Clinical Study Synopsis

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Bayer HealthCare

Clinical Trial Results Synopsis

Study Design Description		
Study Sponsor:	Bayer Healthcare Pharmaceuticals Inc.	
Study Number:	12480	NCT00559650 EudraCT2007-003059-36
Study Phase:	IIb	
Official Study Title:	Placebo controlled, randomized, double-blind, multi-center, multinational Phase IIb study to investigate the efficacy and tolerability of BAY 58-2667 given intravenously in patients with acute decompensated chronic congestive heart failure	
Therapeutic Area:	Cardiology/Coagulation	
Test Product		
Name of Test Product:	Cinaciguat (BAY 58-2667), intravenous (IV) formulation	
Name of Active Ingredient:	Cinaciguat	
Dose and Mode of Administration:	BAY 58-2667 IV infusion in addition to standard therapy A total of 5 dose steps of BAY 58-2667 (50 µg/h, 100 µg/h, 200 µg/h, 400 µg/h, and 600 µg/h), administered intravenously, per subject were planned. A dose of 100 µg/h was the starting dose. In case, the subject did not tolerate the dose of 100 µg/h, the dose could be reduced to a minimum of 50 µg/h. Uptitration: The dose was to be up-titrated if systolic blood pressure (SBP) was ≥ 100 mmHg and if heart rate (HR) was ≤110 beats per minute (BPM) until a dose of 400 µg/h was reached. If SBP was ≥ 110 mmHg and HR was ≤ 110 BPM, the dose could be up-titrated to the maximum dose of 600 µg/h. The maximum volume of infusion administered was 532 mL. No change: The dose was to be maintained if SBP was between ≥90 mmHg and < 100 mmHg and HR was ≤ 110 BPM. Down-titration: If the subject had a sustained SBP fall <90 mmHg and/or a sustained rise of HR to > 110 BPM and was asymptomatic, the pulmonary capillary wedge pressure (PCWP) was to be determined. If PCWP < 16 mmHg, 250 mL of IV fluid was to be given. If PCWP was > 16 mmHg, the study medication was to be down-titrated following the same procedure as the up-titration (the minimum dose was 50 µg/h). Treatment was discontinued if: • Sustained SBP fall to <90 mmHg and/or there was a sustained rise of heart rate to >110 BPM, and the subject suffered from clinical	

	signs such as sweating, nausea and palpitations despite the fact the study medication had been down-titrated and/or IV fluids had been administered • Sustained SBP fall to <90 mmHg and/or there was a sustained rise of HR to >110 BPM was seen and no further dose reduction of study medication was possible • There was a sustained increase of HR to ≥ 120 BPM
Reference Therapy/Placebo	
Reference Therapy:	Matching placebo IV infusion in addition to standard therapy
Dose and Mode of Administration:	Matching placebo IV infusion was administered according to the same regimen as the investigational (test) drug.
Duration of Treatment:	The titration period lasted 8 hours. The maintenance period lasted between 16 and 40 hours, with maximum infusion time of 48 hours.
Studied period:	**Date of first subjects' first visit:** 04 DEC 2007 **Date of last subjects' last visit:** 06 MAR 2009
Premature Study Suspension / Termination:	Yes Following a recommendation by the Data Monitoring Committee (DMC) [formerly: Data Safety Monitoring Board (DSMB)], the study was put on hold and prematurely terminated by the Sponsor after 158 subjects had been screened and 150 subjects had been randomized. The reason for premature suspension was a pronounced pharmacodynamic effect of BAY 58-2667, leading to non-sustained hypotensive events during titration, beginning at doses of 200 µg/h, which was the second titration step. In agreement with the Steering Committee, the Sponsor put this phase IIb dose finding trial with its current design on hold on 09 FEB 2009 following the decision of the Steering Committee which was based on a recommendation of the DMC.
Substantial Study Protocol Amendments:	The study was conducted according to Study protocol latest version from 20 MAR 2009, and included 2 substantial amendments: Amendment no.1 dated 19 MAY 2008 was enacted for the following changes: • To increase safety measures for the subjects in the study, an additional follow-up visit with blood sampling and additional assessments of the scores was instituted. The Steering Committee (committee of external cardiologists who supervised the study) recommended that there should be no up-titration of the study drug from 400 µg/h to 600 µg/h if the subject's SBP was below 110 mmHg. This was added to the titration rules. In addition, subjects with a heart rate above 120 BPM were excluded from the study (new exclusion criteria). • To perform thyroid stimulating hormone (TSH) measurement during

