IM011-077 - An Open-label, Multi-center Extension Study to Evaluate the Long-term Safety and Efficacy of BMS-986165 in Participants with Moderate to Severe Crohn*s Disease or Moderate to Severe Ulcerative Colitis

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Study IM011-077 is a Phase 2 randomized, open-label, multicenter clinical study designed to assess the safety and tolerability, efficacy and biomarker response of deucravacitinib 6 mg BID (twice daily) in subjects with moderate to severe Ulcerative...

Ethical review	Approved WMO
Status	Completed
Health condition type	Gastrointestinal inflammatory conditions
Study type	Interventional

Summary

ID

NL-OMON51428

Source
ToetsingOnline

Brief title
IM011-077

Condition

- Gastrointestinal inflammatory conditions

Synonym
Inflammatory Bowel Disease (IBD); gastro-intestinal tract

Research involving

Human

Sponsors and support

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

Intervention

Keyword: Crohn's Disease, targetted therapy, TYK 2, Ulcerative colitis

Outcome measures

Primary outcome

The primary objective of the study will be to assess the safety and tolerability of long-term use of deucravacitinib in participants with moderate to severe CD.

This will be measured by collecting the number and proportion of participants experiencing Adverse Events (AEs), Serious AEs (SAEs), AEs leading to study discontinuation and AEs of Interest (AEIs).

The number and proportion of participants experiencing abnormalities in the laboratory testing, ECG and vital sign parameters over time.

Changes from Day 1 for laboratory testing, ECG and vital signs will also be measured.

Secondary outcome

Secondary objectives of the study are as follows:

• To assess the effect of long-term use of deucravacitinib in participants with moderate to severe UC and CD

This will be measured by a number of factors including the proportion of participants with clinical remission, clinical response, endoscopic response, endoscopic remission, histologic remission, mucosal healing.

• To assess the effect of long-term use of deucravacitinib on health-related quality of life

This will be measured by a number of factors including the Inflammatory Bowel Disease (IBD) Questionnaire, Stool Frequency (SF) questionnaire and bowel urgency response.

• To obtain data regarding the effect of long-term use of deucravacitinib on healthcare utilisation

This will be measured by the proportion of participants with IBD-related hospitalisation and IBD-related surgery

• To obtain data regarding the effect of long-term use of deucravacitinib on PK.

This will be measured from plasma sample concentrations of deucravacitinib over the course of the study

• To obtain data regarding the effect of long-term use of deucravacitinib on biomarkers.

This will be measured by the change from baseline in faecal calprotectin and faecal lactoferrin over time, in addition to the change from baseline of inflammatory biomarkers over time in circulation and tissues

• To assess the impact of SARS-CoV-2 serologic status on participants receiving deucravacitinib.

This will be measured by checking the levels of SARS-CoV-2 in the blood over the course of the study.

Study description

Background summary

IM011-077 is a multicentre, phase 2, open-label study involving patients with moderate to severe Ulcerative Colitis (UC) and Crohn's Disease (CD). The study will assess the long-term safety and efficacy of deucravacitinib (BMS-986165). Approximately 300 participants are expected to rollover from the parent studies into Study IM011-077. All participants must have completed 1 of the parent studies (Studies IM011-023, IM011-024, or Study IM011-127) and must meet all eligibility criteria.

Approximately 300 participants are expected to rollover from the parent studies into Study IM011077. All participants must have completed 1 of the parent studies (Studies IM011023, IM011024, or Study IM011127) and must meet all eligibility criteria.

Participants will receive deucravacitinib 6 mg twice a day, by mouth, in a tablet formulation.

UC and CD are chronic inflammatory diseases of the gastrointestinal tract which have an impact on mortality and quality of life. The management and treatment of these diseases have placed a huge demand on various healthcare services. Despite new treatment options which have become available over the last several years, significant challenges remain. Current treatments are often ineffective, only inducing are temporary response. In other cases the treatment regimens can cause toxic side effects. There still remains a significant need for well-tolerated and effective treatments.

Deucravacitinib is a selective Tyrosine Kinase 2 (TyK2) inhibitor. TyK2 is an enzyme involved in various signalling pathways found within the cell known as cytokines: interleukin (IL)-12, IL-23 and Type I interferon (IFN) signalling. The TyK2 enzyme works by speeding up the transfer of phosphate groups from high-energy, phosphate-donating molecules to specific proteins. This process is known as phosphorylation. The phosphorylation of these proteins results in the downstream activation of specific responses for these signalling pathways.

