A Randomised Double-Blind Placebo-Controlled Phase III Clinical Study to Evaluate the Efficacy and Safety of Cobitolimod as an Induction and Maintenance Therapy in Participants with Moderate to Severe Active Left-Sided Ulcerative Colitis

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Study Objectives:Primary Objective: InductionTo evaluate the efficacy of cobitolimod treatment compared to placebo in inducing clinical remission, in participants with moderate to severe active left-sided UC.Secondary Objectives: Induction• To...

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

Summary

ID

NL-OMON51406

Source
ToetsingOnline

Brief title
CONCLUDE

Condition

- Other condition

Synonym
chronic inflammation of the lining of the colon, Ulcerative Colitis

Health condition

inflammatory bowel disease

Research involving
Human

Sponsors and support

Primary sponsor: InDex Pharmaceuticals AB
Source(s) of monetary or material Support: farmaceutische industrie

Intervention

Keyword: Cobitolimod, Left-Sided Ulcerative Colitis, Phase 3

Outcome measures

Primary outcome

Primary Efficacy Endpoint: Induction Study

Proportion of participants with clinical remission at I-week 6, defined by the

3-component Mayo score, i) rectal bleeding of 0, ii) stool frequency of 0 or 1

(with at least one (1) point decrease from I-week 0 if 1 at I-week 0), and iii)

endoscopic score of 0 or 1.

Primary Efficacy Endpoint: Maintenance Study

Proportion of participants with clinical remission at M-week 45, defined by the

3-component Mayo score, i) rectal bleeding of 0, ii) stool frequency of 0 or 1

(with at least one (1) point decrease from I-week 0 if 1 at I-week 0), and iii)

endoscopic score of 0 or 1.

Secondary outcome

Key Secondary Efficacy Endpoints: Induction Study

• Proportion of participants with endoscopic improvement at I-week 6 defined by endoscopic subscore of 0 or 1.

• Proportion of participants with symptomatic remission at I-week 6 defined by subscores, i) rectal bleeding of 0, ii) stool frequency of 0 or 1 (with at least one (1) point decrease from I-week 0 if 1 at I-week 0).

Key Secondary Efficacy Endpoints: Maintenance Study

• Proportion of participants with endoscopic improvement at M-week 45.

• Proportion of participants with clinical remission at M-week 45 and steroid-free for at least 8 weeks prior.

• Proportion of participants with clinical remission at M-week 45 among those who achieved clinical remission at I-week 6.

• Proportion of participants with symptomatic remission at M-week 45.

Other endpoints are described in the main protocol.

Safety Endpoints

• incidence of AEs

• incidence of SAEs

• vital signs

• physical examination

• laboratory findings

Study description

Background summary

Background and Rationale: Cobitolimod is a fully synthetic DNA-based 19-mer ODN. The drug functions as an immunomodulatory agent by targeting the TLR9 present in immune cells or on the surface of epithelial cells. These immune cells (e.g., B cells, macrophages and plasmacytoid dendritic cells) reside in high abundance on mucosal surfaces, such as colonic and nasal mucosa. Cobitolimod will be rectally administered at the site of inflammation as a 50 mL enema, placing the drug in close contact with a high number of intended target cells in an area rich in TLR9-expressing cells. Binding of the TLR9 by cobitolimod triggers the cells to produce anti-inflammatory cytokines, such as IL10, which are believed to be important for the clinical effect of cobitolimod.
Based on data from non-clinical studies and five clinical studies, cobitolimod is safe and well tolerated in the treatment of UC.
In the completed phase IIb study, CSUC-01/16 CONDUCT, significantly more patients who received two administrations of cobitolimod 250 mg (2x 250 mg) 3 weeks apart achieved clinical remission at I-week 6 compared with patients who received placebo. The results in several clinically relevant secondary endpoints supported the efficacy of the 2 x 250 mg dose, which was the highest dose of cobitolimod used in the study.
The full phase III programme for cobitolimod in the treatment of moderate to severe UC will include two induction studies (induction 1 and induction 2 study) and one maintenance study. The first protocol (this protocol) will cover the induction 1 study and the maintenance study. The second induction study (induction 2 study) will be developed as a separate protocol. The maintenance study will include participants from both the induction 1 and induction 2 studies.
In the current phase III study, CSUC-01/21 CONCLUDE, the 250 mg dose (administered twice 3 weeks apart) has been selected for induction treatment based on its demonstrated efficacy in the CSUC-01/16 CONDUCT study. However, since the demonstrated efficacy was observed for the highest dose of cobitolimod used in that study, it is possible that a dose higher than 250 mg could provide additional efficacy. Therefore, a 500 mg dose (administered twice 3 weeks apart) will be explored as an additional active study arm for induction treatment in this study in an adaptive design. The selection of the cobitolimod 500 mg dose is justified by previous safety data and toxicology studies. The two active dose arms will be evaluated for induction treatment in induction study 1 whereby only the *winning dose* will be continued after the interim analysis and evaluated for confirmatory efficacy versus placebo at I-week 6. Participants in both active dose arms will be evaluated for safety.
Participants responding to the winning dose at I-week 6 will be re-randomised to maintenance treatment with the winning dose or with placebo.

