A randomized, double-blinded, placebo-controlled, single and multiple ascending dose study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and immunogenicity of BMS-986259 in healthy participants

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

Summary

ID

NL-OMON49614

Source
ToetsingOnline

Brief title
BMS-986259 FIH SAD MAD study

Condition

- Heart failures

Synonym
Heart failure

Research involving

Human

Sponsors and support

Primary sponsor: BritsolMyers Squibb Research and Development
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: BMS-986259, MAD, SAD

Outcome measures

Primary outcome

- Incidence of AEs, SAEs, and AEs leading to discontinuation.

- Results of vital signs, ECGs, physical examinations, and clinical laboratory

tests.

Secondary outcome

- SAD: Cmax, Tmax, kel, T-HALF, AUC(0-T), AUC(INF), CL/F, and Vz/F.

- MAD:

* Day 1: Cmax, Tmax, AUC(TAU).

* Day 13: Cmax, Tmax

* Day 14: Cmax, Tmax, AUC(0-T), AUC(TAU), kel, T-HALF, CL/F, Vz/F, AR(Cmax),

AR(AUC[TAU]).

- NAb and ADAs

Study description

Background summary

BMS-986259 is a new compound that may eventually be used for the treatment of heart failure. Heart failure is characterized by the inability of the heart to deliver a sufficient supply of blood and oxygen to the organs in the body.

Signs and symptoms may include shortness of breath, tiredness, a limited ability to exercise, and leg swelling. Patients with heart failure may have a history of high blood pressure and suffer from chronic kidney disease. BMS-986259 mimics the hormone H2-relaxin which improves kidney function and possibly decreases cardiac fibrosis (thickening of heart valves), and could make BMS-986259 an attractive candidate as a long-term therapy for patients with heart failure.

Study objective

The purpose of this study is to investigate how safe the new compound BMS-986259 is and how well it is tolerated when it is administered as single or multiple doses to healthy volunteers. BMS-986259 has not been administered to humans before. It has been previously tested in the laboratory and on animals. BMS-986259 will be tested at various dose levels.

This study will be performed in approximately 132 healthy male and female volunteers. The study will be performed in 3 parts: Part A and Part B in healthy non-Japanese volunteers, and Part C in healthy Japanese volunteers.

It will also be investigated how quickly and to what extent BMS-986259 is absorbed and eliminated from the body. In addition, the effect of BMS-986259 on the body will be investigated.

The effects of BMS-986259 will be compared to the effects of a placebo.

Study design

Part A:
The study will consist of 1 period during which the volunteer will stay in the research center for 6 days (5 nights) for Groups A1-A2, and 7 days (6 nights) for Groups A3-A5.
Day 1 is the day of administration of the study compound. If the volunteers are in Group A1 or A2, they are expected at the research center at 14:00 h in the afternoon prior to the day of administration of the study compound. If the volunteers are in Group A3, A4, or A5, they are expected at the research center at 14:00 h in the afternoon of Day -2, which is 2 days prior to the administration of the study compound. The volunteer will leave the research center on Day 5 of the study. If the volunteers are in Group A6, they are expected at the research center at 11:00 h in the morning of Day -2, which is 2 days prior to the administration of the study compound. The volunteer will leave the research center on Day 7 of the study. If the volunteers are in Group A7, they are expected at the research center at 11:00 h in the morning of Day -2, which is 2 days prior to the administration of the study compound. The volunteer will leave the research center on Day 5 of the study.

BMS-986259 or placebo will be given as an injection under the skin (subcutaneous) of the belly. The number of injections may count up to 6 per dosing, depending on the dose level.

Part B:
The actual study will consist of 1 period during which you will stay in the research center for 21 days (20 nights).
Day 1 is the day of administration of the study compound. The volunteers are expected at the research center at 14:00 h in the afternoon on Day -3, which is 3 days prior to the administration of the study compound. The volunteers will leave the research center on Day 18 of the study.

BMS-986259 or placebo will be given as an injection under the skin (subcutaneous) of the belly. The number of injections may count up to 6 per dosing, depending on the dose level.

