Clinical Trial Results Disclosure Synopsis

Name of Sponsor: Takeda Pharma GmbH
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Title of Study: Clinical Study to Evaluate the Efficacy and Safety of the Combination Therapy Candesartan Cilexetil 32 mg plus Hydrochlorothiazide 25 mg in Patients with Severe Hypertension

Phase of Development: Phase IV

Name of Active Ingredients:

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

AND:

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

Name of Finished Product: Blopress Plus 32mg/25 mg

Investigators: 18 principal investigators enrolled subjects in the treatment period.

Study Sites: 10 sites in Germany and 8 sites in the Ukraine contributed to the final analysis.

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

Study Period:

Date first subject signed informed consent form: 14 October 2009

Date of last subject's last visit/contact (from the Clinical database): 17 June 2010

Objectives:

To show that the combination therapy Candesartan cilexetil 32 mg plus Hydrochlorothiazide (HCTZ) 25 mg is effective and safe for the treatment of patients newly diagnosed with severe essential hypertension and having received no antihypertensive treatment so far.

Methodology: This trial was a prospective, multi-centre, open-label, single-group study.

Number of Subjects:

Planned: 100 subjects
Screened: 107 subjects
Enrolled in the Treatment Period: 106 subjects
Analyzed: Safety Set: 106 subjects, Full Analysis Set: 105subjects, Per-protocol Set: 97 subjects

Diagnosis and Main Criteria for Inclusion:

- Male and female outpatients of at least 18 years of age with a confirmed diagnosis of essential hypertension.
- Systolic blood pressure (SBP) between 150 mmHg and 200 mmHg AND diastolic blood pressure (DBP) between 110 mmHg and 120 mmHg. Blood pressure was to be measured in sitting position.
- Patients did not receive any antihypertensive treatment so far.
- Negative pregnancy test at baseline (visit 1) in females with childbearing potential. Male or female patients with reproductive potential had to use an approved contraceptive method during study treatment evaluation.
- Written informed consent.

Duration of Treatment:
Since the patients did not receive any antihypertensive treatment before, the dose of Candesartan cilexetil plus HCTZ had to be titrated up. All patients were treated according to the following dose regimen:

Candesartan cilexetil 16 mg once daily. for 1 week followed by

Candesartan cilexetil 16 mg plus HCTZ 12.5 mg once daily for 2 weeks followed by

Candesartan cilexetil 32 mg plus HCTZ 25 mg once daily. for 6 weeks

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	16 mg tablet	16 mg	Oral	18746
Candesartan /HCTZ	16 mg / 12.5 mg tablet	16 mg / 12.5 mg	Oral	18904
Candesartan /HCTZ	32 mg / 25 mg tablet	32 mg / 25 mg	Oral	18611

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

Not applicable

Criteria for Evaluation:

Efficacy:

Primary: Change in SBP and DBP from visit 1 to visit 5

Secondary:

- Percentage of overall responders, i.e., percentage of patients showing a decrease in SBP to < 140 mmHg and/or decrease of SBP by at least 20 mmHg AND a decrease in DBP to <90 mmHg and/or a decrease of DBP by at least 10 mmHg.
- Percentage of diabetics turned out to be responders, i.e., percentage of patients showing a decrease in SBP to < 140 mmHg and/or decrease of SBP by at least 20 mmHg AND a decrease in DBP to <90 mmHg and/or a decrease of DBP by at least 10 mmHg.
- Change in pulse rate from visit 1 to visit 5
- Change in SBP and DBP during the course of the study
- Change of pulse rate during the course of the study

Safety:

- Adverse Events
- Changes in laboratory parameters
- Results of physical examinations

Statistical Methods:

Efficacy: The primary efficacy variable was the change in SBP and DBP from visit 1 to visit 5. With reference to literature, mean decreases by 38 mmHg (SBP) and 29 mmHg (DBP) were expected. For the primary efficacy variable, mean changes and corresponding 95% confidence intervals (two-sided) were given. Additionally, single group t-tests were performed with a 0.0125 one-sided significance level for comparing the mean change from baseline in SBP as well as the mean change from baseline in DBP vs. 0. Further, a longitudinal model was used considering all measurements throughout the observation period.

Standard summary statistics (mean, standard deviation, minimum, lower quartile, median, upper quartile, maximum, number of observations) as well as 95% confidence intervals (two-sided) were calculated for all patients and for the following subgroups:

• Patients <65 years of age versus patients >65 years of age.

• Patients with a body mass index (BMI) ≤30 kg/m^2 versus patients with a BMI >30 kg/m^2

Safety set: All patients who received at least one dose of study medication.

Full Analysis set (FAS): All patients who received at least one dose of study medication and who had a non-missing baseline value and at least one post-baseline efficacy value for at least one variable.

Per-protocol set (PPS): All patients of the FAS who completed the study without any major violation of the protocol and its procedures.

SUMMARY OF RESULTS:

Baseline Demographics and Other Relevant Characteristics:

Patients in the FAS were 52.5 ± 10.1 [53] (mean ± SD [median]) years of age with a BMI of 30.4 ± 4.8 [29.7] kg/m^2. Metabolic and nutrition disorders like obesity, diabetes mellitus and dyslipidaemia, were the most frequent concomitant diseases with 60% of the patients reporting these illnesses. Accordingly, blood-glucose lowering drugs were the concomitant drugs taken most often, ie, by 9.5% of the patients.

