A randomized, double-blinded, placebo-Controlled, single and multiple ascending dose study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of BMS-986224 in healthy subjects and chronic heart failure patients with reduced ejection fraction

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The purpose of this study is to investigate how safe the new compound BMS-986224 is when it is administered as a single dose to healthy subjects and patients with chronic hart failure. It will also be investigated how quickly and to what extent BMS-...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Cardiac disorders, signs and symptoms NEC
Study type	Interventional

Summary

ID

NL-OMON48858

Source
ToetsingOnline

Brief title
BMS-986224 SAD MAD study

Condition

- Cardiac disorders, signs and symptoms NEC

Synonym
chronic heart failure

Research involving
Human

Sponsors and support

Primary sponsor: Britsol-Myers Squibb International Corporation
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: BMS-986224, MAD, SAD

Outcome measures

Primary outcome

Part A:

The primary objective of this study is to assess the safety and tolerability of

single oral doses of BMS-986224 in healthy subjects.

Part B:

To assess the safety and tolerability of multiple oral doses of BMS-986224 in

healthy subjects (including Japanese subjects).

Part C:

To assess the safety and tolerability of multiple oral doses of BMS-986224 in

chronic heart failure patients.

Secondary outcome

Part A:

- To assess the single-dose PK of orally administered BMS-986224 and primary

metabolite, BMT-328934, in healthy subjects.

- To assess the effect of food on BMS-986224 PK following single dose of the drug in capsule (DIC) formulation.

- To assess the effect of a strong CYP3A4 inhibitor (itraconazole) on the single-dose PK of BMS-986224 in healthy subjects.

- To assess the pharmacodynamic (PD) effects of single doses of BMS-986224 in healthy subjects as measured by cardiac magnetic resonance imaging (MRI) (including EF, Left Ventricular Stroke Volume [LVSV], End Diastolic Volume [EDV], End Systolic Volume [ESV], LV mass, Cardiac Output [CO] and Cardiac Index [CI]).

Part B:

To assess the PK of BMS-986224 and BMT-328934 following multiple oral doses of BMS-986224 in healthy subjects (including Japanese subjects).

Part C:

- To assess the PK of BMS-986224 and BMT-328934 following multiple oral doses of BMS-986224 in chronic heart failure patients.

- To assess the PD effects of single and multiple doses of BMS-986224 in chronic heart failure patients as measured by cardiac MRI (including EF, LVSV, EDV, ESV, LV mass, CO and CI).

Study description

Background summary

BMS-986224 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. BMS-986224 is able to bind a protein called human apelin receptor, which is expressed in human heart. Binding of BMS 986224 to this apelin receptor exerts a series of signaling events that may result in enhancement of contractility of cardiac cells and mild dilatation of the blood vessels. In healthy volunteers as well as heart failure patients, evidence suggest that short-term intravenous infusion of a compound with a similar effect on the apelin receptor as BMS 986224 results in improvement of cardiac function.

Study objective

The purpose of this study is to investigate how safe the new compound BMS-986224 is when it is administered as a single dose to healthy subjects and patients with chronic hart failure.

It will also be investigated how quickly and to what extent BMS-986224 is absorbed and eliminated from the body (this is called pharmacokinetics). In addition, the effect of BMS 986224 on the body will be investigated (this is called pharmacodynamics).

Study design

Part A:
For Groups A-1, A-2, A-4, A-5, A-6 the actual study will consist of 1 period during which the volunteer will stay in the research center in Groningen (UMCG) for 6 days (5 nights).
Day 1 is the day of administration of the study compound. The volunteer is expected at the research center at 14:00 h in the afternoon prior to the day of administration of the study compound. The volunteer will leave the research center on Day 5 of the study.

For Group A-3, the actual study will consist of 2 periods during which the volunteer will stay in the research center in Groningen (UMCG) for 6 days (5 nights).
In each period, Day 1 is the day of first administration of the study compound. The volunteer is expected at the research center at 14:00 h in the afternoon prior to the day of administration of the study compound. In each period, the volunteer will leave the research center on Day 5.

