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DRUG PROFILE

Cinaciguat, a soluble guanylate cyclase activator for the potential treatment of acute heart failure

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The nitric oxide (NO)/soluble guanylate cyclase (sGC)/cyclic guanosine-3',5'-monophosphate (cGMP) pathway plays an important role in cardiovascular regulation by producing vasodilation and inhibiting platelet aggregation and vascular smooth muscle proliferation. The NO/SGC/cGMP pathway is disrupted in patients with heart failure as a result of a decrease in NO bioavailability and an increase in NO-insensitive forms of sGC, resulting in insufficient vasodilation. Drugs that activate sGC in a NO-independent manner may provide considerable therapeutic advantages in treating these patients. Cinaciguat (BAY-58-2667), currently in development by Bayer AG, preferentially activates sGC in its oxidized or heme-free state, when the enzyme is insensitive to both NO and nitrovasodilators. Cinaciguat exhibits potent vasodilator and antiplatelet activity, a long-lasting antihypertensive effect and a hemodynamic profile similar to that of nitrates. In clinical trials in patients with acute decompensated heart failure, cinaciguat potently unloaded the heart, increased cardiac output and renal blood flow, and preserved renal function and sodium and water excretion without further neurohumoral activation. The pharmacokinetics of cinaciguat demonstrated dose-proportionality with low individual variability and a low incidence of adverse events. The phase I and II clinical trials performed with cinaciguat so far, however, are insufficient to provide convincing evidence on the efficacy and safety of the drug. Thus, caution should be exerted before extrapolating the present preliminary data to the clinical practice.

Introduction

Activation of the nitric oxide (NO)/soluble guanylate cyclase (sGC)/cyclic guanosine-3',5'-monophosphate (cGMP) pathway plays an important role in the regulation of the cardiovascular system [1108171], [1108175], [1108177], [1108522]. sGC, the intracellular receptor for NO, is a heterodimer consisting of a larger α-subunit and a smaller Fe^{2+}/heme-binding β-subunit [1109175], [1109176]. Under physiological conditions, NO binds to the Fe^{2+}/heme moiety and activates sGC, converting guanosine triphosphate (GTP) to cGMP, which regulates complex signaling pathways, including protein kinases, phosphodiesterases and cyclic nucleotide-gated ion channels [1108171], [1108175], [1108177], [1109178]. As a result, activation of the NO/sGC/cGMP pathway produces vasodilation, inhibition of platelet aggregation, and vascular smooth muscle growth and proliferation [1108171], [1108175], [1108177], [1108522].

Therapeutic Cinaciguat

Originator Bayer AG

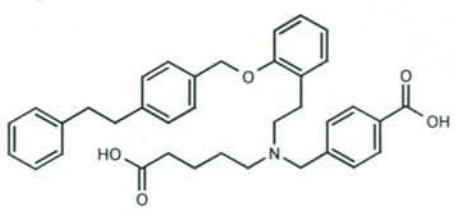
Status Phase II Clinical

Indication Cardiac failure

Actions Cardioprotectant, Guanylate cyclase modulator

Technologies Intravenous formulation, Small-molecule therapeutic

Synonym BAY-58-2667



A major prerequisite for the NO-induced activation of sGC is the presence of the reduced Fe^{2+}/heme moiety, while oxidation to its ferric (Fe^{3+}) form completely prevents NO-mediated sGC stimulation and cGMP production. Thus, it has been hypothesized that, under physiological conditions, sGC exists in equilibrium between its reduced NO-sensitive state and the oxidized/heme-free NO-insensitive state, while pathophysiological conditions associated with oxidative stress shifts this equilibrium toward the NO-insensitive oxidized/heme-free state [839250], [919410], [1109181].

Impaired NO/sGC/cGMP signaling, a condition termed 'endothelial dysfunction', is present in several different

cardiovascular diseases, such as hypertension, atherosclerosis, diabetes and heart failure, in which oxidative stress plays a central role and is associated with a greater risk of cardiac events and poorer disease outcomes [1109182]. Endothelial dysfunction may result from impaired NO production, reduced bioavailability of NO (resulting from excessive NO degradation by reactive oxygen species), downregulation of sGC protein levels, degradation of cGMP by phosphodiesterase activity and/or an increase in oxidized/heme-free forms of sGC, which cannot be activated by NO [839250], [919410], [1108522].