Intervention

Part A:

BMS-986259 or placebo will be given as an injection under the skin (subcutaneous) of the belly. The number of injections may count up to 6 per dosing, depending on the dose level.

Whether the volunteer will receive BMS-986259 or placebo will be determined by chance. Per group, 6 volunteers will receive BMS-986259 and 2 volunteers will receive placebo. Neither the volunteer, nor the responsible doctor knows if BMS-986259 or placebo will be administered.

For safety reasons, initially 2 volunteers will receive the study compound in each group. One volunteer will receive BMS-986259, and 1 will receive placebo. After administration, the safety and tolerability of the study compound in these 2 volunteers will be closely monitored. If there are no concerns about the safety and tolerability 48 hours after administration, then the remaining 6 volunteers (5 will receive BMS-986259 and 1 will receive placebo) in each group will receive the study compound.

In Groups A3-A7, all volunteers will also receive p-aminohippurate as an intravenous infusion (solution of the compound that will be administered directly in a blood vessel) with a duration of 2 hours. P-aminohippurate is a registered diagnostic agent that is given to investigate whether BMS-986259 affects renal blood flow.

Please refer to the table below to see the planned dose levels for each group. The doses of Groups A2 to A7 can be adjusted based on the results of the previous group(s).* However, the dose will not be higher than 30 mg. The dose for the next group will only be increased if the lower dose of the previous

group was found to be well tolerated and in case of no objection by the Medical Research Ethics Committee. The study will be discontinued if, in the opinion of the investigator, unacceptable side effects appear.

Group Day Treatment * Formulation Number of injections How often

A1 1 BMS-986259 0.3 mg or placebo subcutaneous injection 1 once
A2 1 BMS-986259 1 mg or placebo subcutaneous injection 1 once
A3 -1,1 p-aminohippurate ** intravenous infusion once daily
1 BMS-986259 3 mg or placebo subcutaneous injection 1 once
A4 -1.1 p-aminohippurate ** intravenous infusion once daily
1 BMS-986259 5 mg or placebo subcutaneous injection 1 once
A5 -1.1 p-aminohippurate ** intravenous infusion once daily
1 BMS-986259 15 mg or placebo subcutaneous injection 3 once
A6 -1.1 p-aminohippurate ** intravenous infusion once daily
1 BMS-986259 30 mg or placebo subcutaneous injection 6 once
A7 -1.1 p-aminohippurate ** intravenous infusion once daily
1 BMS-986259 0.3 mg or placebo subcutaneous injection 1 once

* In case the dose level will be lower or higher than planned, the volunteer will be informed verbally.
** The actual dose will depend on the volunteers body weight.

Part B:

BMS-986259 or placebo will be given as an injection under the skin (subcutaneous) of the belly. The number of injections may count up to 6 per dosing, depending on the dose level.

Whether the volunteer will receive BMS-986259 or placebo will be determined by chance. Per group, 10 volunteers will receive BMS-986259 and 3 volunteers will receive placebo. Neither the volunteer, nor the responsible doctor knows if BMS-986259 or placebo will be administered.

Please refer to the table below to see the planned dose levels for each group. The volunteer will receive BMS-986259 or placebo once daily from Day 1 up to Day 14. Part B of the study will start after completion of Group A4. The doses of Groups B1 to B4 can be adjusted based on the results of Part A and the previous group(s).* However, the dose will not be higher than 30 mg. The dose for the next group will only be increased if the lower dose of the previous group was found to be well tolerated and in case of no objection by the Medical Research Ethics Committee. The study will be discontinued if, in the opinion of the investigator, unacceptable side effects appear.

All volunteers in Part B will also receive p-aminohippurate on Days -1, 1, and 13 as an intravenous infusion (solution of the compound that will be administered directly in a blood vessel) with a duration of 2 hours.

P-aminohippurate is a registered diagnostic agent that is given to investigate whether BMS-986259 affects renal blood flow.

