Cinaciguat (BAY 58–2667) Improves Cardiopulmonary Hemodynamics in Patients With Acute Decompensated Heart Failure

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Cinaciguat (BAY 58–2667) Improves Cardiopulmonary Hemodynamics in Patients With Acute Decompensated Heart Failure

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Background—Cinaciguat (BAY 58–2667) is the first of a new class of soluble guanylate cyclase activators in clinical development for acute decompensated heart failure. We aimed to assess the hemodynamic effects, safety, and tolerability of intravenous cinaciguat in patients with acute decompensated heart failure (pulmonary capillary wedge pressure ≥18 mm Hg).

Methods and Results—After initial dose finding (part A; n=27), cinaciguat was evaluated in the nonrandomized, uncontrolled proof-of-concept part of the study (part B; n=33) using a starting dose of 100 μg/h, which could be titrated depending on hemodynamic response. Patients were categorized as responders if their pulmonary capillary wedge pressure decreased by ≥4 mm Hg compared with baseline. Final doses of cinaciguat after 6 hours of infusion in part B were 50 μg/h (n=2), 200 μg/h (n=12), and 400 μg/h (n=16). Compared with baseline, a 6-hour infusion of cinaciguat led to significant reductions in pulmonary capillary wedge pressure (−7.9 mm Hg), mean right atrial pressure (−2.9 mm Hg), mean pulmonary artery pressure (−6.5 mm Hg), pulmonary vascular resistance (−43.4 dynes · s · cm^{-5}), and systemic vascular resistance (−597 dynes · s · cm^{-5}), while increasing heart rate by 4.4 bpm and cardiac output by 1.68 L/min. The responder rate was 53% after 2 hours, 83% after 4 hours, and 90% after 6 hours. Cinaciguat was well tolerated, with 13 of 60 patients reporting 14 drug-related treatment-emergent adverse events of mild to moderate intensity, most commonly hypotension.

Conclusions—Cinaciguat has potent preload- and afterload-reducing effects, increasing cardiac output. Further investigation of cinaciguat for acute decompensated heart failure is warranted. (***Circulation*. 2009;119:2781-2788.**)

Key Words: drugs ■ heart failure ■ hemodynamics ■ nitric oxide ■ vasodilation

Improvements in the therapy of acute cardiovascular diseases and an aging population have increased the global prevalence of heart failure (HF). In the 49 member states represented by the European Society of Cardiology, an estimated 10 million people suffer from HF,[1] and an equal number may have asymptomatic left ventricular dysfunction[2]; globally, an estimated 23 million people have HF.[3] HF is the most common cause of hospitalization in the elderly.[4] Patients with HF remain at substantial risk of acute decompensated HF (ADHF), with nearly half of older patients with a discharge diagnosis of HF being readmitted within 6 months.[5] Mortality is high; 10% of patients die within 30 days.[6]

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The underlying pathology of ADHF is characterized by endothelial dysfunction, chronic vasoconstriction, an elevated vascular resistance, and an increase in left ventricular end-diastolic pressure (preload and afterload).[7,8] In the healthy endothelium, vascular tone and vasodilation are regulated by cGMP, a second messenger produced by soluble guanylate cyclase (sGC) in response to endogenous or exogenous nitric oxide (NO).[9] This pathway may be disrupted in ADHF because of a decreased bioavailability of NO, together with increases in oxidized and heme-free forms of sGC that are insensitive to NO, resulting in insufficient vasodilation.[10–12] Furthermore, although direct in vivo evidence for the existence of oxidized/heme-free sGC remains circumstantial, in vivo experiments have shown that oxidative stress and related vascular disease states led to an sGC that was indistinguishable from the in vitro oxidized/heme-free enzyme; thus, the physiological existence of oxidized/heme-free sGC can no longer be rejected.[12–14]

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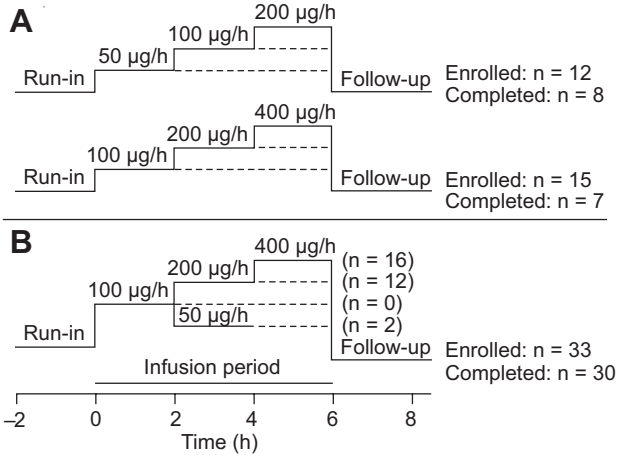

Figure 1. Cinaciguat dosing schedule in parts A and B.

