Clinical Study Report CAESAR	
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An open-label, randomised, 2-arm parallel group, multicentre, 8-week, phase IV study to assess the antihypertensive efficacy and safety of the Candesartan Cilexetil 16mg and Hydrochlorothiazide 12.5mg combination therapy in comparison with Candesartan Cilexetil 16mg monotherapy in hypertensive adults

CAESAR (CAndesartan Effect in Second stage Arterial hyperTension)

Study dates: First patient enrolled: 19 February 2008
Last patient completed: 03 March 2009

Phase of development: IV

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents

SYNOPSIS

An Open-label, Randomised, 2-Arm parallel group, Multicentre, 8-week, Phase IV study to Assess the Antihypertensive Efficacy and Safety of the Candesartan Cilexetil 16 mg and Hydrochlorothiazide 12.5 mg Combination Therapy in Comparison with Candesartan Cilexetil 16 mg Monotherapy in Hypertensive Adults (CAESAR)

Study Centres

Subjects were recruited from a total of 12 centres in Korea. A total of 253 subjects were enrolled, of whom 233 were randomised.

Publications

None at the time of writing this report

Study dates

First patient enrolled	19 February 2008
Last patient completed	03 March 2009

Phase of development

IV

Objectives

Primary:

The primary objective of this study was to compare the changes in mean sitting DBP from baseline after 4 weeks of therapy with either candesartan cilexetil/HCT combination therapy or candesartan cilexetil monotherapy regimen

Secondary:

The secondary objectives of this study were to compare the effects of Cand/HCT Combination and Cand Monotherapy after 4 or 8 weeks of treatment on:

1. To compare the changes in mean sitting SBP from baseline after 4 weeks of therapy with either candesartan cilexetil/HCT combination therapy or candesartan cilexetil monotherapy regimen

2. To compare the proportion of patients achieving goal of mean sitting DBP (<90 mmHg, but <80 mmHg for DM & Chronic kidney disease) and SBP (<140 mmHg, but <130 mmHg for DM & Chronic kidney disease) after 4 weeks of therapy with either candesartan cilexetil/HCT combination therapy or candesartan cilexetil monotherapy
3. To compare the proportion of patients achieving goal of mean sitting DBP (<90 mmHg, but <80 mmHg for DM & Chronic kidney disease) and SBP (<140 mmHg, but <130 mmHg for DM & Chronic kidney disease) after 8 weeks of therapy with either candesartan cilexetil/HCT combination therapy or a candesartan cilexetil monotherapy regimen
4. To compare the changes in mean SBP and DBP from baseline after 8 weeks of therapy with either candesartan cilexetil/HCT combination therapy or candesartan cilexetil monotherapy regimen
5. To compare the changes in hs-CRP level from baseline after 8 weeks of therapy with either candesartan cilexetil/HCT combination therapy or candesartan cilexetil monotherapy regimen
6. To compare the safety of study treatments with regard to adverse events with either candesartan cilexetil/HCT combination therapy or candesartan cilexetil monotherapy regimen
7. To compare the compliance level (rate of compliance by pill count) of study treatments with either candesartan cilexetil/HCT combination therapy or candesartan cilexetil monotherapy regimen

Study design

This was a multi-center, open-label, randomized, 2-arm parallel group, phase IV study with 2 weeks washout period followed by 8 weeks treatment period. Following washout, patients were randomized in a 1:1 fashion to initiate therapy with either candesartan cilexetil 16 mg/HCT 12.5 mg or candesartan cilexetil 16 mg. Following 4 weeks of therapy, antihypertensive efficacy was assessed, and then in each arm, candesartan cilexetil 16 mg was added. After another 4 weeks of therapy, antihypertensive efficacy was compared between the two arms.

Target subject population and sample size

Subjects were male or female, aged from 18 to 70 years, and untreated or taking a maximum of 2 classes of antihypertensive medications at the time of screening.

Subjects with mean sitting DBP ≥ 100 mmHg and/or mean sitting SBP ≥ 160 mmHg at the time of randomisation.

The size of the study was calculated to detect a 2.7 mmHg difference between treatment groups with standard deviation at 7, 107 patients per group were to be included to have 80% power to reach p-value of 0.05.

