SYNOPSIS

Issue Date: 31 August 2012

Document No.: EDMS-ERI-49579610:1.0

Name of Sponsor/Company	Janssen Research & Development, LLC.
Name of Finished Product	To be determined
Name of Active Ingredient(s)	JNJ-39588146 (Stresscopin)

Protocol No.: 39588146AHF2001

Title of Study: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Investigate the Safety, Tolerability, Pharmacodynamics and Pharmacokinetics of JNJ-39588146 in Subjects with Heart Failure

EudraCT Number: 2009-013929-42

NCT No.: NCT01120210

Clinical Registry No.: CR017116

Coordinating Investigator(s): Piotr Ponikowski MD, PhD; [redacted]; Poland.

Study Center(s): The study was conducted at 17 sites in 5 countries: Belgium (3 sites), Germany (3 sites), Italy (5 sites), Poland (3 sites), and Romania (3 sites).

Publication (Reference): None

Study Period: The first visit date for this study was 22 June 2010 with first subject randomized and dosed on 23 June 2010. The last study visit was 05 September 2011.

Phase of Development: 2a

Objectives: The primary objective of the study was to assess the hemodynamic effects, the safety and the tolerability of JNJ-39588146 when administered by intravenous (IV) infusion to male and female subjects of non-childbearing potential with New York Heart Association (NYHA) Class II-IV heart failure.

The secondary objective of the study was to characterize the pharmacokinetics of JNJ-39588146 in subjects with heart failure.

The exploratory objectives of the study were to assess the hemodynamics for an 18-hour extended infusion and to assess the effect of JNJ-39588146 on relevant cardiovascular pharmacodynamic (PD) biomarkers in blood.

Hypothesis: The main hypothesis of the study was that the JNJ-39588146 reduces pulmonary capillary wedge pressure (PCWP) and/or increases cardiac index (CI) in subjects with heart failure as compared with placebo.

Methodology: This was a randomized, double-blind, placebo-controlled, parallel-group multiple ascending dose study consisting of a 3-hour IV infusion of JNJ-39588146 or placebo in all subjects and an 18-hour extended infusion sub-study immediately following the initial 3-hour infusion. All sites and all subjects at participating sites were offered the opportunity to participate in the sub-study.

Eligible subjects were randomly assigned (ratio 3:1) to receive an IV infusion of either JNJ-39588146 or placebo. All subjects underwent right heart catheterization (thermodilution Swan-Ganz pulmonary artery catheter [PAC]). A period of at least 4 hours was required after placement of the PAC before initiating the IV infusion of JNJ-39588146 to allow stabilization of hemodynamic measurements. Hemodynamic parameters were monitored using cardiac catheterization with continuous measurement of cardiac output via a PAC. Echocardiographic parameters were evaluated prior to initiation of the study drug infusion and after 3 hours of infusion. Subjects who participated in the 18-hour extended infusion sub-study underwent an additional echocardiographic evaluation prior to the end of the extended infusion.

Subjects were discharged from the inpatient unit after completion of all the safety procedures and assessments. As part of a post-treatment follow-up phase, subjects returned to the clinic on Day 7 (±3) and Day 28 (±3) after the end of study drug infusion.

Number of Subjects (planned and analyzed): A sample size of 60 subjects was planned to be enrolled in the study. A total of 62 subjects (16 subjects in the placebo group and 46 subjects in the JNJ-39588146 group) were randomized and treated. All subjects were included in the efficacy (modified intent-to-treat population [MITT]) and safety (safety population) analysis.

Diagnosis and Main Criteria for Inclusion: Male subjects or female subjects of non-childbearing potential diagnosed with NYHA Class II-IV heart failure aged 18 to 86 (inclusive) were allowed to participate in the study.

Test Product, Dose and Mode of Administration, Batch No.: JNJ-39588146, Lot No. 09K04/F001 and 10F01/F001.

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo, Lot No. 9087B10 and 0042B19.

