

NCT04985968

CLINICAL STUDY PROTOCOL

Protocol Title: 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

Protocol Number: CSUC-01/21

Compound: Cobitolimod

Phase: III

Acronym: CONCLUDE

Study Sponsor: InDex Pharmaceuticals

Protocol Version: 2.1

Version Date: 09JUN2021

EudraCT Number: 2021-002549-13

IND number: 119141

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[REDACTED]

Statement of Compliance

This study will be conducted in accordance with this Clinical Study Protocol CSUC-01/21 version 2.1, dated 09JUN2021.

No participant may enter the study until approvals have been obtained from Regulatory Authorities and IRB/IECs. Any changes to the protocol will be handled as protocol amendments and if there are substantial changes the amendment will be submitted to the Regulatory Authorities and IRB/IECs for approval.

The study will be conducted, in accordance with the following:

- Declaration of Helsinki (Fortaleza, Brazil, October 2013).
- Good Clinical Practice of the European Community/International Conference on Harmonization (CPMP/ICH/135/95 including e.g., E6 and E8).
- European Clinical Trial Directive 2001/20/EC (EudraLex Vol 10, including e.g. CT-1) and Food and Drug Administration Regulations (e.g., 21 CFR Part 312).
- Respective local laws and regulations.
- Regulatory requirements for reporting of serious adverse events.

Date: _____

Date: _____

Signature Page

The signature below constitutes that I have read and agreed to protocol CSUC-01/21 version 2.1, dated 09JUN2021. I am aware of my responsibilities as an investigator under Good Clinical Practice (GCP), Helsinki Declaration, European Clinical Trials Directives, Food and Drug Administration (FDA) and local regulations (as applicable) and the study protocol.

I agree to conduct the study according to the guidelines mentioned above, and I am aware of my responsibilities to keep the staff that have been delegated to work on the study informed and educated so that they can perform the study according to protocol and guidelines.

I am aware that quality controls can occur during the study, such as monitoring, audit and inspections.

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List of Abbreviations

Abbreviation	Definition
5-ASA	5-aminosalicylate
6-MP	6-mercaptopurine
ADR	adverse drug reaction
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ASAS	all screened analysis set
AST	aspartate aminotransferase
AZA	azathioprine
BP	blood pressure
BUN	blood urea nitrogen
CAI	clinical activity index
CONCLUDE	cobitolimod novel concept for left-sided ulcerative colitis disease evaluation study
CPK	creatine phosphokinase
CRO	contract research organisation
CRP	C-reactive protein
CSR	clinical study report
CSUC	clinical study ulcerative colitis
CD	Crohn's disease
DBL	database lock
DMC	data monitoring committee
DMP	data management plan
DNA	deoxyribonucleic acid
ECG	electrocardiogram
EDC	electronic data capture
eCRF	electronic case report form
EQ-5D-5L	Euroqol-5D-5L health questionnaire
ET	early termination
EU	European Union
FAS	full analysis set
FASM	full analysis set maintenance
FCP	faecal calprotectin
FDA	Food and Drug Administration

Abbreviation	Definition
GCS	glucocorticosteroids
GGT	gamma-glutamyl transpeptidase
GCP	good clinical practice
HBV	hepatitis B virus infection
HCV	hepatitis C virus infection
HIV	chronic human immunodeficiency virus
HR	heart rate
HRQoL	health-related quality of life
I	induction
IAP	interim analysis plan
IB	investigators brochure
IBD	inflammatory bowel disease
IBDQ	inflammatory bowel disease questionnaire
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IL	interleukin
IRB	institutional review board
ITT	intention-to-treat
JAK	Janus kinase
LFT	liver function test
M	maintenance
MCP	multiple comparison procedure
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	no observed adverse effect level
NSAE	non-serious adverse event
NSAID	non-steroidal anti-inflammatory drugs
NRI	non-responder imputation
ODN	oligodeoxyribonucleotide
OR	odds ratio
PE	polyethylene
PD	protocol deviation
PI	principal investigator
PGA	physician's global assessment
PMI	placebo multiple imputation
PPAS	per protocol analysis set
PPASM	per protocol analysis set maintenance

Abbreviation	Definition
PRO	patient-reported outcome
RA	regulatory authorities
RBC	red blood cells
RHI	Robarts histology index
RNA	ribonucleic acid
rINN	recommended international nonproprietary name
RTSM	randomisation and trial supply management
SAE	serious adverse event
SAF	safety analysis set
SAFM	safety analysis set maintenance
SAP	statistical analysis plan
SoA	schedule of activities
SOP	standard operating procedures
SP	sulphasalazine
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TLR9	Toll-like receptor 9
TPMT	thiopurine methyltransferase
TNF α	tumour necrosis factor (alpha)
UC	ulcerative colitis
US	United States
VAS	visual analogue scale
WBC	white blood cells

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Clinical Study Synopsis

CSUC-01/21

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The information in this CLINICAL STUDY SYNOPSIS is property of InDex Pharmaceuticals. It is provided confidentially and should only be disclosed to persons or organisations responsible for execution of the study. You agree to hold such information in confidence and not disclose it to others (except where required by applicable law) nor use for unauthorised purposes.

Synopsis

Name of the Sponsor/Company: InDex Pharmaceuticals AB
Name of Active Ingredient/Product: Cobitolimod
Study Code: CSUC-01/21
Acronym: CONCLUDE
A Phase III 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
Phase of Development: Phase III
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 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:

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.

Selection of Participants:

Inclusion Criteria: Induction

Participants are eligible for inclusion in the study only if all the following criteria apply:

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.

Exclusion Criteria: Induction

Participants are excluded from the study if any of the following criteria apply:

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 pseudopolypsis 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, JAK-inhibitors, 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 $\geq$ 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.

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 Maintenance

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

Planned Study Size:

In stage 1 of the induction 1 study, 44+44+44 participants will be assigned to cobitolimod 250 mg, cobitolimod 500 mg, or placebo. A total of 132 participants will provide reasonable precision in the estimates of posterior probabilities to guide the selection of the winning cobitolimod dose for further allocation and final evaluation in this induction study.

In stage 2, an additional 154+154 participants will be allocated in a 1:1 randomisation to the cobitolimod winning dose or to placebo. The final evaluation for confirmatory efficacy at I-week 6 will compare the cobitolimod winning dose to placebo. Therefore, the power

calculation for the induction 1 study is based on a Chi-square test comparing two treatment arms.

Induction

The goal is to have at least 90% power, with a type I error rate of 0.05, to detect a clinically relevant difference of at least 12 percentage points for the primary endpoint of clinical remission at I-week 6 between cobitolimod and placebo, assuming a placebo clinical remission rate of 10%.

The target is to recruit at least 198 participants to the winning dose of cobitolimod, and at least 198 participants to placebo (total 396 participants), to satisfy the power goal.

Maintenance

Sample size and power calculations are based on the Chi-square test to detect a significant ($p < 0.05$) difference for the primary endpoint of clinical remission at M-week 45 between two study treatment arms, cobitolimod (winning dose) and placebo.

The goal is to have at least 90% power with a type I error rate of 0.05 to detect a clinically relevant difference of at least 20 percentage points between cobitolimod and placebo, assuming a placebo clinical remission rate at M-week 45 of 25%.

In total 236 participants (118 per treatment arm) are needed to satisfy the power goal. The target is to recruit at least 250 participants in total from the induction 1 and induction 2 studies.

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.

Concomitant Therapy:

Participants may receive a therapeutic dose of the following concomitant therapies:

- Oral GCS therapy (≤ 20 mg prednisone or equivalent/day) provided that the dose has been stable for 2 weeks prior to visit 1b and is kept stable up to the primary endpoint of the induction study (I-week 6), or oral Budesonide MMX® therapy (9 mg/day) initiated at least 8 weeks before screening visit

1b provided that the dose has been stable for 2 weeks prior to visit 1b and is kept stable up to the primary endpoint of the induction study (I-week 6). Tapering should start after the I-week 6 visit if the participant is in response.

- Oral 5-ASA and/or 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. The dose should be kept stable up to the end of the maintenance study (M-week 45).
- 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. The dose should be kept stable up to the end of the maintenance study (M-week 45).

During the study, concomitant treatment with immunomodulators such as cyclosporine, tacrolimus and methotrexate, biologics such as infliximab, adalimumab, golimumab, vedolizumab and ustekinumab, JAK-inhibitors, such as tofacitinib or other approved advanced therapy for UC is not allowed. These therapies must have been stopped (due to inadequate response, loss of response or intolerance) at least 8 weeks prior to visit 1b (except for ustekinumab, which must have been discontinued at least 12 weeks prior to visit 1b) *or* have non-measurable serum concentration levels. Use of rectal formulations of GCS, rectal 5-ASA/SP or tacrolimus is not allowed during the study and should have been stopped at least 2 weeks prior to visit 1b.

Outcome Measurements:

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.

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).

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.

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

Statistical Methods:

Planned Interim Analysis

In the induction study, an interim analysis will be performed after approximately 44 participants per treatment arm have been recruited and have completed the I-week 6 visit. The purpose of the interim analysis is to select the winning dose that will be used for treatment allocation throughout the rest of the study and evaluated for efficacy versus placebo for superiority. The primary efficacy endpoint will be tested for futility.

The DMC will perform the comparison for each active treatment dose compared to placebo for the primary and secondary endpoints. The efficacy results will be balanced against safety findings when selecting the winning dose.

No further interim analysis is planned.

Study Population

Induction Study:

For the induction study, the FAS will be based on ITT principles and will consist of all randomised participants who meet the inclusion criteria and none of the exclusion criteria and receive at least one dose of study drug (active or placebo).

The PPAS is defined as FAS participants who do not have major protocol deviations considered to have a major effect on the primary efficacy endpoint, and who have completed the 3-component Mayo subscores assessment to derive the primary endpoint at I-week 6.

The safety population is defined as all participants included in the study and treated with at least one dose of study drug.

Maintenance Study:

For the maintenance study the FASM will be based on all randomised participants. In addition, the PPASM will include all FASM participants with no major protocol deviations.

Primary Efficacy Analysis

Induction:

The primary analysis of the primary endpoint is based on the FAS population and will be performed using logistic regression adjusting for randomisation strata GCS use at I-week 0 and prior use of biologics or JAK-inhibitors. Key secondary endpoints will be analysed using the same principles.

The testing procedure will be controlled using the overall type I error rate of 0.05 with a two-sided test. Adjustment for multiplicity will be done in the key secondary endpoints.

Maintenance:

The primary analysis of the primary endpoint is based on the FASM population and will be performed using logistic regression adjusting for randomisation strata, clinical remission at I-week 6 (Yes/No) and GCS use at I-week 6 (Yes/No). Key secondary endpoints will be analysed using the same statistical approach.

The testing procedure will be controlled using the overall type I error rate of 0.05 with a two-sided test. Adjustment for multiplicity will be done in key secondary endpoints.

Safety:

Safety data will be evaluated using descriptive statistics.

- AEs: Number, frequency, and severity.
- Changes in safety variables, such as laboratory measurements and vital signs, are evaluated at every clinic visit.
- Changes in concomitant medication are recorded at each visit.

Data Monitoring Committee

The DMC will evaluate safety and efficacy data during the study and make recommendations to the sponsor to continue, modify or stop the study. The DMC will also review the interim analysis results from stage 1 of the induction study and make a recommendation to the sponsor on the winning dose of cobitolimod.

Schedule of Activities

Table 1. SoA Induction Study

Study Procedures	Screening		Baseline/Treatment	Treatment	Endpoint
	Visit 1a	Visit 1b	Visit 2	Visit 3	Visit 4a
Guiding principles for visit scheduling ¹		max -10 days before randomisation	I-Week 0 I-Day 1/ randomisation	I-Week 3 I-Day 21 +/- 5 days	I-Week 6 I-Day 42 +/- 5 days
Informed Consent	X				
Review Inclusion/Exclusion Criteria ²	X		X		
Randomisation ²			X		
Demographic, Tobacco History/Use and Medical History ^{3,4}	X				
Prior and Concomitant Therapies ⁵	X				
Vital Signs ⁶	X		X	X	X
Physical Examination ⁷	X		X	X	X
Laboratory:					
-Haematology ⁸	X		X	X	X
-Blood Chemistry including CRP ⁹	X		X	X	X
-Faecal Calprotectin ¹⁰	X		X	X	X
-Pregnancy Test ¹¹	X		X	X	
Biomarkers					
-Serum Protein ¹²			X	X	X
-Mucosal biopsy ¹²		X			X
ECG ¹³	X				
Endoscopy ¹⁴					
-Full Colonoscopy + mucosal biopsy		X			
-Flex Sigmoidoscopy + mucosal biopsy					X
-Mayo Endoscopic subscore ¹⁵		X			X
eDiary instructions ¹⁶	X				
Assessments:					
-eDiary compliance ¹⁶		X	X	X	X
-PGA ¹⁷			X		X
-IBDQ ¹⁸			X		X
-EQ-5D-5L ¹⁸			X		X
Adverse Event (AE) ¹⁹		X	X	X	X
Extraintestinal Manifestation ²⁰			X		X
Study Intervention administration ²¹			X	X	

