Clinical Trial Results Disclosure Synopsis

Name of Sponsor: Takeda Pharma GmbH
Viktoriaallee 3-5
52066 Aachen, Germany

Title of Study: Double-Blind, Randomised Trial To Investigate The Antihypertensive And Metabolic Effects Of Candesartan In Insulin-Resistant Obese Patients With A Hypertension Not Adequately Controlled By Previous ß-Blocker Or Calcium Channel Blocker

Phase of Development: Phase IV

Name of Active Ingredient:

(+) -1-(Cyclohexyloxycarbonyloxy)ethyl-2- ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole- 7-carboxylate (Candesartan cilexetil)

AND:

6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide-1, 1-dioxide (Hydrochlorothiazide; HCT)

Name of Finished Product: Blopress 8mg PLUS 12.5mg and Blopress 16mg PLUS 12.5 mg

Investigators: 29 principal investigators enrolled subjects in the treatment period:

Study Sites: 29 centres in Germany screened at least one patient.

Publication Based on the Study (Citation) at Time of Study Completion: None

Study Period:

Date first subject signed informed consent form: 12 October 2006

Date of last subject's last visit/contact (from the Clinical database): 24 September 2008

Objectives:

Primary:

The primary objective of the study was to determine the efficacy of a six month treatment with candesartan 16 mg + hydrochlorothiazide (HCT) 12.5 mg on blood pressure reduction in comparison to placebo + HCT 12.5 mg both given on top of previously insufficiently effective ß-

blocker or calcium channel blocker therapy.

Secondary:

The secondary objective of the study was to determine the effect of candesartan 16 mg + HCT 12.5 mg on glucose and lipid metabolism, inflammation (assessed by high sensitivity C-reactive protein (hs-CRP)) and coronary risk (assessed by Prospective Cardiovascular Münster (PROCAM) risk score).

Methodology: This study was designed as a prospective, double-blind, parallel, 2-arm, 1:1-randomised, placebo-controlled, multicentre, phase IV trial.

Number of Subjects:

Planned: 180 subjects
Screened: 348 subjects
Enrolled in the treatment period: 188 subjects
Analyzed: Safety Set: 188 subjects, Intention-to-Treat (ITT) Set: 183 subjects, Per Protocol (PP) Set: 147 subjects.

Diagnosis and Main Criteria for Inclusion:

Insulin-resistant obese outpatients aged 35 to 70 years (men) and 45 to 70 years (women) with a hypertension not adequately controlled by ß- blocker or calcium channel blocker. Main inclusion criteria were abdominal obesity with a waist circumference > 102 cm (men) and > 88 cm (women), a body mass index (BMI) > 30 kg/m^2, hypertension with seated diastolic blood pressure (DBP) > 95 mmHg and ≤ 110 mmHg and a Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) index ≥ 2.5.

Duration of Treatment: After a screening phase of 7 days, the treatment of individual patients was planned to last about 6 months (168 ± 7 days).

Test Product, Dose and Mode of Administration, and Lot Number:

Study Medication	Product Dose Strength and Form	Study Dosage	Mode of Administration	Drug Product Lot Number
Candesartan/HCT	8 mg/12.5 mg	8 mg/ 12.5 mg	Oral	10359
Candesartan/HCT	16 mg/12.5 mg	16 mg/ 12.5 mg	Oral	10355
Placebo to HCT			Oral	40264193

Reference Therapy, Dose and Mode of Administration, and Lot Number:

Study Medication	Product Dose Strength	Study Dosage	Mode of Administration	Drug Product Lot Number
Placebo to Blopress			Oral	4015
Placebo to Blopress			Oral	4016
HCT	12.5 mg	12.5 mg	Oral	40268540

Criteria for Evaluation:

Efficacy:

Primary: Blood pressure (mean reduction in DBP measured at "trough") after 6 months of treatment as compared to baseline.

