A double-blind, placebo-controlled, randomized, single and multiple ascending dose study of the safety and tolerability, and pharmacokinetics (including food effect, pH effect and Japanese bridging study) of BMS-986337 following oral administration in healthy participants

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The purpose of this study is to investigate how safe the new compound BMS-986337 is and how well it is tolerated when it is administered as single or multiple doses to healthy volunteers. BMS-986337 has not been administered to humans before. It has...

Ethical review	Approved WMO
Status	Completed
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON49565

Source
ToetsingOnline

Brief title
FIH study with LPA1#3

Condition

- Other condition

Synonym
idiopathic pulmonary fibrosis

Health condition

idiopathic pulmonary fibrosis

Research involving
Human

Sponsors and support

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

Intervention

Keyword: BMS-986337, FiH

Outcome measures

Primary outcome

Incidence of adverse events (AEs), serious adverse events (SAEs), and AEs

leading to discontinuation

Results of clinical laboratory values, vital signs, electrocardiograms (ECGs),

physical examinations

Secondary outcome

Plasma concentrations of BMS-986337, and its acylglucuronide (BMT-405951) and

amine (BMT-385617) metabolites; derived PK parameters as applicable

Plasma concentrations of BMS-986337, and its BMT-405951 and BMT-385617

metabolites, following a high-fat meal and pH modulation; derived

PK parameters as applicable

Plasma concentrations of BMS-986337, and its BMT-405951 and BMT-385617

metabolites in Japanese and non- Japanese participants; derived PK

parameters as applicable

Study description

Background summary

BMS-986337 is a new compound that may potentially be used for the treatment of idiopathic pulmonary fibrosis (IPF). It is a progressive disease in which scarring and lack of elasticity in the lungs continues to increase until the majority of patients die from respiratory failure. Aberrant wound healing responses to lung injury are widely assumed to contribute to the disease. Increased lysophosphatidic acid (LPA) concentrations have been reported in the lungs of IPF patients. LPA has the ability to interfere in many basic cellular functions in several cell types associated with wound healing, and can regulate the transition from normal scar formation to abnormal wound repair. The new compound BMS-986337 is able to block the receptor to which LPA binds and may therefore be beneficial in treating patients with IPF.

Study objective

The purpose of this study is to investigate how safe the new compound BMS-986337 is and how well it is tolerated when it is administered as single or multiple doses to healthy volunteers. BMS-986337 has not been administered to humans before. It has been previously tested in the laboratory and on animals. BMS-986337 will be tested at various dose levels.

Study design

Group A1-A5:
If the volunteer participates in Groups A1 through A5, the volunteer will be given BMS-986337 or placebo once as a small volume drink (between 10 and 30 milliliters depending on the dose level). Immediately after the administration of the study product, the volunteer is asked to complete a questionnaire about the taste, after which the volunteer is given a glass of 240 ml water to drink.
If the volunteer participates in Group A6, the volunteer will receive BMS-986337 three times (once in each period). In this group, all volunteers receive BMS-986337 in each period (no placebo). In Period 1, the volunteer is administered BMS-986337 when the volunteer has been sober before the BMS-986337 dose. In Period 2, the volunteer is also given BMS-986337 when the volunteer has been sober before dosing, but the volunteer is also given one 40 mg tablet

of famotidine 2 hours before the BMS-986337 dose. The famotidine tablet is administered with 240 mL of water after being sober overnight. In Period 3, the volunteer receives a high-fat breakfast before the BMS-986337 dosage.

Group B1-B4
The volunteer is administered BMS-986337 or placebo as a small volume drink (between 10 and 30 mL depending on the dosage) on Day 1 through Day 14. Immediately after administration of the study drug, the volunteer asked to complete a taste test, after which the volunteer should drink a glass of 240 ml water.

Whether the volunteer receives BMS-986337 or placebo is determined by drawing lots. Per group (Group B1 to B4), 6 volunteers receive BMS-986337 and 2 volunteers receive placebo. This means that the volunteer has a 75% chance of getting BMS 986337 and a 25% chance of getting placebo. Both the volunteer and the researcher do not know whether the volunteer is receiving BMS 986337 or placebo.