Some conditions associated with impaired NO/sGC/cGMP signaling are treated with organic nitrates and 'nitrovasodilators', which mimic the actions of endogenous NO by bioconversion to NO or NO-related compounds that nitrosylate the heme of sGC. However, the efficacy of nitrates in this context is limited because of insufficient bioactivation, a progressive diminution of response as a result of *de novo* tissue hypo-responsiveness to NO (ie, NO resistance), progressive diminution of response as a result of pseudotolerance (caused by neurohumoral activation limiting nitrate effects via functional antagonism) [1118814], non-specific interactions of NO with other biological molecules, and an inability to activate sGC when the heme moiety is absent or in the oxidized/heme-free state [839250], [919410], [1109184], [1109185], [1109187]. Moreover, nitrates can increase mitochondrial production of reactive oxygen species (peroxynitrite), which increases the oxidized and heme-free forms of sGC that cannot be activated by NO [919410], [1109184]. Finally, in large randomized clinical trials, nitrates improved symptoms, but not mortality rates, in patients with cardiovascular diseases [1109185].

Acute heart failure syndromes (AHFS), defined as a rapid onset or gradual change in signs and symptoms of heart failure that require urgent therapy, encompass a heterogeneous group of conditions with different clinical presentations, heart failure history, pathophysiology, prognosis and treatment [1024020], [1109188]. AHFS represent a major health problem because of their high prevalence, high rates of associated morbidity and mortality, and significant healthcare costs. They also represent a therapeutic challenge for clinicians because management strategies vary markedly. Traditionally used drugs (eg, diuretics, vasodilators [organic nitrates] and positive inotropics) improve signs and symptoms and hemodynamics [1024020], [1109189], [1118822], [1118829], [1118833], but they fail to reduce, and may even increase, in-hospital and post-discharge mortality [1024020], [1109188], [1109190]. Indeed, it is possible for some vasodilating agents to be harmful in AHF; for example, enalapril and dipyridamole may induce negative inotropic effects or coronary steal, respectively [1118936], [1118940]. Thus, new agents are needed that safely improve the signs and symptoms, hemodynamics and short- and long-term outcomes (hospitalizations/survival) in these patients [1109189], [1109190].

In heart failure, the NO/sGC/cGMP pathway is disrupted either as a result of impaired production of NO or its excessive degradation (NO/redox disequilibrium) [1109191]. Oxidant-producing enzymes are upregulated in congestive heart failure, and either the abundance or spatial localization of NO-producing enzymes is altered. Thus, sGC activators may present important advantages over nitrates in the treatment of acute heart failure because they can activate sGC and produce vasodilatation where endogenous NO and nitrates fail to function, they do not need to be bioactivated, do not induce endothelial dysfunction and do not appear to promote reflex neurohumoral vasoconstriction or tolerance [1085970], [1108522], [1109190], [1109192].

To avoid the disadvantages of nitrate therapy, new types of drugs that activate sGC in an NO-independent manner have been investigated [919410]. These can be divided into two categories: (i) heme-dependent sGC stimulators, such as BAY-41-2272, BAY-41-8543, riociguat (Bayer AG), CFM-1571 and A-350619, that activate the reduced sGC and enhance the sensitivity of sGC to extremely low levels of NO; and (ii) heme-independent sGC activators, such as cinaciguat (Bayer) and ataciguat, that can activate sGC in its NO-insensitive, oxidized ferric (Fe^{3+}) or heme-free state. The development of BAY-41-2272 and BAY-41-8543 has been discontinued as a result of strong inhibition of cytochrome P450 (CYP) enzymes and a poor pharmacokinetic profile, respectively [1011772]. Ataciguat has also been discontinued, although the reasons for this were not reported [1074290]. CFM-1571 and A-350619 also appear to have ceased development, as new information has not been reported for some time.

Cinaciguat (BAY 58-2667) is a potent activator of sGC in its NO-insensitive, oxidized/heme-free state [457509], [839250], [839256]. Cinaciguat directly activates sGC and is the most potent NO-independent sGC activator reported to date. A signal transmission triad (His^{105}, Tyr^{135} and Arg^{139}) located within the heme-binding pocket of the β_1-subunit of sGC appears to be crucial for both the binding of the heme moiety and the activation of sGC by cinaciguat [839251], [839255], [1109194]. The Tyr^{135} and Arg^{139} residues, together with Ser^{137}, form a unique binding motif. The activation of a Ser^{137}Ala mutant sGC by NO was much reduced compared with wild-type sGC, while the activity was enhanced by cinaciguat [839260]. Further crystallization studies with sGC and cinaciguat demonstrated that the β-subunit amino acids Asp^{44}, Asp^{45} and Phe^{74} are also crucially important for functional heme-induced sGC activation [839251], [1109194]. Additionally, cinaciguat protects sGC from heme oxidation-induced ubiquitination and proteasomal degradation, most likely by binding of the unoccupied heme pocket of sGC, thereby stabilizing the heterodimer and preventing its degradation [1109193]. At the time of publication, cinaciguat was undergoing phase II clinical trials for the treatment of cardiac failure [1068831] and phase III trials were planned for later in 2010 [978349].