In the main study, subjects received 3 consecutive escalating IV infusions of either JNJ-39588146 or placebo. Each dose was planned to be infused over 1 hour for a total planned infusion time in the main study of 3 hours. The planned doses were 5, 15 and 30 ng/kg/min. All subjects who participated in the sub-study received an additional 18-hour infusion immediately following the 3-hour infusion at a dose equal to the maximum dose tolerated by that subject during the 3-hour infusion.

Duration of Treatment: The study consisted of 4 periods, a 30-day screening period (from Day -30 to Day 1), a 3-hour infusion (main study) on Day 1, an optional 18-hour extended infusion (sub-study) immediately after the main study and 2 follow-up visits on Day 7 (±3) and Day 28 (±3).

Criteria for Evaluation:

Efficacy: The 2 co-primary endpoints were the post-baseline changes (at 1, 2, and 3 hours post infusion initiation [ie, at the end of 5, 15 and 30 ng/kg/min infusions]) in PCWP and CI. These 2 primary endpoints were used separately to compare JNJ-39588146 with placebo. The pre-specified criterion for a positive outcome was a significant difference for either of the endpoints at the end of at least one of the three well tolerated infusion periods (i.e. at the end of 1, 2 or 3 hours after initiation of the infusion).

The major secondary efficacy variables included change from baseline in heart rate (HR), systemic blood pressure (BP), systemic vascular resistance (SVR), left ventricular (LV) ejection fraction (LVEF), LV end systolic volume (LVESV), LV end diastolic volume (LVEDV), fractional shortening (FS), stroke volume (SV), pulmonary arterial systolic pressure (PASP), pulmonary arterial diastolic pressure (PADP). The other efficacy variables included change from baseline in LV end systolic diameter (LVESD), LV end diastolic diameter (LVEDD), mean pulmonary artery pressure (MPAP), pulmonary vascular resistance (PVR) and right atrial pressure (RAP).

Pharmacokinetics and Biomarkers: Blood samples were collected at pre-specified time points for the measurement of plasma concentrations of JNJ-39588146 and for evaluation PD biomarkers in blood including serum levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP), troponin I (TnI), creatine kinase (CK-MB), and aldosterone and plasma renin activity (PRA).

Safety: The safety assessment included evaluation of adverse events (AEs), clinical laboratory tests, vital signs, physical examinations, pulse oximetry, 12-lead ECG, continuous ECG output and evaluation of anti-drug antibodies.

Statistical Methods:

The calculation of sample size was based on the primary hemodynamic endpoints (post-baseline change in PCWP and CI) and was approximated by a 2-sample t-test with a 1-sided significance level of α=0.05. With the 3:1 randomization ratio (JNJ-39588146 versus placebo), a sample size of 60 provided a power of approximately 90% to detect a difference (JNJ-39588146 versus placebo) of 5.7 mmHg in the post-baseline change of PCWP and a power of approximately 80% to detect a difference (JNJ-39588146 versus placebo) of 0.4 L/min/m^2 in the post-baseline change of CI. In addition, this planned sample size provided a power of more than 90% to detect the assumed post-baseline change in both PCWP and CI within the JNJ-39588146 treatment group.

In the primary analysis, the changes from baseline in PCWP and CI were analyzed to compare JNJ-39588146 with placebo. To support the primary analysis, pair-wise comparisons between JNJ-39588146 and placebo were performed for each of the 3 dose levels (1, 2, and 3 hour time-points) using an analysis of covariance (ANCOVA) model. The ANCOVA model included treatment group, sex and study center as fixed factors and the baseline value as the covariate. Similar analyses were carried out for the other cardiovascular parameters. As a sensitivity analysis, a mixed-effect model with repeated measures was also used to analyze the primary endpoints across the dose levels/time-points.

No adjustments for the multiplicity of doses (time-points) or primary endpoints were made. P values <0.05 1-sided are considered as statistically significant. All p-values presented for the primary efficacy endpoints are 1-sided.

The plasma PK parameters for JNJ-39588146 including peak plasma concentration (C_{max}), time to reach the peak plasma concentration (t_{max}), elimination half-life ($t_{1/2}$), area under the curve (AUC) including AUC_{last}, AUC_{inf}, and AUC_{tau}, clearance (CL), and volume of distribution at steady-state (V_{ss}) were estimated using the standard non-compartmental methods and summarized for each dose level and time-point using descriptive statistics. Biomarkers were summarized by treatment group using descriptive statistics only.