1. Visit window is provided for guidance (and is not an automatic reason for a PD). However, 10 days should be adhered to as the maximum of days between endoscopy and randomisation. The day for visits 3 and 4a should always be calculated from day 1, even if +/- was used the visit before.
2. Inclusion/exclusion criteria will be reviewed at screening visit and again before randomisation to ensure that all collected data e.g., laboratory data, Mayo subscores and potential new symptoms still fulfil the inclusion criteria and do not fulfil any criteria for exclusion.
3. Date of birth, gender, race, height (cm), weight (kg). Tobacco history and/or tobacco use will be collected.
4. Medical History (including UC history) is to include start year of each diagnosis and also the entire screening period, until just prior to the first dose of study intervention, with the exception of AEs related to study procedures. The UC history is to include duration of disease, duration of current flare, number of flares/year and participant's normal number of stools/day when in remission. Post Menopause should be reported on Medical history for post-menopausal women.
5. All non-UC treatment used in the last 8 weeks before screening visit 1b should be recorded with generic name, start and stop date. All UC drug history should be reported with dose, start and stop date (unless treatment is ongoing) for only the last treatment period for each compound, to ensure inclusion criteria 4 and 5 are fulfilled and that exclusion criteria 4, 8 and 9 are not fulfilled. All concomitant medication taken should be reported at each visit; if there are changes ensure no overlaps in dates are reported.
6. Blood pressure and heart rate at every visit (except visit 1b); height and weight only at visit 2.
7. The following system organ classes will be reviewed for any relevant findings and appropriate physical examinations should be performed: general appearance, skin, musculoskeletal, eyes, ears, nose, throat, thyroid, cardiovascular, chest, abdomen, lymph nodes and neurological examination. Clinically significant findings will be reported as medical history prior to first dose of study intervention and thereafter as an AE (preferably a diagnosis term).
8. Haemoglobin, haematocrit, platelet count, RBC, WBC, neutrophil, eosinophil, basophil, lymphocyte and monocyte count in non-fasting samples. Abnormal values that are reported as clinically significant findings (i.e., if the abnormality leads to investigation/action) will be reported as an AE.
9. Albumin, ALP, ALT, AST, BUN, calcium, chloride, CPK, CRP, creatinine, GGT, glucose, phosphate, potassium, sodium, total bilirubin and total protein, in non-fasting samples. Abnormal values that are reported as clinically significant findings (i.e., if the abnormality leads to investigation/action) will be reported as an AE.
10. Morning stool should be used for faecal calprotectin sample; participant should preferably take sampling material home from clinic to be able to collect the next sample on morning stool. For screening visit, participant should preferably take sampling material home so they can provide stool sample at the earliest possible day after the visit.
11. Only for females of childbearing potential, with serum pregnancy test at screening visit 1a and dip-stick tests before each administration of study intervention. Female participants of childbearing potential must have a negative urine pregnancy test prior to receiving each dose of study intervention. If the pregnancy test is positive no further treatment should be administered, and the pregnancy should be considered as an AE.
12. Serum protein samples and colon biopsies will be collected for biomarker analysis. Serum protein samples will only be collected from participants in induction study stage 2.
13. A 12 lead ECG should be done before randomisation, preferably at visit 1a.
14. A full colonoscopy is required during the screening period, and flexible sigmoidoscopy at the primary endpoint (I-week 6). Videos will be sent for central reading and biopsies collected for histopathological grading and biomarker assessment. Four (4) biopsies should be taken from the most inflamed area in sigmoid colon (see protocol section 8.10; separate instructions will be provided). The Mayo endoscopic subscore from local and central reading will be used to determine eligibility; if not in agreement, adjudication reading will be performed.
15. Mayo subscore of endoscopy at I-week 0 and I-week 6 will be based on the centrally read endoscopic subscore for the endoscopy performed during the screening period and at I-week 6.
16. Participant will be prompted to fill in the eDiary daily from screening to I-week 6. Participant should be instructed how to use the eDiary at visit 1a, and compliance monitored during entire study.
17. Physician will assess the PGA at I-week 0 and 6.
18. IBDQ and EQ-5D-5L questionnaires should be filled in by participant.
19. Participant will be questioned about AEs at each clinic visit. Only AEs related to study specific procedures during screening visit will be recorded at visit 1a, 1b and 2.
20. There will be questions regarding extraintestinal manifestation disease/symptoms asked at visit 2 and visit 4a.
21. The study intervention will be self-administered by participant under supervision of site staff. Participant should stay recumbent for at least 30 minutes after administration.

Table 2. SoA Maintenance Study

Study Procedures	Visit #	Treatment period						Endpoint
		Visit 4b ²³	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10/ET
		Week 7	Week 14	Week 22	Week 30	Week 38	Week 46	Week 52
		M-Day 1 M-Week 0	M-Week 7	M-Week 15	M-Week 23	M-Week 31	M-Week 39	M-Week 45
	Type of visit	Clinic visit	Virtual visit	Clinic visit	Virtual visit	Clinic visit	Virtual visit	Clinic visit
	Guiding principles for visit scheduling ²²	21-30 days ²³ after I-Week 3	+/- 7 Days	+/- 7 Days	+/- 7 Days	+/- 7 Days	+/- 7 Days	+/- 7 Days
Review Inclusion/Exclusion Criteria ²⁴		X						
Re-Randomisation ²⁴		X						
Tobacco Use								X
Vital Signs ²⁵				X		X		X
Physical Examination ²⁶				X		X		X
Concomitant Medication ²⁷			X	X	X	X	X	X
Laboratory:								
-Haematology ²⁸				X		X		X
-Blood Chemistry including CRP ²⁹				X		X		X
-Faecal Calprotectin ³⁰				X				X
-Pregnancy Test ³¹		X						
Biomarkers ³³								
-Serum Protein						X		X
-Mucosal biopsy (RNA and histology)								X
Endoscopy ³³								
-Flex sigmoidoscopy + mucosal biopsy								X
-Mayo Score								X
eDiary instructions ³⁴		X						
Assessments:								
-eDiary compliance ³⁴			X	X	X	X	X	
-PGA ³⁵								X
-IBDQ ³⁶				X				X
-EQ-5D-5L ³⁶				X				X
Adverse Event (AE) ³⁷		X	X	X	X	X	X	X
Extraintestinal Manifestation ³⁸				X		X		X
Study Intervention Dispensing ³⁹		X		X		X		
Study Intervention Administration ⁴⁰		X						

22. Visit window is provided for guidance (and is not an automatic reason for a PD) but is preferably followed. The visit window in the maintenance study is calculated from day 1 of maintenance study (M-Day 1).
23. Visit 4b should occur as soon as participant eligibility has been confirmed.
24. Inclusion/exclusion criteria will be reviewed when central reading result has been obtained. If participant fulfils all criteria, a re-randomisation will commence.
25. Blood pressure and heart rate at visit 6, 8 and 10.
26. The following system organ classes will be reviewed for any relevant findings and appropriate physical examinations should be performed: general appearance, skin, musculoskeletal, eyes, ears, nose, throat, thyroid, cardiovascular, chest, abdomen, lymph nodes and neurological examination. Clinically significant findings will be reported as an AE.
27. All concomitant medication taken should be reported at each visit and start and stop dates recorded.
28. Haemoglobin, haematocrit, platelet count, RBC, WBC, neutrophil, eosinophil, basophil, lymphocyte, and monocyte count in non-fasting samples. Abnormal values that are reported as clinically significant findings (i.e., if the abnormality leads to investigation/action) will be reported as an AE.
29. Albumin, ALP, ALT, AST, BUN, calcium, chloride, CPK, CRP, creatinine, GGT, glucose, phosphate, potassium, sodium, total bilirubin and total protein, in non-fasting samples. Abnormal values that are reported as clinically significant findings (i.e., if the abnormality leads to further investigation/action) will be reported as an AE.
30. Morning stool should be used for faecal calprotectin sample.
31. Only for females of childbearing potential. Urine dip-stick tests before each study intervention administration. Female participants of childbearing potential must have a negative urine pregnancy test prior to receiving each dose of study intervention. If the pregnancy test is positive no further treatment should be administered, and the pregnancy should be considered as an AE.
32. Serum protein samples and colon biopsies will be collected to be used for biomarker analysis.
33. Flexible sigmoidoscopy at primary endpoint for the maintenance study, M-week 45. Videos will be sent for central reading and biopsies collected for histopathological grading and biomarker assessment. Four (4) biopsies should be taken from the most inflamed area in sigmoid colon (see protocol section 8.10; separate instructions are provided).
34. Participant will be prompted to complete the e-dairy during the 10 days prior to each maintenance visits. Participant should be re-instructed how to use the eDiary if they are not compliant.
35. Physician will assess the PGA at M-week 45.
36. IBDQ and EQ-5D-5L questionnaires should be filled in by participant.
37. Participant will be questioned about AEs at each visit.
38. There will be questions to the participant regarding extraintestinal manifestation disease/symptoms.
39. Participant will receive study intervention for 4-5 home administration occasions before leaving clinic.
40. Study intervention for M-week 0 will be self-administered by participant at clinic under staff supervision.

Table 3. Schedule of Treatment Activities:

Treatment Procedure Overall weeks counted from Induction week 0.	Week 0	Week 3	Week 7	Week 10	Week 13	Week 16	Week 19	Week 22	Week 25	Week2 8	Week3 1	Week 34	Week 37	Week 40	Week 43	Week 46	Week 49
Self-administration study intervention ⁴¹	at clinic	at clinic	at clinic	home	home	home	home	home ⁴²	home	home	home	home	home	home	home	home	home
Pregnancy test (home) ⁴³				X	X	X	X	X	X	X	X	X	X	X	X	X	X

41. From week 10 and onwards the study intervention will be self-administered by participant at home. Study intervention should be administered while lying on the left side, and participant should stay recumbent for at least 30 minutes, preferably at bedtime.
42. The study intervention at week 22 should be administered after the actual clinic visit have been performed and the faecal calprotectin sample has been collected.
43. Only for females of childbearing potential. Urine dip-stick tests before each study intervention administration. Female participants of childbearing potential must have a negative urine pregnancy test prior to receiving each dose of study intervention. If the pregnancy test is positive no further treatment should be administered, and the pregnancy should be considered as an AE.

Figure 1. Study Design: Induction

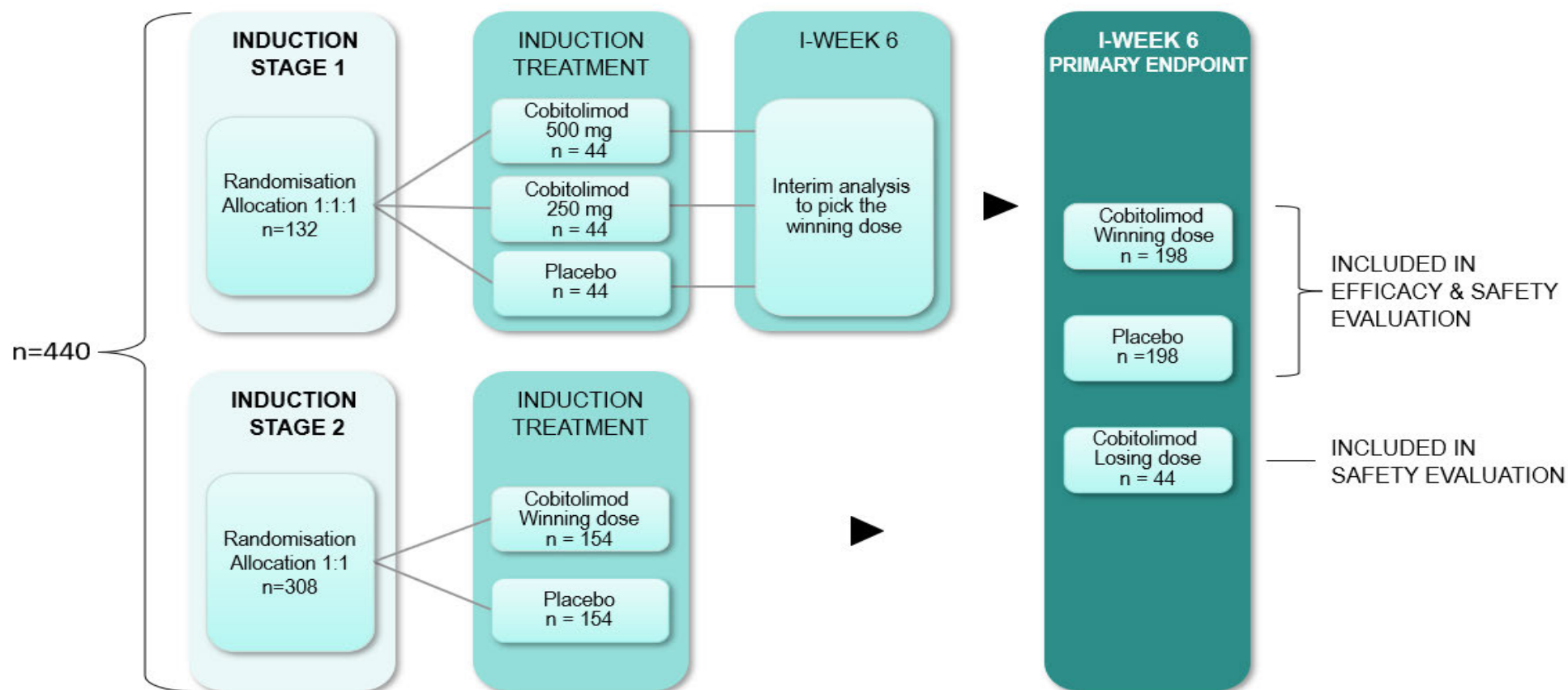
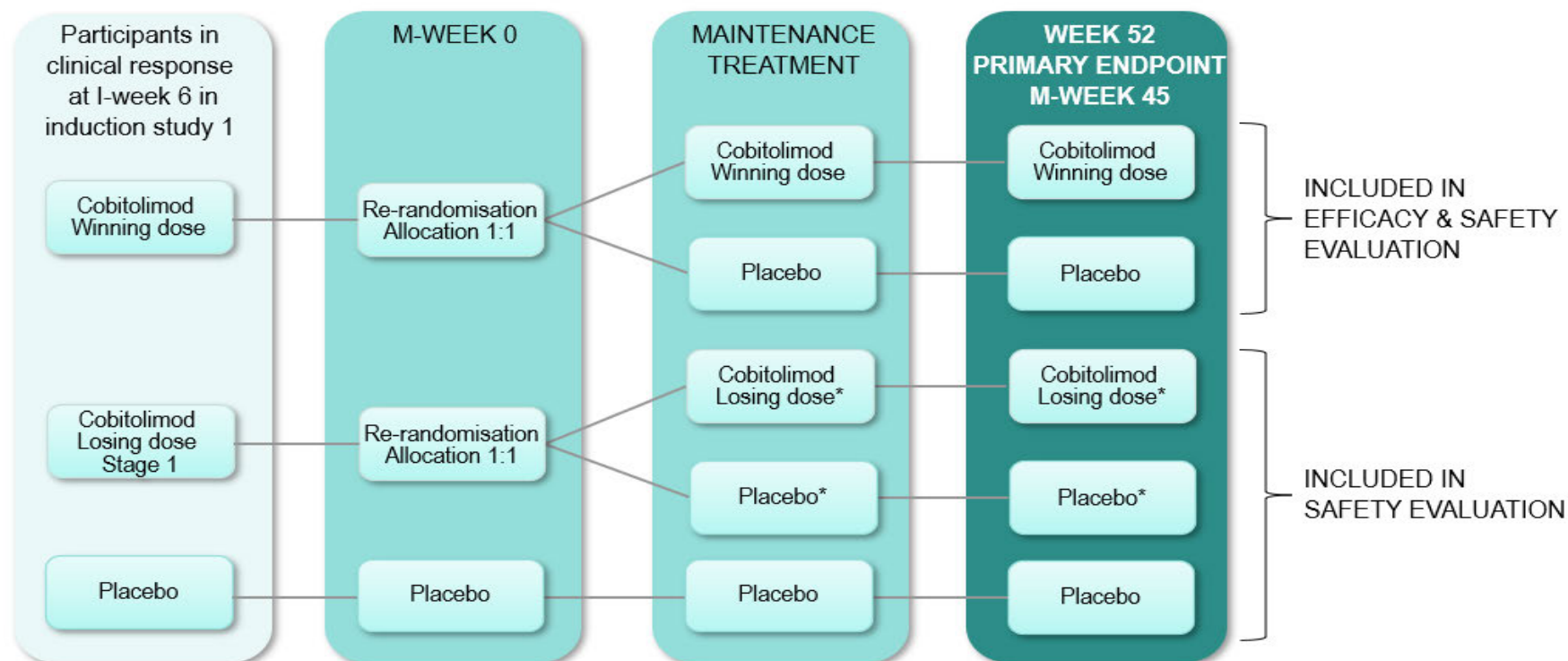


Figure 2. Study Design: Maintenance



**When the winning dose is selected, participants will be switched to the winning dose of cobitolimod.*

Clinical Study Protocol

CSUC-01/21

1 Introduction

Cobitolimod (rINN) is a fully synthetic DNA-based 19-mer ODN. The drug functions as an immunomodulatory agent by targeting the TLR9 present inside 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 IL-10, which are believed to be important for the clinical effect of cobitolimod.

