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A first in human study in healthy volunteers to assess the safety, tolerability, and pharmacokinetics of BMS-986238 in healthy participants

Submission date 25/03/2022	**Recruitment status** Stopped	[X] Prospectively registered [ ] Protocol
Registration date 30/03/2022	**Overall study status** Stopped	[ ] Statistical analysis plan [ ] Results
Last Edited 26/09/2024	**Condition category** Cancer	[ ] Individual participant data [ ] Record updated in last year

Plain English summary of protocol

Background and study aims
The Sponsor is developing the test medicine, BMS-986238, for the potential treatment of various forms of cancer, including solid tumours and lymphomas (cancer of the lymphatic system). Cancer is a disease where cells in the body grow uncontrollably and may spread to other parts of the body. Cancer causes a wide variety of symptoms and can be fatal. This healthy volunteer study is testing the safety and tolerability of 2 different formulations (recipes) of the test medicine, and how these different recipes of test medicine are taken up by the body over time (the pharmacokinetics). It is also looking to assess the different effects of the test medicine when taken with and without food, and to measure the amount of the test medicine that is absorbed by the body when taken by mouth or injection.

Who can participate?
Healthy male and non-lactating female volunteers of non-childbearing potential, aged 18 to 55 years.

What does the study involve?
It was planned that the study would be split into 3 Parts (Parts A, B and C), involving up to 136 healthy volunteers. In Part A, up to 104 volunteers would be split into 9 groups and receive a single dose of test medicine or dummy medicine (placebo) by mouth. In Part B, up to 16 volunteers would receive two single doses of the test medicine by mouth given with or without food. In Part C, up to 16 volunteers would receive a single dose of the test medicine by mouth, and a single dose of test medicine as an injection into the arm. For all study parts, volunteers would enter the clinical unit on Day -2 (2 days before dosing) and are discharged 14 days after dosing. Parts B and C would involve 2 study periods, with a minimum of 35 days between the two single doses. After final discharge from the clinical unit, volunteers in all study parts would return to the clinic on Days 21, 28 and 35 for outpatient study visits, and on Day 42 for a final follow-up visit. Volunteers may return for additional visits if required based on data collected during the study. Volunteer’s blood and urine are collected throughout the study for analysis of

the test medicine and for their safety. Volunteers are expected to be involved in the study for up to 16 weeks, from screening to the final follow up visit.

Please note that the study was terminated prior to Part B and Part C being initiated.

What are the possible risks and benefits of participating?
Participants get no medical benefit from taking part in the study. However, development of a cancer treatment may benefit the population as a whole. It is considered that the risk/benefit evaluation in this study supports the use of healthy volunteers. Full information on the possible side effects is provided to volunteers in the Participant Information Sheet/Informed Consent Form. Volunteers are closely monitored during the study and safety assessments are performed regularly.

Where is the study run from?
Two clinical sites in the United Kingdom: Quotient Sciences Limited (Nottingham) and Labcorp Clinical Research Unit Limited (Leeds).

When is the study starting and how long is it expected to run for?
March 2022 to August 2023

Who is funding the study?
The study Sponsor, Bristol-Myers Squibb Company (USA).

Who is the main contact?
Jay Oza, MD, PhD
Jay.Oza@bms.com

Contact information

Type(s)
Principal investigator

Contact name
Dr Philip Evans

Contact details
Quotient Sciences Limited
Mere Way
Ruddington Fields
Ruddington
Nottingham
United Kingdom
NG11 6JS
+44 (0)330 303 1000
recruitment@weneedyou.co.uk

Type(s)
Scientific

Contact name
Mr Head of Global Submission Management - Clinical Trials

Contact details
Chaussée de la Hulpe 185
Brussels
Belgium
1170
-
mg-gsm-ct@bms.com

Type(s)
Public

Contact name
Mr Head of Global Submission Management - Clinical Trials

Contact details
Chaussée de la Hulpe 185
Brussels
Belgium
1170
-
mg-gsm-ct@bms.com

Additional identifiers

Clinical Trials Information System (CTIS)
2020-004521-23

Integrated Research Application System (IRAS)
1004360

Protocol serial number
Study code: CA037-001

Study information

Scientific Title
A randomized, double-blinded, placebo-controlled, single ascending dose study to evaluate the pharmacokinetics, safety and tolerability, effect of food and absolute bioavailability of BMS-986238 in healthy participants

Study objectives
The following primary and secondary objectives were planned but not achieved due to early termination of the study:

Primary objectives:
1. To assess the safety and tolerability of single ascending doses of BMS-986238 administered using up to 2 different formulations (Formulation A; Formulation B) to healthy male and female participants (Part A).
2. To characterize the pharmacokinetics of single ascending doses of BMS-986238 administered

as an oral formulation(s) to healthy male and female participants (Part A).
3. To assess the safety and tolerability of BMS-986238 administered orally in the fed and fasted states to healthy male and female participants (Part B).
4. To assess the effect of food on the PK of an oral formulation of BMS-986238 administered to healthy male and female participants (Part B).

