CV019-010: A Randomized, Double-Blinded, Placebo-Controlled, Study to Evaluate the Safety and Tolerability of BMS-986259 in Stabilized Patients Hospitalized for Acute Decompensated Heart Failure

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The purpose of this study is to evaluate the effectiveness of the BMS-986259 study drug on blood pressure events in stable participants diagnosed with heart failure admitted to the hospital with Acute Decompensated Heart Failure (ADHF).

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

Summary

ID

NL-OMON49097

Source
ToetsingOnline

Brief title
CV019-010: A study of BMS-986259 in patients with acute heart failure

Condition

- Heart failures

Synonym
Acute Decompensated Heart Failure, Heart Disease

Research involving

Human

Sponsors and support

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

Intervention

Keyword: Acute Decompensated Heart Failure, H2-Relaxin

Outcome measures

Primary outcome

The primary objective of the study is to establish the safety and tolerability of BMS-986259 study drug when initiated in hospital in-patients, who are medically stable after an admission for Acute Decompensated Heart Failure.

The outcome will be measured by the incidence of clinically relevant hypotension. This is defined as:

- Supine Systolic Blood Pressure less than 85mmHg (confirmed by repeat measurement within 30 minutes) regardless of symptoms

OR

- Supine Systolic Blood Pressure less than 90mmHg (confirmed by repeat measurement within 30 minutes) AND symptoms of Hypotension.

Secondary outcome

*The secondary objective of this study is to evaluate serum PK parameters in participants with Heart Failure. This outcome will be measured by trough PK

sampling on day 5 including: serum PK parameters Cmax, Tmax, Area Under the Curve (AUC) and C24.

Additional objectives will be:

*To explore the potential diuretic effects of BMS-986259 study drug. This will be assessed by measuring the change from baseline in natriuresis after IV loop diuretic administration. The total and daily dose of loop diuretics administered during the study will be collected.

*To explore biomarkers related to the mechanism of action of BMS-986259 and related physiolocigal changes which cause Heart Failure. These may include but are not limited to Troponin, NT-proBNP, ST2, eGFR, cystatin C, aldosterone, urine creatinine, urine electrolytes, collagen markers such as ProC6. This will be explored by measuring the change from baseline in these biomarker levels, in blood and urine.

*To evaluate the presence of Anti-Drug Antibodies(ADA) and Neutralising Antibodies(nAb). These antibodies may effect movement of BMS-986259 (relaxin) through the body or cancel-out the therapeutic effects of the study treatment. These will be measured through blood sample collection.

*To evaluate blood pressure changes during daytime and night time. This will be measured and compared between the two arms (treatment vs placebo) using a 48 hours Ambulatory Blood pressure monitor device. The device will measure mean

ambulatory Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP), in addition to daytime and night time mean SBP and DBP.

*To explore patient reported outcomes. These will be measured using the Kansas City Cardiomyopathy Questionnaire (KCCQ) score from baseline (Day 1 of treatment), at the end of treatment (Day 14) and follow-up (Day 30).

Study description

Background summary

CV019-010 is a multicentre, phase 2A, double-blinded study involving adult patients recently admitted to hospital with Acute Decompensated Heart Failure (ADHF). The study will evaluate the effect of BMS-986259 study drug on blood pressure events in stable patients diagnosed with heart failure. The study will be placebo-controlled. Patients are considered for participation if already medically stabilised and before discharge from the hospital. 72 patients will take part in the study globally, approximately 4 of these will be from the Netherlands.

The global burden of heart failure (HF) is substantial. There is an estimated global prevalence of 26 million. In the United States, an estimated 6.5 million people suffer from Heart Failure. This number is projected to increase by approximately 46% by the year 2030. In the recent European data, 12-month all-cause mortality rate for hospitalised and stable ambulatory HF patients were 17% and 7%, respectively and hospitalisation rates were 44% and 32%, respectively.

Current treatment guidelines categorise HF patients based on ejection fraction (EF):
1.)Heart failure with reduced ejection fraction (HFrEF) with an EF less than or equal to 40%. 2.) Heart failure with a mid-range ejection fraction (HFmrEF) with an EF between 41% to 49% 3.) Heart failure with preserved ejection fraction (HFpEF) with an EF greater than or equal to 50%.

The causes of Heart Failure pathophysiology are highly complex and diverse.

