A Multicenter, Randomized, Double-Blind, Placebo- and Active-Controlled, Cross-over Phase 2 Study of Continuous 5-Hour Intravenous Infusions of BMS-986231 in Patients with Heart Failure and Impaired Systolic Function

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Primary* Evaluate the effects of BMS-986231 on the left ventricular (LV) systolic function by stroke volume index (SVI) assessed by echocardiography compared to placebo. Secondary* Evaluate the effects of BMS-986231 on the left ventricular (LV)...

Ethical review	Approved WMO
Status	Completed
Health condition type	Heart failures
Study type	Interventional

Summary

ID

NL-OMON46654

Source
ToetsingOnline

Brief title
BMS CV013-020

Condition

- Heart failures

Synonym
chronic heart failure

Research involving

Human

Sponsors and support

Primary sponsor: Bristol-Myers Squibb
Source(s) of monetary or material Support: Industry

Intervention

Keyword: Chronic Heart failure, Heart failure, Impaired systolic function

Outcome measures

Primary outcome

Mean SVI derived from the velocity time integral at the left ventricular outflow tract (LVOT VTI) at the end of the 5-hours infusion of BMS-986231, versus placebo.

Secondary outcome

* Mean SVI derived from LVOT VTI at the end of the 5-hours infusion of BMS-986231, versus NTG.

* Mean LVEF, computed by Simpson*s method at the end of the 5-hours infusion of BMS-986231, versus placebo and NTG.

* Mean cardiac power index at the end of the 5- hours infusion of BMS-986231, versus placebo and NTG.

* Mean Diastolic indices: E/A, annular e' velocity and E/e' ratio at the end of the 5-hours infusion of BMS-986231, versus placebo and NTG.

* Mean LV global longitudinal strain, computed using STE at the end of the 5-hours infusion of BMS-986231, versus placebo and NTG.

Study description

Background summary

HNO enhances inotropy and lusitropy by direct myocardial effects and causes peripheral vasodilatation. The biological effects of HNO are reversible and mediated by direct post- translational modifications of target proteins, specifically SERCA2a, phospholamban, the ryanodine receptor and myofilament proteins in cardiomyocytes. In vivo, HNO increases the efficiency of calcium cycling and enhances cardiac contractility and relaxation via these proteins. HNO also mediates peripheral vasodilation in a manner dependent on soluble guanylate cyclase in the endothelium, similar to NO. HNO cannot be administered directly and must be delivered as a prodrug (HNO donor). BMS-986231 is a prodrug of HNO that non-enzymatically releases HNO and an inactive byproduct designated BMT-284730. BMS-986231 has been studied in animal models and in humans. In preclinical models, BMS-986231 produces consistent CV effects including peripheral vasodilation, increased inotropy, and enhanced lusitropy. The effects on vasodilation persist for the duration of the infusion and partially resolve within minutes. In canine models of heart failure, produced by microembolization or rapid ventricular pacing, BMS-986231 produced increases in the end-systolic pressure-volume relationship (ESPVR) and preload recruitable stroke work (PRSW), without increased in HR or myocardial oxygen consumption. Diastolic indices, including the left ventricular relaxation time constant (Tau), end-diastolic pressure volume relationship (EDPVR), deceleration time (DT) and the ratio of the time velocity integral of early-to-late ventricular filling (E/A), were improved. BMS-986231 has also been shown to be antiarrhythmic in an in vivo model of programmed electrical stimulation in heart failure dogs. BMS-986231 has been investigated in fluid-overloaded, advanced heart failure subjects for up to 6 hours of continuous infusion, in a phase 2a trial. In this setting, BMS-986231 was hemodynamically active, leading to a decrease in left and right ventricular pressure and systemic vascular resistance, and increase in stroke volume index and cardiac output. Despite these effects, tachycardia, arrhythmia or reflex increase in heart rate were not observed during the infusion of study drug. Cardiac power, assessed non-invasively, increased by 56 % at the highest dose tested. These effects are consistent with either an effect on ventricular loading and/or enhancement of contractility. However, direct measure of the inotropic effect of BMS-986231 would require the use of pressure-volume analysis, an invasive technique not easy to implement in humans.

