Clinical Study Synopsis

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The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

Date of study report:	02 JUN 2008
Study title:	Proof of concept study to investigate the impact of BAY 58-2667 given intravenously in patients with acute decompensated chronic congestive heart failure
Sponsor's study number:	11615
NCT number:	Not applicable
EudraCT number:	2005-004473-14
Sponsor:	Bayer HealthCare
Clinical phase:	Phase II
Study objectives:	**Part A** Primary objective • To investigate the hemodynamic and subjective effects on dyspnea as well as well-being of the subjects following 3 intravenous (IV) doses of BAY 58-2667 given over 2 h per dose step in a dose escalation manner. Secondary objectives • To investigate the safety, tolerability, pharmacodynamics (PD), and pharmacokinetics (PK) of the respective dose levels. **Part B** Primary objective • To investigate the hemodynamic effects of BAY 58-2667 given IV over 6 h. Secondary objectives • To investigate the safety, tolerability, PD, PK, and subjective effects on dyspnea of the respective dose levels of BAY 58-2667.
Test drug:	Cinaciguat (BAY 58-2667)
Name of active ingredient(s):	Cinaciguat
Dose:	**Part A** Doses (D) for **Cohort 1**: D1=50 µg/h/, D2=100 µg/h/, D3=200 µg/h/subject for 2 h per dose step, i.e., 6 h total infusion duration. Doses for **Cohort 2**: D4=100 µg/h/, D5=200 µg/h/, D6=400 µg/h/subject for 2 h per dose step, i.e., 6 h total infusion duration. Planned **Cohort 3 was skipped** and dosing for Part B started based on the results of Cohort 1 and 2.

	Part B: Doses were 100, 200, 400 µg/h/subject (or lower doses following the 100 µg/h starting dose depending on systolic blood pressure [SBP]) for 2 h per dose step, i.e., 6 h total infusion duration.
Route of administration:	IV infusion of solution of BAY 58-2667
Duration of treatment:	In each cohort, infusion duration was of 2 h at each dose level and a total infusion duration of 6 h per subject
Reference drug:	Not applicable
Background treatment:	The basic medication given during the run-in phase consisted of inhalative oxygen, diuretics, and morphine, if required.
Indication:	Decompensated chronic congestive heart failure (CHF)
Diagnosis and main criteria for inclusion:	• Critically ill subjects, male (older than 18 years) and female (older than 55 years), admitted to hospital with decompensated chronic CHF and clinical indication for parenteral pharmacotherapy with invasive hemodynamic monitoring and a Pulmonary capillary wedge pressure (PCWP) of ≥18 mmHg. • Postmenopausal female subjects or women without child bearing potential based on surgical treatment like bilateral tubal ligation, bilateral ovariectomy, or hysterectomy.
Study design:	This was a multicenter, open-label study comprising of 2 parts (Parts A and B). Part A consisted of 2 cohorts (Cohort 1 and 2), where BAY 58-2667 was given intravenously over 2 h per dose step, for a total of 6 h, in a dose escalation manner in each cohort. For Part B, starting dose level of BAY 58-2667 was the optimal dose chosen from Part A. Dose titration in an individual subject in both Part A and B was stopped or the dose reduced once SBP had fallen below the target blood pressure of 100 mmHg.
Methodology:	For each subject the study included a run-in phase in which subjects were admitted to the hospital. Primary diagnostic procedures, indication for the treatments, and selection for the participation in this trial was done along with administration of basic medication. Run-in phase was followed by an investigational part where baseline measurements were taken and study drug administered. For treatment, subjects either entered Part A (Cohort 1or 2) or Part B and received IV infusion of study drug in a dose-escalation manner depending on cohort or part of the study as described above. The investigational part of the study ended 8 h after the start of infusion of the study drug with additional safety measurements about 24 h thereafter. The planned duration of the study was about 3 months for Part A and 4 months for Part B. Hemodynamic measurements and blood sampling (PK) were done at the following time points: • At the end of run in: Baseline measurement: 0d00