	the study, as requested by the German Health Authority (BfArM). • To clarify and resolve a few inconsistencies in the protocol (e.g., titration and stopping rules) as requested by some ethics committees. Amendment no.3 dated 20 MAR 2009 was submitted only for information to the IECs and regulatory authorities. In agreement with the Steering Committee, Bayer put this Phase IIb dose finding trial with its current design on hold on 09 Feb 2009. Amendment no. 3 was enacted to obtain a better understanding of the characteristics of BAY 58-2667 and to generate additional data to provide safety recommendations. It was planned to collect all mean values of blood pressure, heart rate, and right atrial pressure which were documented in the time between the study visits 8 + 30 min and 24 + 30 min.
Study Center(s):	The multinational study was conducted at 32 centers in 13 countries. Number of active centers: Germany (7); Poland (4); Serbia (4); Italy (4); Israel (2); Lithuania (2); Russia (2); the United States (2); Canada (1); Croatia (1); Hungary (1); Slovenia (1); and Spain (1). Sites in Czech Republic, Estonia, United Kingdom and Sweden were terminated.
Methodology:	The study was a randomized, double-blind, placebo-controlled, multi-center, multinational study in subjects with acute decompensated heart failure (ADHF) with the need for parenteral pharmacotherapy and invasive hemodynamic monitoring and PCWP $\geqslant$ 18 mmHg. The study was divided into three periods including screening, treatment, and follow-up period. The screening period included the admission of the subjects to the hospital, the primary diagnostic procedures, and selection of eligible subjects. The baseline assessments were performed at the end of the run-in phase, shortly before the start of study medication infusion, if possible within 60 minutes. The treatment period ranged from 8 to 48 hours. A follow-up visit was performed at 30 + 5 days after inclusion. If this was not possible, a telephone follow-up was performed to assess morbidity and mortality. The subjects were asked to report dyspnea assessments using visual analogue scale (VAS) dyspnea score. Subjective dyspnea was quantified by Likert scale, which was part of a response sheet alongside the VAS Dyspnea score. The overall health status was reported using a European Quality of Life VAS (EQ-5D VAS) score. The assessment of the scores was performed before the hemodynamic measurements. All score assessments were done at baseline, during treatment, at the end of treatment, and at follow-up (if possible). In addition to these timepoints, blood sampling for laboratory tests, hemodynamic measurements, blood pressure, heart rate, and O_2 saturation rate measurements was also done at screening phase. A physician assessment of treatment effect (improvement, unchanged, or worsening) was also obtained. For investigation of study treatment exposure behavior and potential relationships to effects, plasma concentrations of BAY 58-2667 were determined using