Cinaciguat (BAY 58–2667) is a novel sGC activator in clinical development for ADHF. In preclinical studies, cinaciguat has been shown to act on NO-nonresponsive sGC and to induce vasodilation preferentially in diseased vessels.[11,12,15] The aim of this first study of intravenous cinaciguat in patients (proof of concept) was to assess hemodynamic responses, safety, and tolerability in patients with ADHF.

Methods

Study Design

This nonrandomized, uncontrolled, unblinded, multicenter phase II study consisted of an initial dose-finding part (part A) and a proof-of-concept part (part B). Cinaciguat 0.005% (50 µg/mL; Bayer HealthCare AG, Wuppertal, Germany) was administered as an intravenous infusion in 3 ascending dose steps. Each dose step lasted 2 hours, resulting in a total cinaciguat infusion period of 6 hours. This ascending-dose design and the dose were chosen following the results of a previous study in healthy volunteers, with the 2-hour titration step based on the hemodynamic steady-state evaluation in the same study.[16]

Two cohorts of patients participated in part A, with the dose steps being 50, 100, and 200 µg/h per subject in cohort 1 and 100, 200, and 400 µg/h per subject in cohort 2 (Figure 1). Determination of the optimal dose was based on the numbers of responders (defined as a reduction in pulmonary capillary wedge pressure [PCWP] of ≥4 mm Hg compared with baseline without clinically relevant adverse events) for each dose and on the number of patients achieving a reduction of systolic blood pressure (SBP) to 100 to 110 mm Hg. (Note that a response of PCWP ≥4 mm Hg was based on the results of the Vasodilation in the Management of Acute CHF [VMAC] study,[17] and the minimal SBP was 100 mm Hg according to the protocol.) The decision to reduce or stop cinaciguat dose in parts A and B was at the investigators' discretion, although if patients developed symptomatic hypotension or SBP dropped below 80 mm Hg, the dose was stopped. In part B, dose titration started with the optimal dose identified in part A, and individual titration to target blood pressure was allowed after each 2-hour period (Figure 1).

The study was carried out in accordance with the Declaration of Helsinki and adhered to the International Conference of Harmonization good clinical practice guidelines and the German drug law. The study protocol was approved by the Ethics Committee of the Thuringia Medical Council, Jena, Germany, and the Bundesinstitut für Arzneimittel und Medizinprodukte, Bonn, Germany.

Patients

Male and female patients ≥18 years of age who were admitted to hospital for ADHF were eligible for inclusion in this study if they had ongoing New York Heart Association class III or IV symptoms with a PCWP ≥18 mm Hg and if parenteral pharmacotherapy with invasive hemodynamic monitoring was clinically indicated. Unstable patients; women of childbearing potential; patients with New York Heart Association class I or II HF; those with acute HF requiring acute cardiac intervention or surgery, cardiogenic shock, or catecholamines; patients needing invasive mechanical ventilation; and those with renal failure (creatinine ≥2 mg/dL [177 µmol/L]) were excluded.

After admission to hospital with symptoms of ADHF, routine diagnostic tests, administration of basic therapy (eg, inhaled oxygen, diuretics, and morphine), and decisions about treatment (eg, indication for intravenous therapy and invasive hemodynamic monitoring), eligible patients were informed about this study, asked to participate, and allowed to give their informed consent. Before a cinaciguat infusion was started, the patient's medical history was taken, and a physical examination was performed, including measurement of heart rate, blood pressure, and ECG, and blood samples were taken for safety laboratory tests. All long-term oral medications were withheld before the start of the infusion and continued after the end of the invasive part of the study (1-hour run-in, 6-hour cinaciguat infusion, and 2-hour follow-up periods); intravenous diuretics were permitted only if clinically indicated during this period. Inhaled oxygen and morphine were allowed during the invasive period.

Hemodynamic Parameters

Patients underwent hemodynamic monitoring of SBP, diastolic blood pressure, mean arterial pressure (calculated), and heart rate, which were all measured noninvasively. The following parameters were monitored with a Swan Ganz catheter throughout the invasive period of the study: PCWP, mean right atrial pressure (RAP), mean pulmonary artery pressure (PAP), pulmonary (PVR) and systemic vascular resistance (SVR), and cardiac output. Hemodynamic parameters were measured immediately before the cinaciguat infusion was started to establish baseline values. Commercially available routine assay kits were used for hormone determinations.