Secondary:

- Adiponectin
- hs-CRP
- Fasting plasma glucose (FPG)
- Fasting plasma insulin (FPI)
- Insulin resistance (assessed by HOMA-IR index)
- Lipid parameters (total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides)
- Fibrinogen
- PROCAM risk score for the assessment of coronary heart disease
- 24-hour mean blood pressure as assessed by ambulatory blood pressure measurement (ABPM) (optional)
- Daytime and night-time mean blood pressure (as part of the 24-hour ABPM) (optional)
- Systolic blood pressure (SBP)
- Heart rate (pulse rate)

Safety:

- Safety laboratory parameters (haematology, clinical chemistry)

- Adverse events (AEs)

Statistical Methods:

Demographic and baseline characteristics were summarised descriptively for the ITT and PP populations. No statistical tests were performed.

The primary efficacy variable (mean reduction in DBP between baseline and V5 or the last observed value = ΔDBP) was analysed for the ITT and PP populations. The following hypotheses were tested in a confirmatory manner using a one-sided t-test at the significance level of 0.025:

H0: μ C <= μ P

H1: μ C > μ P

with μ C = expected value of ΔDBP under candesartan-HCT and μ P = expected value of ΔDBP under placebo-HCT. Two-sided 95%-confidence intervals were calculated for μ C, μ P and μ C - μ P.

In case of a significant result for the ITT population, a significant result for the PP population was interpreted confirmatorily as well. Supportive analyses include an analysis of variance (ANOVA) including the factor centre as well as an analysis of covariance (ANCOVA) including the baseline value of DBP.

The secondary efficacy parameters were tested between the treatment groups for superiority of candesartan treatment using a one-sided t-test at a significance level of 0.025 using the ITT and PP populations. All tests are to be interpreted as descriptive. No adjustment of p- values was necessary. 95%-confidence intervals were calculated. Descriptive statistics of all secondary efficacy parameters were provided for each time point as well as for the differences between baseline and the following time points stratified by treatment group.

The safety endpoints were analysed for patients in the Safety population. Safety was mainly assessed from the incidence of AEs and the number of laboratory values lying outside predetermined ranges. The AEs were displayed in summary tables using descriptive statistics. They were grouped by MedDRA system organ class (SOC) and preferred term (PT) and analysed with regard to their severity and relationship to study treatment. Laboratory data were presented in shift tables using the ranges of normal values, tabulated descriptive statistics of the raw data and changes from baseline values and by identifying abnormal values in the data listings. No statistical tests were performed.

Descriptive statistics for all recorded and derived variables used appropriate descriptive summary tables (continuous data: sample size, mean, standard deviation (SD), minimum, median, maximum; categorical data: sample size, absolute and relative frequency).

SUMMARY OF RESULTS:

Baseline Demographics and Other Relevant Characteristics:

Of the total of 183 patients in the ITT population, 118 (64.5%) were male and 65 (35.5%) were female. Both treatment groups had a male-to-female ratio of about 2:1. Patients in the ITT were 53.7 (31, 70) [mean (min, max)] years of age with a BMI 34.0 (29.0, 54.2) kg/m^2 in the Candesartan + HCT treatment group and 55.0 (35, 70) years of age with a BMI 34.2 (27.0, 49.3) kg/m^2 in the Placebo + HCT treatment group. The baseline cardiovascular risk assessed by the PROCAM score was similar for both treatment groups at 43.6 (±11.3) [mean (±SD)] for the Candesartan + HCT treatment group and 45.4 (±13.3) for the Placebo + HCT treatment group. The derived risk of suffering a heart attack (myocardial infarction) or dying from an acute coronary event within the next 10 years was 6.9% in the candesartan-HCT group and 7.3% in the placebo-HCT group. The insulin resistance (as assessed by the HOMA-IR) was slightly higher in the placebo-HCT group. This applied also to the mean fibrinogen level. The hs-CRP levels were comparable between the two treatment groups.

