Clinical Trial Results Disclosure Synopsis

Name of Sponsor: Takeda Pharma Vertieb GmbH & Co. KG, Jägerstr.27, 10117 Berlin, Germany

Title of Study: Candesartan "added" Treatment for Optimisation of Heart Failure (HF) Therapy - Effects on BNP and other HF-associated Parameters. An open, non-controlled and multicenter clinical trial.

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: 64 principal investigators enrolled subjects in the open-label treatment period.

Study Sites: 64 sites in Germany enrolled patients in the open-label treatment period.

Study Site 1: Benekestr. 2-8, 61231 Bad Nauheim, Germany
Study Site 2: Neue Str. 91, 89073 Ulm, Germany
Study Site 3: Albert-Einstein-Str. 2, 12489 Berlin, Germany
Study Site 4: Schwarnweberstr. 14, 13405 Berlin, Germany
Study Site 5: Möllendorffstr. 111, 10367 Berlin, Germany
Study Site 6: Apostel-Paulus-Str. 20, 10825 Berlin, Germany
Study Site 7: Rudolf-Seiffert-Str. 11, 10369 Berlin, Germany
Study Site 8: Reichenbergerstraße 3, 13055 Berlin, Germany
Study Site 9: Wingertshecke 6, 35392 Giessen, Germany
Study Site 10: Sturmbäume 3, 37154 Northeim, Germany
Study Site 11: Hauptstr. 55, 28844 Weyhe, Germany
Study Site 14: Marktstr. 2-6, 04177 Leipzig, Germany
Study Site 15: Erlanger Allee 103, 07747Jena, Germany
Study Site 16: Albert-Schweitzer-Str. 10, 79199 Kirchzarten, Germany
Study Site 17: Wiesenbacher Str. 2, 69151 Neckargemünd, Germany
Study Site 18: Königstr. 39, 96253 Untersiemau, Germany
Study Site 19: Pestalozzistr. 38, 10627 Berlin, Germany
Study Site 20: Neuendorfer Str. 70, 13585 Berlin, Germany
Study Site 22: An der Mauer 1, 91785 Pleinfeld, Germany
Study Site 23: Wördemannsweg 25, 22527 Hamburg, Germany
Study Site 24: Bergmannstr. 28, 34121 Kassel, Germany
Study Site 25: Wilhelmshöher Allee 91, 34117 Kassel, Germany

Study Site 26: Friedrichstr. 31, 65185 Wiesbaden, Germany
Study Site 27: Kardiologie Sachsenhausen, Walter-Kolb-Str. 9-11, 60594 Frankfurt/M., Germany
Study Site 28: Am Wall 1, 18273 Güstrow, Germany
Study Site 29: Hitdorfer Str. 10, 40764 Langenfeld, Germany
Study Site 30: Aachener Str. 327, 50931 Köln, Germany
Study Site 33: Odilienplatz 3, 66763 Dillingen, Germany
Study Site 34: Zentrum am Boxberg, 66538 Neunkirchen, Germany
Study Site 35: Max-Braun-Str. 1, 66538 Neunkirchen, Germany
Study Site 37: Enderstr. 59, 01277 Dresden, Germany
Study Site 38: Chemnitzer Str. 7, 09232 Hartmannsdorf, Germany
Study Site 39: Puschkinplatz 4, 01589 Riesa, Germany
Study Site 40: Brühlerwallstr. 4, 99084 Erfurt, Germany
Study Site 41: Brühlerwallstr. 4, 99084 Erfurt, Germany 40, 441, 571-573
Study Site 44: Heilig-Geist-Str. 24, 83022 Rosenheim, Germany
Study Site 46: Salvador-Allende-Str. 2-8, 12559 Berlin, Germany
Study Site 47: Wilhelmshöher Allee 91, 34121 Kassel, Germany
Study Site 49: Friedrichstr. 21, 35392 Gießen, Germany
Study Site 50: Große Parower Str. 53a, 18435 Stralsund, Germany
Study Site 51: Antoniusplatz 10, 49661 Cloppenburg, Germany
Study Site 52: Katschhof 3, 52062 Aachen, Germany
Study Site 53: Chemnitzer Str. 1, 04703 Leisnig, Germany
Study Site 54: Gautschweg 1a, 01309 Dresden, Germany
Study Site 55: Rosengarten 5, 22880 Wedel, Germany
Study Site 56: Hermannstr. 24, 99817 Eisenach, Germany
Study Site 58: Goethestr. 49, 45964 Gladbeck, Germany
Study Site 59: Pfarrstr. 4, 57072 Siegen, Germany
Study Site 60: Goldbergplatz 3, 45894 Gelsenkirchen, Germany
Study Site 61: Voedestr. 79, 44866 Bochum, Germany
Study Site 62: Scheffelstr. 17, 78224 Singen, Germany
Study Site 63: Kaiserstr. 31, 97070 Würzburg, Germany
Study Site 65: Türkenstr. 84, 80799 München, Germany
Study Site 66: Strausberger Platz 19, 10243 Berlin, Germany
Study Site 67: Ziegelkampstr. 37, 31582 Nienburg, Germany
Study Site 68: Dürerstr. 132, 66424 Homburg, Germany
Study Site 69: August Bebel Str. 33, 01219 Dresden, Germany
Study Site 70: LützнerStr. 149, 04179 Leipzig, Germany
Study Site 75: Kösliner Str. 12, 38642 Goslar, Germany
Study Site 76: Bürgerstr. 2, 09113 Chemnitz, Germany
Study Site 77: Liboristr. 1, 33096 Paderborn
Study Site 78: Humboldtallee 6, 37073 Göttingen, Germany
Study Site 79: Grafenstr. 29, 64283 Darmstadt, Germany
Study Site 81: Geschwister-Scholl-Str. 1, 04416 Markkleeberg, Germany