It is important to obtain a better understanding of the relationship between the mechanism of action of BMS-986231 and its effects on myocardial function in humans with impaired contractility and the relative contribution to enhanced myocardial performance mediated by vasodilation (e.g. reduced pre- and post-load). Given the challenges in measuring

contractility directly, as outlined above, the study will examine overall systolic and diastolic function using echocardiography. This imaging study is designed to better characterize the cardiac effects of BMS-986231, its relative effects on systolic and diastolic function and to differentiate from the existing IV vasodilating therapies by comparing BMS-986231, to placebo and to the reference vasodilator nitroglycerin (NTG).
Vasodilators, including nitrates may be added to intravenous diuretics in some patients with acute decompensated heart failure. Generally, vasodilators are used in patients with persistent dyspnea and adequate systolic blood pressures to offset their vasodilatory effects. Nitrates exert their effect by being converted in vivo to nitric oxide (NO), a potent natural vasodilator, whose function is impaired in heart failure (HF) patients. Nitrates have systematically demonstrated short-term decreases in filling pressures. However, evidence supporting their use is apparently scarce, and there is no evidence that nitrates improve outcomes. Despite the limitations, vasodilators particularly NTG are used in acute heart failure syndromes.
Echocardiography represents today the most commonly used imaging modality because of its availability combined with its unique ability to provide real-time images of the beating heart. It became the cornerstone in cardiac imaging and an excellent tool to evaluate changes in cardiac volumes, flows and wall motion. This evolution is due to increasing reproducibility through standardization of the methodology used, as well as technological advances in evaluation of the left ventricular (LV) function through myocardial deformation imaging.
The population of chronic heart failure patients has been chosen for this study in order to standardize as much as possible the loading conditions and background therapies, while ensuring good echogenicity and accurate measures of echocardiographic parameters of interest. While direct transposition of the results to acute and sub-acute heart failure conditions should be done with caution, it will provide important information of the differentiated properties of BMS-986231 on systolic and diastolic LV function.
The results of this study will therefore further clarify the distinctive and differentiated myocardial effects of BMS-986231. Along with an ongoing phase 2b studying the safety, tolerability and effectiveness of BMS-986231 in a population of acute decompensated heart failure patients, this study will help to design confirmatory phase 3 trials in acute and sub-acute heart failure settings.

Study objective

Primary
* Evaluate the effects of BMS-986231 on the left ventricular (LV) systolic function by stroke volume index (SVI) assessed by echocardiography compared to placebo.
Secondary
* Evaluate the effects of BMS-986231 on the left ventricular (LV) systolic function by stroke volume index (SVI) assessed by echocardiography

compared to nitroglycerin (NTG).
* Evaluate the effects of BMS-986231 on selected other left ventricular systolic and diastolic indices compared to placebo and NTG

Study design

This is a multi-center, randomized, cross-over, placebo and active-controlled, double-blind, study of continuous 5-hour intravenous (IV) infusion of BMS-986231 in patients with heart failure and reduced ejection fraction (HFrEF). The trial is designed to evaluate the effects of BMS-986231on systolic and diastolic parameters measured by echocardiography.
Design
A cross-over design will be implemented in this trial, every subject will be exposed to each of the 3 interventions in 3 treatment periods (BMS-986231, NTG and placebo) with one intervention occurring during each treatment period, including the 5-hour infusion, followed by a washout period of at least 7 days, but no more than 4 weeks.

Intervention

Study participants will be randomized to receive BMS-986231, NTG, and placebo, in one of the 6 possible sequences.
NTG, BMS-986231 and placebo: will be administered as a 5-hours infusion according to an up- titration schedule, which is achieved by an increase in the infusion flow rate. All three interventions (NTG, BMS-986231 and placebo) will have the same flow rate as follows: 5 mL/H for 10 min, followed by 10 mL/H for 10 minutes then 20 mL/H for the rest of the infusion. The corresponding doses of the active study medications will be:
* NTG: 20 µg/min for 10 min, followed by 40 µg/min for 10 min, followed by 80 µg/min for the rest of the 5-hour infusion;
* BMS-986231: 3 µg/kg/min for 10 min, followed by 6 µg/kg/min for 10 min, followed by
12 µg/kg/min for the rest of the 5-hour infusion.
In case of decrease in systolic blood pressure, an algorithm will be used to down-titrate /interrupt or discontinue the study drug infusion (see section 7.4 in the protocol).

Study burden and risks

The study drug, the comparator and the study procedurs are associated with certain risks. These are described in the ICF. The study drug, the comparator, the study procedures and the combination thereof can also lead to other unknown risks.
To avoid carry over effects, the treatment days are separated by 1- 4 weeks.

In previous studies, no serious adverse events occured. During the infusions,

the subjects will be carefully monitored and their blood pressure is checked on specified timepoints. Administraton rate will be adjusted or infusion will be stopped if the subject shows signes of hypotension or if the blood pressure falls below specified values.
In addition, the subjects can take their own medication for heartfailure throughout the study, except on the morning of the treatment days.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

* Signed Written Informed Consent
* Age 18 years (or age of majority) or older
* Heart failure with reduced ejection fraction (LVEF on echocardiogram of 40% or less), as assessed by the echocardiographic corelab.