	a sparse sampling approach in all participating subjects. Adverse events (AEs) data was collected througout the study.
Indication/ Main Inclusion Criteria:	Indication: Congestive heart failure. Main inclusion criteria: • Subjects with decompensated acute chronic congestive heart failure, New York Heart Association (NYHA) functional class III–IV, either ischemic or non-ischemic, requiring hospitalization, and with clinical indication for parenteral pharmacotherapy and invasive hemodynamic monitoring (i.e., indwelling Swan-Ganz pulmonary artery catheter) and PCWP ≥ 18 mmHg • Male or female subjects aged 18 years or more
Study Objectives:	**Overall:** To investigate the safety and efficacy of a titration phase (8 hours) and a maintenance phase (maximum 40 hours; in total 48 hours) of BAY 58-2667 administered intravenously in addition to standard therapy in subjects with acute decompensated chronic congestive heart failure with the need for parenteral pharmacotherapy and invasive hemodynamic monitoring (i.e., indwelling Swan-Ganz pulmonary artery catheter) and PCWP ≥ 18 mmHg.
Evaluation Criteria:	**Efficacy (Primary):** • Change of PCWP from baseline to 8 hours (investigational drug vs. placebo) **Efficacy (Secondary):** • Quality of life assessed by EQ-5D VAS (upto 30 days follow-up) • Re-hospitalization (upto 30 days follow-up) • Other hemodynamic measurements: Right atrial pressure (RAP); mean pulmonary artery pressure (PAP mean); pulmonary artery systolic pressure (PASP); pulmonary artery diastolic pressure (PADP); cardiac output (CO); cardiac index (CI); mean arterial pressure (MAP); pulmonary vascular resistance (PVR); pulmonary vascular resistance index (PVRI); systemic vascular resistance (SVR); and systemic vascular resistance index (SVRI) **Safety:** Treatment-emergent adverse events, laboratory parameters, renal function, in-hospital mortality, length of stay at intensive care unit, and 30-day mortality/morbidity.
	Pharmacokinetics: Plasma concentrations during both the titration and maintenance phases were evaluated.
Statistical Methods:	**Efficacy (Primary):** The primary efficacy analysis was performed on the per protocol population of the titration phase (PPT) from baseline to 8 hours/ last observation carried forward (LOCF). Analysis performed on the per protocol population of the maintenance phase (PPM) and the intent-to-

	treat (ITT) population was supportive, as was the time point 48 hours/last observation carried forward (LOCF). In the efficacy analyses, centers were clustered by geographic region (e.g., country). The decision on center pooling was made before unblinding. Statistical analyses were adjusted to these clusters of centers. Change from baseline to 8 hours/LOCF in PCWP in the per protocol population was evaluated using analysis of covariance (ANCOVA), with baseline PCWP as a covariate, treatment group and country/region as main effects, comparing between BAY 58-2667 and placebo. In addition, 95% two-sided confidence intervals of the treatment group differences were calculated. The interaction between treatment group and country/region was also investigated. **Efficacy (Secondary):** Values of PCWP at other time points post-baseline and other efficacy parameters in the per protocol population were considered secondary, and supportive to the primary efficacy comparison. These secondary parameters were analyzed using ANCOVA, as described above. The analysis was also to be performed with the ITT population, supportive to the per protocol analysis. **Safety:** Safety parameters were tabulated using descriptive statistics by treatment group. Adverse events were coded by Medical Dictionary for Regulatory Activities (MedDRA) Version 12.0.
	Pharmacokinetics: Median plasma concentrations during both the titration and maintenance phases were calculated.
Number of Subjects:	Planned: 210 (BAY 58-2667 group: 140, placebo group: 70) Enrolled: 150 (BAY 58-2667 group: 99, placebo group: 51) Analyzed: 148 (BAY 58-2667 group: 97, placebo group: 51)

Study Results

Results Summary — Subject Disposition and Baseline

In total, 158 subjects were screened for study eligibility; 8 subjects were screening failures and were not randomized. Of 150 randomized subjects, two (1.3%) never took study medication and were not included in the safety analyses, resulting in 148 (98.7%) subjects valid for safety analysis. A total of 146 subjects (97.3%) were valid for ITT analysis; 139 subjects (92.7%) were valid for per protocol analysis in the PPT, and 106 subjects (70.7%) were valid for per protocol analysis in the PPM. The rates of subjects valid for ITT analysis (100.0% placebo group vs 96.0% BAY 58-2667 group) and valid for PPT analysis (96.1% vs 90.9%) were similar, but valid for PPM analysis (82.4% vs 64.6%) was different, reflecting the increased withdrawal rate in the BAY 58-2667 group prior to and during the maintenance phase.