Subject Disposition:

One of 106 patients of the Safety Set had no post-baseline efficacy value for at least one efficacy variable so that the FAS consisted of 105 patients. Of those 105 patients, 97 completed the study without any major violations of the protocol and its procedures so that they qualified for the Per-protocol Analysis.

Efficacy Results:

Primary efficacy variable

After treatment with the study drug and based on the FAS, the SBP changed from visit 1 to visit 5 by –45.5 ± 15.9 mmHg while the DPB changed at the same time by –32.6 ± 10.7 mmHg. Using the last observation carried forward (LOCF) method, the SBP change from visit 1 to the individual last visit was –44.4 ± 16.8 mmHg with the DBP change for the same time interval being –32.0 ± 11.3 mmHg. All of these changes were found to be statistically relevant. The results for the PPS were very similar.

Subgroup analyses revealed a slight tendency for female patients and for patients below 50 years of age to have higher changes in blood pressure. However, calculations based on subpopulations by BMI did not reveal any considerable differences.

Secondary efficacy variables

Response to treatment defined as SBP < 140 mmHg and/or a decrease by 20 mmHg AND DBP < 90 mmHg and/or a decrease by 10 mmHg was found in 97/105 (92.4%) of the patients in the FAS. 2/105 (1.9%) non-responders stopped the study during or at the end of the first titration

step so that they never received the combination of Candesartan cilexetil and HCTZ. For the remaining 6/105 (5.7%) non-responders, a final explanation for the treatment failure was not available. All diabetic patients (n=17) were responders.

68/105 (64.8%) FAS patients and 12/17 (70.6%) diabetic patients reached blood pressure values below 140/90 mmHg at their individual last study visit.

The changes of blood pressure during the course of the study and during all titration steps turned out to be of statistical relevance. The highest decrease in the systolic blood pressure was seen during the 2nd titration step while the diastolic blood pressure was lowered most in the first titration step.

The evaluation of the change in pulse rate between visits 1 and 5 with and without LOCF revealed a slight tendency for a decrease over time,i.e. -3.0 ± 14.5 beats per minute (bpm) with LOCF and -3.3 ± 14.6 bpm without LOCF.

The pulse rates generally tended to decrease during the course of the study, but a very minor average increase of 0.5 ± 13.3 bpm was found during the 3rd titration step.

Safety results:

Adverse events

In total, 38 treatment-emergent adverse events (TEAEs) were reported from 30/106 (28.3%) patients. Thereof, a causal relation with the study medication was positively confirmed for 5 TEAEs reported from 4/106 (3.8%) patients. These 5 TEAEs included increases of the Alanine Aminotransferase (ALAT) and Aspartate Aminotransferase (ASAT), vertigo, palpitation and hyperglycaemia and thus were compatible with the known safety profile of the study drug. None of the causal related AEs were severe and/or serious. The outcome of all causally related TEAEs was assessed as recovered.

1 serious TEAE (=SAE) was observed in 1/106 (0.9%) patient. This patient was hospitalised due to chest pain which later turned out to be of non-cardiac origin. This SAE was assessed as not causally related and as recovered.

Most TEAEs were of mild or moderate intensity. There were 2 TEAEs from 2/106 (1.9%) patients that had a severe intensity: the above described SAE and an episode of headache that was severe, but not serious and that had no relation to the study medication.

One TEAE led to premature study termination: an increase of the gamma-glutamyl transferase (γ-GT) to more than 3 x Upper limit of normal (ULN) found at the first study visit caused one immediate withdrawal from the study and retrospectively proved non eligibility of this patient for the study rather than an untoward medical occurrence during the trial.

Laboratory parameters

The analysis of the laboratory results did not provide any remarkable trends. As expected based

on the known safety profile of the study drug, the average results for haemoglobin, haematocrit and red blood cell count decreased very slightly during the study.

A detailed evaluation of the markers of the kidney function, i.e. creatinine and the estimated glomerular filtration rate (eGFR), including analyses of different study periods and subgroups did not reveal any noteworthy changes over the course of the study.

Single, clinically relevant deviations from the normal range were observed for the ASAT and ALAT in one patient.

Physical examination

The physical examinations did not reveal any changes or new findings over time.

Conclusions

The combination of Candesartan cilexetil and HCTZ, initiated in 3 titration steps in patients with freshly diagnosed, severe essential hypertension and no previous anti-hypertensive therapy, turned out to be effective and safe. The anti-hypertensive effect expected to be seen in this study was confirmed and actually slightly exceeded by the actual results. The safety results were compatible with the already known profile.

Significant Changes During Study:

There were no significant changes to the study protocol.

Study ID Number:

BLO K027

Other Study ID Number(s):

DE-CAN-027 [Takeda ID]

2009-011776-30 [EudraCT Number]

U1111-1112-2376 [Registry ID: WHO]

DATE OF DISCLOSURE SYNOPSIS: 13 June 2012