

Clinical Study Synopsis

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Clinical Trial Results Synopsis

Study Design Description		
Study Sponsor:	Bayer Healthcare Pharmaceuticals Inc.	
Study Number:	14836	NCT01064037 EudraCT number: 2009-017082-39
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 (50 µg/h, 100 µg/h, 150 µg/h) given intravenously to subjects with acute decompensated chronic congestive heart failure (ADHF) within 12 hours after hospital admission (pulmonary artery catheter eg, Swan-Ganz not required)	
Therapeutic Area:	Cardiology/Coagulation	
Test Product		
Name of Test Product:	Cinaciguat (BAY 58-2667)	
Name of Active Ingredient:	Cinaciguat	
Dose and Mode of Administration:	50 µg/h, 100 µg/h, or 150 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 needs to be given for at least 24 hours and up to 48 hours.	
Studied period:	Date of first subjects' first visit:	19 APR 2010
	Date of last subjects' last visit:	07 MAR 2011
Premature Study Suspension / Termination:	<p>Yes</p> <p>An ad-hoc meeting of the Data Monitoring Committee (DMC) was held on 03 FEB 2011 to discuss unblinded safety data cinaciguat in ADHF. Following this, the DMC recommended the termination of the three highest doses of cinaciguat (i.e., 50 µg/h, 100 µg/h, and 150 µg/h) being investigated because of adverse effects on blood pressure and renal function. Based on this recommendation and that of the Steering Committee, the Sponsor permanently terminated this study.</p>	
Substantial Study Protocol Amendments:	<p>Amendment no. 1 dated 14 SEP 2010 was enacted for the following changes:</p> <ul style="list-style-type: none"> Inclusion criteria: The following changes were made: The requirement that a subject should have a systolic blood 	

	<p>pressure of ≥ 120 mmHg and a 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.</p> <ul style="list-style-type: none"> Exclusion criteria: The exclusion criteria related to the specific prohibited medications was modified: Use of vasodilating drugs and natriuretic peptides was changed to IV vasodilating drugs and IV natriuretic peptides. Use of any IV inotropic agent (e.g., dobutamine, levosimendan) within the last 3 hours prior to study drug infusion was changed to any IV catecholamine or levosimendan within the last 30 days prior to the study drug infusion. Use of PDE-5 inhibitors was added under prohibited medicines. Safety variables: 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 2 calendar days of starting the infusion.
Study Center(s):	<p>Planned: Approximately 60 centers worldwide.</p> <p>Actual: Twenty investigational sites treated subjects in 12 countries; one center in the United States, two centers in Czech Republic, two centers in Finland, three centers in Germany, three centers in Hungary, one center in Ireland, one center in Israel, one center in Italy, one center in Japan, three centers in Poland, one center in Spain, and one center in South Africa.</p> <p>Thirty-nine additional sites were ready to recruit subjects at the time this study was terminated.</p>
Methodology:	<p>This was a randomized, double-blind, placebo-controlled, fixed-dose, multicenter, multinational study conducted in adult subjects (18 years of age and above) with ADHF who required parenteral pharmacotherapy. The study consisted of 3 groups receiving different doses of cinaciguat (50 $\mu\text{g/h}$, 100 $\mu\text{g/h}$, or 150 $\mu\text{g/h}$), and a placebo group. Eligible subjects received an IV infusion of either one of the three doses of cinaciguat or matching placebo for a minimum of 24 hours and a maximum of 48 hours.</p> <p>Efficacy parameters in this study collected at baseline (defined as within 60 minutes before the start of the study treatment); at various time points during the study drug infusion; at Day 7 or at the time of hospital discharge; and at the follow-up visit (between 30-35 days after the study drug infusion was stopped).</p> <p>For safety parameters, subjects were evaluated during the run-in phase; at baseline; at various time points during the study drug infusion; at Day 7 or at the time of hospital discharge; and at the follow-up visit. In addition, AEs were also recorded at 1, 2, and 8</p>

