Drug product:	Candesartan/HCT	**SYNOPSIS**	
Drug substance(s):	Candesartan/HCT		
Edition No.:	1		
Study code:	D2456C00001		
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A Double Blind, Randomised, 3-arm Parallel Group, Multicentre, 8-week, Phase III Study to Assess the Antihypertensive Efficacy and Safety of the Combination of Candesartan Cilexetil/Hydrochlorothiazide 32/12.5 mg and 32/25 mg in Comparison with Candesartan Cilexetil 32 mg Alone in Patients with Inadequate Blood Pressure Control on Monotherapy with Candesartan Cilexetil 32 mg

Study centres

The study was performed in 11 countries at 165 centres.

Publications

None at the time of the finalisation of this report.

Study dates		**Phase of development**
First patient enrolled	11 September 2006	Therapeutic confirmatory (III)
Last patient completed	17 August 2007	

Objectives

In patients with inadequate blood pressure control at randomisation (sitting diastolic blood pressure (DBP) 90-114 mmHg) on monotherapy with candesartan cilexetil (candesartan) 32 mg:

Primary Objectives

- To compare sitting diastolic blood pressure (DBP) lowering effect of candesartan/HCT 32/25 mg with that of candesartan 32 mg
- To compare sitting systolic blood pressure (SBP) lowering effect of candesartan/HCT 32/25 mg with that of candesartan 32 mg
- To compare sitting DBP lowering effect of candesartan/HCT 32/12.5 mg with that of candesartan 32 mg
- To compare sitting SBP lowering effect of candesartan/HCT 32/12.5 mg with that of candesartan 32 mg

Secondary and Tertiary Objectives

- To compare treatment with candesartan/HCT 32/25 mg to treatment with candesartan/HCT 32/12.5 mg with regard to change in sitting DBP and sitting SBP.
- To compare each of the treatments candesartan/HCT 32/25 mg and candesartan/HCT 32/12.5 mg to monotherapy with candesartan 32 mg and to each other with regard to hypertension control rate at the end of the study (patients with controlled sitting DBP and sitting SBP are defined as having SBP<140 mmHg and 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 each of the treatments candesartan/HCT 32/25 mg and candesartan/HCT 32/12.5 mg to monotherapy with candesartan 32 mg and to each other with regard to change in standing DBP and standing SBP.
- To compare each of the treatments candesartan/HCT 32/25 mg and candesartan/HCT 32/12.5 mg to monotherapy with candesartan 32 mg and to each other with regard to sitting DBP control rate at the end of the study (patients with controlled sitting DBP are defined as having sitting DBP<90 mmHg at the end of the study).
- To compare each of the treatments candesartan/HCT 32/25 mg and candesartan/HCT 32/12.5 mg to monotherapy with candesartan 32 mg and to each other with regard to sitting DBP responder rate (responders are defined as patients having a decrease in sitting DBP≥10 mmHg from baseline to end of study or a sitting DBP<90 mmHg at the end of the study).

Study design

This was a multicentre, multinational, double blind, randomised, 3-arm, parallel group, efficacy and safety study with an 8-week, single-blind, run-in period and a randomised double-blind treatment period of 8 weeks.

Placebo tablets were given during both the run-in and the randomised treatment period in order to maintain blinding (double-dummy technique).

Target patient population and sample size

The target population was hypertensive men and women aged 20-80 years with inadequate blood pressure control (defined as sitting DBP 90-114 mmHg) after an 8-week run-in period with candesartan 32 mg monotherapy. A total of 3953 patients were enrolled, 3521 patients received run-in treatment and 1975 patients were subsequently randomised to double-blind treatment.

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

During the run-in period, all patients received candesartan 16 mg and placebo corresponding to candesartan 32 mg for 2 weeks, then candesartan 32 mg and placebo corresponding to candesartan 16 mg for 6 weeks.

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

1) candesartan/HCT 32/25 mg once daily (given as 2 tablets of 16/12.5 mg, plus 2 placebo tables for double dummy blinding purposes)

or

2) candesartan/HCT 32/12.5 mg once daily (plus 3 placebo tablets for double dummy blinding purposes)

or

3) candesartan 32 mg once daily (plus 3 placebo tablets for double dummy blinding purposes).

All placebo tablets were identical in appearance, smell and taste to the corresponding active tablets. All tablets were taken in the morning with fluid.

Duration of treatment

8 weeks of run-in treatment, 8 weeks of randomised treatment.

