Drug Product		**SYNOPSIS**	
Drug Substance	Candesartan/HCT		
Study Code	D2456C00002		
Edition Number	1		
Date	28 April 2008		

A Double-blind, Randomised, 4-arm Parallel Group, Multicentre, 8-week, Phase III Study to Assess the Antihypertensive Efficacy and Safety of the Combination of Candesartan Cilexetil 32 mg and Hydrochlorothiazide 25 mg in Comparison with Candesartan Cilexetil 32 mg, Hydrochlorothiazide 25 mg and Placebo in Hypertensive Adults

Study centre(s)

The study was performed in 10 countries at 128 centres.

Publications

None at the time of the finalization of this report.

Study dates		**Phase of development**
First patient enrolled	20 January 2007	Therapeutic confirmatory (III)
Last patient completed	09 January 2008	

Objectives

In patients with sitting Diastolic Blood Pressure (DBP) 90-114 mmHg after a 4-week single-blind placebo run-in period:

Primary Objectives (confirmatory analyses)

1. To compare sitting DBP lowering effect of candesartan cilexetil (candesartan)/hydrochlorothiazide (HCT) 32/25 mg with that of candesartan 32 mg.

2. To compare sitting Systolic Blood Pressure (SBP) lowering effect of candesartan /HCT 32/25 mg with that of candesartan 32 mg.

3. To compare sitting DBP lowering effect of candesartan/HCT 32/25 mg with that of HCT 25 mg.

4. To compare sitting SBP lowering effect of candesartan/HCT 32/25 mg with that of HCT 25 mg.

Secondary and Tertiary Objectives

- To compare candesartan/HCT 32/25 mg and each of its components to placebo with regard to change in sitting and standing blood pressures.

- To compare candesartan/HCT 32/25 mg to its components and to placebo with regard to hypertension control rate at the end of the study (patients with controlled sitting SBP and sitting DBP are defined as having sitting SBP <140 mmHg and sitting DBP <90 mmHg at the end of the study).

- To describe safety and tolerability of the study treatments with regard to adverse events including those that lead to treatment discontinuation as well as with regard to pulse rate, laboratory, electrocardiographic and physical examination findings.

- To compare treatment with candesartan/HCT 32/25 mg to each of its components with regard to change from baseline to week 8 in standing DBP and standing SBP.

- To compare candesartan/HCT 32/25 mg to its components and to placebo with regard to sitting DBP control rate at the end of the study (patients with controlled sitting DBP are defined as having a sitting DBP <90 mmHg at the end of the study).

- To compare candesartan/HCT 32/25 mg to its components and to placebo with regard to sitting DBP responder rate (decrease in sitting DBP ≥10 mmHg from baseline to the end of the study or a sitting DBP <90 mmHg at the end of the study).

Study design

This was a multicentre, multinational, randomised, double-blind, placebo controlled, 4-arm parallel group, efficacy and safety study with a 4-week, single-blind run-in period on placebo treatment and an 8-week, double-blind period of randomised treatment.

Following a screening evaluation, patients underwent a 4-week, single-blind treatment with placebo, after which eligible patients were randomly allocated in a 5:5:5:1 ratio to receive 8 weeks of double-blind treatment either with candesartan/HCT 32/25 mg or candesartan 32 mg or HCT 25 mg or placebo, respectively. At the end of the study patients underwent a physical and laboratory safety evaluation.

Blinding of the study medication has been done by using a double-dummy packaging technique.

Target patient population and sample size

The target population was hypertensive men and women aged 20-80 years of age with inadequate blood pressure control (defined as sitting DBP 90-114 mmHg) while untreated or treated with a maximum of two antihypertensive drugs (substances). Patients with inadequate blood pressure control after the 4-week single-blind run-in period with placebo were randomly allocated to one of four double-blind treatment groups. 2207 patients were enrolled in the study, 1772 patients received run in medication and 1524 patients were subsequently randomised to double-blind treatment.

Study treatment and comparator(s): dosage, mode of administration and batch numbers

During the 4-week run-in period, all patients received 5 tablets of placebo corresponding to 2 candesartan/HCT 16/12.5 mg tablets, 1 candesartan 32 mg tablet and 2 HCT 12.5 mg tablets respectively.

