## Clinical Study Synopsis

This Clinical Study Synopsis is provided for patients and healthcare professionals to increase the transparency of Bayer's clinical research. This document is not intended to replace the advice of a healthcare professional and should not be considered as a recommendation. Patients should always seek medical advice before making any decisions on their treatment. Healthcare Professionals should always refer to the specific labelling information approved for the patient's country or region. Data in this document or on the related website should not be considered as prescribing advice.
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.

Bayer HealthCare

# Clinical Trial Results Synopsis

| Study Design Description | | |
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| **Study Sponsor:** | Bayer Healthcare Pharmaceuticals Inc. | |
| **Study Number:** | 14560 | NCT01065077<br>EudraCT Number: 2009-014377-40 |
| **Study Phase:** | IIb | |
| **Official Study Title:** | A placebo controlled, randomized, double-blind, fixed-dose, multicenter, phase IIb study to investigate the efficacy and tolerability of BAY 58-2667 (150 µg/h, 100 µg/h, 50 µg/h) given intravenously to subjects with acute decompensated chronic congestive heart failure (ADHF) | |
| **Therapeutic Area:** | Cardiology/Coagulation | |
| **Test Product** | | |
| **Name of Test Product:** | Cinaciguat (BAY 58-2667) | |
| **Name of Active Ingredient:** | Cinaciguat | |
| **Dose and Mode of Administration:** | The subject received continuous intravenous (IV) infusion of three fixed doses of Cinaciguat (50 µg/h; 100 µg/h; and 150 µg/h). | |
| **Reference Therapy/Placebo** | | |
| **Reference Therapy:** | Matching placebo infusion | |
| **Duration of Treatment:** | Treatment was administered for a minimum of 24 hours and lasted no longer than 48 hours. | |
| **Studied Period:** | **Date of first subjects' first visit:** | 23 MAR 2010 |
| | **Date of last subjects' last visit:** | 22 FEB 2011 |
| **Premature Study Suspension / Termination:** | Yes.<br>The DMC recommended the termination of the three highest doses being investigated (i.e., 50 µg/h, 100 µg/h, and 150 µg/h) because of adverse effects on blood pressure seen with these doses in the present study. Based on this recommendation and that of the Steering Committee, the Sponsor prematurely and permanently terminated this study on 04 FEB 2011. | |
| **Substantial Study Protocol Amendments:** | Amendment no. 1, dated 14 SEP 2010, incorporated the following safety-related changes:<br>• Inclusion criteria: The original protocol required that a subject with systolic blood pressure of ⩾120 mmHg and heart rate of <100 beats per minute would be included in the study. This was modified to require these values at run-in and at baseline. In addition, the criterion was expanded to indicate that the shock index (heart rate/systolic blood pressure) should be <1.<br>• Exclusion criteria: The exclusion criteria addressing specific prohibited medications were modified to (i) restrict the use of intravenous vasodilating drugs and intravenous natriuretic | |

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| | peptides; (ii) revise the exclusion regarding the use of any intravenous inotropic agent (e.g., dobutamine, levosimendan) from within the last 3 hours prior to study drug infusion to exclude any intravenous catecholamine or levosimendan within the last 30 days prior to study drug infusion; and (iii) prohibit the use of phosphodiesterase -5 (PDE-5) inhibitors.<br>• Safety variables: "Length of in hospital stay for the initial admission" was added as an additional safety variable/endpoint in the hope of showing an improvement in the length of hospitalization with Cinaciguat compared with placebo. The definition of a treatment-emergent adverse event (TEAE) was changed from those starting or worsening within 24 hours of starting the study drug infusion to those starting or worsening within two calendar days of starting the infusion.<br>• Events of special interest: The original protocol identified ventricular tachycardia and ventricular extrasystoles as events of special interest. This was changed to provide a broader term, any ventricular arrhythmia, that would encompass both ventricular tachycardia and ventricular extrasystoles, and to identify as events of special interest any such events considered by the investigator as medically important.<br>• Assessment periods: The original protocol defined the "run-in period" as 24 hours from the admission of the subject to the hospital. This was changed such that the run-in period no longer had a time limit and encompassed the entire time from hospital admission to randomization in the study.<br>• Hemodynamic measurements: The statement "The right heart thermo-dilution method will be used for continuous hemodynamic measurements" was removed to allow the study centers to use their routine procedures. |
| **Study Centre(s):** | Planned: approximately 50-60 centers worldwide<br>Actual: 4 sites in Germany, 2 sites in Italy and 1 site in Poland had enrolled subjects. |
| **Methodology:** | This was a randomized, double-blind, placebo-controlled, fixed-dose, multicenter, multinational study in adult subjects with ADHF who had a need for parenteral pharmacotherapy and invasive hemodynamic monitoring (i.e., indwelling pulmonary artery catheter [Swan-Ganz]), PCWP of at least 20 mmHg, and a CI of no more than 2.5. The study comprised a run-in phase which started at the admission of the subject to the hospital (including emergency department) and included the primary diagnostic procedures and selection for participation in the study. Baseline assessments were performed at the end of the run-in phase as soon as possible (i.e., within 60 minutes) before the start of study drug infusion. Treatment was to last a minimum of 24 hours and no longer than 48 hours. A single follow-up visit was conducted between 30 and 35 days after the end of study drug infusion.<br><br>Eligible subjects received an intravenous infusion of one of the three |