The most frequent previous diseases (i.e. diseases not ongoing at the start of study treatment) were surgical and medical procedures (22.0% vs. 26.1% of patients in the candesartan-HCT and placebo-HCT groups, respectively), gastrointestinal disorders (20.9% vs. 16.3% of patients, respectively), and infections and infestations (19.8% vs. 12.0% of patients, respectively). Overall, there were no relevant differences between the treatment groups

For nearly all patients (98.9% and 97.8% of patients in the candesartan- HCT and placebo-HCT groups, respectively), selective beta blocking agents and dihydropyridine derivatives were the most common concomitant antihypertensive medications documented. The vast majority of the patients in the ITT population, i.e. 95.6% of patients in the candesartan-HCT group and 96.7% of patients in the placebo-HCT group showed sufficient compliance ($\geq$ 80%) measured as the percentage of used versus prescribed tablets of study drug during the prescription period of a patient.

Subject Disposition:

One hundred eighty-eight (188) patients were randomised and treated with either candesartan + HCT or placebo + HCT on top of either ß-blocker or calcium channel blocker as antihypertensive co-medication (safety population). In all, 158 patients completed the study, 81/95 patients (85.3 %) in the candesartan-HCT group and 77/93 patients (82.8 %) in the placebo-HCT group. Overall, a slightly higher proportion of patients in the placebo-HCT group had withdrawn during treatment as compared to the candesartan-HCT group. Three patients (2 in the candesartan-HCT group and 1 in the placebo-HCT group) were withdrawn due to AEs

(psychovegetative exhaustion, coronary artery disease and increase of blood potassium, respectively). Five patients were excluded from the ITT population as no Riva-Rocci (RR) measurements post-baseline were available so therefore the ITT population was comprised of 183 patients. From these, 147 patients completed the study without major protocol deviations and showed sufficient compliance (≥80%). These patients constituted the PP population.

Efficacy Results:

Primary efficacy parameter:

Analysis of the primary efficacy variable of the study (mean reduction in diastolic blood pressure between baseline and V5 or the last observed value in the ITT population) resulted in a distinctly higher effect in the candesartan-HCT group (-13.98 mmHg) as compared to the placebo-HCT group (-7.91 mmHg). About 75% of the decrease in mean DBP occurred already in the first two weeks of treatment. The difference between the treatment groups of - 6.07 (± 11.10) mmHg was clinically relevant and statistically significant (p=0.0002, one-sided t-test). Therefore it can be concluded that the treatment with candesartan-HCT is superior to the treatment with placebo-HCT also in obese patients with a hypertension not adequately controlled by ß-blocker or calcium channel blocker. Analysis of the PP population yielded a similar result which can be interpreted confirmatorily as well.

Results of supportive analyses of variance (ANOVA) (considering the influence of the study centre) and of covariance (ANCOVA) (considering the influence of DBP baseline values) were consistent with the results of the confirmatory analysis. Comparable statistically significant differences between the treatment groups were found, suggesting that neither study centres nor baseline values had a relevant effect on the superior DBP-lowering effect of candesartan-HCT as compared to placebo-HCT.

The blood pressure evaluation of subgroups by the type of antihypertensive co-medication points to a clinically relevant difference in the responsiveness to candesartan-HCT, since the efficacy of candesartan-HCT vs. placebo-HCT was more pronounced with underlying calcium channel blocker (ΔDBP -6.84 mmHg) compared to ß-blocker treatment (ΔDBP -4.90 mmHg).

Secondary efficacy parameters:

As changes in metabolism were not expected to occur before 6 to 8 weeks of treatment, results of the PP population are described in the following, as this analysis population comprised only patients who terminated the study as completers.

For the reduction in systolic blood pressure a significant and clinically relevant difference between the treatment groups (-7.50 mmHg in favour of candesartan-HCT) could be observed (p=0.0074, one-sided t-test).

The subgroup analysis of SBP by the type of antihypertensive co-medication resulted in rapid reductions in SBP with initiation of candesartan-HCT and placebo-HCT treatment which were

much more pronounced in the subgroup of patients, who received calcium channel blocker.

Similar as for blood pressure a reduction in heart rate was observed over time which was more pronounced in the candesartan-HCT group (-6.2 beats/minute) than in the placebo-HCT group (-1.6 beats/minute).