For comprehensive non-clinical and clinical information regarding the efficacy and safety of cobitolimod, **please see the latest version of the IB.**

The full phase III programme for cobitolimod in the treatment of moderate to severe UC will include two induction studies and one maintenance study, where the first protocol (this protocol) will cover the first induction study (induction 1) and the maintenance study. The second induction study (induction 2) will be developed as a separate protocol. The maintenance study will include participants from both induction studies.

1.1 Background

A range of non-clinical safety studies have been conducted with cobitolimod according to good laboratory practice and have shown that cobitolimod is well tolerated with no evidence of systemic or local toxicity.

Cobitolimod has been assessed in a total of five controlled clinical studies and in one named patient use programme. In total, 416 patients with IBD have received at least one dose of cobitolimod.

Cobitolimod was first assessed for clinical efficacy and safety in a small exploratory placebo-controlled, double-blind study in steroid-resistant/dependent patients on concomitant steroid treatment with active left-sided UC or colonic CD. In this study, 11 patients (six with UC and five with CD) were randomised to receive a single rectal administration of 3 mg or 30 mg cobitolimod, or placebo. Clinical (stool frequency and rectal bleeding) and endoscopic evaluation at week 1 indicated a combined response rate of 71% in the cobitolimod-treated patients and 25% in the placebo group.

The second study randomised 151 patients with mild to moderate active left-sided UC. Patients were treated with either a single rectal dose of cobitolimod (0.3, 3, 30 or 100 mg) or placebo. The primary endpoint was induction of clinical remission at any of the follow-up visits during the 12-week study period. Cobitolimod did not show a statistically significant superiority to placebo at any of the four dose levels tested. However, at week 4, a numerically higher proportion of patients in the 30 mg and 100 mg groups had achieved clinical remission than in the lower dose groups and the placebo group.

The third study evaluated clinical response and safety following a single rectal dose of 30 mg cobitolimod or placebo in 34 patients with active left-sided UC. Clinical response rates did not show a statistically significant difference between cobitolimod and placebo. However, at week 1, 41.2% of patients in the cobitolimod-treated group compared with 9.1% in the placebo group had a clinical response. Of the week 1 responders in the cobitolimod group, 85.7% were still

responders at week 4, whereas the week 1 responders in the placebo group had relapsed by week 4. In the cobitolimod group, 11.8% and 17.7% of patients were in clinical remission at week 1 and week 4, respectively, whereas no patients receiving placebo were in clinical remission at these time points.

The fourth study assessed the efficacy and safety of two single doses of cobitolimod (administered at week 0 and week 4) in patients with moderate to severe active treatment refractory UC. 131 patients were treated with cobitolimod 30 mg or placebo applied with a spray catheter during endoscopy. The primary efficacy endpoint was defined as a CAI score ≤ 4 at week 12. There was no statistically significant difference between cobitolimod and the placebo group in the proportion of patients that achieved the primary endpoint (44.4% vs 46.5% respectively). However, secondary endpoints showed statistically significant effects for symptomatic remission at weeks 4 and 8, and for registration remission (defined as CAI score of ≤ 4 and endoscopic Mayo score of 0 or 1) at week 4 [1].

The most recent clinical study, CSUC-01/16 (CONDUCT), assessed the efficacy and safety of cobitolimod induction treatment with different dose levels and frequencies compared to placebo in patients with moderate to severe active left-sided UC. The primary endpoint was the proportion of patients achieving clinical remission at week 6, defined as Modified Mayo subscores of rectal bleeding 0; stool frequency 0 or 1, and endoscopy 0 or 1, excluding PGA. Of the randomised patients, 211 received study treatment administered as a standard enema and were included in the efficacy and safety analyses. Significantly more patients achieved clinical remission at week 6 in the group that received two single doses of 250 mg cobitolimod (at week 0 and week 3) than in the placebo group (21.4% vs 6.8% $p=0.025$). Other cobitolimod dose groups showed no significant difference in clinical remission versus placebo. Results in several clinically relevant secondary endpoints supported the efficacy of the 2x 250 mg cobitolimod dose [2].

Based on the data from non-clinical studies and five clinical studies, cobitolimod is safe and well tolerated in the treatment of UC. No safety signals were detected in the clinical studies with cobitolimod.

In the phase IIb study, CSUC-01/16 CONDUCT, 43% of patients in the cobitolimod 2x 250 mg group experienced at least one TEAE compared with 48% of patients in the placebo group. The most common TEAEs were worsening of UC, viral upper respiratory tract infection, headache and pyrexia.

Additional information on the non-clinical and clinical studies is provided in the IB.

1.2 Study Rationale

UC is a disease characterised by chronic inflammation of the rectal and colonic mucosa [3-5]. The disease is recurrent, with both active (flares) and inactive stages that differ in pathology, symptoms and treatment. The underlying cause of UC is not understood, nor is it known what triggers the disease to recur between its inactive and active forms [6].

Current therapy for UC encompasses the treatment of active disease and the maintenance of remission. Treatment of patients with active UC aims to reduce inflammation and promote colonic healing and mucosal recovery. In many cases the disease can be controlled with conventional drugs including 5-ASA/SP [7] and GCS [8]. Left-sided disease, limited to the rectum and the recto-sigmoid or recto-descending area, is often treated with rectal formulations of 5-ASA and GCS. Maintenance treatment with systemic GCS is not advised owing to the

risks associated with long-term use and lacking efficacy [9]. For patients who become refractory to GCS and suffer from severe or moderately severe attacks of UC, immunomodulatory agents such as AZA/6-MP and cyclosporine are sometimes used. However, immunomodulators are slow-acting and induction of remission in these patients is often temporary [10]. These treatments are now used less frequently than in the past in view of their side-effect profile and toxicity issues when used long term and at high doses.

Treatment options for UC have rapidly expanded in recent years, and now include multiple biologic agents and the small molecule drug tofacitinib in addition to the non-biologic options [5, 11]. However, a significant proportion of patients do not respond to these treatments or lose response to biologics over time. TNF α inhibitors carry potential risks associated with their use, and the JAK-inhibitor tofacitinib has also been associated with serious side effects [12, 13].

There is an enduring unmet need for alternative safe and efficacious treatments with new mechanisms of action.

In the phase IIb clinical study, CSUC-01/16 CONDUCT, the group receiving the highest tested dose of cobitolimod, 2x 250 mg, demonstrated a statistically significant higher efficacy compared to placebo in inducing clinical remission, while the lower dose groups did not demonstrate efficacy compared to placebo.

The rationale for selecting the cobitolimod 250 mg dose in the first induction study in the cobitolimod phase 3 programme is based on its demonstrated efficacy in the CSUC-01/16 CONDUCT study. However, since the efficacy was demonstrated for the highest dose group in that study, it is possible that a higher dose could provide an improved efficacy. Therefore, an even higher dose of cobitolimod, 500 mg, will be explored in humans for the first time as an additional active study arm.

The inclusion of the cobitolimod 500 mg dose is justified by previous safety data and toxicology studies. The two active dose arms will be evaluated in the induction 1 study in an adaptive design, where following an exploratory interim analysis only the winning dose will be continued and evaluated for confirmatory efficacy versus placebo at week 6. Participants on both active doses will be evaluated for safety. In the maintenance study, participants with clinical response to the winning dose at I-week 6 will be re-randomised to the winning dose or to placebo for maintenance treatment through M-week 45.

1.3 Potential Risks and Benefits

The target population for the induction study is participants with moderate to severe active left-sided UC in whom previous treatment with conventional drugs, biologics or tofacitinib has not resulted in adequate response. Results from previous clinical studies show that cobitolimod can induce remission in such participants.

Non-clinical safety studies in rodents and cynomolgus monkey support that cobitolimod is well tolerated, and no evidence of systemic or local toxicity has been found.

Safety assessments from the five placebo-controlled studies with cobitolimod have not identified any safety concerns. No administration issues have been reported with rectal administration of cobitolimod or any issues with drug compliance, and overall cobitolimod has been well tolerated.

The overall clinical experience with cobitolimod, as well as with similar oligonucleotides, would therefore support a positive benefit/risk assessment for cobitolimod when administered according to this protocol to participants with moderate to severe active left-sided UC.

More detailed information on the known and expected benefits and risks, and reasonably expected adverse events of cobitolimod, can be found in the IB.

2 Objectives and Endpoints

For endpoint definition see section 16.5.

2.1 Induction

Objectives	Endpoints
Primary Objective: Induction	Primary Efficacy
To evaluate the efficacy of cobitolimod treatment compared to placebo in inducing clinical remission, in participants with moderate to severe active left-sided UC.	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.
Secondary Objectives: Induction	
To evaluate the safety and tolerability of cobitolimod compared to placebo.	Safety: • incidence of AEs • incidence of SAEs • vital signs • physical examination • laboratory findings
To evaluate the efficacy of cobitolimod treatment compared to placebo in clinical symptoms, endoscopy, and histology endpoints.	Key Secondary Efficacy: • Proportion of participants with endoscopic improvement at I-week 6. • Proportion of participants with symptomatic remission at I-week 6. Other Secondary Efficacy: • Proportion of participants with clinical response at I-week 6. • Proportion of participants with normalisation of stool frequency at I-week 6. • Proportion of participants with absence of rectal bleeding at I-week 6. • Mean stool frequency at I-week 6. • Proportion of participants with histologic improvement at I-week 6.

Objectives	Endpoints
	• Proportion of participants with histologic remission at I-week 6. • Proportion of participants with mucosal healing at I-week 6.
To evaluate the efficacy of cobitolimod treatment compared to placebo in other endpoints.	• Mean ln-transformed faecal calprotectin at I-week 6. • Mean 3-component and 4-component Mayo scores at I-week 6.
To evaluate HRQoL and health economics.	• Mean IBDQ total score at I-week 6. • Proportion of participants with an improvement in IBDQ total score at I-week 6 compared to I-week 0.
Exploratory Objectives: Induction	Exploratory
To explore the efficacy of cobitolimod treatment compared to placebo in other efficacy endpoints.	• Proportion of participants with normalisation of faecal calprotectin at I-week 6. • Proportion of participants with normalisation of CRP at I-week 6. • Proportion of participants with endoscopic remission at I-week 6. • Proportion of participants with mucosal improvement at I-week 6. • Proportion of participants with clinical remission at I-week 6, based on the 4-component Mayo score. • Proportion of participants with symptomatic remission at I-week 2 and 4. • Proportion of participants with normalisation of IBDQ total score at I-week 6. • Mean EQ-5D-5L at I-week 6. • Mean ln-transformed CRP value at I-week 6. • Proportion of participants with a 50% reduction in faecal calprotectin at I-week 6 compared to week 0. • Time to major UC-related events (e.g., hospitalisations, colectomies and procedures).

2.2 Maintenance

Objectives	Endpoints
Primary Objective: Maintenance	Primary Efficacy
To evaluate the efficacy of cobitolimod treatment compared to placebo in inducing or maintaining clinical remission, in participants with clinical response at I-week 6 after induction treatment with cobitolimod.	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 Objectives: Maintenance	
To evaluate the safety and tolerability of cobitolimod compared to placebo.	Safety - incidence of AEs - incidence of SAEs - vital signs - physical examination - laboratory findings
To evaluate the efficacy of cobitolimod maintenance treatment compared to placebo in clinical symptoms, endoscopy and in histology.	Key Secondary Efficacy: - 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 Secondary Efficacy: - Proportion of participants with histologic improvement at M-week 45. - Proportion of participants with histologic remission at M-week 45. - Proportion of participants with mucosal healing at M-week 45. - Proportion of participants with clinical response at M-week 45.

Objectives	Endpoints
	• Proportion of participants with absence of rectal bleeding at M-week 45. • Proportion of participants with normalisation of stool frequency at M-week 45. • Mean stool frequency at M-week 45.
To evaluate the efficacy of cobitolimod maintenance treatment compared to placebo in other endpoints.	• Mean ln-transformed faecal calprotectin at M-week 45. • Mean 3-component and 4-component Mayo scores at M-week 45.
To evaluate HRQoL and health economics.	• Mean IBDQ total score at M-week 45. • Proportion of participants with an improvement in IBDQ total score at M-week 45 compared to I-week 0.

Exploratory Objective Maintenance	Exploratory
To explore the efficacy of cobitolimod maintenance treatment compared to placebo in other efficacy endpoints	• Proportion of participants with endoscopic improvement and steroid-free for at least 8 weeks at M-week 45. • Proportion of participants with symptomatic remission and steroid-free for at least 8 weeks at M-week 45. • Proportion of participants with endoscopic improvement at M-week 45 among those who achieved endoscopic improvement at I-week 6. • Proportion of participants with symptomatic remission at M-week 45 among those who achieved symptomatic remission at I-week 6. • Proportion of participants with normalisation of faecal calprotectin at M-week 45. • Proportion of participants with normalisation in CRP at M-week 45. • Proportion of participants with endoscopic remission at M-week 45. • Proportion of participants with mucosal improvement at M-week 45. • Proportion of participants with clinical remission at M-week 45, based on the 4-component Mayo score. • Proportion of participants with normalisation of the IBDQ total score at M-week 45. • Time to loss of response. • Time to major UC-related events (e.g., hospitalisations, colectomies and procedures). • Proportion of participants with a 50% reduction in faecal calprotectin at M-week 45 compared to I-week 0. • Mean dose of GCS through M-week 45 among those on GCS at I-week 6. • Mean ln-transformed CRP value at M-week 45. • Mean EQ-5D-5L at M-week 45.

3 Study Design

3.1 Overview of Study Design

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, where this protocol covers the first induction study and the maintenance study. The maintenance study will include participants from both the induction 1 and the induction 2 studies. We will enrol approximately 800 participants in the induction studies (440 in induction 1 and 300-400 in induction 2) and at least 250 participants in the maintenance study.

CSUC-01/21 CONCLUDE is the first study protocol in the cobitolimod phase III development programme for the treatment of moderate to severe left-sided UC.

Induction

The induction 1 study will use a randomised, double-blind, placebo-controlled, parallel-group, multicentre, adaptive design in two stages. The study will enrol 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) or JAK-inhibitor (tofacitinib) or other approved advanced therapy for UC.