Synthesis and SAR

An automated ultra-HTS system comprising an assay for the detection of intracellular production of cGMP, including a CHO cell line expressing sGC, a cGMP-sensitive cation channel (CNG2) and aequorin (a Ca^{2+}-sensitive luminescence indicator), was used to screen > 900,000 compounds for activity as sGC activators. This resulted in the identification of a class of aminodicarboxylic acids as a new type of sGC activator [839254]. Cinaciguat (4-[[(4-carboxybutyl)[2-[2-[[4-(2-phenylethyl)phenyl]methoxy] phenyl]ethyl]amino]methyl] benzoic acid) was selected from a series of approximately 800 analogs as the first NO-independent activator of sGC, which demonstrated different characteristics to any of the known heme-dependent sGC stimulators (eg, BAY-41-2272 and BAY-41-8543) [839254]. In comparison studies with BAY-41-8543, cinaciguat, BAY-41-8543 and NO were all demonstrated to activate sGC. Cinaciguat in combination with NO increased maximum enzyme reaction velocity (V_{max}) in an additive manner, while the combination of BAY-41-8543 and NO had a synergistic effect on V_{max}, indicating that the two drugs activate sGC via a different mechanism [839256].

Photoaffinity labeling studies demonstrated that cinaciguat targets amino acid residue 371 in the α-subunit of sGC and residues 231 to 310 in the β-subunit [457509].

The synthesis of cinaciguat started with 4-{[(2-methyoxyphenethyl)amino]methyl}benzoate, to which a 5-ethoxy-5-oxopentyl group was added at the central amine via reaction with ethyl 5-bromovalerate in the presence of sodium carbonate and acetonitrile under reflux for 18 h. The 5-ethoxy group was then converted to 5-methoxy and the 2-methoxyphenyl to 2-hydroxyphenyl to form methyl 4-[[(2-hydroxyphenethyl)(5-methoxy-5-oxopentyl)amino]methyl]benzoate. This compound was reacted with 4-(chloromethyl)stilbene in the presence of potassium carbonate and acetonitrile under reflux for 18 h to form the 2-[[4-[(*E*)-2-phenylethenyl]benzyl] oxyphenethyl]amino derivative. This compound was then hydrogenated in the presence of palladium on carbon (Pd/C) catalyst and ethyl acetate to provide the 2-[[(4-phenylethyl) benzyl]oxyphenethyl]amino derivative. Hydrolysis of the two methyl ether groups via dioxane and sodium hydroxide resulted in cinaciguat [US-07517896].

Preclinical development

In a homologous competition binding study using labeled (^3H) and unlabeled cinaciguat, the drug bound to sGC with a K_i value of 8.0 nM. The binding constant K_D in a saturated binding study was calculated, using non-linear regression, as 13.4 nM [839264]. In further binding studies, using non-linear regression for one-site saturation, cinaciguat yielded a dissociation constant K_d of 3.2 nM. In competition binding studies with the sGC inhibitor 1*H*-(1,2,4)-oxadiazolo-(4,3*a*)-quinoxazin-1-one (ODQ), cinaciguat demonstrated K_i values of 6.3 and 6.5 nM, respectively, in the presence and absence of ODQ [457509].

Vasodilator and antihypertensive effects

Cinaciguat inhibited phenylephrine-induced contractions in rabbit saphenous artery rings with a potency several orders of magnitude greater than the NO donors sodium nitroprusside and 3-morpholinosydnonimine (IC_{50} = 0.3 to 0.5 nM versus 635 and 1100 nM, respectively) [457509]. Moreover, cinaciguat inhibited phenylephrine-induced contractions in rabbit saphenous artery rings from wild-type and nitrate-tolerant rabbits with similar potency (IC_{50} = 0.16 and 0.22 μM, respectively). Thus, the vasodilating effect of cinaciguat was not altered by pre-existing nitrate tolerance [457509]. In further studies, cinaciguat was a more potent relaxer of vascular rings from different models of increased oxidative stress (ie, aortae from aged spontaneously hypertensive rats [SHRs] and $ApoE^{-/-}$ mice on a high-fat diet, safenous arteries from Watanabe hyperlipidemic rabbits on a high-fat diet and mesocolon arteries from patients with type 2 diabetes) compared with wild-type vascular rings [839250]. Moreover, exposure of canine coronary arteries to peroxynitrite impaired endothelium-dependent relaxation, increased oxidative stress and reduced cGMP levels; these effects were all reversed by treatment with cinaciguat [1085975].