Secondary objectives:
1. To assess the safety and tolerability of BMS-986238 following single oral and IV administration to healthy male and female participants (Part C).
2. To assess the absolute oral bioavailability of BMS-986238 following single oral and IV administration of BMS-986238 and to characterize BMS-986238 PK after a single IV dose to healthy male and female participants (Part C)

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 29/04/2022, Fast-Track Research Ethics Committee (Health Research Authority, 2 Redman Place, Stratford, London, E20 1JQ, UK; fasttrack.rec@hra.nhs.uk), REC Ref: 22/FT/0033
2. Approved 29/04/2022, MHRA (10 South Colonnade, Canary Wharf, London, E14 4PU, UK; +44 (0) 20 3080 6000; info@mhra.gov.uk), ref: CTA21769/0276/001-0001

Primary study design
Interventional

Study design
Safety, tolerability and pharmacokinetics study in 136 healthy volunteers

Study type(s)
Other

Health condition(s) or problem(s) studied
Cancers, including solid tumours and lymphomas

Interventions
Participants received the following treatments.

1. Single oral dose of placebo for BMS-986238 Formulation A in the fasted state (Part A)
2. Single oral dose of placebo for BMS-986238 Formulation B in the fasted state (Part A)

Participants were randomised according to a computer-generated randomisation scheme so that in Part A, on Day 1 participants were to receive either a single oral dose of BMS-986238 or placebo in up to 9 cohorts (6 active and 2 placebo in Cohort 1A, and 9 active and 3 placebo for all other cohorts).

It was planned that participants would receive the following treatments, however the study was early terminated before the study parts (Part B and Part C) were conducted.
1. Single oral dose of up to 200 mg BMS-986238 Formulation A in the fasted and/or fed state (Parts B and C)

2. Single oral dose of up to 200 mg BMS-986238 Formulation B in the fasted and/or fed state (Parts B and C)
3. Single IV dose of up to 200 mg BMS-986238 in the fasted state (Part C)

The treatment randomisation for Part B and Part C was planned as follows:
Part B - to a treatment sequence on Day 1 in Period 1 (two groups of 8 participants). Participants receive two single oral doses of BMS-986238 in both the fed and fasted state, with a minimum washout period of 35 days between doses.
Part C - to a treatment sequence on Day 1 in Period 1 (two groups of 8 participants). Participants will receive a single oral dose and an IV dose of a formulation of BMS-986238 (Formulation A or B), with a minimum washout period of 35 days between doses.

Participants are expected to be involved in this study for 70 days in Part A, and 105 days in Parts B and C. In all study parts, additional monitoring of participants' wellbeing beyond the final follow-up visit may continue, if required, based on emerging data.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
BMS-986238

Primary outcome(s)
The following primary outcome measures were planned but not achieved due to early termination of the study:
1. Incidence of adverse events, serious adverse events and adverse events leading to discontinuation and deaths from the time of signing the informed consent form until discharge from the study.
2. Incidence of abnormalities in clinical laboratory values measured using participant venous blood or urine samples from the time of signing the informed consent form and at multiple time points until discharge from the study.
3. Pharmacokinetic parameters Tmax, Cmax, AUC(0-T), AUC(INF), T-HALF, CLT/F, and Vz/F (all study parts) and CLR (Part A) and Fed;Fasted geometric mean rations for Cmax and AUC (Part B only) for BMS-986238 in plasma and urine samples from pre-dose and at multiple time points until discharge from the study.

Key secondary outcome(s)
The following secondary outcome measures were planned but not achieved due to early termination of the study: 1. Incidence of adverse events, serious adverse events and adverse events leading to discontinuation and deaths from the time of signing the informed consent form until discharge from the study.
2. Incidence of abnormalities in clinical laboratory values measured using participant venous blood or urine samples from the time of signing the informed consent form and at multiple time points until discharge from the study.
3. Absolute oral bioavailability (F) of BMS-986238 in plasma samples from pre-dose and at multiple time points during the study.
4. Pharmacokinetic parameters Tmax, Cmax, AUC(0-T), AUC(INF), T-HALF, CLT/F (oral), CLT (IV), Vz (IV) and apparent volume of distribution at steady state (Vss) (IV) of BMS-986238 following

an oral dose or an IV infusion in plasma samples from pre-dose and at multiple time points until discharge from the study.

Completion date
27/08/2023

Reason abandoned (if study stopped)
Internal development decisions led to the closure of the CA037001 study. The early termination of the study was in no way related to any adverse events (AEs) or other preclinical/clinical safety concerns associated with BMS-986238.