Stage 1 will explore the efficacy of two different doses of cobitolimod (250 mg and 500 mg, administered twice 3 weeks apart) with placebo as a control, in order to select the most effective dose with no harm in terms of safety. 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 in the selected (winning) dose arm compared to placebo at I-week 6 (Figure 1).

In stage 1, participants will be randomly assigned in a 1:1:1 allocation to receive rectal doses of cobitolimod 250 mg, cobitolimod 500 mg, or placebo. After approximately 44 participants have been randomised into each arm and have eligible efficacy data for the primary endpoint, an interim analysis will be performed. The interim analysis will give guidance regarding which cobitolimod dose (250 mg or 500 mg) will be used in stage 2 of the induction study.

In stage 2, at least 308 (154+154) additional participants will be randomly assigned in a 1:1 allocation to the winning dose of cobitolimod or placebo. The final evaluation for efficacy at I-week 6 will compare the winning dose to placebo, with data from at least 396 (198+198) participants. Participants in the dropped arm will be followed up for safety but will not be included in the final efficacy analysis.

Randomisation in both stages of the induction study will be stratified for concomitant use of GCS treatment at I-week 0 and previous treatment with biologics or JAK-inhibitors.

There will be two screening visits (with one exception described below). At the first screening visit, visit 1a, a written ICF (including consent for the induction and maintenance study) will be obtained before any other study procedure is done. The participant will be assigned a unique participant identification number and enrolment procedures will commence. At the second screening visit, visit 1b, a full colonoscopy will be performed. There is one exception to this schedule. If the participant was already scheduled for an endoscopy and has undergone bowel preparation, visit 1b can be done on the same day as visit 1a provided that informed consent is given before the endoscopy is performed. This is only applicable if bowel preparation is scheduled before study participation was planned for the participant.

Visits during the induction study will be performed during the screening period, with a maximum of 10 days from endoscopy until randomisation, and at I-week 0 (day 1), I-week 3 and I-week 6.

Study intervention will be administered rectally using an enema. Participants will self-administer the study intervention at the clinic under the supervision of the study staff, to ensure they can manage to administer the study intervention appropriately.

All permitted UC-specific medical therapies (e.g., GCS, 5-ASA, AZA/6-MP) must be maintained at a stable dose throughout the study, except for GCS in participants with clinical response at I-week 6; in these participants, GCS should be tapered off from I-week 6.

Maintenance

Participants who demonstrate a clinical response at I-week 6 in the induction study 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.

Participants who are not eligible for the maintenance study, i.e., who do not have clinical response at I-week 6, or not full-filling other inclusion criteria for the maintenance study, will have their last visit at I-week 6, three weeks after the last administration of study intervention.

The maintenance study will evaluate the efficacy and safety of cobitolimod compared to placebo through 46 weeks' maintenance therapy, following 6 weeks of cobitolimod induction therapy (52 weeks' study treatment in total). Cobitolimod or placebo will be administered every 3 weeks.

Participants eligible for the maintenance study will be randomly assigned in a 1:1 allocation (re-randomisation) to receive rectal administrations of the winning dose of cobitolimod (250 mg or 500 mg, as determined by the induction study interim analysis) or placebo. Randomisation will be stratified for clinical remission status at I-week 6 and concomitant use of GCS at I-week 0.

Participants with placebo treatment during induction study will continue with placebo in the maintenance study.

Participants from stage 1 of the induction study 1, who were randomised to active intervention and enters the maintenance study before the winning dose is selected, will be re-randomised to either the same dose of active intervention as in the induction study or to placebo.

After the winning dose is selected, participants that were enrolled into the maintenance study based on clinical response in the losing dose arm, will be switched to the winning dose in the maintenance study at the next visit to the clinic, with the justification to collect further safety data for the winning dose. These participants will not be part of the efficacy evaluation in the maintenance study.

At least 250 participants will be enrolled into the maintenance study from this induction 1 study and the subsequent induction 2 study. Participants will be scheduled for clinic or virtual visits at M-weeks 0, 7, 15, 23, 31, 39 and 45 (further described in [SoA](#)). Evaluation and follow-up of participants will be performed at all visits.

The first maintenance study visit, M-week 0 will occur when the endoscopy result confirms clinical response and other inclusion/exclusion has been reviewed. At this visit the re-

randomisation will occur and the study intervention will be self-administered at the clinic by the participant, supervised by study staff. During all subsequent administration occasions in the maintenance study the study intervention will be self-administered by the participant at home every third week (Table 3).

3.2 End of Study Definition

A participant is considered to have completed the induction/maintenance study if he/she has completed the last scheduled procedure for week 6 (induction) and week 45 (maintenance); see [SoA](#) Table 1 and Table 2.

The end of the induction and maintenance study is defined as the date of the last visit of the last scheduled procedure shown in the [SoA](#), Table 1 and Table 2 for the last participant in the study globally.

4 Study Population

All relevant medical and non-medical conditions should be taken into consideration when assessing suitability for study participation. Participant eligibility should be reviewed and documented by an appropriately qualified member of the investigator's study team prior to inclusion in the study. Endoscopic eligibility and the Mayo subscores for stool frequency and rectal bleeding eligibility will be confirmed centrally and communicated to the investigator before randomisation occurs.

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers, is not permitted.

4.1 Inclusion Criteria: Induction

Participants are eligible for inclusion in the study only if all the following criteria apply:

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.

4.2 Exclusion Criteria Induction

Participants are excluded from the study if any of the following criteria apply:

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 pseudopolypoidosis 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, JAK-inhibitors, 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.

4.3 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.

4.4 Exclusion Criteria Maintenance

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

4.5 Screen Failures

Screen failures in the induction study are defined as participants who consent to participate in the clinical study but are not eligible to subsequently be randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

If a participant fails to fulfil the inclusion/exclusion criteria, they can be re-screened for eligibility at a later date. If the re-screening takes place within a month from the first screening, participants should be assigned the same participant identification number as for the initial screening. Sponsor/CRO will supervise/confirm which screening procedures have to be repeated at the re-screening visit to ensure that the participant fulfils the inclusion criteria for the study. If the re-screening is performed more than 1 month after the first screening, the participant will receive a new participant identification number and all procedures need to be re-done.

5 Study Intervention and Concomitant Therapy

The active ingredient cobitolimod is a fully synthetic DNA-based 19-mer ODN. [REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

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

5.1 Study Intervention Administration

Cobitolimod and matching placebo will be provided to the study clinics by InDex Pharmaceuticals or its representative. Cobitolimod rectal solution is provided at two different strengths (250 mg/50 mL or 500 mg/50 mL) or as matching placebo solution.

Female participants of childbearing potential must have a negative urine pregnancy test prior to receiving each dose of study intervention.

At I-weeks 0 and 3 and M-week 0, the study intervention will be self-administered at clinic by the participant under the supervision of study staff. The participant should be lying in a left-sided position and stay recumbent for at least 30 minutes after study intervention administration.

The following study interventions will be self-administered by the participant at home every third week until the end of the maintenance study (Table 3). The participant should be lying on the left side when administering the study intervention, preferably at bedtime, and stay recumbent for at least 30 minutes, preferably overnight. The participant will receive a take-home instruction/guide regarding at-home study intervention administration.

The visit schedule allows/guides for a +/- 5-day visit window from the planned visit date during the induction study and should be calculated from day 1 of induction study. During the maintenance study a +/-7-day visit window can be allowed (except M-week 0). The visit window in the maintenance study is calculated from day 1 of maintenance study.

All participants and study personnel will be blinded to study intervention assignment for the entire study.

5.2 Study Intervention Packaging, Labelling, Shipment and Storage

5.2.1 Study Intervention Packaging

The study intervention is a [REDACTED]

5.2.2 Study Intervention Labelling

The batch number and unique enema identification number is printed on each enema. Each blister will be labelled according to the GMP/GCP and the regulatory requirements for the countries participating in the study. Labelling of the enema and the blister is performed by [REDACTED].

5.2.3 Shipment of Study Intervention

[REDACTED] will prepare individual participant supplies according to a computer-generated randomisation code. Study intervention will be shipped to the investigational clinics or depot at 2-8°C under controlled conditions.

5.2.4 Storage of Study Intervention

The study intervention should at clinic be stored under controlled conditions, 2-8°C. When taken home by the participant, the study intervention is preferably stored in the fridge (2-8°C,

non-controlled). Before administration the enema should be placed in room temperature for approximately 30 minutes.

The shelf life of the study intervention is 18 months at 2-8°C.

5.3 Study Intervention Accountability and Compliance

The investigator and the pharmacy must keep an inventory of all study intervention received and administered during the study in the intervention accountability log (e.g., drug dispensing and return forms). Prior to site closure, the investigator and pharmacy (if involved) will provide 100% accountability for all enemas received and dispensed.

Participants will be given a treatment card to report when the study intervention was self-administered at home and administration compliance. Participants should bring the card to each clinic visit, together with their empty (used) or unused enemas. After compliance checks and documentation, the used enemas can be destroyed at site. Site staff will enter the information into the eCRF.

After study completion, all unused study intervention packs should have been destroyed according to the approved procedure, and the destruction documented.

A participant will be considered compliant to the study intervention if they have applied all (two) study intervention enemas in the induction study and at least 80% of all protocolised maintenance study intervention enemas.

5.4 Blinding and Unblinding

The study is double-blind to study treatment. Blinding is accomplished by giving all study products identical appearance, packaging, and labelling.

If the treatment assignment must be revealed for safety reasons, the investigator may break the blind through RTSM. There is no antidote for cobitolimod, so interruption of study intervention is recommended as the first option if a drug-related AE is suspected, before considering breaking the code. Further details of the unblinding procedure are described in the separate manual. Any unblinding must be fully documented. The required information includes date and reason for unblinding as well as the name and an electronic signature of the person who performed the unblinding. If the reason for unblinding is an AE, it should be reported on the AE form.

The RTSM will retain an audit trail of all unblinding that has occurred during the study. All relevant parties per the RTSM specification will be notified.

Whenever possible, the study Medical Monitor should be contacted before breaking the code or informed of any intended unblinding.

If a need for unblinding arises when the investigator is unavailable, further contact information is provided on the emergency card handed out to the participant at randomisation.

The induction study will remain blinded until a clean file has been declared for the entire induction study population. The only exception is for information needed for the DMC, as reflected in the DMC charter and IAP. The maintenance study will remain blinded until a clean file has been declared for the entire maintenance study population.

For the interim analysis, an independent statistical support group will provide the DMC with relevant efficacy and safety data (see section 10.4 and 13.1).

5.5 Overdose

Deliberate or accidental study intervention overdose should be treated symptomatically and should be reported as an AE. Definition of overdose is treatment with more than one enema at each treatment occasion or administration of two or more doses within a week. If an overdose occurs the medical monitor should be contacted.

5.6 Concomitant Medications

Any medications that the participant has taken during the study (prescribed or over the counter) must be recorded in the eCRF. Any changes need to be reported in the eCRF.

The following concomitant UC medications are allowed:

- 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 screening visit 1b and kept stable up to the primary endpoint of the induction study (week 6). Tapering should start after the I-week 6 visit if the participant is in response; see tapering scheme in section [5.8](#).
- Oral 5-ASA and/or 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. The dose should be kept stable up to the end of the maintenance study (M-week 45).
- 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. The dose should be kept stable up to the end of the maintenance study (M-week 45).

5.7 Prohibited Medications

The following concomitant medications are prohibited throughout the duration of study:

- immunomodulators such as cyclosporine, tacrolimus and methotrexate
- biologics such as infliximab, adalimumab, golimumab, vedolizumab and ustekinumab
- JAK-inhibitors such as tofacitinib, or other approved advanced therapies

Any prior treatment with these drugs must be discontinued at least 8 weeks prior to visit 1b (except for ustekinumab, which must be discontinued at least 12 weeks prior to visit 1b) *or* have non-measurable serum concentration levels.

Use of rectal formulations of the following medications are also prohibited throughout the duration of study:

- GCS
- 5-ASA/SP
- tacrolimus

Any prior treatment with these drugs must be discontinued at least 2 weeks prior to visit 1b.

5.8 Oral Corticosteroid Tapering Regimen

For participants that are treated with oral GCS (≤ 20 mg prednisone or equivalent/day) at inclusion, tapering should start when the participant has reached clinical response, but at the earliest after the I-week 6 visit. Once the decision to initiate steroid tapering is taken, reduction

of the oral steroid dosage should follow the schedule outlined below in Table 4 and Table 5. It is permitted to taper more slowly than in the schedule, e.g., to allow more weeks at each tapering step, but tapering should be completed at latest 8 weeks before M-week 45. The risk of adrenal gland insufficiency should be considered, especially when the daily dose is lowered to less than 10 mg.

During the corticosteroid taper, participants may experience worsening of UC signs or symptoms that in the opinion of the investigator is attributable to the reduction in corticosteroid dose. The investigator can instruct the participant to revert to the preceding week's daily dosage or to a maximum of the dose at randomisation. If the participant's dose is increased to more than the dose at randomisation the participant should be discontinued from the study intervention but should continue to be followed according to the protocol.

Table 4. Schedule of Oral Prednisolone or Equivalent Dose Reduction.

Tapering frequency	Starting dose Prednisolone or equivalent		
	20 mg/day	15 mg/day	10 mg/day
2 weeks	15	10	7.5
2 weeks	10	7.5	5
2 weeks	7.5	5	2.5
2 weeks	5	2.5	0
2 weeks	2.5	0	0
	0	0	0

Table shows dose (mg/day) of prednisolone or equivalent.

Table 5. Schedule of Oral Budesonide MMX® Dose Reduction

Tapering frequency	Starting Budesonide MMX® dose	
	9mg/day	6mg/day
3 weeks	6	3
3 weeks	3	0
	0	0

Table shows dose (mg/day) of budesonide MMX®.

5.9 Rescue Medication

If rescue medication during study is needed, a flexible sigmoidoscopy should be performed before the initiation of rescue therapy. When rescue medication is initiated, the participant should be discontinued from the study intervention but should continue in the study.

Rescue medications should not be withheld if, in the opinion of the investigator, failure to prescribe them would compromise participant safety. It is at the investigator's discretion to decide what treatment is best for the participant.

6 Discontinuation

There will be two types of discontinuation: discontinuation from study intervention (where the participant stops taking the study intervention but continues with protocol visits), and discontinuation from the study (where the participant does not want to attend further follow-up). Study discontinuation is not the same as withdrawn consent. The participant should be

informed of the safety aspects and scientific value of completing the study and all reasonable efforts should be made to collect as much protocol related data as possible up to M-week 45.

6.1 Discontinuation from Study Intervention

A participant may discontinue from the study intervention at any time at their own request or may be discontinued at any time at the discretion of the investigator for safety, behavioral or compliance reasons.

If a decision has been made to discontinue the study intervention, the participant should be asked to continue in the study according to the protocol. All reasonable efforts should be made to collect as much protocol related data as possible up to M-week 45.

