Table 14: Predicted, Raw and their difference of Reduction from Baseline in SiSBP in mmHg✣

		Candesartan (mg)					
		0	2	4	8	16	32
HCTZ (mg)	0	5.37, (5.62) -0.25	7.06, (9.01) -1.95	8.56, (8.56) 0.00	11.05, (9.67) 1.38	13.95, (15.36) -1.41	11.36, (9.29) 2.07
	6.25	8.52, (4.09) 4.43	10.28, (—) —	11.85, (14.07) -2.22	14.48, (—) —	17.66, (—) —	15.63, (—) —
	12.5	10.35, (9.91) 0.44	12.17, (12.90) -0.73	13.82, (19.09) -5.27	16.59, (17.66) -1.07	20.04, (18.03) 2.01	18.57, (21.19) -2.62
	25	10.01, (10.95) -0.94	11.97, (12.84) -0.87	13.76, (10.71) 3.05	16.81, (16.25) 0.56	20.82, (21.09) -0.27	20.47, (—) —

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

For the case of D_SiSBP, due to marginally significant Lack of Fit (P = 0.0718; significant at $\alpha = 0.05$ but not at $\alpha = 0.10$) somewhat larger differences between the fitted and predicted means than the case of D_SiDBP should be expected. Table 14, shows the $D_{(P-R)}$ = 4.43 mmHg for CC 0/HCTZ 6.25 mg and $D_{(P-R)}$ = -5.27 mmHg for CC 4/HCTZ 12.5.

Here also, in the pooled data there were no actual treatment arms, and hence the observations, for the treatment combinations CC 2/HCTZ 6.25, CC 8/HCTZ 6.25, CC 16/HCTZ 6.25, CC 32/HCTZ 6.25; however, the response surface provided the predicted means by the interpolation. Also, the response_surface provided an extrapolated predicted mean for treatment combination CC 32/HCTZ 25 that was not an arm of the pooled data. That predicted number is greater than predicted for 16/12.5 mg, but raw data do not exist to support an additional benefit for a combination of CC 32 mg with 25 mg HCTZ. The raw data for the 16/25 mg combination do not rule out an added antihypertensive benefit over 16/12.5 mg, though that difference was not significant.

As was discussed for the case of D_SiDBP, here also we are interested to determine the CC/HCTZ combination therapy at which the D_SiSBP response will reach its maximum. This CC/HCTZ is the combination with the maximum effect on D_SiSBP. We also, use similar graphical procedure, as discussed for D_SiDBP, for the determination of CC/HCTZ for maximum D_SiSBP.

Figure 5 presents the profiles of D_SiSBP response surface as function of CC doses for fixed 0, 12.5 and 25 mg HCTZ. Visual inspection shows that, for the three HCTZ curves, the maximum of D_SiSBP, approximately, occurred within the range of 22 to 24 mg of CC doses (also confirmed by mathematical calculation).

Figure 5: Profiles of D_SiSBP Response Surface for Given HCTZs as Functions of CC Doses

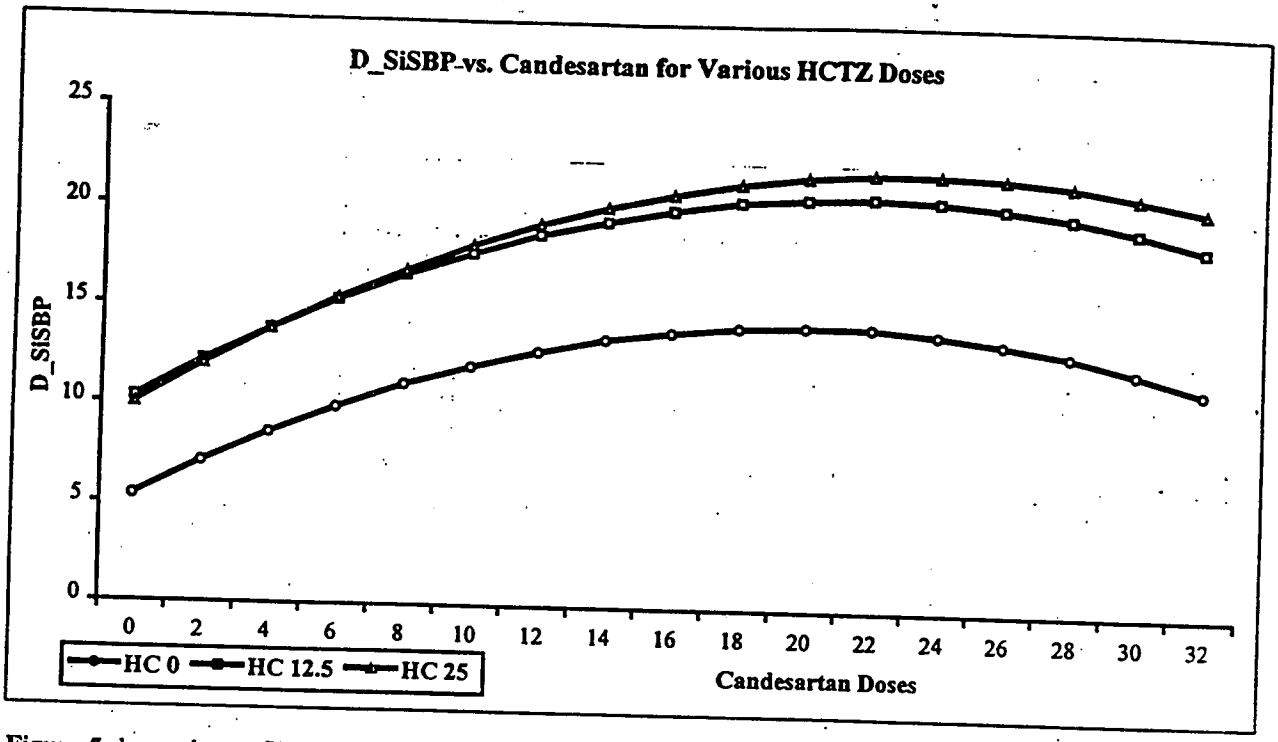
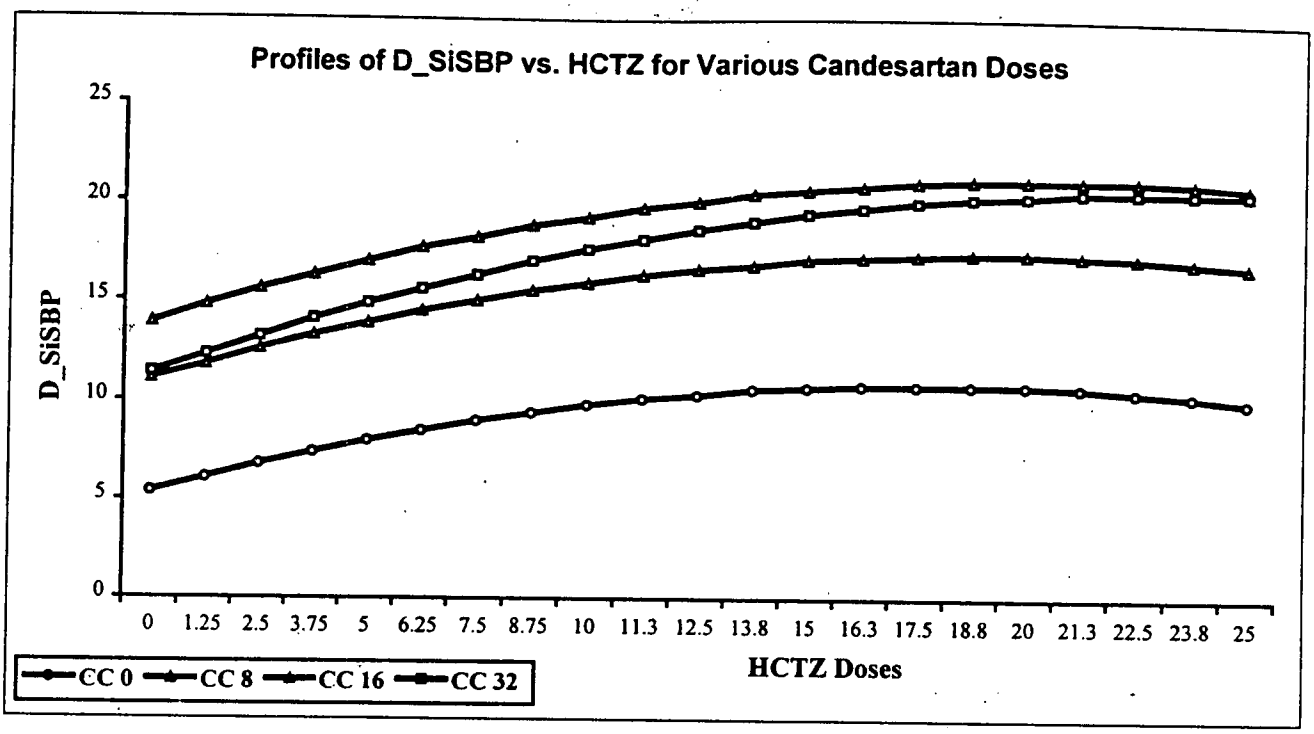


Figure 5 shows the profiles of D_SiSBP response surface as function of HCTZ doses for fixed 0, 8, 16, 32 mg CC. Visual inspection shows that, for the three HCTZ curves, the maximum of D_SiDBP, approximately, occurs within the range of 18 to 23.5 mg of HCTZ doses (also confirmed by mathematical calculation).

Figure 6: Profiles of D_SiSBP Response Surface for Given CCs as Functions of HCTZ Doses

APPEARS THIS WAY
ON ORIGINAL



In conclusion, the maximum of D_SiDBP occurred within the range of 22 to 24 for CC and within 18 to 23.5 mg for HCTZ on the surface.

Results on D_StDBP:

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

Table 15: Summary of Quadratic Response Surface Analysis on D_StDBP

Variable	Parameter (Coefficient)	Parameter Estimate	Standard Error	P-Value for Testing Ho: Para. = 0 vs. Ha: Para. ≠ 0
Intercept	α	4.1970	0.3820	<0.0000
Candesartan	β	0.5025	0.0653	< 0.0000
HCTZ	δ	0.2542	0.0704	0.0003
Candesartan*Candesartan	θ	-0.0095	0.0022	< 0.0000
HCTZ*HCTZ	λ	-0.0077	0.0027	0.0046
Candesartan*HCTZ	ρ	0.0015	0.0031	0.6237
Lack of Fit P-Value = 0.4920 Hence, the null hypothesis of quadratic fit (Test a) cannot be rejected, at $\alpha = 0.05$				

Table 15 shows that:

- The statistical test for testing "Lack of Fit" (Test a) produced a P-Value = 0.4920, indicating that the null hypothesis of quadratic fit cannot be rejected at $\alpha = 0.05$ (fitted model is not a poor fit).
- Except for the coefficient of the interaction term (ρ), the P-values of the statistical tests (Test b) on the other parameters (α, β, δ, θ, and λ) indicate that the parameter estimates are statistically significantly different from zero (P-Values $\leq$ 0.0046, for all parameters). With respect to the interaction, the P-Value = 0.6237 indicates that the interaction is not statistically significant.

Therefore, the fitted model will be:

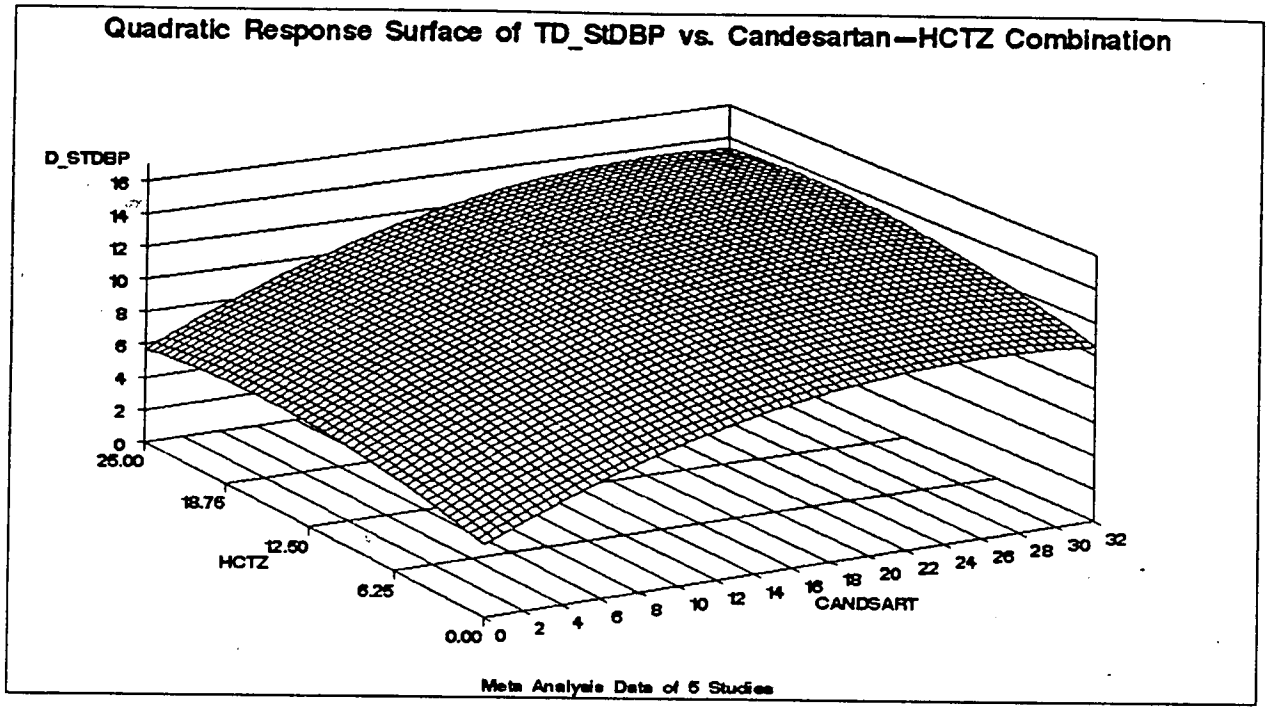
(3) $D\_StDBP_i = 4.1970 + 0.5025CC + 0.2542HCTZ - 0.0095CC^2 - 0.0077HCTZ^2 + 0.0015CC*HCTZ.$

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

The graph of the response surface is presented in Figure 7.

APPEARS THIS WAY
ON ORIGINAL

Figure 7: Quadratic Response Surface for Reduction from Baseline in StDBP
As a Function of Candesartan/HCTZ Combination Therapy



As was discussed earlier, the response surface presents the predicted values of the mean response (here for D_StDBP) for the CC/HCTZ combination, rather than the raw means. It is useful to examine the differences between the raw and predicted means. Table 16 presents the predicted means, raw means and the difference between the predicted and raw means ($D_{(P-R)}$ = Predicted - Raw) for the CC/HCTZ combinations. Comparisons of the predicted and the raw means of D_SiDBP indicate that the maximum difference is $D_{(P-R)}$ = 2.76 mmHg for the CC 0/HCTZ 6.25 mg therapy. So, in general, the predicted and raw means are close to each other.