Although current standard of care treatment (beta-blockers, angiotensin converting enzyme inhibitors and other renin angiotensin-aldosterone system

(RAAS) inhibitors, as well as mineral corticoid receptor antagonists) have led to a decrease in mortality rates in Heart Failure patients with reduced ejection fraction (HFrEF), unmet medical need remains high. The overall benefit of these treatments is often limited by co-morbidities and undesired effects such as kidney disease, hyperkalemia, and high blood pressure. For Heart Failure patients with preserved ejection fraction (HFpEF), no therapy has yet been proven in a placebo-controlled clinical trial to reduce mortality rates.

Human relaxin (H2-relaxin) is a peptide hormone believed to be, at least in part, responsible for the many physiological adaptations that occur during human pregnancy. These changes include an increase in global arterial compliance and a decrease in total systemic vascular resistance (SVR). Renal blood flow (RBF) and glomerular filtration rate (GFR) are increased by up to 80% and 50% respectively.

In previous clinical studies a short-acting recombinant form of H2-relaxin (serelaxin), administered in the form of an IV was demonstrated to have vasodilatory properties and to enhance both RBF and estimated GFR in patients with HF. In a large phase 3 clinical study, serelaxin when administered as a short-term 48 hour continuous IV infusion, failed to improve long-term clinical outcomes in patients with ADHF, compared with placebo. Although this failure represents a setback for the advancement of novel therapeutics to treat HF, learnings from the multitude of serelaxin clinical trials, indicate that chronic administration of a therapeutic with H2-relaxin-like activity (ie, beyond 48 hours) could potentially benefit HF patients. In a separate double-blind and placebo-controlled study in which serelaxin was given to chronic HF patients as a continuous 48-hour IV infusion, statistically significant increases in eGFR were observed for serelaxin when compared to placebo. Hemodynamic effects of serelaxin were also studied in a double-blind, placebo-controlled trial in patients hospitalised for ADHF. When serelaxin was given as a 20-hour IV infusion, hemodynamic effects were detected early (within 30 minutes), and were characterised by statistically significant reductions in pulmonary capillary wedge pressure (PCWP) and pulmonary arterial pressure (PAP), with a concomitant decrease in SVR. Serelaxin administration also improved renal function and decreased circulating levels of N-terminal pro-brain natriuretic peptide (NT-proBNP), a biomarker of cardiac stress.

As short term IV injections cannot be expected to exhibit lasting effects, there has been a need to develop a formulation of the peptide hormone that allows for chronic administration. BMS-986259, is a recombinant form of H2-relaxin that contains a covalently attached fatty acid chain which binds to circulating albumin, to extend its half-life. It has a pharmacokinetic (PK) profile that supports once daily dosing and exhibits H2-relaxin-like activity. This has been tested in vitro-cell based assays, as well as in vivo. These activity data, together with the preclinical PK and toxicology data, indicate that BMS-986259 can be safely administered subcutaneously. Preliminary data from an ongoing first in human (FIH) study also support safe subcutaneous use

up to 14 days.

Study objective

The purpose of this study is to evaluate the effectiveness of the BMS-986259 study drug on blood pressure events in stable participants diagnosed with heart failure admitted to the hospital with Acute Decompensated Heart Failure (ADHF).

Study design

DESIGN
This is a randomised, double-blind, placebo-controlled phase 2a study to Evaluate the Safety and Tolerability of BMS-986259 study drug in stabilised patients hospitalised for Acute Decompensated Heart Failure (ADHF). The study is divided into a screening period, study treatment period and a follow-up period.

The screening period may last anywhere from 24 hours and up to 8 days from the time of presentation to the emergency room. Time of presentation is defined as the time of the first dose of IV diuretic in the hospital.

After signing the consent form and completing the screening tests to determine eligibility, patients eligible for the study will be randomised to one of the following treatment arms in a 1:1 ratio:

Arm A
BMS-986259 (3mg or 1mg down-titrated as a 1ml sub-cutaneous injection) administered daily for 14 days

Arm B
BMS-986259 placebo (subcutaneous injection) administered daily for 14 days

Patients will be randomised at least 24 hours and no later than 8 days after presentation to the hospital. Patients will only begin treatment at least 12 hours after the last dose change of IV loop diuretics. In addition at least 24 hours must have passed since the last dose of positive inotropes and at least 12 hours since the last dose of IV vasodilators.

Randomisation will be done by an automated sorting process through IVRS (a telephone based computer system). This ensures that both the treatment arm and the placebo arm are equally balanced with subject numbers for comparison at time of analysis, while maintaining the integrity of the randomisation itself.