Intervention

Part A:

If the volunteer participate in Groups A1 to A5, the volunteer will be given BMS-986337 or placebo once as a drink with a small volume (between 10 and 30 mL, this is dependent on the dose). Immediately after administration of the study compound, the volunteer will be asked to complete a taste questionnaire, then the volunteer will be asked to drink a glass of water (240 mL). If the volunteer participate in Group A6, the volunteer will be given BMS-986337 3 times (once in each period). In this group, all subjects will receive BMS 986337 in all 3 periods (no placebo). In Period 1 the volunteer will receive BMS-986337 when the volunteer has fasted before BMS-986337 dosing. In Period 2 the volunteer will also receive BMS 986337 when the volunteer has fasted before dosing but the volunteer also will be given a tablet 40 mg famotidine 2 hours before BMS-986337 dosing. The famotidine tablet will be administered with 240 mL of water after an overnight fast. In Period 3 the volunteer will receive a high-fat breakfast before BMS-986337 dosing.

Part B:

The volunteer will be given BMS-986337 or placebo as a drink with a small volume (between 10 and 30 mL, this is dependent on the dose) on Days 1 to 14 of the study. Immediately after administration of the study compound, the volunteer will be asked to complete a taste questionnaire, then the volunteer will be asked to drink a glass of water (240 mL).

Study burden and risks

The study compound may cause side effects.

As BMS-986337 will be administered to man for the first time in this study, side effects of BMS-986337 in man have not been reported to date. However, BMS-986337 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.

Contacts

Public
Bristol-Myers Squibb Research and Development

Princeton Pike 3401
Lawrenceville NJ 08648
US
Scientific
Bristol-Myers Squibb Research and Development

Princeton Pike 3401
Lawrenceville NJ 08648
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1) Signed Written Informed Consent
a) Participants must be willing and able to participate in the study and sign

the informed
consent form (ICF).
b) Participants must be willing and able to complete all study-specific procedures and visits.

2) Type of Participant and Target Disease Characteristics
a) Healthy participant, as determined by no clinically significant deviation from normal in
medical history, physical examination, ECGs, and clinical laboratory determinations.
b) Participants in the Japanese cohorts in Part C must be first-generation Japanese (born in
Japan, not living outside of Japan for more than 10 years, and both parents are ethnically
Japanese).
c) Body mass index (BMI) of 18.0 kg/m2 to 30.0 kg/m2, inclusive, at screening. BMI = weight (kg)/height (m)2
d) Body weight between 50 kg and 120 kg, inclusive, at screening.
e) Normal renal function at screening (and study admission) as evidenced by an estimated glomerular filtration rate (eGFR) >= 80 mL/min/1.732 m2 calculated with the Chronic Kidney Disease Epidemiology Collaboration formula.
GFR = 141 × (min(SCr/*,1)α × max (SCr/*,1) -1.209 × 0.993Age × 1.018 [if female] ×
1.159 [if black]) Where SCr is serum creatinine (mg/dL), * is 0.7 for females and 0.9 for males, α
is -0.329 for females and -0.411 for males, min indicates the minimum of SCr/* or 1, and max indicates the maximum of SCr/* or 1.

3) Age and Reproductive Status
a) Female Participants:
i) Females, ages 21 to 65 years, inclusive.
ii) Women participants must have documented proof that they are not of childbearing potential (refer to APPENDIX 4).
iii) A female participant is eligible to participate if she is not pregnant or breastfeeding, and is not a WOCBP.
iv) Women who are not of childbearing potential are exempt from contraceptive requirements.
b) Male Participants:
i) Males, ages 21 to 65 years, inclusive.
ii) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception defined in APPENDIX 4 and as described below.
iii) Azoospermic males are not exempt from contraceptive requirements and will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with WOCBP even if the participant has undergone a successful vasectomy or if the partner is pregnant.
iv) Male participants will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with WOCBP; even if

the participants have undergone a successful vasectomy or if their partner is already pregnant or breastfeeding. Males should continue to use a condom during the study treatment period and for at least 5 days after the last dose of study treatment.
v) Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from sexual activity or use a male condom during any sexual activity (eg, vaginal, anal, oral) even if the participants have undergone a successful vasectomy, during the study treatment period and for at least 5 days after the last dose of study treatment.
vi) Female partners of males participating in the study should be advised to use highly effective methods of contraception during the study treatment period and for at least 5 days after the last dose of study treatment in the male participant (refer to APPENDIX 4).
vii) Male participants must refrain from donating sperm during the study treatment period and for at least 5 days after the last dose of study treatment.
viii) Breastfeeding partners should be advised to consult their healthcare providers about using appropriate highly effective contraception during the time the participant is required to use condoms.

