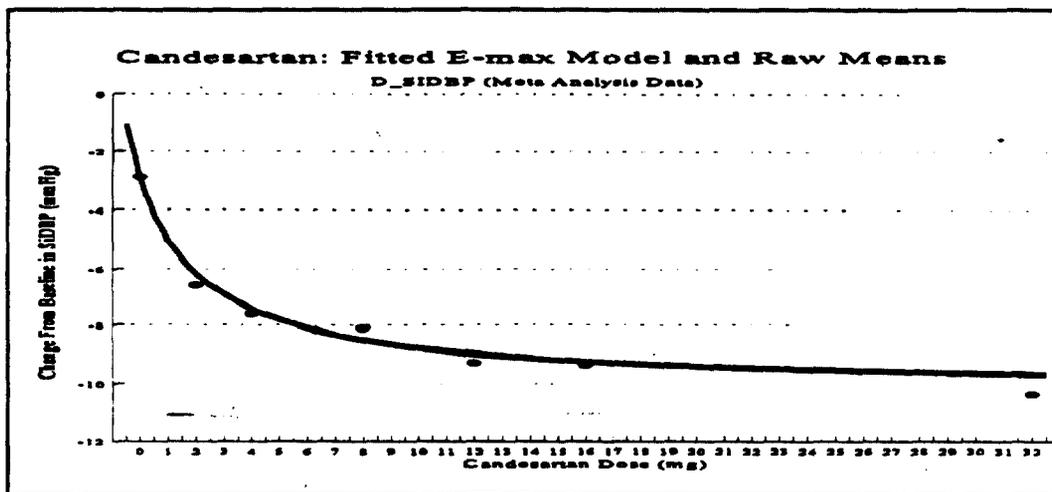
**Candesartan: Least Square Means Profile of Change From Baseline in SiSBP  
All Studies in the Meta Analysis Data**



The circles are the Least Square means of the meta analysis data (all studies combined). The ANCOVA model used to calculate the Least Square Means contained the class variables and covariates (which were statistically significant in the model): Study, Dose, Sex, Race and age ( $\leq 65$  or  $> 65$ ) as class variables and the baseline SiSBP as the covariate.

Using the observed changes from baseline, an  $E_{max}$  model was fitted to those data.

**Candesartan: Fitted E-max Model and the Raw Means  
Change From Baseline in SiDBP (Meta Analysis Data)**



Dots are the raw means of the meta analysis data (all studies combined) and the solid line is the fitted curve.

The mathematical equation of the E-max model is:

$$D\_SiDBP = P_{Effect} + \frac{E_{max} * Dose}{D_{50} + Dose}$$

where:

$P_{effect}$  = Placebo effect,

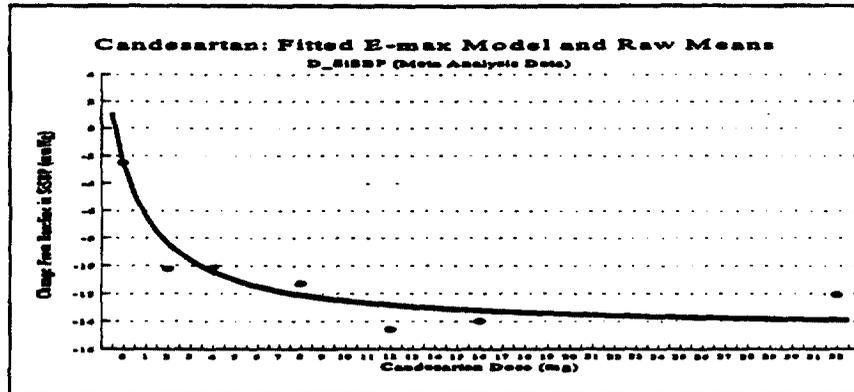
$E_{max}$  = Placebo adjusted maximum drug effect, and

$D_{50}$  = Dose corresponding to placebo adjusted half of maximum drug effect.

By using the SAS non-linear procedure (proc nonlin), the fitted Least Square E-Max model is:

$$D\_SiDBP = -2.92 + \frac{-7.31 * Dose}{2.49 + Dose}$$

**Candesartan: Fitted E-max Model and the Raw Means  
Change From Baseline in SISBP (Meta Analysis Data)**



Dots are the raw means of the meta analysis data (all studies combined) and the solid line is the fitted curve.

The mathematical equation of the E-max model is:

$$D\_SISBP = P_{Effect} + \frac{E_{max} * Dose}{D_{50} + Dose}$$

where:

$P_{effect}$  = Placebo effect,

$E_{max}$  = Placebo adjusted maximum drug effect, and

$D_{50}$  = Dose corresponding to placebo adjusted half of maximum drug effect.

By using the SAS non-linear procedure (proc nonlin), the fitted Least Square E-Max model is:

$$D\_SISBP = -2.56 + \frac{-12.00 * Dose}{2.14 + Dose}$$

Analyses of these data for age, race and sex are provided in the following two charts.