Safety Monitoring

All patients underwent screening evaluations before participation in the study. Subjective tolerability was monitored by reporting of patients' well-being, adverse events, New York Heart Association class, and dyspnea score (using a 7-point Likert scale ranging from 3 [clear improvement] to −3 [clear deterioration/worsening]) as described previously.[17] As defined in the study protocol, patients were questioned about their well-being compared with their baseline condition, and their dyspnea score before hemodynamic measurements was assessed in a nonpersuasive manner by a person not involved in (or aware of) hemodynamic measurements and results. Thus, patient-assessed dyspnea and well-being were blinded to hemodynamic measurement.

Clinical adverse events were graded as mild, moderate, or severe and according to whether or not they were considered serious. Objective tolerability was measured by monitoring of vital signs and ECGs, and laboratory parameters were assessed throughout the study. Blood samples were taken at 0, 6, and 8 hours after the start of cinaciguat infusion for measurement of atrial natriuretic peptide, N-terminal prohormone brain natriuretic peptide (NT-proBNP), and renin and noradrenaline concentrations. Follow-up monitoring (physical examination, adverse event questioning, safety laboratory tests, heart rate, blood pressure, and ECG) was carried out 8, 24, and 48 hours after the first administration of cinaciguat, with a final examination at least 2 days after administration of cinaciguat or before hospital discharge. The follow-up period for adverse events was until final examination for all adverse events with active follow-up and 5 days for serious adverse events with active follow-up; after a further 25 days, the investigator reported any serious adverse event that had occurred.