TyK2 is widely expressed. TYk2-dependent signalling pathways and the chemical messengers that they modulate are thought to be involved in the onset and development of various immune-mediated diseases including UC, CD, psoriasis, psoriatic arthritis and systemic lupus erythematous (SLE).

Data from this study will be analysed to:
(i) Assess the safety and tolerability of long-term sue of deucravacitinib in participants with moderate to severe UC and CD

(ii) Assess the long-term use of deucravacitinib in participants with moderate to severe UC and CD

(iii) Assess the effect of long-term use of deucravacitinib on health-related quality of life.

(iv) Obtain data regarding the effect of long-term use of deucravacitinib on healthcare utilization.

(v) Obtain data regarding the PK long-term use of deucravacitinib following long-term use in participants

(vi) Obtain data regarding the effect of long-term use of deucravacitinib on biomarkers

(vii) To assess the safety impact of SARS-CoV-2 serologic status on participants receiving deucravacitinib

Study objective

Study IM011-077 is a Phase 2 randomized, open-label, multicenter clinical study

designed to assess the safety and tolerability, efficacy and biomarker response of deucravacitinib 6 mg BID (twice daily) in subjects with moderate to severe Ulcerative Colitis and Crohn's Disease.

Study design

Approximately 300 patients will participate in the study. The total number patients that take part in the Netherlands will depend on the number of eligible participants that have completed one of the parent studies. There are 3 BMS parent phase 2 deucravacitinib studies - one for participants with moderate to severe Crohn's Disease (CD) (Study IM011023) and two for participants with moderate to severe ulcerative colitis (UC) (Studies IM011024 and IM011127).

Participation on the study will last about 6 years. The exact duration will depend on how well the participant tolerates the study treatment.

The study is divided into three periods:

• Screening
• Treatment: up to 6 years
• Follow-up: 4 weeks (28 days)

During the screening visit the participant will undergo test to confirm whether they can participate. These tests include a physical examination, ECG, measurement of weight and vital signs, and collection of blood, urine and stool samples. An endoscopy with biopsy may also be performed.

When this screening visit occurs less than 14 days from the last visit of the parent study, only one set of samples will be taken, and the results will be used in both studies. If this visit occurs greater than or equal to 14 days and less than or equal to 28 days from the last visit of the parent study, certain procedures will need to be repeated except the endoscopy with biopsy. When this visit occurs greater than 28 days from the last visit in the parent study, all procedures will need to be repeated and the study investigator will inform the participant if the endoscopy with biopsy needs to be repeated.

All participants will receive deucravacitinib 6 mg daily in the form of a tablet. The study drug should be taken once in the morning and once in the evening.

After patients have completed the treatment period or for those who permanently discontinue the study drug before the end of the treatment period, they will enter a 4 week post treatment follow-up period.

DMC
A Data Monitoring Committee will provide oversight on the safety of trial

participants within this study. The DMC will regularly review accumulating data from this study and advise the Sponsor regarding the continuing safety of trial participants, as well as the continuing validity and scientific merit of the trial.

Data summaries and listings will be provided to the DMC to assist their safety assessment of the study, at regularly scheduled meetings and on an ad hoc basis if needed. The DMC will also be provided with suspected, unexpected serious adverse reaction (SUSAR) reports relating to deucravacitinib and recommendations from other DMCs supporting the deucravacitinib clinical development program.

Regular DMC safety reviews will include all AEs, SAEs, and AEIs. Based on their review of safety data, the DMC will make recommendations regarding the appropriateness of continuing the study, with or without study modifications, or stopping the study. The DMC may request select efficacy data from the blinded parent studies for benefit-risk assessment and study continuation.

Intervention

Patients who have completed screening procedures (up to 28 days duration) and meet inclusion/exclusion criteria will be randomized on Day 1 of the treatment period.

All participants will receive deucravacitinib 6mg twice daily by mouth (PO) in a tablet formulation, for up to 6 years.

Participants will undergo the same on treatment study evaluation procedures: assessments of medical history, prior medications, concomitant medications, tobacco use, baseline Stool Frequency; blood, stool and urine collection for checking safety, pharmacokinetics, and biomarkers, vital signs monitoring, endoscopy with biopsies, ECG, additional efficacy assessments, questionnaires and patient collection of PROs in daily electronic diaries.

