A double-blind randomized placebo-controlled single and multiple ascending doses study of the safety and tolerability, pharmacokinetics (including bioavailability comparison and food effect) and pharmacodynamics of oral BMS-986251 administration in healthy subjects, with efficacy assessment of multiple doses in patients with moderate-to-severe psoriasis

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The purpose of Part A of this study is to investigate how safe the new compound BMS 986251 is when it is administered as a single dose to healthy subjects. The purpose of Part B of this study is to investigate how safe the new compound BMS 986251 is...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Autoimmune disorders
Study type	Interventional

Summary

ID

NL-OMON44577

Source
ToetsingOnline

Brief title
BMS-986251 SAD (including BA and FE), MAD and proof of mechanism study

Condition

- Autoimmune disorders

Synonym
auto immune disorder, Psoriasis

Research involving
Human

Sponsors and support

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

Intervention

Keyword: BMS-986251, MAD, SAD

Outcome measures

Primary outcome

Safety and tolerability

- Number and percent of subjects that experience the following: SAE, death or an AE leading to study discontinuation, during the study participation or up to 1 month post discontinuation of dosing or last participation in the study for SAE.

- Number and percent of subjects with potentially clinically significant changes in ECG parameters, vital signs, or clinical laboratory parameters from Day 1 through the final follow visit.

Pharmacokinetics

PK parameters will be derived from BMS-986251 concentration versus time data measured at the time points specified in the schedule of assessments for each

part of the study. The PK parameters to be assessed are listed in Section 8.5.3. The PK parameters to be evaluated in each part include but are not limited to the following:

- Part A: Cmax, tmax, AUC0-t, AUC0-inf, t1/2, CL/F, Vz/F, Aet, Feurine%, CLR

- Part B:

Day 1: Cmax, tmax, AUC0-t, AUC0-24

Days 2-14: Cpre

Day 14: Cmax, tmax, AUC0-t, AUC0-24, CL/F, Vz/F, t1/2, ARAUC0-24, ARCmax, Aet, Feurine%, CLR

Secondary outcome

The secondary objective to assess PD of single and multiple oral doses of BMS 986251 in healthy subjects will be measured by evaluating the percentage ex-vivo inhibition (I) of IL-17 secretion in whole blood. PD parameters will be derived from inhibition versus time data measured at the time points specified in the schedule of assessments for each part of the study. The PD parameters to be assessed are listed in Section 8.5.4. The PD parameters to be evaluated in each part include:

- Part A: Imax, tImax, tI>50%, tI>90%

- Part B: Imax, tImax, tI>50%, tI>90% (Day 1 and Day 14); Ipre (Days 2, 4, 7, and 14); It (Days 16, 20, and 24)

The secondary objectives to evaluate the oral BA of an oral suspension of BMS 986251 relative to a liquid dosage form at a single dose level in healthy subjects, and to evaluate the effect of a high-fat meal on the PK of an oral

suspension of BMS-986251 at a single dose level in healthy subjects will be evaluated by comparing the PK parameters listed for the SAD part in Section 9.3.1.

The secondary objective to evaluate the efficacy of multiple doses of BMS 986251 in patients with moderate-to-severe psoriasis will be evaluated by evaluating the following endpoints:

• PASI score at baseline, and Days 7, 14, and 28

• PGA score at baseline, and Days 7, 14, and 28

• DLQI at baseline, and Days 7, 14, and 28

Study description

Background summary

BMS-986251 is a new compound that may eventually be used for the treatment of psoriasis and other (auto)immune disorders. In this type of disorder the immune system is overactive. BMS-986251 binds within cells in the body to a protein called ROR-gamma-t. This protein plays an important role in activating immune reactions. One part of these immune reactions is an increased production of specific signaling proteins such as interleukins. By binding to ROR-gamma-t, BMS-986251 is able to counteract the effects of this protein. By doing so BMS-986251 may decrease the production of interleukins (among others). Experience with antibodies against interleukins have shown that by interfering with these interleukins a good clinical result can be obtained in immune disorders such as psoriasis and rheumatoid arthritis. BMS-986251 can be taken by mouth, which is an important advantage over other treatments for the same diseases.

Study objective

The purpose of Part A of this study is to investigate how safe the new compound BMS 986251 is when it is administered as a single dose to healthy subjects.

The purpose of Part B of this study is to investigate how safe the new compound

BMS 986251 is when it is administered as multiple doses to healthy subjects.

BMS 986251 has not been administered to humans before.

It will also be investigated how quickly and to what extent BMS-986251 is absorbed and eliminated from the body (this is called pharmacokinetics). In one of the groups of Part A, it will also be investigated what the pharmacokinetics of BMS 986251 are when it is administered in another dosage form and whether this will be influenced by food. In addition, in all parts of the study, the effect of BMS 986251 on the body will be investigated (this is called pharmacodynamics).