Study objective

Study Objectives:
Primary Objective: Induction
To evaluate the efficacy of cobitolimod treatment compared to placebo in inducing clinical remission, in participants with moderate to severe active left-sided UC.
Secondary Objectives: Induction
• To evaluate the safety and tolerability of cobitolimod compared to placebo.
• To evaluate the efficacy of cobitolimod treatment compared to placebo in clinical symptoms, endoscopy and histology endpoints.
• To evaluate the efficacy of cobitolimod treatment compared to placebo in other secondary endpoints.
Exploratory Objectives: Induction
• To explore the efficacy of cobitolimod treatment compared to placebo in other exploratory endpoints.
Primary Objective: Maintenance
To evaluate the efficacy of cobitolimod maintenance treatment compared to placebo in inducing or maintaining clinical remission, in participants with clinical response at I-week 6 after induction treatment with cobitolimod.
Secondary Objectives: Maintenance
• To evaluate the safety and tolerability of cobitolimod compared to placebo.
• To evaluate the efficacy of cobitolimod maintenance treatment compared to placebo in clinical symptoms, endoscopy and histology endpoints.
• To evaluate the efficacy of cobitolimod maintenance treatment compared to placebo in other secondary endpoints.
• To evaluate HRQoL and health economics.
Exploratory Objectives: Maintenance
To explore the efficacy of cobitolimod maintenance treatment compared to placebo in other efficacy endpoints.

Study design

Study Design:
This phase III protocol includes an induction and a maintenance study. These are randomised, double-blind, placebo-controlled, parallel-group, multicentre studies of cobitolimod in participants with moderate to severe active left-sided UC who demonstrate an inadequate response to or intolerance of conventional, biological (infliximab, adalimumab, golimumab, vedolizumab, ustekinumab), JAK-inhibitor (tofacitinib) or other approved advanced therapy for UC.
Induction Study
Induction study 1 will have an adaptive design in two stages. Stage 1 will explore the efficacy of two different doses of cobitolimod, 250 mg and 500 mg, with placebo as a control. In stage 2, the study will drop-the-loser and continue with the winning dose of cobitolimod. The primary objective of the

induction study is to confirm a superior efficacy compared to placebo of the winning dose of cobitolimod.
In stage 1, participants will be randomly assigned in a 1:1:1 allocation to receive two rectal doses (3 weeks apart) of cobitolimod 250 mg, cobitolimod 500 mg, or placebo. When 44 participants in each arm have eligible efficacy data for the primary endpoint at I-week 6, an interim analysis will be performed. This will give guidance which dose (cobitolimod 250 mg or 500 mg) will be dropped, and which dose will be used in stage 2 of this induction study.
The interim analysis will also include a futility analysis.
In stage 2, additional 154 participants per remaining arm will be recruited and randomly assigned in a 1:1 allocation to the winning dose of cobitolimod or to placebo. Existing participants in the losing dose cobitolimod dose arm will be followed up for safety but will not be included in the final efficacy evaluation at I-week 6.
Randomisation in stage 1 and stage 2 will be stratified for concomitant use of GCS treatment and for previous treatment with biologics, JAK-inhibitors or other approved advanced therapy. Induction study clinic visits will take place at screening, I-week 0, I-week 3 and I-week 6. A full colonoscopy will be done during screening, with a maximum of 10 days between colonoscopy and randomisation. At I-week 6 a flexible sigmoidoscopy will be performed. Endoscopies will be centrally read.
Participants will self-administer the study drug at clinic under supervision of study staff, to ensure that participants can manage to self-administer the study drug at home during the maintenance study.
Maintenance Study
Participants who achieve clinical response at I-week 6 after starting induction treatment will be eligible for the maintenance study. Clinical response is defined by a decrease in the 3-component Mayo score (rectal bleeding, stool frequency, and endoscopy) of at least two (2) points and at least 35% from I-week 0 with either a decrease in the rectal bleeding subscore of at least one (1) point or a rectal bleeding subscore of 0 or 1. Eligible participants (I-week 6 responders) will be re-randomised in a 1:1 allocation to the winning dose of cobitolimod or to placebo, administered once every 3 weeks.
Participants who were treated with placebo or the losing dose in the induction study who meet the responder*s criterion at I-week 6 assessment will continue into the maintenance study but will be excluded from the efficacy analysis.
At least 250 responders to the winning dose of cobitolimod will be enrolled into the maintenance study from the induction 1 study and the subsequent induction 2 study (which is outside the scope of this protocol).
Participants in the maintenance study will be scheduled for clinic or virtual visits at M-weeks 0, 7, 15, 23, 31, 39 and 45 (see SoA).
At the first administration occasion in the maintenance study (following re-randomisation), the study intervention will be self-administered at the clinic by the participant under supervision of study staff. During all subsequent administration occasions, the study intervention will be self-administered by the participant at home every third week.
Evaluation and follow-up of participants will be performed at all visits. If