For Group A-7, the actual study will consist of 1 period during which the

volunteer will stay in the research center in Groningen (UMCG) for 20 days (19 nights).
Day 1 is the day of administration of the study compound. The volunteer is expected at the research center at 14:00 h in the afternoon prior to the day of administration of the study compound. The volunteer will leave the research center on Day 19 of the study.

For Group A-8, the actual study will consist of one period during which the volunteer will stay in the research center in Groningen (UMCG) for 13 days (12 nights).
Day 1 is the day of first administration of the study compound. The volunteer is expected at the research center at 14:00 h in the afternoon prior to the day of administration of the study compound. The volunteer will leave the research center on Day 12.

For Groups A-PD1, A-PD2 and A-PD3, the actual study will consist of 1 period during which the volunteer will stay in the research center in Groningen (UMCG) for 6 days (5 nights).
Day 1 is the day of administration of the study compound. The volunteer is expected at the research center at 10:00 h in the afternoon prior to the day of administration of the study compound. The volunteer will leave the research center on Day 5 of the study.

Part B:
The actual study will consist of 1 period during which the volunteer will stay in the research center in Groningen (UMCG) for 19 days (18 nights).
Day 1 is the day of first administration of the study compound. The volunteer is expected at the research center at 14:00 h in the afternoon prior to the day of administration of the study compound. The volunteer will leave the research center on Day 18 of the study.

Group B5:
The actual study will consist of 1 period during which the volunteer will stay in the research center in Groningen (Martini Hospital) for 10 days (9 nights).
Day 1 is the day of first administration of the study compound. The volunteers is expected at the research center at 14:00 h in the afternoon prior to the day of administration of the study compound. The volunteer will leave the research center on Day 9 of the study.

Part C:
The actual study will consist of 2 periods during which the volunteer will stay in the research center for 3 days (2 nights).
In each period, Day 1 is the day of administration of the study compound. The volunteer is expected at the research center at 14:00 h in the afternoon prior to the day of administration of the study compound. The volunteer will leave the research center on Day 2 of both periods. The volunteer will be asked to return for a short visit to the research center on Days 4, 7 and 10 of Period

1.

BMS-986224 and placebo will be given as oral capsules with 240 milliliters (mL) of (tap) water.

Intervention

Part A:

The planning of the study is as follows:

Group Day Treatment Formulation Condition How often
A-1 1 BMS-986224 1 mg or placebo capsule fasting once
A-2 1 BMS-986224 5 mg or placebo capsule fasting once
A-3 1 BMS-986224 15 mg or placebo capsule fasting once
8 BMS-986224 15 mg or placebo capsule after breakfast
A-4 1 BMS-986224 45 mg or placebo capsule fasting once
A-5 1 BMS-986224 90 mg or placebo capsule fasting once
A-6* 1 BMS-986224 XX mg or placebo capsule fasting once
A-PD1 1 BMS-986224 15 mg or placebo capsule fasting once
A-PD2 1 BMS-986224 90 mg or placebo capsule fasting once
A-PD3* 1 BMS-986224 XX mg or placebo capsule fasting once
A-7 1 BMS-986224 3 mg capsule fasting once
8,9,10 itraconazol 200 mg capsule fasting or fed after breakfast once daily
11 BMS-986224 3 mg and itraconazol 200 mg cupsules fasting once
12-15 itraconazol 200 mg capsule fasting of fed after breakfast once daily
A-8* 1 BMS-986224 15 mg capsule fasting once
8 BMS-986224 15 mg capsule fasting once

*) Groups A-6, A-PD3 and A-8 are optional; the dose levels for these groups will be determined based on results from the previous group(s) and will not be higher than 90 mg. The dose levels in the other groups may be adapted to a lower dose or a repeated dose based on the results of the previous dose cohorts.

Part B:

The planning of the study is as follows:

Group Day Treatment Formulation Condition How often
B-1 1-14 BMS-986224 3 mg or placebo capsule fasting once daily*
B-2 1-14 BMS-986224 10 mg or placebo capsule fasting once daily*
B-3 1-14 BMS-986224 30 mg or placebo capsule fasting once daily*
B-4 1-14 BMS-986224 90 mg or placebo capsule fasting once daily*
B-5 1-14 BMS-986224 90 mg or placebo capsule fasting once daily*
B-J1 1-14 BMS-986224 10 mg or placebo capsule fasting once daily*

B-J2 1-14 BMS-986224 30 mg or placebo capsule fasting once daily*
B-J3 1-14 BMS-986224 XX mg* or placebo capsule fasting once daily*

*) The dose levels in this group will be determined based on the results of the previous dose cohorts. Based on the outcome of Part A of the study, it may be decided if drug administration will be once daily, twice daily or 3 times a day. Should the dosing frequency exceed more than once daily, then a single morning dose will be given on Days 1 and 14.