Cinaciguat produced a dose-dependent and durable antihypertensive effect in aged SHRs and, in contrast to nitrates, no tolerance was observed [457509], [839250]. In hypertensive (*m*REN2)27 transgenic rats, cinaciguat reduced blood pressure and decreased plasma B-type natriuretic peptide, creatinine, urea and renin activity levels, reflecting a cardiorenal protecting effect [839250].

Cinaciguat decreased acute hypoxic pulmonary vasoconstriction in isolated perfused mouse lungs and in rodent models of pulmonary hypertension (hypoxia- or monocrotaline-induced); it also reduced right ventricular systolic pressure and hypertrophy, and attenuated structural remodeling of pulmonary vasculature (reducing fully muscularized and decreasing non-muscularized arteries) [839252]. In newborn lambs with persistent pulmonary hypertension, cinaciguat (0.1 to 100 μg iv over 10 min) caused potent pulmonary vasodilation, increased pulmonary blood flow and cGMP plasma levels, and reduced pulmonary vascular resistance for > 1.5 h [1085982]. However, treatment of pulmonary hypertension with vasodilating agents can be associated with arterial hypotension and deterioration of arterial oxygenation resulting from pulmonary ventilation-perfusion mismatching [1109197]. Inhalation of vasodilating agents can provide targeted drug delivery to the lungs, thereby avoiding or reducing the risk of systemic side effects. Inhalation of lipid-protein-sugar microparticles containing cinaciguat produced potent selective pulmonary vasodilation and enhanced arterial oxygenation in lambs with acute pulmonary hypertension without any adverse effects on pulmonary gas exchange [1109197]. Thus, inhaled cinaciguat might be an effective agent in treating pulmonary hypertension, particularly when responsiveness to NO is impaired.

Studies have demonstrated that administration of the PDE5 inhibitor sildenafil, in combination with cinaciguat and ODQ, suppressed $TGF\beta_1$-induced differentiation of human lung fibroblasts to myofibroblasts, a feature of fibrotic lung diseases [838141]. This finding suggests that sGC activators might represent a new therapeutic approach to this type of disease (eg, idiopathic pulmonary fibrosis, asthma and COPD) [919410], although clinical efficacy for cinaciguat in this context has not been investigated.

Cardiac effects

In isolated perfused rat hearts (Langendorff), cinaciguat decreased coronary perfusion pressure, with no effects on left ventricular (LV) pressure or heart rate [457509]. In isolated rabbit and rat hearts exposed to regional ischemia (30 min) and reperfusion (120 to 180 min), cinaciguat (1 to 50 nM; infused for 60 min starting 5 min prior to reperfusion) decreased infarct size, an effect abolished by protein kinase G (PKG) or mitochondrial K_{ATP} channel antagonists [1025909]. This finding confirmed that cinaciguat exerted a cardioprotective effect similar to that of ischemic pre-conditioning.

In a rat model of isoproterenol-induced myocardial infarction, cinaciguat (10 mg/kg bid for 4 days, with isoproterenol administered on days 3 and 4) improved histopathological lesions (ie, the degree of necrosis, fiber fragmentation and inflammatory infiltrate) and cardiac performance (improved LV contractility and relaxation), reduced oxidative stress (demonstrated by reduced plasma lactate dehydrogenase and TBARS), ameliorated intracellular enzyme release, and decreased COX2, $TGF\beta_1$ and β-actin mRNA expression [1085975]. In isoproterenol-treated rats, the slope (E_{max}) of the LV end-systolic pressure-volume relationship and preload recruitable stroke work were markedly reduced. Treatment with cinaciguat resulted in a significant increase in these parameters, indicating an improvement in LV contractility. Isoproterenol treatment also resulted in impaired ventricular relaxation (as determined by a prolonged time constant of LV decay τ), which was again significantly increased by cinaciguat treatment. The rate of mortality within 30 min in the cinaciguat-treated group was 0%, compared with 6% in controls. Over the course of the study, mortality rates were 33 and 56% for cinaciguat and control groups, respectively [1085975].