	• Thereafter 0.5, 1.0, and 2.0 h after each dose step, i.e., ▪ D1: 0d00:30, 0d01, 0d02 ▪ D2: 0d02:30, 0d03, 0d04 ▪ D3: 0d04:30, 0d05, 0d06 • After stop of infusion: 0d06:30, 0d07, 0d08. The same schedule was applicable for Cohort 2 and Part B. In case the dose was not changed at 0d02 and 0d04, the measurements at 0d02:30 and 0d04:30 were skipped in Part B. Blood sampling for biochemical analyte measurement was done up to 24 h after start of infusion. Two days after administration of study drug or before discharge from hospital, a follow-up was performed. Safety and tolerability of investigational product were monitored throughout the study.
Study center(s):	The study was conducted at 7 centers in Germany.
Publication(s) based on the study (references):	Lapp H, Mitrovic V, Franz N, Heuer H, Buerke M, Wolfertz J, et al. BAY 58–2667, a soluble guanylate cyclase activator, improves cardiopulmonary haemodynamics in acute decompensated heart failure and has a favourable safety profile. BMC Pharmacol. 2007;7(Suppl 1): S9. Lapp H, Mitrovic V, Franz N, Heuer H, Buerke M, Wolfertz J, et al. Cinaciguat (BAY 58-2667) improves cardiopulmonary hemodynamics in patients with acute decompensated heart failure. Circulation. 2009 Jun 2;119(21):2781-8. Boerrigter G and Burnett JC Jr. Soluble guanylate cyclase: not a dull enzyme. Circulation. 2009 Jun 2;119(21):2752-4.
Study period:	**Study Start Date:** 03 MAY 2006 **Study Completion Date:** 21 MAY 2007
Early termination:	Not applicable
Number of subjects:	**Planned:** 30 subjects in Part A (10 subjects in each planned 3 cohorts); 30 subjects in Part B **Analyzed:** 60 subjects (27 subjects in Part A [12 in Cohort 1 and 15 in Cohort 2] and 33 subjects in Part B)
Criteria for evaluation	
Efficacy:	Not applicable
***Safety*:**	Subjective tolerability was evaluated by recording of AEs. AEs were

classified according to their seriousness, severity (mild, moderate, severe), relationship to investigational product. The AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 8.1. The objective tolerability was evaluated by the incidence of abnormal findings in measurements of vital parameters (HR and blood pressure), ECG, and laboratory findings (hematology, clinical chemistry).

Clinical pharmacology: Pharmacodynamics:

Primary PD parameter

- Pulmonary capillary wedge pressure (mmHg)

Secondary PD parameters:

- Subjective dyspnea and well-being score (7-point Likert Scale)
- Hemodynamic measurements
  - Swan-Ganz hemodynamics
    - ✓ **Measured**: Mean right atrial pressure (RAPmean, mmHg); systolic, diastolic, and mean pulmonary artery pressure (PAPsyst, PAPdiast, PAPmean), HR, cardiac output (CO); systemic blood pressure, i.e., systolic, diastolic blood pressure and mean arterial pressure (SBP, DBP, MAP)
    - ✓ **Calculated**: Pulmonary vascular resistance (PVR); pulmonary vascular resistance index (PVRI); systemic vascular resistance (SVR); systemic vascular resistance index (SVRI); cardiac index = CO/body surface area (BSA)
  - Impedance cardiography: Stroke volume (SV_{imp}), cardiac output (CO_{imp}), heart rate (HR_{imp}), cardiac index
- Biochemical parameters: Noradrenaline, adrenaline, N-terminal ANP, N-terminal BNP, cyclic guanosine monophosphate (cGMP), and plasma renin activity (PRA)
- Functional classification according to NYHA (New York Heart Association)

Pharmacokinetics:

Primary PK parameters (for both Part A and B)

- Drug concentration in plasma after 2,4, and 6 h of start of infusion (C_2 h, C_4 h, and C_6 h); area under curve (AUC) from time 0-2 h, 2-4 h, and 4-6 h after start of infusion (AUC_{0-2}, AUC_{2-4}, and AUC_{4-6}); and AUC_{0-2}, AUC_{2-4}, and AUC_{4-6} divided by dose (AUC_{0-2}/D, AUC_{2-4}/D, and AUC_{4-6}/D)

Secondary PK parameters (for both Part A and B)

- Area under the plasma concentration vs time curve from zero to infinity

after single dose (AUC), AUC divided by dose per kg body weight

- (AUC_{norm}), AUC from time 0 to the last data point (AUC_{0-tn}), maximum drug concentration in plasma after single dose (C_{max}), maximum drug concentration in plasma after single dose administration divided by dose (mg) per kg body weight ($C_{max,norm}$), mean residence time after an IV administration (MRT_{iv}), time to reach maximum drug concentration in plasma after single dose (t_{max}), half-life associated with the terminal slope ($t_{1/2}$), total body clearance of drug from plasma calculated after IV administration (CL), apparent volume of distribution at steady state (V_{ss}), and apparent volume of distribution during terminal phase (V_z).

Statistical methods: Analysis sets

All subjects who pass the intended dosage regimens over the complete period of 6 h without major changes vs protocol were included in the evaluation of pharmacodynamics.

All subjects with valid pharmacokinetic data were included in the evaluation of pharmacokinetics.

All subjects who received at least one dose of the trial medication were included in the safety evaluation.

Demographic and other baseline characteristics

Summary statistics (arithmetic mean, standard deviation [SD], median, minimum and maximum for quantitative variables) were presented by dosage regimen. Frequency tables for qualitative data were provided.

Safety variables

Descriptive methods used for quantitative data were summary statistics (arithmetic mean, SD, median, minimum, and maximum) for the original data as well as for the difference to baseline. Frequency tables were provided for qualitative data. The incidence of treatment-emergent AEs were summarized by dosage regimen using MedDRA.

An interim safety assessment was planned after the completion of each cohort in Part A before starting with the next cohort or Part B.