Part C:

The planning of the study is as follows:

Group Day Treatment Formulation Condition How often
C-1 1-14 BMS-986224 15 mg or placebo capsule fasting or fed once daily*
C-2 1-14 BMS-986224 90 mg or placebo capsule fasting or fed once daily
C-3 1-14 BMS-986224 XX mg* capsule fasting or fed once daily*
*) The dose levels in this group will be determined based on the results of the previous dose cohorts. Based on the outcome of Part A of the study, it may be decided if drug administration will be once daily, twice daily or 3 times a day. Should the dosing frequency exceed more than once daily, then a single morning dose will be given on Days 1 and 14. Whether the study compound will be administered under fasted or fed conditions will be based on the outcome of Part A of the study.

Study burden and risks

As BMS-986224 will be administered to humans for the first time in this study, side effects of BMS-986224 in humans have not been reported to date. However, BMS-986224 has been studied in animals. There were no findings related to BMS-986224 in dogs treated with oral doses up to 300 mg/kg/day for 2 weeks, which was the highest dose tested.

Based on the mechanism of action of BMS-986224, side effects may occur that are observed with a similar compound, apelin.

Apelin has been infused in approximately 58 people at doses that are similar (or higher) than those to be used in this study. No significant bad reactions were reported in these previous studies. Apelin causes blood vessels to open which results in lower blood pressure and faster heart rate. Low blood pressure may cause dizziness, fainting, sweating, nervousness, nausea and chest or abdominal pain. Increased heart rate may cause a sensation of pounding in the chest (palpitations) which may cause feelings of anxiety or nervousness. Apelin also causes the heart to beat more forcefully. This may also cause a sensation of pounding in the chest. Apelin effects are expected to go away

within 30 minutes after stopping the infusion.

Contacts

Public
Britsol-Myers Squibb International Corporation

Chaussee de la Hulpe 185
Brussels 1170
BE
Scientific
Britsol-Myers Squibb International Corporation

Chaussee de la Hulpe 185
Brussels 1170
BE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Part A and B
- Males and females, ages 18 to 55 years, inclusive, female subjects should be of non childbearing potential, at screening.
- BMI of 18.0 to 30.0 kg/m2, inclusive, at Screening. BMI = weight (kg)/height m2.;Part C
1. Signed written informed consent.
2. Subjects must be willing to participate in the study and sign the ICF.
3. Subjects must be willing and able to complete all study-specific procedures and visits.
4. Males and females, ages 18 years or older, at screening; female subjects should be of non childbearing potential (see Inclusion Criterion 12).

5. BMI of 18.0 to 35.0 kg/m2, inclusive, at screening. BMI = weight (kg)/height m2.
6. New York Heart Association class II or III.
7. Left ventricular EF <45%, as assessed by cardiac MRI within 3 months of first dose of study drug; or left ventricular EF <40% as assessed by echocardiogram, multiple gated acquisition (MUGA) or single photon emission computed tomography (SPECT) at screening or within 3 months of first dose of study drug
8. Have not had a myocardial infarction within 3 months of first dose of study drug, or have not had any other acute cardiovascular (CV) event or hospitalization (including emergency room visits) for CV causes within 1 month of first dose of study drug and are considered to have stable heart failure at the discretion of the Investigator (also refer to Exclusion Criteria #21 for Part C).
9. Stable guideline directed therapy for HF (could include oral diuretics, ACEi, ARBs, ARNi, MRAs, and β-blockers as tolerated), and stable medications for other chronic comorbidities (as cleared by the PI and PRA Medical Monitor), with no dose changes of these medications in the past 1 month prior to start of study drug. The use of pre-determined patient-managed flexible oral loop diuretics is permitted.
10. Have screening values of NT pro-BNP >= 300 pg/mL (35 pmol/L) or BNP >= 100 pg/mL (29 pmol/L).
11. Regular sinus rhythm at screening and no history of atrial fibrillation in the past 12 months.
12. Postmenopausal women (12 months or more amenorrhea and over 45 years of age in the absence of other biological or physiological causes). Females under 55 years of age require FSH >40 mIU/mL at screening.
13. Women must not be breastfeeding.
14. Males that meet one of the following:
Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of the study and a minimum of 3 months after dosing has been completed. In addition, male subjects must be willing to refrain from sperm donation during this time.

