A double-blind, placebo-controlled, randomized, single and multiple ascending dose study (including food effect, pH effect, and Japanese bridging Study) of the safety, pharmacokinetics, and exploratory pharmacodynamics of oral BMS-986278 administration in healthy participants

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Congenital respiratory tract disorders
Study type	Interventional

Summary

ID

NL-OMON46573

Source
ToetsingOnline

Brief title
BMS-986278 SAD MAD FE pH Japanese study

Condition

- Congenital respiratory tract disorders

Synonym
Idiopathic pulmonary fibrosis

Research involving
Human

Sponsors and support

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

Intervention

Keyword: BMS-986278, MAD, SAD

Outcome measures

Primary outcome

To evaluate the safety and tolerability of single and multiple ascending oral

doses of BMS-986278 in healthy participants.

Secondary outcome

- To evaluate the plasma PK of single and multiple ascending oral doses of

BMS-986278 in healthy participants.

- To evaluate the effect of a high-fat meal and of a modified gastric pH on the

plasma PK of a single dose of BMS-986278 in healthy participants.

Study description

Background summary

BMS-986278 is a new compound that may eventually be used for the treatment of idiopathic pulmonary fibrosis (IPF). IPF is a chronic and fatal lung disease with an unknown cause (idiopathic). It is characterized by worsening shortness of breath and loss of lung function caused by scarring in the lungs. The scarring and loss of long function get worse over time and most patients die of respiratory failure.
There are two approved drugs that slow down this decline in some patients.

However, in addition to not being very effective, these drugs are not tolerated well.
Abnormal wound healing is thought to contribute to fibrotic lung diseases like IPF. Fibrosis is similar to scarring, but in case of fibrosis an excess scar tissue is formed. The so-called lysophosphatidic acid (LPA) is involved in many functions that regulate wound healing. LPA can regulate the transition from normal scar tissue to abnormal wound repair (fibrosis).
BMS-986278 targets the LPA1 receptor, and blocks LPA from stimulating the formation of fibrotic tissue. It is therefore expected that BMS-986278 will help treating patients with IPF.

Study objective

The purpose of this study is to investigate how safe the new compound BMS-986278 is when it is administered as a single dose to healthy subjects. BMS-986278 has not been administered to humans before. It has been previously tested in the laboratory and on animals. BMS-986278 will be tested at various dose levels.

It will also be investigated how quickly and to what extent BMS-986278 is absorbed and eliminated from the body (this is called pharmacokinetics). Additionally, it will also be investigated what the effect is of a high-fat meal on the pharmacokinetics of BMS-986278.
The effect of famotidine on the pharmacokinetics of BMS-986278 will be investigated when it is given shortly before BMS-986278. Famotidine is already being used for the treatment of heartburn.

In addition, the effect of BMS-986278 on biomarkers will be investigated (this is called pharmacodynamics). Biomarkers are substances in the body that can be used as a sign of a specific disease, or condition or as a method to predict how you respond to or tolerate treatment with BMS-986278.

The effects of BMS-986278 will be compared to the effects of a placebo. A placebo is a medicine without any active ingredient. It is a *fake* medicine.

Study design

Part A:

For Groups A1 -A6:
The actual study will consist of 1 period during which the volunteer will stay in the research center in Groningen Martini Hospital for 6 days (5 nights). This will be followed by 2 short visits which will take place on Day 7 and 11 between 10.00 and 12.00 hour.

For Group A7:

The actual study will consist of 3 periods during which you will stay in the research center in Groningen Martini Hospital for 6 days (5 nights) each period. After Period 1 and Period 2 there will also be a one short visit on Day 7. After Period 3 there will be short visits on Day 7 and Day 11. For the short visits, you are expected at the research center between 10:00 and 12:00 hour.

Part B:
The actual study will consist of 1 period during which the volunteer will stay in the research center in Groningen Martini Hospital for 19 days (18 nights). This will be followed by 2 days during which the volunteer will visit the research center for a short visit. These short visits will take place on Days 20 and 24 between 10.00 and 12.00 hour.

Intervention

Part A:
BMS-986278 or placebo will be given in the morning as a suspension with a volume between 6 mL and 50 mL. After administration of the study compound, the vial will be rinsed three times with 5 or 10 mL, taken from 240 mL of (tap)water, which the volunteer will also be required to drink. Then the volunteer will be given the remainder of the 240 mL of water which he/she will also have to drink.

