AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Candesartan cilexetil
Study Code	D2451C00007
Edition Number	1
Date	15 October 2009

A Single Dose, 2-Period, Cross-over, Bioequivalence Study in Healthy Subjects to Evaluate the Proposed Commercial Oral Suspension of Candesartan Cilexetil

Study dates:	First healthy volunteer enrolled:	17 March 2009
	Last healthy volunteer completed:	04 June 2009
Phase of development:	Clinical pharmacology (I)	

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

Study centre(s)

Early Phase Clinical Unit – London, PAREXEL International, Northwick Park Hospital, Harrow, Middlesex, United Kingdom.

Study period		Phase of development
First healthy volunteer enrolled	17 March 2009	I
Last healthy volunteer completed	04 June 2009	

Publications

None at the time of writing this report

Objectives

The primary objective of the study was to assess bioequivalence of the proposed commercial oral suspension of candesartan cilexetil and the oral suspension of candesartan cilexetil used in the paediatric clinical programme, after single dose administration.

The secondary objectives of the study were to investigate the safety and tolerability of the proposed commercial oral suspension of candesartan cilexetil and the oral suspension of candesartan cilexetil used in the paediatric clinical programme, after single dose administration.

Study design

This was a Phase-I, 2-period, cross-over, randomised, open-label, group-sequential, single-centre study with an interim analysis to determine bioequivalence of a single 32 mg dose of the proposed commercial oral suspension of candesartan cilexetil (1 mg/mL) and a single 32 mg dose of the candesartan cilexetil oral suspension (1.6 mg/mL) used in the paediatric programme in healthy volunteers.

Target healthy volunteer population and sample size

A total of 52 healthy male and female volunteers (females to constitute at least 20% of all subjects; pregnant or lactating female volunteers were excluded), aged between 18 to 55 years old (inclusive).

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

Drug: Candesartan cilexetil (proposed commercial oral suspension)
Formulation: Oral suspension
Strength: 1.0 mg/mL
Dose: 32 mg, single dose (32 mL)
Batch number: 08-003268AZ

Drug: Candesartan cilexetil (clinical paediatric oral suspension)
Formulation: Oral suspension
Strength: 1.6 mg/mL
Dose: 32 mg, single dose (20 mL)
Batch number: 2439191

Duration of treatment

The study included 2 periods with blood sampling up to 36 hours post-dose which were separated by a wash-out period of 6 to 14 days (from the Investigational Product (IP) administration on Day 1 of the first period until IP administration on Day 1 of the second period). Considering a Screening period of 21 days and a Follow-up visit between 2 to 5 days after final candesartan cilexetil administration in the second study period, the total duration of this study for a healthy volunteer was 11 days at minimum and 42 days at maximum.

Criteria for evaluation - efficacy and pharmacokinetics (main variables)

For candesartan uncorrected and corrected for potency: C_{max}, AUC and AUC_{0-t}.

Criteria for evaluation - safety (main variables)

Adverse events, laboratory variables (clinical chemistry, haematology, and urinalysis) and vital signs.

Statistical methods

A group sequential method was applied. In the first step healthy volunteers were dosed with the aim that 32 male and female healthy volunteers completed, and were included in the interim analysis. If bioequivalence for candesartan was declared based on data obtained in this step, the study was to be stopped. In case bioequivalence was not declared at this step, the study was to continue and further healthy volunteers were dosed up to a maximum of 52 with the goal of including at least 48 healthy volunteers who completed the study. For the bioequivalence testing the log-transformed variables C_{max}, AUC and AUC_{0-t} 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. Symmetric confidence intervals (CIs) for the mean treatment difference (Treatment A, test minus Treatment B, reference) for log(AUC), log(AUC_{0-t}) and log(C_{max}) of candesartan were calculated. If the 95% CIs for the ratio of geometric means for candesartan AUC, AUC_{0-t} and C_{max} after the first step were all contained in the interval [0.8, 1.25] then the study was to be stopped and bioequivalence declared. Upon continuation of the study, bioequivalence was to be declared after the second step if the 92% CIs for the ratio of geometric means for AUC, AUC_{0-t} and C_{max} were all contained in the interval [0.8, 1.25].

Descriptive statistics for all subjects together were given for all pharmacokinetic, demographic and vital signs variables.

Adverse events and laboratory variables were presented descriptively.

Subject population

A total of 36 healthy male and female subjects from a single-centre were enrolled and randomised to receive the study drug in the first step of this sequential study. One subject discontinued from the study due to AEs in the first treatment period so that 35 subjects completed the first step of this clinical study. Thus, the safety and PK analysis sets each comprised all 36 subjects, while only 35 subjects were included in the bioequivalence analysis set. Demographic characteristics and gender balance of the subjects in the present study were suitable for the purposes of assessing the study variables and in accordance with the clinical study protocol.

Summary of pharmacokinetic results

Bioequivalence between candesartan cilexetil proposed commercial oral suspension 1.0 mg/mL and candesartan cilexetil clinical suspension 1.6 mg/mL was assessed by AUC, AUC_{0-t} and C_{max} of candesartan plasma concentrations. The results of the mixed model ANOVA are shown in Table S1.

Table S1 Intra-individual bioequivalence comparison between candesartan cilexetil commercial (test) and paediatric oral suspension 32 mg (reference)

Parameter	Unit	Geometric Mean (Treatment B) N=35	Geometric Mean (Treatment A) N=35	Geometric Mean Ratio (A:B) [%]	95% CI [%]
Candesartan					
AUC	nmol.h/L	6544.39	6786.96	96.43	90.29; 102.99
AUC_{0-t}	nmol.h/L	6179.60	6327.10	97.70	91.08; 104.79
C_{max}	nmol/L	598.45	579.03	103.57	94.91; 113.01

Treatment A: Candesartan Cilexetil proposed commercial oral suspension 1.0 mg/mL (oral)
Treatment B: Candesartan Cilexetil clinical suspension 1.6 mg/mL (oral)
Ratios are calculated from the ANOVA and calculated as EXP(diff), where diff is the mean treatment difference estimated by the ANOVA.

Bioequivalence between 32 mg candesartan cilexetil proposed commercial oral suspension 1.0 mg/mL and 32 mg candesartan cilexetil clinical suspension 1.6 mg/mL after single dose administrations was demonstrated based on the candesartan PK parameters AUC, AUC_{0-t} and C_{max}. All geometric mean ratios of the test and reference PK parameters were slightly below or above unity and the respective 95% CIs were all within the pre-defined limits of bioequivalence [0.8:1.25].

Summary of safety results

Single dose administration of 32 mg candesartan cilexetil proposed commercial oral suspension 1.0 mg/mL and 32 mg candesartan cilexetil clinical suspension 1.6 mg/mL was safe and well tolerated.

Altogether, 44.4% of the subjects reported a total of 31 AEs which were all judged by the Investigator to be of mild intensity except 3 AEs which considered of moderate intensity. There was no relevant difference between the profile and incidence of AEs between both treatments. There were no clinically relevant treatment related changes in clinical laboratory, vital sign and ECG parameters and in physical examination data. The observed safety profiles of candesartan cilexetil given as candesartan cilexetil proposed commercial oral suspension 1.0 mg/mL and 32 mg candesartan cilexetil clinical suspension 1.6 mg/mL were consistent with the results of previous studies.