Once participants complete the study treatment period, they will begin the last part of the study, the follow-up period. During this period the investigator will continue to assess the patients' health. The follow-up period includes 1 visit at the study center. If the investigator thinks it's necessary additional visits may be necessary to further evaluate the safety or efficacy of the drug.

Study burden and risks

Several sources of research suggest that inhibition of TYK 2 signalling by deucravacitinib may be beneficial to patients with Ulcerative Colitis (UC) and Crohn's Disease (CD).

Deucravacitinib has previously been studied in parent studies IM011-023 (for participants with moderate to severe CD), IM011-024 and IM011-127 (for participants with moderate to severe UC).

Study IM011-127 was the first study involving patients with moderate to severe UC. In this placebo controlled study participants received deucravacitinib at doses 6-12 mg twice daily, for up to 52 weeks. The current study (IM011-077) has been designed to closely monitor patients' safety throughout, over a longer period (6 years). Participants enrolling in the study will have had 1 to 2 years of safety monitoring while receiving deucravacitinib. Safety monitoring will continue at study sites, by the Sponsor, and also by an external, independent Data Monitoring Committee.

The inclusion/ exclusion criteria, tests and procedures for this study are aligned with the parent studies. The similarity between the studies will allow for data from the current study to be analysed alone, and compared with the data collected in the parent studies. This may also help to determine dose selection for phase 3 trials of deucravacitinib.

The safety and tolerability of deucravacitinib has been investigated at multiple doses (including 6mg) in healthy volunteers and patients with psoriasis in phase 2 studies. The results from these studies indicate and overall favourable benefit-risk assessment for investigating further treatment of patients with CD and UC.

Adverse Events of Interest (AEIs) have been defined, based on the mechanism of action of BMS-986165 (deucravacitinib) and the observed safety profile in the BMS-986165 clinical trial program. The eligibility and randomization criteria have been clearly defined to ensure to minimize the risk for AEIs such as infections or malignancy, which may be associated with immunomodulator use. (Deucravacitinib is an immunomodulatory Investigational Product and potential Immunosuppressant). Frequent study visits and safety assessments, with monitoring of subject safety by investigators, the Sponsor, and the Data Monitoring Committee are designed to promote the safety of subjects within this study. Furthermore all participants may remain on permitted background Standard of Care (SOC) therapy. The protocol provides details on how to manage treatment failure and increase in Inflammatory bowel disease activity.

Testing will be done to exclude participants with COVID-19 infection prior to enrollment. Study treatment will be interrupted in the event there is a positive test for SARS-CoV-2 or clinical suspicion for COVID-19 infection.

Data Monitoring Committee (DMC)
An external, independent DMC will provide oversight on the safety of patients within this study, The DMC will regularly review accumulating data from this study, and advise the Sponsor regarding the continuing safety of trial subjects and those yet to be recruited to the trial, as well as the continuing validity

and scientific merit of the trial.

Data summaries and listings will be provided to the DMC to facilitate their safety assessment at regularly scheduled meetings and on an ad hoc basis if needed. The DMC will also be provided with suspected, unexpected serious adverse reaction (SUSAR) reports relating to deucravacitinib.

Regular DMC safety reviews will include all AEs, SAEs, and AEs of special interest. Based on their review of safety data, the DMC will make recommendations regarding the appropriateness of continuing the study, with or without study modifications, or stopping the study.

Deucravacitinib could provide clinical benefit and improvements in the outcomes for patients with UC and CD. However, with all experimental drugs and clinical trials, there are known and unknown risks. Study medication and procedure related risks are outlined in the patient information sheet in detail to ensure the patients are fully informed before agreeing to take part in the study.

As part of the trial, patients will be expected to attend multiple clinic visits where they will undergo physical examinations, vital sign measurements, endoscopy, biopsy, ECG, blood, stool and urine tests for safety assessment, pregnancy testing (for females of child bearing potential) and monitoring for adverse events.

Blood will also be collected at certain visits for research purposes (PK, and biomarker studies).

Patients will be asked to complete an electronic diary about their stool frequency, daily throughout the screening and treatment periods. They will also be required to complete questionnaires about their UC and CD and quality of life at various points throughout the study.

Patients will be required to take tablets twice daily for up to 6 years, during the treatment period. The diary and pill bottle will be reviewed by site-staff.