Pharmacodynamic parameters

Results for PD data were displayed utilizing summary statistics and figures. The exploration of the results for Swan-Ganz hemodynamics included the evaluation of a possible PCWP-reducing effect of BAY 58-2667. Therefore the change of this variable from baseline (calculated as “PCWP end of infusion-PCWP start of infusion”) was displayed. The associated one-sided 90% confidence interval ($-\infty$, c) was calculated for Part B assuming that the observations for PCWP followed a normal distribution.

Pharmacokinetic parameters

The concentration vs time courses of BAY 58-2667 were summarized

	separately for each dosage regimen. The following statistics were calculated for each of the sampling points: arithmetic mean; SD and coefficient of variation (CV); geometric mean; geometric standard deviation (retransformed SD of the logarithms) and CV; and minimum, median, and maximum value and the number of measurements. Individual and mean plasma-concentration vs time curves were plotted using both linear and semi-logarithmic scale. PK characteristics (t_{max} excluded) were summarized by the statistics mentioned above. T_{max} was described utilizing minimum, maximum, and median as well as frequency counts.
Substantial protocol changes:	The study was conducted according to the final study protocol, Version 3 from 20 FEB 2006 and included no substantial amendments.

Subject disposition and baseline

Out of the 71 subjects enrolled into the study, 11 subjects failed screening and a total of 60 subjects were included in the study and were valid for safety analysis. Forty-five subjects were valid for PD analysis and 44 subjects (88%) were valid for PK analysis. Mean overall age of the subjects was 65.8 years (range 36.0-87.0) with a BMI of 27.98 kg/m^2 (5.18 SD). In Part A, Cohort 1, 12 subjects, 10 men and 2 women (mean age 69.2 years, range: 50-87 years), were included and completed the study. In Part A, Cohort 1, 8 subjects were valid for PD and PK analyses, and 12 subjects were valid for safety analyses. In Part A, Cohort 2, 15 subjects, 14 men and 1 woman (mean age 65.5 years, range: 41-84 years), were included. Seven subjects (47%) discontinued study drug prematurely, 6 subjects (40%) due to adverse events and 1 subject (7%) was lost to follow-up. In Part A, Cohort 2, 7 subjects were valid for PD and PK analyses, and 15 subjects were valid for safety analyses. In Part B, 33 subjects, 31 men and 2 women (mean age 64.7 years, range: 36-81 years), were included; 30 subjects (91%) completed the study; 1 subject discontinued study drug permanently due to an adverse event; 1 subject died; and 1 subject was lost to follow-up. In Part B, 29 subjects were valid for PD analyses; 30 subjects for PK analyses; and 33 subjects were valid for safety analyses.

Efficacy evaluation

Not applicable

Safety evaluation

Twenty-four of 60 subjects (40%) reported 42 treatment-emergent AEs (TEAEs). Twenty-seven AEs were of mild, 13 of moderate, and 2 of severe intensity. Thirteen subjects experienced 14 drug-related, TEAEs. Eleven drug-related AEs were of mild and 3 of moderate intensity. The 3 moderate drug-related AEs were hypotension (n=2) and dyspnea (n=1).

Tables 1 and 2 below display the proportion of subjects with incidence of TEAEs and drug-related TEAEs, respectively.

Table 1: Proportion of subjects with treatment-emergent adverse events (all subjects valid for safety, n=60)

MedDRA Primary System Organ Class Preferred Term	Part A Cohort 1 (n=12)	Part A Cohort 2 (n=15)	Part B (n=33)	Total (n=60)
Number of subjects with any adverse event	8 (67%)	10 (67%)	6 (18%)	24 (40%)
CARDIAC DISORDERS	3 (25%)	1 (7%)	2 (6%)	6 (10%)
Angina pectoris	1 (8%)		1 (3%)	2 (3%)
Atrial thrombosis	1 (8%)			1 (2%)
Cardiac failure			1 (3%)	1 (2%)
Intracardiac thrombus		1 (7%)		1 (2%)
Myocardial infarction	1 (8%)			1 (2%)
Myocardial ischemia	1 (8%)			1 (2%)
Pericardial effusion		1 (7%)		1 (2%)
GASTROINTESTINAL DISORDERS	3 (25%)	1 (7%)		4 (7%)
Nausea	2 (17%)	1 (7%)		3 (5%)
Vomiting	1 (8%)			1 (2%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		2 (13%)	4 (12%)	6 (10%)
Asthenia		1 (7%)		1 (2%)
Injection site edema			1 (3%)	1 (2%)
Malaise			1 (3%)	1 (2%)
Pyrexia		1 (7%)	2 (6%)	3 (5%)
INFECTIONS AND INFESTATIONS		1 (7%)		1 (2%)
Influenza		1 (7%)		1 (2%)
METABOLISM AND NUTRITION DISORDERS			1 (3%)	1 (2%)
Gout			1 (3%)	1 (2%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	2 (17%)	3 (20%)		5 (8%)
Back pain	1 (8%)	2 (13%)		3 (5%)
Muscle spasms	1 (8%)			1 (2%)
Musculoskeletal chest pain		1 (7%)		1 (2%)
Neck pain	1 (8%)			1 (2%)
NERVOUS SYSTEM DISORDERS	1 (8%)	2 (13%)		3 (5%)
Headache		2 (13%)		2 (3%)
Somnolence	1 (8%)			1 (2%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		2 (13%)	1 (3%)	3 (5%)
Dyspnea		2 (13%)		2 (3%)
Respiratory failure			1 (3%)	1 (2%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (8%)			1 (2%)
Erythema	1 (8%)			1 (2%)
VASCULAR DISORDERS	3 (25%)	4 (27%)	2 (6%)	9 (15%)
Hot flush	2 (17%)			2 (3%)
Hypotension		4 (27%)	2 (6%)	6 (10%)
Thrombophlebitis	1 (8%)			1 (2%)