The cardiovascular risk (as assessed by the PROCAM score) showed a slight decrease over time which was similar in both treatment groups (-2.6 vs. -2.1 in the candesartan-HCT and placebo-HCT groups, respectively), mainly reflecting the decrease in SBP as all other parameters influencing the PROCAM score stayed relatively unchanged in the course of the study.

Regarding the effect of the study treatment on glucose homeostasis, a slight reduction in FPG, FPI and HOMA estimates was found. A worsening of FPG values from normal at baseline to above normal at study end occurred in 1 patient in the candesartan-HCT group compared to 7 patients in the placebo-HCT group.

Analysis of adiponectin levels revealed no difference in changes from baseline until end of the trial in between the treatment groups.

The hs-CRP levels showed a slight increase during the study which was somewhat more pronounced in the candesartan-HCT group (0.71 mg/L) than in the placebo-HCT group (0.53 mg/L), possibly due to lower screening values in the candesartan-HCT group. Statistical comparison of changes between the treatment groups revealed no significant differences (p=0.4279, one-sided t-test).

Statistical evaluations of lipid parameters (changes in total cholesterol, the respective HDL- and LDL-fractions and in serum triglyceride levels from baseline until end of the trial) were not significant.

Fibrinogen assessment revealed no significant difference in changes from baseline until end of the trial between treatment groups.

As the 24-hour ABPM was not conducted as planned (only for two patients pre and post values were available) these data were not analysed.

Safety Results:

Overall, the incidence of AEs and the number of patients experiencing AEs was similar between the two treatment groups: After the start of study treatment a total of 125 AEs in 56.8% of candesartan-HCT-treated patients (54/95) and 105 AEs in 52.7% of placebo-HCT- treated patients (49/93) were reported, irrespective of any causal relationship with the trial medication.

AEs from the MedDRA SOCs ‘infections and infestations’ (50/188 patients, 26.6%), ‘musculoskeletal and connective tissue disorders’ (30/188 patients, 16.0%) and ‘nervous system disorders’ (18/188 patients, 9.6%) were reported most frequently with only minor differences between the treatment groups.

No patient died in the study. A total of 6 SAEs occurred in 3 patients, all of them in the candesartan-HCT group. However, none of the SAEs was related to the study medication (based on the causal relationship assessment).

The incidence of those AEs, which were related to study medication (based on investigators' assessment), was very low, i.e. 9 AEs in 4 patients of the candesartan-HCT group (4.2%) and 2 AEs in 2 patients in the placebo-HCT group (2.2%). The number of patients withdrawn due to AEs was also very low, two early withdrawals in the candesartan-HCT group were due to unrelated SAEs and one early withdrawal in the placebo-HCT group due to an unrelated non-serious AE.

Regarding haematological or biochemistry parameters, no apparent differences between the treatment groups were observed, neither evaluating mean changes from screening to last value nor comparing numbers of individual patients with clinically relevant abnormalities.

Conclusion:

In conclusion, the diastolic (and systolic) blood pressure was further lowered by candesartan-HCT to a clinically relevant degree in patients, being on a basal insufficiently effective β-blocker or calcium channel blocker therapy. No influence of candesartan-HCT on glucose and lipid metabolism, inflammation or coronary risk was found. With respect to safety, both treatments were found to be safe and generally well tolerated.

Significant Changes During Study:

The final version of the study protocol, was amended once based on the high rate of screening failures due to very restrictive eligibility criteria in regard to lipid metabolism, HOMA-IR and age. Therefore the eligibility criteria for these parameters were expanded, as described in the criteria for inclusion section above. All changes were restricted to selection criteria without affecting the profile of morbidity of the study population and were not likely to have a significant impact on the safety or physical or mental integrity of the subjects. Furthermore they did not inflict the primary parameter and endpoint of this study; therefore, it was not expected that they would have a significant impact on the scientific value of the trial.

Study ID Number:

BLO K025

Other Study ID Number(s):

2006-001998-25 [EudraCT Number]

D-CAN-545 [Takeda ID]

U1111-1113-9336 [Registry ID: WHO]

DATE OF DISCLOSURE SYNOPSIS: 13 June 2012