In a mouse model of ischemia/reperfusion injury, cinaciguat (10 μg/kg ip) was administered both with and without the PKG inhibitor KT-5283. Cinaciguat reduced infarct size compared with controls when administered alone, but the effect was reduced with coadministration of KT-5283. This suggests that the cardioprotective effect of cinaciguat is mediated by PKG signaling [958739].

Hemodynamic effects

The effects of cinaciguat and glyceryl trinitrate were compared in anesthetized dogs under autonomic blockade. Both drugs decreased LV end-diastolic, central venous and diastolic pulmonary arterial pressures and mean right atrial pressures with a compensatory increase in heart rate, but the vasodilator effect lasted longer with cinaciguat [457509].

The cardiorenal effects of cinaciguat (0.1 or 0.3 μg/kg/min iv) were studied in a canine model with tachypacing-induced severe chronic heart failure. Cinaciguat reduced systemic and pulmonary vascular resistances and mean arterial, right atrial, pulmonary artery and pulmonary capillary wedge (PCWP) pressures, and increased cardiac output and renal blood flow [513877], [802144], [839261]. Urinary flow, glomerular filtration rate, sodium and water excretion, plasma renin activity and aldosterone levels remained unchanged. Consistent with cardiac unloading, atrial and B-type natriuretic peptides decreased with administration of the higher dose [513877], [802144].

In rats with subtotal (5/6) nefrectomy (a model of chronic renal failure), treatment with cinaciguat (3000 ppm in feed; ~ 50 mg/day) for 18 weeks reduced blood pressure (146 ± 11 versus 189 ± 14 mmHg in untreated rats), LV weight, cardiac myocyte diameter, media-lumen ratio of renal and cardiac arteries, and arterial wall thickness. Kidney function and morphology were significantly improved as assessed by creatinine clearance, glomerulosclerosis, and interstitial and perivascular fibrosis of intrarenal arteries [693379], [839258]. These data suggest that cinaciguat slowed renal disease progression and thus may have potential clinical value in the treatment of chronic renal disease.

Antiplatelet and anticoagulant activity

Cinaciguat dose-dependently inhibited platelet aggregation induced by the thromboxane A_2 mimetic U-46619 (IC_{50} = 0.046 μM), collagen (IC_{50} = 1.1 μM) and ADP (IC_{50} = 7.5 μM) in human platelet-rich plasma. Moreover, cinaciguat dose-dependently prolonged rat tail bleeding time and significantly increased cGMP content in washed rat platelets 1 h after oral administration. Cinaciguat inhibited arterial thrombus formation induced in the left common carotid artery with iron(III) chloride (ED_{50} = 0.9 mg/kg po) [457509]. Furthermore, cinaciguat reduced tissue factor protein expression and activity in human monocytes stimulated with lipopolysaccharide, and reduced tissue-factor-dependent procoagulant activity in HUVECs stimulated with TNFα. Cinaciguat also suppressed transcriptional activity of NFκB [1085971]. These effects might present therapeutic advantages in treating cardiovascular diseases associated with enhanced procoagulant and inflammatory response.

Toxicity

No toxicity data were available at the time of publication.

Metabolism and pharmacokinetics.

In healthy male volunteers (n = 72), the T_{max} of cinaciguat (50 to 250 μg/h over 2 or 4 h) was 30 min, and plasma concentration declined rapidly below 1.0 μg/l within 30 min of cessation of infusion (terminal $t_{1/2}$ = 0.30 to 3.58 h) [1085963]. C_{max} was 1.25 to 6.63 μg/l and AUC

was 2.08 to 24.40 μg·h/l. Pharmacokinetics demonstrated dose-proportionality with low interindividual variability. Cinaciguat did not interact with CYP enzymes and the biliar route accounted for 94% of total clearance (renal clearance < 1%) [1085963].