Exclusion criteria

1) Medical Conditions
a) Women who are of childbearing potential.
b) Women who are breastfeeding.
c) Any significant acute or chronic medical condition that presents a potential risk to the participant and/or that may compromise the objectives of the study, including active, or history of, liver disease, or intestinal disorder including irritable bowel syndrome.
d) History or presence of malignancy including hematological malignancies; participants with a history of basal cell or squamous cell carcinoma that has been treated with no evidence of recurrence within 5 years will be allowed for inclusion, as judged by the investigator.
e) History of significant cardiac disease (eg, hospitalization for congestive heart failure, myocardial infarction, unstable angina, coronary angioplasty, or coronary artery bypass graft within 6 months of screening) or uncontrolled atrial or ventricular cardiac arrhythmias.
f) History of significant left ventricular dysfunction (ie, echocardiography with ejection fraction of < 40%).
g) Current or recent (within 3 months of study treatment administration) gastrointestinal disease that could impact upon the absorption of study treatment.
h) Any major surgery within 6 weeks of study treatment administration.
i) Any gastrointestinal surgery, including cholecystectomy, that, in the opinion of the investigator, could impact upon the absorption of study treatment.

j) Documented congenital QT syndrome, and/or corrected QT-interval (Fridericia correction,
QTcF) at screening or first admission > 450 msec.
k) Donation or loss of more than 450 mL of blood within 2 months prior to (the first) study
treatment administration.
l) Blood transfusion within 4 weeks of study treatment administration.
m) Inability to tolerate oral medication.
n) Inability to be venipunctured and/or tolerate venous access.
o) Participants 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 treatment.
p) Recent (within 6 months of study treatment administration) drug or alcohol abuse as defined in Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV),13 Diagnostic Criteria for Drug and Alcohol Abuse.
q) Average intake of more than 21 units of alcohol (1 unit of alcohol equals approximately 12 oz of beer, 5 oz of wine, or 1.5 oz of spirits) per week within the last 6 months at the screening visit. After screening, participants are permitted to consume an average intake of <= 14 units of alcohol per week until the day of study admission.
r) Any other medical, psychiatric, and/or social reason as determined by the investigator.

2) Prior/Concomitant Therapy
a) Prior exposure to BMS-986278.
b) Inability to comply with restrictions and prohibited treatments as listed in Section 6.7.
c) Use of any prescription drugs or over-the-counter (OTC) gastric acid controllers within 4
weeks prior to study treatment administration except those medications cleared by the investigator and PRA Medical Monitor.
d) Use of any OTC medications and herbal preparations within 2 weeks prior to study treatment administration (except OTC gastric acid controllers which are not allowed within 4 weeks prior to study treatment administration), except those medications cleared by the investigator and PRA Medical Monitor.

3) Physical and Laboratory Test Findings
a) Evidence of organ dysfunction or any clinically significant deviation from normal in physical examination, vital signs, ECG, or clinical laboratory determinations beyond what is consistent with the target population of healthy volunteers.
b) Resting HR < 50 bpm at any of the screening or predose vital sign measurements. Refer to BP manual.
c) Seated SBP of < 100 mmHg or seated DBP of < 60 mmHg at screening or prior to

Day 1 study treatment. Refer to BP manual.
d) Orthostatic intolerance, orthostatic hypotension, or orthostatic tachycardia (as defined in Section 8.4.2) at screening or prior to Day 1 study treatment.
e) Positive results at screening or admission to the CRU from urine screen for drugs of abuse
(amphetamines, methamphetamines, barbiturates, benzodiazepines, cocaine, methadone, oxycodone opiates, and cannabinoids), urine cotinine, or alcohol urine test.
f) Positive blood screen for hepatitis C antibody, hepatitis B surface antigen (HBsAg), or human immunodeficiency virus (HIV) 1 or 2 antibodies.
g) Positive nasopharyngeal RT-PCR test for SARS-CoV-2 on Day -2.

4) Allergies and Adverse Drug Reaction
a) History of any significant drug reactions and/or food allergies (such as anaphylaxis or
hepatotoxicity).

5) Other Exclusion Criteria
a) Prisoners or participants who are involuntarily incarcerated. (Note: Under certain specific
circumstances and only in countries where local regulations permit a person who has been imprisoned may be included or permitted to continue as a participant. Strict conditions apply and BMS approval is required.)
b) Participation in a drug study or exposure to any investigational drug or placebo within 4 weeks prior to (the first) study treatment administration in the current study.
c) Employees of PRA or BMS and their first-line relatives.
d) Inability to comply with protocol procedures, assessments, restrictions, and prohibited treatments.
e) Legal incapacity or limited legal capacity.
f) Inability to comply with restrictions as listed in the section on lifestyle restrictions in the protocol.

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):	17-09-2020
Enrollment:	78
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:	24-04-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-09-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-12-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-01-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	03-03-2021
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	EUCTR2019-004518-32-NL
CCMO	NL73466.056.20

Study results

Date completed:	03-03-2021
Results posted:	18-03-2022

First publication
06-02-2022