All volunteers will also receive iohexol on Days -1, 2, and 12 as an intravenous injection. Iohexol is a registered diagnostic agent that is given before BMS-986259 administration to investigate whether BMS-986259 affects renal function.

The planned dose levels for Part B are as follows:

Group Day Treatment* Formulation Number of injections How often

B1 -1, 1 p-aminohippurate** intravenous solution once daily
-1, 2, 12 iohexol, 5 mL containing 3.236 grams intravenous solution once daily
13 p-aminohippurate** intravenous solution twice daily
1-14 BMS-986259 1 mg or placebo subcutaneous injection 1 once daily

B2 -1, 1 p-aminohippurate** intravenous solution once daily
-1, 2, 12 iohexol, 5 mL containing 3.236 grams intravenous solution once daily
13 p-aminohippurate** intravenous solution twice daily
1-14 BMS-986259 3 mg or placebo subcutaneous injection 1 once daily

B3 -1, 1 p-aminohippurate** intravenous solution once daily
-1, 2, 12 iohexol, 5 mL containing 3.236 grams intravenous solution once daily
13 p-aminohippurate** intravenous solution twice daily
1-14 BMS-986259 10 mg or placebo subcutaneous injection 2 once daily

B4 -1, 1 p-aminohippurate** intravenous solution once daily
-1, 2, 12 iohexol, 5 mL containing 3.236 grams intravenous solution once daily
13 p-aminohippurate** intravenous solution twice daily
1-14 BMS-986259 30 mg or placebo subcutaneous injection 6 once daily

* In case the dose level will be lower or higher than planned, the volunteer will be informed verbally.
** The actual dose will depend on the volunteers body weight.

Study burden and risks

As BMS-986259 will be administered to man for the first time in this study,

side effects of BMS-986259 in man have not been reported to date. However, BMS-986259 has been studied extensively in the laboratory and in animals.

The dose which can be given first and the dose-increase regimen was calculated based on the doses that did not cause side effects in various animal studies.

Throughout the study the volunteer will be under careful medical observation. Any change in your state of health is monitored, evaluated and documented, and any medically necessary action can be taken immediately. All adverse events (including changes in laboratory values) are recorded until they return to normal, are stable, or can be explained by other causes (concomitant illness or medication) and the doctor no longer considers further examination necessary. If necessary, your investigator will refer you to other diagnostic procedures or treatments. The next higher dose will only be used if the previous dose was tolerated well and there are no medically noticeable symptoms or changes in medical parameters.

To date, only experience from animal studies on the risks of BMS-986259 is available. However, another similar peptide H2-relaxin, serelaxin (Novartis), was administered to healthy participants and over 4000 patients with heart failure with no concerning safety findings or no clinical significant abnormal laboratory findings. Most commonly observed was a drop in blood pressure (hypotension) which were mostly asymptomatic (> 95%), and resolved spontaneously without treatment (> 85%).

BMS-986259 was well tolerated in rats and monkeys using single and repeated doses, which were considerably higher compared to the present study. Although a mild change of an ECG parameter (QTc) was observed in monkeys at higher doses, no signs of cardiovascular toxicity were observed at lower doses and the volunteer will be closely monitored by ECG during treatment.

While BMS-986259 is considered to have a low risk of producing drug-induced liver injury (DILI), there was no evidence of hepatotoxicity (toxic damage to the liver) in any of the nonclinical studies so far. Due to its properties to widen blood vessels, drop in blood pressure (hypotension) is an expected adverse event.

Following treatment with BMS-986259 antibodies against BMS-986259 (anti-drug antibodies, ADAs) may form. They may also respond to the endogenous hormone relaxin, which circulates at higher levels during pregnancy. Although it is not currently known whether ADAs will be formed, women of childbearing potential are excluded from participation in the present study to avoid any risk to future pregnancies.

This is the first time that the investigational product BMS-986259 is been used in humans and therefore unexpected adverse events can also occur. If new findings from this or other studies, including animal studies, emerge

that could potentially influence the decision of the volunteer to participate in this study, the volunteer will be informed immediately.