There is no data available on the risk of clinically significant hypotension with relaxin administered to medically stabilised patients admitted for ADHF, especially in patients with systolic blood pressure (SBP) less than 125 mmHg.

For this reason a sentinel group of patients will be treated initially. These patients must have a SBP greater than or equal to 115 mmHg and less than 130 mmHg to qualify. They will be randomized 1:1 to receive 3 mg subcutaneous Relaxin or placebo daily. After approximately 8 participants have completed the treatment period, a Safety Review Committee will review the safety data from this sentinel group. The main group will consist of patients with a SBP greater than or equal to 100mg. The number of patients with SBP greater than 125 mmHg will be capped at 48 patients.

Approximately 72 participants will be randomised to have at least 60 patients complete the study by the last patient last visit date, assuming a potentially high dropout rate due to the long treatment period.

VISITS AND ASSESSMENTS
Patients will receive treatment in hospital after the first treatment dose for a minimum of 5 days. If patients are discharged from the hospital before the end of the study treatment they will complete study visits at an outpatient clinic or at home, where they will receive the remainder of the study treatment. A home nurse or healthcare provider will carry out daily study visits at home.

Exploratory blood samples (study drug blood levels and biomarkers [taken to measure substances in the blood such as cells, DNA, RNA and other markers]) will be collected from all patients at certain visits throughout the study. Study drug blood levels will be measured to assess plasma concentration at various points. Biomarkers will be collected to further explore biological activities and the mechanism of action of BMS-986259.

Vital signs and blood pressure monitoring will be performed daily throughout the treatment period as per the protocol, to monitor patient safety and measure the effect on the study drug on blood pressure events. If the patient is discharged before the end of the treatment period, the home nurse or healthcare provider will be responsible to measure pre-dose blood pressure, administer study treatment and to collect pharmacokinetic, immunogenicity and biomarker blood samples. A home nurse will install an Ambulatory Blood Pressure Monitoring device on day 6 and day 12. The device will collect blood pressure monitoring data over a 48 hour period.

Patients will visit the hospital on day 8 and day 14 of the treatment period, for ambulatory visits. During these visits patients will undergo a physical examination, ECG and body weight assessment, in addition to routine blood and urine tests, vital sign measurements and study drug administration.

Patients will be asked to complete a questionnaire about how they feel and any symptoms they are having on Day 1, Day 14 and Day 30. This is called the Kansas City Cardiomyopathy Questionnaire (KCCQ).

Treatment will be discontinued if the subject withdraws consent, if their condition gets worse, if it is no longer safe for the subject to continue in the trial or if the sponsor decides to discontinue development of the study medication for any reason.

The follow-up visit will take place 30 days (+/-2 days) after the first treatment dose. During this visit patients will undergo an ECG, blood and urine tests and they will be asked to complete the KCCQ. In the event that patients develop any Anti-Drug Antibodies, they will return to the hospital 3 months later for an additional follow-up visit.

SAFETY MONITORING COMMITTEE
To assure an ongoing favourable risks/benefit assessment for participants enrolled into this study, an internal Safety Review Committee will assess blood pressure data after completion of the Sentinel Group. The committee may request access to unblinded treatment codes for individual participants. The Committee will consist of senior clinical development individuals not directly involved in the study conduct and overseeing, including (but not limited to) senior Worldwide Patients Safety representative, a statistician, and a senior clinician.

Intervention

Patients will undergo screening tests and assessments to determine eligibility. Those eligible to participate in the study will be randomised to the treatment arm or the placebo-controlled arm in a 1:1 ratio:

Arm A (Treatment arm)

BMS-986259 (3mg or 1mg down-titrated as a 1ml sub-cutaneous injection) administered daily for 14 days

Arm B (Control arm)

BMS-986259 placebo (subcutaneous injection) administered daily for 14 days

Patients in both arms will undergo the same on treatment study evaluation procedures: blood and urine collection for checking safety, pharmacokinetics, immunogenicity and biomarkers, vital signs monitoring, ambulatory blood pressure assessments and ECG. Patients will be asked to complete the KCCQ questionnaire which will measure quality of life and disease symptoms.

After patients complete the treatment period, they will return to the hospital on Day 30 (+/- 2 days) for the follow-up visit.