During the 8-week double-blind treatment period, patients received either:

1. candesartan/HCT 32/25 mg (given as 2 candesartan/HCT 16/12.5 mg tablets, plus 1 placebo tablet corresponding to candesartan 32 mg tablet and 2 placebo tablets corresponding to HCT 12.5 mg tablets for double dummy blinding purposes)

   or

2. candesartan 32 mg (given as 1 candesartan 32 mg tablet plus 2 placebo tablets corresponding to candesartan/HCT 16/12.5 mg tablets and 2 placebo tablets corresponding to HCT 12.5 mg tablets for double dummy blinding purposes)

   or

3. HCT 25 mg (given as 2 HCT 12.5 mg tablets plus 2 placebo tablets corresponding to candesartan/HCT 16/12.5 mg tablets and 1 placebo tablet corresponding to a candesartan 32 mg tablet for double dummy blinding purpose)

   or

4. placebo (given as 2 placebo tablets corresponding to candesartan/HCT 16/12.5 mg tablets, 1 placebo tablet corresponding to a candesartan 32 mg tablet and 2 placebo tablets corresponding to HCT 12.5 mg tablets for double dummy blinding purpose)

The daily dose (5 tablets) was to be taken in the morning. On the day of a clinic visit, the tablets were not to be taken until all blood pressure measurements were performed.

Duration of treatment

4 weeks of run-in treatment (placebo), 8 weeks of randomised treatment.

Criteria for evaluation (main variables)

Primary outcome variables:

- Change in sitting DBP (24 hours after dose) from baseline (randomisation) to the end of the study (8 weeks)

- Change in sitting SBP (24 hours after dose) from baseline (randomisation) to the end of the study (8 weeks)

Secondary and tertiary outcome variables:

- Change in sitting DBP and sitting SBP (24 hours after dose) from baseline (randomisation) to the end of the study (8 weeks)

- The proportion of patients with controlled sitting SBP and sitting DBP in each treatment group at the end of the study (8 weeks)

- Occurrence of Adverse Events (AEs) and discontinuations of study medication due to AEs from baseline (randomisation) to the end of the study (8 weeks). Changes in laboratory variables, physical status, vital signs and electrocardiogram (ECG) from baseline (randomisation) to the end of the study (8 weeks)

- Change in standing DBP and standing SBP (24 hours after dose) from baseline (randomisation) to the end of the study (8 weeks)

- The proportion of patients with controlled sitting DBP in each treatment group at the end of the study (8 weeks)

- The proportion of responders in each treatment group at the end of the study (8 weeks)

Statistical methods

Efficacy variables were analysed according to the intention-to-treat (ITT) principle. The ITT population is defined as all randomised patients who have received at least one dose of randomised study treatment, with a baseline blood pressure measurement and with at least one post-randomisation blood pressure measurement. The analyses were done according to the randomised treatment. The safety population was defined as all patients who received at least one dose of the randomised treatment, and for whom any post randomisation data were available. The analyses of safety were done according to actual treatment given.

The family-wise type I error for testing the treatment effects related to the primary objectives was controlled at the 5% level by using a step-wise closed test procedure.

Nominal p-values are reported without any adjustments for multiple comparisons. Similarly, the confidence intervals were calculated at the nominal confidence level of 95% without any adjustments. Where appropriate, the Last Value Carried Forward (LVCF) principle is used, to impute missing end-of-study values.

Changes in sitting and standing DBP and SBP were analysed using an ANCOVA (analysis of covariance) model with treatment group as a factor and baseline blood pressure as a covariate. Pairwise treatment group differences were determined from Student's t-distribution using least squares estimates from the model. The statistical significance of the pairwise comparisons for the primary objectives was determined according to a step-wise closed test procedure.

For dichotomous efficacy variables (controlled sitting DBP and sitting SBP, controlled sitting DBP and treatment response), Fisher's exact test was used for pairwise treatment group comparisons.