Table 2: Proportion of subjects with treatment-emergent, drug-related adverse events (all subjects valid for safety, n=60)

MedDRA Primary System Organ Class Preferred Term	Part A Cohort 1 (n=12)	Part A Cohort 2 (n=15)	Part B (n=33)	Total (n=60)
Number of subjects with any adverse event	4 (33%)	6 (40%)	3 (9%)	13 (22%)
GASTROINTESTINAL DISORDERS	1 (8%)	1 (7%)		2 (3%)
Nausea	1 (8%)	1 (7%)		2 (3%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			1 (3%)	1 (2%)
Malaise			1 (3%)	1 (2%)
NERVOUS SYSTEM DISORDERS	1 (8%)	1 (7%)		2 (3%)
Headache		1 (7%)		1 (2%)
Somnolence	1 (8%)			1 (2%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		1 (7%)		1 (2%)
Dyspnea		1 (7%)		1 (2%)
VASCULAR DISORDERS	2 (17%)	4 (27%)	2 (6%)	8 (13%)
Hot flush	2 (17%)			2 (3%)
Hypotension		4 (27%)	2 (6%)	6 (10%)

The 2 severe TEAEs were also serious AEs (SAEs): cardiac failure, which resulted in death, and myocardial infarction, which resolved after remedial drug therapy. Cardiac failure occurred 5 days after the last dose of study drug following elective surgery for implantable cardioverter defibrillator exchange. One subject experienced an SAE, i.e., moderate intracardiac thrombus. The investigators considered all SAEs as not related to study drug treatment. Four subjects discontinued study drug treatment permanently due to 5 AEs: hypotension (n=2), dyspnea (n=1), back pain (n=1), and respiratory failure (n=1). The investigators considered all events apart from back pain and respiratory failure as related to study drug treatment.

Laboratory abnormalities were typical of the study population selected, i.e., critically ill subjects admitted to hospital with decompensated chronic CHF, and the study population did not reveal any suspicion for a specific laboratory abnormality related to BAY 58-2667 treatment. In particular, there was no indication of serum creatinine increases related to BAY 58-2667 treatment. Mean changes vs baseline in HR, SBP, DBP, and MAP during the 6-h BAY 58-2667 treatment and the subsequent 2-h follow-up period were limited in all 3 treatment groups as were changes in HR, SBP, and DBP up to 05d00h00min. Although changes vs baseline in single subjects were pronounced, increases in HR and decreases in SBP, DBP, and MAP did not result in critically high HR or low blood pressure values. It is of note that, in Part B, maximum HR values detected at baseline and after 6 h of infusion were virtually identical, i.e., 116 and 115 bpm. No clinically relevant influence of BAY 58-2667 on ECG parameters including QTc was detected.

Clinical pharmacology evaluation

Pharmacodynamic evaluation:

Single IV infusion doses of 50-400 µg/h BAY 58-2667 over 2 h per dose level were administered (total infusion time: 6 h). Part A was a dose-escalation in 2 cohorts and served as dose finding for Part B. In Part B, “real-life” dose-titration of BAY 58-2667 was performed, i.e., all subjects started on 100 µg/h

BAY 58-2667 IV for 2 h. Subsequently, the dose was individually titrated to achieve a clinically relevant decrease in PCWP >4 mmHg, whereas SBP was to remain >100 mmHg.

Swan-Ganz hemodynamic results of Part A are summarized for Cohort 1 (50, 100, 200 µg/h for 2 h per dose step) and Cohort 2 (100, 200, 400 µg/h for 2 h per dose step) in Tables 3 and 4 below. (Please note that, in Tables 3-5, the mean difference between 00d00h00min and 00d06h00min was calculated as the mean of the individual differences and not as the difference of the means at 00d00h00min and 00d06h00min).

Based on the pronounced hemodynamic effects at a dose of 400 µg/h in Cohort 2 and the assessment of safety by the data and safety monitoring board, skipping the originally planned third cohort of Part A with higher doses and proceeding with Part B was recommended. Swan-Ganz hemodynamic results for the entire group of subjects treated in Part B are summarized in Table 5. This analysis included the results of the 3 subgroups, i.e., subjects with a final dose of 400 µg/h (n=16), 200 µg/h (n=12), and 50 µg/h (n=2).