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

Study Period:

Date first subject signed informed consent form: February 16, 2005

Date of last subject's last visit/contact (from the Clinical database): August 24, 2006

Objectives:

Determination of the course of B-type Natriuretic Peptide (BNP) over 4 months of constant therapy and its correlation to other objective heart failure (HF)-parameters (e.g. left ventricular ejection fraction (LVEF), New York Heart Association (NYHA)-class, Selbstbeurteilungs-Fragebogen 36 (SF-36) health survey questionnaire scores) in order to generate further efficacy data for the angiotensin-II type-I receptor-blocker Candesartan Cilexetil (CC) in the treatment of heart failure when administered in an "added" regimen to standard HF-therapy with at least Angiotensin-Converting Enzyme (ACE)-inhibitors.

Methodology: Open-label, non-controlled and multicenter clinical trial

Number of Subjects:

Planned: 400 patients to be enrolled in order to achieve 360 evaluable cases
Screened: 473 patients screened and enrolled
Treated: 414 patients (safety analysis set)
Analyzed: 383 patients eligible for the full-analysis set, 355 patients for the per-protocol set

Diagnosis and Main Criteria for Inclusion:

Male or female patients of at least 18 years of age suffering from heart failure with systolic dysfunction and LVEF $\leq$ 40% since at least 4 weeks and without any expected deterioration in the next 4 months according to clinical experience. BNP of more than 200 pg/ml at baseline. NYHA class II or III in stable condition since 3 months and a 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 treatment phase with test preparation was defined to be 22 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	8 mg tablets	8 mg QD	Oral	242H05
Candesartan	16 mg tablets	16 mg QD	Oral	246H07, 258H02, 274I03
Candesartan	2 x 16 mg tablets	32 mg QD	Oral	

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

Study Medication	Product Dose Strength	Study Dosage	Mode of Administration	Drug Product Lot Number
N/A	N/A	N/A	N/A	N/A

Criteria for Evaluation:

Efficacy:

Primary

Course of BNP determined by evaluation of the mean change from baseline (V1) to the final study visit (V6) measured by the Biosite "Triage Cardiac System".

Secondary

Mean change from V0/V1 to V6 for LVEF, NYHA-class, SF-36-scores and N-terminal pro-B-type Natriuretic Peptide (NT-proBNP), mean change from V4 to V6 for NYHA-class, BNP and NT-proBNP, correlations of BNP with LVEF, NYHA-class, SF-36-scores and NT-proBNP, subgroup evaluation regarding ß-blocker therapy (yes / no) and NYHA-class (II / III), subgroup evaluation for the different possible dosages of study medication during the 16 weeks of constant therapy (i.e. 8, 16 or 32 mg).