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**Candesartan Meta Analysis Data**  
**Subgroup Analysis Relative to Reduction From Baseline in Sitting Diastolic Blood Pressure**  
**For Gender, Race (Blacks and Whites only) and Age Class**  
**Sorted by Treatment (all candesartan doses combined and placebo)**

		All Candesartan Doses Combined				Placebo				Placebo Adjusted Comparisons			
		N	Mean (mmHg)	SE (mmHg)	P-Value	N	Mean (mmHg)	SE (mmHg)	P-Value	Contrast	Mean of Contrast	SE of Contrast	P-Value
Gender □	Male	1085	-8.26	0.27	0.0972	360	-2.10	0.47	0.0108	(Male) - (Female)	-1.09	0.83	0.1927
	Female	651	-8.99	0.25		271	-3.92	0.54					
Race ⊙	White	1578	-8.71	0.23	0.0006	589	-2.84	0.37	0.8724	(White) - (Black)	-3.41	1.74	0.0498
	Black	116	-3.54	0.89		36	-3.09	1.31					
Age Class	≤ 65	1437	-8.46	0.24	0.4387	513	-2.72	0.39	0.3655	(Younger) - (Older)	-0.38	1.06	0.7210
	> 65	299	-8.90	0.52		118	-3.54	0.82					

⊠: The means are the Least Square adjusted means and the SE's are the standard errors of the Least Square adjusted means, based on the model described in the next line.  
□: For each subgroup, and for each treatment separately, the results are based on an ANOVA model which contains: baseline blood pressure as covariate and the study and the subgroup as the class variables. For instance, for gender, the ANOVA model contains baseline blood pressure, study and gender.  
⊙: For race only the comparison between whites and blacks was considered.

**Candesartan Meta Analysis Data**  
**Subgroup Analysis Relative to Reduction From Baseline in Sitting Systolic Blood Pressure**  
**For Gender, Race (Blacks and Whites only) and Age Class**  
**Sorted by Treatment (all candesartan doses combined and placebo)**

		All Candesartan Doses Combined				Placebo				Placebo Adjusted Comparisons			
		N	Mean (mmHg)	SE (mmHg)	P-Value	N	Mean (mmHg)	SE (mmHg)	P-Value	Contrast	Mean of Contrast	SE of Contrast	P-Value
Gender □	Male	1085	-11.67	0.45	0.1290	360	-1.95	0.77	0.3450	(Male) - (Female)	-0.004	1.37	0.9974
	Female	651	-12.77	0.58		271	-3.05	0.89					
Race ⊙	White	1578	-12.35	0.38	0.0016	589	-2.32	0.61	0.3871	(White) - (Black)	-6.97	2.85	0.0146
	Black	116	-7.57	1.50		36	-4.53	2.47					
Age Class	≤ 65	1437	-12.64	0.39	0.0004	513	-2.98	0.64	0.0202	(Younger) - (Older)	0.12	1.74	0.9428
	> 65	299	-9.26	0.87		118	0.51	1.36					

⊠: The means are the Least Square adjusted means and the SE's are the standard errors of the Least Square adjusted means, based on the model described in the next line.  
□: For each subgroup, and for each treatment separately, the results are based on an ANOVA model which contains: baseline blood pressure as covariate and the study and the subgroup as the class variables. For instance, for gender, the ANOVA model contains baseline blood pressure, study and gender.  
⊙: For race only the comparison between whites and blacks was considered.

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Pairwise p values for CC versus placebo, and between doses were:

**Candesartan Meta Analysis Data**  
**Least Square Means and Standard Errors of Least Square Means and P-Values Resulting from Pairwise Comparisons Among Doses**  
**With Respect to Reduction From Baseline in Sitting Diastolic Blood Pressure (in mmHg)**

Dose	Placebo n = 631 mean = -2.2 SE = 0.80	Candesartan					
		2 mg n = 134	4 mg n = 352	8 mg n = 695	12 mg n = 154	16 mg n = 374	32 mg n = 54
Placebo: n = 631, mean = -2.2, SE = 0.80		0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
Candesartan	2 mg: n = 134, mean = -6.8, SE = 1.06	0.0001	0.6515	0.1897	0.1745	0.0066	0.0212
	4 mg: n = 352, mean = -6.4, SE = 0.86	0.0001	0.6515	0.0139	0.0305	0.0001	0.0060
	8 mg: n = 695, mean = -8.0, SE = 0.78	0.0001	0.1897	0.0139	0.6761	0.0218	0.1013
	12 mg: n = 154, mean = -8.3, SE = 1.04	0.0001	0.1745	0.0305	0.6761	0.2605	0.2250
	16 mg: n = 374, mean = -9.4, SE = 0.86	0.0001	0.0066	0.0001	0.0218	0.2605	0.5547
	32 mg: n = 54, mean = -10.2, SE = 1.43	0.0001	0.0212	0.0060	0.1013	0.2250	0.5547

Note: The Results is based on the ANCOVA model on reduction from baseline in sitting diastolic blood pressure (D\_SDBP) which contained:  
 Class Variables: Dose, Sex, and Race.  
 Covariate: Baseline Sitting Diastolic Blood Pressure (B\_SDBP).