The subjects in safety population had a mean age of 61.3 ±11.24 years and a mean BMI of 29.0 ± 5.54 kg/m^2. Majority of the subjects were male (85.1%) and Caucasians (white; 98.6%). For the safety population, 13 of 51 (25.5%) subjects in the placebo group were female as compared 9 of 97 (9.3%) subjects in the BAY 58-2667 group. A difference in sex was seen between the treatment groups. This observation was most likely due to chance. The

demographic data for subjects valid for the PPT were similar to those in the safety population.

Results Summary — Efficacy

Primary efficacy

The absolute values, change from baseline and the statistical analyses for the per protocol populations, are summarized in the table below **(Table** 1). There was a statistically significant (P < 0.0001) difference between BAY 58-2667 and placebo for the change in PCWP from baseline to 8 hours (or to last observation in this period) in both the per protocol populations. In the primary PPT population, the least squared (LS) mean reduction in PCWP was 7.66 mmHg in the BAY 58-2667 group compared to 3.69 mmHg in the placebo group, a mean difference of 3.97 mmHg. Hence, the primary aim of the study was met. The mean difference in the PPM population was slightly higher, possibly due to all the subjects in this population having received study medication for the full 8 hour titration period. The results in the ITT population were consistent with the PPT population.

At 48 hours (or last observation in the maintenance period), there was no statistically significant difference (P = 0.56) between the two treatment groups. The LS mean reduction from baseline to 48 hours/LOCF was slightly higher in the BAY 58-2667 group at 6.52 mmHg compared to 5.82 mmHg in the placebo group.

Table 1: PCWP (mmHg) - Summary statistics at baseline, 8 hours/LOCF and 48 hours/LOCF (ANCOVA with baseline assessment as covariate**)**

Time	Placebo LS Mean	BAY 58-2667 LS Mean
PPT population	(n = 49)	(n = 90)
Baseline	25.30	25.87
Change 8 hours/LOCF	-3.69	-7.66
Difference BAY 58-2667-Placebo [95% CI] at 8 hours/LOCF		3.97 [2.10; 5.83]
P value		<0.0001
PPM population	(n = 42)	(n = 64)
Baseline	25.37	25.74
Change 8 hours/LOCF	-3.99	-8.18
Difference BAY 58-2667-Placebo [95% CI] at 8 hours/LOCF		4.19 [2.16;6.21]
P value		<0.0001
Change 48 hours/LOCF	-5.82	-6.52
Difference BAY 58-2667-Placebo [95% CI] at 48 hours/LOCF		0.70 [-1.65;3.04]
P value		0.56

Abbreviations: PCWP = pulmonary capillary wedge pressure; LOCF = last observation carried forward; ANCOVA = analysis of covariance; LS = least squared; CI = confidence interval; PPT = per protocol titration population; PPM = per protocol maintenance population

Secondary efficacy

Other hemodynamic measurements: A beneficial effect was found during titration at 8 hours in all the secondary hemodynamic parameters (nominal P < 0.0001, except RAP, P=0.0019). The beneficial effect (LS mean change from baseline) was maintained until the end of hemodynamic measurements (48 hours) in PVRI, PVR, and MAP (nominal P ≤ 0.05), and it

was most pronounced in SVR (-549 vs. -179 dyn s/cm^5), SVRI (-1075 vs. -356 dyn s/cm^5/m^2), CO (+1.47 vs. +0.17 L/min), and CI (+0.73 vs. +0.08 L/min/m^2), each with nominal P < 0.0001.

Quality of life and overall health status of the subjects were assessed by the EQ-5D VAS. The estimated (LS mean) increases from baseline were larger in the BAY 58-2667 group than in the placebo group, but did not reach statistical significance in any of the exploratory tests. The maximum difference between groups on the EQ-5D VAS (LS mean 5.57 points) was found at 48 hours/LOCF (nominal P = 0.092).