Safety:

Incidence of adverse events, change of routine and safety laboratory parameters, changes in physical examination and vital signs, ECG recording and the rate of premature withdrawals.

Statistical Methods:

The statistical software used was SAS® version 8.2, the MedDRA dictionary Version 8.1 was used for coding of adverse events, medical history and previous/concomitant diseases. Previous and concomitant medication/therapy were coded according to the WHO terminology using version 2006/01 of the WHO-DRL dictionary.

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 BNP during the 22-week period of study treatment, i.e. the mean change for V6-V1. Data from all clinical assessments and combined for all participating centers, whether explicitly referred to in the statistics section or not, were presented in summary tables and in individual

patient data listings. Data were summarized with respect to demographic and baseline characteristics as well as efficacy and safety observations and measurements.

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 centre, patient number and visit.

The primary confirmatory analysis of the primary efficacy variable has to be distinguished from supporting exploratory analyses of the primary and secondary variables. All p-values and confidence levels of additional inferential statistical methods are to be interpreted in the exploratory sense only.

SUMMARY OF RESULTS:

Baseline Demographics and Other Relevant Characteristics:

Parameter	Items	Total (n=414)	Male (n=336)	Female (n=78)
Sex	Male (%)	336 (81.2)	336 (100.0)	---
	Female (%)	78 (18.8)	---	78 (100.0)
Age (years)	Mean (SD)	68.2 (9.7)	67.8 (9.7)	70.2 (9.7)
Height (cm)	Mean (SD)	171.3 (8.5)	173.9 (6.8)	160.3 (6.0)
Weight (kg)	Mean (SD)	81.4 (14.9)	83.8 (13.8)	71.4 (15.1)
BMI (kg/m2)	Mean (SD)	27.7 (4.5)	27.7 (4.0)	27.8 (6.1)
Ethnic Origin	Caucasian (%)	414 (100.0)	336 (100.0)	78 (100.0)
Smoking Habits	Never (%)	182 (44.0)	121 (36.0)	61 (78.2)
	Ex-Smoker (%)	189 (45.7)	179 (53.3)	10 (12.8)
	Currently (%)	43 (10.4)	36 (10.7)	7 (9.0)
Use of Alcohol	No (%)	286 (69.1)	217 (64.6)	69 (88.5)
	Yes (%)	128 (30.9)	119 (35.4)	9 (11.5)

Percentages based on the total number of patients per group; SD = standard deviation

Subject Disposition:

A total of 473 patients were enrolled of which 414 patients were treated with at least one dose of study medication. The primary reason of termination in the 59 patients screened and enrolled but not treated was patient's decision to withdraw in three patients, adverse event in one case and different protocol violations in 55 patients. From the 414 treated patients, a total of 96 patients (23.2%) discontinued the study prematurely.

Premature study discontinuation (all patients treated; n=414)

Patients with	All patients treated; n = 414
Regular study termination	318 (76.8%)
Premature discontinuation	96 (23.2%)
Reason for discontinuation	

Adverse events	40 (9.7%)
Patient's decision for withdrawal	16 (3.9%)
Death	12 (2.9%)
Protocol violation	12 (2.9%)
Non-compliance	9 (2.2%)
Study drug intolerance	3 (0.7%)
Change to NYHA-class IV	2 (0.5%)
Others	2 (0.5%)

The statistical analysis of the primary study efficacy parameter was carried out using the group of patients with at least one baseline and one post-baseline BNP-value. This condition was not fulfilled in a total of 31 patients which were to be excluded from the all-patients-treated set, thus leading to a full-analysis-set of 383 patients. Moreover, a total of 59 patients presented major protocol violations and were excluded as well from the all-patient-treated set, leading to 355 patients allocated to the per-protocol analysis set.

Efficacy Results: (Full-Analysis-Set: n=383; Per-Protocol-Set: n=355)

In the following, study results for primary and secondary efficacy parameters are presented, providing the difference in BNP between the visits as Means (SD) and Medians together with pertinent 95%-CIs and p-values for the changes.