Patient population

Table S1 Patient disposition and characteristics

		Candesartan/ HCT 32/25 mg	Candesartan 32 mg	HCT 25 mg	Placebo
Patient disposition					
N randomised		492	465	470	97
N who completed randomised treatment		464	431	441	89
N who completed study		478	457	461	90
Patient characteristics					
N (ITT population)		**486**	**457**	**464**	**92**
Sex N (%)	Male	201 (41.4)	202 (44.2)	191 (41.2)	41 (44.6)
	Female	285 (58.6)	255 (55.8)	273 (58.8)	51 (55.4)
Age, (years)	Mean (SD)	52.7 (10.2)	51.7 (10.5)	50.9 (10.2)	52.7 (11.3)
	Range	22-77	21-79	21-78	28-76
Race, N (%)	Caucasian	427 (87.9)	397 (86.9)	398 (85.8)	81 (88.0)
	Black	44 (9.1)	47 (10.3)	48 (10.3)	8 (8.7)
	Oriental	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
	Other	15 (3.1)	13 (2.8)	17 (3.7)	3 (3.3)

		Candesartan/ HCT 32/25 mg	Candesartan 32 mg	HCT 25 mg	Placebo
Sitting DBP at randomisation (mmHg)[a]	Mean (Range)	97.5 (90-113)	97.4 (80-115)	97.8 (90-114)	97.8 (90-112)
Sitting SBP at randomisation (mmHg)	Mean (Range)	154.0 (124-198)	152.9 (120-185)	153.2 (122-214)	153.8 (127-175)
BMI at randomisation (kg/m^2)	Mean (Range)	30.8 (19-53)	30.7 (17-58)	30.8 (19-51)	31.1 (21-47)
Medical history of diabetes, N (%)	No	471 (96.9)	442 (96.7)	443 (95.5)	89 (96.7)
	Yes	15 (3.1)	15 (3.3)	21 (4.5)	3 (3.3)

a Table 11 provides information about numbers of patients with DBP out of range at randomisation in each treatment group.

Efficacy results

The 4 primary objectives were tested using a confirmatory step-wise closed test procedure. Results showed a statistically significantly greater reduction of mean sitting DBP and mean sitting SBP with candesartan/HCT 32/25 mg as compared with candesartan 32 mg monotherapy (LS mean -4.6 mmHg; $p<0.001$ and LS mean -8.3 mmHg; $p<0.001$, respectively). Similarly, there was a statistically significantly greater reduction of mean sitting DBP and mean sitting SBP in candesartan/HCT 32/25 mg treated patients when compared to the HCT 25 mg monotherapy group (LS mean: -6.3 mmHg; $p<0.001$ and LS mean: -9.8 mmHg; $p<0.001$, respectively).

Further, comparisons of each of the active treatment groups with placebo showed greater reductions both of mean sitting DBP and of mean sitting SBP. Comparisons of mean sitting DBP and mean sitting SBP showed greater reduction with candesartan/HCT 32/25 mg compared with placebo (LS mean -10.6 mmHg; $p<0.001$ and LS mean -17.7 mmHg; $p<0.001$, respectively), comparisons of mean sitting DBP and mean sitting SBP showed greater reduction with candesartan 32 mg compared with placebo (LS mean -6.0 mmHg; $p<0.001$ and LS mean -9.4 mmHg; $p<0.001$, respectively) and comparisons of mean sitting DBP and mean sitting SBP showed greater reduction with HCT 25 mg compared with placebo (LS mean -4.4 mmHg; $p<0.001$ and LS mean -7.9 mmHg; $p<0.001$, respectively).

The results for standing blood pressure were consistent with the results for sitting blood pressure.

In addition, a higher proportion of patients achieved controlled sitting DBP and sitting SBP in the candesartan/HCT 32/25 mg group (62.6%) as compared with candesartan 32 mg (43.3%) and HCT 25 mg (36.2%). The difference in proportions between candesartan/HCT 32/25 mg and candesartan 32 mg was 19.2% ($p<0.001$), between candesartan/HCT 32/25 mg and HCT 25 mg 26.3% ($p<0.001$) and between candesartan/HCT 32/25 mg and placebo 53.9% ($p<0.001$).

Safety results

The overall frequency of AEs and SAEs was low and similar in all treatment groups. Headache was the most common AE in both monotherapy treatment groups and in the placebo group. Hypotension and vertigo were infrequent but more common in the combination treatment group. Dizziness was the most common AE in the candesartan/HCT 32/25 mg group but caused permanent treatment discontinuation in only 1 patient.

Adverse events leading to discontinuation of study treatment were infrequent with similar distribution between the treatment groups.

Two patients died during the course of the study. One patient died during the run-in period (due to septic shock) and one patient died during the randomised period (reported as sudden death). The investigators considered the deaths unrelated to study treatment.

An increase of mean serum uric acid was observed during the study in the HCT 25 mg and the candesartan/HCT 32/25 mg treatment groups. Otherwise there were no apparent changes in the clinical laboratory variables.