Drug Substance	Candesartan cilexetil/ Hydrochlorothiazide	**SYNOPSIS**	(For national authority use only)
Study Code	D2456C00004		
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A single dose, 4-period, cross-over, bioequivalence and drug-drug interaction study in healthy subjects to evaluate the fixed combination tablet of candesartan cilexetil/hydrochlorothiazide 32/25 mg

Study centre

This study was conducted in the United Kingdom (one centre).

Study dates		**Phase of development**
First subject enrolled	13 June 2007	Clinical pharmacology (I)
Last subject completed	05 September 2007	

Objectives

The primary objective of the study was to assess the bioequivalence of one candesartan cilexetil/hydrochlorothiazide (HCT) 32/25 mg tablet and two candesartan cilexetil/HCT 16/12.5 mg tablets after single dose administration.

The secondary objective of the study was to assess the pharmacokinetics of candesartan cilexetil 32 mg and HCT 25 mg after single dose administration of the fixed combination tablet and after each monocomponent (ie one candesartan cilexetil tablet 32 mg tablet and two HCT 12.5 mg tablets).

Study design

This was a Phase-I, single-centre, open-label, randomised, group-sequential, four-way cross over study to determine bioequivalence of a candesartan cilexetil/HCT 32/25 mg tablet and two candesartan cilexetil/HCT 16/12.5 mg tablets and to evaluate drug-drug interaction between candesartan cilexetil 32 mg and HCT 25 mg after single dose administration of the fixed combination tablet compared with administration of each component as monotreatment tablets in healthy male and female subjects, all aged between 18 and 80 years inclusive.

Target subject population and sample size

According to the group-sequential design, 53 healthy male and female subjects, aged between 18 and 59 years, with female subjects comprising at least 20% per treatment group, were enrolled in the first step, to ensure completion by at least 48 subjects. A total of 48 subjects completed the study. If bioequivalence could not have been declared according to the group-sequential analysis criteria, further healthy male and female subjects were to be enrolled in the second step of the study up to a maximum of 80 subjects in total to ensure evaluable datasets of 72 subjects after completion of both steps of the study. Bioequivalence could be concluded at the interim analysis if the 95% confidence intervals for C_{max} and AUC were within 0.8 to 1.25. With a total sample of 72 subjects (18 in each sequence in the four-way crossover design) and with an interim analysis after 48 subjects, the power was to be 88% to conclude bioequivalence for C_{max}. The power had been calculated assuming a true C_{max} ratio of 1.15 and a residual standard deviation of 0.17, which had been obtained in a previous study. Under these assumptions about C_{max}, the study was to be stopped concluding bioequivalence with a probability of 0.65 at the interim analysis.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Drug:	Candesartan cilexetil/Hydrochlorothiazide
Formulation:	tablets
Mode of administration:	oral
Strength:	32 mg/25 mg
Single dose:	32 mg/25 mg
Batch number:	H 1865-01-01-02

Drug:	Candesartan cilexetil/Hydrochlorothiazide
Formulation:	tablets
Mode of administration:	oral
Strength:	16 mg/12.5 mg
Single dose:	2 x 16 mg/12.5 mg
Batch number:	H 1332-02-01-06

Drug:	Candesartan cilexetil
Formulation:	tablets
Mode of administration:	oral
Strength:	32 mg

Single dose:	32 mg
Batch number:	H 1308-01-01-07
Drug:	Hydrochlorothiazide
Formulation:	tablets
Mode of administration:	oral
Strength:	12.5 mg
Single dose:	2 x 12.5 mg
Batch number:	H 0425-07-01-12

Duration of treatment

Four treatment periods with one day of IP administration each and with a washout period between successive treatments (investigational product (IP) administrations) between six and 14 days.

Variables

- **Pharmacokinetic**

  Primary variables:
  For candesartan and HCT (combined treatment):
  AUC, AUC_{0-t}, C_{max}.

  Secondary variables:
  For candesartan and HCT (fixed combined treatment and monotreatment):
  AUC, AUC_{0-t}, C_{max}, t_{max}, $t_{1/2}$.

- **Safety**

  Adverse events, laboratory variables and vital signs.

Statistical methods

The log-transformed variables AUC and C_{max} for both candesartan and HCT were analysed using a mixed model analysis of variance (ANOVA) with fixed effects for sequence, period and treatment, and a random effect for subject within sequence.

ANOVA was also employed to test for possible candesartan/HCT interactions.

Descriptive statistics for all subjects together were given for all pharmacokinetic, demographic and vital sign variables who received the study drug in the first step of this group sequential study. Adverse events and laboratory variables were presented descriptively.

Subject population

A total of 53 healthy male and female subjects from a single-centre were enrolled and received the study drug in the first step of this sequential study. The first subject signed informed consent for the study on 13 June 2007, and the last subject of the first step of the

study completed the study on 05 September 2007. All subjects fulfilled the inclusion/exclusion criteria. A total of five subjects discontinued from the study due to personal reasons (n=3) and need for concomitant medication (n=2). Altogether, a sufficient number of subjects was recruited and randomised to assess the study objectives. Demographic characteristics of the subjects in the present study were suitable for the purposes of assessing the study variables and the details are summarised in Table S1.