Criteria for evaluation (main variables)

Primary outcome variable:

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

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

Secondary outcome variables:

- Change (reduction) in sitting DBP (24 hours after dose) from baseline of the randomised period to the end of the study (8 weeks)
- Change (reduction) in sitting SBP (24 hours after dose) from baseline of the randomised period) 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
- Occurrence of Adverse Events and discontinuations of study medication due to Adverse Events from baseline of the randomised period to the end of the study (8 weeks). Changes in laboratory variables, physical status, vital signs and electrocardiogram (ECG) from baseline of the randomised period to the end of the study (8 weeks)

Tertiary outcome variables:

- Change (reduction) in standing DBP (24 hours after dose) from baseline of the randomised period to the end of the study (8 weeks)
- Change (reduction) in standing SBP (24 hours after dose) from baseline of the randomised period 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
- The proportion of responders in each treatment group at the end of the study

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 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 study 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 and the first two secondary objectives was controlled at the 5% level by using a confirmatory stepwise 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 a Student's t-distribution using least squares estimates from the model. The statistical significance of the pairwise comparisons for the primary objectives and the first 2 secondary 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 hypertension 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/ HCT 32/12.5 mg	Candesartan 32 mg
Patient disposition				
N randomised (N planned)		665 (600)	656 (600)	654 (600)
N who completed randomised treatment		621	598	581
N who completed study		651	638	629
Patient characteristics				
N (ITT population)		**659**	**648**	**638**
Sex, N (%)	Male	387 (58.7)	381 (58.8)	363 (56.9)
	Female	272 (41.3)	267 (41.2)	275 (43.1)
Age, (years)	Mean (SD)	54.6 (10.0)	54.6 (9.9)	54.9 (10.2)
	Range	21 to 79	26 to 80	22 to 77
Race, N (%)	Caucasian	654 (99.2)	643 (99.2)	627 (98.3)
	Black	4 (0.6)	2 (0.3)	4 (0.6)
	Oriental	0 (0.0)	2 (0.3)	4 (0.6)
	Other	1 (0.2)	1 (0.2)	3 (0.5)
Sitting DBP at randomisation (mmHg)[a]	Mean (Range)	97.0 (81-118)	96.6 (89-114)	96.8 (85-115)

		Candesartan/ HCT 32/25 mg	Candesartan/ HCT 32/12.5 mg	Candesartan 32 mg
Sitting SBP at randomisation (mmHg)	Mean (Range)	153.1 (122-196)	152.6 (119-191)	154.1(119-207)
BMI at randomisation (kg/m^2)	Mean (Range)	30.0 (18.4-54.6)	30.1 (18.0-53.6)	30.3 (18.9-51.6)
Medical history of diabetes, N (%)	No	626 (95.0)	608 (93.8)	599 (93.9)
	Yes	33 (5.0)	40 (6.2)	39 (6.1)

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 and the 2 first secondary objectives were tested using a confirmatory stepwise closed test procedure. Results showed a statistically significantly greater reduction of mean sitting DBP and mean sitting SBP with candesartan/HCT 32/25 mg compared with candesartan 32 mg monotherapy (LS mean -4.3 mmHg; p<0.001 and LS mean -9.4 mmHg; p<0.001, respectively). Similarly, there was a statistically significantly greater reduction of sitting DBP (LS mean: -3.2 mmHg) and sitting SBP (LS mean: -6.9 mmHg) in candesartan/HCT 32/12.5 mg treated patients when compared to the candesartan 32 mg monotherapy group (p<0.001 and p<0.001, respectively). Comparisons of sitting DBP and sitting SBP showed statistically significantly greater reductions with candesartan/HCT 32/25 mg compared with candesartan/HCT 32/12.5 mg (LS mean -1.2 mmHg; p=0.01 and LS mean -2.5 mmHg; p<0.001, respectively).

The proportion of patients with controlled sitting DBP and sitting SBP was higher in both the candesartan/HCT 32/25 mg group and the candesartan/HCT 32/12.5 mg group when compared with candesartan 32 mg monotherapy (differences in proportions: 23.8% and 18.3% respectively; p<0.001 for both comparisons). The candesartan/HCT 32/25 mg group had a higher control rate as compared to the candesartan/HCT 32/12.5 mg group (difference in proportions: 5.5%; p=0.052).

The results for standing blood pressure were consistent with the results of the confirmatory analysis.

Overall, in patients with hypertension not controlled on candesartan 32 mg monotherapy, addition of HCT led to improved efficacy. Both candesartan/HCT 32/25 mg and candesartan/HCT 32/12.5 mg showed greater blood pressure lowering effects than continued treatment with candesartan 32 mg monotherapy and candesartan/HCT 32/25 mg showed a greater effect than candesartan/HCT 32/12.5 mg.

Safety results

There were slightly more patients with AEs in the candesartan/HCT 32/25 mg group as compared with the candesartan/HCT 32/12.5 mg or the candesartan 32 mg monotherapy

group. SAEs and adverse events leading to discontinuation of a patient from treatment were infrequent and similar in all treatment groups. Two patients died during the run-in period (the reasons were: sudden death and road traffic accident) . The investigators considered the deaths as unrelated to the run-in treatment. No deaths occurred during the randomised period.

The overall pattern of AEs was similar to findings from previous hypertension studies with combinations of candesartan and HCT. The most common AEs in the candesartan/HCT combination treatment arms were dyslipidaemia and dizziness. The frequency of dyslipidaemia was a baseline observation with no signs of deterioration during the study period. Headache was the most common AE in the candesartan 32 mg monotherapy arm.

No clinically relevant changes in mean levels of laboratory variables or vital signs were observed during the study period. For uric acid, a pattern suggestive of a dose-response relationship with HCT emerged. Also for mean creatinine and mean calculated GFR minor numerical changes were observed.