Table 3: Swan-Ganz hemodynamic parameters (mean values, all patients of Part A, Cohort 1 [50, 100, 200 µg/h for 2 h per dose step], valid for PD, n=8)

Parameter	Unit	00d00h00min (start of infusion)	00d06h00min (end of infusion)	Difference between 00d00h00min and 00d06h00min
RAPmean	mmHg	9.4	6.8	-2.6
PAPsyst	mmHg	54.0	48.5	-5.5
PAPdiast	mmHg	23.3	18.3	-5.0
PAPmean	mmHg	35.1	30.6	-4.5
PCWP	mmHg	23.3	18.3	-5.0
HR	BPM	67.0	73.1	6.1
SBP	mmHg	126.8	116.8	-10
DBP	mmHg	67.3	62.9	-4.4
MAP[a]	mmHg	87.0	80.9	-6.1
CO	L/min	3.63	4.46	0.84
PVR[a]	$dyn*sec*cm^{-5}$	291.3	253.1	-38.20
PVRI[a]	$dyn*sec*cm^{-5}*m^2$	554.0	484.6	-69.44
SVR[a]	$dyn*sec*cm^{-5}$	1803	1481	-321.9
SVRI[a]	$dyn*sec*cm^{-5}*m^2$	3469	2882	-587.3
Cardiac index[a]	$L/min/m^2$	1.85	2.29	0.44

a calculated parameter

Table 4: Swan-Ganz hemodynamic parameters (mean values, all patients of Part A, Cohort 2 [100, 200, 400 µg/h for 2 h per dose step], valid for PD, n=7)

Parameter	Unit	00d00h00min (start of infusion)	00d06h00min (end of infusion)	Difference between 00d00h00min and 00d06h00min
RAPmean	mmHg	9.3	7.2	-2.2
PAPsyst	mmHg	42.9	37.9	-5.0
PAPdiast	mmHg	21.0	16.1	-3.5
PAPmean	mmHg	29.7	25.0	-4.7
PCWP	mmHg	21.6	13.4	-8.1
HR	BPM	73.7	85.1	11.4
SBP	mmHg	121.6	115.3	-6.3
DBP	mmHg	72.4	60.7	-11.7
MAP[a]	mmHg	88.7	79.0	-9.7
CO	L/min	5.08	6.36	1.29
PVR[a]	$dyn*sec*cm^{-5}$	146.4	154.6	8.18
PVRI[a]	$dyn*sec*cm^{-5}*m^2$	299.5	317.3	17.75
SVR[a]	$dyn*sec*cm^{-5}$	1236	936.6	-298.9
SVRI[a]	$dyn*sec*cm^{-5}*m^2$	2579	1993	-585.6
Cardiac index[a]	$L/min/m^2$	2.32	2.95	0.62

a calculated parameter

Table 5: Swan-Ganz hemodynamic parameters (mean values, all patients of Part B (starting dose 100 µg/h for 2 h titrated up to 200 µg/h for 2 h and 400 µg/h for 2 h if SBP >110 mmHg], valid for PD, n=30)

Parameter	Unit	00d00h00min (start of infusion)	00d06h00min (end of infusion)	Difference between 00d00h00min and 00d06h00min
RAPmean	mmHg	13.0	10.1	-2.9
PAPsyst	mmHg	54.1	48.1	-6.0
PAPdiast	mmHg	23.6	17.9	-5.7
PAPmean	mmHg	36.0	29.4	-6.5
PCWP	mmHg	25.0	17.2	-7.9
HR	BPM	76.7	81.1	4.4
SBP	mmHg	119.0	105.7	-13.9
DBP	mmHg	72.6	57.9	-14.5
MAP[a]	mmHg	88.1	73.8	-14.3
CO	L/min	4.24	5.92	1.68
PVR[a]	$dyn*sec*cm^{-5}$	223.1	179.7	-43.4
PVRI[a]	$dyn*sec*cm^{-5}*m^2$	445.3	360.8	-84.5
SVR[a]	$dyn*sec*cm^{-5}$	1581	971.0	-596.6
SVRI[a]	$dyn*sec*cm^{-5}*m^2$	3167	1944	-1198
Cardiac index[a]	$L/min/m^2$	2.07	2.88	0.82

a calculated parameter

Subjective well-being in comparison to baseline was assessed by the dyspnea score. Results are presented in Tables 6, 7, and 8 for Part A Cohort 1, Part A Cohort 2, and Part B, respectively.