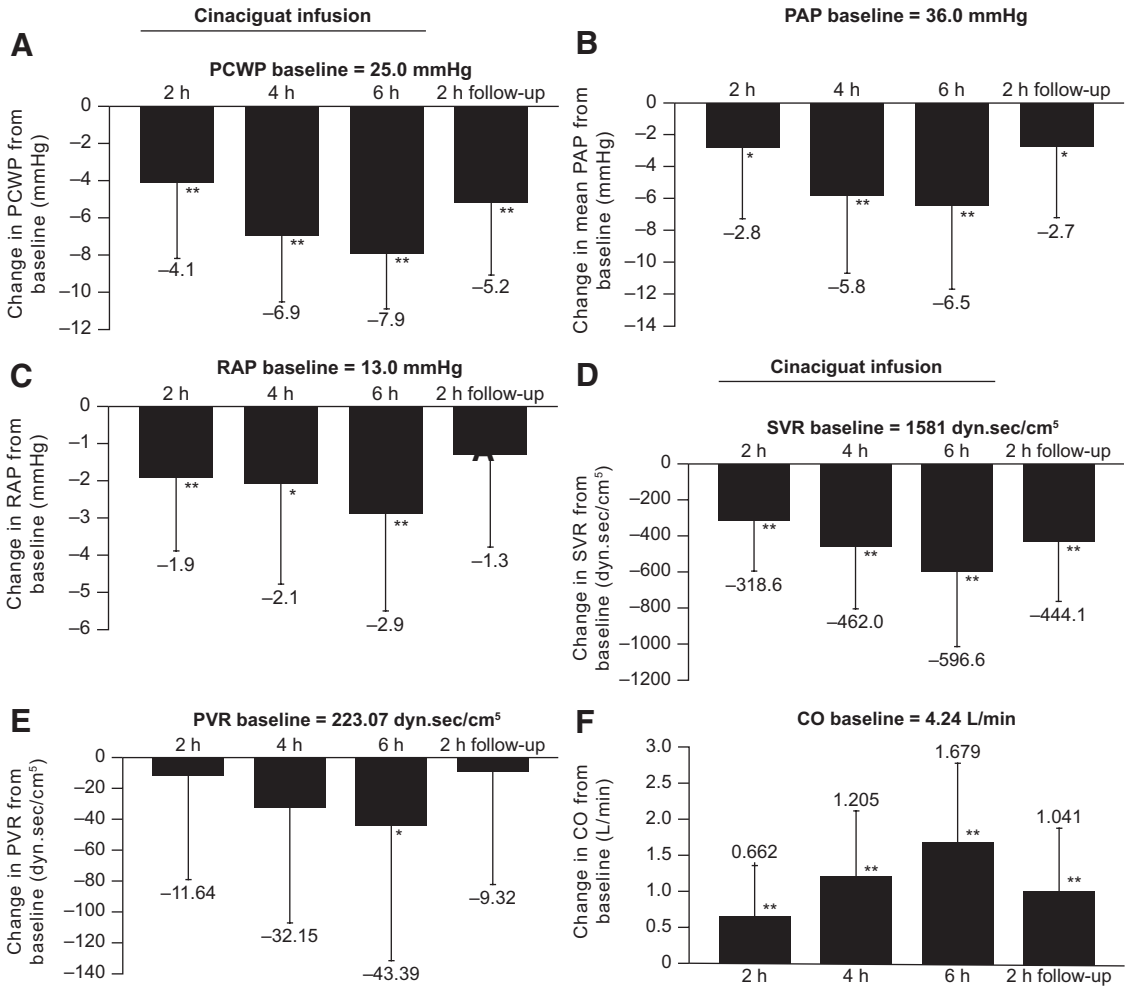

Figure 2. Effect of intravenous infusion of cinaciguat on (A) PCWP, (B) mean PAP, (C) mean RAP, (D) SVR, (E) PVR, and (F) cardiac output (CO) in patients with ADHF (n=30). *$P<0.0125$, **$P<0.000125$ vs baseline. Note that the distribution of patients to the doses in part B is shown in Figure 1B.

Statistical Analyses

The primary target prespecified in the protocol was the change in PCWP observed 6 hours after the start of infusion compared with the corresponding baseline value before administration. The statistical analysis of all other changes was exploratory. Probability values were calculated by means of a paired *t* test. Two-tailed probability values ($\alpha=0.05$) were calculated independently, and no adjustment for multiple tests of different variables was performed. For tests within a variable, the Bonferroni correction was applied, and $P<0.05/4=0.0125$ was required for statistical significance of any given time point (Figure 2). Analyses were performed with the SAS 9.1 package (SAS Institute Inc, Cary, NC).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Patient Demographics

In total, 60 patients with ADHF were enrolled from 7 study centers and received the study drug: 12 patients in cohort 1 of part A, 15 patients in cohort 2 of part A, and 33 patients in part B (Table 1). Patient demographics were similar among the 3 groups (Table 1), with the overall mean age being 65.8 years (range, 36 to 87 years) and the large majority (92%) of the study population being male. All 60 patients were valid for safety evaluation. In part B, 30 of 33 subjects were valid for hemodynamic evaluation. The median time between admission and first dose of cinaciguat was 2.08 days for patients participating in part B.

Comorbidities

In line with the critically ill nature of the patient population, a high level of comorbid disorders was recorded at study entry. Comorbidities recorded in at least one quarter of the study population included arterial hypertension (73%), hyperlipidemias (45%), renal failure and impairment (45%), diabetes mellitus (43%), and mitral valvular disorders (38%). Surgical and medical procedures that had been performed in at least one quarter of the study population before study entry included cardiac device implants (42%) and coronary artery bypass grafts or percutaneous coronary interventions (38%). Recorded drug use (medications taken on admission to hospital before the infusion and/or during or after the invasive part of the study) included medications for diseases of the cardiovascular system (100%) and anticoagulation or platelet inhibition (93%). Specifically, for part B (n=33), the number of patients with recorded drug use, categorized by drug type, was as follows: angiotensin-converting enzyme inhibitors/an-

Table 1. Demographics and Patient Characteristics at Baseline

	All Patients Valid for Safety (n=60)		
	Part A		
	Cohort 1 (n=12)	Cohort 2 (n=15)	Part B (n=33)
Male, n (%)	10 (83)	14 (93)	31 (94)
Mean age (range), y	69.2 (50–87)	65.5 (41–84)	64.7 (36–81)
Mean (SD) BMI, kg/m^2	27.0 (5.9)	27.4 (5.9)	28.6 (4.6)
Mean (SD) NT-proBNP, pg/mL*	19 059 (8119)	18 140 (7676)	21 199 (11 029)
HF origin, n (%)			
Ischemic	6 (50)	9 (60)	21 (64)
Nonischemic	6 (50)	6 (40)	12 (36)

BMI indicates body mass index.

*The numbers of patients with values for mean NT-proBNP were as follows: part A cohort 1, n=8; part A cohort 2, n=4; part B, n=28.

giotensin II receptor blockers, 31 (94%); β-blockers, 28 (85%); spironolactone, 27 (82%); diuretics, 32 (97%); and digitalis, 13 (39%). Corresponding values for all patients (parts A and B; n=60) were angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, 56 (93%); β-blockers, 52 (87%); spironolactone, 50 (83%); diuretics, 58 (97%); and digitalis, 28 (47%).

Part A: Dose Finding

Overall, 27 patients participated in part A, the dose-finding part of the study. Responses in PCWP and SBP were analyzed to determine the optimal starting dose for part B of the study.