Study burden and risks

Only patients currently hospitalised for acute decompensated heart failure will be considered for the study. The average length of stay for patients with this condition is 5 days. Patients may be considered and screened for the study anywhere from 24 hours and up to 8 days after presentation to the emergency room. During the screening period patients will be asked questions about their medical history, including smoking history and alcohol consumption, ethnic origin and medication use. If a patient provides consent and is eligible for the study, they will be expected to remain in hospital as an in-patient for up to a minimum of 5 days from the start of study treatment. The entire treatment duration is 14 days.

Patients may be discharged from hospital from day 6 of the treatment period, to continue the 14 day treatment at home with the assistance of the home nurse. If patients are discharged before the end of the 14 day treatment period they will be provided with the remaining supply of the study medication to store in refrigerated conditions, at home. Patients must allow nurses or healthcare professionals to administer the study medication daily, via subcutaneous injection, at their home. Patients must also give their consent for home nurses to complete the study assessments. Timings of these visits will be based on the protocol schedule but will be mutually agreed with both the study research staff and the patient to avoid patient and/or staff attending at unsocial hours, and to minimise any inconvenience to the patient. Patients will be reimbursed for reasonable travel expenses incurred for attending study visits.

As part of the study patients will be expected to attend hospital visits on day 8 and day 14, where they will undergo a physical examination, body weight assessment, ECG and blood and urine test for safety assessments. Blood samples will also be collected for research purposes. Patients will be asked to complete a questionnaire about their quality of life (Kansas City Cardiomyopathy Questionnaire (KCCQ)).

The number of procedures carried out during this study would typically be considered over and above standard of care. The procedures are carried out by trained medical professionals and every effort will be made to minimise any risks or discomfort to the patient.

Patients will be required to wear an Ambulatory Blood Pressure Monitoring device on day 6 and day 12. The device will be installed and removed by a home nurse or a member of the study research team. The device will collect ambulatory systolic and diastolic blood pressure monitoring data to compare blood pressure changes between the group of patients receiving the study drug and the group receiving the placebo.

The study drug may cause side effects. BMS-986259 will be administered to

patients with Heart Failure for the first time in this study. However BMS-986259 administration was generally safe and well-tolerated when administered to normal health volunteers, in an ongoing phase 1 study. To ensure an ongoing favourable risk/benefit assessment for participants enrolled onto the study, an independent Safety Review Committee will be established to provide oversight of safety and efficacy considerations. Sites and study investigators will receive training on the adiminstration of BMS-986259 and adverse event manafement strategies.

BMS-986259 could provide clinical benefit and improvements in the outcomes for patients with acute heart failure. However, with all experimental drugs and clinical trials, there are known and unknown risks. Study medication and procedure related risks are outlined in the patient information sheet in detail to ensure the patients are fully informed before agreeing to take part in the study.

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

* Patients currently hospitalized for ADHF, regardless of Left Ventricular Ejection Fraction (LVEF) 24 hours or greater since presentation to the Emergency Room defined as the time of the first dose of IV diuretic administered at the hospital, maximum of 8 days since presentation to ER and before hospital discharge.
* Acute Decompensated Heart Failure is the main reason for admission and there is no other potential cause for congestive symptoms leading to index hospitalization (eg, concurrent pneumonia, acute COPD exacerbation)
* Dyspnea at rest or with minimal exertion upon presentation to ER, plus signs and symptoms of fluid overload that require IV therapy with loop diuretics
* NT-proBNP greater than or equal to 1400 pg/mL OR BNP greater than or equal to 350 pg/mL upon presentation to the hospital; NT-proBNP greater than or equal to 2000 pg/mL OR BNP greater than or equal to 500 pg/mL if Atrial Fibrillation (AFib) present at presentation. For participants on Entresto, NT-proBNP should be used.
* Patients must be hemodynamically stable, as assessed by the investigator, and as defined by the following criteria:
- * 12 hours since the last dose change of IV loop diuretics (ie, participants may still be on IV loop diuretics at randomization, as long as dose is stable for 12 hours or greater).
- * 24 hours since last dose of positive inotropes.
- * 12 hours since the last dose of IV vasodilators.
- Absence of symptoms of hypotension (eg, dizziness, lightheadedness, etc),
- Supine Systolic Blood Pressure (SBP) must remain within the following range*, on at least 2 routine consecutive measurements, over the 12 hours before randomization:
1.) Sentinel Group: SBP greater than or equal to 115 mmHg
2.) Main Group: SBP greater than or equal to 100 mmHg