Investigational product and comparator: dosage and mode of administration

During the first 4-week treatment period, all patients received either:

1. One candesartan cilexetil 16 mg/HCT 12.5 mg tablet once daily or

2. One candesartan cilexetil 16 mg tablet once daily

For the following 4-week treatment period

3. Patients who received treatment 1 in the previous treatment period received one candesartan cilexetil 16 mg/HCT 12.5 mg tablet and one candesartan cilexetil 16 mg tablet once daily or

4. Patients who received treatment 2 in the previous treatment period received two candesartan cilexetil 16 mg tablets daily

Duration of treatment

8 weeks of randomised treatment.

Outcome variables

Primary outcome variable:

Changes in mean sitting DBP from baseline after 4 weeks of therapy

Secondary outcome variables:

1. Changes in mean sitting SBP from baseline after 4 weeks of therapy
2. Proportion of patients achieving goal of mean trough sitting DBP (<90 mmHg, but <80 mmHg for DM & Chronic kidney disease) and SBP (<140 mmHg, but <130 mmHg for DM & Chronic kidney disease) after 4 weeks of therapy
3. Proportion of patients achieving goal of mean trough sitting DBP (<90 mmHg, but <80 mmHg for DM & Chronic kidney disease) and SBP (<140 mmHg, but <130 mmHg for DM & Chronic kidney disease) after 8 weeks of therapy
4. Changes in mean sitting DBP and SBP from baseline after 8 weeks of therapy
5. Changes in hs-CRP level from baseline after 8 weeks of therapy
6. Occurrence of Adverse Events (AE) and discontinuation of study medication due to AE's from baseline (randomisation) to the end of the study (8 weeks)
7. Compliance levels at 4 weeks and 8 weeks of therapy

Statistical methods

Efficacy data were evaluated based on an intention-to-treat (ITT) population. The ITT population consisted of subjects who had a baseline reading and at least one post-randomisation blood pressure measurement and had taken at least one dose of study treatment. The per protocol (PP) population as secondary analysis set consisted of all subjects in the ITT population who did not have a major protocol violation or deviation that would likely to affect the efficacy outcomes.

The safety population consisted of all subjects who took at least 1 dose of study medication.

The mean change between the combinations and the monotherapy was compared in an ANCOVA model with treatment as a factor and the BP at randomization as a covariate. The proportion of patients with controlled BP was analyzed using Fisher's exact test.

The occurrence of patients with AE and patients who discontinued investigational product due to AE from randomization to the end of the study (8 weeks) were calculated as the proportion of patients at randomization who experience an AE or discontinue the investigational treatment before 8 weeks, respectively.

The proportion of patients with at least one AE and the proportion of patients who discontinued the investigational product were both analyzed using Fisher's exact test.

Study population

The subject population and disposition are presented in Table S1. A total of 253 subjects were enrolled in the study at 12 centres, of whom 233 were randomised in approximately 1:1 ratio to treatment with Cand/HCT Combination (n=117) or Cand Monotherapy (n=116). Among the 20 subjects not randomised, the most common reason for not proceeding was a failure to meet the eligibility criteria. A total of 198 subjects completed this study and 35 were dropped out during the treatment period.

Two-hundred-twenty-seven (227) subjects took at least one dose of study medication. The ITT set comprised 224 subjects and 211 subjects were included in PP set.

Table S1 Subject population and disposition

		Cand/HCT Combination	Cand Monotherapy	Total
All enrolled subjects				253
Randomised		117	116	233
	Completed	97	101	198
	Discontinued	20	15	35
Safety set (treated subjects)		113	114	227
Full analysis set (ITT)		111	113	224
Per-protocol (PP)		102	109	211

The demographic and background characteristics of study subjects are summarised in Table S2. There were more (65.7%) men than women, and all subjects were Oriental (Korean). The mean age 49.4years, and ages ranged from 20 to 76. The mean weight and height at baseline was 68.9kg and 165.4cm.