the participant*s disease deteriorates or does not improve, it is at the discretion of the investigator to judge if an alternative treatment is needed, and if so to take the necessary action.

Intervention

Investigational Therapy and Treatment:
In the induction study 1, cobitolimod 250 mg or 500 mg or placebo will be self-administered with a rectal enema at I-week 0 and I-week 3, under supervision of study staff.
The first dose of study intervention in the maintenance study (M-week 0) will be self-administered at clinic under supervision of study staff. All subsequent doses will be self-administered at home.
The primary endpoint for induction will be assessed after 6 weeks. The primary endpoint for maintenance will be assessed after 46 weeks of maintenance treatment (approximately 52 weeks from induction study, I-week 0).
Safety evaluation and disease monitoring will be performed at each visit after the first dose.

Reference Therapy:
Placebo is the same aqueous solution as the drug product apart from cobitolimod.

Study burden and risks

Abdominal Pain 2.4%
Headache 11.3%
Anaemia/Haemoglobin decreased 4.6%
Haemorrhoids 1.2%
Arthralgia (joint pain) 1.2%
Nausea 2.2%
Blood in urine 2.2%
Protein in urine 1.4%
Common Cold/Upper Respiratory Infections 7.7%
Fever 3.1%
CRP increased (blood test marker for inflammation in the body) 1.7%
Rash 2.9%
Diarrhoea 1.2%
Ulcerative Colitis, Worsening 7.7%
Dyspepsia (upset stomach) 1.9%
Vomiting 1.2%

If new information about side effects for the study drug becomes known, you will be informed about them.

You can experience the following discomforts from the study procedures:

• Taking blood samples: This involves a needle prick which can feel unpleasant and painful and can lead to a transient bruise, dizziness, and rarely haematoma, infections, and nerve damage.
• Endoscopy and biopsies: Possible complications include infection, perforation (piercing or tearing) of the bowel or excessive bleeding.
You can feel discomfort during and for a little bit after the procedure as air is inflated, and water is flushed for better visibility during the examination.
• Investigational treatment administration: you can feel discomfort during and for a little bit after the administration of the enema.
• ECG: Patches may cause skin reactions such as redness, itching and hair loss associated with the placement of the ECG electrodes.

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

Inclusion Criteria: Induction
1. Male or female >= 18 years of age.
2. Established diagnosis of UC, with minimum time from diagnosis of at least 3 months before screening visit 1b.
3. Moderate to severe active left-sided UC (disease should extend 15 cm or more above the anal verge and not beyond the splenic flexure) determined by a 3-component Mayo score of 5 to 9 with an endoscopic subscore >=2 (in sigmoid or descending segments) assessed by central reading of endoscopy, and with stool frequency and rectal bleeding subscores, assessed by eDiary, each >=1.
4. Have inadequate response, loss of response or be intolerant of at least one of the following treatments:
a. Oral GCS
b. AZA/6-MP
c. Biologics, JAK-inhibitors, or other approved advanced therapies for UC
5. Allowed to receive a therapeutic dose of the following UC drugs during the study:
a. Oral GCS therapy (<=20 mg prednisone or equivalent/day) provided that the dose has been stable for 2 weeks prior to visit 1b, or oral Budesonide MMX® therapy (9 mg/day) initiated at least 8 weeks before visit 1b, provided that the dose has been stable for 2 weeks prior to visit 1b.
b. Oral 5-ASA/SP compounds, provided that the dose has been stable for 2 weeks prior to visit 1b and initiated at least 8 weeks before visit 1b.
c. AZA/6-MP provided that the dose has been stable for 8 weeks prior to visit 1b and initiated at least 3 months before visit 1b.
6. Ability to understand the treatment, willingness to comply with all study requirements, and ability to provide informed consent.

