Clinical Trial Results Disclosure Synopsis

Name of Sponsor: Takeda Pharma GmbH
Viktoriaallee 3 – 5
52066 Aachen / Germany

Title of Study: Candesartan 'Added' Therapy For Treatment Optimization Of Symptomatic Heart Failure With Diastolic Dysfunction In Diabetic And Hypertensive Patients. A Randomized, Placebo-Controlled, Double-Blind, Parallel-Group And Multicentre Clinical Phase III Study Investigating The Effects On NT-ProBNP Over 6 Months.

Phase of Development: Phase IIIb

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)

Name of Finished Product: BLOPRESS®

Investigators: 14 principal investigators enrolled subjects in the screening phase:

Study Sites: 8 sites in Germany randomized patients in the double-blind treatment phase.

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

Study Period:

Date first subject signed informed consent form: 16 January 2008

Date of last subject's last visit/contact (from the Clinical database): 02 December 2008

Objectives: Determination of N-terminal pro-B-type natriuretic peptide (NT-proBNP) and its correlation to other heart failure (HF)-parameters (New York Heart Association (NYHA)- class, 36-Item Short Form Health Survey (SF-36)-score, Blood Pressure (BP)-control, kidney function, metabolic state) to generate valid efficacy data for optimization of therapy in heart failure with preserved ejection fraction over a 6-month treatment with the angiotensin-II type-I receptor-blocker (ARB) Candesartan Cilexetil (CC) compared to placebo. CC or placebo were to be given in an "added" regimen to a constant background-HF-therapy with at least ACE-inhibitors (or

further drugs) for the treatment of symptomatic heart failure with diastolic dysfunction in diabetic and hypertensive patients.

Methodology: Randomized, placebo-controlled, double-blind, multicentre, parallel-group trial

Number of Subjects:

Planned: 300 subjects
Screened: 42 subjects
Enrolled in the double-blind treatment Period: 22 subjects
Analyzed: 22 patients were enrolled, randomized, and treated (safety analysis set); 6 patients completed the planned study period regularly; 7 patients showed premature termination due to whole trial discontinuation.

Diagnosis and Main Criteria for Inclusion: Male or female patients of at least 45 years of age suffering from a non-insulin dependent diabetes mellitus type 2 orally treated for at least 3 months and showing normotension or controlled hypertension with sitting systolic blood pressure (sSBP) < 140 mmHg and/or sitting diastolic blood pressure (sDBP) < 90 mmHg. Evidence of an abnormal left ventricular relaxation, diastolic distensibility or diastolic stiffness confirmed by echocardiography under the prerequisite of a preserved Left ventricular ejection fraction (LVEF) ≥ 45%. NT-proBNP ≥ 250 pg/ml at baseline, NYHA class II or III in stable condition since 3 months, and standard HF- therapy with an ACE-inhibitor alone or with further preparations in a constant regimen since at least 1 month (3 months in terms of β-blockers). Signed written informed consent available.

Duration of Treatment: The total study period was planned to be about 12 months. The individual study period for a single patient was defined with about 6.5 months including screening (1 week maximum) and treatment phase (24 weeks). The treatment comprised a titration period of 6 weeks and a period of constant study therapy of at least 18 weeks. Study visits were planned for screening (V0; day -7), baseline (V1; day 0), three times during titration (V2, V3, V4, i.e. weeks 2, 4, 6) and twice during the period of constant therapy with Candesartan (V5 and V6, i.e. weeks 16 and 24).

After the initially planned period of one year (2008), the study was terminated prematurely as a whole by the sponsor in December 2008 since randomization of patients was very poor until that date (low and slow recruitment (n=42) with a high number (n=20) of screening failures).

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	8 mg	8 mg	Oral	13585
Candesartan	16 mg	16 mg	Oral	13232 and 13233
Candesartan	32 mg	32 mg	Oral	N/A

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 8 mg	N/A	N/A	Oral	2007054801
Placebo to 16 mg	N/A	N/A	Oral	2007054901

Criteria for Evaluation:

Efficacy:

Primary: Course of NT-proBNP (log-transformed; determination by central laboratory) defined as the mean change from baseline (V1) to final visit (V6)

Secondary: Mean change V1/V4 and V4/V6 for NT-proBNP (log-transformed); mean change V0/V1 to V6 for SF-36, Adiponectin, Cystatin C, HbA1c, UAE, kidney function (based on estimated glomerular filtration rate (eGFR)/Cystatin C), NYHA-, body weight-, BP- and echocardiographic results; subgroup evaluations regarding ß- blocker (yes/no), NYHA-class (II/III), the different dosages of study medication during constant therapy (i.e. 8, 16, or 32 mg; V4 to V6), and on baseline eGFR, Cystatin C, and NT-proBNP; correlations of NT-proBNP with NYHA, SF-36, and BP; comparison between V1, V4 and V6 on concomitant use of loop diuretics; transition from sinus rhythm to permanent atrial fibrillation (based on ECG); progression of preserved (LVEF $\geq$ 45%) to impaired systolic dysfunction (LVEF < 45%) based on the echocardiographic results.

