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.

Bayer HealthCare

Clinical Trial Results Synopsis

Study Design Description		
Study Sponsor:	Bayer HealthCare Pharmaceuticals Inc.	
Study Number:	14663	NCT01067859 EudraCT number: 2009-014378-16
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 low dose BAY 58-2667 (25 µg/h, 10 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 (BAY58-2667)	
Name of Active Ingredient:	Cinaciguat	
Dose and Mode of Administration:	10 µg/h or 25 µg/h administered as continuous intravenous (IV) infusion	
Reference Therapy/Placebo		
Reference Therapy:	Matching placebo	
Dose and Mode of Administration:	Matching placebo was administered as continuous IV infusion	
Duration of Treatment:	Treatment was given for at least 24 hours and up to 48 hours.	
Studied Period:	**Date of first subjects' first visit:**	15 MAR 2010
	Date of last subjects' last visit:	05 NOV 2010
Premature Study Suspension / Termination:	Yes This study was terminated on 01 Mar 2011, in view of (i) the inconclusive risk-benefit balance for the 10 µg/h and 25 µg/h doses and (ii) recruitment difficulties experienced by the study sites.	
Substantial Study Protocol Amendments:	Amendment no. 1, dated 14 SEP 2010, was enacted for the following substantial changes: • Inclusion criteria: The following changes were made: ○ The requirement that a subject should have systolic blood pressure of ≥120 mmHg and heart rate of <100 beats per minute at inclusion in the study was modified, and the subjects were required to have these values during the run-in phase and at baseline. In addition, the criterion was also expanded to indicate that the shock index (heart	

	rate/systolic blood pressure) should be <1.
	• Exclusion criteria: The exclusion criteria related to the specific prohibited medications was modified to:
	  ○ restrict the use of IV vasodilating drugs and IV natriuretic peptides
	  ○ revise the exclusion regarding the use of any IV inotropic agent (e.g., dobutamine, levosimendan) from within the last 3 hours prior to the study drug infusion to exclude any IV catecholamines or levosimendan within the last 30 days prior to study drug infusion
	  ○ prohibit the use of PDE-5 inhibitors.
	• Safety variables: The following changes were made:
	  ○ The safety variable "Length of in-hospital stay for the initial admission" was added as an additional safety variable/endpoint in the hopes of showing an improvement in the length of hospitalization with BAY 58-2667 compared with placebo.
	  ○ The definition of a treatment-emergent adverse event (TEAE) was changed from those starting or worsening within 24 hours of start of the study drug infusion to those starting or worsening within two calendar days of starting the infusion.
	• Events of special interest: The events ventricular tachycardia and ventricular extrasystoles were identified as events of special interest. These were changed to provide a broader term, any ventricular arrhythmia (encompassing both ventricular tachycardia and ventricular extrasystoles) that were considered by the investigator as medically important.
	• Assessment periods: The run-in period of 24 hours from the admission of the subjects to the hospital was changed such that the run-in period no longer had a time limit of 24 hours and encompassed the entire time from hospital admission to randomization in the study. Specific restrictions regarding the use of some drugs during the run-in period were modified/added to reflect the changes made to the exclusion criteria and the use of prior and concomitant therapy.
	• Information regarding restricted therapy during the treatment was clarified/expanded to include prohibition of IV vasodilators, IV natriuretic peptides, oral or topical nitrates, and non-invasive ventilation during the infusion period. A statement was added that these drugs could be used as rescue medication once the infusion had been stopped. The statement regarding the use of IV diuretics during the treatment was modified to allow any diuretic.
	• Hemodynamic measurements: The statement "The right heart thermodilution method will be used for continuous hemodynamic measurements" was removed to allow the study sites to use their routine procedures.