Table 16: Predicted, Raw and their difference of Reduction from Baseline in StSBP in mmHg✣

		Candesartan (mg)					
		0	2	4	8	16	32
HCTZ (mg)	0	4.20, (4.22) -0.02	5.16, (7.16) -2.00	6.06, (5.88) 0.18	7.61, (7.27) 0.34	9.81, (10.19) -0.38	10.55, (9.88) 0.67
	6.25	5.48, (2.72) 2.76	6.47, (---) ---	7.38, (9.17) -1.79	8.97, (---) ---	11.24, (---) ---	12.14, (---) ---
	12.5	6.17, (6.57) -0.40	7.18, (5.08) 2.10	8.10, (7.25) 0.85	9.73, (10.41) -0.68	12.08, (11.39) 0.69	13.12, (14.08) -0.96
	25	5.47, (6.41) -0.94	6.78, (4.80) 1.98	7.75, (6.13) 1.62	9.45, (9.68) -0.23	11.95, (12.03) -0.08	13.29, (---) ---

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

Although in the pooled data there were no actual treatment arms, hence the observations, for the treatment combinations CC 2/HCTZ 6.25, CC 8/HCTZ 6.25, CC 16/HCTZ 6.25, CC 32/HCTZ 6.25, however, the response

surface provided the predicted means by the interpolation. Also, the response surface provided an extrapolated predicted mean for treatment combination CC 32/HCTZ 25 that was not an arm of the pooled data.

Results on D_StSBP:

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

Table 17: Summary of Quadratic Response Surface Analysis on D_StSBP

Variable	Parameter (Coefficient)	Parameter Estimate	Standard Error	P-Value for Testing Ho: Para. = 0 vs. Ha: Para. ≠ 0
Intercept	α	4.4127	0.6461	< 0.0001
Candesartan	β	1.0093	0.1104	< 0.0001
HCTZ	δ	0.5964	0.1190	< 0.0001
Candesartan*Candesartan	θ	-0.0243	0.0036	< 0.0001
HCTZ*HCTZ	λ	-0.0161	0.0046	0.0005
Candesartan*HCTZ	ρ	0.0030	0.0053	0.5742
Lack of Fit P-Value = 0.6683 Hence, the null hypothesis of quadratic fit (Test a) cannot be rejected, at $\alpha = 0.05$				

Table 17 shows that:

- The statistical test for testing "Lack of Fit" (Test a) produced a P-Value = 0.6683, indicating that the null hypothesis of quadratic fit cannot be rejected at $\alpha = 0.05$ (fitted model is not a poor fit).
- Except for the coefficient of the interaction term (ρ), the P-values of the statistical tests (Test b) on the other parameters (α, β, δ, θ, and λ) indicate that the parameter estimates are statistically significantly different from zero (P-Values $\leq$ 0.0005, for all parameters). With respect to the interaction, the P-Value = 0.5742 indicates that the interaction is not statistically significant.

Therefore, the fitted model will be:

$$(3)\quad D\_StSBP_i = 4.4127 + 1.0093CC + 0.5964HCTZ - 0.0243CC^2 - 0.0161HCTZ^2 + 0.0030CC*HCTZ.$$

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

The graph of the response surface is presented in Figure 7.

Here also, since the response surface presents the predicted values of the mean response rather than the raw means for StSBP, it is useful to examine the differences between the raw and predicted means.

Figure 7: Quadratic Response Surface for Reduction from Baseline in StSBP As a Function of Candesartan/HCTZ Combination Therapy

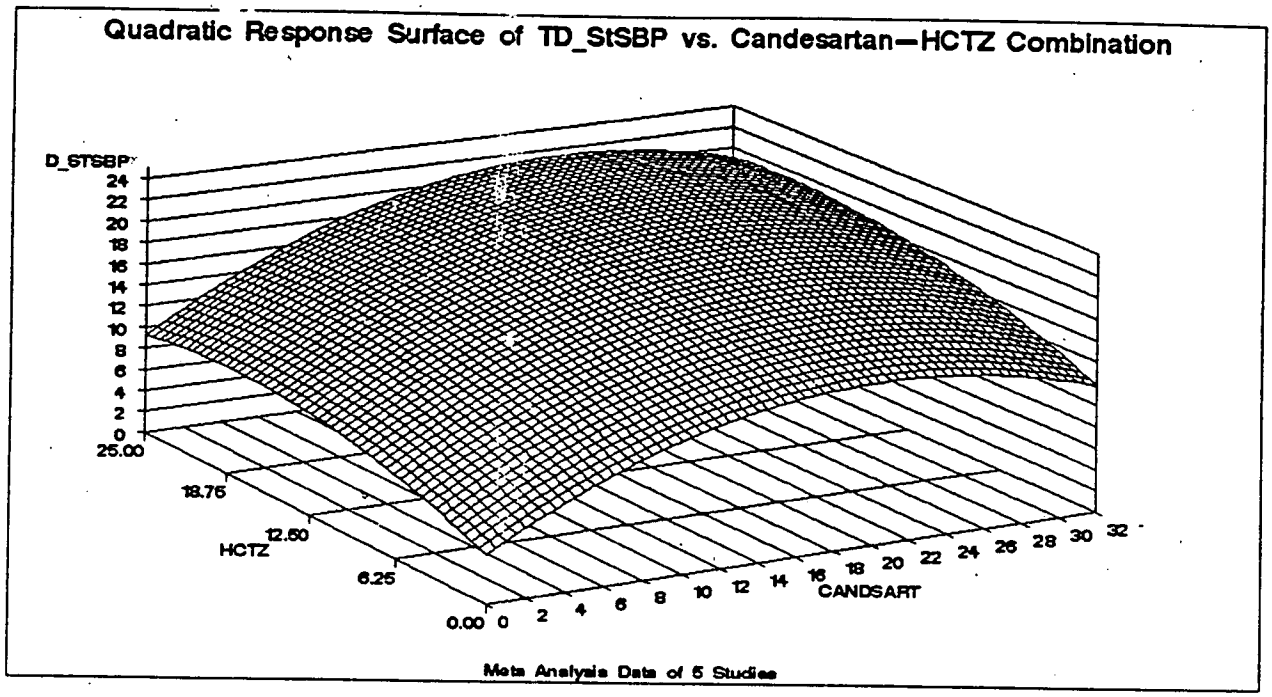


Table 18 presents the predicted means, raw means and the difference between the predicted and raw means ($D_{(P-R)}$ = Predicted - Raw) for the CC/HCTZ combinations. Comparisons of the predicted and the raw means of D_SiDBP indicate that the maximum difference is $D_{(P-R)}$ = 2.88 mmHg for the CC 2/HCTZ 6.25 mg combination. Therefore, in general, the predicted and raw means are close to each other.

Table 18: Predicted, Raw and their difference of Reduction from Baseline in StSBP in mmHg✣

		Candesartan (mg)					
		0	2	4	8	16	32
HCTZ (mg)	0	4.41, (4.66) -2.25	6.33, (3.45) 2.88	8.06, (8.43) -0.37	10.93, (9.88) 1.05	14.34, (15.72) -1.38	11.83, (9.92) 1.91
	6.25	7.51, (5.09) 2.42	9.47, (---) ---	11.23, (13.01) -1.78	14.18, (---) ---	17.74, (---) ---	15.53, (---) ---
	12.5	9.35, (8.96) 0.39	11.35, (11.87) -0.52	13.15, (17.32) -4.17	16.17, (17.43) -1.26	19.88, (17.45) 2.43	17.97, (20.58) -2.61
	25	9.26, (9.84) -0.58	11.33, (11.32) 0.01	13.21, (11.27) 1.94	16.38, (16.26) 0.12	20.39, (20.79) -0.40	19.07, (---) ---

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

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

Comparisons of the predicted and the raw means of D_StSBP indicate that, in general, the differences between the raw and predicted means are small.

3.7.3 CONCLUSION

From the pooled analyses we would conclude that CC/HCTZ combinations from 8/12.5-32/12.5 mgs are superior to placebo and the individual components.
While the pairwise statistical comparisons do not establish the superiority of the 32/12.5 mg strength to the 16/12.5 mg strength, the response surface analyses suggest that the antihypertensive effect goes above 16/12.5 mg. There appears to be little benefit in increasing the HCTZ to 25 mg for the CC 16 mg combination, and little orthostatic change was demonstrated for the various combinations.

3.8

OTHER STUDIES

The sponsor has included 14 studies in the NDA, which, while adding safety information, add little to the determination that the combination drug is superior to its components. They will be briefly considered in the following categories and order:

3.8.1:Unresponsive patients: AHK-0011

3.8.2:Severe Hypertension: AM 117

3.8.3:Various CC doses: EC 016

3.8.4:Titrated by response: EC 406, AM 140, AHK-0003

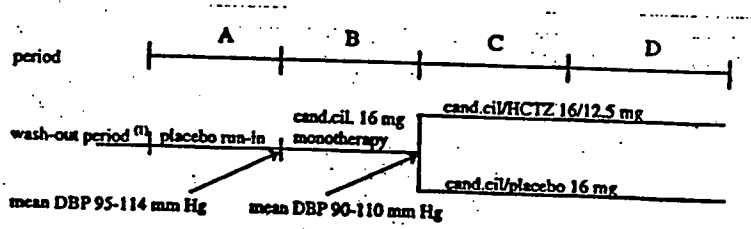
3.8.5:Other active comparisons: EC 033 (Enalapril), EC 407 (Enalapril), AHK-0006 (Lisinopril), AHK-0012 (Losartan), EC 015 (Amlodipine)

3.8.6:Long-term safety:AM116OL

3.8.7:Clinical Pharmacology: EC 415.

3.8.1
Unresponsive Patients
Study AHK-0001
The Antihypertensive Effect of the Fixed Combination of Candesartan Cilexetil and Hydrochlorothiazide 16/12.5 mg Once Daily in Hypertensive Patients Uncontrolled on Monotherapy with Candesartan Cilexetil 16 mg Once Daily

The protocol was finalized on 12/4/98, and was executed in Poland, Hungary, and the United Kingdom. The objective of the study was to determine if adding HCTZ to CC in hypertensive patients, who were inadequately responsive to CC 16 mg alone after a 4 week placebo run-in, treatment with CC/HCTZ 16/12.5 mg would have a superior antihypertensive effect than CC 16 mg alone. The plan for the study was outlined as follows:



Visit	①	②	③	④	⑤	⑥	⑦
Weeks	-8/-6	-4	-2	0	2	4	8
Medical history	X						
Physical examination	X	X		X			X
BP and HR (24h post dose)	X	X	X	X	X	X	X
Body weight		X		X			X
Height		X					
AE		X	X	X	X	X	X
ECG		X		X			X
Laboratory assessments	X(2)	X	X(2)	X	X(2)		
Pregnancy test		X					X

(1) To check for inclusion/exclusion criteria (S-creatinine, potassium, sodium, ASAT, ALAT).
(2) S-creatinine, sodium, potassium.
⑥ Randomisation (visit 4).

While the protocol stipulated that 260 patients would need to be randomized to demonstrate a significant treatment difference of 3 mmHg with a standard deviation of 8.3 mmHg, 329 patients were randomized at 41 centers. One patient had no efficacy data and was excluded from the ITT analysis. Of the 328 patients analyzed, 190 patients

male, all caucasian, mean age 52.8 years. 106 patients had not been treated with antihypertensive drugs prior to enrollment, and the mean duration of hypertension was 7.2 years.
The results for the ITT/LOCF analyses of change from baseline to last visit of trough SiDBP were:

Table 12. Mean sitting DBP (mm Hg) at baseline and last visit, 24 h post dose. ITT population (LVCF).

Treatment	N	Baseline		Last visit		Change	
		Mean	SD	Mean	SD	Mean	SD
cand.cil/HCTZ	164	98.2	5.7	90.4	8.5	-7.8	8.3
cand.cil/placebo	164	97.5	5.2	92.0	9.1	-5.5	8.4

A minus sign (-) in the mean change indicates a reduction from baseline.

Table 13. Adjusted mean and 95% confidence interval for each treatment for the change from baseline to last visit in sitting DBP (mm Hg), 24 h post dose. ITT population (LVCF).

Treatment	N	Adjusted Mean	Lower 95% CI	Upper 95% CI
cand.cil/HCTZ	164	-7.5	-8.8	-6.1
cand.cil/placebo	164	-5.5	-6.8	-4.2

A minus sign (-) in the adjusted mean indicates a reduction from baseline.

Table 14. Comparison of treatments for the change in sitting DBP (mm Hg) from baseline to last visit, 24 h post dose. ITT population (LVCF).

Treatment Comparison	Adjusted Mean	Lower 95% CI	Upper 95% CI	p-value
cand.cil/HCTZ vs cand.cil/placebo	-2.0	-3.8	-0.1	0.037

A minus sign (-) in the adjusted mean indicates that the first indicated treatment is the most effective.

For difference in trough SiSBP from baseline to last visit, the results were:

Table 15. Mean sitting SBP at baseline and last visit (mm Hg), 24 h post dose. ITT population (LVCF).

Treatment	N	Baseline		Last visit		Change	
		Mean	SD	Mean	SD	Mean	SD
cand.cil/HCTZ	164	153.0	13.3	140.8	16.2	-12.1	15.7
cand.cil/placebo	164	153.4	13.1	145.7	17.7	-7.7	15.3

A minus sign (-) in the mean change indicates a reduction from baseline.

Table 16. Adjusted mean and 95% confidence interval for each treatment for the change from baseline to last visit in sitting SBP (mm Hg) 24 h post dose. ITT population (LVCF).

Treatment	N	Adjusted Mean	Lower 95% CI	Upper 95% CI
cand.cil/HCTZ	164	-12.0	-14.5	-9.6
cand.cil/placebo	164	-7.5	-9.9	-5.1

A minus sign (-) in the adjusted mean indicates a reduction from baseline.

Table 17. Comparison of treatments for the change in sitting SBP (mm Hg) from baseline to last visit, 24 h post dose. ITT population (LVCF).

Treatment Comparison	Adjusted Mean	Lower 95% CI	Upper 95% CI	p-value
cand.cil/HCTZ vs cand.cil/placebo	-4.5	-8.0	-1.1	0.010

A minus sign (-) in the adjusted mean indicates that the first indicated treatment is the most effective.

The protocol stated that a per protocol analysis was also to be done, but the sponsor notes that, because of the greater number of premature discontinuations in the CC monotherapy group (20.3% versus 5.8% in the CC/HCTZ group) and that these patients had the least reduction in blood pressure, the per protocol analysis was not as positive as the ITT.
Subgroup analysis of the SiDBP ITT results for age, sex and country showed a consistent numerical difference favoring the combination over monotherapy.

For the secondary endpoint where in the ITT analysis % of responders (i.e. trough SiDBP ≤ 90 mmHg or reduction from baseline of 10 mmHg from baseline to last visit) were compared between groups 61% were responders in the CC/HCTZ group compared to 47.6 in the CC monotherapy group. The Mantel-Haenszel chi-square statisitic was noted to give a p=0.015.
Heart rate from baseline to last visit was not much changed within or between groups. No orthostatic hypotension was noted within or between groups.

Safety was evaluated for all 329 randomized patients. There were no deaths.
The most common adverse experiences were headache and URI.
There were 4 serious adverse experiences noted: 2 for CC alone, 2 for the combination. Of these one patient on CC/HCTZ experienced a cerebrovascular disorder, and two on CC monotherapy had cardiac complaints(AF in one, CAD in the other).
Two patients, one in each group, was withdrawn for an adverse experience. The CC/HCTZ patient had headache and hypertension given as the reason; the CC alone patient had dyspepsia, nausea and somnolence.
Laboratory changes were minimal. Slightly decreased hemoglobin in both groups, an increase in uric acid in the CC/HCTZ group. Liver function and renal function did not become abnormal.