Eligibility

Key inclusion criteria
1. Must provide written informed consent
2. Healthy males healthy females of non-childbearing potential
3. Aged 18 - 55 years, inclusive, at the time of signing the informed consent form
4. Body mass index (BMI) of 18.0 - 32.0 kg/m² as measured at screening
5. A negative PCR or rapid antigen test for COVID-19 at screening and admission
6. Participants with a previous history of COVID-19 infection, must have been symptom-free for a minimum of 4 weeks before dosing, and did not experience a serious complication of the infection
7. Has received all doses of COVID-19 vaccines in compliance with national vaccination policy
8. Must agree to adhere to the contraception requirements defined in the protocol

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Upper age limit
55 Years

Sex
All

Total final enrolment
24

Key exclusion criteria
1. Any significant acute or chronic medical illness, including viral infection or seasonal allergies
2. History of diabetes mellitus, severe hypertriglyceridemia, acute or chronic pancreatitis, pancreatic exocrine disorder

3. Known or suspected autoimmune disorder, including but not limited to rheumatoid arthritis, fibromyalgia, systemic lupus erythematosus, polymyalgia rheumatic, giant cell arteritis, Behcet's disease, dermatomyositis, multiple sclerosis, moderate to severe asthma, any autoimmune vasculitis, autoimmune hepatitis, autoimmune uveitis, autoimmune thyroiditis, or any other active autoimmune disease for which a participant requires medical follow-up or medical treatment
4. Any history of known or suspected congenital or acquired immunodeficiency state or condition that may compromise the participant's immune status (eg, history of splenectomy)
5. Have been treated with systemic steroids, immunosuppressant therapies, or chemotherapeutic agents within 3 months prior to screening or is expected to receive these agents during the study (eg, corticosteroids, immunoglobulins, and other immune- or cytokine-based therapies)
6. Any participant with clinically significant symptoms of COVID-19 in the last 4 weeks, including but not limited to fever, new and persistent cough, breathlessness or loss of taste or smell, as per the judgement of the investigator
7. Any participant with a temperature of >37.5°C (confirmed by repeat after 15 minutes) at screening or admission
8. History of Gilbert's syndrome
9. Current or recent (within 3 months of study intervention administration) gastrointestinal disease, including severe peptic ulcer disease, gastroesophageal reflux disease, or other gastric acid hypersecretory conditions requiring treatment
10. Any major surgery within 12 weeks of study intervention administration
11. Any gastrointestinal surgery that could impact upon the absorption of study drug. Appendectomy and cholecystectomy performed > 12 weeks prior to study intervention administration are permissible
12. Malignancy within 5 years prior to screening, with the exception of specific cancers that are cured by surgical resection (eg, basal cell skin cancer). Participants under evaluation for possible malignancy are not eligible
13. Donation of blood to a blood bank or in a clinical study (except a screening visit) within 90 days of study intervention administration (within 2 weeks for plasma only) or loss of greater than 400 mL of blood
14. Blood transfusion within 6 weeks of study intervention administration
15. Inability to be venipunctured and/or tolerate venous access
16. Inability to tolerate oral medication
17. Have received inactivated vaccinations (eg, pneumococcal) within 30 days prior to randomization or received live vaccinations within 30 days prior to screening. The use of inactivated seasonal influenza vaccines (eg, Fluzone®) will be permitted on the study without restriction. COVID-19 vaccines are permitted as long as they are not administered within 7 days prior to Day 1 (of Period 1, when applicable), during the study, and until at least Day 42 after the last dose or until receptor occupancy (RO) is at or projected to be at baseline level or at a level deemed clinically safe based on emerging PK, RO, and safety data, whichever is longer
18. Current smokers or user of any tobacco- or nicotine-containing products within 3 months of study intervention administration
19. Recent (within 6 months of study intervention administration) drug or alcohol abuse as defined in DSM IV, Diagnostic Criteria for Drug and Alcohol Abuse
20. Regular alcohol consumption in males >21 units per week and females >14 units per week (1 unit = ½ pint beer, or a 25 mL shot of 40% spirit, 1.5 to 2 units = 125 mL glass of wine, depending on type).
21. Inability to comply with all protocol assessments including follow-up visits
22. Any other sound medical, psychiatric and/or social reason as determined by the investigator
23. Inadequate veins for multiple venepunctures/cannulation (all study parts) or for IV infusion (Part C only)