The effects of BMS-986251 will be compared to the effects of a placebo.

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 (location Martini Hospital) for 8 days (7 nights). Day 1 is the (first) 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 7 of the study. This will be followed by 2 days during which you will visit the research center for a short visit. These short visits will take place on Day 9 and Day 11, between 9 and 12 AM.

For Group A7
The actual study will consist of 3 periods during which the volunteer will stay in the research center in Groningen (location Martini Hospital) for 8 days (7 nights). Day 1 of each period 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. In each period, the volunteer will leave the research center on Day 7 of the study. 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 Day 9 and Day 11 of each period, between 9 and 12 AM. There will be at least 2 weeks between each of the 3 study drug administrations.

Part B:

The actual study will consist of 1 period during which the volunteer will stay in the research center in Groningen (location Martini Hospital) for 17 days (16 nights). Day 1 is the first 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 first administration of the study compound. The volunteer will

leave the research center on Day 16 of the study. This will be followed by 3 days during which the volunteer will visit the research center for a short visit. These short visits will take place on Days 18, 20 and 24, between 9 and 12 AM.

Intervention

Part A:

If the volunteer participate in Groups A1 to A6, the volunteer will be given BMS-986251 or placebo once as a drink with a small volume (maximally approximately 6 mL). After administration of the study compound, the volunteer is required to drink a glass of water (240 mL).

If the volunteer participate in Group A7 (see below), the volunteer will be given BMS-986251 3 times (once in each period). In this group all subjects will receive BMS 986251 in all 3 periods (no placebo). Only if the volunteer participate in Group A7 the volunteer will receive during the study 2 different types of drinks, one of which is a clear solution (Period 1) and one of which is a suspension (Period 2 and Period 3). After administration of the study compound, the volunteer is required to drink a glass of water (240 mL).

All volunteers in Group A7 will receive the study compound once with a standardized high-fat breakfast (Period 3) and twice after an overnight fast of at least 10 hours as described above (Period 1 and Period 2). In Period 3 the volunteer will receive a high-fat breakfast which has to be eaten at a specific time and will have to be finished within 20 minutes. The entire breakfast must be consumed

Group Day Period Treatment How often Condition
A1 1 1 BMS-986251 2 mg or placebo once fasting
A2 1 1 BMS-986251 6 mg or placebo once fasting
A3 1 1 BMS-986251 15 mg or placebo once fasting
A4 1 1 BMS-986251 30 mg or placebo once fasting
A5 1 1 BMS-986251 60 mg or placebo once fasting
A6 1 1 BMS-986251 120 mg or placebo once fasting
A7 1 1 BMS-986251 30 or 60 mg or placebo once fasting
1 2 BMS-986251 30 or 60 mg or placebo once fasting
1 3 BMS-986251 30 or 60 mg or placebo once high-fat breakfast

Part B:

The volunteer will be given BMS 986251 or placebo as a drink with a small volume (maximally approximately 6 mL) on Days 1 to 14 of the study. After administration of the study compound, he/she is required to drink a glass of water (240 mL).

Group Days Treatment How often Condition
B1 1-14 BMS-986251 6 mg or placebo once daily fasting
B2 1-14 BMS-986251 x mg or placebo once daily fasting
B3 1-14 BMS-986251 y mg or placebo once daily fasting
B4 1-14 BMS-986251 60 mg or placebo once daily fasting

Study burden and risks

As BMS-986251 will be administered to humans for the first time in this study, side effects of BMS-986251 in humans have not been reported to date. However, BMS-986251 has been studied in animals. There were no findings related to BMS-986251 in monkeys treated with oral doses up to 8 mg/kg/day for 2 weeks and in rats treated with oral doses up to 150 mg/kg/day for 2 weeks, which were the highest dose tested. In the animal studies in monkeys and rats, large intestine inflammation was seen. However, the findings were minimal, in general fully reversible and not associated with clinical signs. In the rat the large intestine inflammation was persistent only in the highest dose group (150 mg/kg). This is a much higher dose than will be administered to humans.

Based on the mechanism of action of BMS-986251 and its possible effects on the immune system, it is possible that the volunteer may be more susceptible to infections during participation in the study. You will be closely monitored for any signs and symptoms of infection.

Procedures: pain, minor bleeding, bruising, possible infection

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 males and females, ages 18 to 55 years, inclusive, at screening
- BMI of 18.0 to 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 or being a blood donor within 60 days from the start of the study. In case of donating more than 1.5 liters of blood in the 10 months prior the start of this 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):	31-10-2017
Enrollment:	88
Type:	Actual

Ethics review

Approved WMO Date:	17-10-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-10-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-04-2018
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	EUCTR2017-003408-38-NL
CCMO	NL63534.056.17