Comments:
The study did not include a hydrochlorothiazide alone or placebo arm, but, unless one believes that HCTZ 12.5 mg once daily could alone be responsible for the superior performance of the combination, this study is supportive of the conclusion that CC/HCTZ 16/12.5 mg is superior to CC 16mg alone for the treatment of mild to moderate hypertension. Whether these were truly unresponsive patients is difficult to determine without a placebo group, and the continued response to CC alone undercuts that notion. Adverse experiences did not appear to be worse for the combination compared to continued monotherapy.

3.8.2
Severe Hypertension
Study AM 117
Evaluation of Safety and Efficacy of adding Candesartan Cilexetil (8 to 16 mg) to HCTZ in Patients with Severe (JNC-V) Hypertension.

This U.S. study was a multicenter (37 sites), randomized, double-blind, placebo controlled, parallel design study with a four week controlled period followed by open label long term extension.
The protocol was approved August 30, 1996; amended January 19, 1996 and June 3, 1996. The study was initiated April 9, 1996, and completed December 12, 1996.
The 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.

Male or female (without child-bearing potential) patients, 18-80 years of age, with severe hypertension (sitting DBP ≥ 110 mm Hg at entrance) on antihypertensive treatment were eligible, but would be excluded if the systolic BP was ≥ 210 mm Hg; for organic cardiovascular, renal, hepatic, pulmonary or hemotologic disease; if taking steroids, NSAIDS or ASA exceeding 1 gm daily.

Randomization (2:1, active: placebo) was via a computer generated list blocked by investigative site. Race (black, non-black) was also considered in the randomization program. A sample size of 210 entering the double blind phase was considered adequate to provide [redacted] 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 α 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. Secondarily, standing trough DBP, sitting and standing trough SBP, and proportion of responders (< 90 mm Hg or ≥ 10 mm Hg drop in sitting trough DBP) by Mantel-Haenszel stratified by site.

Safety was also evaluated. Compliance was 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	Weeks		Week	Weeks				Weeks									Weeks
	0	1	2	1	1	2	3	4	6	8	12	16	24	32	40	48	52	2
Informed Consent	X																	
Medical History	X																	
Chest X-ray	X																	
12-lead ECG	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
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	
AE Assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Final Report																	X	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 ≥ 110 mm Hg on or without antihypertensive therapy prior to the open label HCTZ 12.5 mg 1 week treatment period, but a SIDBP 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 > 90 mm Hg.

289 patients were screened, and of these 217 patients were randomized into the double blind period.

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.
For the primary endpoint using the ITT population, the results were:

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

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

Results by baseline SIDBP were:

	Placebo + HCTZ		CC + HCTZ	
Baseline DBP (n)	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)

For sitting SBP, the results for the ITT groups were:

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

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

Safety

Heart rate was assessed in both groups and showed little change.
Tachycardia associated with decreases in blood pressure was not found, and orthostatic hypotension was not 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 patient having chest pain and lightheadedness, the other stroke. The following patients 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
001/003	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

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.

The open label extension lasted 48 weeks followed by 2 weeks off drug. All patients who completed the double-blind period were allowed to enter the extension study where they all were given treatment with the CC/HCTZ 8/12.5mg drug. If after two weeks their trough SiDBP was≥ 90 mmHg, the dose was changed to 16/12.5mg. If after an additional two weeks the SiDBP was still ≥90 mmHg, the dose was raised to 16/25 mg.
143 patients entered this extension study, and 68 completed it. 28% discontinued for lack of response, and 15 for an adverse experience. Over the course of the study 49% of the patients were titrated up to the 16/25mg dose, while 37.8% stayed at the 8mg/12.5 dose. The mean number of days on drug was 33 weeks(median 45.1), ranging from 0.1 to 58.7 weeks.
While there was no control group in this oper label study, there was continued decrease for the trough sitting blood pressures throughout the 48 week extension.
Of the 143 patients who participated there was one death. A 42 year old non-black male with mitral regurgitation and hypertension since 1985 entered the initial study on 7/31/96. He had a heart rate of 88 bpm and blood pressures of 146/116 mmHg. In the double blind phase he was on the CC/HCTZ combination, and on 9/3/96 entered the open label extension in which he was titrated up to the 16/25mg dose. On 11/26/96 his heart rate was 96 bpm with blood pressure readings of 124-130/86-88 mmHg. On 1/20/97 he developed hemoptysis and pneumonia. The CC/HCTZ drug was stopped and he was hospitalized and improved. On 1/31/97 he developed ventricular tachycardia and died.
Of the 8 other patients with serious adverse experiences, 3 had angina or chest pain, 1 had an aortic aneurysm, 1 had thrombophlebitis, 1 headache, dizziness and paresthesias(bp 138/96 mmHg the previous day), 1 pyelonephritis, and 1 pyschosis. Additionally one patient developed orthostatic hypotension, but did not leave the study.
Without some randomized comparator, it is not possible to assess whether these experiences are more or less than would have occurred in the course of hypertension, treated or not. That problem also confounds interpretation of the sporadic laboratory abnormalities that occurred in LFTs, BUNs, uric acid, glucose, and hemoglobin.

Comments

The double-blind part of this study demonstrated effectiveness of CC 8mg titrated to 16mg for inadequate control in a relatively severe hypertensive population also treated with HCTZ. Since there is no CC alone and no placebo arm, one cannot tell what contribution HCTZ makes to the effect. Safety analysis, however, showed few problems with the combination in this part of the study. The long-term extension study is of limited value since it lacks control arms, but no unexpected signal was found.

3.8.3
Various CC doses
Study EC016
Efficacy and Safety of Candesartan Cilexetil in Combination with HCTZ in the Treatment of Patients with Mild to Moderate Hypertension, Not Responding to Low dose Monotherapy with HCTZ.

This French randomized, placebo controlled, double-blind multicenter study compared 4mg to 8mg of Candesartan cilexetil in hypertensive patients treated with hydochlorothiazide.

To be eligible for the placebo run-in, patients had to be ≥18 years, male or female and have been unsatisfactorily treated for mild to moderate essential hypertension (sitting DBP 95-109 mm Hg). For the HCTZ monotherapy period a trough sitting DBP 95-109 mm Hg and sitting SBP < 200 mm Hg had to be present.

For inclusion into the DB treatment study, a trough sitting DBP 90 mm Hg or more had to be present. Malignant hypertension, cardiac, hepatic, GI, renal, autoimmune, or metabolic disease were exclusions.

The visit schedule for the study was.

Flow-Chart of Study EC 016

	Placebo Run-In Period			HCTZ Monotherapy		"Add-On" Treatment	
Week	0	2	4	7	10	14	18
Visit	1	2	3	4	5	6	7
Medical history	x						
Incl./excl. criteria	x		x		x		
Concomitant medication	x	x	x	x	x	x	x
Extensive physical examination	x				(x)		x
Brief physical examination		x	x	x	x	x	
Blood pressure/heart rate	x	x	x	x	x	x	x
Adverse events		x	x	x	x	x	x
Laboratory tests (blood)[1]	x			x[2]		x[3]	
Urinalysis (dipstick)	x		x		x		x
ECG	x		x		x		x
Distribution of medication	x		x	x	x	x	
Drug accountability		x	x	x	x	x	x
Global assessment of efficacy and safety					(x)		x

[1] taken at patients' home
[2] results had to be available at visit 5
[3] results had to be available at visit 7

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

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

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

Of the 325 patients enrolled, 262 entered the HCTZ treatment period, and of these 234 were randomized.

All 234 were included in the ITT and safety analyses, but 39 were excluded from the per protocol analyses, most for major protocol violations.
In the double-blind portion of the study,123 patients were male, 111 female; mean age 56.2 years; mean duration of hypertension was greater than 3 years for approximately one-half of the patients in each treatment group. More than one-half had previously received antihypertensive therapy in each group.

The results for the primary endpoint were:

T-Table 7
Primary efficacy evaluation: Mean (± SD) and 95% confidence intervals (in brackets) of reduction in sitting diastolic blood pressure (mmHg) at the individual endpoint of eight scheduled weeks of randomised treatment compared to baseline (= start of randomised treatment, Visit 5).

	HCTZ + Placebo	HCTZ + Cand. cil. 4 mg	HCTZ + Cand. cil. 8 mg
ITT	-3.3 ± 10.1 [-6.198, -0.402] n = 49	-7.0 ± 8.0 [-8.648, -5.352] n = 94	-7.9 ± 9.6 [-9.905, -5.895] n = 91
PP	-3.4 ± 10.5 [-6.668, -0.132] n = 42	-7.6 ± 8.2 [-9.457, -5.743] n = 78	-8.5 ± 9.6 [-10.704, -6.296] n = 75

T-Table 8
Primary efficacy evaluation: ANOVA on reduction in sitting diastolic blood pressure at the individual last value versus baseline (= start of randomised treatment, Visit 5).).

Comparison of the "add-on" therapy A *versus* B			Estimate [a] (mmHg)	95% Confidence interval (mmHg)	p-value (2-sided)
Candesartan cilexetil 4 mg	placebo	ITT	-3.90	[-6.974, -0.826]	0.0127 *
		PP	-4.90	[-8.401, -1.399]	0.0061 *
Candesartan cilexetil 8 mg	placebo	ITT	-5.00	[-8.096, -1.904]	0.0017 *
		PP	-5.60	[-9.105, -2.095]	0.0018 *
Candesartan cilexetil 4 mg	Candesartan cilexetil 8 mg	ITT	1.10	[-1.474, 3.674]	0.4086
		PP	0.70	[-2.244, 3.644]	0.6362

ANOVA with "treatment" and "centre" as factors. Centres with less than 4 patients were pooled.
[a] A minus B; i.e. a negative estimate indicates greater reduction for A.
* p-value < 5%.

While Candesartan was clearly superior to placebo, the doses were not significantly different.

No deaths occurred during the study. And there were two serious adverse experiences (one in each of the CC groups) during the double blind study: one of removal of nasal polyps, one epistaxis. There were four adverse experiences leading to withdrawal (two in each of the CC groups). They were: headache and muscle cramp in the 4 mg group, vertigo and anxiety in the 8 mg group.

Comments:
This study has little relevance for efficacy in this NDA. It was presented and more fully reviewed in the monotherapy NDA 20-838. There is no CC alone arm, and it is feasible that CC monotherapy could have been as effective. Safety experience was as expected.

3.8.4.
Titrated by Response
3.8.4.1
Study EC 406
Long-term Safety and Efficacy of Candesartan Cilexetil/HCTZ Combination (4 or 8 mg CC; 6.25 or 12.5 mg HCTZ) in Patients with Mild to Moderate Essential Hypertension. An Open Prospective Multi-centre Study with Response-Dependent Dose Titration.

This was a German multicenter (58 sites) 12 month open study of hypertensive patients (previously enrolled in EC 040 and EC 403) treated with 4/6.25 mg of CC/HCTZ once daily with a response-dependent titration to 8/12.5 mg if response to the initial dose was unsatisfactory.

The plan for the study was outlined as follows:

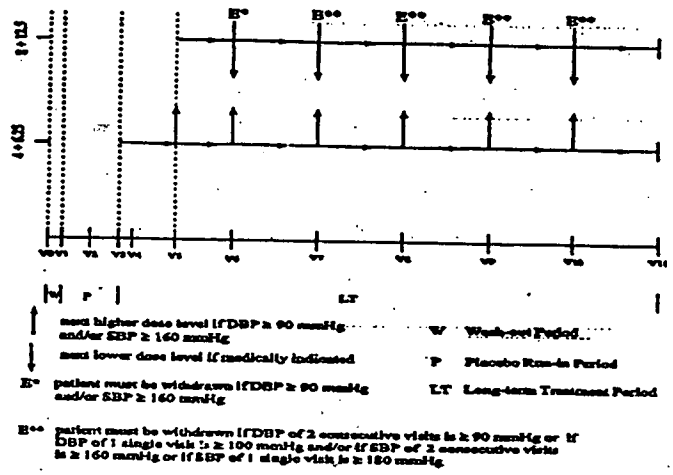
Study Period	Wash-Out Period	Placebo Run-In Period			Long-Term Treatment Period							
Week	-1	0	2		1							
End of month				1		1	2	4	6	8	10	12
Visit	V0*	V1	V2**	V3	V4	V5	V6	V7	V8	V9	V10	V11
Medical history		X										
Inclusion/Exclusion criteria	X	X		X								
Concomitant medication check	X	X	X	X	X	X	X	X	X	X	X	X
Extensive physical examination		X										X
Brief physical examination	X		X	X	X	X	X	X	X	X	X	
Blood pressure/Heart rate	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events		X*	X	X	X	X	X	X	X	X	X	X
Laboratory tests		X		X	X	X	X	X	X	X	X	X
ECG		X		X	X	X	X	X	X	(X)	(X)	X
Dose titration (if necessary)						X	X	X	X	X	X	
Distribution of medication		X		X		X	X	X	X	X	X	
Drug accountability				X		X	X	X	X	X	X	X
Assessment of efficacy/safety												X

* to be performed only in case of antihypertensive pre-treatment other than candesartan cilexetil alone or in combination with HCTZ

** Patients previously treated with candesartan cilexetil and/or HCTZ showing at Visit 2 a mean DBP ≥ 90 mmHg were allowed to proceed directly to Visit 3 and enter the long-term treatment period after all examinations scheduled for Visit 3 had been performed

( ) optional

The plan for dose adjustment was:



APPEARS THIS WAY
ON ORIGINAL

Of the 602 patients enrolled into this study, 559 entered the long-term treatment period, although 5 had no post-baseline data. 111 withdrew during that 12 month period, leaving 448 who provided sufficient data for analysis. The demographic characteristics of the 559 patients who entered included 239 males, 320 females; average age 59.2 years; 99.6% Caucasian.
Results for the primary endpoint were stratified by final dose for 448 patients:

T-Table 8: Mean sitting diastolic blood pressure in patients with diastolic hypertension stratified by last dose – Efficacy analysis (n=448)

	Candesartan cilexetil/HCTZ	
	Low dose	High dose
	n=186	n=262
Baseline (Visit 3) [mmHg]	99.8 ± 3.2	102.0 ± 4.3
Last value* [mmHg]	83.9 ± 7.1	88.5 ± 7.1
Decrease between baseline and last value [mmHg]	15.9 ± 7.0	13.5 ± 7.5
Response (last value)	88.7%	68.3%
Normalisation (last value)	88.7%	67.9%

* Blood pressure at Visit 11 or at the time of premature discontinuation (only values under medication)

For these patients the results by visit independent of stratification were provided:

T-Table 7: Mean sitting diastolic blood pressure (mean ± SD) and changes in mean sitting diastolic blood pressure (mean ± SD) between baseline (Visit 3) and each subsequent visit – Efficacy analysis – Patients with diastolic hypertension (n=448)

Time point	Number of patients	Mean sitting diastolic blood pressure [mmHg]	Change in mean sitting diastolic blood pressure versus baseline [mmHg]
Visit 1	448	102.2 ± 4.2	NA
Visit 2	435	101.1 ± 4.0	NA
Visit 3 (Baseline)	448	101.1 ± 4.1	NA
Visit 4	437	94.4 ± 7.3	-6.7 ± 6.5
Visit 5	432	90.5 ± 6.7	-10.6 ± 6.4
Visit 6	413	86.4 ± 5.4	-14.6 ± 5.9
Visit 7	398	85.0 ± 5.3	-15.9 ± 6.0
Visit 8	390	85.0 ± 5.4	-15.9 ± 6.0
Visit 9	383	84.6 ± 5.4	-16.2 ± 5.9
Visit 10	372	84.6 ± 4.5	-16.2 ± 5.6
Visit 11	363	85.0 ± 5.4	-15.8 ± 5.9
Last value	448	86.6 ± 7.4	-14.5 ± 7.4

NA = Not applicable

None of these results provide efficacy data, since they are uncontrolled, but are descriptive a patient population treated long-term with the combination products.