(SD: standard deviation; CI: confidence interval; MPB: minimal post-baseline value; LVEF: left ventricular ejection fraction; SF-36: health-survey-questionnaire; PCS/MCS: physical/mental component score of SF-36; NYHA: New York Heart Association)

Primary parameter:

BNP; V6-V1 [pg/ml]:	**Mean ± SD**	**95% CI†**	**p-value†**	**Medians (Min. – Max.)**	**95% CI§**	**p-value§**
Full-Analysis-Set						
Baseline (V1)	539.7±443.5			394.0 (60.0 - 3890.0)		
Final Visit (V6)	447.6±481.7			295.0 (6.0 - 3520.0)		
Change (V6-V1)	-92.0 ±446.4	-136.9 to -47.2	<0.0001	-102.0 (-1946.0 - 2477.0)	-117.0 to -73.0	<0.0001
Per-Protocol-Set						
Baseline (V1)	535.4±445.4			382.0 (158.0 - 3890.0)		
Final Visit (V6)	454.4±490.4			297.0 (6.0 - 3620.0)		
Change (V6–V1)	-80.9±446.1	-127.5 to -34.4	0.0004	-94.0 (-1946.0 - 2477.0)	-112.0 to -69.0	<0.0001

† - t-test for paired samples, H_0: $\mu \geq 0$; § - Wilcoxon signed rank test, H_0: $\mu \geq 0$

Secondary parameters (Full-Analysis-Set)

Parameter	Mean ± SD	95% CI[†]	p-value[†]	Medians (Min. – Max.)	95% CI[§]	p-value[§]
BNP; V6-V4 [pg/ml]						
End of Titration (V4)	427.1±420.6			316.5 (5.0 - 3150.0)		
Final Visit (V6)	448.5±495.6			290.0 (6.0 - 3620.0)		
Change (V6-V4)	21.4±416.8	-23.2 to 66.0	0.8275	-5.5 (-2173 - 2320.0)	-20.0 to 11.0	0.5136
BNP; MPB-V1 [pg/ml]						
Baseline (V1)	539.7±443.5			394.0 (60.0 - 3890.0)		
Minimum post-baseline	313.7±283.2			235.0 (5.0 - 1830.0)		
Change (MPB-V1)	-226.0±344.5	-260.6 to -191.4	<0.0001	-155.0 (-2070.0 - 679.0)	-177.0 to -133.0	<0.0001
NT-proBNP; V6-V1 [pg/ml]						
Baseline (V1)	2625.6±2454.5			1809.0 (1809.0 - 15175.0)		
Final Visit (V6)	2262.1±2506.1			1412.5 (1412.5 - 19293.0)		
Change (V6 – V1)	-363.5±1742.6	-540.7 to -186.3	<0.0001	-231.5 (-231.5 - 12775.0)	-352.0 to -146.0	<0.0001
NT-proBNP; V6-V4 [pg/ml]						
End of Titration (V4)	2256.7±2833.6			1497.5 (23.1 - 30937.0)		
Final Visit (V6)	2205.9±2553.5			1322.5 (11.7 - 19293.0)		
Change (V6-V4)	-50.8±2277.7	-303.7 to 202.1	0.3465	-8.5 (-18771.0 - 11305.0)	-106.4 to 73.0	0.5119
LVEF; V6-V0 [%]						
Screening (V0)	30.5±6.7			31.0 (10.0 - 62.0)		
Final Visit (V6)	36.2±10.2			36.0 (5.0 - 67.0)		
Change (V6-V0)	5.7 ± 9.2	4.7 to 6.7	<0.0001	5.0 (-33.0 - 49.0)	4.0 to 5.0	<0.0001
SF-36-PCS; V6-V1 [score]						
Baseline (V1)	39.3±8.5			38.5 (15.7 - 60.3)		
Final Visit (V6)	42.0±8.7			42.4 (19.6 - 60.3)		

Parameter	Mean ± SD	95% CI†	p-value†	Medians (Min. – Max.)	95% CI§	p-value§
Change (V6-V1)	2.6±8.0	1.7 to 3.6	<0.0001	2.0 (-24.5 - 27.6)	1.4 to 3.4	<0.0001
SF-36-MCS; V6-V1 [score]						
Baseline (V1)	45.0±11.0			45.4 (5.5 - 72.1)		
Final Visit (V6)	46.8±10.9			47.4 (13.4 - 64.8)		
Change (V6-V1)	1.8±11.3	0.5 to 3.1	0.0039	1.1 (-35.4 - 43.5)	-0.1 to 3.0	0.0049