COMMENT: An initial ANCOVA model was conducted which contained: class variables (main effects) dose, sex, class age, and race; covariate B\_SDBP; and the interactions dose\*study, dose\*sex, dose\*c\_age, and dose\*race. It was found that the interaction and the class age were not statistical significant. Then, a second ANCOVA model was run after exclusion of the non-significant effects, with the following ANCOVA results with the following results.

Source	DF	Type III SS	Mean Square	F Value	Pr > F
STUDY	8	3057.63	382.20	5.02	0.0001
DOSE	6	16391.85	2731.90	35.86	0.0001
SEX	1	701.73	701.73	9.21	0.0024
RACE	3	928.21	309.40	4.06	0.0069
B_SDBP	1	7036.19	7036.19	92.36	0.0001

**Candesartan Meta Analysis Data**  
**Least Square Means and Standard Errors of Least Square Means and P-Values Resulting from Pairwise Comparisons Among Doses**  
**With Respect to Reduction From Baseline in Sitting Systolic Blood Pressure (in mmHg)**

Dose	Placebo n = 631 mean = -0.0 SE = 1.34	Candesartan					
		2 mg n = 134	4 mg n = 352	8 mg n = 695	12 mg n = 154	16 mg n = 374	32 mg n = 54
Placebo: n = 631, mean = -0.0, SE = 1.34		0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
Candesartan	2 mg: n = 134, mean = -8.3, SE = 1.77	0.0001	0.4770	0.3503	0.2150	0.0097	0.0834
	4 mg: n = 352, mean = -7.2, SE = 1.45	0.0001	0.4770	0.0203	0.0221	0.0001	0.0205
	8 mg: n = 695, mean = -9.6, SE = 1.31	0.0001	0.3503	0.0203	0.5137	0.0083	0.2060
	12 mg: n = 154, mean = -10.6, SE = 1.74	0.0001	0.2150	0.0221	0.5137	0.2566	0.4523
	16 mg: n = 374, mean = -12.3, SE = 1.44	0.0001	0.0097	0.0001	0.0083	0.2566	0.9426
	32 mg: n = 54, mean = -12.4, SE = 1.38	0.0001	0.0834	0.0205	0.2060	0.4523	0.9426

Note: The Results is based on the ANCOVA model on reduction from baseline in sitting systolic blood pressure (D\_SISBP) which contained:  
 Class Variables: Study, Dose, Class Age, Sex, and Race.  
 Covariate: Baseline Sitting Systolic Blood Pressure (B\_SISBP).

COMMENT: An initial ANCOVA model was conducted which contained: class variables (main effects) dose, sex, class age, and race; covariate B\_SISBP; and the interactions dose\*study, dose\*sex, dose\*c\_age, and dose\*race. It was found that the interaction were not statistical significant. Then, a second ANCOVA model was run after exclusion of the non-significant effects, with the following ANCOVA results with the following results.

Source	DF	Type III SS	Mean Square	F Value	Pr > F
STUDY	8	6761.82	845.22	4.11	0.0001
DOSE	6	47213.01	7868.83	38.31	0.0001
SEX	1	852.34	852.34	4.64	0.0314
RACE	3	1624.77	541.59	2.64	0.0482
C_AGE	1	4021.03	4021.03	19.59	0.0001
B_SISBP	1	54352.01	54352.01	264.61	0.0001

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2. For responders, pairwise Fisher's exact test p values were:

Dose	Placebo n = 631 (PR = 24.3%)	Candesartan						All Candesartan Doses Combined n = 1736 (PR = 48.6%)
		2 mg n = 134 (PR = 38.1%)	4 mg n = 352 (PR = 29.9%)	8 mg n = 695 (PR = 46.6%)	12 mg n = 154 (PR = 50.0%)	16 mg n = 374 (PR = 56.5%)	32 mg n = 54 (PR = 57.4%)	
Placebo: n = 631, (PR = 24.3%)		0.0017	0.0018	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Candesartan	2 mg: n = 134, (PR = 38.1%)	0.0017		0.102	0.072	0.044	0.0004	0.022
	4 mg: n = 352, (PR = 29.9%)	0.0018	0.102		1.000	0.499	0.010	0.146
	8 mg: n = 695, (PR = 46.6%)	<0.0001	0.072	1.000		0.476	0.0031	0.157
	12 mg: n = 154, (PR = 50.0%)	<0.0001	0.044	0.499	0.476		0.206	0.429
	16 mg: n = 374, (PR = 56.5%)	<0.0001	0.0004	0.010	0.0031	0.206		1.000
	32 mg: n = 54, (PR = 57.4%)	<0.0001	0.022	0.022	0.157		1.000	
	All Candesartan Doses Combined n = 1736, (PR = 48.6%)	<0.0001						