For Groups A1 to A6
If the volunteer participate in Groups A1 to A6 (see below), he/she will be given BMS-986278 or placebo once.
When BMS-986278 or placebo is administered, the volunteer should have fasted for at least 10 hours (no eating and drinking). Also after administration of the study compound, the volunteer will be required to fast for 4 additional hours on Day 1. Then he/she will be served lunch. The volunteer will receive dinner approximately 10 hours after administration of the study drug. All meals on this day must be consumed entirely. On this day the volunteer is not allowed to eat or drink between lunch and dinner. During fasting the volunteer is allowed to drink water, exception during 2 hours before and 1 hour after administration of the study compound.

For group A7:
If the volunteeer participate in Group A7 he/she will be given BMS-986278 3 times (once in each period). In Period 1 the volunteer will receive BMS-986278 without breakfast. In Period 2 the volunteer will receive famotidine 2 hours before receiving BMS-986278, again without breakfast. Famotidine will be given as a tablet with 240 mL of water. In Period 3 the volunteer will receive a high fat breakfast 30 minutes before dosing with BMS-986278. This standardized high fat breakfast has to be started exactly on time and will have to be finished within 20 minutes.

Part B:

BMS-986278 or placebo will be given in the morning as a suspension with a volume between 6 mL and 50 mL for 14 consecutive days. After administration of the study compound, the vial will be rinsed three times with 5 or 10 mL, taken from 240 mL of (tap)water, which the volunteer will also be required to drink. Then the volunteer will be given the remainder of the 240 mL of water which he/she will also have to drink.

Study burden and risks

BMS-986278 has been administered to humans for the first time in this study. Single doses of BMS-986278 up to a dose level of 150 mg have been administered to volunteers in previous cohorts in the current study. BMS-986278 was well tolerated. Several volunteers had a transient lowering of blood pressure, however they did not experience any symptoms. To study this further, if you participate in Cohort A6, additional blood pressure measurements (while you are standing up) will be included.
In addition, BMS-986278 has been studied in animals. In the studies performed in animals few abnormalities have been observed. After multiple administrations of high doses in monkeys mild elevations in some liver enzymes in the blood were observed; and after very high doses given to rats an increase in the weight of the liver and inflammation of the lining of the stomach were seen. Abnormalities in bone formation were observed in monkeys after repeated dosing, however this was only observed in monkeys that still had growing bones.

The study compound may also have adverse effects that are still unknown.

Procedures: pain, minor bleeding, bruising, possible infection

Group A7:
Side effects which might occur after use of the heart burn medicine famotidine are given below. As this will be given only once in this study the chances on the mentioned effects are judged to be minimal.

Common side effects are (occurring in less than 1 in 10 users): Headache, dizziness, constipation, diarrhea.

Uncommon side effects are (occurring in less than 1 in 100 users): Dry mouth, nausea, vomiting, abdominal discomforts or distension, flatulence, lack of appetite, taste disorder, rash, itching (pruritus), fatigue.

Rare side effects (occurring in less in 1 in 1000 users):
Hypersensitivity reactions (anaphylaxis (allergic reactions), angioneurotic edema (swelling of face and throat), bronchospasm (trouble breathing), liver enzyme abnormalities, hepatitis cholestatic jaundice, urticaria (hives), arthralgia (joint pain), increase in laboratory values (transaminases, gamma GT, alkaline phosphatase, bilirubin).

Very rare side effects (occurring in less than 1 in 10,000 users):
Changes in blood: reduction in different type of blood cells (pancytopenia, leucopenia, agranulocytosis) or platelets (thrombocytopenia), which can lead to weakness, fatigue, sudden fever, sore throat, nose bleed, bruises. Reversible psychological disturbances (including hallucinations, disorientation, confusion, anxiety, disorders, agitation, depression, insomnia), reduced libido, impotence, paraesthesia, drowsiness, convulsions, grand mal seizures (particularly in patients with impaired renal function), alopecia, Stevens-Johnson
Syndrome/toxic epidermal necrolysis, muscle cramps, chest tightness.

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

- healthy volunteers
- 21-65 yrs, inclusive, at screening
- BMI: 18.0-30.0 kg/m2, inclusive, at screening
- body weight: between 55 and 105 kg, inclusive, at screening

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. Donation or loss of more than 100 mL of blood within 2 months prior to (the first) drug administration. Donation or loss of more than 1.5 L of blood (for male participants)/more than 1.0 L 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:	Recruitment stopped
Start date (anticipated):	06-02-2018
Enrollment:	62
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Famotidine

Generic name:	N/A
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	22-01-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	31-01-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-08-2018
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	EUCTR2017-004136-10-NL

Register	ID
CCMO	NL64641.056.18