Patients with liver cirrhosis (Child-Pugh A [n = 8] and Child-Pugh B [n = 8]) and healthy volunteers (n = 16) were treated with cinaciguat. The Child-Pugh A and a group of the healthy volunteers received 100 μg/h cinaciguat over 4 h, while the Child-Pugh B group and the remainder of the healthy volunteers received 50 μg/h cinaciguat over 4 h. Compared with healthy volunteers, the mean exposure to cinaciguat in the Child-Pugh A group was increased by 1.5-fold, while in the Child-Pugh B group exposure was > 4-fold higher. In both patient groups, the mean apparent volume of distribution at steady-state increased by approximately 50%. The mean drug clearance was < 15% in the Child-Pugh B group and approximately 67% in the Child-Pugh A group compared with healthy volunteers, reflecting the considerably prolonged $t_{1/2}$ in patients with hepatic impairment. Thus, adaptation of dosing is required for patients with reduced liver function [1109201]. Impaired renal function (creatinine clearance between < 30 and > 80 ml/min), however, had minimal effects on the mean AUC, C_{max} (2.2 to 3.1 μg/l) and $t_{1/2}$ (1.0 to 1.7 h) of cinaciguat (100 μg/h for 4 h) [1109202].

In a phase II clinical trial performed in patients (n = 56) with acute decompensated heart failure (ADHF; PCWP ≥ 18 mmHg), the pharmacokinetics of cinaciguat were linear, with moderate interindividual variability [1077071]. The mean estimates for the clearance and volume of distribution at steady-state were 26.4 l/h and 18.4 l, respectively. A 50% recovery to pharmacodynamic baseline values occurred within 1 h and a complete return to baseline was estimated to occur 3 to 4 h after the end of infusion. Cardiac output significantly affected clearance, whereas patient age, body weight and renal function did not [1077071].

Clinical development

Phase I

In a phase I, placebo-controlled, randomized, dose-escalation clinical trial, up to five separate doses of cinaciguat (50, 100, 150, 200 or 250 μg/h) were administered to healthy volunteers (n = 39) intravenously over 2 or 4 h [1085963]. Cinaciguat significantly decreased diastolic blood pressure, without reducing systolic blood pressure, and increased cardiac output as a result of an increase in stroke volume and heart rate (increased significantly by 4 to 14 bpm in the 2-h infusion 150 and 200 μg/h groups, and all of the 4-h infusion groups). At higher doses (150 to 250 μg/h), cinaciguat significantly decreased mean arterial pressure and increased cGMP, renin and noradrenaline, but not aldosterone plasma levels. Dose escalation was stopped at the dose level of 250 μg/h cinaciguat for 4 h [1085963].

Phase II

A phase II, non-randomized, unblinded, uncontrolled, multicenter clinical trial investigated the effects of cinaciguat in patients (n = 60) with ADHF (New York Heart Association [NYHA] functional class III to IV, PCWP ≥ 18 mmHg) [1085966]. In an initial dose-finding part of the trial, two cohorts of patients (total n = 27) received three ascending dose steps of cinaciguat (50, 100 and 200 μg/h or 100, 200 and 400 μg/h iv), with each dose step lasting 2 h (total infusion = 6 h). The decrease from baseline in mean PCWP at the end of the 6-h infusion was 5.0 and 8.2 mmHg in patients treated with the first and second schedule of cinaciguat, respectively; the decrease in mean systolic blood pressure was 10.0 and 6.3 mmHg, respectively. On the basis of the results of this part of the trial, a starting dose of 100 μg/h (iv) was selected for patients (n = 33; evaluable n = 30) enrolled in the second part of the trial. Doses were titrated individually in each 2-h period according to blood pressure levels to 50 (n = 2), 100 (n = 12) and 400 μg/h (n = 16) after 6 h. Compared with baseline, a 6-h infusion of cinaciguat produced a potent venous and arterial dilation, leading to a significant reduction in PCWP (reduced by 7.9 mmHg; $p < 0.0001$), right atrial and pulmonary artery pressures (reduced by 2.9 and 6.5 mmHg, respectively; $p < 0.0001$), pulmonary and systemic vascular resistances (reduced by 43.4 [$p = 0.0117$] and 597 dynes·s·cm^{-5} [$p < 0.0001$], respectively), and increased heart rate (by 4.4 bpm; $p = 0.0246$) and cardiac output (by 1.68 l/min; $p < 0.0001$), and improved dyspnea score, but no change in renal function (creatinine plasma levels) was observed. The response rate (ie, PCWP reduced by ≥ 4 mmHg versus baseline) was 53, 83 and 90% after 2, 4 and 6 h of cinaciguat, respectively [1085966].