Table S1 Subject population and disposition

Demographic or baseline characteristic			**Total (N = 53)**
Demographic characteristics (SD)			
Sex [n]	Male	(% of subjects)	33 (62.3%)
	Female	(% of subjects)	20 (37.7%)
Age [years]	Mean	(SD)	28.9 (9.04)
	Range		18 – 59
Race [n]	Caucasian	(% of subjects)	31 (58.5%)
	Black	(% of subjects)	11 (20.8%)
	Other	(% of subjects)	11 (20.8%)
Baseline characteristics			
Height [cm]	Mean	(SD)	173.3 (9.92)
	Range		148 – 189
Weight [kg]	Mean	(SD)	71.0 (10.55)
	Range		51 – 92
BMI [kg/m^2]	Mean	(SD)	23.6 (2.06)
	Range		20 – 27
Disposition of all dosed subjects			
Candesartan cilexetil/HCT 32/25 mg			49
Candesartan cilexetil/HCT 2x 16/12.5 mg			52
Candesartan cilexetil 32 mg			52
HCT 2x 12.5 mg			50
Completed study			48
Discontinued study			5

Note: Given is the number of subjects who took at least 1 dose of study treatment and had at least 1 data point after dosing.

Summary of pharmacokinetic results

The pharmacokinetic parameters are summarized for bioequivalence of one candesartan cilexetil/HCT 32/25 mg tablet and two candesartan cilexetil/HCT 16/12.5 mg tablets along with the 95 % confidence intervals in Table S2.

Table S2 Intra-individual bioequivalence comparison between one candesartan cilexetil/HCT 32/25 mg tablet (test) and two 16/12.5 mg tablets (reference)

Parameter	Unit	Geometric mean ratio (test : reference) [%]	95% CI [%]
Candesartan			
AUC	ng·h/mL	107.71	101.40; 114.42
AUC_{0-t}	ng·h/mL	107.87	101.71; 114.39
C_{max}	ng/mL	106.15	96.85; 116.34
HCT			
AUC	ng·h/mL	101.97	98.54; 105.52
AUC_{0-t}	ng·h/mL	102.00	98.49; 105.64
C_{max}	ng/mL	106.06	99.23; 113.37

The 95% CIs of geometric mean ratios of all candesartan and HCT PK parameters were completely contained within the pre-defined bioequivalence limits of 0.8 to 1.25 demonstrating that one 32/25 mg tablet was bioequivalent to two 16/12.5 mg tablets of candesartan cilexetil/HCT.

The corresponding pharmacokinetic parameters for drug-drug interaction along with the 90% confidence intervals for comparison of one candesartan cilexetil/HCT 32/25 mg tablet versus one candesartan cilexetil 32 mg tablet and two HCT 12.5 mg tablets are summarised in Table S3.

Table S3 Intra-individual comparison of exposure to candesartan and HCT after treatment with one candesartan cilexetil/HCT 32/25 mg tablet versus one candesartan cilexetil 32 mg tablet and two HCT 12.5 mg tablets

Parameter	Unit	Geometric mean ratio (test : reference) [%]	90% CI [%]
Candesartan			
AUC	ng·h/mL	112.31	106.76; 118.14
AUC_{0-t}	ng·h/mL	111.67	106.31; 117.31
C_{max}	ng/mL	102.87	95.26; 111.08
HCT			
AUC	ng·h/mL	98.06	95.27; 100.93
AUC_{0-t}	ng·h/mL	98.54	95.67; 101.49
C_{max}	ng/mL	105.04	99.30; 111.10

The 90% CIs of geometric mean ratios of all candesartan and HCT PK parameters were completely contained within the pre-defined limits of 0.8 to 1.25 indicative of no drug-drug interaction.

The secondary PK parameters of candesartan and HCT were in accordance to the known PK characteristics. For candesartan and HCT, the median t_{max} values were 4 and 2 hours and the geometric mean $t_{1/2}$ values were about 10 and 8.5 hours, respectively.

Summary of safety results

Single dose administration of candesartan cilexetil and hydrochlorothiazide was well tolerated, and no new safety issues were identified during the study regardless of the administration schedule. Headache and dizziness were the most frequently observed adverse events (AE). No deaths, serious adverse events, or adverse events classified as "other significant AEs" occurred during the study. No subject discontinued study treatments due to an AE. There were no clinically relevant changes in laboratory safety variables or physical examinations. An expected blood pressure lowering effect was observed reaching mean minimum SBP and DBP values at around 8 hours after dosing of 32 mg candesartan cilexetil, ie, after one candesartan cilexetil/HCT 32/25 mg tablet, after two candesartan cilexetil/HCT 16/12.5 mg tablets or after one candesartan cilexetil 32mg tablet. This blood pressure lowering effect was less evident after treatment with two HCT 12.5 mg tablets.