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| | doses of Cinaciguat or placebo for a minimum of 24 hours and a maximum of 48 hours. Subjects were evaluated at baseline (defined as close to the start of study drug infusion as possible; time = 0 h) at various time points during the study drug infusion, within the immediate hours after the stop of the study drug infusion, at hospital discharge, and at 30 days after the stop of the infusion. Assessments included hemodynamic measurements, blood pressure, heart rate, adverse events (AEs), and the need for concomitant medications.<br><br>The subjective well-being was assessed by the European Quality of Life (EuroQoL) Visual Analogue Scale (VAS), Kansas City Cardiomyopathy Questionnaire (KCCQ), and the physician's assessment. For determining systemic exposure with IV infusion, blood samples were taken at several time points during infusion and at 1 and 2 hours, respectively, after the stop of the study drug infusion.<br><br>Blood samples for biomarker analysis were collected before infusion; at 24 hours and end of infusion; at hospital discharge; and at the follow-up visit. |
| **Indication / Main Inclusion Criteria:** | Indication:<br>Acute decompensated chronic congestive heart failure<br><br>Main inclusion criteria:<br>• Male and non-pregnant, non-lactating female subjects or women without childbearing potential (defined as postmenopausal women aged 55 years or older, women with bilateral tubal ligation, women with bilateral ovarectomy, and women with a hysterectomy)<br>• Subjects aged 18 years and above<br>• Subjects with a clinical diagnosis of congestive heart failure (CHF) made at least 3 months prior to enrollment<br>• Subjects who had experienced worsening dyspnea and had clinical evidence of volume overload leading to hospitalization at the time of hospital admission up to study run-in phase |
| **Study Objectives:** | **Primary:**<br>To investigate the safety and efficacy of a fixed dose of intravenous Cinaciguat given over at least 24 hours and up to 48 hours in subjects with ADHF with the need for parenteral pharmacotherapy and invasive hemodynamic monitoring (i.e., indwelling pulmonary artery catheter [Swan-Ganz]) and PCWP ≥20 mmHg with CI ≤2.5.<br><br>**Secondary:**<br>To evaluate the potential effects of the three fixed doses of Cinaciguat (50 µg/h, 100 µg/h, and 150 µg/h) or placebo given intravenously on QT/QTc prolongation. |
| **Evaluation Criteria:** | **Efficacy (Primary):** |

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| | • Change in PCWP from baseline to 8 hours after starting the study drug infusion (or last observation carried forward [LOCF]).<br><br>**Efficacy (Secondary):**<br>Exploratory efficacy variables included:<br>• Cardiac Index<br>• EuroQoL VAS, KCCQ scores, and physician's assessment<br>• Right atrial pressure (RAP)<br>• Change in PCWP at 48 hours and responder rate (i.e., proportion of subjects experiencing a PCWP reduction of ≥4 mmHg)<br>• Pulmonary artery pressure (PAP); mean arterial pressure; cardiac output; systemic vascular resistance; and pulmonary vascular resistance<br>• Change in concomitant medications during the treatment phase<br><br>**Safety:**<br>Safety assessments included change in heart rate; systolic and diastolic blood pressure; frequency of treatment-emergent adverse events (TEAEs; adverse events were considered to be treatment-emergent if they started after the start of study drug infusion up to two calendar days after the end of the study drug infusion); treatment-emergent serious adverse events; deaths; evaluation of renal and cardiac function; laboratory parameters; electrocardiogram (ECG) assessments; in-hospital mortality; length of in-hospital stay for the initial admission; days in hospital (from first admission until the follow-up visit); re-hospitalization until the follow-up visit; and 30-days mortality. |
| | **Pharmacokinetics:**<br>For the investigation of pharmacokinetics (PK), the plasma concentrations of Cinaciguat were determined using a sparse sampling approach, in all participating subjects. |
| **Statistical Methods:** | **Population:**<br>A randomized subject was valid for the safety population if he/she had received any study drug. A subject was valid for the intent-to-treat (ITT) population if he/she was valid for the safety population and had at least one valid efficacy measurement (primary or secondary) at both baseline (if required) and post-baseline. A per protocol (PP) population was planned in the original study protocol. However, because the study was prematurely terminated and comprised of only 12 randomized subjects, no PP population was defined for the purposes of reporting the study data.<br><br>**Efficacy (Primary):**<br>No planned inferential statistical analyses were conducted. The data were presented only by descriptive or summary statistics and listings. The number of data available (i.e., N), mean, standard deviation, minimum, quartiles, median, and maximum were calculated for continuous data. |