As with other medicines, allergic reactions may occur after taking BMS-986259. These can manifest themselves in skin redness, itching, fever, breathing difficulties, circulatory problems and even life-threatening shock (massive heart failure). Suitable medicines and equipment are available to treat these symptoms. If the volunteer is allergic to medication or suffer from allergic asthma, he/she is not allowed to participate in this study.

P-aminohippurate
To measure kidney blood flow, small doses of a substance called p-aminohippurate are used. P-aminohippurate was previously approved by the FDA and has been used to conduct studies of blood flow through the kidneys for over 60 years. As the prior manufacturer no longer produces p-aminohippurate, the researchers have obtained permission from the FDA to use p-aminohippurate as an investigational product in this study. Allergic reactions to p-aminohippurate are rare but have been observed in people (itchy rash and/or breathing problems). This reaction is usually not serious and can be easily reversed with antihistamine medications. If the volunteer develop such symptoms, the study will be discontinued, and he/she will be treated. Other side effects which the volunteer may experience occur rarely (in less than 1 out 100 persons): Abnormal heartbeat, chest pain, low blood pressure, dizziness, lightheadedness, pain, blurred vision, headache, and bad taste in your mouth. In addition, the volunteer may have a sensation of warmth, tingling or the desire to pee during or shortly after receiving p-aminohippurate. For measurement of renal blood flow, small doses of p-aminohippurate are used which minimize these risks of these reactions.

Iohexol
Iohexol is a substance used to measure kidney blood flow. Allergic reactions to iohexol have been observed in people allergic to iodine (itchy rash and/or breathing problems). This reaction is usually not serious and can be easily reversed with antihistamine medications. Nevertheless, we recommend that the volunteer will not receive iohexol if he/she is known to be allergic to iodine containing compounds used during X-ray examinations. Participants with shellfish or iodine allergy will not be allowed to participate in this study due to their higher risk of an allergic reaction. Other side effects which the volunteer may experience occur rarely (in less than 1 out 100 persons): Abnormal heartbeat, chest pain, low blood pressure, dizziness, lightheadedness, pain, blurred vision, headache, and bad taste in the mouth.

Possible discomforts due to procedures
Drawing blood and/or insertion of the indwelling cannula may be painful or cause some bruising.

In total, we will take about 500 mL of blood from the volunteer.

To make a heart tracing, electrodes will be pasted at specific locations on the arms, chest and legs. To monitor the heart rate, electrodes will be pasted at specific locations on the chest and abdomen. Prolonged use of these electrodes can cause skin irritation (rash and itching).

A sample for the coronavirus test will be taken from the back of the nose and throat using a swab. Taking the sample only takes a few seconds, but can cause discomfort and can give an unpleasant feeling. Taking a sample from the back of the throat may cause the volunteer to gag. When the sample is taken from the back of the nose, the volunteer may experience a stinging sensation and your eyes may become watery.

Contacts

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Healthy males and females not of childbearing potential, aged 18 to 54 years at time of consent, inclusive.
- Body mass index (BMI) of 18.0 to 30.0 kg/m2, inclusive, at screening.

Exclusion criteria

Suffering from hepatitis B, hepatitis C, cancer or HIV/AIDS. Participation in an investigational drug study within 2 months prior to (the first) drug administration in the current study, or 4 months prior to (the first) drug administration in case of exposure to long-acting biological investigational drug. Participation in more than 4 other drug studies in the year prior to (the first) drug administration in the current study.
Donation or loss of more than 100 mL of blood within 60 days prior to (the first) drug administration. Donation or loss of more than 1.5 liters of blood (for male participants)/more than 1.0 liter of blood (for female participants) in the 10 months prior to (the first) drug administration in the current study.

Study design

Design

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):	18-06-2019
Enrollment:	82
Type:	Actual

Ethics review

Approved WMO Date:	05-06-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-06-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-10-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-11-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-12-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-05-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-05-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	12-06-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2019-001266-15-NL
CCMO	NL70161.056.19

Study results

Date completed:	24-07-2020
Results posted:	05-01-2022

First publication
16-12-2021