6.2 Discontinuation from Study

A participant may discontinue from the study at any time at their own request. This means that the participant has decided not to attend further visits. If the participant makes a final decision to no longer attend study visits, they should be asked to attend a termination visit (M-week 45 visit procedures).

If a participant in the maintenance study agrees to attend the M-week 45 visit only, the patient will be reported as discontinued from study intervention and the visits up to M-week 45 should be entered as not performed, and only M-week 45 visit data will be collected.

6.3 Reason for Discontinuation

If a participant discontinues from the study intervention or from the study prematurely, the primary reason for discontinuation should be reported in the eCRF. Potential reasons are:

- Loss of Response confirmed by 3-component Mayo score (maintenance study only).

Participant is experiencing worsening of the UC disease, investigator identifies an increase of at least 2 points in the 2-component Mayo score from I-week 6, with a rectal bleeding subscore of at least 1 reported for two consecutive visits (at least 2 weeks apart), and investigator confirms loss of response with a flexible sigmoidoscopy, with an endoscopic score of 2 or 3.

- Lack of Efficacy

The participant reports worsening or no improvement of the UC disease, confirmed by 2-component Mayo score, but not confirmed by endoscopy. This reason is primarily intended for the induction study but can also be used in the maintenance study if the definition of loss of response is not fulfilled e.g., participant refuses to perform an endoscopy.

- TEAE

Clinical (other than loss of response/lack of efficacy) or laboratory events that in the judgment of the investigator, DMC, or the sponsor, and in the best interest of the participant, constitute grounds for discontinuation. This includes SAEs/NSAEs regardless of relation to study intervention.

- Lost to Follow Up

A participant will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and the site has made at least three (3) attempts to contact them. The contact attempts need to be documented in source documents.

- **Withdrawal of Consent**

If a participant withdraws consent for disclosure of future information at the discontinuation of the study or after completion of the study then; no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use data collected before the participant withdrew their consent. The withdraw consent reason is only applicable if the participant denies any further contact with site and there is no further data collection. Participant's decision should be documented in source documents.

- **Unwilling**

The participant is unwilling or unable to comply with the protocol.

- **Other**

Termination for other reason (should only be used if the reasons above do not apply).

7 Study Schedule

For details about each procedure performed at the different visits, see section 8.

All obtained study related information will be reported in the eCRF.

7.1 Visit 1a- and 1b– Screening Visits

The screening period will be divided into two separate visits, visit 1a and 1b (see exception below). Visit 1b should be performed within 10 days from randomisation (visit 2).

At the first screening visit, visit 1a, the participant will be informed about the study in detail; if they agree to participate, an ICF will be signed before any study-specific procedures occur (it is also acceptable for a participant to sign the ICF before the first screening visit, maximum 1 week ahead, and be provided with repeated information at the first screening visit). Every participant will be given a unique participation identification number. During the screening visit 1a, procedures to assess participant eligibility for the study will be performed. Demographics (date of birth, gender, and race), vital signs (BP, HR, height, weight, and smoking status), and medical history including UC history (including duration of disease, duration of current flare, number of flares/year and participant's normal number of stools/day when in remission) will be obtained. A physical examination and a 12-lead ECG will also be conducted.

Non-fasting blood samples will be collected for haematology and blood chemistry including CRP. Faecal calprotectin should preferably be assessed on morning stool, and participants should be provided with stool sampling material so that they can provide a stool sample at the earliest possible day after the visit. Females of childbearing potential will have a serum pregnancy test taken. Concomitant medications will be recorded. Prior UC treatment will be recorded with used dose, start/stop date and reason why not re-started to ensure that inclusion criteria are fulfilled. Only the last treatment period for each UC medication will be collected. It is important that all concomitant UC medications are recorded with start date and dose to ensure that a stable dose is used during the entire study (or for GCS, up to I-week 6). Treatment with cyclosporine, methotrexate, tacrolimus, advanced therapies (infliximab, adalimumab, golimumab, vedolizumab, ustekinumab, tofacitinib), or similar immunomodulatory/immunosuppressant drugs should have been stopped at least 8 weeks before visit 1b (except for ustekinumab, which must have been discontinued 12 weeks before visit 1b). These drugs should have been stopped because of inadequate response, loss of response or intolerable side effects. When laboratory results are available and if the participant remains suitable for the study, the participant will be informed about the bowel cleaning preparation for colonoscopy (separate instructions will be provided to the participant). The colonoscopy will be performed at screening visit 1b.

The participant will receive training and instructions on how to use an eDiary for daily assessment of data up to the day before the randomisation visit 2.

At the second screening visit, visit 1b, a full colonoscopy will be performed to determine the extent and severity of inflammation. This visit can be done on the same day as visit 1a if the endoscopy was planned for the patient before the participant was informed of the study. Informed consent must be signed before endoscopy is performed. The colonoscopy will be recorded according to the site operation imaging manual, and the local endoscopist should evaluate and report the endoscopic Mayo score and thereafter send the video for central reading. Further instruction is provided in the investigator site operation imaging manual. During the endoscopy, four (4) mucosal biopsy samples should be taken at the most inflamed area in the

sigmoid colon. These biopsies will be used for centrally read histopathological evaluation and for biomarker assessment.

All inclusion and exclusion criteria will be reviewed at the screening visit and before randomisation.

Any AEs related to study specific procedures will be recorded at the randomisation visit.

7.2 Visit 2 – Randomisation Visit

The participant must be scheduled for the visit 2/1-week 0 visit within 10 days from the performed endoscopy (including the day of endoscopy and first treatment). Participant must have at least 3 days of eDiary data for evaluation of inclusion criteria regarding rectal bleeding and stool frequency. The investigator should review the inclusion and exclusion criteria including receipt of central approval regarding the endoscopic subscore and stool frequency and rectal bleeding subscores (3-component Mayo score). If the participant is eligible for study participation based on all information collected, the investigator will follow a central randomisation procedure using the RTSM system. If the participant fails to fulfil the inclusion/exclusion criteria, the participant can be re-screened later. If the re-screening will take place more than 1 month after visit 1a, all procedures need to be re-done; otherwise, the sponsor/CRO will supervise/confirm which screening procedures need to be repeated at the re-screening visit to ensure that the participant fulfils the eligibility criteria for the study. If the re-screening is performed more than 1 month after the first screening, the participant will receive a new participant identification number.

Before administration of the study intervention, all other procedures should be done. Vital signs (HR, BP) will be collected, physical examination conducted, and dipstick urinary pregnancy test for females of childbearing potential tested. The participant will be asked to complete IBDQ and EQ-5D-5L questionnaires. Information on extra-intestinal manifestations will also be collected. Non-fasting blood samples will be collected for haematology, blood chemistry including CRP assessment and for biomarker (serum protein) analysis, Stool sample for faecal calprotectin taken on morning stool at home will be collected. Repeated training and instructions for participant eDiary handling will be given. It is important to ensure the participant understands that eDiary data are necessary to evaluate the study. Information on concomitant medication will be collected. Any AEs related to study-specific procedures will be recorded.

The participant will then be educated on how to use the study intervention and will administer the study intervention him/herself under the supervision of study staff. The participant should lie on the left side during administration and will be asked to remain recumbent for at least 30 minutes.

7.3 Visit 3

This visit should occur on day 21 (± 5 visit days as a recommendation). Vital signs (BP and HR) will be collected, and physical exam will be conducted. Non-fasting blood samples will be collected for haematology, blood chemistry including CRP assessment and biomarker (serum protein) analysis. Stool sample for faecal calprotectin taken on morning stool at home will be collected. A dipstick urine pregnancy test should be checked (females of childbearing potential). Repeated instructions for eDiary handling will be given if necessary. It is important to ensure the participant understands that eDiary data are necessary to evaluate the study. Changes in concomitant medication or new medications should be reported. The participant will thereafter administer the study intervention him/herself using the allocated rectal enema under the supervision of study staff. Following study intervention administration, the participant will be asked to remain recumbent for at least 30 minutes. The participant will be asked if any AE has occurred since the last visit.

Participants will be instructed on the bowel cleaning procedure that is needed to undergo the flexible sigmoidoscopy at next visit.

7.4 Visit 4a - Primary Endpoint Induction

This visit should occur on day 42 (± 5 days recommendation). Vital signs (BP and HR) will be collected, and physical exam will be conducted. Non-fasting blood samples will be collected for haematology, blood chemistry, including CRP assessment and biomarker (serum protein) analysis. Stool sample for faecal calprotectin taken on morning stool at home will be collected. A dipstick urine pregnancy test should be checked (females of childbearing potential). The participant will be asked to complete IBDQ and EQ-5D-5L questionnaires. Information on extra-intestinal manifestations will also be collected. Changes in concomitant medication or new medications should be reported. The participant will be asked if any AE has occurred since the last visit.

A flexible sigmoidoscopy will be performed, and four (4) biopsies should be taken from the most inflamed area of the sigmoid part of colon according to imaging guidelines. These biopsies will be used for central read histopathological evaluation and for biomarker assessment.

7.5 Visit 4b

This clinic visit should occur as soon as eligibility for the maintenance study is confirmed, including central confirmation of I-week 6 clinical response based on local and central reading of endoscopy e.g., fulfils all inclusion criteria and is not fulfilling any exclusion criteria for the maintenance study. This visit is the M-week 0 for the maintenance study. If the participant is eligible, a re-randomisation will occur via RTSM.

The participant will be asked if any AE has occurred since the last visit.

The participant will receive instructions on dipstick urine pregnancy testing to be conducted before study intervention administration at home (females of childbearing potential), and further instructions about study intervention administration. The participant will administer the study intervention themselves under the supervision of study staff, lying on the left-side and staying recumbent for 30 minutes before leaving the clinic.

Repeated training and instructions for use of the participant eDiary will be given if needed. It is important to ensure that the participant understands that eDiary data are necessary to evaluate the study. Information on concomitant medication will be collected.

The participant will receive study intervention for 4-5 treatment occasions according to allocation to take home.

7.6 Visit 5

This visit can preferably be performed as a virtual visit.

The participant will be asked if any AE has occurred since the last visit. Changes in concomitant medication or new medications should be reported. eDiary compliance will be checked.

7.7 Visit 6

This visit should be performed as a clinic visit. Vital signs (BP and HR) will be collected, and physical exam will be conducted. Non-fasting blood samples will be collected for haematology, blood chemistry including CRP assessment. Changes in concomitant medication or new medications should be reported.

The participant will be asked to complete IBDQ and EQ-5D-5L questionnaires. Information on extra-intestinal manifestations will also be collected. The participant will be asked if any AE has occurred since the last visit.

The participant (if female of childbearing potential) should be reminded about dipstick urine pregnancy testing to be conducted before study intervention administration at home. Further instructions about study intervention administration should be given if needed. The participants will receive study intervention for 4-5 treatment occasions according to allocation to take home. Repeated training and instructions for participant eDiary handling will be given if needed. It is important to ensure the participant understands that eDiary data are necessary to evaluate the study.

7.8 Visit 7

This visit can preferably be performed as a virtual visit. The participant will be asked if any AE has occurred since the last visit. Changes in concomitant medication or new medications should be reported. eDiary compliance should be checked.

7.9 Visit 8

This visit should be performed as a clinic visit. Vital signs (BP and HR) will be collected, and physical exam will be conducted. Non-fasting blood samples will be collected for haematology and blood chemistry including CRP assessment and biomarker (serum protein) analysis. Stool sample for faecal calprotectin taken on morning stool at home will be collected. Changes in concomitant medication or new medications should be reported.

The participant will be asked if any AE has occurred since the last visit.

The participant (if female of childbearing potential) should be reminded about dipstick urine pregnancy testing to be conducted before study intervention administration at home. Further instructions about study intervention administration should be given if needed. The participant will receive study intervention for 4-5 treatment occasions according to allocation to take home. Repeated training and instructions for participant eDiary handling will be given if needed. It is important to ensure the participant understands that eDiary data are necessary to evaluate the study.

7.10 Visit 9

This visit can preferably be performed as a virtual visit.

The participant will be asked if any AE has occurred since the last visit. Changes in concomitant medication or new medications should be reported. eDiary compliance should be checked.

The participant will be instructed about the bowel cleaning procedure that is needed to undergo the flex sigmoidoscopy at next visit.

7.11 Visit 10 – Primary Endpoint/Early Termination

This visit should be performed as a clinic visit. Vital signs (BP and HR) will be collected, and physical exam will be conducted. Non-fasting blood samples will be collected for haematology, blood chemistry, including CRP assessment and biomarker (serum protein) analysis. Stool sample for faecal calprotectin taken on morning stool at home will be collected. A dipstick urine pregnancy test should be checked (females of childbearing potential). The participant will be asked to complete IBDQ and EQ-5D-5L questionnaires. Information on extra-intestinal manifestations will also be collected. Changes in concomitant medication or new medications should be reported. The participant will be asked if any AE has occurred since the last visit.

A flexible sigmoidoscopy will be performed according to imaging guidelines. All obtained information will be reported in the eCRF.

7.12 Unscheduled Visit

An extra visit (clinic or virtual) can be performed at any time when there is a need for it, as judged by the investigator. In case of values outside the normal range, the DMC can request an extra visit where additional examinations should be conducted, and blood sample(s) drawn as agreed with the DMC.

8 Study Assessments and Procedures

Study procedures and their timing are summarised in the [SoA](#), Table 1, Table 2 and Table 3. Study assessments will be performed by the investigator, delegated study personnel and central reader. Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. When a protocol-required test or procedure cannot be performed, the reason should be documented.

Procedures are presented in **alphabetic order**.

8.1 Biomarker Analysis

Serum samples will be collected for assessment of disease and drug mechanism-associated serum proteins as well as for proteins associated with proinflammatory and anti-inflammatory effects, the recruitment and proliferation of cells associated with inflammation, drug mechanism of action and for prediction of clinical response. Serum samples will be collected at visits 2, 3, 4a, 8 and 10.

Mucosal biopsy samples for biomarker assessment will be collected at visit 1b, 4a and 10. Two of the biopsies for biomarkers will be placed in RNAlater solution and thereafter frozen at -20°C, and the left over material from the histopathological evaluation samples will be used. Total RNA will be isolated and used to identify messengerRNA expression patterns that are relevant to cobitolimod treatment and/or UC, and to evaluate markers that can predict clinical response. The mucosal biopsy samples collected will also be used for immunohistochemical assessment of disease, healing, and drug mechanism of action.

Serum protein samples will be collected only for participants recruited in stage 2 of the induction 1 study. These analyses will be performed after unblinding has occurred and will be presented in a separate report, and not included in the CSR. The biopsy samples will be collected for all participants.

8.2 Collection of Adverse Events (NSAEs and SAEs)

Collection of AEs will start directly after an ICF is signed. During the screening period only AEs related to study procedure will be reported as AEs. Definitions, documentation and reporting of AEs are described in detail in section 9.