Safety was evaluated for 559 patients. 403 of these were treated for at least 360 days.
There was a death in a 53 year old obese,male with a history of coronary artery disease on the low dose combination for 4 days. After the first dose of drug the patient's blood pressure was 152/102. Myocardial infarction was given as the cause of death.

28 patients withdrew from the long-term treatment period for a variety of reasons as given below:

		Age at onset [years]	Gender	Adverse event (Verbatim translated into English)	Adverse event (Preferred term)
* Long-term treatment period (n=28)					
Pat.	Dose				
007	high	81	female	Dizziness	Dizziness
				Headaches	Headache
048	high	62	male	Increase of transaminases	Hepatic function abnormal
051	low	53	male	Fatal myocardial infarction*†	Myocardial infarction
049	low	63	female	Absolute arrhythmia with atrial fibrillation*	Arrhythmia
062	low	57	female	Glaucoma	Glaucoma
066	high	66	male	Phlebothrombosis*	Thrombophlebitis
				Subsequent pulmonary embolism*	Embolism pulmonary
085	low	59	female	Acoustic neurinoma*	Brain neoplasm benign
121	high	52	female	Hypertensive crisis	Hypertension
136	low	71	male	Empyema in the knee joint*	Abscess
183	high	72	female	Increasing complaints due to coxarthrosis left (total hip replacement planned) *	Arthrosis
191	high	57	male	Pancreatic carcinoma (mechanical jaundice) *	Pancreas neoplasm malignant
225	high	55	male	Apoplexy*	Cerebrovascular disease
316	high	86	female	AV block grade I	AV block
324	low	60	male	Attacks of dizziness, short attacks	Dizziness
328	low	66	female	Constipation	Constipation
335	low	72	male	Acute myocardial infarction*	Myocardial infarction
344	low	56	female	Pain in ears	Earache
				Restlessness	Agitation
374	high	89	female	Disturbance of orthostatic regulation	Hypotension postural
408	low	58	female	Pain in left leg	Pain
435	high	47	female	Generalised pruritus	Pruritus
446	low	37	male	Increase of the transaminases	Hepatic function abnormal
456	low	86	female	Hypokalaemia	Hypokalaemia
498	low	82	female	Exsiccosis	Dehydration
				Extrasystoles	Extrasystoles
555	low	67	female	Breast cancer right side*	Breast neoplasm malignant female
557	low	68	male	Elevated liver values	Hepatic function abnormal
586	low	44	female	Acute lumbar spine syndrome with intervertebral disk prolapse*	Back pain
587	high	64	female	Extrasystole at night (subjective)	Extrasystoles
590	low	52	female	Cholelithiasis	Cholelithiasis

* reported as serious adverse event

† Premature discontinuation due to death

Some events seem unrelated to the drug (e.g. pancreatic carcinoma); some may indicate inadequate control of disease (e.g. hypertensive crisis); some possibly due to the drug (e.g. postural hypotension, hypokalemia); and others due to underlying disease and/or drug toxicity (e.g. abnormal hepatic function). Were there a placebo group, it might be found that the drug was associated with fewer serious events leading to withdrawal, but given the open, uncontrolled design this cannot be determined from this study. It is interesting to note that in the placebo run-in period, three patients withdrew for adverse events: one for angina, another for abnormal liver function, and the third for hypertension. The more frequently noted adverse experiences (i.e. incidence> 2%) included back pain, influenza-like illnesses, and inflicted injury. Of more relevance were findings of abnormal liver function in 14 patients, hyperuricemia in 13, symptomatic hypotension in 12, and dizziness in 19. Other changes in laboratory values were minor and not clinically relevant.

Comments:

This open uncontrolled study is descriptive of clinical experience with the drug, and as such provides no surprising findings for safety or efficacy.

3.8.4.2

Study AM 140

The ABC* Study of Hypertension. Efficacy and Safety of Candesartan Cilexetil in Hypertensive Black Patients: a Double-blind, randomized, Placebo Controlled, Parallel Group Design Study with an Open Label, Long Term Extension (*Association of Black Cardiologists)

This U.S multicenter (38 sites contributing in the controlled portion of the study) was a randomized, placebo controlled study of the antihypertensive effect of Candesartan Cilexetil in adult, male or female Black patients with a SiDBP of 91-105 mmHg at randomization.

After the placebo run-in, patients were randomized to CC 16 mg once daily or placebo. After four weeks those not having a satisfactory response (i.e. trough SiDBP <90 mmHg) had their dose doubled. After the 8th week, those not having a satisfactory response either doubled the 16 mg dose or placebo, or if on 32 mg or placebo had HCTZ 12.5 mg added to both arms.

304 patients were randomized: 154 males, 150 females with an average age of 52.3 years and 10.2 years for the average duration of hypertension.

The results for trough SiDBP and SiSBP by weeks were:

Trough Sitting Diastolic Blood Pressure (mm Hg) by Treatment and Visit (ITT/LOCF Population)

Treatment		Baseline	DB Wk 2	DB Wk 4	DB Wk 8	DB Wk 8 (LOCF)	DB Wk 12
Candesartan cilexetil	N	151	148	143	134	151	124
	Mean	96.3	91.9	91.8	90.7	91.5	88.6
	SD	4.4	8.7	8.0	8.5	9.0	8.2
Placebo	N	145	144	138	129	145	119
	Mean	97.0	94.3	93.4	94.6	95.1	90.8
	SD	4.7	7.5	7.3	9.5	9.2	8.3

Trough Sitting Systolic Blood Pressure (mm Hg) by Treatment and Visit (ITT/LOCF Population)

Treatment		Baseline	DB Wk 2	DB Wk 4	DB Wk 8	DB Wk 8 (LOCF)	DB Wk 12
Candesartan cilexetil	N	151	148	143	134	151	124
	Mean	147.7	142.3	141.9	141.2	142.5	137.0
	SD	14.3	16.0	15.5	16.4	17.6	16.4
Placebo	N	145	144	138	129	145	119
	Mean	151.2	148.4	147.9	148.9	149.7	143.4
	SD	15.3	15.0	15.6	16.3	16.0	15.8

At week 4, 42.4% of the CC group were uptitrated compared to 53.8% of the placebo group.

At the end of week 12, 24.6% were on placebo, 24.3% placebo + HCTZ, 23.6% CC 16 mg, 13.5% CC 32 mg, and 13.8% on CC 32 mg + HCTZ.

The sponsor determined that the difference between the CC and placebo arm for change from baseline to week 8 for trough SiDBP was significant. This effect on blood pressure occurred by week 4 when patients were on either CC 16 mg or placebo, and doubling the dose did little.

For the safety analysis, 304 patients were evaluated. The mean time on treatment assignment was 78.8 days. No deaths occurred.
13 patients withdrew from the double-blind portion of the study for reasons cited below:

Patient	Treatment	Adverse Event (Included Term)	Days on Treatment Prior To Event Start Date
002/001	Placebo	Drug Abuse Hypertension	35
007/001	Placebo	Allergic Reaction	4
041/007	Placebo	Pregnancy	55
016/001	Candesartan cilexetil	Depression	-3
021/002	Candesartan cilexetil	Blood Pressure Increased Fibrillation Atrial Pain	40 40 40
026/007	Candesartan cilexetil	Heart Pounding	4
026/014	Candesartan cilexetil	Hypertension Aggravated Numbness Localized	32 32
029/005	Candesartan cilexetil	Impotence	5
043/012	Candesartan cilexetil	Blood Pressure Increased Breath Shortness Heart Murmur	14 14 14
045/016	Candesartan cilexetil	Breath Shortness Coughing Breath Shortness Coughing	2 2 17 28
046/009	Candesartan cilexetil	Chest Pain Headache	29 29
053/005	Candesartan cilexetil	Headache	14
053/006	Candesartan cilexetil	Hypertension	21

2.7% of those assigned to CC withdrew for treatment failure compared to 0.7% of those on placebo.
Headache was the most frequently reported adverse experience(12.8%). Two asymptomatic orthostatic episodes were reportcd; one patient assigned to CC (at trough measurement at baseline), the other on placebo.
Laboratory changes were slight, and did not lead to clinical intervention. Once again, a slight decrease in mean hemoglobin from baseline to weeks 8 and 12 was noted for CC treated patients and not for those on placebo. Renal and liver function tests did not vary from baseline significantly for either group, and hypokalemia was noted in two patients on placebo alone.
The results of the 40 week long-term extension were reported in an amendment dated 2/28/00. 208 patients continued into this part of the study. Final treatment given was CC 16 mg-45 (21.6%), CC 32 mg-20 (9.6%), CC/HCTZ 16/12.5 mg-39 (18.8%), CC/HCTZ 32/12.5 mg57 (27.4%), and CC 32 mg/HCTZ 12.5mg/Plendil-47 (22.6%).
One patient on CC 16 mg died of a gunshot wound.
12 patients withdrew for AEs; 4 on the combination 32/12.5 (3 including Plendil). Reasons in the combination patients were headache, hypertension, CPK increased, and cramps.
Serious AEs were reported in 3 patients on the 32/12.5 mg combination (1 with Plendil). They were uterine fibroid, bladder carcinoma, and abdominal pain.
Laboratory changes of potential significance included 8 patients with CPK elevation app[roximately 3Xnl or greater, 4 with elevated glucose, 5 with elevated uric acid (4 on the combination), 1 with elevated BUN, 2 with creatinine> 2 mg/dL, 0 with LFT elevations, and 2 with low hematocrits.

Comments:
The primary objective of this study was to assess the safety and efficacy of Candesartan Cilexetil monotherapy as an antihypertensive in black patients. Although HCTZ 12.5 mg was added based on inadequate response in weeks 8-12, such addition was made in both the CC and placebo arm. From the perspective of this combination product NDA, little data from this study are useful, and the safety data do not signal a problem other than expected from the monotherapies or overall results with the combination products.

3.8.4.3

Study AHK-0003

Antihypertensive Effect and Tolerability of the Fixed Combination of Candesartan Cilexetil and Hydrochlorothiazide, Compared with the Individual Components

This multicenter(7) Swedish study was a double-blind, three way randomized crossover study comparing antihypertensive efficacy and safety of once daily Candesartan Cilexetil (CC) 4 or 8 mg titrated by response, HCTZ 6.25 or 12.5 mg titrated by response and the fixed combination of CC+HCTZ (4 mg+6.26 mg or 8 mg+12.5 mg) for 12 week periods of treatment. 69 adult male or female patients with SiDBP 95-114 mmHg during the placebo run-in phase were randomly assigned to one of 6 treatment sequences, each drug being given for 12 week periods of treatment without washout between drugs with dose doubling at 6 weeks for SiDBP >90 mmHg. 47 patients comprised the per protocol population.

Of the 69 randomized, 42 were male, all caucasian, and 72.5% were less than 65 years of age. 40% had not been on previous antihypertensive medication.

The primary endpoint was mean trough SiDBP at the end of each 12 week treatment period for the ITT and per protocol populations. The objective was to determine if the fixed combination was superior to the components. The ITT results for trough SiDBP were provided in the following tables:

Table 34. Sitting DBP (mmHg) 24 hours post-dose, summarized after 6 and 12 weeks in each treatment period. All centres. ITT population.

Treatment		baseline	6 weeks	6 weeks (LVCF)	12 weeks	12 weeks (LVCF)
cand.cil.	N		63	64	61	62
	Missing		1	0	3	2
	Mean		93.0	92.9	92.5	92.6
	SD		8.1	8.1	8.4	8.4
	Min		74.0	74.0	68.0	68.0
	Median		93.0	93.0	93.0	93.5
	Max		111.0	111.0	108.0	108.0
HCTZ	N		65	65	61	63
	Missing		1	1	5	3
	Mean		96.8	96.8	95.7	96.0
	SD		8.1	8.1	6.9	7.1
	Min		80.0	80.0	85.0	85.0
	Median		96.0	96.0	95.0	95.0
	Max		113.0	113.0	114.0	114.0
cand.cil./HCTZ	N		62	62	61	61
	Missing		0	0	1	1
	Mean		91.6	91.6	89.9	89.9
	SD		8.5	8.5	6.6	6.6
	Min		64.0	64.0	69.0	69.0
	Median		92.0	92.0	90.0	90.0
	Max		109.0	109.0	107.0	107.0
placebo	N	69				
	Missing	0				
	Mean	101.7				
	SD	5.8				
	Min	84.0				
	Median	101.0				
	Max	114.0				

APPEARS THIS WAY
ON ORIGINAL

For sitting trough systolic blood pressure the ITT results were:

Table 36. Sitting SBP (mmHg) 24 hours post-dose, summarised after 6 and 12 weeks in each treatment period. All centres. ITT population.

Treatment		baseline	6 weeks	6 weeks (LVCF)	12 weeks	12 weeks (LVCF)
cand.cil.	N		63	64	61	62
	Missing		1	0	3	2
	Mean		151.2	151.3	151.2	151.4
	SD		14.2	14.1	14.1	14.2
	Min		125.0	125.0	126.0	126.0
	Median		152.0	152.0	150.0	150.0
	Max		182.0	182.0	183.0	183.0
HCTZ	N		65	65	61	63
	Missing		1	1	5	3
	Mean		156.6	156.6	154.9	155.2
	SD		16.2	16.2	13.2	13.5
	Min		121.0	121.0	120.0	120.0
	Median		156.0	156.0	154.0	154.0
	Max		196.0	196.0	180.0	181.0
cand.cil/HCTZ	N		62	62	61	61
	Missing		0	0	1	1
	Mean		148.7	148.7	145.4	145.4
	SD		12.6	12.6	14.8	14.8
	Min		119.0	119.0	122.0	122.0
	Median		150.5	150.5	146.0	146.0
	Max		174.0	174.0	187.0	187.0
placebo	N	69				
	Missing	0				
	Mean	164.4				
	SD	13.0				
	Min	140.0				
	Median	164.0				
	Max	192.0				

At 12 weeks 66.1% were taking high dose CC, 76.2% high dose HCTZ, and 57.4% high dose combination CC+HCTZ. The combination drug was statistically superior to its components at 12 weeks, but at 6 weeks the combination was not demonstrably superior to CC alone for the ITT trough SiDBP results.

69 patients were evaluated for safety. No patient died, two had the drug discontinued for an adverse experience (asthenia-CC alone, fatigue-HCTZ), and three patients had non-fatal serious adverse experiences (cholecystitis-on HCTZ, pneumonia-on CC+HCTZ, and syncope after blood donation-on CC alone). Heart rate did not significantly change or differ within or between groups.
In the laboratory analyses, increased uric acid was noted for patients on HCTZ alone or in the combination compared to CC alone. ALAT was above the critical limit in 5% of those on HCTZ, 3% on the combination and 0% on CC alone.