Inclusion Criteria: Maintenance
Participants are eligible to be included in the maintenance study if they have achieved clinical response at I-week 6 and have adhered to the protocol procedures of the induction study.
Clinical response is defined by a decrease in the 3-component Mayo score (rectal bleeding, stool frequency, and endoscopy) of at least two (2) points and at least 35% from I-week 0 with either a decrease in the rectal bleeding subscore of at least one (1) point or a rectal bleeding subscore of 0 or 1.

Exclusion criteria

Exclusion Criteria: Induction
1. Suspicion of differential diagnosis such as Crohn*s enterocolitis, ischaemic colitis, radiation colitis, indeterminate colitis, infectious colitis, diverticular disease, associated colitis, microscopic colitis, massive

pseudopolyposis or non-passable stenosis.
2. Acute fulminant UC, toxic megacolon and/or signs of systemic toxicity.
3. UC limited to the rectum (disease extending <15 cm above the anal verge) or extending beyond the splenic flexure.
4. Have failed treatment with more than three advanced therapies (infliximab, adalimumab, golimumab, vedolizumab, ustekinumab or tofacitinib) of two different therapeutic classes (anti-TNF, anti-integrins, anti-IL12/23, JAKinhibitors, or other approved advanced therapies for UC).
5. Have had surgery for treatment of UC.
6. History of malignancy, unless treated with no relapse of the disease and >= 5 years since last treatment (cured) or treated (cured) basal cell or squamous cell in situ carcinoma.
7. History or presence of any clinically significant disorder that, in the opinion of the investigator, could impact on the participant*s ability to adhere to the protocol and protocol procedures, or would confound the study result or compromise participant safety.
8. Concomitant treatment with cyclosporine, methotrexate, tacrolimus, or advanced therapies such as infliximab, adalimumab, golimumab, vedolizumab, ustekinumab or tofacitinib, or similar immunosuppressants and immunomodulators at enrolment.
Any prior treatment with such drugs must have been discontinued at least 8 weeks prior to visit 1b (except for ustekinumab, which must have been discontinued at least 12 weeks prior to visit 1 b) or have non-measurable serum concentration levels.
9. Treatment with rectal GCS, 5-ASA/SP or tacrolimus within 2 weeks before visit 1b.
10. Long-term treatment (>14 days) with antibiotics or NSAIDs within 2 weeks prior to visit 1b (one short treatment regimen for antibiotics, occasional use of NSAIDs and low dose NSAIDs as prophylactic therapy is allowed).
11. Serious known active infection including history of latent or active tuberculosis, documented history of past or current tuberculosis, or living with or having frequent close contact with people with active tuberculosis or with a positive tuberculosis test according to current regulations for 12 weeks preceding randomisation. Serious infections include, but is not limited to, HIV, HBV, or HCV infections.
12. Gastrointestinal infections including positive Clostridium difficile stool assay. (Local laboratory reports must be available in accordance with normal clinic practice, to confirm that the current episode of disease exacerbation is not due to infection).
13. Females who are lactating or have a positive serum pregnancy test during the screening period.
14. Women of childbearing potential not using highly effective (failure rate < 1%) contraceptive methods throughout the duration of the study.
15. Concurrent participation in another clinical study with investigational therapy or previous use of investigational therapy within 5 half-lives and within at least 30 days after last treatment of the experimental product prior to enrolment.

16. Previous exposure to cobitolimod

Exclusion Criteria Maintenance:
Participants will not be eligible for the maintenance study if they are not willing to comply with all further study requirements.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-08-2022
Enrollment:	5
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	cobitolimod
Generic name:	cobitolimod

Ethics review

Approved WMO

Date:	28-04-2022
Application type:	First submission

Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	11-10-2022
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	31-10-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	12-09-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	07-11-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2021-002549-13-NL
CCMO	NL80916.091.22