PR = Proportion of Responders

3. For normalizers, results were:

Dose	Placebo n = 631 (PN = 17.6%)	Candesartan						All Candesartan Doses Combined n = 1736 (PN = 38.9%)
		2 mg n = 134 (PN = 29.9%)	4 mg n = 352 (PN = 39.8%)	8 mg n = 695 (PN = 36.8%)	12 mg n = 154 (PN = 37.0%)	16 mg n = 374 (PN = 44.7%)	32 mg n = 54 (PN = 53.7%)	
Placebo: n = 631, (PN = 17.6%)		0.0018	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Candesartan	2 mg: n = 134, (PN = 29.9%)	<0.0001		0.046	0.140	0.213	0.0004	0.0027
	4 mg: n = 352, (PN = 39.8%)	<0.0001	0.046		0.381	0.314	0.221	0.056
	8 mg: n = 695, (PN = 36.8%)	<0.0001	0.140	0.381		1.000	0.022	0.019
	12 mg: n = 154, (PN = 37.0%)	<0.0001	0.213	0.314	1.000		0.141	0.037
	16 mg: n = 374, (PN = 44.4%)	<0.0001	0.0004	0.221	0.022	0.141		0.240
	32 mg: n = 54, (PN = 53.7%)	<0.0001	0.0027	0.056	0.019	0.037	0.240	
	All Candesartan Doses Combined n = 1736, (PN = 38.9%)	<0.0001						

PN = Proportion of Normalized Patients

CC clearly has a treatment effect. There is a dose response, and with the information thus far available, 16mg Q.D. seems to be the most effective dose.

An unplanned analysis to determine the percentage of patients with no benefit was done.

Using the following definitions of benefit, no benefit, the number and proportion for each category was determined.

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Definitions

Benefit: D<sub>Si</sub> DBP ≤ -1 mm Hg (decrease from baseline of at least 1 mm Hg)  
No Benefit: D<sub>Si</sub> DBP > -1 mm Hg (decrease from baseline of less than 1 mm Hg- includes patients who had no change or increased BP).

	CC mg						
	Pl n=631	2 n=134	4 n=352	8 n=695	12 n=154	16 n=347	32 n=54
Benefit	392 62%	104 78%	283 80%	581 84%	134 87%	287 83%	49 91%
No Benefit	239 38%	30 22%	69 20%	114 16%	20 13%	60 17%	5 9%

Age, sex and race were not predictive factors for no benefit in this limited database.

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## 7.0 Conclusions and Recommendations

1. Candesartan cilexetil is an effective antihypertensive as shown by numerous studies, e.g. EC047, AM113, EC011.
2. Candesartan cilexetil doses of 2 mg to 32 mg have been shown to be statistically superior to placebo.
3. There is a dose response which may have plateaued at 12-16 mg.
4. There is no evidence in the database that titrating the drug is as effective as starting with the "best" dose (e.g. 16 mg). At 16 mg the drug can be given once daily.
5. Effects on systolic and diastolic blood pressure levels were similar.
6. There were approximately 17% of patients who showed no response to Candesartan.
7. For those who have a blood pressure response, the onset of effect was noted at 2 weeks with a "maximal" effect at 4-6 weeks.
8. From placebo controlled combination studies, Candesartan can be used with other antihypertensives.
9. From randomized withdrawal studies, Candesartan's long term effect to reduce blood pressure has been supported.
10. Candesartan has not been shown superior or equivalent to other sartans. Dose response comparisons in controlled clinical studies have not been provided.
11. While a comprehensive safety analysis will be provided by Dr. U, a review of the individual studies suggests a safety profile similar to placebo. However, patients entered were without serious concomitant problems. Additional review of the carcinogenicity studies are pending.
12. The kidney appears to be the target organ of toxicity, and a trend to anemia was noted in the elderly.
13. The RESOLVD studies raises the question of safety in CHF patients. Until the issue is resolved, a precaution that safety and efficacy in patients with CHF have not been demonstrated is suggested.
14. At 2-16 mg, no overall change in heart rate or serious orthostatic effects were demonstrated compared to placebo.
15. Based on the clinical data submitted, approval is recommended.

Stephen Fredd, M.D. 1/29/98

Kooros Mahjoob, Ph.D. 1/29/98

George Chi, Ph.D. 1/29/98

cc:

Dr. Lipicky  
Dr. Ganley  
Dr. U  
Dr. Mahjoob  
Dr. Chi  
Ms. Bongiovanni  
NDA 20 838

K. Bonfiovanni

DIVISION OF CARDIO-RENAL DRUG PRODUCTS  
MEDICAL OFFICER REVIEW OF CLINICAL SAFETY

MAY - 8 1998

NDA #: 20-838 Document ID: BM  
DRUG NAME: Atacand™ (Candesartan cilexetil) Tablets SPONSOR: Astra Merck  
TYPE OF DOCUMENT: Amendment to an approvable NDA Application: Case Report Forms  
MEDICAL OFFICER: Khin Maung U, M.D. DATE COMPLETED 08-May-1998

"Addendum to Review"

Further to my "Addendum to Review" filed 20-Mar-1998, regarding two patients with "hepatitis" in study EC040 on 26-Mar-1998, the following is a narrative of the 5 patients who dropped out for abnormal liver function tests (LFTs).

**Patient #1 (EC012/00008/0345):** This 67 year-old white female patient with history of basal cell carcinoma (1974), and newly diagnosed hypertension (not on antihypertensive drugs) at the time of screening (Nov-1994) was placed on therapy with *candesartan cilexetil 4 mg po qd* (titrated to 16 mg qd) for the treatment of hypertension in Dec-1994.