8.3 Concomitant Medication

All changes to concomitant treatments must be recorded during the study, e.g., stop date, change of dose, or initiation of a new treatment. The start date of change of dose or treatment should reflect the day when the new dose/treatment was started; overlaps should be avoided.

8.4 Contraceptive Methods

All female participants who, are biologically capable of having children and are sexually active must agree to use a highly effective method of contraception for the duration of the study. Female participants of non-childbearing potential must meet at least one of the following criteria:

- Postmenopausal females are defined as over the age of 45 years who have been amenorrhea for at least 12 months with no alternative pathological or physiological cause.
- Females who had a physician documented hysterectomy and/or bilateral oophorectomy.

Highly effective birth control methods include:

- combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: ¹
 - oral
 - intravaginal
 - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation ¹
 - oral
 - injectable
 - implantable ²
- intrauterine device (IUD) ²
- intrauterine hormone-releasing system (IUS) ²
- bilateral tubal occlusion ²
- vasectomised partner ^{2,3}
- sexual abstinence ⁴

¹ Hormonal contraception may be susceptible to interaction with the investigational medicinal product, which may reduce the efficacy of the contraception method.

² Contraception methods that are considered to have low user dependency.

³ Vasectomised partners are a highly effective birth control method provided that partner is the sole sexual partner of the woman of childbearing potential and that the vasectomised partner has received medical assessment of the surgical success.

⁴ In this context sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptom-thermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Adapted from Clinical Trials Facilitation Group (CTFG)

8.5 C-reactive Protein

CRP has been demonstrated to be a useful marker of inflammation in participants with UC. CRP will be measured in terms of absolute values. Because of the typical skewness of the data, values will be ln-transformed for statistical analysis. CRP values that are below the lower detection limit specified will be replaced with a nominal value for the presentation of descriptive statistics.

Samples will be collected at visits 1a, 2, 3, 4a, 6, 8 and 10.

8.6 Demographics

Participant sex, age, and race will be collected at the screening visit 1a.

8.7 eDiary Completion and Review

A participant eDiary will be used for assessment of daily symptoms (Appendix 16.2). The following symptoms will be assessed daily from visit 1a to visit 4a in the induction study, and daily during 10 days prior to each visit in the maintenance study:

- Absolute number of stools
- Daily stool frequency (according to the Mayo subscore)

- Daily blood in stool (according to the Mayo subscore)

eDiary data will be used to calculate the Mayo subscores of stool frequency and rectal bleeding.

Site staff should check the eDiary entry compliance continuously, and participants should be reminded if they do not enter data during the expected entry period. The eDiary should be reviewed by the investigator at each visit. If the eDiary data indicate worsening of disease at two (2) consecutive visits, the investigator should take appropriate actions, e.g., perform an endoscopy to confirm loss of response.

8.8 Electrocardiogram

A 12-lead ECG will be performed and assessed preferably at visit 1a, but at the latest at randomisation. The ECG will be reviewed by the investigator. In the case of ECG abnormalities, the findings should be reported as medical history.

8.9 Eligibility and Evaluation

At visit 1a, the investigator should assess the participant's eligibility for potential enrollment into the study based on medical history, UC history of left-sided disease and concomitant therapy, according to the inclusion and exclusion criteria. The participant should also be asked about number of daily stools and presence of rectal bleeding. The combined information informs whether the participant is eligible for further evaluation to be enrolled in the study.

At visit 1b a full colonoscopy will be performed. The endoscopic findings will be assessed by the local endoscopist during the procedure, and by the central reader when reviewing a video of the endoscopy. Participant eligibility at I-week 0 will be based on the final reported endoscopic Mayo subscore as determined by the following process:

- If the local endoscopist and the central reader agree on the endoscopic subscore, the agreed subscore will be the final reported endoscopic subscore.
- If there is disagreement between the local endoscopist and the central reader, a second central reader (designated for adjudication) will review. The final decision of the endoscopic Mayo score will be the score that two of the three readers agree on.

Inclusion in the induction study requires a 3-component Mayo score between 5 and 9 at visit 2 (I-week 0), which will be calculated by summarising the visit 1b Mayo endoscopic subscore and the Mayo subscores of blood in stool and stool frequency. The Mayo subscores rectal bleeding and stool frequency will be calculated from eDiary.

At visit 4a (I-week 6) and visit 10 (M-week 45), a sigmoidoscopy will be performed. The endoscopic findings will be assessed by the local endoscopist during the procedure and by the central reader when reviewing a video of the endoscopy using the same reading paradigm as described in bullets one and two above.

At visit 4b (M-week 0), the investigator should assess the participant's eligibility for the maintenance study based on clinical response (the 3-component Mayo score will be calculated by summarising the visit 4a endoscopy subscore and the Mayo subscores assessed from eDiary excluding the last two days before the visit) and participant's adherence to protocol procedures and willingness to comply with all further study requirements.

8.10 Endoscopy Procedures

A full colonoscopy will be performed with a video endoscope at the screening visit (visit 1b). The endoscope should inspect the whole bowel, up to the cecum. Flexible sigmoidoscopy with a video endoscope will be performed at I-week 6 (visit 4a) and M-week 45 (visit 10).

Four (4) biopsies should be taken from the most inflamed area of the sigmoid colon. Separate instruction regarding endoscopy, central reading, adjudication, and biopsies will be provided to the site.

Separate instructions for endoscopy preparations will be provided to the participants.

8.11 EQ-5D-5L, Health Questionnaire

EQ-5D-5L is a validated self-rated QoL to assess impact on quality of life in five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. EQ-5D-5-L also includes a participant self-rated health VAS score [14, 15].

The VAS can be used as a quantitative measure of health outcome that reflects the participant's own judgment. The participant will be asked to fill in the questionnaire at visit 2 (before study drug administration) and at visits 4a, 6 and 10.

The questionnaire shall be checked for completeness by study staff before the participant leaves the site.

8.12 Extraintestinal Manifestation Assessment

The participant will be asked questions (Appendix 16.4) about specific diseases at visit 2 (before study intervention administration) and at visits 4a, 6, 8 and 10 [16].

8.13 Faecal Calprotectin

Faecal calprotectin is considered to be a sensitive and specific marker identifying inflammation and response to UC treatment. Faecal calprotectin will be measured in terms of absolute values. Because of the typical skewness of the data, the values will be ln-transformed.

Stool samples will be collected on morning stool in connection to visits 1a, 2, 3, 4a, 8 and 10.

8.14 Genetics

Genetics are not evaluated in this study.

8.15 Histopathology

Histopathology is an emerging treatment target in UC. The Robarts Histologic Index will be used to score inflammation in the mucosa [17, 18].

Two (2) of the four (4) biopsies taken (visit 1b, 4a and 10) from the most inflamed area of sigmoid colon will be used for centrally read histopathological evaluation (Appendix 16.3). Further instruction will be found in the investigator laboratory manual.

Centrally read histopathological evaluation will be done in batches, and results will not be sent to site until the end of the study. Biopsies collected for biomarker evaluation will be analysed after the study is unblinded.

8.16 Inflammatory Bowel Disease Questionnaire

IBDQ is a validated 32-item participant questionnaire used to evaluate disease-specific health-related quality of life in people with IBD. The IBDQ comprises four dimensions: bowel

function (loose stools, abdominal pain), systemic symptoms (fatigue, altered sleep pattern), social function (work attendance, need to cancel social events), and emotional status (anger, depression, irritability) [19, 20].

The total IBDQ score ranges from 32 to 224, and an increase from I-week 0 to I-week 6 or from I-week 0 to M-week 45 of at least 16 points is considered to indicate a clinically meaningful improvement.

The IBDQ will be completed at visit 2 (before study intervention administration), and at visits 4a, 6, and 10. The questionnaire should be checked for completeness by study staff before the participant leaves the site.

8.17 Informed Consent

All participants will receive written and verbal information concerning the study prior to any study-related procedures. The given information emphasises that participation in the study will be voluntary and that the participant might discontinue and/or withdraw consent from the study at any time and for any reason. It is important to inform the participant of the importance of following the protocol and of the scientific value of all data collected in accordance with the protocol. All participants will be given the opportunity to ask questions about the study and will be given sufficient time to decide whether to participate. Participants will not be identifiable from the data collected. Participants will give consent for both the induction and maintenance study in same consent.

A copy of the participant information, including the signed ICF, will be given to the participant.

8.18 Laboratory Procedures

Blood, urine, and stool samples will be collected at the time point identified in the [SoA](#) (Table 1, Table 2 and Table 3). All samples will be collected in a non-fasting state. The clinical analyses to be performed are listed in Table 6. Unscheduled clinical laboratory testing may be conducted at any time during the study to assess any perceived safety concerns.

In the induction study, the total blood volume to be collected from each participant is approximately 80 mL. In the maintenance study, the total blood volume to be collected from each participant is approximately 60 mL. All females of child-bearing potential will have a serum pregnancy test at visit 1a, and a urine dipstick test should be done prior to each dosing of study intervention (during the maintenance study the dipstick test will be performed by the participant at home).

A central laboratory will be used to perform safety tests for haematology and blood chemistry. Safety laboratory reports will show the reference range for each variable. In the event of an unexplained clinically noteworthy abnormal laboratory test value, the test should be immediately repeated and followed-up until it has returned to the normal range and/or an adequate explanation of the abnormality is found. Clinically significant abnormal findings should be recorded as AEs. Abnormal findings associated with the UC are not considered clinically significant unless judged by the investigator to be more severe than expected for the participant's condition.

All clinically significant abnormal laboratory values should be followed up.

The signed and interpreted laboratory results will be kept together with the participant's source documents.

Table 6. Clinical Laboratory Analysis

Haematology	Blood Chemistry		Other
Hemoglobin ¹	Albumin ¹	CRP ¹	Faecal calprotectin ²
Hematocrit ¹	ALP ¹	GGT ¹	Serum protein ^{1,3}
Platelet count ¹	ALT ¹	Glucose ¹	Serum and urine pregnancy test ⁴ Colon biopsies ⁵
RBC s ¹	AST ¹	Phosphate ¹	
WBCs ¹	BUN ¹	Potassium ¹	
-Neutrophils ¹	Calcium ¹	Sodium ¹	
-Eosinophils ¹	Chloride ¹	Total bilirubin ¹	
-Monocytes ¹	CPK ¹	Total protein ¹	
-Basophils ¹	Creatinine ¹		
-Lymphocytes ¹			

¹ Non-fasting state

² Stool sample for faecal calprotectin should be collected from a morning stool. Sampling material should be given to participant at visits to return at the next visit. At screening visit, participant should return with the sample at the earliest possible day.

³ Serum protein samples will be collected only from participants recruited in stage 2 of the induction 1 study.

⁴ For women of childbearing potential

⁵ For histopathological evaluation and biomarker assessment, four(4) biopsies from the most inflamed are of the sigmoid colon Two (2) in paraffin and two (2) in RNA-later.

8.19 Mayo Score

The Mayo score disease activity index was developed to assess mild, moderate and severe UC (Appendix 16.1) [21].

- 2-component Mayo score (range 0–6)

A 2-component Mayo score includes the stool frequency and rectal bleeding subscores.

The stool frequency and rectal bleeding subscores will be evaluated during the screening period, using eDiary data. The 2-component Mayo score will also be used to assess loss of response or lack of efficacy.

- 3-component Mayo score (range 0-9)

A 3-component Mayo score includes the stool frequency, rectal bleeding, and endoscopy subscores. A 3-component Mayo score of 3-4 points indicates mild disease, of 5-7 points indicates moderate disease, and of 8-9 points indicates severe disease.

The 3-component Mayo Score will be used to evaluate eligibility to the induction study to assess efficacy and to assess loss of response.

- 4-component Mayo score (range 0-12)

A 4-component Mayo score includes the stool frequency, rectal bleeding, endoscopy and PGA subscores. A 4-component Mayo score of 3 to 5 points indicates mild disease, of 6 to 10 points indicates moderately active disease, and of 11 to 12 points indicates severe disease.

8.20 Medical History

A complete medical history will be collected covering up to the first dose of study intervention. Diagnosis/symptoms/signs and the start year of each diagnosis will be collected. Findings and/or abnormalities detected by physical exam and ECG interpretation at Visit 1a should be reported on medical history, preferably as a diagnosis. Information regarding postmenopausal status will be collected as medical history. A broader UC history will be collected to obtain information on the “normal” number of stools per day (when not having a flare) and number of flares/year.

8.21 Medical Resource Utilization

Medical resource utilisation measures such as UC-related hospitalisations and UC-related surgeries will be collected for evaluation of the health economics of cobitolimod treatment.

8.22 Physical Examination

A complete physical examination should be performed at site visits (except visit 4b) and should include the following body system evaluations: general appearance, skin, musculoskeletal, eyes, ears, nose, throat, thyroid, cardiovascular, chest, abdomen, lymph nodes and neurological examination. If a clinically significant abnormality is observed, it should be reported either as medical history (during screening) or as an AE (after first dose).

8.23 Physicians Global Assessment

The PGA is a clinician-reported assessment that reflects the participant’s abdominal discomfort and general sense of wellbeing, and other observations, such as physical findings and the participant’s performance status. The PGA information will be collected at visits 2, 4a and 10.

8.24 Pregnancy Test

Pregnancy tests will be performed on all females of childbearing potential before all study intervention occasions. A serum pregnancy test will be carried out at Visit 1a. Urine dipstick pregnancy tests should be done at site before treatment at visits 2, 3 and 4a, and by the participant themselves before each self-administrated treatment at home. If the pregnancy test is positive no further treatment should be administered, and the pregnancy should be considered as an AE.

8.25 Prior Therapies

The prior used therapy will be recorded with preferably the generic name and with start and stop date. For all non-UC therapy, the last 8 weeks’ treatment prior to screening visit 1a must be recorded. For UC treatment, such as GCS, Budesonide MMX[®], 5-ASA/SP, AZA/6-MP, TNF- α inhibitor, anti-integrins, cyclosporine, tacrolimus, JAK-inhibitors, anti-IL-12/23 or other immunomodulatory/immunosuppressant drugs, the generic name, start date and stop date (if applicable) and dose should be recorded independently when treated. Only the last treatment period for each drug should be recorded. The reason why these drugs were not re-started when the participant relapsed should also be reported.

8.26 Randomisation and re-randomisation

8.26.1 Induction

At stage 1 of the induction study, a total of 132 participants will be randomly assigned using permuted blocks in a 1:1:1 allocation to receive rectal doses of cobitolimod 250 mg, cobitolimod 500 mg, or placebo.

After interim analysis of stage 1, the winning dose will be continued in stage 2 of the induction study, in which an additional 308 participants will be randomly assigned using permuted blocks in a 1:1 allocation to the winning dose of cobitolimod or to placebo (Figure 1).

The final evaluation for efficacy will compare the winning dose versus placebo including participants from both stage 1 and stage 2.