Pulmonary Capillary Wedge Pressure

Mean±SD PCWP of patients in cohort 1 of part A was 23.3±4.7 mm Hg at baseline, decreasing to 18.3±5.9 mm Hg at the end of the 6-hour infusion period with cinaciguat and increasing slightly again to 19.6±6.7 mm Hg at the end of the 2-hour postinfusion follow-up period. For patients in cohort 2 of part A, the mean±SD PCWP at these 3 time points was 21.6±3.8, 13.4±4.5, and 15.7±5.4 mm Hg, respectively. The proportion of patients responding to cinaciguat was 75% (6 of 8 patients) in cohort 1 and 100% (7 of 7 patients) in cohort 2. For the 100-μg/h dose, the starting dose for part B, the proportion of responders in both cohorts was 53.3% (8 of 15 patients), whereas for the 200-μg/h dose, it was 80.0% (12 of 15 patients).

Systolic Blood Pressure

Mean±SD SBP of patients in cohort 1 of part A was 126.8±23.2 mm Hg at baseline, decreasing to 116.8±20.2 mm Hg at the end of the 6-hour infusion period with cinaciguat and increasing again to 125.8±22.4 mm Hg at the end of the 2-hour postinfusion follow-up period. For patients in cohort 2 of part A, the mean±SD SBP at these 3 time points was 121.6±11.2, 115.3±20.5, and 128.1±20.5 mm Hg, respectively. In the 100-μg/h dose group, the starting dose for part B, 40.0% (6 of 15) of patients achieved a reduction of SBP to <110 mm Hg. In the 200-μg/h dose group, the proportion was 46.7% (7 of 15 patients).

Table 2. Cinaciguat Dosing Distribution in Part B

Study Time				
0 h	2 h	4 h	6 h	Patients, n
100	100/50	50/50	50	2
100	100/200	200	200	12
100	100/200	200/400	400	16

Doses were measured in μg per hour.

Part B: Hemodynamic Responses

On the basis of the results from part A, an intravenous infusion starting dose of 100 μg/h cinaciguat was chosen for patients in part B, the proof-of-concept part of the study. Individual titration to target blood pressure was allowed after each 2-hour period. The final doses of cinaciguat after 6 hours of infusion were 50 μg/h (n=2), 200 μg/h (n=12), and 400 μg/h (n=16) (Table 2).

Hemodynamic Parameters

Six-hour infusions with cinaciguat in part B resulted in a decrease in SBP, diastolic blood pressure, mean arterial pressure, PCWP, PAP, RAP, SVR, and PVR and an increase in cardiac output, without a marked increase in heart rate (Table 3). Values for these hemodynamic parameters started returning toward baseline levels once the cinaciguat infusion was stopped (Table 3). Hemodynamic parameters worsened again within 2 hours of the end of infusion, even though other interventions such as treatment diuretics and oxygen were still being provided. Figure 2 shows changes from baseline in PCWP, mean PAP, RAP, SVR, mean PVR, and cardiac output at 2, 4, and 6 hours of infusion with cinaciguat and at 2 hours after infusion. Changes from baseline were significant at all time points during infusion with cinaciguat for these parameters except for PVR, for which changes from baseline did not reach significance at the 2- and 4-hour infusion time points, and RAP during the 2-hour follow-up period (Figure 2).

Responder Rate

Six-hour infusions with cinaciguat in part B significantly decreased the mean±SD PCWP from 24.1±5.4 mm Hg at baseline to 17.2±5.2 mm Hg at the end of the infusion period ($P<0.0001$ versus baseline). The proportion of patients responding to cinaciguat was 53% after 2 hours, 83% after 4 hours, and 90% after 6 hours (Figure 3).

Dyspnea score

Of the 30 patients with valid dyspnea score data in part B, 26 reported an improvement in dyspnea score at the end of the infusion period, and 28 reported an improvement at the end of the 18-hour follow-up period.

Neurohormones

At baseline, plasma values of vasoconstrictors (represented by plasma renin activity and noradrenaline) and vasodilators (represented by atrial natriuretic peptide and NT-proBNP) were pathologically elevated as a result of HF (Table 3).

Table 3. Effect of 6-Hour Intravenous Infusion of Cinaciguat on Hemodynamic Parameters and Biomarkers in Part B