She had elevated baseline LFTs (table below) on 09-Dec-1994 and occasionally elevated serum uric acid levels. Peak abnormal laboratory values in LFTs and uric acid were observed in May and June of 1995. She was withdrawn from the study on 1-Jun-1995 for these abnormal LFTs. At follow up > one month later in Aug-1995, the transaminases and  $\gamma$ -GT had returned to half their peak values, and the remaining LFTs and uric acid levels were within the normal range.

Test	Baseline (09-Dec-1994) (IU/L)	Peak (11-May-1995) (IU/L)
ALAT (GPT)	72	189
ASAT (GOT)	79	232
$\gamma$ -GT	219	323 (01-Jun-1995)
Alk. Phosphatase	104	100
LDH	600	856
Bilirubin	19 mmol/l	20 mmol/l (01-Jun-1995)
Uric Acid	377 mmol/l	484 mmol/l (01-Jun-1995)

**Patient #2 (EC012/00028/0233):** This 56-year old white female patient with history of hemorrhoidectomy (Aug-1986) and new onset HTN (not on antihypertensive drugs) at the time of screening (24-Nov-1994), was placed on therapy with *candesartan cilexetil 4 mg po qd* (titrated to 16 mg qd) for the treatment of hypertension on 26-Dec-1994. She was also suffering from bronchitis at screening (Nov-1994) and was taking erythromycin 1G/day, which was changed to Ampicillin 1 G/day on 14-Dec-1994. She had normal baseline LFTs (table below). On 12-Jan-1995, she complained of pain in the right hypochondrium and loss of appetite, and was found on physical examination to have an enlarged liver. This was accompanied by abnormal LFTs, and the patient was withdrawn on 12-Jan-1995 for abnormal LFTs. The patient also had a serum potassium level of 5.7 mmol/l on 12-Jan-1995 which was attributed to a hemolysed specimen. No follow up clinical or laboratory data were available.

Test	Baseline (24-Nov-1994) (IU/L)	Peak (12-Jan-1995) (IU/L)
ALAT (GPT)	37	173
ASAT (GOT)	48	220
$\gamma$ -GT	59	191
Alk. Phosphatase	72	76
LDH	595	706
Bilirubin	13 mmol/l	11 mmol/l

**Patient #3 (EC040/0015/0088):** This 63-year old white male patient with hyperlipidemia (since 1987), hypertension (27-Apr-1993) and recurrent gastritis was placed on therapy with *candesartan cilexetil 4 mg po qd* on 22-Nov-1994 for the treatment of hypertension. Concomitant medication included metoclopramide. On 07-Aug-1995, he was hospitalized for atypical chest pain and elevated creatine kinase (peak = 783 U/L) with an MB fraction of 76 U/L about 20 hours after the onset of pain. A posterior myocardial infarction was diagnosed. PTCA was performed on the proximally occluded right coronary artery, and the patient became symptom free. He was discharged on 23-Aug-1995. On 28-Aug-1995, he experienced angina pain, and was hospitalized. His ECG findings were unchanged, cardiac enzymes were normal, and a

repeat angiography excluded re-stenosis. An EGD revealed a moderate erosive antrum gastritis; ranitidine 150 mg qd was added. He was discharged on 31-Aug-1995. At follow up, he was reported to be well.

In reviewing this patient's laboratory results, he had abnormal LFTs during the period of his participation in Study EC040. In the adverse event forms, he was reported on 30-Mar-1995 to have clinical symptoms of cholangitis, and reported again on 29-Jun-1995 with cholangitis with elevated  $\gamma$ -GT and alkaline phosphatase. The LFTs reported on 09-Aug-1995 gave the highest values as shown below. The primary reason for his discontinuation (on 7-Aug-1995) was not because of abnormal LFTs but because of acute myocardial infarction requiring hospitalization and treatment including PTCA.

Test	Baseline (27-Oct-1994) (IU/L)	Peak (09-Aug-1995) (IU/L)
ALAT (GPT)	8	31
ASAT (GOT)	9	88
$\gamma$ -GT	23	33
Alk. Phosphatase	205	198
LDH	150	611
Bilirubin	0.6 mg/dl	0.6 mg/dl

Patient #4 (EC040/00016/0249): This 60 year-old white female with history of varicose veins both legs (15-Jun-1992, on Antistax drops and Vetren ointment daily), hypercholesterolemia since 11-Dec-1993 (on low-fat diet), bladder prolapse of several years duration (not requiring treatment), was known to be hypertensive since Jan-94 (on low-sodium diet). She was enrolled on 30-Sep-1994, and was placed on therapy with *candesartan cilexetil 4 mg qd* for the treatment of hypertension in Oct-1994. She had normal baseline LFTs (table below), occasional elevation of serum uric acid levels, and proteinuria and eosinophilia (5%-8%) that persisted throughout her course of participation in the study. She was discovered to have repeatedly elevated blood glucose levels; on 23-Dec-94, she was diagnosed with diabetes mellitus and diet therapy was initiated. On 11-Jul-1995, she had abnormal LFTs. The patient withdrew from the study on 11-Jul-1995 on her own desire because she did not want to undergo laboratory tests. No follow up clinical or laboratory data were available.