Randomisation at both stages of the induction study will be stratified for concomitant use of GCS treatment at I-week 0 and previous treatment with biologics (infliximab, adalimumab, golimumab, vedolizumab or ustekinumab) or JAK-inhibitors (tofacitinib).

8.26.2 Maintenance

In the maintenance study, participants who were randomised into the induction study and have demonstrated a clinical response to induction treatment with the cobitolimod winning dose at I-week 6 will be randomly assigned using permuted blocks (re-randomised) in a 1:1 allocation to receive rectal doses of the cobitolimod winning dose or placebo. Randomisation will be stratified for clinical remission status (Yes/No) and concomitant use of GCS treatment (Yes/No) at M-week 0.

Participants treated with placebo who achieve clinical response in the induction study will continue with placebo in the maintenance study but will be excluded from the efficacy analysis. Participants with no clinical response in the induction study will not continue into the maintenance study. Participants with a clinical response in the induction stage 1 losing dose arm will be re-randomised to the same dose of cobitolimod or to placebo in the maintenance study until the decision has been taken on the winning dose. After that, all these participants, will be switched to the winning dose, and will continue on that dose throughout the study. They will be excluded from the efficacy analysis but included in the safety analysis.

8.27 Tobacco Use

The participant's tobacco history/use will be collected at screening visit 1a and at M-week 45.

8.28 Ulcerative Colitis History and Assessment

A detailed history of UC, including month and year of diagnosis and disease severity, will be collected. Information on the participant's normal stool frequency when in remission, and duration of flare and number of flares per year, will also be collected, as well as the participant's stool frequency prior to the initial onset of signs and symptoms of UC.

Definition of stool:

Participants should be instructed that a stool is defined as a trip to the toilet where the participant has either a bowel movement or passes blood alone, blood and mucus, or mucus only.

Definition of remission reference stool frequency:

The participant should be asked to identify at visit 1a how many stools he or she had in a 24-hour period when in remission from UC.

If the participant does not report that he or she has never achieved remission, the participant should be asked to identify the number of stools he or she had per day before the initial onset of signs and symptoms of UC.

8.29 Vital Signs

Systolic and diastolic BP (mmHg) and HR (beats/min) will be measured in a sitting position and after 5 minutes' rest at site visits. The use of automated devices is acceptable. BP and HR should be measured before blood samples are taken. Weight and height will be measured or reported by participants at the randomisation visit.

9 Adverse Event

Investigators are responsible for recording all AEs/SAEs observed during the study period, i.e., from the time the participant signs the ICF until the participant has completed the study. (In the screening period, only AEs/SAEs related to study-specific procedures, occurring after ICF signing up to randomisation, will be reported at the randomisation visit; any other medical findings during the screening period will be recorded in the medical history section of the eCRF rather than the AE section). Participants will be questioned about AEs/SAEs at every virtual or clinic visit and should be encouraged to contact the site when a new AE occurs for further guidance.

9.1 Adverse Event Definition

An AE is any untoward medical occurrence associated with the use of a drug, whether considered drug-related or not. An AE can be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study intervention, whether it is study intervention-related or not. This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of study intervention. Loss of Response and Lack of Efficacy of study intervention should not be reported as an AE, unless the disease has worsened compared to its level at randomisation.

9.2 Adverse Drug Reaction Definition

An ADR is an AE suspected to be causally related to a product. In clinical studies this means that the investigator has judged that there is a likely relationship to the study intervention.

9.3 Serious Adverse Event Definition

An SAE is any AE, occurring at any dose and regardless of causality, defined as:

- death
- a life-threatening AE (immediate risk of death)
- participant hospitalisation or prolongation of existing hospitalisation
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- a congenital anomaly or birth defect
- regarded as medically important without meeting the above-mentioned criteria

9.4 Adverse Events by Intensity

Intensity for each AE, including any laboratory abnormality, will be defined according to the following criteria:

MILD: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
MODERATE: An event that is sufficiently discomforting to interfere with normal everyday activities.
SEVERE: An event that prevents normal everyday activities.

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the experience should be noted. If the intensity category changes over a number of days, those changes should be recorded separately (with distinct onset dates).

9.5 Classification of Adverse Events by Relationship to Study Intervention

UNLIKELY RELATED: This category applies to those AEs that are judged to be unrelated to the study intervention.
LIKELY RELATED: This category applies to those AEs that the investigator feels are with high probability related to the study intervention.

9.6 Reporting of Adverse Events

At each visit, the participant will be asked if any new signs or a symptom has occurred since the last visit. For all AEs, the investigator must obtain information to determine the outcome of the AE and to assess whether it meets the criteria for classification as a SAE.

All AEs, serious and non-serious, should be recorded in the eCRF. If no AE has occurred during the study period, this should also be recorded in the eCRF. AEs that occur after the first dose of study intervention will be reported as TEAEs.

Preferably all AEs should be recorded in standard medical terminology rather than the participant's own word; if possible, diagnosis instead of symptoms should be recorded.

UC is associated with certain characteristic signs and symptoms including diarrhoea and rectal bleeding that may be present at the screening visit and may fluctuate based on the individual participant's disease history during the course of the study. These signs and symptoms are considered medically anticipated clinical events for the condition under study and will only be collected as an AE if clinically significant. These characteristics of disease activity will be regularly captured.

Exacerbations of disease activity (increase in the daily amount of rectal bleeding beyond the participant's normal fluctuation, or new signs or symptoms of UC) will be collected as AEs and reported according to regulatory reporting requirements.

The following evaluations are to be done by the investigator in connection with the AE:

- type of event
- seriousness

- degree of severity
- duration (start - end)
- action taken
- causality with study product
- outcome of the AE

9.7 Reporting of Serious Adverse Events

All SAEs must be reported to the [REDACTED] Drug Safety Services within 24 hours from knowledge by the investigator or delegate, regardless of the time that may have elapsed from the time the event occurred to when the investigator first learns of it. The initial report should contain as a minimum: participant identification, AE term, date of event and reporting person.

SAEs should be reported to [REDACTED] Drug Safety Services even after the clinical study has been finished if, in the judgment of the investigator, there might be an association between the event and previous use of the study product, or as a result of the study procedures.

Only SAEs that are both unexpected and related to the study intervention, SUSARs, are subject to expedited reporting.

The sponsor is responsible for informing all investigators concerned of relevant information about SUSARs that could adversely affect the safety of participants. The appropriate EC and regulatory authorities, as per local requirements, should be informed by the sponsor about SAEs associated with the use of the product.

9.8 Follow-up Period after an Adverse Event

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution and/or stabilisation, the event is otherwise explained, or the participant is lost to follow up.

In case of pregnancy during the study, the participant and offspring must be monitored for AEs during the entire pregnancy. Any AE occurring to the offspring during pregnancy or at birth must be reported. The pregnancy should be reported in eCRF as an AE and reported to [REDACTED] via the Pregnancy report form.

9.9 Coding of Adverse Events

All AEs will be coded according to medical dictionary for regulatory activities (MedDRA).

10 Statistical Considerations

The principal features of the statistical analysis of the data are described in this section. A more technical and detailed elaboration of the principal features will be written in the SAP which will be finalised prior to DBL.

This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

Mock table, figure, and listing (TFL) shells will be provided in a separate supporting document along with details for the practical implementation of the analyses.

10.1 Statistical Hypothesis

The primary objective of the induction study is to confirm a superior efficacy for the cobitolimod induction treatment compared to placebo using an adaptive design; i) stage 1 of the induction 1, is to choose the winning dose of 250 mg or 500 mg compared to placebo in the primary endpoint of clinical remission at I-week 6 for participants with moderate to severe active left-sided UC and to test for futility, and ii) in stage 2, to compare the cobitolimod winning dose to placebo regarding the primary endpoint. The null hypothesis to be tested is that there is no difference between cobitolimod winning dose and placebo, i.e., the odds ratio, OR=1. The same statistical hypothesis, OR=1, will be used for key secondary endpoints.

In the maintenance study the primary objective is to confirm a superior efficacy for the cobitolimod winning dose compared to placebo in the primary endpoint of clinical remission at M-week 45 for participants who achieved clinical response after induction treatment with cobitolimod, where the null hypothesis to be tested for the primary and key secondary endpoints is 'no difference between cobitolimod 'winning' dose and placebo.

$$H_{01}: OR = 1 \quad \text{versus} \quad H_{11}: OR \neq 1$$

10.1.1 Multiplicity Adjustment

The overall type I error rate for testing the primary and the key secondary efficacy endpoints will be controlled at the type I error rate of 0.05 using appropriate methods for adjustment for multiplicity but separately for the induction and the maintenance study.

All hypothesis tests will be two-sided. Details of the methods for adjustment in terms of the selection of endpoints to include in the testing sequence and the criteria for rejecting (or not rejecting) individual hypotheses are provided in the SAP. Nominal p-values will be displayed for all treatment comparisons.

10.2 Analysis Sets

10.2.1 Induction

10.2.1.1 All Screened Analysis Set

All participants who gave their written informed consent and entered into the screening visit will be included in ASAS.

10.2.1.2 Full Analysis Set

All efficacy analyses will be based on the ITT principle. The FAS, include participants who were randomised and received at least one dose of the study intervention.

10.2.1.3 Per-Protocol Analysis Set

The PPAS, consists of all participants in FAS who do not violate the protocol in terms of study intervention intended, major inclusion or exclusion criteria or other deviations that will be identified to have a major impact on the possible efficacy outcome. Decisions regarding exclusion from the PPAS will be made during the Blinded Data Review Meeting and documented before the study data are unblinded for final analysis.

10.2.1.4 Safety Analysis Set

The SAF consists of all participants who received at least one administration of study intervention. Participants will be analysed according to the treatment that they actually received.

10.2.2 Maintenance

10.2.2.1 Full Analysis Set Maintenance

All efficacy analyses will be based on the ITT principle. The FASM, is defined as all participants who were randomised into the maintenance study.

10.2.2.2 All Screened Analysis Set Maintenance

The ASASM, consists of all participants who were eligible to enter the maintenance study.

10.2.2.3 Per-Protocol Analysis Set Maintenance

PPASM, consists of all participants in FASM who do not violate the protocol in terms of study intervention intended or other deviations that will be identified to have a major impact on the possible efficacy outcome, which must be documented prior to unblinding.

10.2.2.4 Safety Analysis Set Maintenance

SAFM, consist of all participants who received at least one administration of the study intervention in the maintenance study. Participants will be analysed according to the treatment they received.

10.2.3 Subgroups

There are specific subgroups of interest which will be explorative analysed for the primary endpoint, the key secondary endpoints in both the induction and maintenance evaluation, and a selection of other secondary endpoints. The main purpose of these subgroup analyses is to check the consistency of results across subgroups, rather than to make inferences within subgroups. These subgroups are listed below:

- Prior use of biologics or JAK-inhibitors (Yes/No)
- GCS use at baseline, I-week 0 (Yes/No)
- GCS use at baseline, M-week 0 (Yes/No)
- Disease severity at baseline, I-week 0, (5-7 and 8-9)
- Clinical remission status at M-week 0 (Yes/No)

10.3 Statistical Analyses

10.3.1 General Considerations

Baseline and participant characteristics will be presented in tables by group and in total.

All continuous variables will be described using standard statistical measures, i.e., number of observations, mean and median value, standard deviation, and minimum and maximum value. All categorical variables will be summarised in frequency tables.

In general, analysis for categorical data in terms of binary data (Yes/No) will be presented as the proportion of participants with the frequency of presence or absence by treatment group of the characteristics of interest and analysed using logistic regression, where the parameter used for the statistical hypothesis testing will be the OR, as a measure of the relative difference in odds between treatment arms.

Continuous outcome variables will be analysed using ANCOVA, unless otherwise specified. Estimates will be presented using least square means for differences between treatment arms. Variables used for adjustment will be defined with each analysis.

All statistical testing will be performed at the type I error rate of 0.05, using two-sided tests with appropriate multiplicity adjustment employed for the primary and key secondary endpoints. Nominal p-values will be displayed for all treatment comparisons, i.e., for analysis to be considered as exploratory.

10.3.2 Induction

10.3.2.1 Primary Efficacy Endpoint Analysis

The primary analysis of the primary endpoint is based on the FAS population and will be performed using logistic regression adjusting for randomisation strata GCS use at I-week 0 (Yes/No) and prior use of biologics or JAK-inhibitors (Yes/ No) to compare the winning dose of cobitolimod against placebo. There will be no adjustment for multiplicity as there is only one primary endpoint.

The primary endpoint proportion of participants with clinical remission at I-week 6 will be tested using an overall type I error rate of 0.05, and a two-sided test. Results will be presented using the frequency and the proportion by treatment group and the OR together with its corresponding 95% confidence interval. Data will be presented for NRI, in all summary presentations and analyses.

The p-value for testing the null hypotheses must be less than 0.05 (i.e., 0.04999 adjusted for the futility analysis) to be considered to have met the primary objective.

To support the interpretation of the primary analysis, several exploratory sensitivity analyses will be performed for the primary endpoint. An identical analysis as described above will be conducted using the analysis populations selected and different methods for imputation of missing data, which will be described in the SAP.

10.3.2.2 Subgroup Analyses of the Primary Efficacy Endpoint

Subgroup analyses will be performed using the same approach as described above for the FAS population and applied for subgroups described in section 10.2.3.

10.3.2.3 Secondary Efficacy Endpoint Analyses

Key Secondary Efficacy

There are two key secondary endpoints: proportion of participants with endoscopic improvement at I-week 6 and proportion of participants with symptomatic remission at I-week 6.

Both will be analysed and summarised using the same statistical methods as for the primary endpoint, including the exploratory sensitivity analyses. The type I error rate for the two key secondary endpoints will be appropriately controlled for multiplicity using the methods described in the SAP. However, they will only be appropriately adjusted if the hypothesis of the primary endpoint is rejected, i.e., demonstrates a statistically significant result ($p < 0.05$).

Other Secondary Efficacy

Other secondary binary endpoints will be analysed for the FAS population and summarised using the same methods as those for the primary endpoint.

Other secondary continuous endpoints will be analysed for the FAS population and will be performed using ANCOVA, adjusting for randomisation strata GCS use at I-week 0 (Yes/No) and prior use of biologics or JAK-inhibitors (Yes/No) and treatment, as fixed factors in the model, and I-week 0 levels as a covariate in the model.

All other secondary endpoints will be tested using an explorative type I error rate of 0.05, and a two-sided test. Results will be presented using the least square means by treatment group and difference between groups together with the corresponding 95% confidence intervals. Data will be presented for the observed data in all summary presentations and analyses. There will be no adjustment for multiplicity.

Nominal p-values will be displayed for all efficacy endpoint treatment comparisons.

10.3.2.4 Exploratory Endpoint Analyses

Exploratory endpoints will be analysed and summarised using the same methods as those for the secondary endpoints. There will be no adjustment for multiplicity. Nominal p-values will be displayed for all treatment comparisons.