	<p>hours after the study drug infusion was stopped; blood pressure and heart rate were assessed at 0.5, 1, 2, 4, 6, and 8 hours after the the study drug infusion was stopped.</p> <p>Blood samples for determining the systemic exposure with IV infusion were taken at several time points during the infusion and at 1 and 2 hours after the study drug infusion was stopped.</p>
<p>Indication/ Main Inclusion Criteria:</p>	<p>Indication: Acute decompensated chronic congestive heart failure (ADHF)</p> <p>Main inclusion criteria:</p> <ul style="list-style-type: none"> • Adult subjects (age ≥ 18 years) admitted to the hospital with symptoms of ADHF and a clinical indication for parenteral pharmacotherapy • Subjects who were able to commence treatment within 12 hours of hospital administration (including emergency department) • Male and non-pregnant, non-lactating female subjects, age ≥ 18 years; or women without childbearing potential (defined as postmenopausal women aged 55 years or older, women with bilateral tubal ligation, women with bilateral ovariectomy, 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 and a history of heart failure hospitalization or IV diuretic treatment required within the last 12 months • Subjects must have had experienced worsening of both dyspnea and clinical evidence of volume overload leading to hospitalization at the time of entry into the study
<p>Study Objectives:</p>	<p><u>Primary:</u> Using the dyspnea Visual Analogue Scale (VAS), to investigate the safety and efficacy of a fixed dose of cinaciguat (50 $\mu\text{g/h}$, 100 $\mu\text{g/h}$, or 150 $\mu\text{g/h}$) given intravenously over at least 24 hours and up to 48 hours in subjects with ADHF with the need for parenteral pharmacotherapy.</p> <p><u>Secondary:</u> To evaluate the potential effects of the three fixed doses of cinaciguat (50 $\mu\text{g/h}$, 100 $\mu\text{g/h}$, and 150 $\mu\text{g/h}$) and placebo given intravenously on QT/QTc prolongation.</p>
<p>Evaluation Criteria:</p>	<p><u>Efficacy (Primary):</u> The primary efficacy outcome measure was the change in the dyspnea VAS from baseline to 8 hours after start of infusion or last observation carried forward (LOCF).</p> <p><u>Efficacy (Secondary):</u> Other efficacy outcome measures included:</p> <ul style="list-style-type: none"> • Changes in the dyspnea VAS at other time points • Dyspnea assessment through Likert scale at various time points

	<p>up to the follow-up visit</p> <ul style="list-style-type: none"> • Overall health status assessment through EQ-5D Health Questionnaire up to the follow-up visit • Global clinical assessment by the physician • Change in concomitant medications during treatment <p><u>Safety:</u></p> <p>Safety variable included:</p> <ul style="list-style-type: none"> • Frequency of TEAEs (AEs were considered to be treatment emergent if they started after the start of the study drug infusion to up to 2 calendar days after the end of the study drug infusion); treatment-emergent serious adverse events (SAEs); deaths; evaluation of renal and cardiac function • Change in heart rate • Change in systolic and diastolic blood pressure • Laboratory parameters (including parameters related to hematology, clinical chemistry, urinalysis, and biomarkers) • ECG assessments <p><u>Efficacy (other):</u></p> <ul style="list-style-type: none"> • 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
	<p><u>Pharmacokinetics:</u></p> <p>Plasma concentrations of cinaciguat.</p>
Statistical Methods:	<p><u>Population:</u></p> <p>A randomized subject was considered valid for the safety analysis set if he/she had received any study drug.</p> <p>A subject was considered valid for the intent-to-treat (ITT) population if he/she was considered valid for the safety analysis set and had at least one valid efficacy measurement (primary or secondary) at both baseline (if required) and post-baseline.</p> <p>A per protocol (PP) population was planned in the original study protocol. However, because the study was prematurely terminated and comprised of only 62 treated subjects, no PP population was defined for the purposes of reporting the study data.</p> <p><u>Efficacy (Primary):</u></p> <p>No statistical analyses were performed. All data were presented by the use of summary statistics only.</p> <p><u>Efficacy (Secondary):</u></p> <p>No statistical analyses were performed. All data were presented by</p>