Table 6: Dyspnea score (all subjects of Part A, Cohort 1 [50, 100, 200 µg/h for 2 h per dose step], valid for PD, n=8)

Time	Median	Unchanged		Slight improvement		Improvement		Significant improvement	
00d02h00min	0.50	4/8	(50%)	2/8	(25%)	2/8	(25%)	0/8	(0%)
00d04h00min	1.00	3/8	(38%)	2/8	(25%)	3/8	(38%)	0/8	(0%)
00d06h00min	1.50	2/8	(25%)	2/8	(25%)	3/8	(38%)	1/8	(13%)
00d08h00min	1.00	3/8	(38%)	2/8	(25%)	2/8	(25%)	1/8	(13%)
01d00h00min	1.00	2/8	(25%)	3/8	(38%)	2/8	(25%)	1/8	(13%)

Table 7: Dyspnea score (all subjects of Part A, Cohort 2 [100, 200, 400 µg/h for 2 h per dose step], valid for PD, n=7)

Time	Median	Unchanged		Slight improvement		Improvement		Significant improvement	
00d02h00min	1.00	3/7	(43%)	3/7	(43%)	1/7	(14%)	0/7	(0%)
00d04h00min	1.00	1/7	(14%)	3/7	(43%)	3/7	(43%)	0/7	(0%)
00d06h00min	2.00	1/7	(14%)	2/7	(29%)	3/7	(43%)	1/7	(14%)
00d08h00min	1.00	1/7	(14%)	3/7	(43%)	2/7	(29%)	1/7	(14%)
01d00h00min	2.00	1/7	(14%)	2/7	(29%)	3/7	(43%)	1/7	(14%)

Table 8: Dyspnea score (n/n [%], all subjects of study Part B [starting dose 100 µg/h for 2 h titrated up to 200 µg/h for 2 h and 400 µg/h for 2 h if SBP >110 mmHg] valid for PD, n=30)

Time	Median	Unchanged	Slight improvement	Improvement	Significant improvement	Not available
00d02h00min	0.00	22/30 (73)	5/30 (17)	2/30 (7)	1/30 (3)	0/30 (0)
00d04h00min	1.00	8/30 (27)	17/30 (57)	4/30 (13)	1/30 (3)	0/30 (0)
00d06h00min	1.00	4/30 (13)	15/30 (50)	10/30 (33)	1/30 (3)	0/30 (0)
00d08h00min	1.00	3/30 (10)	14/30 (47)	10/30 (33)	1/30 (3)	2/30 (7)
01d00h00min	2.00	2/30 (7)	11/30 (37)	15/30 (50)	2/30 (7)	0/30 (0)

In all subjects valid for PD in Part B (n=30), mean PCWP was reduced from 25.0 mmHg at baseline to 17.2 mmHg after 6 h of BAY 58-2667 infusion, mean HR increased by 4.4 beats per minute (bpm) (range: -23-28), and SBP decreased by 13.9 mmHg (range: -44 to19) during that time. It is of note that maximum HR values detected at baseline and after 6 h of infusion were virtually identical, i.e., 116 and 115 bpm.

Similar results were determined in the 2 subgroups of subjects with a final dose of 400 µg/h (n=16) and 200 µg/h (n=12). In the 2 subjects with a final dose of 50 µg/h, PCWP decreased by 7 and 14 mmHg during the 6 h of infusion. The upper 90% confidence limit of -7.15 mmHg showed that the PCWP results after 6 h of infusion differed significantly from PCWP results at baseline (00d00h00min) (all subjects valid for PD in Part B). For 27 of 30 subjects (90%), the decrease in PCWP from baseline to end of infusion was ≥4 mmHg. Similar results were detected in the subgroup of subjects with a final dose of 400 µg/h (n=16). Both subgroups with a final dose of 200 µg/h and 400 µg/h were homogeneous with regard to demographic data and baseline values of Swan-Ganz hemodynamics.

Subjects were asked about their well-being in comparison to their baseline conditions. Questioning was done before hemodynamic measurements of the respective time point were performed. Please note that this assessment was neither double-blinded nor placebo-controlled. After 6 h of BAY 58-2667 infusion in Part B, 26 of 30 subjects (87%) reported an improvement in their well-being; 18 h after end of infusion (01d00h00min), 28 of 30 subjects (93%) reported an improvement. No clear dose-response relationship was detected in CHF patients and their NYHA classification. No subject reported deterioration in the dyspnea score.

Stroke volume, cardiac output (SV_{imp}*HR_{imp}), and cardiac index measured by impedance cardiography were poorly correlated to Swan-Ganz hemodynamics with Spearman correlation coefficients of 0.4046, 0.4754, and 0.3330, respectively. Although changes vs baseline in some vasoactive hormones, such as adrenaline, noradrenaline, and PRA, were statistically significant in Part B, neurohormonal activation by BAY 58-2667 was limited and clinically irrelevant. There were virtually no changes vs baselines in mean N-terminal ANP and N-terminal BNP in either cohort of Part A or in Part B. Consistent mean increases in plasma cGMP were detected in both cohorts of Part A and in Part B at the end of infusion (00d06h00min). These changes lasted up to 01d00h00min in Cohort 2 of Part A and Part B.

Pharmacokinetic evaluation:

Tables 9 and 10 summarize the results as geometric means, geometric coefficients of variation (%CV), and ranges of the PK parameters for BAY 58-2667 by treatment in all subjects valid for PK (n=44) and the 3 subgroups of subjects valid for PK in Part B (n=29), respectively.