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| | **Efficacy (Secondary):**<br>The secondary efficacy variable data were presented similarly to primary efficacy variable. Frequency tables were generated for categorical data. No planned inferential statistical analyses were conducted.<br><br>**Safety:**<br>Incidence of all AEs, SAEs, and events of special interest were reported using the hierarchy of MedDRA code. |
| **Number of Subjects:** | Planned: A total of 100 subjects were planned to be enrolled and randomized; 25 subjects each to receive one of the 3 doses of the study drug or matching placebo.<br><br>Analyzed: A total of 14 subjects were screened, and 12 were randomized and treated. |

**Study Results**

**Results Summary — Subject Disposition and Baseline**

By the time when this study was prematurely terminated by the Sponsor, a total of 14 subjects were screened (ie, provided a signed and dated informed consent form) and 12 subjects were randomized. Both of the subjects who were not randomized did not meet the study inclusion/exclusion criteria. These subjects were recorded in the data base as having failed screening for a "protocol violation".

Twelve subjects were treated as follows:

Placebo – 3 subjects

50 µg/h – 4 subjects

100 µg/h – 2 subjects

150 µg/h – 3 subjects

Of the 12 randomized subjects, 8 completed the treatment phase and 11 completed the follow-up phase.

Of the 12 randomized subjects, 4 prematurely discontinued study treatment. 3 subjects, all of whom were treated with cinaciguat, reported an adverse event as the primary reason for discontinuation.

**Results Summary — Efficacy**

Upon premature termination of this study on 04 February 2011, no inferential efficacy analyses were performed.

Only minor changes in the mean PCWP were observed in the placebo group; there was no change in median PCWP at 8 hours/LOCF and a median (min/max) change of 1.00 mm Hg (-5.00 mm Hg/ 2.00 mm Hg) at 48 hours/LOCF. Median (min/max) PCWP decreased in all cinaciguat groups over the course of treatment. At 8 hours/LOCF, the median (min/max) change was -6.00 mm Hg (-9.00 mm Hg/-2.00 mm Hg), -10.00 mm Hg (13.00 mm Hg/-7.00 mm Hg), and -4.00 mm Hg (-4.00 mm Hg/-3.00 mm Hg) in subjects receiving 50 µg/h, 100 µg/h, and 150 µg/h, respectively.

Because of the small number of subjects randomized and treated in this terminated study, no definitive conclusions can be drawn regarding the efficacy of cinaciguat at the dosages investigated, including dose relationship or treatment differences versus placebo.

**Results Summary — Safety**

**Adverse events**

Most subjects (n=10) experienced an adverse event (AE) at some point after signing the study informed consent form and approximately half of the subjects (n=7) experienced TEAEs. Study drug-related TEAEs were reported by three subjects, all of whom were treated with cinaciguat, and protocol-required procedure-related TEAEs were reported by two subjects, both of whom were treated with cinaciguat.

Of the three subjects experiencing drug-related TEAEs, two experienced severe events and one experienced mild events. The most common TEAEs were in the Cardiac Disorders system organ class (SOC; 5 subjects) and included the preferred terms of atrial fibrillation (n=3) and ventricular tachycardia (n=4). All other cardiac preferred terms (PTs) were reported by only a single subject each.

Five subjects overall experienced treatment-emergent serious adverse events (SAEs), including one subject who received 150 µg/h and subsequently died as the result of event. Five subjects experiencing treatment-emergent SAEs. Three SAEs were considered by the investigator as not related to the study drug, and each SAE resolved.

**Laboratory parameters**

Generally, none of the assessments of laboratory parameters (hematology, clinical chemistry, urinalysis, biomarkers, and endocrinology) suggested a trend for an increase or decrease in mean/median values from baseline, for the study population as a whole or by treatment group. The incidence of high and low laboratory abnormalities was low in all treatment groups. No changes in clinical laboratory parameters suggestive of a treatment effect were observed.