* Stable guideline directed therapy for heart failure (could include oral diuretics, ACEi, ARBs, ARNi, MRAs , and * blockers as tolerated), with no dose changes of these medications in the past 2 weeks
* Have screening values of NT pro-BNP * 125 pg/mL (15 pmol/L) or BNP * 35 pg/mL (10 pmol/L).
* In sinus rhythm at the start of the infusion

Exclusion criteria

* Body weight < 45 kg or * 140 kg
* Low quality echocardiographic visualization windows and image acquisition
* Systolic blood pressure (SBP) < 110 mm Hg at screening or pre-randomization
* Heart rate < 50 beats per minute (bpm) or > 90 bpm at screening or pre-randomization
* Permanent Atrial Fibrillation, Atrial Flutter or having Atrial Fibrillation, Atrial Flutter before start of the infusion
* Parmanent paced rhythm (VVI, DDD or BiV pacing)
* Ventricular assist device or prior heart transplant
* Primary HF etiology attributable to either restrictive/obstructive cardiomyopathy, idiopathic hypertrophic or uncorrected severe valvular disease as defined by AHA/ACC/ESC criteria.
* (Note: A restrictive mitral inflow pattern is NOT exclusionary)
* Large post-MI Left Ventricular aneurisms
* Intra-cardiac thrombus
* Prior mitral valve repair, mitral or aortic prosthesis
* Treatment with oral phosphodiesterase type 5 (PDE5) inhibitor sildenafil, vardenafil or avanafil within 24 hours of study drug infusion or treated with tadalafil within 4 days of study drug infusion
* Hospitalized for acute decompensated heart failure in the previous month
* Hospitalized with acute coronary syndrome, coronary revascularization or acute myocardial infarction during the previous 90 days prior to screening
* Have a history of a cerebral vascular accident (CVA or stroke) or of a transient ischemic attack (TIA) during the previous 90 days prior to screening
* NYHA Class IV symptoms of heart failure
* Treatment with intravenous inotropic therapy (dobutamine, milrinone, leveosimendan) in the previous month or planned treatment in the next 3 months.
* Current treatment with chronic oral, transdermal or sublingual nitrates, except at the discretion of the investigator and treating physician, nitrates could be temporarily interrupted. In which case, an
interruption of 3 days is required prior to start of study drug.
* Prior solid organ transplant
* Estimated glomerular filtration rate (eGFR) < 15 ml/min/1.73 m2
* Have persistent abnormal serum electrolytes not resolved between screening and start of the study drug infusion, as defined by any of the following:
o A sodium (Na+) concentration < 130 or >145 mEq/L (mmol/L)
o A potassium (K+) concentration < 3.5 or >5.5 mEq/L (mmol/L)
* Have severe anemia, as documented by a hemoglobin < 9 g/dL (< 5.59 mmol/L)

* Liver disease defined as history of cirrhosis with evidence of portal hypertension such as varices, or encephalopathy, or total bilirubin > 3 mg/dL (> 51 *mol/L) or significant elevation of liver enzymes (AST, ALT > 3 times the upper limit of normal)
* Considered clinically unstable for any condition
* Serious comorbid non cardiovascular disease in which the life expectancy of the subject is < 3 months;Other Exclusion Criteria
a) Prisoners or participants who are involuntarily incarcerated. (Note: under certain specific circumstances a person who has been imprisoned may be included or permitted to continue as a participant. Strict conditions apply and Bristol-Myers Squibb's approval is required.
b) Participants who are compulsorily detained for treatment of either a psychiatric or physical (e.g., infectious disease) illness
c) Participation in an investigational clinical drug study within 30 days or 5 elimination half-lives, (whichever is longer) prior to randomization.
d) Prior participation and treatment in a study using BMS-986231, CXL-1427, or CXL 1020
e) Alcohol beverage consumption within 6 hours prior to randomization.
f) Low quality echocardiographic visualization windows and image acquisition
g) Body weight < 45 kg or 140 kg
h) Known hypersensitivity or contra-indication to the intravenous echocardiography contrast agent, in the event contrast echocardiography is used.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	15-06-2018
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	HNO (NITROXYL) PRODRUG
Generic name:	BMS-986231
Product type:	Medicine
Brand name:	potassium acetate
Generic name:	potassium acetate
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Solinitrina
Generic name:	Nitroglycerin

Ethics review

Approved WMO Date:	12-03-2018
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-05-2018
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-08-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-10-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	13-12-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO	

Date:	05-04-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2016-003586-26-NL
ClinicalTrials.gov	NCT03357731
CCMO	NL64906.042.18

Study results

Date completed:	18-04-2019
Results posted:	10-06-2020

First publication
22-05-2020