On an average, subjects with acute decompensated chronic CHF had a reduced BAY 58-2667 clearance, most probably due to impaired cardiac output and reduced liver blood flow in these patients, leading to higher AUC and C_{max} values (individually up to 50%) than reported previously in healthy young male subjects. Otherwise, PK behavior was similar, especially the fast increase in plasma concentrations after start of infusion and rapid decline of concentrations after stop of infusion with concentrations at or below 1 µg/L at 1-2 hours after end of infusion. BAY 58-2667 pharmacokinetics were of moderate inter-individual variability. Plasma concentration and AUC results suggested dose-proportionality in the dose range administered, i.e., 50-400 µg/h. In deviation from the protocol, the pharmacokinetic parameter C_{max}/D was not determined.

Table 9: Pharmacokinetic parameters of BAY 58-2667 in plasma (geometric mean/%CV [range], all subjects valid for PK, n=44)

Parameter	Unit	Part A Cohort 1 (n=8)	Part A Cohort 2 (n=7)	Part B (n=24-29)
AUC	µg*h/L	25.61 / 32.2 (9.554 - 37.96)	43.06 / 22.2 (26.95 - 65.87)	37.28 / 34.1 (16.20 - 125.1)
AUC(0-2)	µg*h /L	3.431 / 27.0 (1.631 – 4.911)	5.401 / 30.5 (2.988 - 8.880)	4.945 / 37.4 (1.855 - 14.06)
AUC(2-4)	µg*h /L	7.410 / 34.0 (2.628 - 10.86)	11.61 / 25.8 (5.771 - 16.48)	10.96 / 27.3 (4.623 - 27.52)
AUC(4-6)	µg*h /L	11.63 / 42.4 (3.261 - 20.16)	20.16 / 27.1 (10.80 - 31.16)	15.30 / 47.4 (3.772 - 61.99)
AUC_{norm}	kg*h/L	3.207 / 20.1 (2.036 – 4.809)	2.981 / 10.4 (2.335 - 3.596)	2.886 / 29.4 (1.488 - 6.253)
AUC(0-2)/D	h/L	0.034 / 26.0 (0.016 – 0.045)	0.027 / 31.1 (0.014 - 0.044)	0.026 / 47.8 (0.009 - 0.254)
AUC(2-4)/D	h/L	0.040 / 19.4 (0.026 – 0.054)	0.029 / 26.2 (0.014 - 0.041)	0.030 / 27.8 (0.017 - 0.074)
AUC(4-6)/D	h/L	0.035 / 19.7 (0.023 – 0.050)	0.028 / 32.0 (0.013 - 0.051)	0.029 / 31.2 (0.013 - 0.077)
AUC(0-tn)	µg*h /L	25.36 / 32.0 (9.515 - 37.80)	42.09 / 22.3 (26.82 - 63.12)	36.36 / 32.9 (16.01 - 123.1)
C_2h	µg/L	2.127 / 29.1 (1.146 - 3.932)	3.819 / 29.8 (1.909 - 5.812)	3.086 / 85.9 (0.025 - 16.07)
C_4h	µg/L	4.400 / 40.3 (1.529 - 7.682)	6.553 / 31.2 (3.186 - 10.41)	5.192 / 94.9 (0.025 - 15.14)
C_6h	µg/L	4.872 / 54.2 (1.613 - 9.963)	8.875 / 24.3 (4.936 - 14.82)	7.243 / 65.5 (0.690 - 36.93)
C_{max}	µg/L	7.392 / 46.8 (1.703 - 13.28)	12.60 / 22.9 (7.578 - 18.65)	10.04 / 36.3 (3.337 - 36.93)
$C_{max,norm}$	kg/L	0.926 / 24.1 (0.681 – 1.765)	0.872 / 8.2 (0.704 - 0.984)	0.777 / 34.0 (0.438 - 3.629)
$t_{1/2}$	h	0.637 / 18.9 (0.403 – 0.860)	0.863 / 25.0 (0.504 - 1.353)	0.868 / 43.7 (0.224 - 5.150)
MRT_{iv}	h	1.088 / 20.5 (0.739 – 1.651)	1.255 / 11.8 (0.906 - 1.504)	0.933 / 89.7 (0.010 - 5.133)
V_z	L	22.44 / 20.3 (15.66 - 32.65)	38.81 / 33.9 (25.82 - 83.53)	37.37 / 51.8 (9.117 - 141.0)
CL	L/h	24.41 / 16.2 (18.30 - 31.40)	31.16 / 23.8 (21.69 - 50.96)	29.86 / 33.1 (11.19 - 60.76)
V_{ss}	L	26.55 / 17.7 (21.12 - 47.42)	39.09 / 31.5 (25.42 - 76.65)	27.85 / 108.0 (0.153 - 136.6)
t_{max} [a]	h	4.758 (4.000- 6.083)	4.500 (4.500- 5.983)	5.000 (2.000 - 6.217)

a Median (range)