The safety analyses included the incidence and type of AEs, changes in ECG measurements, laboratory values, vital signs, digoxin level, and potential allergic reactions to IV infusions. All AEs were coded and tabulated by system organ class (SOC) and preferred term. Adverse events were tabulated by severity and relationship to the study drug. Serious adverse events (SAEs) were summarized separately.

RESULTS:

STUDY POPULATION

A total of 62 subjects (16 subjects in the placebo group and 46 subjects in the JNJ-39588146 group) were randomized and treated. Sixty subjects completed the study. One subject in the placebo group was withdrawn from the study due to serious adverse event which occurred 30 days after the start of infusion (prior to last visit). One subject in the JNJ-39588146 group was withdrawn from the study due to withdrawal of consent.

Of the total 62 subjects, 10 subjects (3 subjects in the placebo group and 7 subjects in the JNJ-39588146 group) chose to participate in the 18-hour extended infusion sub-study. All subjects continued the infusion with the study high dose (30 ng/kg/min) and completed the entire sub-study.

The majority of subjects were male (90.3%) with median age of 58.0 years and median body mass index (BMI) of 27.8 kg/m^2. All subjects, except 2, were White, non-Hispanic or Latino. All subjects who participated in the 18-hour extended dose sub-study were White males, with a median age of 49.5 years and median BMI of 27.1 kg/m^2. The study population was well balanced with regard to demographic parameters and baseline medication.

Four subjects (6%) had major protocol deviations due to being enrolled despite meeting exclusion criterion. Eight additional subjects (13%) had other protocol deviations. None of the deviations were judged to affect the study outcome.

All subjects who were randomized (ie, 62 subjects) received at least 1 dose of the study drug (either placebo or JNJ-39588146). The median (range) duration of exposure was 3.10 (3.0 to 21) hours in the placebo group and 3.01 (2.0 to 21) hours in the JNJ-39588146 group.

EFFICACY RESULTS:

The MITT analysis set was used for the efficacy analyses. It included all randomized subjects who received at least 1 dose of the study drug or placebo and had baseline and at least one post baseline measurement value for at least one of the primary endpoints. All randomized subjects were included in the MITT analysis. The changes from baseline in PCWP and CI were analyzed to compare JNJ-39588146 with placebo. Pair-wise comparisons between JNJ-39588146 and placebo were performed for each of the 3 individual dose levels (1, 2, and 3 hour time-points). For the primary endpoint analysis, an ANCOVA model was used to compare treatments using baseline values as the covariate and treatment group, sex and study center as fixed factors. The estimated least-squares (LS) means and appropriate 90% confidence intervals for the difference in LSMs between active and placebo in change from baseline for CI and PCWP were calculated and one-sided p-values were reported. Sensitivity analyses with repeated measures analysis were also performed and presented. The mixed-effect model included treatment group, sex, study center, baseline, time and time by treatment interaction as fixed effects and a random subject effect. Secondary variables were analyzed using the same ANCOVA model.

Throughout this report, the results presented by dose group (ie, 5, 15 and 30 ng/kg/min) for the main-study represent 1, 2, and 3 hours post-infusion initiation.

Primary Endpoints:

Cardiac index (CI): A statistically significant and dose-dependent increase in CI was observed at the end of 15 ng/kg/min and 30 ng/kg/min infusions of JNJ-39588146. The placebo-subtracted LS mean change from baseline CI was 0.33 L/min/m^2 at the end of the 15 ng/kg/min infusion (p=0.0215) and 0.57 L/min/m^2 at the end of the 30 ng/kg/min infusion (p=0.0049).

Pulmonary capillary wedge pressure (PCWP): The placebo-subtracted LS mean changes from baseline appeared to decrease numerically in a dose-dependent fashion with a decrease of 2.58 mmHg observed at the end of the 30 ng/kg/min infusions; however, none of the changes were statistically significant.