Safety: Incidence of adverse events, change of routine and safety laboratory parameters (haemoglobin, hematocrit, sodium, potassium, calcium, alanine transaminase (ALAT), aspartate aminotransferase (ASAT), gamma-glutamyl transpeptidase (γ-GT), creatinine, urea, fasting glucose and HbA1c), changes in physical examination and vital signs including monitoring of Body Weight, Eelectrocardiogram recordings (12-lead), echocardiography V0/V6 with appropriate evaluation, and the rate of premature withdrawals.

Statistical Methods: The study was stopped due to poor recruitment based on Ethics Committee approval of September 25, 2009 after Sponsor's petition from September 15, 2009. Only 42 of 350 patients planned were enrolled. Therefore, it was decided to prepare an abbreviated 'synopsis-format' Clinical Study Report (CSR) according to the requirements of the Guidance for Industry for abbreviated reports providing summary tables only for those efficacy variables considered to be relevant and complete safety parameters usually presented in a standard CSR. Confirmatory and exploratory statistics (as initially planned in the study protocol) were not calculated due to the small number of 22 evaluable patients. Interim and subgroup analyses were not performed.

In general, summary tables are displayed by treatment group as the main classification variable and for the total of the sample in the respective analysis set. According to protocol an all patients treated set, a full analysis set and a per-protocol analysis set were planned to be analyzed. The data of all patients enrolled were listed. However, due to the premature study discontinuation, only selected summary tables were calculated for the all patients treated set and a determination of major violations of the study protocol and its procedures was not done. Thus, a specific per-protocol analysis was not performed.

Study visit V1 (day 0) was defined as baseline and study visit V6 (week 24 ± 8d) was used as endpoint for analysis of the primary efficacy parameter. In case of premature termination the last available observation after baseline served for further evaluation (LOCF approach).

The primary statistical analysis applied was the testing on intra-individual differences in the mean change from baseline (V1) compared to last visit (V6) of the objective primary study endpoint NT-proBNP of which all values were listed. Display of summary descriptive statistics were given for absolute values of NT-proBNP and changes from baseline. Because of the expected skewed distribution of NT-proBNP values, the geometric mean and the geometric coefficient of variation were calculated. No log-transformation was performed.

All values and data on secondary parameters were listed. Display of summary descriptive statistics was given for absolute values and changes from baseline visit (V1) for Adiponectin, Cystatin C, HbA1c, eGFR, and urinalysis. The estimated glomerular filtration rate (eGFR) was calculated in addition to the study protocol.

Standard descriptive summary statistics were calculated for continuous variables (i.e. arithmetic mean, standard deviation, minimum value, lower quartile, median, upper quartile, maximum value, number of non-missing values). Categorical data were presented in frequency tables using counts and percentages. Individual patient data listings were presented parameterwise and were sorted by treatment group, centre, patient number and study visit. Data from all clinical assessments and combined for all participating centres, whether explicitly referred to in the statistics section or not, were presented in relevant summary tables only and in complete individual patient data listings.

The statistical analysis and generation of summary tables and data listings was performed using the SAS® software package version 9.2 The MedDRA dictionary Version 11.0 was used for coding of adverse events, medical history and previous/concomitant diseases. Previous and concomitant medication/therapy was coded according to the World Health Organisation terminology using version 2008/01 of the WHO-DRL dictionary.

SUMMARY OF RESULTS:

Baseline Demographics and Other Relevant Characteristics:

Of the 22 (11 vs. 11) treated patients, 13 (7 vs. 6) were male and 9 (4 vs. 5) were female. Mean age was 67.0 ± 16.8 vs. 69.0 ± 7.1 years, mean height was 167.3 ± 9.1 vs. 170.4 ± 8.4 cm, mean weight was 88.0 ± 16.2 vs. 87.7 ± 21.7 kg, and the calculated mean BMI was 31.4 ± 5.0 vs. 30.0 ± 5.7 kg/m^2. Demographic and baseline findings did not show clinically relevant differences between the two treatment groups with the exception that there were more male than female patients (13 vs. 9).