Parameter	Baseline	End of 6-Hour infusion	2 h After Infusion	6-h Infusion Versus Baseline	*P*
SBP, mm Hg	119.0 (±18.7)	105.7 (±16.6)	112.0 (±16.9)	−13.9 (±13.9)	<0.0001
DBP, mm Hg	72.6 (±12.0)	57.9 (±14.1)	62.6 (±10.2)	−14.5 (±12.9)	<0.0001
MAP, mm Hg	88.1 (±12.6)	73.8 (±12.8)	79.1 (±10.7)	−14.3 (±12.4)	<0.0001
PCWP, mm Hg	25.0 (±4.5)	17.2 (±5.2)	19.4 (±5.6)	−7.9 (±3.0)	<0.0001
Mean PAP, mm Hg	36.0 (±6.0)	29.4 (±6.2)	32.8 (±6.3)	−6.5 (±5.2)	<0.0001
RAP, mm Hg	13.0 (±4.0)	10.1 (±4.1)	11.5 (±4.2)	−2.9 (±2.6)	<0.0001
SVR, dynes · s · cm^{-5}	1581 (±603)	971 (±438)	1133 (±462)	−597 (±424)	<0.0001
PVR, dynes · s · cm^{-5}	223 (±104)	180 (±87)	215 (±71)	−43 (±88)	0.0117
Cardiac output, L/min	4.24 (±1.34)	5.92 (±1.79)	5.24 (±1.36)	1.68 (±1.10)	<0.0001
Heart rate, bpm	76.7 (±17.0)	81.1 (±16.7)	78.7 (±15.8)	4.4 (±1.2)	0.0246
ANP, nmol/L	11.86 (±6.64)	11.14 (±5.68)	11.10 (±5.14)	−0.73 (±2.94)	0.2032
NT-proBNP, pg/mL	21 199 (±11,029)	22 148 (±11,915)	21 189 (±10,953)	−948 (±3694)	0.1855
cGMP, nmol/L	15.28 (±7.31)	18.22 (±8.49)	17.17 (±9.07)	−2.94 (±4.84)	0.0034
PRA, ng · mL^{-1} · h^{-1}	6.12 (±6.48)	10.65 (±9.52)	8.37 (±8.72)	−4.53 (±6.73)	0.0014
Noradrenaline, ng/L	605.4 (±315.3)	822.6 (±350.8)	783.7 (±363.5)	−217.3 (±294.9)	0.0006

DBP indicates diastolic blood pressure; MAP, mean arterial pressure; ANP, N-terminal atrial natriuretic peptide; and PRA, plasma-renin activity. Values are mean (±SD) unless indicated otherwise.

Although there was no significant change in atrial natriuretic peptide and NT-proBNP levels 6 hours after cinaciguat infusion, noradrenaline (217.3 ng/L) and plasma renin activity (4.53 ng · mL^{-1} · h^{-1}) increased significantly compared with baseline.

Safety

Of the 60 patients who were treated and were valid for the safety evaluation, 36 did not report any adverse events. Twenty-four patients reported a total of 42 treatment-emergent adverse events (intensity: mild, n=27; moderate, n=13; severe, n=2). The most frequently reported treatment-emergent adverse event was hypotension (6 patients, all with symptomatic hypotension; Table 4). Three adverse events were serious: cardiac failure after elective surgery for an implantable cardioverter-defibrillator occurring 5 days after the last dose of study drug and resulting in death, non–ST-elevation myocardial infarction (without preceding hypotension) that resolved after remedial drug therapy, and intracardiac thrombus. None of the serious adverse events were considered related to the study drug. Fourteen treatment-emergent adverse events in 13 patients were considered to be drug related (intensity: mild, n=11; moderate, n=3 [hypotension, n=2; dyspnea, n=1]). Four patients discontinued treatment with the study drug as a result of 5 adverse events. Of these, hypotension (n=2) and dyspnea (n=1) were considered drug related; back pain (n=1) and respiratory failure (n=1) were considered not drug related.

Laboratory values were typical for this study population and did not show any specific abnormality related to cinaciguat treatment. In particular, there did not appear to be increases in serum creatinine levels in response to cinaciguat treatment. Mean creatinine levels in part B (n=33) at baseline (1.34 mg/dL) had changed little by 24 hours after the start of the cinaciguat infusion (1.45 mg/dL) or 48 hours after the start of the infusion (1.40 mg/dL).

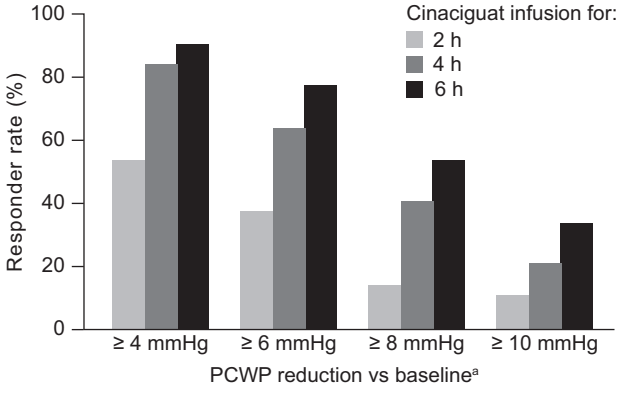

Figure 3. Proportion of patients with ADHF responding to intravenous cinaciguat according to the magnitude in reduction of PCWP (n=30). [a]Decrease in PCWP of at least 4 mm Hg.