Study Center(s):	Planned: Approximately 60 centers worldwide. Actual: At the time of study termination, two sites in Germany had screened the subjects, and two sites had randomized a total of five subjects.
Methodology:	This study consisted of three groups: two groups receiving different doses of cinaciguat (10 µg or 25 µg) and a placebo group. Eligible subjects received an IV infusion of either one of the two doses of cinaciguat or matching placebo for a minimum of 24 hours and a maximum of 48 hours. Subjects were evaluated at run-in phase (time from hospital admission to randomization of subjects), baseline (defined as: as close to the start of study drug infusion as possible), at various time points during the study drug infusion, within the immediate hours after the stop of study drug infusion, at hospital discharge, and at 30 days after the stop of the infusion (follow-up visit). Assessments included hemodynamic measurements, blood pressure, heart rate, adverse events (AEs), and the need for concomitant medications. The subjective well-being of the subject was assessed by the EuroQol Visual Analogue Scale (VAS) and Kansas City Cardiomyopathy Questionnaire (KCCQ). For determining systemic exposure to IV infusion, blood samples were taken at several time points during the infusion and at 1 and 2 hours after the stop of the study drug infusion. Blood samples for biomarker analysis were collected before infusion, at 24 hours, at the end of the infusion, at hospital discharge, and at the 30-day follow-up visit.
Indication / Main Inclusion Criteria:	Indication: Acute decompensated chronic congestive heart failure (ADHF) Main inclusion criteria: • Subjects with ADHF New York Heart Association functional class III-IV, either ischemic or non-ischemic, requiring hospitalization and with clinical indication for parenteral pharmacotherapy and invasive hemodynamic monitoring (i.e., in-dwelling pulmonary artery catheter [Swan-Ganz]) and pulmonary capillary wedge pressure [PCWP] ≥20 mmHg with cardiac index (CI) ≤2.5 at run-in and baseline • Subjects aged 18 years and above • 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 • Subjects must have had a clinical diagnosis of congestive heart failure (CHF) made at least 3 months prior to enrollment

	• Subjects must have experienced worsening of both dyspnea and clinical evidence of volume overload leading to hospitalization at the time of entry into the study
Study Objectives:	**Primary:** To investigate the safety and efficacy of a fixed dose over at least 24 hours and up to 48 hours of intravenous cinaciguat (25 µg/h, 10 µg/h) in subjects with ADHF with the need for parenteral pharmacotherapy and invasive hemodynamic monitoring (i.e., in-dwelling pulmonary artery catheter [Swan-Ganz]) and pulmonary capillary wedge pressure (PCWP) ≥20 mmHg with cardiac index (CI) ≤2.5. **Secondary:** To evaluate the potential effects of the two fixed doses of cinaciguat (10 µg/h, 25 µg/h) and placebo given intravenously on QT/QTc prolongation.
Evaluation Criteria:	**Efficacy (Primary):** The primary efficacy outcome measure was the change in PCWP from baseline to 8 hours after the start of the infusion (or last observation carried forward [LOCF]). **Efficacy (Secondary):** Exploratory efficacy outcome measures included: • Change in PCWP from baseline to 48 hours after the start of infusion • Cardiac index at various time points up to the follow-up visits (including at 8 hours and 48 hours after the start of the infusion) • Right arterial pressure (RAP) at various time points up to the follow-up visits (including at 8 hours and 48 hours after the start of the infusion) • Other hemodynamic parameters including pulmonary artery pressure (PAP), mean arterial pressure, cardiac output, systemic vascular resistance, and pulmonary vascular resistance at various time points up to the follow-up visit • Change in PCWP from baseline to maximal effect • Responder rate (i.e., proportion of subjects experiencing a PCWP reduction of ≥4 mmHg) • Change in overall health status through EuroQol VAS from baseline to 24 hours and 48 hours after the start of the infusion, and up to the follow-up visit • Change in overall health status through KCCQ scores from baseline to the follow-up visit • Physician's assessment at different time points during the treatment phase **Safety:**