Major Secondary Efficacy Variables:

- A statistically significant increase (14.2 mL/beat) in SV compared with placebo was observed at the end of the 30 ng/kg/min infusion of JNJ-39588146 (p=0.0180).
- Statistically significant and dose-dependent reductions in calculated SVR were observed at the end of 15 ng/kg/min and 30 ng/kg/min infusions of JNJ-39588146. The placebo-subtracted LS mean change from baseline in calculated SVR was -383.32 dyne/s/cm^{-5} at the end of the 15 ng/kg/min infusion (p=0.0006) and -527.77 dyne/s/cm^{-5} at the end of the 30 ng/kg/min infusion (p=0.0001).

- Statistically significant and apparently dose-related reductions in DBP were observed at the end of 15 ng/kg/min and 30 ng/kg/min infusions of JNJ-39588146. The placebo-subtracted LS mean change from baseline in DBP was -5.55 mmHg at the end of the 15 ng/kg/min (p=0.0282) and -7.08 mmHg at the end of the 30 ng/kg/min (p=0.0043) infusions.
- Although small numerical trends were observed towards increase in HR (up to 2.16 bpm) and decrease in SBP (up to 3.77 mmHg), these changes were not statistically significant at any dose level.
- JNJ-39588146 had no statistically significant effects on PASP, PADP, LVEF, FS, LVESV or LVEDV compared with placebo.

Other Efficacy Variables:

JNJ-39588146 had no statistically significant effects on MPAP, PVR, RAP, LVESD, and LVEDD compared with placebo.

Exploratory extended-infusion sub-study:

The hemodynamic effects were variable but appeared to be overall sustained over the additional 18-hour infusion time, when compared to baseline. However due to substantial variability, limited data and no apparent difference when compared to placebo, no conclusion could be made.

PHARMACOKINETIC AND IMMUNOGENICITY RESULTS:

Systemic clearance of JNJ-39588146 following continuous intravenous infusion in subjects with heart failure (HF) averaged at about 0.8-0.9 L/h/kg but was variable (up to 89% CV). Steady-state volume of distribution averaged at about 1.8-3.0 L/kg but was also variable (up to 61% CV). In virtually all subjects at the end of the infusion, plasma concentrations of JNJ-39588146 showed an initial rapid decline, followed by a distinctive slower terminal elimination phase. The apparent alpha and beta half-lives for subjects in the main study were approximately 15 min and 4 hours, respectively. The apparent alpha and beta half-lives for subjects in the sub-study were approximately 25 min and 8.5 hours, respectively.

All antidrug antibody samples were negative; indicating immunogenicity for JNJ-39588146 was not detected.

PD BIOMARKERS in BLOOD:

No apparent differences in changes from baseline in the JNJ-39588146 group compared with the placebo group were noted for NT-proBNP, TnI, CK-MB, aldosterone and PRA values (descriptive statistics). Substantial variability precludes definitive conclusion.

SAFETY RESULTS: All subjects who received at least 1 dose of the study drug were included in the safety population (ie, 62 subjects).

Treatment-emergent adverse events (TEAEs) were reported in 9 subjects (56%) in the placebo group and in 18 subjects (39%) in the JNJ-39588146 group. The most common System or Organ Class (SOC) TEAEs was “cardiac disorders,” reported in 6 (38%) subjects in the placebo group and in 8 (17%) subjects in the JNJ-39588146 group.

None of the TEAEs in the placebo group were considered to be “severe”. The majority of TEAEs in the JNJ-39588146 group were considered to be ‘mild’ or ‘moderate’ in intensity.

The majority of TEAEs were considered to be not related to the study drug. Few TEAEs were considered to be "doubtfully related" or "possibly related" to the study drug. None of the TEAEs were considered to be "probably related" to the study drugs. Only 1 TEAE (flushing) in the placebo group was considered to be "very likely related" to the study drug. TEAEs considered to be "very likely related" to the study drug in the JNJ-39588146 group included: feeling hot (2 subjects) and erythema (2 subjects), arrhythmia supraventricular (1 subject), ventricular arrhythmia (1 subject), somnolence (1 subject), heart rate

increased (1 subject), pulmonary arterial pressure increased (1 subject), flushing (1 subject), and hypotension (1 subject).