Subject Disposition:

Enrolled: n=42; Screening failures: n=20; Randomized/treated: n=22 (11 Candesartan vs. 11 Placebo); Premature termination: n=16 (8 vs. 8); Full study completion: n=6 (3 vs. 3); Reasons for screening failures were NT-proBNP < 250 pg/ml (10 patients), not allowed concomitant diseases (5), no diabetes (3), withdrawal of consent (1), and no reason given (1). Among the 5 patients with not acceptable diseases there were clinical findings in 2 cases specified as serious adverse events: unstable angina pectoris with hospitalization in one case; progressive pulmonary failure with subacute alveolitis and following death in the other case. Study medication was not administered in any case. Reasons for premature termination in 16 (8 vs. 8) patients were discontinuation of the complete study in 7 (3 vs. 4) patients, adverse events in 5 (3 vs. 2) patients, randomization/enrolment error in 2 (1 vs. 1) patients, not available parameters of echocardiography in one patient of the Candesartan group, and withdrawal of consent in one patient of the placebo group. The 42 patients screened were enrolled by 14 centres, of which in 8 sites the 22 (11 vs. 11) treated patients were randomized as follows: one centre with 8 patients, two centres with 4, one centre with 2, and 4 centres with 1 patient each. Regarding extent of exposure the 6 (3 vs. 3) patients with full completion showed a duration of study therapy between 160 and 168 days and thus fulfilled the requirements for a complete treatment phase. The highest achieved dose of study drug in the Candesartan group was 32 mg in 7/11 (63.6%) patients, 16 mg in 2/11 (18.2%) patients, and 8 mg in again 2/11 (18.2%) patients.

Efficacy Results: The present clinical study was prematurely terminated as a whole in September 2008 after inclusion of only 22 treated patients evaluable for efficacy and safety (11 in each treatment group), which is less than 10% of the patients initially planned for final evaluation (n=300). Therefore, clinically relevant and reliable conclusions regarding the

therapeutic potential of an 'add-on-regimen' with Candesartan Cilexetil for optimization of therapy in heart failure patients with preserved ejection fraction cannot be postulated.

Primary:

The heart failure associated parameter NT-proBNP showed a slight increase during study therapy (i.e., V1 vs. V6) in both treatment groups with a minimal higher rise for treatment with Candesartan.

Efficacy Results	**Candesartan**				**Placebo**			
	Means (SD)		**Medians**		**Means (SD)**		**Medians**	
Primary Parameter	**Baseline/V1**	**V6/LOCF**	**V1**	**V6**	**Baseline/V1**	**V6/LOCF**	**V1**	**V6**
NTproBNP [pg/ml]	712.5 (452.1)	879.4 (553.8)	584.5	957.0	582.3 (432.0)	694.9 (563.1)	465.5	573.2

Secondary:

Differences between the treatment groups were seen for HbA1c (decrease under Candesartan), urine albumin, and urine albumin/creatinine ratio (both with more increase under Candesartan). No particular changes occurred for adiponectin, cystatin C, urine creatinine, and the estimated GFR.

Efficacy Results	**Candesartan**				**Placebo**			
	Means (SD)		**Medians**		**Means (SD)**		**Medians**	
Secondary Parameters	**Baseline/V1**	**V6/LOCF**	**V1**	**V6**	**Baseline/V1**	**V6/LOCF**	**V1**	**V6**
Adiponectin [µg/ml]	11.90 (6.22)	13.69 (6.13)	12.0	12.9	14.84 (15.42)	17.77 (19.88)	9.20	8.90
Cystatin C [mg/l]	0.90 (0.14)	0.97 (0.12)	0.88	0.94	0.99 (0.30)	0.85 (0.20)	0.92	0.83
HbA1c [%]	7.40 (0.54)	6.89 (0.50)	7.20	6.70	6.56 (0.90)	6.71 (0.84)	6.40	6.70
Urine albumin [mg/dl]	11.30 (19.0)	15.20 (25.6)	2.90	6.20	5.40 (`115.0)	12.2 (22.6)	0.70	0.60

Efficacy Results	Candesartan				Placebo			
	Means (SD)		Medians		Means (SD)		Medians	
Secondary Parameters	**Baseline/V1**	**V6/LOCF**	**V1**	**V6**	**Baseline/V1**	**V6/LOCF**	**V1**	**V6**
Urine creatinine [mg/dl]	81.0 (34.5)	74.90 (25.5)	76.6	73.1	80.6 (79.2)	89.2 (80.4)	48.4	52.2
U.-Alb./Crea.-ratio [mg/g]	150.5 (240.6)	259.2 (521.1)	30.1	67.5	185.4 (458.9)	184.0 (351.7)	11.2	32.7
Estimated GFR [ml/min]	59.9 (15.3)	58.40 (15.9)	55.1	52.4	55.8 (16.2)	60.3 (15.0)	56.3	56.8