Re-hospitalization: According to the hospital ward information provided by the investigators, 12 subjects were re-hospitalized, notably two subjects (3.9%) in the placebo group and 10 subjects (10.3%) in the BAY 58-2667 group. Except for one subject in the placebo group where no details were given, the re-hospitalization was due to serious adverse events, and the reasons were cardiac failure in eight subjects; and cholecystolithiasis, endocarditis, and implantation of a biventricular pacemaker with defibrillator in one subject each.

Results Summary — Safety

Extent of exposure

The duration of treatment with study drug, expressed as mean ± standard deviation (range), was 29.5 ± 15.5 hours (0.5 – 56.8 hours) in the BAY 58-2667 group and 37.1 ± 13.6 hours (4.6 – 48.9 hours) in the placebo group.

Adverse Events

The reason for premature termination of the study was a pronounced pharmacodynamic effect of test drug, leading to hypotensive events during titration beginning at doses of 200 µg/h, which s the second titration step.

A brief summary of treatment-emergent adverse events is given in the table below (Table 2). Any such events were recorded for 71.1% of subjects in the BAY 58-5667 group and 45.1% in the placebo group. Treatment-emergent serious adverse events were reported for 9.3% of subjects receiving BAY 58-2667 and for 2.0% subjects receiving placebo. The most common treatment-emergent adverse event, by preferred term, was hypotension (BAY 58-2667: 50.5%; placebo 11.8%); it was considered drug-related in most subjects (BAY 58-2667: 48.5%; placebo 7.8%).

There were 5 deaths during the course of the study (within 30 + 5 days), notably in two subjects (2.1%) receiving BAY 58-2667 and three subjects (5.9%) receiving placebo. The fatalities in the BAY 58-2667 group were a 70yearold man who died of treatment-emergent worsening of heart failure, and a 60yeaold man who died of post-treatment ischemic stroke. Neither of these fatal adverse events w considered to be related to study medication. The causes of death in the placebo group were mesenteric ischemia, worsening of heart failure, and bradycardia/cardiogenic shock following renal failure and cardiac arrest; none of these fatal events were regarded as drug-related. All five subjects died in hospital.

Table 2: Adverse event summary - Safety Analysis

Incidence of	Placebo N=51 (100%)	BAY 58-2667 N=97 (100%)
Any adverse event [a]	30 (58.8%)	75 (77.3%)
Any treatment-emergent adverse event [a]	23 (45.1%)	69 (71.1%)
Any drug-related treatment-emergent adverse event [a]	9 (17.6%)	58 (59.8%)
Any treatment-emergent adverse event resulting in permanent discontinuation of study drug [a]	4 (7.8%)	24 (24.7%)
Any adverse event starting more than 2 days after stop of study drug [a]	14 (27.5%)	37 (38.1%)
Any serious adverse event [a]	6 (11.8%)	22 (22.7%)
Any serious treatment-emergent event	1 (2.0%)	9 (9.3%)
Any drug-related serious treatment-emergent adverse event	0 (0.0%)	5 (5.2%)
Any serious adverse event starting more than 2 days after stop of study drug	5 (9.8%)	14 (14.4%)
Any treatment-emergent serious adverse event resulting in death	0 (0.0%)	1 (1.0%)
Any death [b]	3 (5.9%)	2 (2.1%)

A: including serious adverse events
b: as a result of post-treatment (not treatment-emergent) serious adverse events
Treatment-emergent: adverse events starting after first application of double-blind study drug up to 2 days after stop of double-blind study drug

Other observations related to safety

The value of serum creatinine was found to be above the upper limit of normal (ULN) in 20.9% of subjects receiving test drug and in 14.6% of placebo subjects. In addition, troponin I was found to be above the upper limit of normal (ULN) in 7.7% of subjects receiving BAY 58-2667 compared 0.0% in placebo subjects. The creatinine clearance determined based on the Modification of Diet in Renal Disease (MDRD) formula decreased in the BAY°58-2667 group at 24 hours (−8.96 mL/min), while it was largely unchanged in the placebo group. At the follow-up visit, the change from baseline was comparable in both groups. Decrease in B-type natriuretic peptide (BNP) under treatment was faster and more pronounced in the BAY 58-2667 group.