A phase IIb, placebo-controlled, randomized, double-blind, multicenter clinical trial investigated the safety and efficacy of cinaciguat (iv) as add-on to standard therapy in patients (n = 139) with ADHF (NYHA class III to IV; PCWP ≥ 18 mmHg) [1109200]. Patients received placebo (n = 49) or cinaciguat (n = 90; titrated according to systolic blood pressure from 100 up to 600 μg/h for the first 8 h, and then maintained for up to 40 h). The primary endpoint was a change in PCWP after 8 h compared with placebo. Secondary endpoints included hemodynamic and safety parameters, organ protection and 30-day mortality. Cinaciguat treatment was associated with a rapid and sustained decrease in PCWP, increased cardiac output and reduced pulmonary vascular resistance without causing a significant change in heart rate or impairing cardiac function. No effects on renal function or 30-day mortality were observed [1109200].

Two phase IIb, placebo-controlled, randomized, double-blind, parallel-assignment clinical trials to investigate the efficacy and tolerability of cinaciguat (10, 25, 50, 100 and 125 μg/h iv for 48 h) in patients with acute decompensated chronic congestive heart failure are currently in recruitment. A similar third trial is planned, but not yet in recruitment. In the COMPOSE 1 (ClinicalTrials.gov identifier:

NCT01065077; EudraCt: 2009-014377-40; 14560) and COMPOSE 2 (NCT01067859; 2009-014378-16; 14663) trials, recruitment of 100 and 60 patients, respectively, was planned, and the primary endpoint was a change in PCWP at 8 h. Secondary endpoints included cardiac index and right atrial pressure after 8 and 48 h and well-being using the Kansas City Cardiomyopathy Questionnaire. In the third trial, known as COMPOSE EARLY (NCT01064037; 2009-017082-39), an estimated 160 patients would be enrolled and the primary outcome was to be dyspnea at 8 h using a visual analog scale. Secondary endpoints included dyspnea assessment (Likert Scale) and overall health status assessment (EQ-5D) after 30 to 35 days of treatment. Bayer anticipated that all three of these trials would be completed in January 2011.

A fourth phase II, placebo-controlled, randomized, double-blind, parallel-assignment clinical trial (NCT00559650; 2007-003059-36; 12480) in patients (n = 149) with congestive heart failure began in December 2007. Patients were to receive cinaciguat (100 to 600 μg/h iv for a maximum of 48 h) or placebo. This trial was later terminated. The reasons for this were unreported at the time of publication.

Side effects and contraindications

In the phase I clinical trial, 26 out of 76 volunteers assessed for safety reported mild adverse effects related to the pharmacodynamic effects of the drug, which resolved by the end of the trial. No relevant effects on hematology or clinical chemistry parameters were noted, nor were any ECG abnormalities [1085963]. In patients (n = 34) with variable renal function, adverse events were mostly mild, with headache being the most frequently reported [1109202]. In patients (n = 16) with liver cirrhosis, the most frequent adverse events were headache (n = 4) and spontaneous penile erection (n = 2), but there was no indication of a higher incidence of adverse events than in healthy volunteers [1109201].

In the phase II clinical trial, 24 patients presented 42 adverse effects (27 mild, 13 moderate and 2 severe), most commonly hypotension (10%), hot flush (3%) and nausea (3%). Three serious adverse events were recorded, although none were considered drug-related. Four patients discontinued the trial as a result of five adverse effects, two of which were considered non-drug-related. No changes in laboratory levels and serum creatinine levels or evidence of tachyphylaxis were observed [1085966]. In the phase IIb clinical trial, no adverse effects on cardiac or renal function were observed, despite an increased occurrence of asymptomatic hypotension at high doses of cinaciguat; thus, further dose titration trials are required to establish the optimal dosing strategy [1109200].

Patent summary

Cinaciguat was first claimed by Bayer in WO-0119780. This patent has been granted in Europe as EP-01216225 and in the US as US-07087644 and US-07517896. The patent should retain solid protection in the EU until August 2020 and in the US until March 2021.

PCT application WO-2004006975, assigned to Bayer, discloses a stent specifically claimed for use with cinaciguat.

WO-2005011727 claims combinations of ACE inhibitors and activators of sGC. This case is especially interesting in that it is assigned to Pfizer Inc and specifically claims cinaciguat for use. The disclosure cites the WO-0119780 product case and a journal reference. This was followed by another combination case (WO-2006037491), this time assigned to Bayer and claiming combinations with NO for treating asthma and other forms of bronchoconstriction.

A series of new use applications for cinaciguat were published early in 2007: WO-2007025595, for the treatment of reperfusion damage; WO-2007003435, for the treatment of wounds; WO-2007009589, for the treatment of Raynaud's disease; WO-2007009607, for the treatment of renal disorders; and WO-2007039155, for the treatment of lung disorders, all assigned to Bayer.