Table 4. Patients With Treatment-Emergent, Drug-Related Adverse Events

	Part A, n (%)			
	Cohort 1 (n=12)	Cohort 2 (n=15)	Part B (n=33), n (%)	Total (n=60), n (%)
Total patients*	4 (33)	6 (40)	3 (9)	13 (22)
Nausea	1 (8)	1 (7)		2 (3)
Malaise	…	…	1 (3)	1 (2)
Headache	…	1 (7)	…	1 (2)
Somnolence	1 (8)	…	…	1 (2)
Dyspnea	…	1 (7)	…	1 (2)
Hot flush	2 (17)	…	…	2 (3)
Hypotension	…	4 (27)	2 (6)	6 (10)

Patients valid for safety: n=60.
*With any treatment-emergent, drug-related adverse event.

Discussion

These first clinical results with cinaciguat in patients with ADHF clearly demonstrate the clinical potential of cinaciguat. Results from a recently completed phase I clinical trial showed that cinaciguat had a favorable safety profile and was well tolerated in healthy male volunteers.[16] In the present proof-of-concept study, cinaciguat had a favorable hemodynamic efficacy and was well tolerated in patients with ADHF. Administration of cinaciguat resulted in potent unloading of the heart with venous and arterial vasodilatation, which was associated with a decrease in PCWP, RAP, SVR, and PVR and an increase in cardiac output in patients with ADHF with a modest increase in heart rate. The decrease of PCWP and RAP is a consequence primarily of venous vasodilatation, whereas the decrease in SVR is a result of arterial vasodilatation. Importantly, there did not appear to be increases in serum creatinine levels in response to cinaciguat treatment, indicating that renal function was preserved.

As a result of arterial vasodilatation, the observed increase in noradrenaline and plasma renin activity levels during cinaciguat infusion was probably a result of arterial vasodilatation. The small changes in heart rate, which are clinically insignificant, also have to be regarded in this setting. Reduced left ventricular filling pressure at 6 hours is not reflected in decreased plasma NT-proBNP concentrations. Reductions in right and left ventricular filling pressures may result in a reduction of NT-proBNP with a time-lag phase[18] shown in a large number of patients in the Safety and Efficacy of an Intravenous Placebo-Controlled Randomized Infusion of Ularitide in a Prospective Double-blind (SIRIUS) II study.[19] NT-proBNP secretion usually requires a long-term stimulus.[20] Therefore, abrupt reductions in right and left ventricular filling pressures may not directly result in a reduction of NT-proBNP. The half-life of NT-proBNP is 120 minutes, suggesting that hemodynamic changes could be reflected by this test every ≈12 hours.[20]

The large majority of patients (90%) responded to cinaciguat by the end of the 6-hour infusion period, as defined a priori by a reduction in PCWP of at least 4 mm Hg compared with baseline. Dyspnea scores also improved in the majority of patients, but the effect of cinaciguat on dyspnea remains speculative in the absence of a control group. The dyspnea scoring assessment used here is not validated but has been used previously.[17,19] Patient self-assessment, however, may be affected by confounding variables (eg, if the patient has a right heart catheter in place or if hemodynamic parameters are known). We reduced potential bias by performing dyspnea self-assessment before hemodynamic measurements and by prohibiting investigators from discussing these measurements or assisting patients in completing their symptom evaluation. However, knowledge of the degree of PCWP reduction by the nursing and medical staff still may have affected a patient's self-assessment.

The observed clinical improvement is likely to be a result of the study drug in addition to other interventions such as diuretics and oxygen. Moreover, it is important to note that the positive hemodynamic effects observed during the cinaciguat infusion worsened after the infusion stopped, despite ongoing general treatment. This implies that the hemodynamic benefits observed were largely related to cinaciguat rather than the general treatment.

A potential criticism of the study is that its uncontrolled design may have resulted in an overestimation of the beneficial hemodynamic effects of cinaciguat, given that the placebo group in VMAC had a 2-mm Hg, albeit insignificant, decrease in PCWP by 3 hours. Moreover, failure of the hemodynamic parameters to return fully to baseline levels by 2 hours after the infusion ceased may suggest that factors other than the cinaciguat infusion (eg, bedrest and general treatment) account for a proportion of the hemodynamic improvements. Although this is a possibility, the half-life of cinaciguat (12 to 18 minutes) means that residual cinaciguat activity also may partly explain this phenomenon.[16]