Comments:
This complex study supports the finding that the combination of CC+HCTZ is superior in antihypertensive efficacy to its components which was more clearly demonstrated in studies AHK0004, AM 124, EC 408, AM 153, and EC 403. All drugs were well tolerated.

3.8.5
Other active comparisons
3.8.5.1
Study EC 033
Long Term Comparison of the Safety and Efficacy of Candesartan cilexetil in Different Dosages (4,8,12 mg) with Placebo and Enalapril (10 mg) in Patients with Mild to Moderate Hypertension.
Follow up to Study EC011 - Comparative, double-blind randomized, multicenter (FRG), placebo controlled study of Candesartan cilextetil at a dose of 4 mg or 8 mg or 12 mg once daily, or enalapril 10 mg once daily in patients with mild to moderate hypertension (DBP 95-114 mm Hg).

Study EC011 was reported and reviewed in NDA 20838, not in this NDA. In that study 336 patients were randomized to either once daily placebo, CC 4 mg, CC 8 mg, CC 12 mg or Enalapril 10 mg. For trough SiDBP, all actives but for CC 4 mg were statistically superior to placebo and all were well tolerated.
EC 033 was also reported in the monotherapy NDA and reviewed there, but since HCTZ could be added during the course of the long term study, it is represented by the sponsor in this combination product NDA.
In the 40 week continuation study, 176 patients participated: placebo-24, CC 4 mg-32, CC 8 mg-41, CC 12 mg-35, Enalapril 10 mg-44. Of these 165 were eligible for the ITT analysis while all 176 were included in the safety evaluation. Relevant to this NDA was the provision that if the mean SiDBP was ≥95 mmHg, HCTZ 12.5 mg could be added, and if still at that level at the next evaluation the HCTZ dose could be doubled to 25 mg.
The numbers given HCTZ were presented as follows:

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

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

Comments:
Since only 35 patients were given HCTZ, in most cases Placebo,CC or Enalapril monotherapy was clinically adequate. There was little additive blood pressure response after HCTZ was added, but these were by design patients not responding as well. The long term benefits of monotherapy were better addressed by the randomized withdrawal studies in NDA 20-838, and the safety and efficacy of the fixed combination better evaluated in the factorial studies cited above. Indeed the sponsor has not provided the safety data for those who received CC+HCTZ in this study separate from the monotherapy assignment. More detail about this study can be found in the full review that was provided in the monotherapy NDA.

3.8.5.2

Study EC 407

The Antihypertensive Effect of the Fixed Combination Dose of Candesartan Cilexetil and Hydrochlorothiazide 8/12.5 mg Once Daily in Comparison to the Market Dose of the Fixed Combination of Enalapril and Hydrochlorothiazide 10/25 mg Once Daily in Patients with Mild to Moderate Essential Hypertension. A Double-blind, Randomized, Placebo-controlled, Parallel Group, Multi-centre Study.

This 12 week, German multi-center(40), 279 patient study was done to compare the antihypertensive efficacy of CC+HCTZ to Enalapril+HCTZ and both to placebo for change in trough SiDBP from baseline to week 12. A single dose level of each active was chosen for this study: 8/12.5 for CC combination (not proposed for marketing in this NDA) and 10/25 for the Enalapril combination (which is marketed in the U.S.).The randomization was unbalanced so that 139 were assigned to CC+HCTZ, 72 to Enalapril+HCTZ, and 68 to Placebo.
136 males, 143 females, mean age 56.4 years were randomized. Approximately 59% had previously been on antihypertensive treatment.
The ITT results for SiDBP, SiSBP and pulse were:

Table 10 Time courses of sitting systolic/diastolic blood pressure and pulse rate
ITT population

	Candesartan cilexetil/HCTZ			Enalapril/ HCTZ			Placebo		
	n	mean	SD	n	mean	SD	n	mean	SD
	Systolic Blood Pressure (mmHg)								
Visit 1 Screening	138	160.7	11.2	72	162.6	10.7	67	161.2	11.8
Visit 2, baseline	138	161.1	11.6	72	162.2	12.1	67	159.9	11.6
Visit 3	138	147.9	13.5	70	147.4	15.6	65	158.1	14.0
Visit 4	136	143.1	11.7	67	143.4	14.7	61	153.6	12.3
Visit 5	130	140.1	12.7	63	138.4	14.1	46	149.4	13.7
Visit 6, 12 weeks post baseline	136	138.9	13.1	70	139.4	14.6	64	150.9	14.8
Individual last value	138	139.0	13.0	72	139.3	14.8	67	151.5	14.1
	Diastolic Blood Pressure (mmHg)								
Visit 1 Screening	138	101.7	4.2	72	101.3	4.3	67	102.0	4.1
Visit 2, baseline	138	101.1	4.3	72	100.9	4.6	67	101.3	4.7
Visit 3	138	92.6	7.8	70	91.5	9.6	65	98.5	7.5
Visit 4	136	86.8	6.2	67	87.2	8.3	61	92.9	7.9
Visit 5	130	84.9	6.1	63	84.3	8.0	46	90.0	5.9
Visit 6, 12 weeks post baseline	136	85.2	7.6	70	85.6	8.6	64	93.7	8.9
Individual last value	138	85.2	7.6	72	85.7	8.5	67	93.7	9.3
	Pulse rate (bpm)								
Visit 1 Screening	138	74.9	9.9	72	74.8	9.2	67	75.9	9.6
Visit 2, baseline	138	75.4	9.5	72	75.8	8.8	66	75.2	10.9
Visit 3	138	75.6	9.2	70	76.3	10.0	64	76.2	9.5
Visit 4	136	75.4	9.8	67	75.1	9.2	60	75.3	9.7
Visit 5	130	74.8	9.0	63	75.8	12.1	46	75.8	9.4
Visit 6, 12 weeks post baseline	136	74.3	9.9	70	74.6	10.0	64	75.7	9.7
Individual last value	138	74.2	9.8	72	74.7	9.8	67	75.3	9.7

For change in SiDBP, both actives were statistically superior to placebo ($p<0.001$), and not statistically different from each other ($p=0.4972$).

ABPM was done in a 62 patient subset of patients with the following results:

Table 14 ABPM: Changes from baseline to Visit 6 for trough / peak levels and AUC
ABPM population

		Candesartan cilexetil/HCTZ n=30		Enalapril/ HCTZ n=15		Placebo n=17	
		mean	SD	mean	SD	mean	SD
Trough level mmHg	DBP	-5.9	11.7	-4.3	12.4	0.9	10.3
	SBP	-8.0	13.6	-7.7	17.7	1.6	13.2
Peak level mmHg	DBP	-4.1	9.8	-13.1	12.0	-2.1	13.7
	SBP	-3.2	16.0	-17.7	18.3	4.5	18.3
AUC h x mmHg	DBP	-130.2	154.2	-145.5	219.1	38.6	177.6
	SBP	-188.4	230.1	-253.7	350.6	93.1	293.1

trough level = highest hourly BP mean during the time interval 20-24 h post dose
peak level = lowest hourly BP mean during the time interval 4-8 h post dose

Table 15 ABPM: p-values for trough / peak levels and AUC
Analysis of covariance based on changes from baseline (Visit 2) to Visit 6. ITT population

		Candesartan cilexetil/HCTZ versus Placebo	Enalapril/ HCTZ versus Placebo	Candesartan cilexetil/HCTZ versus HCTZ + Enalapril
Trough level	SBP	0.0639	0.1218	0.9651
	DBP	0.0302*	0.4895	0.1788
Peak level	SBP	0.1911	0.0027*	0.0185*
	DBP	0.2334	0.0224*	0.1223
AUC	SBP	<0.001*	<0.001*	0.3202
	DBP	<0.001*	0.0022*	0.9440

trough level = highest hourly BP mean during the time interval 20-24 h post dose
peak level = lowest hourly BP mean during the time interval 4-8 h post dose
* p-value < 0.05

At the dose chosen, the data suggested that CC+HCTZ 8/12.5 had a significant effect on change in trough SiDBP compared to placebo, but not peak. It is unlikely that a drug effective at trough would not be effective at peak, though the reverse is possible. Overall both combinations were superior to placebo.

279 patients formed the safety database. Mean duration of treatment was 65 days, 78 days and 82 days for the placebo, Enalapril+HCTZ, and CC+HCTZ groups respectively. No deaths occurred. No serious adverse experiences were noted in the CC+HCTZ group, while there were 2 in the Enalapril+HCTZ group and 2 in the placebo group, none plausibly related to the drug assignment. Dizziness and vertigo were noted most frequently for those assigned to Enalapril+HCTZ.
Of the laboratory findings, there was a decrease of hemoglobin in the CC+HCTZ group, an increase from baseline in uric acid and decrease in serum potassium in both groups taking HCTZ.

Comments:
CC+HCTZ 8/12.5 was shown to be effective and well-tolerated as an antihypertensive. Since the components were not studied, it cannot be asserted from this study that the combination performed better than CC or HCTZ alone, but there are other data.

3.8.5.3

Study AHK 000(

The Antihypertensive Effect of the Fixed Combination of Candesartan Cilexetil and Hydrochlorothiazide 8/12.5 mg Once Daily, in Comparison with the Fixed Combination of Lisinopril and Hydrochlorothiazide 10/12.5 mg Once Daily

This multicenter (42) study was performed in Norway, Finland, The Netherlands and England. 355 patients were randomized in a 2:1 manner to either CC+HCTZ 8/12.5 (n=238) or Lisinopril+HCTZ 10/12.5 (n=117). A double-dummy technique was used to maintain the blind, and the duration of the study was 26 weeks. 2 patients were excluded from the ITT analysis due to lack of efficacy information. Of the 353 patients in the ITT analysis 195 were male, 158 female. All but 5 were Caucasian, and the average age was 58.2 years in the CC+HCTZ group and 56 years in the Lisinopril+HCTZ group. All but 3 had been on prior antihypertensive treatment.

For 1 or 2 weeks prior to randomization previous blood pressure medication was discontinued, and if the mean SiDBP was ≥95 mmHg and <115 mmHg the patient was randomized. The primary endpoint was change from baseline to 26 weeks of treatment for trough mean SiDBP.

The results were:

Table 38. Sitting diastolic BP (mmHg) summarised by visit. All centres. ITT population.

Treatment	Statistics	Baseline	Week 2	Week 6	Week 12	Week 19	Week 26	Week 26 (LVCF)
cand.cil./HCTZ	N	237	233	227	211	198	190	233
	Missing	0	4	10	26	39	47	4
	Mean	102.9	93.8	91.6	91.5	90.3	90.3	93.0
	SD	5.5	8.6	8.5	9.0	8.2	7.5	9.3
	Min	86.0	66.0	69.0	66.0	66.0	71.0	71.0
	Median	103.0	93.0	92.0	91.0	90.0	90.0	91.0
	Max	115.0	118.0	113.0	122.0	121.0	116.0	124.0
lisinopril/HCTZ	N	116	115	110	106	100	96	115
	Missing	0	1	6	10	16	20	1
	Mean	101.8	92.6	90.6	90.0	89.2	90.2	91.2
	SD	4.9	7.9	7.5	7.7	7.9	8.1	8.4
	Min	95.0	75.0	71.0	71.0	62.0	72.0	72.0
	Median	101.0	91.0	90.0	89.0	89.0	90.5	91.0
	Max	114.0	114.0	125.0	113.0	105.0	111.0	111.0

There was no statistically significant difference in the magnitude of change from baseline between the two actives, and no placebo and/ or component arms were included. Results for SiSBP were similar between the arms. There was little change in heart rate during the course of the study.

Safety analysis was provided the 355 patients randomized..

No deaths occurred.

14 patients in each group withdrew for adverse experiences (5.9% of the CC+HCTZ group; 12% of the Lisinopril+HCTZ group). Listed reasons in the CC+HCTZ group included MI, syncope, coughing, flushing, rash, hypertension, arrhythmia and dizziness. In the Lisinopril+HCTZ group, coughing was frequently listed as well as 1 case of angioedema. 23.1% of patients assigned to Lisinopril+HCTZ complained of coughing compared to 4.6% in the CC+HCTZ group.

1 patient in the CC+HCTZ group had hypokalemia listed as a severe adverse experience, and hypokalemia was reported in 1.3% of those on the CC combination versus 0.9% of the Lisinopril combination group.

Elevation of uric acid from baseline was reported in both groups, but there were few changes in LFTs.

Comments:

Little can be said of efficacy from this study, and the safety findings were consistent with what is already known for these drugs.

3.8.5.4
Study AHK 0012
The Antihypertensive Effect of the Fixed Combination of Candesartan Cilexetil and Hydrochlorothiazide 16/12.5 mg Once Daily, in Comparison with the Fixed Combination of Losartan and Hydrochlorothiazide 50/12.5 mg.

This multicenter (34) 12 week comparison of the antihypertensive effect of CC+HCTZ and Losartan+HCTZ was conducted in France, Norway and Sweden. 300 patients with inadequately controlled blood pressure were randomized to once daily doses of 16/12.5 mg CC+HCTZ or 50/12.5 mg Losartan+HCTZ. The dose of the Losartan combination is noted in the U.S. approved labeling to be the usual starting dose which can be doubled if needed. The commercially available Losartan combination drug was ground and put in gelatin capsules, and a double-dummy technique was used to maintain blinding. The encapsulated Losartan combination was said to be bioequivalent to the marketed tablet.

151 patients were randomized to CC+HCTZ and 149 to Losartan+HCTZ. 1 Losartan patient had no efficacy data available so that the ITT population was 299. Of these there were 155 males and 144 females; 297 Caucasian; 64.2% less than 65 years of age. To be randomized the trough had to be SiDBP ≥90mmHg and ≤ 110mmHg with the mean SiSBP ≤200mmHg.

The primary endpoint was change in trough mean SiDBP from randomization to 12 weeks of treatment. The statistical analysis was a comparison of the change for the ITT and PP results of the two arms.

The results of the trough mean diastolic and systolic blood pressure evaluations through the course of the study were:

Table 39. Sitting DBP (mm Hg), 24 h post dose, by visit. ITT population.

Treatment	Statistics	Week -2	Baseline	Baseline (LVCF)	Week 2	Week 6	Week 12	Week 12 (LVCF)
losartan/HCTZ	N	148	148	148	144	134	132	148
	Missing	0	0	0	4	14	16	0
	Mean	99.8	98.5	98.5	91.7	89.3	90.1	90.9
	SD	5.5	5.4	5.4	8.1	7.1	7.1	8.3
	Min	90.3	90.0	90.0	72.7	71.0	70.3	70.3
	Median	99.7	97.7	97.7	91.8	89.2	90.0	90.3
	Max	115.7	110.3	110.3	122.3	108.3	108.0	129.0
cand.cil/HCTZ	N	151	151	151	147	142	139	151
	Missing	0	0	0	4	9	12	0
	Mean	99.9	98.4	98.4	89.9	88.3	88.1	88.4
	SD	5.2	5.8	5.8	9.0	8.1	9.0	9.3
	Min	90.3	89.7	89.7	66.3	70.0	65.0	65.0
	Median	99.3	93.0	98.0	89.7	87.5	87.3	88.0
	Max	109.7	110.3	110.3	109.3	113.0	113.0	120.3

Table 43. Sitting SBP (mm Hg), 24 h post dose, by visit. ITT population.