**Renal function – Serum creatinine and estimated glomerular filtration rate (eGFR)**

Clinically significant changes in renal function were predefined as (i) changes from baseline in serum creatinine of >0.3 mg/dL; or (ii) changes from baseline in serum creatinine of >0.5 mg/dL. In addition, throughout the study, renal function was investigated using the Modification of Diet Renal Disease (MDRD) formula. A decrease from baseline in eGFR of > 10 ml/min/1.73 m2 was also considered to be a clinically significant change in renal function. Eight subjects had experienced clinically significant changes in renal function. However, there were no indications of an effect of cinaciguat on renal function in this study.

**Cardiac function – Ultrasensitive Troponin I (UsTnI) values**

Eight subjects experienced at least one UsTnI value above this threshold during or after treatment. There was no indication of an effect of cinaciguat on UsTnI levels in the study.

**Vital signs**

Minor changes in median systolic blood pressure were observed during treatment in the placebo group, while subjects in all three cinaciguat groups experienced decreases in systolic pressure. Similarly, minor fluctuations in median diastolic blood pressure were observed during treatment in the placebo group, while subjects in all three cinaciguat groups experienced fairly consistent decreases in diastolic pressure over the course of treatment. Two subjects reported TEAEs of hypotension and had prematurely discontinued study drug in response to the TEAE. No clinically relevant changes in median heart rate were observed during treatment in any treatment group

**ECGs**

Based on the ECG tracings collected at these specified time points, the central reader identified three subjects with tachycardia (placebo n=2; 150 µg/h n=1) and one with sustained supraventricular tachycardia (150 µg/h n=1) as treatment-emergent ECG findings. No other treatment-emergent ECG findings suggestive of a ventricular arrhythmia were reported by the central reader.

Two subjects, one receiving 100 µg/h and one receiving 150 µg/h, experienced prolonged QTc at least one time point assessed, including discharge and/or follow-up. Both of these subjects, however, had a prolonged QT interval before the start of treatment and in neither case the QT interval changed appreciably.

**Holter Monitoring**

In summary, the pattern of Holter recordings was similar to the expected pattern for this population of subjects with ADHF.

**Hospitalization and Mortality**

Median (min/max) length of hospital stay for the initial admission was 12.0 days (9 days/20 days) in the placebo group and ranged from 8.0 days (3 days/10 days; 150 µg/h) to 10.5 days (6 days/14 days; 50 µg/h) in the cinaciguat groups. One subject who had received 150 µg/h died during the initial hospitalization; therefore, mortality during the initial hospitalization and by the 30-day follow-up was 0% in the placebo group and 11.1% in the combined cinaciguat group. By the follow-up visit, no subject had required rehospitalization.

**Results Summary — Pharmacokinetics**

A general trend of increasing plasma concentrations of Cinaciguat with increasing Cinaciguat dose was observed such that the median values for plasma concentrations of Cinaciguat in subjects receiving 150 µg/h were consistently higher than those in subjects treated with 50 µg/h.

**Conclusion(s)**

In this study, changes in PCWP suggested a treatment effect of Cinaciguat compared to placebo. Higher decreases in PCWP were seen with Cinaciguat than placebo, a greater maximum effect was achieved with Cinaciguat than with placebo, and a higher responder rate was observed with Cinaciguat than with placebo. However, due to the small number of subjects, no definitive conclusions could be drawn regarding the efficacy of Cinaciguat at the dosages investigated, including dose relationship or treatment differences versus placebo.

In general, the safety findings (i.e., AEs and laboratory parameters) observed in this study were consistent with the known safety profile of Cinaciguat and with the behavior of the patient population (i.e., subjects with ADHF), as described in the literature. While a fall in blood pressure was a common occurrence during infusion of Cinaciguat (reported as a TEAE by five subjects, and three additional subjects experienced predefined clinically relevant changes in systolic blood pressure), no clinically significant reflex tachycardia was reported.

Hypotensive events were expected in the Cinaciguat treatment groups and were consistent with the mode of action of the drug. However, the decrease of blood pressure seen in this study exceeded the acceptable range of vasodilation. Finally, in this study, there was no clinically significant difference in change of renal function between the placebo group and the Cinaciguat groups.

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| **Publication(s):** | None | | |
| **Date Created or Date Last Updated** | 10 MAY 2013 | **Date of Clinical Study Report:** | 05 JAN 2012 |