Subjects are required to fast for a minimum of 10 hours before the randomization visit (Day 1) and the Week 48 (visit 5), as fasting lipid and glucose samples will be obtained at those times.

Women of child-bearing potential must agree to follow instructions for methods of contraception for the duration of treatment with the study drug.

Use of tobacco products will be assessed at each study visit.

Study treatment may be taken without regard to meals.

The investigation medicinal products could provide clinical benefit and

improvements in the outcomes for patients with UC & CD. However, with all experimental drugs and clinical trials, there are known and unknown risks. Study medication and procedure related risks are outlined in the patient information sheet in detail to ensure the patients are fully informed before agreeing to participate.

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

1) Signed Written Informed Consent
a) Participants must be willing to participate in Study IM011077 and must have the ability to sign the informed consent form.
b) Willing and able to complete all study specific procedures and visits.

2) Type of Participant and Target Disease Characteristics
a) Previously completed OLE treatment in 1 of the parent CD or UC studies;
b) Be in clinical response or clinical remission at Week 104 of Study IM011023 or Study IM011024, or Week 52 of Study IM011127;
• Evidence of clinical response or clinical remission (compared with baseline in the parent study) as defined by CDAI or modified Mayo score;
AND
• No worsening of endoscopy (by SES-CD or Mayo endoscopic subscore) from the parent study baseline (as assessed by local read).

3) Age and Reproductive Status
Investigators shall counsel women of childbearing potential (WOCBP) participants, and male participants who are sexually active with WOCBP, on the importance of pregnancy prevention and the implications of an unexpected pregnancy.
• The investigator shall evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.
• Local laws and regulations may require the use of alternative and/or additional contraception methods.

a) Female Participants
• Females, age 18 or local age of majority and older at the time of enrollment.
• Women who are not of childbearing potential are exempt from contraceptive requirements.
• Women participants must have documented proof that they are not of childbearing potential.
• WOCBP must have a negative highly sensitive urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) within 24 hours prior to the start of study treatment.
If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
• The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.
• WOCBP must agree to follow instructions for method(s) of contraception as described below and included in the ICF.
• WOCBP are permitted to use hormonal contraception methods as described.
• A female participant is eligible to participate if she is not pregnant or breastfeeding and at least one of the following conditions applies:
(1) Is not a WOCBP, OR
(2) Is a WOCBP and using a contraceptive method(s), during the treatment period (at a minimum until after the last dose of study treatment).

b) Male Participants
• Males, age 18 or local age of majority and older at the time of enrollment.
• Male participants should maintain their usual practice with regard to

contraception (if any); however, no specific contraceptive measures are required.

Exclusion criteria

Exclusion Criteria
1) Medical Conditions
a) Women who are pregnant or breastfeeding.

2) Gastrointestinal Exclusion Criteria
a) Current colonic adenomas or dysplasia diagnosed at the endoscopy performed at the end of treatment visit of the parent study or past confirmed colonic dysplasia in the parent study that has not been eradicated.
A participant with adenomatous polyps may be eligible if the polyps have been completely removed (documented) and the participant is free of polyps at enrollment (Day 1).
A participant with mucosal dysplasia may be eligible if the dysplasia has been completely removed/resected/eradicated (as applicable, documented), and the participant is free of dysplasia at enrollment (Day 1). This should be discussed with the BMS Medical Monitor/designee prior to enrollment.
Participants must be current with surveillance for dysplasia and screening for colorectal cancer (based on local guidelines).
3) Immune and Infectious Disease Exclusion Criteria
a) Known serious infection, defined as any infection requiring hospitalization or treatment with parenteral (intramuscular [IM] or IV) antimicrobial agents (eg, antibiotics, antiviral, antifungal, or antiparasitic agents) within 30 days of the first dose of study treatment.
Antibiotics used to cover a procedure such as endoscopy would not exclude the participant. Prophylactic antibiotic use should be discussed with the BMS Medical Monitor/designee.
Additionally, in the case of prior SARS-CoV-2 infection, symptoms must have resolved and, based on investigator assessment in consultation with the BMS Medical Monitor/designee, there are no sequelae that would place the participant at a higher risk by receiving investigational treatment.