Test	Baseline (01-Oct-1994) (IU/L)	Peak (12-Jul-1995) (IU/L)
ALAT (GPT)	8	28
ASAT (GOT)	10	17
$\gamma$ -GT	12	28
Alk. Phosphatase	109	131
LDH	186	252
Bilirubin	0.2 mg/dl	0.9 mg/dl

Patient #5 (EC040/00028/0192): This 58-year old female patient with history of anal eczema (since 1993), allergic dermatosis(1993), herpes labialis (05-Dec-1994), febrile respiratory infections (05-Dec-1994), fatty infiltration of liver (Jul-1993) and hypertension (May-1993, not on antihypertensive drugs) was placed on therapy with *candesartan cilexetil 4 mg po qd* for the treatment of hypertension on 29-Dec-1994. She had had a pace maker implanted for syncope, rotatory vertigo, third degree AV block and complete SA block.

She had elevated baseline alkaline phosphatase and bilirubin (table below) on 07-Dec-1994. Peak abnormal lab values in LFTs were observed on 18-Jan-1995. The laboratory abnormality was at first presumed by the investigator to be due to fatty infiltration of the liver with disturbed fat metabolism and cholestasis. A subsequent record dated 05-May-1995 stated that the patient's first hepatitis serology of 12-Apr-1995 suggested post-hepatitis A, with post hepatic hepatopathy. Serology was positive for Anti-HAV IgG and negative for anti-HAV IgM, and for HBs antigen, anti-HBC, anti-HBs, and anti-HCV IgG. She was reported as no sign of fresh or resolved hepatitis B, no immunity against hepatitis B, sign of resolved hepatitis A or condition after vaccination with sufficient immunity against hepatitis A, and recommended to re-test in a few months for hepatitis C. She was discontinued on 14-Jan-1995 (after 29 days of treatment) for abnormal LFTs.

Test	Baseline (05-Dec-1994) (IU/L)	Peak (18-Jan-1995) (IU/L)
ALAT (GPT)	23	95
ASAT (GOT)	10	42
$\gamma$ -GT	46	57
Alk. Phosphatase	204	301 (17-Jan-1995)
LDH	168	198 (17-Jan-1995)
Bilirubin	1.4 mg/dl	1.9 mg/dl

Comments:

Of these 5 withdrawals, Patient #3 was withdrawn primarily for the serious adverse event of myocardial infarction requiring PTCA; his abnormal LFTs were coincidental findings.

Thus, four patients (Patients #1, #2, #4 and #5) were withdrawn primarily because of abnormalities in their LFTs.

In Patient #5, the abnormal LFTs could be attributed to post-hepatitis A; the presumed fatty liver and cholestasis earlier reported by the investigator could be a feature of hepatitis.

Patient #1 had abnormal LFTs at baseline, and they worsened after about 5 months of treatment with Candesartan cilexetil, and improved one month after withdrawal. It is possible that "worsening of LFTs" in a patient with abnormal baseline LFTs occur with administration of Candesartan over a prolonged period.

Patient #2 had confounding factors that may contribute to her abnormal LFTs: concomitant medications (erythromycin, ampicillin) and hepatomegaly. A viral hepatitis antibody profile was not reported, and no follow up report was available.

In Patient #4, her abnormal LFTs were minimal. That she had been put on several diet regimens (low-fat diet on 11-Dec-1993 for hypercholesterolemia, low sodium diet in Jan-1994 for hypertension, and low carbohydrate diet on 23-Dec-1994 for diabetes mellitus - and all these dietary restrictions around the time of Christmas and New Year!) together with repeated blood tests with kept revealing one laboratory abnormality after another, and requiring her to cut off her fat, salt and carbohydrate in her diet, could have compelled her to refuse any more laboratory tests and withdraw from the study.

Overall, none of the abnormal LFTs in these 5 withdrawals were extremely high (the highest values of SGPT, SGOT,  $\gamma$ -GT, LDH and bilirubin being found in patient #1 and alkaline phosphatase in Patient #5). Elevated bilirubin was found in patients #1 and #5, both associated with elevated transaminases.

Khin Maung U, MBBS, MMedSc, MD(NSW), MD, FACP

cc: orig.  
Dr. Robert Temple  
HFD 110  
HFD-110 / CSO / R. Lipicky / A. Karkowsky / C. Ganley / S. Fredd / K.M.U

Kibung'u

DIVISION OF CARDIO-RENAL DRUG PRODUCTS  
MEDICAL OFFICER REVIEW OF CLINICAL SAFETY

MAR 31 1998

NDA #: 20-838 Document ID: BM  
DRUG NAME: Atacand™ (Candesartan cilexetil) Tablets  
SPONSOR: Astra Merck  
TYPE OF DOCUMENT: Amendment to a Pending NDA Application: Case Report Form  
DATE OF CORRESPONDENCE: 25-Mar-1998 DATE ASSIGNED: 26-Mar-1998  
DATE RECEIVED: 25-Mar-1998 DATE COMPLETED: 27-Mar-1998  
MEDICAL OFFICER: Khin Maung U, M.D