	<p>the use of summary statistics only.</p> <p>Safety: Safety data were described using summary tables.</p>
	<p>Pharmacokinetics: For the investigation of PK, the plasma concentrations of cinaciguat were determined using a sparse sampling approach in all participating subjects. Plasma concentration of cinaciguat were presented using summary statistics.</p>
Number of Subjects:	<p>Planned: Approximately 160 subjects were to be randomized; 40 subjects per treatment group.</p> <p>Actual: A total of 62 subjects were randomized and treated (matching placebo, n=19; 50 µg/h, n=14; 100 µg/h, n=15; 150 µg/h, n=14).</p>
Study Results	
Results Summary — Subject Disposition and Baseline	
<p>Of the 62 randomized and treated subjects, 50 subjects completed the treatment phase, and 57 subjects completed the follow-up phase. Most subjects (n=37; all treatment groups) were treated for between 24 and 48 hours and 14 subjects (9 in the placebo group and 5 in all cinaciguat treatment groups) were treated for 48 hours. 12 subjects prematurely discontinued the study treatment because of an AE of hypotension. Other events leading to premature discontinuation included bradycardia (with hypotension).</p> <p>The average age of the subjects at the time of enrollment was 69.7 ± 13.9 years in the placebo group and 68.3 ± 12.5 years in the combined cinaciguat treatment groups.</p>	
Results Summary — Efficacy	
<p>This study was prematurely terminated on 04 FEB 2011 following recommendations from the DMC and Steering Committee. No inferential efficacy analyses were conducted. The primary efficacy outcome measure was the change in dyspnea VAS scores from baseline to 8 hours/LOCF. The greatest reduction in the mean dyspnea VAS scores at this time was seen in the placebo group.</p> <p>Overall, neither the EuroQol VAS data nor the Likert scale data suggested a treatment effect of cinaciguat on breathing ability. The physicians' assessments did not suggest a treatment effect of cinaciguat at any of the doses tested.</p>	
Results Summary — Safety	
<p>In this study, half of the subjects enrolled (50.0%) experienced TEAEs. The study drug-related TEAEs were more often reported by the subjects receiving cinaciguat (32.6%) than subjects receiving placebo (5.3%). Additionally, the study drug-related TEAEs (24.2%) were reported more often than the events considered to be related to a protocol-specified procedure (8.1%). Most TEAEs were of either mild or moderate intensity; severe TEAEs were reported by less than 5% of the study subjects. There was one death reported in the follow-up phase of the study (approximately 5 days after the end of treatment).</p> <p>Overall, nine subjects experienced treatment-emergent SAEs including two subjects in the placebo group. There were no treatment-emergent SAEs related to the protocol-required procedures, and three subjects experienced drug-related treatment-emergent SAEs. The</p>	

drug-related treatment-emergent SAEs were hypotension (50 µg/h and 150 µg/h) and shock (100 µg/h).

Six subjects experienced treatment-emergent AEs that were classified as ventricular arrhythmias, including four subjects with ventricular extrasystoles (placebo, n=2; 100 µg/h, n=1; 150 µg/h, n=1) and three subjects with ventricular tachycardia (placebo, n=1; 150 µg/h, n=2). In most cases, the event was reported as an SAE and resolved.

Generally, none of the assessments of laboratory parameters (related to hematology, clinical chemistry, urinalysis, biomarkers, and endocrinology) suggested a trend for an increase or decrease in the mean/median values from baseline, for the study population as a whole or by treatment group.

There were no obvious differences in the number of subjects experiencing changes in renal function between the placebo and individual cinaciguat treatment groups. In addition, there were no obvious differences between the treatments in the magnitude or extent of changes in the renal function that would suggest a treatment effect.