4) Prior/Concomitant Therapy
a) Have received any of the following therapies since the first dose of study treatment in the parent study or before Day 1 in Study IM011077:
i) Treatment with an immunomodulatory or biologic agent for the treatment of IBD.
ii) Treatment with an investigational agent other than deucravacitinib.
iii) Treatment with D-penicillamine, leflunomide, thalidomide, S1P inhibitors (eg, ozanimod, fingolimod, and etrasimod), or JAK inhibitors (eg, tofacitinib, upadacitinib, and filgotinib).
b) Are currently receiving or require initiation of any of the following

therapies:
i) Treatment with corticosteroids at a dose that exceeds the prednisone equivalent of
7.5 mg/day for adrenal insufficiency.
ii) Treatment with immunomodulatory agents (eg, azathioprine, 6-mercaptopurine, or methotrexate).
c) Treatment with a live vaccine or live attenuated vaccine within 90 days prior to Visit 1 of this trial.
d) Prophylactic antibiotic use should be discussed with the BMS Medical Monitor/designee.

5) Physical and Laboratory Test Findings
a) Evidence of active or latent tuberculosis
Participants diagnosed with latent TB infection (LTBI) in the parent study are eligible to continue in this study if (1) there are no current signs or symptoms of active TB, (2) the participant has received adequate documented treatment for LTBI within 5 years of screening in the parent study.
b) Evidence of active hepatitis B virus (HBV) infection as defined.
Participants who were required to have HBV deoxyribonucleic acid (DNA) tested every 3 months in the parent study will continue to be tested every 3 months throughout this study.
c) Clinically significant abnormalities in laboratory testing at the second to last visit in the parent study or most current result available prior to Day 1 including (but not limited to):
i) Hematology:
(1) Hemoglobin level < 8.5 g/dL
(2) White blood cell (WBC) count < 3.0 × 109/L (< 3000/mm3)
(3) Lymphocyte count < 0.75 × 109/L (< 750/mm3)
(4) Neutrophil count < 1.0 × 109/L (< 1000/mm3) (5) Platelet count < 100 × 109/L (< 100,000/mm3)
ii) Renal Function:
(1) Serum creatinine > 2 × upper limit of normal (ULN) or renal impairment based on an estimated glomerular filtration rate < 45 mL/min/1.73 m2 (calculated using the Modification of Diet in Renal Disease equation)
iii) Liver-related Blood Tests and Liver Function:
(1) Serum alanine aminotransferase (ALT) > 2 × ULN
(2) Serum aspartate aminotransferase (AST) > 2 × ULN
(3) Serum total bilirubin > 1.5 × ULN
Participants with total bilirubin > 1.5 × ULN who have a confirmed diagnosis of Gilbert*s syndrome are not excluded from this study but must be discussed with the BMS Medical Monitor/designee.
(4) Alkaline phosphatase (ALP) > 1.5 × ULN
d) Any other findings on physical examination, vital signs, or clinical laboratory testing that, in the opinion of the investigator, may place the participant at an unacceptable risk for participation in this study.

Allergies and Adverse Drug Reaction

e) History of any significant drug allergy (eg, anaphylaxis) or significant adverse drug reaction (eg, hepatotoxicity).

6) Other Exclusion Criteria
a) Participants with cancer screening or surveillance that is suspicious for malignancy, or where the possibility of malignancy cannot be reasonably excluded after additional clinical, laboratory, or other diagnostic evaluations. Participants with non-melanoma skin cancer are not excluded.
b) Class III or IV congestive heart failure, as classified by the New York Heart Association (NYHA) Functional Classification or any recent onset of heart failure resulting in NYHA Class III/IV symptoms.
c) Acute coronary syndrome (eg, myocardial infarction, unstable angina pectoris) and/or any history of significant cerebrovascular disease (eg, stroke, cerebral hemorrhage, transient ischemic attack) within 24 weeks before enrollment.
d) Known history of hereditary galactose intolerance, total lactase deficiency, or glucose- galactose malabsorption.
e) 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 Bristol-Myers Squibb approval is required.

Eligibility criteria for this study have been carefully considered to ensure the safety of the study participants and that the results of the study can be used. It is imperative that participants fully meet all eligibility criteria.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL
Recruitment status: Completed

Start date (anticipated):	11-11-2022
Enrollment:	1
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Deucravacitinib
Generic name:	Deucravacitinib

Ethics review

Approved WMO Date:	20-07-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-10-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-12-2022
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	EUCTR2020-004461-40-NL
ClinicalTrials.gov	NCT04877990
CCMO	NL81621.056.22

Study results

Date completed: 03-08-2023

Results posted: 29-08-2024

First publication
01-01-1900