The hemodynamic goals of effective therapy for ADHF are a decrease in end-diastolic pressure of the left ventricle (preload) and a decrease in afterload, resulting in an increase of cardiac output. Furthermore, to be effective in ADHF, it may be desirable for such a therapy to act independently of NO because of conditions of oxidative stress in diseased tissues. In recent decades, there has been only limited advancement in the treatment of ADHF.[21,22] Existing treatment options include positive inotropic agents, vasodilators, and diuretic drugs, as well as ultrafiltration and mechanical support of ventilation.[23,24] Although the vasodilator nesiritide improves hemodynamics and symptoms in patients with ADHF,[17] it also has been linked to worsening renal function in this patient group.[25] Nesiritide may even increase premature mortality rates, although this is a subject of some controversy and ongoing studies.[26,27] Organic nitrates such as nitroglycerin are widely used in the treatment of ADHF even though there are limited data from clinical trials. Cotter et al[24] reported that a strategy of high-dose isosorbide dinitrate and low-dose furosemide was associated with improved outcomes in ADHF compared with low-dose isosorbide dinitrate and high-dose furosemide. However, the well-recognized development of tolerance,[28] together with their lack of effect on oxidized and heme-free sGC, may limit the therapeutic value of organic nitrates.[10] Many preclinical observations indicate that cinaciguat represents a new class of therapeutics that may be useful in overcoming the tolerance developed during sustained nitroglycerin therapy.[14,29]

Results from the present study show that cinaciguat has promising cardiovascular effects resulting in a potent unloading of the heart. They are also consistent with preclinical data that suggested that patients with enhanced vasodilator responses to cinaciguat, but probably blunted vasodilator response to NO donors, appear to be ideally suited for therapies directed at restoring redox homeostasis, sGC activity, and NO sensitivity.[11–14] Cinaciguat thus has the potential to provide important therapeutic advantages in ADHF.[11] It is important to acknowledge, however, that further studies are required because this proof-of-concept study lacks placebo control or comparison groups.

With regard to the pharmacokinetics of cinaciguat, it should be noted that the plasma concentration–time profiles of cinaciguat suggest dose-proportional pharmacokinetic behavior, with low interindividual variability in healthy volunteers.[16] The plasma concentrations reached near-maximum

levels within 30 minutes of the beginning of an infusion, declining rapidly after the end of the infusion (dominant half-life, 0.2 to 0.3 hours), with the hepatic biliary pathway accounting for 94% of total clearance.[16] Cinaciguat does not appear to interact with cytochrome P450.[16] Furthermore, no potential clinically significant off-target effects have been detected for cinaciguat, as tested with radioligand binding assays (data on file at Bayer HealthCare AG). Thus, the interaction between cinaciguat and sGC is highly specific. This contrasts with the lack of specificity observed with nitrovasodilators.[30]

Conclusions

Results from this first clinical study with cinaciguat in patients with ADHF clearly demonstrate its promise. Cinaciguat has potent preload- and afterload-reducing effects, as well as other cardiovascular benefits, and further investigation of this promising new therapeutic strategy for HF is warranted. A phase II study with infusion periods of 24 to 48 hours is currently enrolling patients.

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CLINICAL PERSPECTIVE

Therapies for managing acute decompensated heart failure are far from ideal; hospitalization rates and disease morbidity continue to increase, as does the need for more treatment resources, and current pharmacotherapy has its limitations. Thus, there is still a need for better therapies. Cinaciguat (BAY 58–2667) is the first of a new class of soluble guanylate cyclase activators in clinical development for acute decompensated heart failure. It has a promising and novel mode of action, stimulating cGMP synthesis by targeting soluble guanylate cyclase in its nitric oxide–insensitive, oxidized-ferric (Fe^{3+}), or heme-free state. Therefore, cinaciguat also may be effective under oxidative stress conditions refractory to traditional organic nitrate therapies for acute decompensated heart failure. The nonrandomized, uncontrolled, proof-of-concept study described here is the first to investigate cinaciguat in patients with acute decompensated heart failure, demonstrating potent preload- and afterload-reducing effects and maintenance of renal function. A 6-hour infusion of cinaciguat 50 to 400 μg/h led to significant reductions compared with baseline in pulmonary capillary wedge pressure (−7.9 mm Hg), mean right atrial pressure (−2.9 mm Hg), mean pulmonary artery pressure (−6.5 mm Hg), pulmonary vascular resistance (−43.4 dynes · s · cm^{-5}), and systemic vascular resistance (−597 dynes · s · cm^{-5}), while increasing heart rate by 4.4 bpm and cardiac output by 1.68 L/min. The responder rate (pulmonary capillary wedge pressure decrease of ≥4 mm Hg compared with baseline) was 90% after 6 hours. Cinaciguat was well tolerated. Thus, further investigation of cinaciguat is warranted in this patient group.