# Clinical Trial Results Disclosure Synopsis

**Name of Sponsor:** Takeda Italia farmaceutici SpA
Via Elio Vittorini 129, 00144 Rome – Italy

**Title of Study:** Effects Of Candesartan Cilexetil Vs. Standard Therapy On Serum Levels Of Brain Natriuretic Peptide In Patients Suffering From Chronic Heart Failure With Depressed Or Preserved Left Ventricular Systolic Function (CANDHEART)

**Phase of Development:** Phase III

**Name of Active Ingredient:** (+/)-1-(cyclohexyloxycarbonyloxy)ethyl-2-ethoxy-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-yl] methyl-1 –benzimidazole-7-carboxylate (Candesartan cilexetil)

**Name of Finished Product:** Blopress®

**Investigators:** 74 principal investigators in Italy enrolled subjects for screening

**Study Sites:** 70 sites in Italy randomized subjects into the open-label treatment period

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

**Study Period:**

Date first subject signed informed consent form: 09 December 2005

Date of last subject's last visit/contact (from the Clinical database): 18 July 2008

**Objectives:**

**Primary:**

Assessment of the effects of the maximum tolerated dose of Candesartan cilexetil up to 32 mg once daily, added to on-going standard therapy, vs. standard therapy, on the 3-month changes of brain natriuretic peptide (BNP) from baseline in patients suffering from chronic heart failure (CHF) with depressed or preserved left ventricular (LV) systolic function

**Secondary:** to assess after a 48-week treatment period:

- change of BNP from baseline;
- changes from baseline of aldosterone, Pentraxin-3 (PTX3), C-Reactive Protein (CRP);
- changes from baseline of New York Heart Association (NYHA) class;
- changes from baseline of left ventricular ejection fraction (LVEF), left ventricular internal diastolic diameter (LVIDD), E wave peak velocity/A wave peak velocity (E/A), deceleration

time of E wave (E-DT), atrial dimensions, blood pressure (BP) and heart rate (HR);

- persistence of active treatment and discontinuation rate;
- quality of life by blind evaluation through Kansas City Cardiomyopathy Questionnaire (KCCQ).

**Methodology:** Add-on, multi-centre, open-label, randomised, parallel groups study.

**Number of Subjects:**

Planned: 1500 subjects
Screened: 571 subjects
Randomized in the open-label treatment period: 514 subjects
Analyzed: Safety Population: 513 subjects, Intent-to-treat Population (ITT): 514 subjects, Per Protocol Population (PP): 361 subjects

**Diagnosis and Main Criteria for Inclusion:** Patients with CHF treated at study entry with their appropriate therapy.

Inclusion criteria:

- Age ≥ 18 years; both sexes
- Stable, symptomatic NYHA II-IV CHF with LVEF < or ≥40% treated with standard therapy including Angiotensin Converting Enzyme (ACE)-inhibitors and/or beta-blockers. Patients with LVEF>40% had to be hospitalized for cardiovascular events during the past 12 months;
- Written informed consent

Exclusion criteria:

- Prior treatment with Angiotensin-Receptor Blocker (ARBs) within two weeks from visit 1;
- Severe or malignant hypertension (systolic blood pressure (SBP)/diastolic blood pressure (DBP)>180/110 mmHg);
- Symptomatic hypotension;
- Angina pectoris or acute myocardial infarction within one month from visit 1;
- Stroke or transient ischemic attack (TIA) within one month from visit 1;
- Percutaneous transluminal coronary angioplasty (PTCA) or coronary artery by-pass graft (CABG) within one month from visit 1;
- Haemodynamically relevant arrhythmias or cardiac valvular defect;
- Implant of pacemakers, cardiac resynchronization therapy (CRT) or cardioverters (ICD) within 6 months prior the randomization;
- Constrictive pericarditis or active miocarditis;

- Likelihood of cardiac surgical intervention (of any type) during the overall treatment period;
- Poorly controlled diabetes mellitus, untreated thyroid dysfunction, renal artery stenosis, angio-oedema of any aetiology, significant liver or renal impairment, anaemia of any aetiology or any other clinically relevant haematological disease; any disease with malabsorption
- Pregnant or lactating females or females at risk of pregnancy
- any non-cardiac (e.g. cancer) disease likely to shorten life expectancy
- Chronic alcohol or drug/substance abuse
- Known allergy, sensitivity or intolerance to study drugs
- Patients unlikely to comply with the protocol
- Participation in another trial in the month preceding study entry