†- t-test for paired samples, H0: $\mu \geq 0$; § - Wilcoxon signed rank test, H0: $\mu \geq 0$

NYHA-ratings	NYHA I	NYHA II	NYHA III	Improved	Unchanged/ Deteriorated	p-value†
NYHA V6-V0 [n (%)]	23 (6.0)/0 (0.0)	242 (63.2)/151 (39.4)	118 (30.8)/232 (60.6)	140 (36.6)	243 (63.4)	≥0.9999
NYHA V6-V4 [n (%)]	22 (6.5)/4 (1.2)	218 (64.5)/195 (57.7)	98 (29.0)/139 (41.1)	68 (20.1)	270 (79.9)	≥0.9999

†p-value (H_0: $\pi 1 \geq \pi 2$) of chi-square test with $\pi 1$ = percent unchanged/deteriorated and $\pi 2$ = percent improved

Exploratory subgroup analyses in terms of primary and secondary parameters for the V6-V0/V1 change revealed predominantly similar results as already described above for the total sample with the exception of BNP, NT-proBNP and SF-36 changes for the subgroups 'without β-blocker' and 'constant dose 8 mg'.

The calculation of correlations for the BNP changes (V6-V0/V1 and V6-V4) to the secondary parameters NT-proBNP, NYHA-Class, LVEF and SF-36-Scores is displayed below (r = correlation coefficient):

BNP-change V6-V1 correlations	r-value	p-value	n patients
NT-proBNP V6 - V1:	0.58463	<0.0001	374
LVEF V6 - V0:	-0.10245	0.0552	351
NYHA-Class V6 - V0:	0.17555	0.0006	383
SF-36-PCS V6 - V1:	-0.10023	0.0868	293
SF-36-MCS V6 - V1:	-0.01805	0.7538	293
BNP-change V6-V4 correlations			
NT-proBNP V6 - V4:	0.64242	<0.0001	314
NYHA-Class V6 - V4:	0.12480	0.0217	338

The pertinent results for calculation of correlations of the BNP change V6-V0/V1 to secondary variables regarding the different subgroups β-blocker therapy, NYHA-class and constant dosage group revealed obvious correlations again only for NT-proBNP without any clear differences between the subgroups.

The corresponding per-protocol analysis of the main demographic variables as well as of the primary and secondary efficacy parameters (per-protocol set of patients: n=355) did not show any major difference to the results calculated on the basis of the full analysis set presented above.

Safety Results: (All-Patients-Treated-Set: n=414)

Adverse events (AEs) occurred in 223/414 (53.9%) patients with 510 individual events classified as treatment emergent adverse events (TEAEs). Most frequently reported were hypotension in 47 (11.4%), dizziness in 37 (8.9%) and serum creatinine increase in 26 (6.3%) patients. Serious adverse events (SAEs) occurred in 84 (20.3%) cases with 130 individual events mainly based on hospitalization (120 events). The SAEs were described as cardiac (39 patients), nervous system (14 patients) or renal/urinary (11 patients) disorders. SAEs with assumed relationship to study drug were predominantly specified as hypotension, headache, dizziness, increase of serum creatinine/potassium, and renal failure/insufficiency. This distribution also applies to premature termination due to AE observed in 58/414 patients (14.0%) reporting 84 single events. During the study course 13 cases of death were recorded (3.1%) based on a total of 17 single events which were all assessed as not related to the administration of study medication by the investigators.

The AE-course was unique for 170, intermittent for 151 and continuous for 184 events. Regarding severity 215 events were assessed as mild, 190 as moderate and 100 as severe. Relationship to study drug administration was rated as unlikely/not related in 307, as possibly related in 82, as probably related in 78 and as definitely related in 43 single events. Mostly AEs were classified as recovered during study (n=379), whereas 91 events did not yet recover at study end or recovered with sequelae (n=11). The incidence of TEAEs continuously increased from 8 over 16 until the 32 mg dosage. Within these dose groups, incidence was further raised in

patients without beta-blocker therapy, but relevant differences in terms of relationship to study medication could not be observed between the individual subgroups.