Table S2 Demographic and baseline characteristics (Randomised set)

		Cand/HCT Combination n=117	Cand Monotherapy n=116	Total n=233
Sex	Male	75(64.1%)	78(67.2%)	153(65.7%)
(n and % of subjects)	Femle	42(35.9%)	38(32.8%)	80(34.3%)
Age(years)	Mean (SD)	51.0(10.2)	47.8(10.7)	49.4(10.6)
	Range	26 to 76	20 to 70	20 to 76
Origin	Oriental	117(100.0%)	116(100.0%)	233(100.0%)
(n and % of subjects)	Other	0	0	0
Smoking	Non-smoker	65(55.6%)	63(54.3%)	128(54.9%)
(n and % of subjects)	Ex-smoker	26(22.2%)	31(26.7%)	57(24.5%)
	Occasional smoker	3(2.6%)	3(2.6%)	6(2.6%)
	Habital smoker	23(19.7%)	19(16.4%)	42(18.0%)
Weight(kg)	Mean (SD)	69.6(12.2)	68.2(11.9)	68.9(12.1)
	Range	42 to 101	42 to 104	42 to 104
Height(cm)	Mean (SD)	165.7(8.1)	165.2(8.0)	165.4(8.0)
	Range	147 to 184	145 to 182	145 to 184
BMI(kg/m^2)	Mean (SD)	25.2(3.3)	24.8(2.9)	25.0(3.1)
	Range	17.8 to 34.6	18.4 to 34.9	17.8 to 34.9

Efficacy results

Cand/HCT Combination was significantly more effective than Cand Monotherapy in reducing DBP and SBP after 4 weeks (-17.8 vs -14.1 for DBP; -28.2 vs -21.0 for SBP, $p<0.01$ in each case). Similarly, Cand/HCT Combination was significantly more effective than Cand Monotherapy in reducing DBP and SBP after 8 weeks (-21.1 vs -16.1 for DBP; -31.6 vs -24.9 for SBP, $p<0.01$ in each case).

A significantly greater proportion of subjects receiving Cand/HCT Combination reached their DBP and SBP goal at week 8 than did so receiving Cand Monotherapy (68.5% vs 52.2%, $p=0.0143$), whereas there was no statistically difference in DBP and SBP goal at week 4 ($p=0.0608$). But, the proportion of patients achieving goal of DBP and SBP after 4 weeks in Cand/HCT Combination (54.1%) is higher than that in Cand Monotherapy (40.7%).

Table S3 Summary of major efficacy results (ITT set)

		Cand/HCT Combination N=111	Cand Monotherapy N=113
Change in DBP after 4 weeks	LS mean change	-17.8	-14.1
		p=0.0032 (ANCOVA)	
Change in SBP after 4 weeks	LS mean change	-28.2	-21.0
		p=0.0004 (ANCOVA)	
Proporton of patients achieving goal of DBP and SBP after 4 weeks	n(%)	60(54.1)	46(40.7)
		p=0.0608 (Fisher's exact test)	
Proporton of patients achieving goal of DBP and SBP after 8 weeks	n(%)	76(68.5)	59(52.2)
		p=0.0143 (Fisher's exact test)	
Change in DBP after 8 weeks	LS mean change	-21.1	-16.1
		p=0.0002 (ANCOVA)	
Change in SBP after 8 weeks	LS mean change	-31.6	-24.9
		p=0.0018 (ANCOVA)	

Safety results

Both study treatments were generally well tolerated, and the incidence of adverse events (AEs), and possibly related AEs, serious AEs, and AEs that led to their permanently discontinuing study treatment were low (Table S4). Only 3 subjects (1.3%) in the Cand/HCT Combination or Cand Monotherapy treatment reported a non-fatal treatment-emergent SAE during the course of the study. These SAEs were assessed by investigator as having been unrelated to study medication.

Table S4 Summary of adverse events during treatment period (Safety set)

	Cand/HCT Combination n=113	**Cand Monotherapy n=114**
Number of subjets	n(%)	n(%)
Any adverse event	24(21.2%)	20(17.5%)
Possibly related adverse event	8(7.1%)	4(3.5%)
Serious adverse event	1(0.9%)	2(1.8%)
Discontinuation of study treatment due to AEs	3(2.7%)	4(3.5%)
Number of adverse events		
Any adverse event	29	27
Possibly related adverse event	10	5
Serious adverse event	1	2
Discontinuation of study treatment due to AEs	4	4

All p-values >0.05 from Fisher's exact test.