**Duration of Treatment:** 48 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 cilexetil | 4 mg tablet | 4 mg QD | Oral | 149H07<br>9100017A |
| Candesartan cilexetil | 8 mg tablet | 8 mg QD | Oral | 8962<br>10747 |
| Candesartan cilexetil | 16 mg tablet | 16 mg QD | Oral | 8862<br>10749 |
| Candesartan cilexetil | 16 mg tablet | 32 mg QD (2 x 16 mg QD) | Oral | 8862<br>10749 |

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

| Study Medication | Product Dose Strength | Study Dosage | Mode of Administration | Drug Product Lot Number |
|---|---|---|---|---|
| Standard therapy for CHF | As needed | As needed | N/A | N/A |

**Criteria for Evaluation:**

Efficacy:

Primary: changes of BNP between baseline and three months of treatment

Secondary:

- change of BNP from baseline to 48 weeks,
- change from baseline of aldosterone, PTX3, CRP, NYHA class, LVEF, LVIDD, E wave peak velocity/A wave peak velocity (E/A) ratio, Deceleration Time of E wave (E-DT) time, atrial dimensions, BP, HR
- persistence and discontinuation rate of active treatment
- quality of life (KCCQ)

Safety:

Adverse events' profile, abnormal laboratory parameters.

**Statistical Methods:**

Efficacy:

Efficacy data were analysed in order to observe intragroup and intergroup differences of all the efficacy parameters considered, in the Candesartan cilexetil group and in the comparative group, after completion of the study. Each group was also divided in the two subsets (preserved and non-preserved cardiac function).

Continuous parameters were analysed according to an analysis of variance (ANOVA) model. Mean changes from baseline with 95% confidence interval (CI) were also calculated and multiple comparisons performed according to the Bonferroni's correction.

Data recorded as discrete scores or non-normally distributed were analysed according to nonparametric tests to assess changes from baseline (Friedman test or McNemar test).

Effects of Candesartan cilexetil and standard therapy on BNP was also evaluated by stratifying patients 1) into subsets of Angiotensin Converting Enzyme (ACE) inhibitors and beta ( $\beta$ )-blockers users and non-users, 2) into subsets above and below the median of baseline values of BNP, 3) into subsets with and without an aldosterone antagonist at baseline.

An interim analysis was introduced with Amendment 3, to be done after 350 and after 700 subjects enrolled.

Safety:

Safety data were presented and analysed in order to observe intragroup and intergroup differences of all the safety parameters considered, in the group of patients treated with

Candesartan cilexetil and in the comparative group, after completion of the study. Laboratory tests were analysed according to an ANOVA model. Mean changes from baseline with 95% confidence interval (CI) were also calculated.

**SUMMARY OF RESULTS:**

**Baseline Demographics and Other Relevant Characteristics:**

All patients reported signs of cardiac failure in their medical history, mostly of mild intensity (NYHA class II), with mean ejection fraction of 36.6 ± 10.2 (%).

All patients were on specific therapy addressed at the correction of heart failure, in particular with ACE-inhibitors, beta-blockers, aldosterone receptor antagonists, diuretics, digitalis.

During the study, the patients received Candesartan cilexetil for an overall exposure of 258 ± 127 days.

The study was well balanced between the two groups as for the demographic characteristics, medical history, cardiovascular parameters and hematology / biochemistry data.

Demographic characteristics of randomized subjects and other clinical information is reported in the following table:

| Parameter at baseline | CANDESARTAN (N = 256) | CONTROL (N= 258) |
|---|---|---|
| Male (n)<br>Female (n) | 195 (76%)<br>61 (24%) | 196 (76%)<br>62 (24%) |
| Age (mean years ± standard deviation (SD)) | 66 ± 11 | 66 ± 11 |
| SBP (mean mmHg ± SD)<br>DBP (mean mmHg ± SD) | 129 ± 18<br>78 ± 9 | 129 ± 17<br>78 ± 9 |
| HR (mean b/min ± SD) | 69 ± 13 | 69 ± 14 |
| BMI (mean kg/$m^2$ ± SD) | 27.6 ± 4.5 | 27.4 ± 4.2 |
| Cause of CHF (%)<br>Ischemic<br>dilated<br>arterial hypertension<br>Other | <br>48.8 %<br>21.5 %<br>19.5 %<br>10.2 % | <br>50.8 %<br>23.3 %<br>18.2 %<br>7.8% |
| NYHA class (%) II<br>III-IV | 72.3 %<br>27.7 % | 74.4 %<br>25.6 % |
| LVEF (mean % ± SD)<br>LVEF ≥ 40 %<br>LVIDd/BSA (mean ± SD) | 36.6 ± 10.2<br>27.2 %<br>33.1 ± 5.3 | 35.7 ± 9.2<br>22.7 %<br>33.8 ± 5.5 |