24. Participants who have received any IMP in a clinical research study within the 90 days prior to Day 1 (of the first study period, when applicable)
25. History of clinically significant cardiovascular, renal, hepatic, dermatological, chronic respiratory or gastrointestinal disease, neurological or psychiatric disorder, as judged by the investigator
26. Participants with a history of cholecystectomy or gall stones (Part B only)
27. Any history or risk for tuberculosis (TB), specifically participants with: 1) current clinical or laboratory evidence of active TB (based on a QuantiFERON® test at screening or within 1 month prior to Day 1 [of the first study period, when applicable]); 2) history of active TB unless there is documentation that the prior anti-TB treatment was appropriate in duration and type; 3) latent TB which has not been successfully treated; a QuantiFERON® test at screening or within 1 month prior to Day 1 (of the first study period, when applicable) is acceptable as long as there is documentation of a negative result
28. Any history of retinopathy or the presence of any clinically significant retinal abnormality detected during ophthalmologic evaluation
29. Women who are of childbearing potential
30. Women who are breastfeeding
31. Participants who are taking, or have taken, any prescribed or over-the-counter drug or herbal remedies (other than up to 4 g of paracetamol per day, or HRT) in the 14 days before IMP administration
32. No concomitant medications (prescription, over-the-counter or herbal) are to be administered during study unless they are prescribed for treatment of specific clinical events by the investigator and/or the BMS medical monitor, or specifically required as part of the protocol-specified ophthalmological examinations (eg, eye drops)
33. Vaccination or plans for vaccination with any live vaccine within 30 days before screening (or 30 days before randomization for non-live vaccines), during the course of the study, or 30 days after last study intervention administration. The use of inactivated seasonal influenza vaccines (eg, Fluzone®) will be permitted on the study without restriction. COVID-19 vaccines are permitted as long as they are not administered within 7 days prior to Day 1 (of Period 1, when applicable), during the study, and through at least Day 42 after the last dose or until RO is at or projected to be at baseline level or a level deemed clinically safe based on emerging PK, RO, and safety data, whichever is longer
34. 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
35. Any of the following on 12-lead ECG prior to administration of study intervention, confirmed by 1 repeat:
35.1. PR ≥210 msec
35.2. QRS ≥120 msec
35.3. QT interval ≥500 msec
35.4. QTcF ≥450 msec
36. Laboratory test findings as follows:
36.1.White Blood Cell count <LLN or >ULN
36.2.Neutrophil count <LLN or >ULN
36.3. ALT>ULN
36.4. Direct bilirubin >ULN
36.5. Lipase >ULN
36.6. Platelet count <LLN
36.7. INR >ULN
36.8. Albumin <LLN
36.9. HbA1C ≥6.5%
36.10. Hemoglobin outside of the normal reference range, unless considered not clinically

significant by the investigator
36.11. Creatinine Clearance (CLcr) < 80 mL/min (using the Cockcroft-Gault [C-G] method) based on serum creatinine and actual body weight as measured at the screening evaluation
36.12. Positive urine screen for cotinine and drugs of abuse
36.13. Positive alcohol breath test
36.14. Positive blood screen for hepatitis C antibody, hepatitis B surface antigen, HIV-1 antibody, or HIV-2 antibody
36.15. Positive blood screen for asymptomatic and potential autoimmune diseases according to the normal reference ranges and/or standards of the local laboratory, including but not limited to ANA, anti-SMA, AMA, RF, and anti-TPO
37. Known history of allergy to macrocyclic peptides
38. Known allergy to corn or legumes (eg, dextrose allergy)
39. History of significant allergy or hypersensitivity to PEGylated products (eg, SARS-CoV-2 mRNA vaccine)
40. History of any significant drug allergy (such as anaphylaxis or hepatotoxicity)
41. Presence or history of clinically significant allergy requiring treatment, as judged by the investigator. Hay fever is allowed unless it is active
42. Prior exposure to any medicinal products with the same mechanism of action as the investigational medicinal product, including in the current study. Participants who have taken part in Part A are not permitted to take part in Parts B or C. Participants who have taken part in Part B are not permitted to take part in Part C, and vice versa
43. Prisoners or participants who are involuntarily incarcerated
44. Inability to comply with restrictions and prohibited activities/treatments
45. Participants who are, or are immediate family members of, a study site or sponsor employee

Date of first enrolment
05/07/2022

Date of final enrolment
01/08/2023

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Quotient Sciences Limited
Trent House
Mere Way
Ruddington Fields
Nottingham
United Kingdom
NG11 6JS

Study participating centre
Labcorp Clinical Research Unit Limited
Drapers Yard, Marshall Street, Holbeck
Leeds
United Kingdom
LS11 9EH

Sponsor information

Organisation
Bristol-Myers Squibb (Belgium)

ROR
https://ror.org/03c09ma81

Funder(s)

Funder type
Industry

Funder Name
Bristol-Myers Squibb

Alternative Name(s)
Bristol-Myers Squibb Company, Bristol Myers Squibb, Bristol-Myers Company, BMS

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study are not expected to be made available because of their high commercial sensitivity and the negligible benefit to the public of publication of results of non-therapeutic clinical trials.

IPD sharing plan summary

Not expected to be made available