The first formulation case for cinaciguat, WO-2008003414, describes an aqueous parenteral formulation. This was followed by two new use applications for cinaciguat later in the year; WO-2008138483, for treating urological disorders, and WO-2008148474, for perfusing and preserving organs and tissues. The application WO-2009138165 claims cinaciguat for treating hearing impairments. The most recent application, WO-2010049078, claims gas mixtures containing helium and oxygen for the treatment of pulmonary hypertension. These mixtures are claimed to contain active pharmaceutical ingredients, including, among others, cinaciguat. Again, the assignee in each of these cases is Bayer.

Current opinion

Cinaciguat is a potent, direct sGC activator that is being developed as a first-in-class treatment for ADHF. In preclinical studies, cinaciguat exerted potent arterial and venous vasodilator, platelet anti-aggregant and antiremodeling properties, which persisted in nitrate-tolerant tissues. In patients with ADHF, phase II clinical trials demonstrated that intravenous cinaciguat produced a hemodynamic benefit and improved signs and symptoms of disease, without increasing oxidative stress or development of tolerance, two potentially adverse actions of conventional nitrovasodilators. Moreover, cinaciguat appears to be a promising, effective and safe new therapeutic intervention for several other cardiovascular disorders, including systemic and pulmonary hypertension, chronic kidney disease and, perhaps, other cardiovascular diseases. Preclinical studies of cinaciguat in combination with PDE5 inhibitors have also hinted at a possible application in the treatment of COPD, idiopathic pulmonary fibrosis and asthma.

However, its long-term efficacy and safety still needs to be defined in randomized, double-blind phase III clinical trials focusing principally on determining whether cinaciguat can confer mortality benefits in patients with ADHF and other cardiovascular diseases. Furthermore, the effects of cinaciguat on certain forms of ADHF, such as pulmonary edema, cardiogenic shock and right HF, or ADHF with renal failure (creatinine ≥ 2 mg/dl) are presently unknown.

Cinaciguat appears to be the only sGC activator currently in development, if ataciguat has indeed been discontinued. The published data indicate that cinaciguat is a potent sGC activator; however, the mechanisms and signaling pathways involved in its cardio- and nefro-protective effects are presently unknown.

Oxidative stress occurring during various vascular disease states interferes with the NO/sGC/cGMP signaling pathways through scavenging of NO and formation of peroxynitrite, making vasodilator therapy with NO donors less effective [839250]. Under these circumstances, cinaciguat not only activates sGC in its NO-unresponsive oxidized or heme-free state, but also preferentially induces vasodilation in diseased vessels without the development of tolerance [802144] [839250], [919410]. Thus, it is possible that cinaciguat may help to circumvent nitrate resistance; however, this assessment must be corroborated in long-term clinical trials.

In preclinical studies, cinaciguat produced a concentration-dependent inhibition of platelet aggregation induced by U-46619, collagen and ADP. However, currently there is no clinical data available on the anti-aggregant effects of cinaciguat in patients with heart failure. In the report from Lapp *et al*, despite 93% of patients receiving anticoagulation therapy or platelet inhibition prior to and during cinaciguant therapy, there was no evidence discussed of hematological/bleeding side effects [1085966]. However, in this paper there was no indication that the anti-aggregant effects or safety of cinaciguat in this context had been investigated.

If phase IIb and III clinical trials confirm the efficacy and safety of the drug, cinaciguat could become a competitor to nitrates in the treatment of AHFS. The phase I and II clinical trials performed with cinaciguat so far, however, are insufficient to provide convincing evidence on the efficacy and safety of the drug. Phase II trials included a reduced number of patients followed for only a very short period of time (up to 48 h), therefore it is too early to venture a possible role that this drug may play in the treatment of AHFS. Additionally, it should also be noted that all of the drugs developed in the last two decades for the treatment of AHFS improved the signs and symptoms of the patient, but they had limited effects on overall outcome (ie, hospitalization and survival) [1118899]. Thus, caution should be exerted before extrapolating the present preliminary data to the clinical practice.

Development status

Developer	Country	Status	Indication	Date	Reference
Bayer AG	Germany	Phase II	Cardiac failure	29-NOV-06	789193

Associated patent

Title Novel derivatives of dicarboxylic acid having pharmaceutical properties.
Assignee Bayer AG
Publication WO-00119780 22-MAR-01
Inventors Alonso-Alija C, Heil M, Flubacher D, Naab P, Pernerstorfer J, Stasch J-P, Wunder F, Dembowsky K, Perzborn E, Stahl E.

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• of special interest

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