* Males and Females at least 18 years of age
* Males who are sexually active with Woman of Child-Bearing Potential (WOCBP) must agree to follow instructions for method(s) of contraception defined in the protocol, during the study and for at least 6 days after the last dose of the study treatment
* Female Participants:
- Are eligible to participate if they are not pregnant or breast feeding and if they are not a WOCBP
- Women must have documented proof that they are not of childbearing potential

Exclusion criteria

* At randomisation Systolic Blood Pressure (SBP) less than 100 mmHg or greater than 145 mmHg
* At randomisation Heart Rate (HR) greater than 120 bpm
* Acute cardiovascular condition other than HF decompensation either contributing to hospitalisation or making the participant unstable, such as acute MI/acute coronary syndrome, myocarditis, or arrhythmia with the exception of atrial fibrillation if HR within criteria limit.
* Cardiogenic shock (defined as SBP below 90 mmHg, signs of end-organ hypoperfusion plus need for intubation, mechanical circulatory support and other life-sustaining emergency measures) at presentation to Emergency Room or at any time before randomisation.
* History of heart or any other solid organ transplant or currently on the transplant list.
* Recipient of ventricular assist devices.
* Use of any cardiac extracorporeal devices, within 12 weeks of study randomisation. Cardiac Resynchronization Therapy Defibrillator (CRTD) and pacemakers / Implantable Cardioverter-Defibrillator (ICDs) are allowed, if implanted at least 4 weeks before randomization and no discharge within 4 weeks prior to randomisation.
* Participants with contraindications to vasodilator therapy such as restrictive or obstructive cardiomyopathy, severe mitral or aortic stenosis.
* Women cannot be pregnant or breastfeeding.
* Any major surgery within 12 weeks of study randomization.
* Suspected acute pulmonary disease such as pneumonia, exacerbation of asthma or COPD or severe chronic, pulmonary disease (eg. severe COPD , pulmonary fibrosis, patients with hypercapnia or requiring home oxygen or chronic systemic steroids).
* Hereditary or idiopathic pulmonary hypertension.
* History of stroke, or transient ischemic attack (TIA) within the 30 days prior to screening (according to the participants' records) or during screening.
* Acute coronary event within 30 days prior to screening or during screening (myocardial infarction, acute coronary syndrome, or unstable angina; according to the participants' records).
* Terminal non-cardiovascular disease such as cancer with a life expectancy for less than 6 months.
* Severe liver disease such as cirrhosis with evidence of portal hypertension, or acute viral hepatitis.
* Participant is on dialysis or history of chronic or intermittent dialysis or ultrafiltration.
* Need for mechanical ventilation any time before screening or non-invasive ventilation (CPAP, BiPAP) less than 2 hrs prior to screening.
* Inability to comply with restrictions and prohibited treatments as listed in the protocol.
* Exposure to any investigational drug or placebo, including serelaxin; within

30 days of initial study drug administration or 4 months prior to the first dose of investigational product, in case of exposure to long-acting biological investigational drug.
* Persistent electrolytes abnormalities not corrected before randomization
- (1) A sodium concentration less than 130 or greater than 145 mEq/l
- (2) A potassium concentration less than 3.1 or greater than 5.5 mEq/l

* Haemoglobin less than 9 g/dL, which is defined as severe anaemia.
* eGFR less than 30 ml/min./1.73 m2.
* Liver abnormalities including total bilirubin greater than 2 mg/dL (greater than 34.2 micromol/L) or significant elevation of liver enzymes (AST, ALT greater than 3 x ULN).
* Positive blood screen for hepatitis C antibody, hepatitis B surface antigen, or human immunodeficiency virus (HIV)-1 and -2 antibodies.
* History of any significant drug allergy or drug-related serious AE (SAE) (such as anaphylaxis or hepatotoxicity).
* History of ADAs to relaxin (eg, while in a serelaxin development program).
* History of adverse reactions to aminoglycosides.
* Prisoners or participants who are involuntarily incarcerated.
* Employees of CRO or BMS and their first-line relatives
* Legal incapacity or limited legal capacity

Study design

Design

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	12-03-2021
Enrollment:	6

Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	BMS-986259
Generic name:	n/a

Ethics review

Approved WMO Date:	26-05-2020
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	12-03-2021
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-06-2021
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	EUCTR2019-004186-40-NL
ClinicalTrials.gov	NCT04318093
CCMO	NL73330.042.20

Study results

Date completed: 19-07-2021

Results posted: 11-07-2022

First publication
01-01-1900