Treatment	Statistics	Week -2	Baseline	Baseline (LVCF)	Week 2	Week 6	Week 12	Week 12 (LVCF)
losartan/HCTZ	N	148	148	148	144	134	132	148
	Missing	0	0	0	4	14	16	0
	Mean	163.1	160.5	160.5	149.5	144.8	145.6	147.0
	SD	16.5	16.1	16.1	17.2	14.7	16.6	17.9
	Min	132.7	124.0	124.0	116.0	107.0	116.3	116.3
	Median	161.5	159.2	159.2	148.8	142.3	143.3	144.2
	Max	206.3	198.0	198.0	194.0	182.7	192.0	202.3
cand.c/HCTZ	N	151	151	151	147	142	139	151
	Missing	0	0	0	4	9	12	0
	Mean	161.7	159.5	159.5	144.8	141.2	138.5	140.3
	SD	15.1	15.4	15.4	17.6	15.6	17.5	19.2
	Min	131.0	123.0	123.0	96.0	104.3	97.7	97.7
	Median	160.7	159.7	159.7	144.7	141.0	137.0	137.7
	Max	197.3	193.7	193.7	196.0	192.0	190.0	220.0

For the ITT analysis of change in SiDBP comparing the two arms the CC arm was statistically superior to the Losartan arm (p=0.016). The significance was not maintained for the PP analysis.
There was no significant change in heart rate within or between arms.

300 patients were included in the safety analysis.
No deaths occurred.
20 patients discontinued the drug assigned for an adverse experience (CC/HCTZ-8; Losartan/HCTZ-12). The reasons for disconinuation in the CC/HCTZ group included dizziness, headache, TIA, sweating and tachycardia. No TIAs were reported in the Losartan/HCTZ group, although one patient discontinued for inadequate control of hypertension. Other reasons given for this group were similar to the CC/HCTZ group. It might be noted that the TIA reported in the CC/HCTZ patient occurred after 2 days on that assignment.
Of the other serious adverse experiences, one 59 year old female patient taking CC/HCTZ for 36 days had a TIA (BP-145/100), but continued on treatment with the addition of aspirin therapy.
Of the most frequent adverse experiences reported, dizziness/vertigo was complained of in 14 (9.3%) of CC/HCTZ patients and 8 (5.4%) of Losartan/HCTZ patients.
For the laboratory evaluations, uric acid increased in both groups, but to a somewhat greater extent in the CC/HCTZ patients. Hemoglobin decreased slightly in both groups, while BUN increased slightly but without change in creatinine. SGPT increased in 1 CC?HCTZ patient, and SGPT and bilirubin were elevated in 1 patient in each group, none resulting in change of therapy.

Comments:
The lack of placebo and component arms limit conclusions that could be drawn from this study. With HCTZ present in both arms, it is essentially a comparison of CC 16 mg to Losartan 8 mg given once daily. A study (AHM 0001) presented in the monotherapy NDA for CC compared CC 8 or 16 mg once daily to Losartan 50 mg and placebo once daily and found that CC 8 mg was comparable in antihypertensive effect to Losartan 50 mg, while CC 16 mg was somewhat more effective.
While both CC 16 mg and Losartan 50 mg are noted to be usual starting doses of the monotherapy drugs, such designations are somewhat arbitrarily determined since the drugs are to be titrated according to patient response. No superiority of one combination compared to the other can be supported based on this study.
From a safety perspective, both combinations were reasonably well tolerated with no unexpected adverse experiences reported.

3.8.5.5
Study EC 015
Efficacy and Safety of Candesartan Cilexetil alone or in Combination with Amlodipine and Hydrochlorothiazide in Patients with Moderate to Severe Essential Hypertension

This study was presented and more fully reviewed in the CC monotherapy NDA 20-838. It was a multicenter (18)study done in the UK and Israel had two phases. The first was an open, response dependent dose titration for 12 weeks which had been preceeded by a 2 week placebo run-in. The second was a double-blind, placebo-controlled 4 week withdrawal study at the end of which, change in SiDBP from Entrance into the withdrawal phase to end of that phase was compared for the two arms.
In the open response–dependent phase patients with SiDBP 100-114 mm Hg were started on CC 8 mg once daily. Patients were evaluated every 2 weeks, and if th SiDBP was ≥95 mm Hg they were given CC 16 mg; then CC 16 mg+amlodipine 5 mg; and finally if not controlled CC 16 mg+amlodipine 5 mg+HCTZ 25 mg.
181 patients were in the ITT analysis of this phase: CC 8 mg-36 patients (19.9%), CC 16 mg- 33 patients (18.2%), CC+amlodipine- 47 patients (26%), CC+amlodipine +HCTZ- 30 patients (16.6%), and 35 patients in a lack of efficacy group (S group-19.3%).
Of these 159 patients entered the double-blind withdrawal phase where they were randomized to continued treatment on last open assignment or placebo instead of CC+ other drugs assigned.
While the results in the withdrawal phase supported the long-term antihypertensive effectiveness of CC, it does not address the effectiveness of any combination treatment.
For safety, 185 patients were considered in the open dose-escalation phase, and 159 in the withdrawal phase.
One patient on CC 8 mg was stabbed to death while pursuing a burglar.
15 patients were withdrawn for an adverse experience or laboratory abnormality. The reasons included bradycardia, myalgia, diabetes worsened, rash, headache, coughing and increased CK.
One case of a serious adverse experience was a 46 year old male with an MI found on pyrophosphate scan during the withdrawal phase. He had been treated with CC 16 mg+amlodipine 5 mg for 3.5 months which assignment continued. At the time of the event, hypotension was noted (BP 117/78). It had been 184/114 prior to entrance. Follow-up blood pressure on continued therapy was 117/78.
Scattered laboratory abnormalities were found, but not clustered in any one treatment group.

Comments:
Whatever observational information was provided by this result, since no arm of any CC/HCTZ combination was included, the data are not useful to the CC/HCTZ combination NDA.

3.8.6

Long-term safety

Study AM 116

Evaluation of the Safety and Comparative Efficacy of Candesartan Cilexetil, Force-Titrated from 8 mg to 16 mg once daily or 8 mg BID, in the treatment of Patients with Hypertension: A multicenter, Randomized, Double-blind, placebo-controlled, Parallel-design Study with an Open-label Extension.

The controlled trial was reported and reviewed in the monotherapy NDA 20-839. Presented here is the open-label extension.

Patients who completed the 8 week double-blind study without an adverse experience were eligible for the 44 week open label safety study. 256 patients were eligible, and 187 participated. All were placed on CC 8 mg once daily. If the blood pressure response was inadequate at 4 weeks, they were titrated up to 16 mg once daily. After another 4 weeks if BP response was inadequate HCTZ 12.5 mg was added.

The number of patients in each of the three final treatment groups was:

CC 8 mg-57 (30.5%); CC 16 mg-111 (59.4%); CC/HCTZ-19 (10.2%).

While 187 entered the open label study, 137 completed that period(7-LTFU,20-lack of response, 14-AE, 5-withdrew consent, 4-sponsor/investigator decision).

Of the 19 in the CC/HCTZ group, 7 were included in the "ITT" analysis of change from open label entry to week 44.

The mean number of weeks on each final treatment was:

CC 8mg-39.1; CC 16mg-38.5; CC/HCTZ-27.4.

For safety all 187 were included in the analysis.

One patient died. This was a 65 year old, non-black on CC 16 mg who died of pneumonia.

One patient ingested 160 mg of CC along with other drugs in a suicide attempt who survived after gastric lavage. Hypotension was not noted in this case.

10 patients had serious adverse experiences in the open label portion of the study:

Patient	Treatment	Preferred Term	Days on Treatment
005/008	CC 8 mg	Inflicted Injury Arrhythmia	128 294
015/003	CC 8 mg	Appendicitis Peritonitis	325 325
002/008	CC 16 mg	Basal Cell Carcinoma	62
003/015	CC 16 mg	Suicide Attempt	111
004/009	CC 16 mg	Myocardial Infarction	142
004/010	CC 16 mg	Pneumonia (death)	57
005/013	CC 16 mg	Coronary Artery Disorder	162
005/032	CC 16 mg	Dyspnea Sweating Increased	87 87
021/005	CC 16 mg	Cerebrovascular Disorder	72
009/011	CC 16 mg/ HCTZ 12.5 mg	Sepsis Renal Calculus	58 58

14 withdrew or died:

Patient	Treatment	Adverse Event (Included Term)	Days on Treatment
014/012	CC 8 mg	BUN Increased	173
		Glycosuria	173
		Proteinuria	173
014/025	CC 8 mg	Carbohydrate Craving	10
		Polydipsia	10
		Polyuria	10
		Infection	17
		Abdominal Pain	18
		Headache	18
		Gustatory Sense Diminished	45
		Skin Dry	45
002/022	CC 16 mg	AV Block Second Degree (Mobitz Type II)*	92
003/015	CC 16 mg	Suicide Attempt	111
004/009	CC 16 mg	Arrhythmia	142
		Myocardial Infarction	142
004/010	CC 16 mg	Pneumonia (death)	57
005/004	CC 16 mg	Rash	94
005/013	CC 16 mg	Coronary Artery Disorder	162
005/032	CC 16 mg	Diaphoresis	87
		Dyspnea	87
		Numbness	87
		Skin Discoloration	87
		Hemorrhoids	89
		Herpes Zoster	89
		Proteinuria	92
		Urinary Retention	113
021/005	CC 16 mg	Stroke	72
002/030	CC 16 mg/HCTZ 12.5 mg	Gamma-GT Increased	145
		Headache	161
005/011	CC 16 mg/HCTZ 12.5 mg	SGPT Increased	147
005/030	CC 16 mg/HCTZ 12.5 mg	Azotemia	144

Headache and dizziness were frequently reported adverse experiences (15.5% and 8.0% respectively). Laboratory abnormalities included the abnormal LFTs cited above, although these did not resolve after discontination of the drug assignment. 5 patients had elevated CKs during treatment without a consistent pattern. Few elevated uric acids and glucose were reported.

Comments:
From a safety perspective for the majority of patients all treatments were well tolerated. There were few patients on the CC/HCTZ combination, and fewer who completed the 44 week open label study.

3.8.7

Clinical Pharmacology

Study EC 415

Assessment of the Safety of the First Dose of the Combination of 16 mg Candesartan Cilexetil and 25 mg Hydrochlorothiazide Given Orally in Patients with Mild to Moderate Essential Hypertension. Double-blind, Single Dose Administration, versus 25 mg Hydrochlorothiazide.

23 Caucasian, male or female adult patients with SiDBP ≥95 mmHg and ≤110 mmHg entered the single center French study. 17 were male, 6 female. Average age of the males was 50.3 years, and for the females 47.7 years. Mean SiDBP at entrance was 101.7 mmHg. The study period was 36 hours in-hospital.
A 2:1 randomization provided 16 patients in the combination group, and 7 for HCTZ monotherapy.
The primary objective of the study was to evaluate safety of the first dose of CC/HCTZ 16/25 mg.
Secondarily PK/PD was to be evaluated.
Safety was evaluated by clinical events and BP study (both by cuff and ABPM), including orthostatic changes.
PK samples were collected every half hour for the first 6 hours and then every 2 hours to T+24 hrs. The PK results were not included in this report.
PD activity was measured through evaluation of the renin angiotensin system, including measurements of renin, angiotensin I, II, and aldosterone.
A primary safety measure was orthostatic blood pressure, defined as the BP measured within 1 minute after abrupt standing following supine measurements. Those results for mean orthostatic diastolic blood pressure in mmHG for all treated patients (n=23) were presented as follows:

	Combination Therapy Group (N=16)	HCTZ Monotherapy Group (N=7)	P- Value[b]
T0 hour[c] (mmHg)			
n	16	7	0.943
Mean ± SD	97.56 ± 14.44	98.00 ± 9.98	
T+1 hour (mmHg)			
n	16	7	0.691
Mean ± SD	100.00 ± 9.45	97.71 ± 17.98	
T+2 hour (mmHg)			
n	16	7	0.207
Mean ± SD	87.69 ± 12.85	94.71 ± 9.16	
T+2.5 hours (mmHg)			
n	16	7	0.327
Mean ± SD	86.69 ± 10.66	91.43 ± 9.80	
T+3 hours (mmHg)			
n	16	7	0.856
Mean ± SD	87.31 ± 13.07	88.57 ± 19.37	
T+3.5 hours (mmHg)			
n	16	7	0.223
Mean ± SD	88.25 ± 10.41	94.57 ± 12.66	
T+4 hours (mmHg)			
n	16	7	0.321
Mean ± SD	86.13 ± 13.58	92.71 ± 15.97	
T+4.5 hours (mmHg)			
n	16	7	0.192
Mean ± SD	84.88 ± 14.95	93.71 ± 13.21	
T+5 hours (mmHg)			
n	16	7	0.049*
Mean ± SD	86.38 ± 11.70	97.71 ± 12.72	
T+5.5 hours (mmHg)			
n	16	7	0.999
Mean ± SD	88.56 ± 9.94	88.57 ± 22.78	
T+6 hours (mmHg)			
n	16	7	0.019*
Mean ± SD	82.56 ± 9.44	92.71 ± 6.97	
T+24 hours (mmHg)			
n	16	7	0.044*
Mean ± SD	82.13 ± 12.38	94.71 ± 14.42	
T+ 36 hours (mmHg)			
n	8	2	0.043*
Mean ± SD	89.00 ± 12.14	115.50 ± 9.19	

Combined therapy = Candesartan cilexetil 16 mg + HCTZ 25 mg.
Monotherapy = HCTZ 25 mg. N (n) = Number. SD = Standard deviation.
a Orthostatic BP measurements within 1 minute standing directly after supine measurement.
b P-values based on the analysis of variance (ANOVA).
c Predose (baseline)
* Indicates a statistically significant difference ($p \leq 0.05$).

The results for orthostatic systolic blood pressure were:

	Combination Therapy Group	HCTZ Monotherapy Group	P- Value[b]
T0 hour[c] (mmHg)			
n	16	7	
Mean ± SD	164.63 ± 19.03	158.86 ± 15.36	0.489
T+1 hour (mmHg)			
n	16	7	
Mean ± SD	167.56 ± 15.17	150.43 ± 19.11	0.031*
T+2 hour (mmHg)			
n	16	7	
Mean ± SD	155.38 ± 16.17	155.14 ± 11.14	0.973
T+2.5 hours (mmHg)			
n	16	7	
Mean ± SD	148.63 ± 14.75	153.29 ± 21.27	0.549
T+3 hours (mmHg)			
n	16	7	
Mean ± SD	147.13 ± 17.44	146.86 ± 20.64	0.975
T+3.5 hours (mmHg)			
n	16	7	
Mean ± SD	147.06 ± 20.45	149.14 ± 18.48	0.820
T+4 hours (mmHg)			
n	16	7	
Mean ± SD	143.38 ± 16.71	148.86 ± 18.85	0.493
T+4.5 hours (mmHg)			
n	16	7	
Mean ± SD	141.81 ± 20.35	147.71 ± 11.06	0.482
T+5 hours (mmHg)			
n	16	7	
Mean ± SD	146.19 ± 17.85	161.14 ± 23.95	0.110
T+5.5 hours (mmHg)			
n	16	7	
Mean ± SD	145.00 ± 14.80	150.43 ± 24.48	0.515
T+6 hours (mmHg)			
n	16	7	
Mean ± SD	140.31 ± 15.81	151.14 ± 19.07	0.170
T+24 hours (mmHg)			
n	16	7	
Mean ± SD	142.94 ± 19.57	155.71 ± 24.13	0.193
T+36 hours (mmHg)			
n	8	2	
Mean ± SD	155.75 ± 19.72	147.50 ± 0.12	0.587

Combined therapy = Candesartan cilexetil 16 mg + HCTZ 25 mg;
Monotherapy = HCTZ 25 mg; N (n) = Number; SD = Standard deviation.
a Orthostatic BP measurements taken within 1 minute standing directly after supine measurement.
b P-values based on the analysis of variance (ANOVA).
c Predose (baseline).
* Indicates a statistically significant difference (α= 0.05)

Ambulatory blood pressure monitoring results suggested a more pronounced antihypertensive effect with the single dose combination drug versus HCTZ 25 mg.