A clinically meaningful increase in troponin I (defined as troponin I levels ⩾1.0 ng/mL [⩾ 2.5 X ULN] or higher) either at baseline or during study drug infusion was observed in 17 subjects (11.5%) and was more frequent in subjects receiving BAY 58-2667 (13.4%) than placebo (7.8%). In 11 (7.4%) subjects (BAY 58-2667: 7.2%; placebo: 7.8%), troponin I was elevated already before administration of study drug (normal range ⩽0.4 ng/mL); 6 (4.1%) experienced treatment-emergent troponin I increases ⩾1.0 ng/mL. Increases in troponin I may be indicative of an acute myocardial injury, which was supported by concomitant increase in creatine kinase or serum glutamic oxaloacetic transaminase/alanine transaminase in 6 subjects (BAY 58-2667 5.2%; placebo 2.0%). Only two (1.4%) subjects (BAY 58-2667 1.0%; placebo 2.0%) had electrocardiogram (ECG) recordings which showed evidence of myocardial ischemia present at the time of troponin I elevations. The comparative data vs placebo indicate a slightly higher incidence of treatment-emergent troponin I increase in the BAY 58-2667 group. However, none of the subjects with either troponin I increase at baseline or during study drug infusion showed clinical signs or symptoms of myocardial ischemia.

In other laboratory parameters, there was no clinically important difference between treatment groups in the incidence rates of treatment-emergent abnormalities. In accordance with the more frequently observed hypotensive events, there was a more pronounced and sustained decrease in systolic and diastolic blood pressure in the BAY 58-2667 group in comparison to placebo. The HR at baseline was already higher in the BAY 58-2667 group in comparison to placebo (81.9 BPM vs 76.2 BPM). The largest increase in HR in the BAY 58-

2667 group was 5.4 BPM and observed 8 hours after start of study drug infusion.

No clinically important differences between treatment groups were detected in the ECG parameters including the QT interval corrected for HR (QTc). Thirty day mortality and morbidity defined as either death within 30 + 5 days of randomization or re-hospitalization occurred in 5 subjects of the placebo group (9.8%) and 12 subjects of the BAY 58-2667 group (12.4%).

Results Summary — Pharmacokinetics

Median BAY 58-2667 plasma concentrations during both the titration and maintenance phases increased dose-dependently, and were in the range previously reported for BAY 58-2667 plasma exposure data in ADHF patients.

Conclusion(s)

This study supports the clinical efficacy of BAY 58-2667 intravenous formulation in subjects with ADHF. Regarding the primary efficacy outcome, a highly significant difference between test drug and placebo was demonstrated in the change from baseline to 8 hours in PCWP. This effect occurred in conjunction with very similar changes in all the secondary hemodynamic measures. There were particularly beneficial and sustained effects on cardiac index, which were seen over the entire period of hemodynamic observation.

Evaluation of safety showed that some dosages administered to subjects with ADHF in this study were above the therapeutic range. BAY 58-2667 is a guanylate cyclase activator with vasodilating properties; therefore, blood pressure lowering is an expected pharmacodynamic effect of BAY 58-2667. However, in this trial, the incidence of hypotension exceeded the acceptable level starting from the second dosage step corresponding to 200 µg/h. Consequently, further clinical studies will use the lower dosages (<°200°µg/h) to investigate whether subjects benefit from additional treatment with BAY 58-2667 on top of standard therapy when used in the therapeutic dose range.

Publication(s):	Erdmann E, Semigran MJ, Nieminen MS, Gheorghiade M, Agrawal R, Mitrovic V, Mebazaa A. Cinaciguat, a soluble guanylate cyclase activator, unloads the heart but also causes hypotension in acute decompensated heart failure. Eur Heart J. 2013 Jan;34(1):57-67.		
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