| Parameter at baseline | CANDESARTAN (N = 256) | CONTROL (N= 258) |
|---|---|---|
| Previous (%) | | |
| myocardial infarction: | 35.3 % | 42.6 % |
| unstable angina: | 11.8 % | 10.9 % |
| stroke: | 2.0 % | 3.1 % |
| arterial hypertension: | 53.3 % | 48.4 % |
| diabetes: | 26.6 % | 25.2 % |
| revascularization: | 32.4 % | 32.6% |
| Hospitalization in last year due to cardiovascular events (%) | 58.6 % | 57.4 % |
| Electrocardiogram (ECG) (%) | | |
| QRS > 120 msec | 31.5 % | 33.1 % |
| atrial fibrillation | 15.5 % | 15.1 % |
| pacemaker | 7.8 % | 4.9 % |

**Subject Disposition:**

This study screened consecutive patients with chronic heart failure, for a 48-month treatment with Candesartan cilexetil in comparison with standard therapy for CHF, to evaluate changes of BNP and other biological and functional parameters related to the cardiac status.

Overall, 569 patients from 74 centers were screened and 514 randomized to Candesartan cilexetil (n = 256) or control therapy (n = 258). 322 patients completed the study. The study was suspended on 05 June 2008 because of too slow patients' recruitment rate, in the presence of non significant differences between groups as for the primary end-point in an interim evaluation on first 350 patients enrolled. The re-estimation of the sample size raised the eventual number of patients needed up to 4500, therefore, the continuation of the trial in such conditions was deemed unethical. At the time of study interruption, 142 patients were still on study and were treated for their disease following the best clinical practice in the treatment of heart failure, according to the evaluation of the investigator.

Five Amendments were submitted and received approval (Am 1, Am 2, Am 3 were substantial; Am 4, Am 5 were non substantial).

**Efficacy Results:**

Treatment with both candesartan and standard therapy determined a progressive reduction of BNP; however, this effect was statistically non significant by Mann Whitney test (p=0.35 between baseline and 12 weeks; p = 0.98 between baseline and end of study):

| (median; pg/mL) | Baseline | 12 weeks | End of study |
|---|---|---|---|
| Candesartan (n = 256) | 141.0 | 104.5 | 93.5 |
| Control (n = 258) | 157.0 | 119.5 | 110.0 |

Patients showed an improvement of LVEF, which was statistically significant between baseline and end of study (p=0.01), but no differences were detected between groups:

| (median; %) | Baseline | 12 weeks | End of study |
|---|---|---|---|
| Candesartan (n = 256) | 36 | 39 | 40 |
| Control (n = 258) | 35 | 37 | 37 |

A significant improvement was also observed for diastolic left ventricular diameter.

No significant changes occurred in NYHA class during the study.

No significant changes occurred for plasma aldosterone.

No significant differences were found between groups for all cause mortality or cardiovascular mortality, nor for the hospitalization rate.

Data on quality of life showed a mild improvement of almost all parameters in the KCCQ test. Improvements in Quality of Life Score reached significance ($p<0.05$) while physical domain and overall KCCQ Summary Score showed a p value lower than 0.1. No statistically significant differences between groups at 48 weeks.

PTX3 and CRP (secondary end-points) were not evaluated.

**Safety Results:**

Safety data in the 256 patients treated with candesartan indicated 10.5 % discontinuation of treatment, overall, including 6 % discontinuation for adverse events (most frequently hypotension, hyperkalemia, asthenia). There were five serious, adverse reactions related to the study drug in four patients.

**Conclusions:**

The study was addressed at the verification of the effect of candesartan cilexetil in patients with congestive heart failure, in comparison with standard therapy, with special focus on BNP. This biological marker has been identified as a sensitive and specific prognostic index for morbidity and mortality in patients with left ventricular dysfunction and may also be used to check the

improvement of left ventricular function in response to a pharmacological treatment. The study did not recruit enough patients within the scheduled timelines therefore it was interrupted prematurely. Available data showed well balanced population between the two groups on study.

12-week Candesartan treatment (up to 32 mg daily) on top of recommended treatment did not significantly modify the circulating levels of BNP, although a reduction of median values was observed. However, the treatment was associated with a significant improvement of LV size and function.

Candesartan and standard therapy were well tolerated.

**Study ID Number:**

CANc-CHF14-TIF

**Other Study ID Number(s):**

2005-001306-87 [EudraCT Number]

U1111-1114-0042 [Registry ID: WHO]

**DATE OF DISCLOSURE SYNOPSIS:** 25 June 2012