	Combination Therapy Group	HCTZ Monotherapy Group	P- Value[b]
Overall Ambulatory Blood Pressure Monitoring			
Systolic BP (mmHg)			
n	16	7	
Mean ± SD	133.50 ± 13.14	145.38 ± 15.57	0.073
Diastolic BP (mmHg)			
n	16	7	
Mean ± SD	75.46 ± 8.87	86.39 ± 8.93	0.013*
Daytime Blood Pressure Monitoring			
Systolic BP (mmHg)			
n	16	7	
Mean ± SD	139.77 ± 12.96	151.11 ± 15.91	0.085
Diastolic BP (mmHg)			
n	16	7	
Mean ± SD	79.58 ± 9.64	90.69 ± 9.35	0.018*
Night-time Blood Pressure Monitoring			
Systolic BP (mmHg)			
n	16	7	
Mean ± SD	125.66 ± 14.41	138.82 ± 15.54	0.062
Diastolic BP (mmHg)			
n	16	7	
Mean ± SD	70.31 ± 8.66	81.47 ± 9.02	0.011*

Combined therapy = Candesartan cilexetil 16 mg + HCTZ 25 mg;
Monotherapy = HCTZ 25 mg; BP = Blood pressure; N (n) = Number; SD = Standard deviation.
a Measurements were recorded every 30 minutes from 2 PM-10 PM and every 30 minutes from 10 PM to 8 AM.
b P-values based on the analysis of variance (ANOVA).
* Indicates a statistically significant difference (α= 0.05)

Heart rate did not differ significantly between the groups.

The measures of the renin angiotensin system showed increases in angiotensin I, II and renin with a decrease in aldosterone in the combination group with little change in the HCTZ group.

No deaths or serious adverse reactions were reported. The most common complaints in the combination group were weakness and headache. 7 (44%) combination group patients had complaints compared to 2 (29%) HCTZ treated patients.

4.0
Safety

4.1 General

The safety database consisted of 6426 patients from the 19 Phase II/III studies presented in section 3.0. Of these 2831 patients received at least 1 dose of CC+HCTZ. The frequencies of patients exposed to the various CC, HCTZ or placebo regimens was:

Treatment (mg)	Number of Patients	Percent of Total
CC 2 + HCTZ 12.5	45	0.7
CC 2 + HCTZ 25	38	0.6
CC 4 + HCTZ 6.25	364	5.7
CC 4 + HCTZ 12.5	153	2.4
CC 4 + HCTZ 25	71	1.1
CC 8 + HCTZ 12.5	1117	17.4
CC 8 + HCTZ 25	126	2.0
CC 12 + HCTZ 12.5	2	0.0
CC 12 + HCTZ 25	5	0.1
CC 16 + HCTZ 12.5	676	10.5
CC 16 + HCTZ 25	129	2.0
CC 32 + HCTZ 12.5	105	1.6
CC 2	43	0.7
CC 4	203	3.2
CC 8	413	6.4
CC 12	28	0.4
CC 16	646	10.1
CC 32	113	1.8
HCTZ 6.25	110	1.7
HCTZ 12.5	623	9.7
HCTZ 25	215	3.3
PBO	722	11.2
CC 16 + AML 5	27	0.4
CC 16 + AML 5 + HCTZ 25	21	0.3
AML 5 + HCTZ 25	18	0.3
ENA 10 + HCTZ 12.5	4	0.1
ENA 10 + HCTZ 25	77	1.2
LIS 10 + HCTZ 12.5	117	1.8
LOS 50 + HCTZ 12.5	149	2.3
ENA 10	35	0.5
AML 5	31	0.5
Total	6426	100.0

53.4% were male, 46.6% female. 11.3%were black, 88.7% non-black. Mean age was 55.5 years, and the duration of hypertension ranged from <year 7.5% to>10 years 27.1 years.

Duration of exposure for the CC, HCTZ, CC+HCTZ, and placebo treatments were:

Treatment (mg)	Numbers of Patients								Mean (days)	Med (days)
	≥ 1 day	≥ 1 wk	≥ 2 wk	≥ 4 wk	≥ 8 wk	≥12 wk	≥24 wk	≥48 wk		
CC+HCTZ	2831	2782	2751	2689	2364	1488	789	502	133	84
CC	1446	1426	1406	1350	1222	688	204	7	100	83
HCTZ	948	925	914	877	757	405	2	0	68	82
PBO	722	704	696	650	558	327	16	0	71	82

The distribution of duration of exposure for the CC+HCTZ 8/12.5, 16/12.5 and 32/12.5mg combination regimens were:

DOSE	≥1 day	≥1 week	≥2 weeks	≥4 weeks	≥8 weeks	≥12 weeks	≥24 weeks	≥48 weeks	Med.(d)
8/12.5	1117	1101	1091	1071	1001	809	496	262	167
16/12.5	676	673	665	646	502	274	24	11	73
32/12.5	105	104	104	103	84	34	0	0	67

The majority of combination drug safety data comes from a regimen not proposed for marketing.

4.2 Deaths

6 deaths occurred in the trials; 3(0.1%) in those assigned to CC+HCTZ, and 3(0.1%) on CC monotherapy.
3 deaths were non-cardiovascular: one patient dying of carcinoma of the pancreas, another of pneumonia, and the third of a gunshot wound.
The 3 cardiovascular deaths were summarized in the following chart:

Trial Center Patient	Age Gender Race	Randomized Treatment	Verbatim Term	Days on Therapy
AM1170L 022 254	42 Male Caucasian	CC 8 mg + HCTZ 12.5 mg	Ventricular tachycardia Hypertensive heart disease Pneumonia* Hemoptysis*	150 Prior to study start 138 138
EC406 42 051	53 Male Caucasian	CC 4 mg + HCTZ 6.25 mg	Fatal MI	3
EC403 001 0551	78 Female Caucasian	CC 8 mg	Sudden death (Suspected pulmonary embolism)	20

* Nonfatal serious adverse event

4.3 Non-Fatal Serious AEs

Non-fatal serious adverse reactions in 2 or more patients in the placebo controlled trials were the following:

Adverse Event Preferred Term	Treatment Group[a]									
	CC+ HCTZ (n=2831)		CC (n=1446)		HCTZ (n=948)		PBO (n=722)		CC+ AML (n=27)	
	n	%	n	%	n	%	n	%	n	%
Inflicted Injury[b]	8	0.3	3	0.2	1	0.1	2	0.3	0	0.0
Chest Pain	3	0.1	0	0.0	2	0.2	0	0.0	0	0.0
Procedures, NOS[c]	3	0.1	1	0.1	1	0.1	0	0.0	0	0.0
Back Pain	2	0.1	0	0.0	0	0.0	0	0.0	0	0.0
Renal Calculus	4	0.1	0	0.0	0	0.0	0	0.0	0	0.0
Dizziness	3	0.1	0	0.0	2	0.2	0	0.0	1	3.7
Arthrosis	3	0.1	0	0.0	0	0.0	0	0.0	0	0.0
Hernia Inguinal	2	0.1	1	0.1	0	0.0	0	0.0	0	0.0
Cerebrovascular Disorder	3	0.1	1	0.1	3	0.3	0	0.0	0	0.0
Transient Ischemic Attack	2	0.1	0	0.0	0	0.0	0	0.0	0	0.0
Myocardial Infarction	3	0.1	2	0.1	0	0.0	0	0.0	1	3.7
Aneurysm	2	0.1	0	0.0	0	0.0	0	0.0	0	0.0
Hypertension	0	0.0	2	0.1	2	0.2	1	0.1	0	0.0
Fibrillation Atrial	2	0.1	1	0.1	0	0.0	0	0.0	0	0.0
Tachycardia Supraventricular	2	0.1	0	0.0	0	0.0	0	0.0	0	0.0
Pancreas Neoplasm Malignant	2	0.1	0	0.0	0	0.0	0	0.0	0	0.0
Epistaxis	2	0.1	1	0.1	0	0.0	0	0.0	0	0.0
Pneumonia	2	0.1	0	0.0	1	0.1	0	0.0	0	0.0
Coronary Artery Disorder	0	0.0	2	0.1	0	0.0	0	0.0	0	0.0

[a] There were no nonfatal SAEs reported in the CC+AML+HCTZ treatment group.

[b] Injuries or accidents that were reported on the AE CRF and were reported by the investigator as serious.

[c] Procedures for elective surgery that were recorded on the AE CRF and were reported by the investigator as serious.

The frequencies by drug and dose were:

	Patients Treated	Patients With a Non-fatal Serious Adverse Event	
		N	%
Study Treatment			
CC2 +HCTZ12.5	45	0	0.0
CC2 +HCTZ25	38	0	0.0
CC4 +HCTZ6.25	91	1	1.1
CC4 +HCTZ12.5	56	4	7.1
CC4 +HCTZ25	65	0	0.0
CC8 +HCTZ12.5	357	4	1.1
CC8 +HCTZ25	124	3	2.4
CC16+HCTZ12.5	206	5	2.4
CC16+HCTZ25	43	1	2.3
CC32+HCTZ12.5	64	0	0.0
CC2	43	0	0.0
CC4	150	4	2.5
CC8	268	1	0.4
CC16	280	8	2.9
CC32	73	0	0.0
HCTZ6.25	92	1	1.1
HCTZ12.5	377	2	0.5
HCTZ25	206	5	2.4
PBO	592	14	2.4
EMA10+HCTZ25	72	2	2.8
Total	3250	55	1.7

4.4 Withdrawals Due To an AE

In all trials withdrawals due to an adverse event in ≥0.2% of patients were:

Adverse Event Preferred Term	Treatment Group											
	CC+ HCTZ (n=2831)		CC (n=1446)		HCTZ (n=948)		PBO (n=722)		CC+ AML (n=37)		CC+ AML+ HCTZ (n=21)	
	n	%	n	%	n	%	n	%	n	%	n	%
Dizziness	17	0.6	2	0.1	4	0.4	0	0.0	0	0.0	1	4.8
Headache	12	0.4	7	0.5	5	0.5	0	0.0	0	0.0	0	0.0
Fatigue	6	0.2	0	0.0	1	0.1	1	0.1	0	0.0	0	0.0
Hepatic Function Abnormal	6	0.2	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0
Hypertension	5	0.2	5	0.3	5	0.5	3	0.4	0	0.0	0	0.0
Abdominal Pain	5	0.2	7	0.5	0	0.0	0	0.0	0	0.0	0	0.0
Hypokalemia	5	0.2	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0
Upper Respiratory Tract Infection	5	0.2	2	0.1	0	0.0	0	0.0	0	0.0	0	0.0

The frequencies by drug and dose were:

Study Treatment	Patients Treated	Patients Withdrawing due to an Adverse Event	
		N	%
CC2 +HCTZ12.5	45	1	2.2
CC2 +HCTZ25	38	1	2.6
CC4 +HCTZ6.25	91	1	1.1
CC4 +HCTZ12.5	56	3	5.4
CC4 +HCTZ25	65	1	1.5
CC8 +HCTZ12.5	357	13	3.6
CC8 +HCTZ25	124	5	4.0
CC16+HCTZ12.5	206	6	2.9
CC16+HCTZ25	43	1	2.3
CC32+HCTZ12.5	64	3	4.7
CC2	43	4	9.3
CC4	158	2	1.3
CC8	268	7	2.6
CC16	280	7	2.5
CC32	73	1	1.4
HCTZ6.25	92	2	2.7
HCTZ12.5	377	8	2.1
HCTZ25	206	7	3.4
PBO	592	10	1.7
EMA10+HCTZ25	72	2	2.8
Total	3250	85	2.6

4.5 Non-Serious AEs

From the placebo controlled trials, adverse events occurring in more than 1% of CC+HCTZ patients and more frequent than placebo patients were displayed in the following chart:

Body System Preferred Term	Treatment Group			
	CC+ HCTZ (n=1089)	CC (n=822)	HCTZ (n=675)	PBO (n=592)
	%	%	%	%
Respiratory System Disorders				
Upper Respiratory Tract Infection	3.6	4.5	6.2	3.0
Rhinitis	1.1	1.2	1.2	0.3
Body as a Whole				
Back Pain	3.3	3.6	4.3	2.4
Influenza-Like Symptoms	2.5	2.2	3.4	1.9
Inflicted Injury	2.0	2.2	2.5	1.4
Chest Pain	1.0	0.7	1.3	0.7
Central Peripheral Nervous System Disorders				
Dizziness	2.9	2.9	2.8	1.2
Gastrointestinal System Disorders				
Nausea	1.5	1.0	0.9	0.7
Abdominal Pain	1.1	1.3	0.9	0.8
Urinary System Disorders				
Urinary Tract Infection	1.4	1.1	1.2	0.5
Musculo-Skeletal System Disorders				
Arthralgia	1.3	1.0	1.2	0.8
Heart Rhythm Disorders				
Tachycardia	1.2	0.9	0.9	0.5
Cardiovascular Disorders				
ECG Abnormal	1.0	1.2	0.3	0.7
Metabolic Nutritional Disorders				
Hyperglycemia	1.0	0.6	0.6	0.7
Hyperuricemia	1.0	0.5	0.7	0.3

While a number of these adverse experiences are not likely to have been related to the drug assigned, some such as vertigo might be drug and/or disease related.

Using **vertigo and dizziness** as examples for further analysis, for the first day of dosing the incidence of dizziness and vertigo in all studies involving the combination drug was:

	CC+HCTZ N=2831	CC N=1446	HCTZ N=948	Placebo N=722	CC+AML N=27	CC+AML+ HCTZ N=21
dizziness	9 (0.3%)	1 (0.1%)	2 (0.2%)	1 (0.1%)	0	0
vertigo	2 (0.1%)	1 (0.1%)	0	0	0	0

For males and females, similar rates of dizziness were found in those taking the combination drug. For those ≥65 years of age compared to those under 65 and for blacks versus non-blacks, a similar rate of dizziness was noted, but

compared to a 3.5% rate in the elderly and 3.3% in blacks taking the combination, there was a 0% rate in those on placebo.