	Safety assessments included: • Change in heart rate from baseline to different time points up to the follow-up visit • Change in systolic and diastolic blood pressure from baseline to different time points up to the follow-up visit • Frequency of TEAEs; treatment-emergent serious adverse events (SAEs); and deaths during the study • Evaluation of renal and cardiac function through assessments of different biomarkers at different time points up to the follow-up visit • Laboratory parameters at different time points up to the follow-up visit • Electrocardiogram (ECG) assessments at different time points up to the follow-up visit • 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 • 30-days mortality
	Pharmacokinetics: Blood samples were collected periodically during the treatment period, at the end of the study drug infusion, and during the follow-up visit to determine the plasma concentrations of cinaciguat.
Statistical Methods:	**Population:** A randomized subject was considered valid for the safety population if he/she had received any study drug. A subject was considered valid for the intent-to-treat (ITT) population if he/she was considered 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 four treated subjects, no PP analysis set was defined. **Efficacy (Primary):** No statistical analyses were performed, and no descriptive statistics were prepared because of the small number of subjects enrolled in the study. **Efficacy (Secondary):** No statistical analyses were performed, and no descriptive statistics

	were prepared because of the small number of subjects enrolled in the study. **Safety:** Safety results were described individually for each subject due to the small number of subjects enrolled in the study. No statistical analyses were performed.
	Pharmacokinetics: Plasma concentration of cinaciguat was reported for all the enrolled subjects to determine whether the concentration was above or below the lower limit of quantification (LLOQ). No statistical analyses were performed.
Number of Subjects:	Planned: A total of 60 subjects were to be randomized, 20 subjects per treatment group, or a total of 60 subjects valid for the protocol. Actual: Seven subjects were screened; five subjects were randomized; and four subjects were treated (placebo group n = 1; 10 µg/h group n = 2; 25 µg/h group n = 1).

Study Results

Results Summary — Subject Disposition and Baseline

Of the five randomized subjects, four subjects were treated (placebo group n = 1; 10 µg/h group n = 2; 25 µg/h group n = 1), and one subject did not receive the study treatment. In this study, three subjects were males, and one subject was female; all subjects were Caucasian. The age of the subjects ranged from 58 to 75 years. Only one subject (25 µg/h) completed the treatment phase. The three other subjects discontinued the treatment phase because of insufficient therapeutic effect.

Results Summary — Efficacy

This study was prematurely terminated; therefore, no inferential efficacy analyses were conducted, and no summary statistics for the efficacy variables were prepared.

Results Summary — Safety

Two subjects (one subject each in the 10 µg/h group and 25 µg/h group) reported AEs, all of which were either mild or moderate in severity. Adverse events considered related to the study drug were nausea and decreased blood pressure. No SAEs or deaths were reported.

Clinically significant changes in serum creatinine, creatinine clearance, and ultrasensitive troponin I (UsTnI) were not evaluated.

Two subjects had high serum creatinine at baseline; both of these subjects had a history of chronic renal failure. In both the cases, serum creatinine remained high and similar to baseline at 24 hours. All four treated subjects had high serum creatinine and low eGFR at the follow-up visit.

Two subjects (10 µg/h group) experienced elevated UsTnI only at the follow-up visit. A third subject (25 µg/h group) had elevated UsTnI values at all time points assessed (including

baseline).

For the most part of the study, vital signs remained relatively stable and within the expected ranges throughout the treatment, and at 1 and 2 hours post-treatment in all subjects. One subject (10 µg/h group) experienced a TEAE of decreased blood pressure that was considered to be related to the study drug. The event resolved upon withdrawal of the study drug without remedial drug therapy.

The most common ECG findings included rhythm and rate disorders which were reported in three subjects.

Results Summary — Pharmacokinetics

No appreciable difference in the plasma concentrations of cinaciguat was observed in the subjects who received 10 µg/h and in the subject who received 25 µg/h. The single subject who received 25 µg/h had detectable concentrations at 1 and 2 hours post-treatment, while concentrations were below the LLOQ at 2 hours post-treatment in both the subjects treated with 10 µg/h of the study drug.

Conclusion(s)

In this study, due to the small number of subjects, no definitive conclusions could be drawn regarding the efficacy or safety of cinaciguat at the doses tested.

Publication(s):	None		
Date of Clinical Study Report:	10 MAY 2013	**Date Created or Date Last Updated:**	16 APR 2013