Total of 29 subjects experienced at least one Ultrasensitive Troponin I (UsTnI) value above 0.040 ng/mL during or after treatment (placebo, n=8; 50 µg/h, n=7; 100 µg/h, n=6; 150 µg/h, n=8). Of these 23 subjects (placebo, n=7; 50 µg/h, n=5; 100 µg/h, n=5; 150 µg/h, n=6) also had high values at baseline.

Minor changes in the median systolic blood pressure values were observed during treatment in the placebo group. However, subjects in all the three cinaciguat groups experienced decrease in the systolic pressure. Similarly, minor fluctuations in the median diastolic blood pressure were observed during treatment in the placebo group. However, subjects in all the three cinaciguat groups experienced fairly consistent decrease in the diastolic pressure over the course of treatment.

Nine subjects reported non-serious TEAEs of hypotension (placebo, n=1; 50 µg/h, n=5; 100 µg/h, n=3; 150 µg/h, n=2), most of which were either mild or moderate in severity and considered to be related to study treatment. Two additional subjects (50 µg/h, n=1; 150 µg/h, n=1) experienced SAEs of hypotension, considered to be related to the study treatment.

Twelve subjects also experienced the pre-defined significant changes in systolic blood pressure of ≤ 40 mmHg or a systolic blood pressure of < 90 mmHg (placebo, n=3; 50 µg/h, n=2; 100 µg/h, n=5; 150 µg/h, n=2).

The most common ECG findings reported by the Central Reader were rhythm and rate disorders. No ventricular arrhythmias were reported as treatment-emergent ECG findings by the Central Reader.

Nineteen subjects (placebo, n=3; 50 µg/h, n=4; 100 µg/h, n=5; 150 µg/h, n=7) experienced prolonged QTc (Bazett) at least at one time point (excluding run-in) during the study, including 14 subjects who had prolonged QTc (Bazett) at baseline (placebo, n=1; 50 µg/h, n=3; 100 µg/h, n=4; 150 µg/h, n=6). There was no consistency in the occurrence of prolonged QTc (Bazett) in the remaining subjects that was suggestive of a treatment effect.

The mean (\pm SD) length of stay for the initial hospitalization was 7.3 ± 3.4 days in the placebo group and ranged from 5.8 ± 2.3 days to 8.5 ± 8.0 days in the cinaciguat groups. A total of seven subjects (placebo, n=2; 50 μ g/h, n=2; 100 μ g/h, n=1; 150 μ g/h, n=2) required re-hospitalization. One subject died during the initial hospital stay (50 μ g/h group); this death contributed to mortality during the initial hospitalization and 30 day mortality.

Results Summary — Pharmacokinetics

At all time points assessed, all samples from the cinaciguat groups were above the lower limit of quantification [LLOQ=0.05 μ g/L]. A general trend of increasing plasma concentrations of cinaciguat with increasing cinaciguat dose was observed.

Conclusion(s)

In this study, the dyspnea VAS scores did not suggest a treatment effect of cinaciguat compared to placebo. Similarly, neither the EuroQol VAS nor the Likert Scale suggested a treatment effect of cinaciguat on breathing ability.

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 behaviour of the population (i.e., subjects with ADHF) as described in the literature. While a fall in blood pressure did occur during the infusion of cinaciguat (reported as a TEAE by 11 subjects, and 10 additional subjects experienced the pre-defined clinically relevant changes in systolic blood pressure) and placebo (4 subjects experienced the pre-defined clinically relevant changes in systolic blood pressure). However no clinically significant reflex tachycardia was reported. The study was terminated because of the negative effects seen on blood pressure. In this study, there was no clinically significant difference in the change of renal function between the placebo group and the cinaciguat group.

This study was prematurely terminated by the sponsor on 04 FEB 2011 following recommendations from the DMC and Steering Committee.

Publication(s):	None		
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