Further to my telephone conversation with Dan Cushing and Eric Michelson of Astra Merck on 20-Mar-1998, and my "Addendum to Review" filed 20-Mar-1998, regarding two patients with "hepatitis" in study EC040 on 26-Mar-1998, the sponsor submitted the case report forms for the following patients:

**EC040/0015/0088:** This 63-year old male patient with hyperlipidemia (since 1987) and recurrent gastritis was placed on therapy with *candesartan cilexetil* 4 mg po qd on 22-Nov-1994 (or 25-Oct-1994) for the treatment of hypertension. Concomitant medication included metoclopramide. On 07-Aug-1995, he was hospitalized for atypical chest pain and elevated creatine kinase (peak = 783 U/L) with an MB fraction of 76 U/L about 20 hours after the onset of pain. A posterior myocardial infarction was diagnosed. PTCA was performed on the proximally occluded right coronary artery, and the patient became symptom free. He was discharged on 23-Aug-1995. On 28-Aug-1995, he experienced angina pain, and was hospitalized. His ECG findings were unchanged, cardiac enzymes were normal, and a repeat angiography excluded re-stenosis. An EGD revealed a moderate erosive antrum gastritis; ranitidine 150 mg qd was added. He was discharged on 31-Aug-1995. At follow up, he was reported to be well.

In reviewing his laboratory results, this patient had elevated liver function tests during the period of his participation in Study EC040. In the adverse event forms, he was reported on 30-Mar-1995 to have clinical symptoms of cholangitis, and reported again on 29-Jun-1995 with cholangitis. The LFTs reported on 09-Aug-1995 gave the highest values as shown below. The primary reason for his discontinuation is not because of elevated LFTs but because of chest pain requiring hospitalization and treatment.

Test	Baseline value (IU/L)	Peak (09-Aug-1995) (IU/L)
ALAT (GPT)	8.0	31.0
ASAT (GOT)	9.0	88.0
γ-GT	23.0	33.0
Alk. Phosphatase	205	198
LDH	150	613
Bilirubin	0.6 mg/dl	0.6 mg/dl

**EC040/00028/0192:** This 52-year old female patient with history of anal eczema, allergic dermatosis, herpes labialis and febrile respiratory infections was placed on therapy with *candesartan cilexetil* 4 mg po qd for the treatment of hypertension. She had had a pace maker implanted for syncope, rotatory vertigo, third degree AV block and complete SA block.

She had elevated baseline LFTs (table below) on 07-Dec-1994. Peak lab values were observed on 18-Jan-1995. The laboratory abnormality was at first presumed by the investigator to be due to fatty infiltration of the liver with disturbed fat metabolism and cholestasis. A subsequent record dated 05-May-1995 stated that the patient's first hepatitis serology of 12-Apr-1995 suggested post-hepatitis A, with post hepatic hepatopathy. Serology was positive for Anti-HAV IgG and Ig M, negative for anti-HAV IgM, and for HBs antigen, anti-HBC, anti-HBs, and anti-HCV IgG. She was reported as no sign of fresh or resolved hepatitis B, no immunity against hepatitis B, sign of resolved hepatitis A or condition after vaccination with sufficient immunity against hepatitis A, and recommended to re-test in a few months for hepatitis C. She was discontinued for abnormal liver enzymes.

Test	Baseline value (IU/L)	Peak (18-Jan-1995) (IU/L)
ALAT (GPT)	23.0	95.0
ASAT (GOT)	10.0	42.0
γ-GT	46.0	57.0
Alk. Phosphatase	204	301 (17-Jan-1995)
LDH	168	198 (17-Jan-1995)
Bilirubin	1.4 mg/dl	1.9 mg/dl

Khin Maung U, MBBS, MMedSc, MD(NSW), MD, FACP

cc: orig.  
HFD-110  
HFD-110 / CSO / A. Karkowsky / C. Ganley / S. Fredd / K.M.U

T. BONNELLUARD

**DIVISION OF CARDIO-RENAL DRUG PRODUCTS**  
**MEDICAL OFFICER REVIEW OF CLINICAL SAFETY** MAR 31 1998

NDA #: 20-838 Document ID: BM  
DRUG NAME: Atacand™ (Candesartan cilexetil) Tablets  
SPONSOR: Astra Merck  
TYPE OF DOCUMENT: Amendment to a Pending NDA Application: Case Report Form  
DATE OF CORRESPONDENCE: 20-Mar-1998 DATE ASSIGNED: 24-Mar-1998  
DATE RECEIVED: 23-Mar-1998 DATE COMPLETED: 25-Mar-1998  
MEDICAL OFFICER: Khin Maung U, M.D

Further to my telephone conversation with Dan Cushing and Eric Michelson of Astra Merck on 20-Mar-1998, and my "Addendum to Review" filed 20-Mar-1998, regarding report of a patient reported as "seafood allergy" from the NDA study 116, the sponsor submitted the case report form for patient 116-021-027.

A 54-year old Caucasian female patient with hypertension since 1994, and history of angina pectoris, peptic ulcer, kidney stones, asthma, rheumatoid arthritis, hiatal hernia, hypothyroidism and hysterectomy, and allergy to penicillin and Ilosone, was enrolled on 16-Apr-1996. The patient was later known to be randomized to receive Candesartan cilexetil. Concomitant or prior medications include Hyzaar, Carafate, Prilosec, Motrin, Synthroid and Premarin. The patient completed the study on 17-Oct-1996.