There were no deaths reported during the study. Three subjects (19%) in the placebo group and 6 subjects (13%) in the JNJ-39588146 group experienced SAEs. All these adverse events resolved. The majority of SAEs in both placebo and JNJ-39588146 groups were considered to be not related by the investigator. Two SAEs were considered by the investigator to be doubtfully related to study therapy by the investigator; 1 SAE (cardiac failure) in the placebo group and 1 SAE (cardiac failure [worsening of heart pump failure]) in JNJ-39588146 groups; both of them resolved.

One subject in the placebo group was withdrawn from the study due to an SAE (ventricular tachycardia) which occurred 30 days after the start of infusion (prior to last visit).

There were no treatment- or dose-related changes from baseline throughout the study in any of the clinical laboratory tests, or vital sign parameters of respiratory rate and temperature. There were no apparent or consistent treatment- or dose-related changes noted from time matched baseline in mean ECG parameters (HR, PR, QRS, QT, QTcB, and QTcF intervals).

There were no allergic or anaphylactic type reactions reported during the study.

STUDY LIMITATIONS: Limitations of this study include a short duration of study drug infusion (3 hours in main study) and only 10 subjects opted to participate in the extended infusion sub-study (21 hours total infusion time). However, these characteristics were in-line with the purpose of this study as a proof of concept trial to determine if the effects and safety seen with JNJ-39588146 in prior animal studies with short IV infusions of JNJ-39588146 could be qualitatively replicated in a larger population of HF subjects receiving guideline-based standard HF therapies.

CONCLUSION(S):

- In subjects with systolic HF, JNJ-39588146 induced statistically significant and dose-dependent increases in CI. The placebo-subtracted LS mean change from baseline in CI was 0.33 L/min/m^2 at the end of the 15 ng/kg/min infusion (90% confidence interval: 0.064, 0.595; p=0.0215) and 0.57 L/min/m^2 at the end of the 30 ng/kg/min infusion (90% confidence interval: 0.214, 0.921; p=0.0049).
- Though a trend towards an improvement (decrease) in PCWP was observed, no statistically significant reductions in PCWP were seen with any dose tested in the primary analysis.
- JNJ-39588146 induced increases in SV (up to 14.16 mL/beat; p=0.0180) and dose dependent decreases in calculated SVR (up to -527.8 dyn.s.cm^{-5}; p=0.0001) and DBP (up to -7.08 mmHg; p=0.0043).
- Although small numerical trends were observed towards increase in HR (up to 2.16 bpm) and decrease in SBP (up to 3.77 mmHg), these changes were not statistically significant at any dose level.
- No effect was observed on secondary or other hemodynamic endpoints RAP, PASP, PADP, MPAP, and PVR and multiple echocardiographic parameters, including, LVEF, FS, LVESV, LVEDV, LVESD, and LVEDD suggesting suboptimal accuracy and precision of echocardiographic methodology in the setting of this study.
- In subjects with severe systolic HF, systemic clearance of JNJ-39588146 averaged at about 0.8-0.9 L/h/kg but was variable (up to 89% CV). Steady-state volume of distribution averaged at about 1.8-3.0 L/kg but was also variable (up to 61% CV).
- At constant infusion rates (between 5 ng/kg/min to 30 ng/kg/min), steady-state plasma levels of JNJ-39588146 appeared to be dose proportional.

- All antidrug antibody results were negative; indicating immunogenicity to JNJ-39588146 was not detected.
- In subjects with severe systolic HF, continuous infusions of JNJ-39588146 (up to 30 ng/kg/min dose for 3 hours or 21 hours) were generally safe and well tolerated.
- JNJ-39588146 has demonstrated an ability to increase CI and reduce SVR in a dose and plasma concentration-dependent manner, without adversely affecting HR and SBP.
- Further studies are required to characterize the effects of longer-term infusions JNJ-39588146 on clinical outcomes in appropriate patient populations.

Disclaimer

Information in this posting shall not be considered to be a claim for any marketed product.
Some information in this posting may differ from, or not be included in, the approved labeling for the product. Please refer to the full prescribing information for indications and proper use of the product.