Exclusion criteria

Suffering from hepatitis B, hepatitis C, cancer or HIV/AIDS.
In case of participation in another drug study within 90 days before the start of this study.
Being a blood donor (Part A & B)/Loss of more than 100 mL blood (Part C) within 60 days prior to the first study drug administration. In case of donating more than 1.5 liters of blood (male subjects)/1 liter (female subjects) in the 10 months prior the first study drug administration.
We refer to section 9.3.2 if the protocol for a complete overview of all the exclusion criteria.;Part C:
1. Current or recent (within 3 months of study treatment administration) gastrointestinal disease that could affect absorption. Patients who suffer from an episode of acute gastroenteritis without an underlying chronic GI condition can be enrolled if the acute event occurred more than 1 month prior to the first dose of study drug.
2. Major surgery within 4 weeks of (first) study treatment administration.
3. Loss of more than 100 mL of blood within 2 months prior to the first drug administration.

Loss of more than 1.5 L of blood (for male subjects) / more than 1.0 L of blood (for female subjects) in the 10 months prior to the first drug administration in the current study.
4. Inability to be venipunctured and/or tolerate venous access.
5. Not applicable per Protocol Amendment 4: Subjects who have smoked or used smoking cessation or nicotine containing products (including, but not limited to, e-cigarettes, pipes, cigars, chewing tobacco, nicotine patches, nicotine lozenges, or nicotine gum, varenicline, bupropion) within 3 months of the first dose of study drug.
6. Abuse or drug addiction (including cannabis products) within one year from screening.
7. Positive drug screen (opiates, methadone, cocaine, amphetamines [including ecstasy], cannabinoids or barbiturates) at screening or admission to the CRU. Any positive drug screen test will be discussed with the Medical Monitor for further assessment. If justified in the opinion of the PI and Medical Monitor, the patient can be eligible for the study, despite a positive urinary drug screen.
8. Average intake of more than 21 units of alcohol per week (1 unit of alcohol equals approximately 250 mL of beer, 100 mL of wine or 35 mL of spirits).
9. Participation in a drug study or exposure to investigational drug or placebo within 2 months prior to the first drug administration in the current study.
10. Any contraindication to MRI scanning (eg, claustrophobia, implantable devices, etc).
11. Systolic blood pressure >180 mmHg or <100 mmHg.
12. Heart rate <50 beats per minute (bpm) or >90 bpm at screening or pre-randomization. A patient is eligible if clinically stable as per PI*s assessment and if heart rate at rest is at least 50 bpm, up to a maximum of 90 bpm, on vital signs taken at both the screening visit and the Day -1 visit (or pre dose Day 1 if patient admits to the clinic on Day 1 instead of Day -1), regardless of the heart rate reported on ECG.
13. Atrial arrhythmia (fibrillation, flutter) at screening or pre-randomization.
14. Significant ventricular arrhythmia (eg more than one couplet, triplets, or any VT-runs of 6 consecutive beats or more) on baseline or screening ECG. Note that a history of (ie, anterior to screening) couplets, triplets or non-sustained VT (<6 consecutive beats) does not exclude a patient from participation.
15. Presence of pacemakers/implantable cardioverter-defibrillator/cardiac resynchronization therapy device.
16. Ventricular assist device or prior heart transplant.
17. Any LV aneurism or intra-cardiac thrombus.
18. Any cardiac valve prosthesis.
19. Current treatment with antiarrhythmic drugs. For the purpose of this study, beta-blockers (excluding sotalol) and digoxin are permitted.
20. Hospitalization for acute decompensated HF in the previous 1 month prior to the first dose of study drug.
21. Hospitalization for coronary revascularization or unstable angina during the previous 1 month prior to the first dose of study drug, or hospitalization for acute myocardial infarction (ST-segment elevation myocardial infarction [STEMI] or non-ST-segment elevation myocardial infarction [NSTEMI]) during the previous 3 months prior to the first dose of study drug.
22. History of transient ischemic attack or stroke during the previous 3 months prior to the first dose of study drug.
23. Treatment with intravenous inotropic therapy (dobutamine, milrinone, levosimendan) in the previous 3 months or planned treatment for the duration of the study.
24. Prior solid organ transplant.

25. Estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m2.
26. Severe anemia, as documented by a hemoglobin <9 g/dL (<5.59 mmol/L).
27. Liver disease defined as history of cirrhosis with evidence of portal hypertension such as varices, or encephalopathy.
28. Liver abnormalities including total bilirubin >2 mg/dL (>34.2 µmol/L) or significant elevation of liver enzymes (AST, ALT >3x upper limit of normal [ULN]) or serum albumin <3.5 g/dL.
29. Considered clinically unstable for any condition in the opinion of the PI.
30. NYHA Class IV.
31. Serious comorbid non-cardiovascular disease in which the life expectancy of the subject is <3 months in the opinion of the PI.
32. Positive blood screen for hepatitis C antibody, hepatitis B surface antigen (HBsAg), or human immunodeficiency virus (HIV) 1 or 2 antibodies.
33. History of allergy to BMS 986224 or related compounds.
34. History of any significant drug allergy (such as anaphylaxis or hepatotoxicity).
35. Inability to comply with protocol procedures, assessments, restrictions, and prohibited treatments.
36. Employees of PRA or the Sponsor.
37. Not applicable per Protocol Amendment 4: Prior exposure to BMS 986224.
38. Not applicable per Protocol Amendment 4: Use of OTC medications within 1 week and herbal preparations within 2 weeks prior to study drug administration, except those medications cleared by the PI and PRA Medical Monitor.
39. Use of any oral or injected (IV, intramuscular [IM], SC) glucocorticoids within 3 months of study treatment. Topical and intra-articular injection of glucocorticoids is acceptable.
40. Not applicable per Protocol Amendment 4: Concomitant medications (prescription, OTC, or herbal) outside the stable standard of care regimens for HF and chronic comorbidities administered during the study unless prescribed by the Investigator for treatment of specific clinical events.
41. Not applicable per Protocol Amendment 4: Concomitant medications that are strong inducers of CYP3A4 or strong inhibitors or inducers of OATP administered within 2 weeks prior to the start of the study and throughout the study. Patients on stable standard of care medications that are moderate inhibitors or inducers of CYP3A4 or OATP will be cleared for use by the PI and PRA Medical Monitor. Strong CYP3A4 inhibitors are permitted.
42. Not applicable per Protocol Amendment 4: Consumption of any nutrients known to modulate cytochrome P450 (CYP) enzymes activity (eg, grapefruit or grapefruit juice, pomelo juice, star fruit, or Seville [blood] orange products) within 14 days prior to first administration of study drug until after Discharge in the last treatment period.
43. Women of childbearing potential (WOCBP).
44. Concomitant medications (prescription, OTC or herbal) outside the stable standard of care regimens for HF and chronic comorbidities unless prescribed by the Investigator for treatment of specific clinical events during the study; AND concomitant medications that are strong CYP3A4 inducers (i.e. rifampin, St. John*s Wort, etc.) administered within 2 weeks prior to the start of the study and throughout the study. Patients who are on stable standard of care medications that are moderate CYP3A4 inducers will be cleared for use by the PI and PRA Medical Monitor.

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:	Recruitment stopped
Start date (anticipated):	18-09-2017
Enrollment:	165
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Itraconazol
Generic name:	N/A
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	05-09-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-09-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	23-02-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-03-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-04-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-05-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-06-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-06-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-08-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-09-2018

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-09-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-10-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	31-10-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-02-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-02-2019
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	EUCTR2017-002970-38-NL
ClinicalTrials.gov	NCT03281122
CCMO	NL63128.056.17