4.6 EKG Analyses

Cardiovascular adverse experiences such as MIs, AF, SVT, abnormal ECG were numerically more frequent for the combination treatment than placebo. The sponsor conducted a comprehensive review of the EKG data available. As part of that review analyses of QT changes were performed. Studies AM 153 and AM 124 contained comprehensive EKG data that could be analyzed for heart rate, QTc and other changes. AM 153 was an 8 week placebo-controlled double-blind study which evaluated the antihypertensive effect of CC 32 mg+HCTZ 12.5 mg and the individual components. AM 124 was a 12 week study of similar design that evaluated CC 8 mg+HCTZ 12.5 mg and the individual components as well as CC 16 mg.

The following charts present the results from the sponsor's analysis based on the computerized readings of the EKGs:

	CC 8 mg + HCTZ 12.5 mg					CC 32 mg + HCTZ 12.5 mg					CC 8 mg				
	Baseline		Chg from BL			Baseline		Chg from BL			Baseline		Chg from BL		
ECG variable	Mean	SD	n	Mean	SD	Mean	SD	n	Mean	SD	Mean	SD	n	Mean	SD
Heart Rate (bpm)	68.4	10.4	150	0.4	8.9	72.7	12.3	63	2.0	10.6	70.9	12.0	132	0.0	9.2
PR Interval (msec)	161.4	23.5	150	-0.5	20.0	158.8	23.9	63	-2.7	24.0	161.7	26.7	132	-1.2	21.2
QRS Interval (msec)	83.2	14.5	150	2.4	12.1	83.1	11.3	63	3.2	11.7	82.7	16.2	132	2.8	12.2
QT Interval (msec)	387.8	35.5	150	5.6	32.1	374.4	52.8	63	1.3	37.6	387.5	35.4	132	0.5	29.2
QTc Interval (msec)	410.9	31.3	150	7.5	33.2	408.4	53.1	63	7.2	40.3	418.0	34.2	132	0.9	25.9

	CC 16 mg					CC 32 mg					HCTZ 12.5 mg				
	Baseline		Chg from BL			Baseline		Chg from BL			Baseline		Chg from BL		
ECG variable	Mean	SD	n	Mean	SD	Mean	SD	n	Mean	SD	Mean	SD	n	Mean	SD
Heart Rate (bpm)	69.9	12.2	74	1.4	11.0	70.8	11.6	71	1.9	10.8	70.6	11.6	134	0.2	8.3
PR Interval (msec)	160.8	23.5	74	0.7	17.8	161.6	32.2	71	-0.7	17.6	158.7	23.7	134	1.2	18.0
QRS Interval (msec)	83.0	18.1	74	2.7	14.4	85.1	17.4	71	1.0	12.5	86.3	14.6	134	1.9	9.9
QT Interval (msec)	390.2	39.8	74	1.7	27.9	388.7	32.6	71	-7.0	27.5	387.4	36.7	134	-1.4	33.0
QTc Interval (msec)	417.6	37.2	74	4.7	30.2	418.7	25.8	71	-2.5	24.3	416.8	33.4	134	-1.0	34.4

	HCTZ 25					PBO				
	Baseline		Chg from BL			Baseline		Chg from BL		
ECG variable	Mean	SD	n	Mean	SD	Mean	SD	n	Mean	SD
Heart Rate (bpm)	72.1	9.8	78	-1.5	9.8	70.5	11.0	133	0.8	9.5
PR Interval (msec)	159.3	26.5	78	2.0	20.2	162.0	28.5	133	-2.2	17.1
QRS Interval (msec)	85.2	16.2	78	-0.2	8.4	85.1	15.3	133	-0.2	10.1
QT Interval (msec)	385.2	29.4	78	4.6	27.1	385.8	42.0	133	2.0	33.9
QTc Interval (msec)	418.8	24.0	78	-0.0	25.0	414.4	36.8	133	4.3	30.4

Although when the combination drug mean change from baseline QTc results are compared with placebo there are numerical differences, given the large standard deviations these are not significant differences as per analysis by Dr. Mahjoob:

Variable	Candesartan/HCTZ Treatment (C/H) Sample Size, Mean and SD of Reduction from Baseline				Placebo Treatment (P) Sample Size, Mean and SD of Reduction from Baseline			Difference (C/H – P)	T-Test Value	P-Value
	C/H Combination	N	Mean	SD	N	Mean	SD			
QT	C 00/H 25.0	78	4.6	27.1	133	2.0	33.9	2.6	0.57755	0.56419
	C 00/H 12.5	134	-1.4	33.0	133	2.0	33.9	-3.4	-0.83040	0.40706
	C 08/H 00.0	132	0.5	29.2	133	2.0	33.9	-1.5	-0.38580	0.69996
	C 16/H 00.0	74	1.7	27.9	133	2.0	33.9	-0.3	-0.06486	0.94835
	C 32/H 00.0	71	-7.0	27.5	133	2.0	33.9	-9.0	-1.92384	0.05578
	C 08/H 12.5	150	5.6	32.1	133	2.0	33.9	3.6	0.91711	0.35987
	C 32/H 12.5	63	1.3	37.6	133	2.0	33.9	-0.7	-0.13030	0.89646
QTC	C 00/H 25.0	78	0.0	25.0	133	4.3	30.4	-4.3	-1.05683	0.29181
	C 00/H 12.5	134	-1.0	34.4	133	4.3	30.4	-5.3	-1.3336	0.18348
	C 08/H 00.0	132	0.9	25.9	133	4.3	30.4	-3.4	-0.97966	0.32815
	C 16/H 00.0	74	4.7	30.4	133	4.3	30.4	0.4	0.09073	0.92780
	C 32/H 00.0	71	-2.5	24.3	133	4.3	30.4	-6.8	-1.62705	0.10529
	C 08/H 12.5	150	7.5	33.2	133	4.3	30.4	3.2	0.84184	0.40059
	C 32/H 12.5	63	7.2	40.3	133	4.3	30.4	2.9	0.55966	0.57636

The QRS mean change for the combination drugs compared to a negative change for placebo may influence the results of the QT and QTc analyses by providing a good deal of the numerical change seen.

The sponsor had a cardiologist manually and in a blinded fashion reread the EKGs from study AM 153. Considering that a QTc prolongation > 460 msec was clinically significant, 11 patients with that finding were identified. In 8 EKGs were available for rereading. In 3 they were not. The findings in those 11 patients were summarized as follows:

Site/ Patient Number	Treatment Group (mg)	QTc Interval			Potassium Values (mEq/L)		Other Potential Confounding Factors
		Baseline	Final	ΔQTc	Baseline	Final	
004/004	Placebo	459	465	6	4.3	4.3	Ventricular bigeminy
020/002	HCTZ 12.5	465	468	3	3.9	3.5	None
020/003	CC 32 + HCTZ 12.5	458	469	11	4.6	3.9	Nonspecific ST-T-U wave changes
019/004	Placebo	453	466	13	4.3	4.3	Nonspecific ST-T-U wave changes; prominent U wave changes
002/005	CC 32	464	478	14	4.5	4.0	None
032/004	CC 32	447	461	14	4.3	4.1	Nonspecific ST-T-U wave changes
030/003	HCTZ 12.5	461	505	44	4.3	3.4	Heart rate change from 77 to 56 affecting QTc calculation
025/013	CC 32	442	460	18	3.9	4.1	None
Tracings were not available for the remaining three patients							
008/017	CC 32 + HCTZ 12.5	474	509	35	4.4	4.0	None evident in CRF
012/011	PBO	473	499	26	4.9	4.5	None evident in CRF
032/011	HCTZ 12.5	453	460	7	4.9	4.5	None evident in CRF

None of these patients had adverse experiences noted in the CRFs.

In all trials where EKG data were available the % of patients with a prolonged QTc was:

12.5%-CC+HCTZ, 6.9%-CC monotherapy, 10.1%-HCTZ monotherapy and 6.7%-Placebo.

The incidence rates for those experiencing cardiac rate and/or rhythm adverse events was provided:

Adverse Event	Treatment Group*								
	CC+ HCTZ (n=2831)	PBO (n=722)	CC (n=1446)	HCTZ (n=948)	AML (n=31)	CC+ AML (n=27)	ENA+ HCTZ (n=81)	LIS+ HCTZ (n=117)	LOS+ HCTZ (n=149)
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Heart Rate Rhythm Disorders									
Tachycardia	26 (0.92)	3 (0.42)	7 (0.48)	6 (0.63)	0 (0.00)	0 (0.00)	1 (1.23)	0 (0.00)	3 (2.01)
Palpitation	23 (0.81)	1 (0.14)	9 (0.62)	3 (0.32)	0 (0.00)	0 (0.00)	1 (1.23)	4 (3.42)	2 (1.34)
Extrasystoles	21 (0.74)	5 (0.69)	6 (0.41)	1 (0.11)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Bradycardia	13 (0.46)	2 (0.28)	3 (0.21)	3 (0.32)	0 (0.00)	1 (3.70)	0 (0.00)	0 (0.00)	0 (0.00)
Arrhythmia	10 (0.35)	2 (0.28)	5 (0.35)	2 (0.21)	0 (0.00)	1 (3.70)	2 (2.47)	3 (2.56)	0 (0.00)
AV Block	10 (0.35)	0 (0.00)	4 (0.28)	1 (0.11)	1 (3.23)	0 (0.00)	1 (1.23)	0 (0.00)	0 (0.00)
Fibrillation Atrial	6 (0.21)	0 (0.00)	3 (0.21)	0 (0.00)	0 (0.00)	1 (3.70)	0 (0.00)	0 (0.00)	2 (1.34)
Bundle Branch Block	4 (0.14)	1 (0.14)	2 (0.14)	2 (0.21)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
QT Prolonged	3 (0.11)	0 (0.00)	4 (0.28)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Supraventricular Tachycardia	3 (0.11)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.67)

* There were no ECG-related treatment-emergent AEs in the AML+HCTZ group, CC+AML+HCTZ group, and the enalapril group.

While unexpected, the QTc findings do not establish that the combination poses an increased risk for torsade or VT/VF. Nor do the findings rule it out.

4.7 Chemistry Results

Since chemistry results in the placebo-controlled trials for BUN, Alkaline Phosphatase, LDH, Uric acid, Sodium, Potassium and Chloride for the combination drug were significantly different from the placebo, these results were provided in the following chart:

	CC+HCTZ					Placebo					CC					HCTZ				
		Baseline		Chg from BL			Baseline		Chg from BL			Baseline		Chg from BL			Baseline		Chg from BL	
Serum Chemistry Test	n	Mean	SD	Mean	SD	n	Mean	SD	Mean	SD	n	Mean	SD	Mean	SD	n	Mean	SD	Mean	SD
Urea (mg/dL)	973	23.3	11.7	2.3	6.6	466	19.3	10.1	-0.2	4.9	689	21.6	11.5	0.7	6.2	554	20.5	11.3	1.3	5.5
Alkaline Phosphatase (IU/L)	972	93.8	37.7	-4.5	17.1	466	84.0	37.0	1.7	17.3	689	92.7	39.0	-1.9	15.4	553	90.0	36.4	-0.9	23.8
LDH (IU/L)	895	167.6	32.3	-3.8	34.1	402	169.2	34.4	-0.5	30.0	608	169.1	30.7	-1.6	34.2	474	169.2	32.3	-0.7	31.7
Uric Acid (mg/dL)*	975	8.3	31.3	-0.2	4.1	466	11.1	43.4	-0.2	4.0	690	8.9	34.4	0.3	4.1	554	9.9	39.0	0.6	3.5
Sodium (mEq/L)	836	140.4	2.7	-0.4	3.1	436	140.6	2.7	0.3	3.2	608	140.0	2.5	0.3	2.9	513	140.0	2.5	0.3	3.1
Potassium (mEq/L)	333	4.3	0.4	-0.1	0.4	434	4.3	0.4	0.0	0.4	607	4.3	0.4	0.0	0.4	509	4.3	0.4	-0.2	0.4
Chloride ((mEq/L)*	973	104.6	2.9	-1.3	3.4	466	104.9	2.9	-0.3	3.6	689	104.9	2.8	-0.3	3.2	557	105.0	2.7	-1.5	3.3

* Candesartan cilexetil monotherapy and HCTZ monotherapy were not statistically significantly different from CC+HCTZ combination therapy.
* HCTZ monotherapy was not statistically significantly different from CC+HCTZ combination therapy.

Statistically significant differences of the combination drug compared to placebo for hematology tests were:

	CC+HCTZ					Placebo				
		Baseline		Chg from BL			Baseline		Chg from BL	
Hematology Test	n	Mean	SD	Mean	SD	n	Mean	SD	Mean	SD
Hemoglobin	965	15.7	13.1	-0.2	1.1	458	16.8	17.7	-0.0	1.3
Hematocrit	962	41.8	4.9	-0.4	2.7	456	41.8	6.0	0.6	2.9
Neutrophils	504	58.6	8.6	-1.0	7.5	342	57.1	8.6	1.2	7.1
Lymphocytes	963	32.2	7.8	0.7	7.1	459	33.3	8.1	-0.9	6.6

These small mean numerical differences, although termed statistically significant, were not of clinical significance in terms of altering therapy or determined to be an adverse experience but for the following

Percentages in the various drug groups:

Adverse Event (preferred term)	CC+HCTZ (n=2831)		PBO (n=722)		CC (n=1446)		HCTZ (n=948)	
	n	%	n	%	n	%	n	%
Hyperuricemia	38	1.34	2	0.28	7	0.48	5	0.53
Hyperglycemia	30	1.06	4	0.55	10	0.69	5	0.53
Hypokalemia	18	0.64	1	0.14	2	0.14	10	1.05
Hepatic Function Abnormal	27	0.95	2	0.28	6	0.41	3	0.32
SGPT Increased	19	0.67	0	0.00	9	0.62	3	0.32
Hematuria	17	0.60	2	0.28	5	0.35	2	0.21
Creatine Kinase Increased	14	0.49	5	0.69	12	0.83	7	0.74
Hypercholesterolemia	10	0.35	3	0.42	9	0.62	3	0.32
Hypertriglyceridemia	9	0.32	4	0.55	16	1.11	4	0.42

As expected there was hypokalemia noted most frequently in the HCTZ group, and hepatic function abnormalities in the combination drug group. Hyperuricemia was noted most frequently in the combination drug group. Although there was some mean decrease of hemoglobin and hematocrit compared to placebo, anemia was not noted.

4.8 Comments

5 pages redacted from this section of the approval package consisted of draft labeling

6.0
Conclusions and Recommendation

The sponsor has provided substantial evidence that CC/HCTZ in fixed combination doses of 4/6.25 mg to 32/12.5 mg is safe and effective for the treatment of hypertension. Pooled analyses of the 5 placebo-controlled factorially designed studies supports the conclusion that there is a dose response for the combination drug that continues beyond the 16/12.5 mg dose.

The sponsor requests approval for two strengths: 16/12.5 and 32/12.5 mg. The safety database, while small for the 32/12.5 mg combination, does not indicate dose related toxicities beyond those expected from the monotherapies. Since many of the patients who might be put on a CC/HCTZ combination would already have failed to CC 32 mg, the higher strength is needed.

Approval is recommended with labeling revisions as indicated in Section 5.0 and others suggested by the other reviewers.

/S/ /S/

Stephen Fredd, M.D. 3/15/00 Kooros Mahjoob, Ph.D. 3/15/2000

Concur:

James Hung, Ph.D. /S/ 3/22/00

George Chi, Ph.D. /S/

Raymond J. Lipicky, M.D.

CC: Dr. Fredd
Dr. Mahjoob
Mr. Fromm