The following adverse events were listed in the CRF:

	Adverse event	Onset	Resolution	Severity	Action taken
1.	Dizziness	17-May-1996	26-May-1996	mild	none
2.	Tiredness	17-May-1996	26-May-1996	mild	none
3.	Edema both feet	17-May-1996	04-Jul-1996	mild	none
4.	Nausea	08-Jun-1996	06-Jul-1996	mild	none
5.	Headache	10-Jul-1996	10-Jul-1996	mild	none
6.	Anaphylactic shock	10-Jul-1996	10-Jul-1996	moderate	none

On a note regarding verbatim change for the adverse event dated 17-Jan-1997, the 6th AE of "Anaphylactic Shock" was changed to "Allergic Reaction to Seafood".

**Comment:** The above report is to be considered in the light of a recent report by the sponsor as follows:

At 3:21 p.m. today 20-Mar-1997, Dr. Dan Cushing of Astra Merck called to report the following SAE he had received by phone from Germany.

A female patient with hypertension was treated with Candesartan cilexetil orally in hospital. The patient's medical history and the reason for her being in hospital was not known. The dose, frequency and duration of treatment with Candesartan cilexetil were not known. The patient was discharged from hospital. She visited the hospital as an out patient for angioedema. The presenting symptom for angioedema was not known. She was referred to another hospital. The patient died. There was no information regarding the cause of death, concomitant medications nor the treatment given for angioedema.

**Action:** At present, there is not adequate information to determine what caused the patient's death, or what confounding factors are present that led to angioedema and to her death. I have requested the sponsor to provide more information as soon as it becomes available.

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cc: orig.  
HFD-110

HFD-110 / CSO / A. Karkowsky / C. Ganley / S. Fredd / K.M.U

*K. Bong'anni*

DIVISION OF CARDIO-RENAL DRUG PRODUCTS  
MEDICAL OFFICER REVIEW OF CLINICAL SAFETY

MAR 23 1998

NDA #: 20-838  
DRUG NAME: Atacand™ (Candesartan cilexetil) Tablets  
SPONSOR: Astra Merck  
TYPE OF DOCUMENT: New NDA (Clinical Safety Review)  
DATE OF CORRESPONDENCE: 30-Apr-1997 DATE ASSIGNED: 08-Aug-1997  
DATE RECEIVED: 30-Apr-1997 DATE COMPLETED: 26-Jan-1998  
MEDICAL OFFICER: Khin Maung U, M.D. DATE of ADDENDUM: 20-Mar-1998

ADDENDUM TO SAFETY REVIEW

After completion of the review, the following information are received from the sponsor.

1. Angioedema

At 3:21 p.m. today 20-Mar-1997, Dr. Dan Cushing of Astra Merck called to report the following SAE he had received by phone from Germany.

A female patient with hypertension was treated with Candesartan cilexetil orally in hospital. The patient's medical history and the reason for her being in hospital was not known. The dose, frequency and duration of treatment with Candesartan cilexetil were not known. The patient was discharged from hospital. She visited the hospital as an out patient for angioedema. The presenting symptom for angioedema was not known. She was referred to another hospital. The patient died. There was no information regarding the cause of death, concomitant medications nor the treatment given for angioedema.

Comment: At present, there is not adequate information to determine what caused the patient's death, or what confounding factors are present that led to angioedema and to her death. I have requested the sponsor to provide more information as soon as it becomes available.

I mentioned that there was no report of angioedema in the new NDA submission. Dr. Eric Michelson with whom I spoke on the speaker phone reported that there was a first case of angioedema in a patient (a nurse) who was on Candesartan cilexetil in study 116. On the last day of her treatment period, she took sea food, and had facial swelling. She sought treatment at the ER, and was given benedryl which provided relief. She did not report this episode, but at a later visit, mentioned about this casually. She had had similar reactions following ingestion of seafood. The adverse event was reported under "Allergic reaction to seafood".

2. Two patients with hepatitis in study EC040.

Patient # EC040/00015/0088: This patient was on Candesartan cilexetil 4 mg. A narrative is given on page 150 of Safety Review. His liver function tests were abnormal as follows:

Test	Baseline value (IU/L)	Peak/final value (IU/L)
ALAT (GPT)	13.0	31.0
ASAT (GOT)	10.0	88.0
γ-GT	26.0	33.0
Alk. Phosphatase	205	198
LDH	152	613

Patient # EC040/00028/0192: This patient was on Candesartan cilexetil 4 mg. A brief narrative is given on page 95 of Safety Review. His liver function tests were abnormal as follows:

Test	Baseline value (IU/L)	Peak/final value (IU/L)
ALAT (GPT)	23.0	95.0
ASAT (GOT)	10.0	42.0
γ-GT	46.0	59.0
Alk. Phosphatase	204	301
LDH	168	198

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cc: orig.  
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HFD-110 / CSO / A. Karkowsky / C. Gangley / S. Fredd / K.M.U