Table 10: Pharmacokinetic parameters of BAY 58-2667 in plasma (geometric mean/%CV [range], all subjects of Part B valid for PK, n=29)

Parameter	Unit	Last dose 50 µg/h (n=2)	Last dose 200 µg/h (n=9)	Last dose 400 µg/h (n=13-14)
AUC	µg*h/L	20.76 / 25.2 (16.20 - 26.61)	35.82 / 33.4 (18.84 - 70.57)	41.93 / 32.4 (22.32 - 125.1)
AUC(0-2)	µg*h /L	8.862 / 48.7 (5.586 - 14.06)	5.336 / 38.7 (2.096 - 10.89)	4.305 / 32.4 (1.855 - 13.56)
AUC(2-4)	µg*h /L	5.857 / 24.0 (4.623 - 7.422)	10.90 / 23.3 (6.739 - 20.52)	12.03 / 25.4 (7.322 - 27.52)
AUC(4-6)	µg*h /L	4.309 / 13.4 (3.772 - 4.921)	11.64 / 33.2 (5.357 - 23.71)	21.84 / 30.8 (11.88 - 61.99)
AUC_{norm}	kg*h/L	4.128 / 38.9 (2.835 - 6.011)	3.005 / 31.7 (1.639 - 5.911)	2.649 / 26.2 (1.488 - 6.253)
AUC(0-2)/D	h/L	0.084 / 154.4 (0.028 - 0.254)	0.026 / 38.3 (0.010 - 0.054)	0.022 / 32.4 (0.009 - 0.068)
AUC(2-4)/D	h/L	0.059 / 24.0 (0.046 - 0.074)	0.027 / 22.9 (0.018 - 0.051)	0.030 / 26.1 (0.017 - 0.069)
AUC(4-6)/D	h/L	0.043 / 13.4 (0.038 - 0.049)	0.029 / 32.9 (0.013 - 0.059)	0.027 / 31.3 (0.016 - 0.077)
AUC(0-tn)	µg*h /L	20.47 / 24.9 (16.01 - 26.17)	34.08 / 31.6 (18.72 - 68.44)	41.34 / 31.1 (21.73 - 123.1)
C_2h	µg/L	7.322 / 92.4 (3.337 - 16.07)	2.586 / 148.4 (0.025 - 9.209)	3.168 / 28.8 (1.775 - 8.511)
C_4h	µg/L	2.195 / 0.8 (2.177 - 2.214)	4.527 / 177.1 (0.025 - 15.14)	6.498 / 29.1 (3.734 - 14.32)
C_6h	µg/L	1.617 / 34.7 (1.155 - 2.265)	5.625 / 66.5 (0.690 - 13.66)	10.65 / 40.7 (2.940 - 36.93)
C_{max}	µg/L	7.322 / 92.4 (3.337 - 16.07)	8.006 / 27.0 (4.655 - 15.14)	12.55 / 31.0 (7.102 - 36.93)
$C_{max,norm}$	kg/L	1.456 / 114.2 (0.584 - 3.629)	0.672 / 28.3 (0.438 - 1.261)	0.803 / 25.1 (0.488 - 1.846)
$t_{1/2}$	h	1.079 / 9.1 (0.986 - 1.182)	0.972 / 49.8 (0.562 - 5.150)	0.763 / 41.1 (0.224 - 1.562)
MRT_{iv}	h	nc	1.002 / 60.6 (0.212 - 5.133)	1.336 / 13.6 (0.880 - 2.065)
V_z	L	30.92 / 12.8 (27.23 - 35.12)	39.91 / 53.0 (13.03 - 141.0)	36.29 / 56.5 (9.117 - 103.7)
CL	L/h	19.86 / 22.0 (15.97 - 24.69)	28.48 / 35.5 (14.12 - 60.76)	32.96 / 31.1 (11.19 - 54.78)
V_{ss}	L	nc	28.52 / 62.7 (6.241 - 136.6)	44.02 / 29.9 (17.18 - 77.92)
t_{max} [a]	h	2.125 (2.000- 2.250)	5.000 (2.517- 6.217)	6.000 (4.500 – 6.083)

a Median (range)
nc not calculated

Overall conclusions

In this study, Swan-Ganz hemodynamics and dyspnea score demonstrated that single IV infusion doses of 50-400 µg/h BAY 58-2667 over 2 h per dose level (total infusion time: 6 hours) were effective in decreasing PCWP and increasing subjective well-being.

Subjects with acute decompensated chronic CHF had on average a reduced BAY 58-2667 clearance, most probably due to impaired cardiac output and reduced liver blood flow in these patients, leading to higher AUC and C_{max} values (individually up to 50%) than previously reported in healthy young male subjects. Otherwise, PK behavior was similar to that reported in the healthy young male subjects.

Single IV infusion doses of 50-400 µg/h BAY 58-2667 over 2 h per dose level (total infusion time: 6 h) were safe and generally well tolerated in critically ill subjects admitted to hospital with decompensated chronic CHF. No maximum tolerated dose of BAY 58-2667 was detected in this study.