Safety Results:

Adverse events (AEs) under study treatment (i.e., treatment emergent adverse events, TEAEs) occurred in 12/22 (54.5%; 7 vs. 5) treated patients showing the following 22 (13 vs. 9) individual events:

Cardiac failure (2 vs. 0), peripheral oedema (2 vs. 0), and pruritus (1 vs. 1) in 2 patients each. Chest pain, constipation, bile duct cancer, dementia, dyspnoea, hypertensive crisis, cystitis, and pain in extremity in one patient each treated with Candesartan. Bradycardia, rash, diarrhoea, nausea, breast cancer, cough, hypertension, and tremor in 1 patient each of the placebo treatment group.

Course of AE: 5 events unique (3 vs. 2); 8 events intermittent (3 vs. 5); 9 events continuous (7 vs. 2).

AE intensity: 5 events mild (2 vs. 3 in 1 vs. 2 patients), 13 events moderate (7 vs. 6 in 5 vs. 4 patients), 4 events severe (4 vs. 0 in 3 vs. 0 patients).

Relationship: 19 events unlikely/not related (11 vs. 8 in 7 vs. 4 patients), 2 events possibly related in 1 vs. 1 patients specified as constipation and hypertension. One event in one Candesartan patient probably related and specified as pruritus.

Outcome: 17 events recovered during study (9 vs. 8). 4 events did not yet recover at study end (3 vs. 1; dementia, bile duct cancer, cardiac failure vs. breast cancer). One Candesartan patient recovered with persistent damage from a severe and serious unique episode of cystitis without any relationship to study drug.

Serious adverse events (SAEs) occurred in 4/22 (18.2%; 3 vs. 1) patients with 8 (7 vs. 1) single events always due to hospitalization (all treatment emergent). The SAEs were assessed as not related to study drug for all 8 events, with moderate intensity in 4 vs. 1 events and severe intensity in 4 vs. 0 events (3 vs. 0 patients). In 3 of the 4 patients with SAEs, premature termination due to SAE was documented.

In general, laboratory analyses did not show clinically noticeable changes during the study course with the exception of slightly elevated serum potassium and creatinine in some patients of both treatment groups. Furthermore, the evaluation of ECGs, echocardiography, physical examinations, and vital signs did not reveal distinct clinical differences both between and within the treatment groups.

Conclusions

The present clinical study was prematurely terminated as a whole in September 2008 after inclusion of only 22 treated patients evaluable for efficacy and safety (11 in each treatment group), which is less than 10% of the patients initially planned for final evaluation (n=300). Therefore, clinically relevant and reliable conclusions regarding the therapeutic potential of an 'add-on-regimen' using Candesartan Cilexetil for optimization of therapy in heart failure patients with preserved ejection fraction cannot be postulated. The specific heart failure associated parameter NT-proBNP showed only slight differences for both treatment groups and thus, remained mainly stable during study therapy. In terms of selected relevant secondary variables differences between the groups were seen for HbA1c (decrease with Candesartan), urine albumin, and urine albumin/creatinine ratio (both with more increase under Candesartan).

No particular changes occurred for adiponectin, cystatin C, urine creatinine, and the estimated GFR. With respect to safety, potentially new or unexpected signs and symptoms allocated to the active study drug in comparison to the known range of ARB-specific adverse reactions could not be observed including the results on laboratory parameters, ECG, echocardiography, and vital signs. Developments of serum creatinine and potassium, urine creatinine and albumin, albumin/creatinine ratio, and estimated GFR have always to be regarded in line with the known influence of ARBs like Candesartan on blood pressure and renal function, i.e. considering possible renal failure or insufficiency.

Significant Changes During Study:

Due to poor patient recruitment, the study was prematurely terminated as a whole after inclusion of only 22 treated patients evaluable for efficacy and safety (11 in each treatment group) based on an EC approval of September 25, 2009 following Sponsor’s petition from September 15, 2009.

Study ID Number:

BLO K026

Other Study ID Number(s):

2007-003070-26 [EudraCT Number]

D-CAN-546 [Takeda ID]

U1111-1113-9515 [Registry ID: WHO

DATE OF DISCLOSURE SYNOPSIS: 13 June 2012