For laboratory analyses the variables with a noticeable change during study course in the sense of raised values after being normal or lowered at screening were serum creatinine, potassium, glucose and urea. A slight decrease could be observed for the calculated estimated Glomerular Filtration Rate (eGFR). An increase of creatinine and potassium with a depending slight decrease in eGFR can be expected for HF-patients within a clinical study collective treated with Angiotensin-Receptor Blockers (ARBs) considering the known influence on the renal function.

The evaluation of vital signs showed a further slight lowering of both systolic and diastolic blood pressure during the study course as expected for this study-specific add-on-treatment with Candesartan.

Conclusions

The present clinical study confirms the therapeutic potential of Candesartan Cilexetil to improve the leftventricular function in heart failure patients by lowering blood pressure and the systemic vascular resistance, and thus optimizing heart failure treatment using the 'add-on-regimen'. In this context, the heart failure associated parameters BNP, NT-proBNP, LVEF and patient's general health (SF-36-scores) can be regarded as strong markers for the onset of the effect already at the start of therapy and during the recommended titration period, respectively. A comparable 'early effect' for the NYHA-stage could not be verified and the best responses were seen in patients with a basic therapeutic regimen including -blockers and for a constant dose of more than 8 mg Candesartan (i.e., for either 16 mg or 32 mg). The reported mean improvement of LVEF of 5% absolute (16% relative) has a definite clinical relevance since it is in accordance with the improvement of the NYHA-stage in NYHA-III patients.

An obvious correlation of BNP-changes was only confirmed regarding the development of NT-proBNP. In terms of safety results the study did not reveal any potential new or unexpected signs or symptoms allocated to the study drug in comparison to the known range of ARB-specific adverse reactions including changes in laboratory parameters and vital signs. Observations like hypotension, headache, dizziness, increase of serum creatinine or potassium, and renal failure/insufficiency are consistent with the expected safety profile of the used ARB. In contrast, cardiovascular disorders like cardiac failure, angina pectoris, myocardial infarction, tachy-/bradyarrhythmia or syncope but also findings like cerebral infarction, gastroenteritis and osteoarthritis must be clearly associated with the specific clinical conditions in the patients considered for this study and are therefore causally unrelated to the use of ARBs.

Serum creatinine/potassium increase and renal failure/insufficiency have to be regarded in connection with the known influence of ARBs like Candesartan on the blood pressure but also on the renal function. The conditions of patients with such events in this study can be attributed to the specific study population with a more advanced stage of heart failure at study entry than in previous clinical trials, confirmed by high portions of NYHA III patients (60.6%) and of patients under -blocker therapy (91.3%) at study start. Hence, monitoring of renal function especially

during titration must remain an important issue for heart failure therapy with Candesartan which is, however, already the well-established current clinical practice.

Significant Changes During Study:

Changes to the study protocol or the conduct of the clinical trial in the sense of officially approved substantial amendments were not issued during the entire study period.

As laid down in the final statistical analysis plan the following modifications of planned statistical evaluations described in the protocol were made:

- In contrast to study protocol, it was decided that the change for the objective primary study endpoint BNP was to be calculated as the BNP-value at the final visit (V6; day 154 ± 6) minus the BNP-value at baseline (V1; day 0) instead of BNP-value at baseline minus BNPvalue at the final visit. The reason was to have a correlated negative result for the expected decrease of the BNP- (and also NT-proBNP-) values during the study treatment period.
- In addition to the protocol, the mean change from baseline (V1) of the minimum post-baseline BNP-value ('best response value') was to be analyzed as further secondary efficacy variable.
- In addition to the protocol, the exploratory analysis of secondary efficacy variables was also to be done with Wilcoxon signed-rank tests for the secondary endpoints NT-proBNP, LVEF, SF-36 scores (PCS, MCS), and the minimum post-baseline BNP-value.
- In addition to the protocol, the eGFR (estimated Glomerular Filtration Rate) was to be calculated and analyzed analogously to serum creatinine.

Study ID Number:

BLO K022

Other Study ID Number(s):

2004-003962-14 [EudraCT Number]

DATE OF DISCLOSURE SYNOPSIS: 30 April 2013