10.3.3 Maintenance

All efficacy analyses will be based on the FASM. Data for non-randomised participants, i.e., participants in clinical response to placebo and participants responding to the cobitolimod losing dose in the induction studies at I-week 6, will be summarised and presented using descriptive statistics only.

10.3.3.1 Primary Efficacy Endpoint Analysis Maintenance

The primary analysis of the primary endpoint is based on the FASM population and will be performed using logistic regression adjusting for clinical remission at I-week 6 (Yes/No), and randomisation strata GCS use at I-week 6 (Yes/No). There will be no adjustment for multiplicity as there is only one primary endpoint.

The primary endpoint proportion of participants with clinical remission at M-week 45 will be tested using an overall type I error rate of 0.05, and a two-sided test. Results will be presented using the frequency and the proportion by treatment group and the OR together with its

corresponding 95% confidence interval. Data will be presented for NRI, in all summary presentations and analyses.

The p-value for testing the null hypotheses must be less than 0.05 to be considered to have met the primary objective of the maintenance study.

To support the interpretation of the primary analysis, several sensitivity analyses will be performed for the primary endpoint. An identical analysis as described above will be conducted using the analysis populations selected and different methods for imputation of missing data, which will be described in the SAP.

10.3.3.2 Subgroup Analyses of the Primary Efficacy Endpoint

Subgroup analyses will be performed using the same approach as described above for the FASM population and applied for subgroups described in section 10.2.3.

10.3.4 Secondary Endpoint Analyses

Key Secondary Efficacy

There are four key secondary endpoints: proportion of participants with endoscopic improvement at M-week 45, proportion of participants with steroid-free remission at M-week 45 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 (which is only a subgroup of participants but balanced according to the stratification design), and proportion of participants with symptomatic remission at M-week 45.

They will be analysed and summarised using the same methods as those for the primary endpoint (except the endpoint of clinical remission at M-week 45 among those who achieved clinical remission at I-week 6, which will drop the stratification factor of clinical remission status), including the sensitivity analyses. The type I error rate for the four key secondary endpoints will be appropriately controlled for multiplicity using the methods described in the SAP. However, they will only be confirmatory if the hypothesis of the primary endpoint is rejected, i.e., demonstrates a statistically significant result ($p < 0.05$).

Other Secondary Efficacy

Other secondary binary endpoints will be analysed for the FASM population and summarised using the same methods as those for the primary endpoint.

Other secondary continuous endpoints will be analysed for the FASM population and will be performed using ANCOVA, adjusting for randomisation strata clinical remission at I-week 6 (Yes/No) and GCS use at baseline, M-week 0 (Yes/No) and treatment, as fixed factors in the model, and M-week 0 levels as a covariate in the model.

The endpoints will be tested using the type I error rate of 0.05, and a two-sided test. Results will be presented using the least square means by treatment group and difference between groups together with the corresponding 95% confidence intervals. Data will be presented for the observed data in all summary presentations and analyses. There will be no adjustment for multiplicity.

Nominal p-values will be displayed for all efficacy endpoint treatment comparisons.

10.3.5 Exploratory Endpoint Analyses

Exploratory endpoints will be analysed and summarised using the same methods as those for the secondary endpoints. There will be no adjustment for multiplicity. Nominal p-values will be displayed for all treatment comparisons.

10.3.6 Safety Analyses

Safety analyses will be provided separately for the induction and maintenance studies and will be based on SAF and SAFM, including participants who received at least one dose of study intervention in each respective study.

Participants in the losing cobitolimod treatment arm, and non-randomised participants in the maintenance study will be summarised separately using descriptive statistics.

10.3.6.1 Analyses of Adverse Events

The number and percentage of participants reporting AEs, and the number of AEs (events) reported, will be presented. The events will be tabulated by system organ class and preferred term. In addition, summaries by relationship to study drug and severity will be presented. SAEs will also be presented in separate tabulations. The number of participants experiencing an AE will be compared descriptively between groups. All participants with AEs will be listed individually with participant number in addition to type of event, start and stop time, duration, seriousness, severity, action taken, relationship to study drug and outcome of AE.

10.3.6.2 Other Safety Assessments

All continuous safety variables, such as laboratory measurements, vital signs, ECG parameters and body weight will be described using summary statistics. Changes from baseline will also be summarised as appropriate. All categorical variables, such as physical examination, will be summarised using frequencies and percentages. The safety will include laboratory safety variables and/or adverse clinical findings as appropriate. Laboratory data will also be presented in shift tables for selected parameters, where the number of values within, below and above laboratory reference range will be displayed.

10.3.7 Other Analyses

10.3.7.1 Medical Resource Utilisation Analyses

Data will be summarised using descriptive statistics.

10.3.8 Covariates

The stratification factors used in the induction study are prior treatment with biologics or JAK-inhibitors (Yes/No), and GCS use at I-week 0 (Yes/No). These factors will be used as covariates to assess the treatment effect in the induction study. If a participant was assigned to the wrong stratum at randomisation, their actual stratum will be used for the statistical analyses. In addition, the I-week 0 value of continuous efficacy endpoints will be used as a covariate when the treatment effect is assessed on the change from baseline for the efficacy endpoint.

In the efficacy evaluation of the maintenance study, the clinical remission status (Yes/No) and use of GCS at M-week 0 (Yes/No) be used as covariates in the statistical analyses.

10.3.9 Missing Data

For the primary and key secondary efficacy analyses, missing data will be replaced using the NRI method. NRI will be used where missing data are replaced with a negative outcome, i.e.,

interpreted as a non-responder to the intervention, e.g., no clinical remission in the primary endpoint. Additional methods for imputation of missing data, such as the PMI method [22] assuming that the statistical behaviour of placebo and cobitolimod treated participants after dropout is the statistical behaviour of placebo treated participants, and more, will be used as a sensitivity analysis for evaluation of study data. All methods for handling missing data and the estimands will be described more comprehensively in the SAP.

Treatment failures override missing data rules. If a participant has an event which can be considered as a treatment failure e.g., use of rescue medications, baseline values will be assigned from the point of treatment failure and onward for continuous endpoints, and participants will be considered as not achieving the respective endpoints for binary endpoints, including the primary endpoint, regardless of whether the data were observed or missing.

Missing data for safety endpoints will not be imputed and will be left as missing.

10.4 Interim Analysis

The DMC will evaluate the interim analysis and its members will be independent from the study team and the sponsor. The criteria for dropping the loser arm will be based on the primary endpoint, secondary endpoints and available safety data. Selection criteria and decision scenarios will be presented in detail in the IAP. Posterior probabilities for the efficacy in the cobitolimod 250 mg and 500 mg treatment arms compared to placebo regarding the primary endpoint will be calculated. A posterior probability of 95% or more will be the preferable choice to be selected as the winning dose. If both dose-arms do not meet the posterior probability of >95%, the dose with the highest efficacy with absence of harm in safety is selected. If both dose-arms are meeting a posterior probability >95%, the dose with the best efficacy with the absence of harm is preferable.

Also, a futility analysis during the induction study is planned; this will be based on the primary endpoint of clinical remission at I-week 6 and will be performed using the same data set used for the exploratory dose selection. The study may be stopped for futility when the conditional power (i.e., the predictive probability of success at the end of the study, given the data at the interim analysis) is less than 15%.

This futility analysis will result in minimal loss in power ($\leq 2\%$ when the treatment effect is in the range of 12%) and will affect the overall type I error rate (0.05, and 2-sided test) for the primary endpoint analysis and key secondary endpoints, marginally. A small alpha of 0.00001 will be allocated for this interim analysis. Further details of the futility analysis will be presented in the IAP.

There will be a blinded monitoring of data in the maintenance study after approximately 100 participants have passed M-week 45 after randomisation in the maintenance study. The aims are to estimate the amount of discontinuations (missing data), to control the assumptions made in terms of subgroup and stratification factors, and to check the blinded overall event rates for the primary and key secondary endpoints.

If the outcome of the monitoring indicates a potential weakened statistical power for the primary endpoint, the study sample size in the induction 2 and the subsequent maintenance study may be extended to maintain the targeted study power of the maintenance study.

The monitoring does not require access to information on comparative treatment effects, nor unblinding of data, and therefore has no impact on the type I error.

10.5 Sample Size Determination Induction

Sample size and power calculations were based on the Chi-square test to detect a significant ($p < 0.05$) difference for the primary endpoint of clinical remission at I-week 6 between two study treatment arms, cobitolimod and placebo.

The goal is to have at least 90% power to detect a clinically relevant difference of at least 12 percentage points between cobitolimod and placebo, assuming a placebo clinical remission rate of 10%.

Assumptions:

- a 7-10% remission rate for the placebo
- a type I error rate of 0.05
- an 18-24% remission rate for the active cobitolimod treatment arm
- a power of 90%
- a two-sided test for differences between treatment arms

The target is to recruit at least 396 participants (198 per group) to the one and finally selected winning dose arm of cobitolimod and one placebo arm, to satisfy the power goal (Table 7).

Sample size calculation for the key secondary endpoint of proportion of participants with endoscopic improvement, to detect a difference of at least 12 percentage points between cobitolimod and placebo, assuming a placebo endoscopic improvement rate of 18% (vs 30% in the cobitolimod arm), with at least 80 % power, reveals that the study requires at least 396 participants (198 per group).

It is assumed that there will be 5% missing data in the induction study.

Table 7. Power and Sample Size calculations for Detecting a Difference Between Treatments at I- week 6.

Proportion of Clinical Remission (Two arms)					
Placebo	Cobitolimod 250 mg/500 mg	Power	n/group	n Total	
7%	18%	90%	188	376	
7%	19%	90%	163	326	
7%	20%	90%	144	288	
8%	19%	90%	201	402	
8%	20%	90%	174	348	
9%	20%	90%	214	428	
9%	21%	90%	184	368	
10%	22%	90%	195	390	
10%	23%	90%	170	340	
10%	24%	90%	150	300	

Power calculation was performed using the Chi-square test for independent groups. Nquery 7.0 was used for power calculation.

10.6 Sample Size: Induction, Stage 1

The induction study will consist of two stages: stage 1 for exploratory purposes to select one of the two cobitolimod treatment arms and to drop-the-loser dose arm, where the winning cobitolimod treatment arm and the placebo arm will continue until the end of the study in stage 2.

The exploratory evaluation of stage 1, regarding efficacy, will be done after approximately 132 (44+44+44) participants have been randomised and have available data for the primary endpoint. Based on simulations with a Bayesian statistical approach using a non-informative Beta-distribution, this sample is considered sufficiently large to achieve reasonable precision in the estimation of effect size for calculation of posterior probabilities for the cobitolimod 250 mg and 500 mg dose arms. An interim analysis outcome where 11 of 44 participants in a cobitolimod treatment arm and 5 of 44 participants in the placebo arm will have a posterior probability > 95%, i.e., a delta (difference) of 13.6%.

10.6.1 Sample Size: Maintenance

Sample size and power calculations were based on the Chi-square test to detect a significant ($p < 0.05$) difference for the primary endpoint of clinical remission at M-week 45 between two study treatment arms, cobitolimod (winning dose) and placebo.

The goal is to have at least 90% power to detect a clinically relevant difference of at least 20 percentage points between cobitolimod and placebo, assuming a placebo clinical remission rate at M-week 45 of 25%.

Assumptions

- a 25% remission rate for placebo
- a type I error rate of 0.05
- a 45% remission rate for the active cobitolimod treatment arm
- a power of 90%
- a two-sided test for differences between treatment arms

In total 236 participants (118 per treatment arm) are needed to satisfy the power goal. The target is to recruit at least 250 participants from the induction 1 and 2 studies.

It is assumed that 15% of the participants in cobitolimod group and 30% of the participants in the placebo group will discontinue from the maintenance study.

11 Data Handling

11.1 Data Handling

██████████ will be responsible for the processing and quality control of the data. Data management will be carried out as described in ██████████ SOPs for clinical studies. Handling of data, including data quality control, will comply with regulatory guidelines (e.g., ICH and GCP) and ██████████ SOP and working instructions. The Data Management procedures will be detailed in a written Data Management Plan approved by InDex Pharmaceuticals.

All source data will be identified at the start of the study. Participant eDiary data and laboratory data will be considered as source data, and all other data (if not noted on the source data log) will be entered in the eCRF by site staff based on the source data. Data Management routines include procedures for handling the eCRF, database set up and handling, data verification and entry, data validation, database quality control and documentation of activities performed, including information on discrepancies in the procedure.

The investigator must ensure the accuracy, completeness, legibility, and timeliness of data reported in the eCRF and all required reports. Any change or correction to the eCRF must be dated, signed, and explained (if necessary) and must not obscure the original entry. This process applies to both written and electronic changes.

eCRF reported data that are derived from source documents should be consistent with the source documents, or the discrepancies must be explained.

Within three (3) days of completion of each participant visit, the investigator should agree to have completed and entered data into the eCRF for review.

The initial notification of SAEs will also be entered in ██████████ safety database for coding, medical evaluation and notification to the health authorities and independent EC according to national regulatory requirements.

11.2 Data Management

The Data Management routines include procedures for handling of eCRFs, database setup and management, data entry and verification, data validation, quality control of database, and documentation of the performed activities, including handling of discrepancies in the process. The database, data entry screens and programme will be designed in accordance with the clinical study protocol and will be described in a Data Management guideline.

11.2.1 Electronic Case Report Form

Clinical data (including AEs and concomitant medications) will be entered into a 21 CFR Part 11-compliant electronic data capture system. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete or inaccurate. Clinical data will be entered directly from the source documents.

Authorised study site personnel designated by the PI will complete data collection. Appropriate training and security measures will be completed with the PI and all authorised study site personnel, prior to the study being initiated and any data being entered into the system for any study participants.

11.2.2 Entry of Data

All data must be entered in English. The eCRFs should always reflect the latest observations of participants participating in the study. Therefore, the eCRF is to be completed as soon as

possible during or after the participant's visit (within 3 days). All terms will be coded using the MedDRA Dictionary. The PI must verify that all data entries in the eCRF are accurate and correct. If some assessments are not done, or if certain information is not available, not applicable or unknown, the PI should indicate this in the eCRF. The PI will be required to electronically sign off the clinical data.

Guidelines for CRF completion will be provided before study start.

The participant will fill in eDiary data on a daily basis during the induction study. During maintenance, the participant will be asked to enter data 10 days prior to each visit (virtual/site).

11.2.3 Query Process

The CRA will review the eCRF and evaluate for completeness and consistency. Each eCRF will be compared with the respective source documents to ensure that there are no discrepancies between critical data. All entries, corrections and alterations are to be made by the PI or his/her designee. The CRO staff cannot enter data in the eCRFs. Once clinical data of the eCRF have been submitted to the central server, corrections to the data fields will be audit trailed, meaning that the reason for change, the name of the person who performed the change, and the time and date will be logged. Rules and rights of the site personnel responsible for entering the clinical data into the eCRF will be determined in advance. If additional corrections are needed, the responsible monitor or Data Manager will raise a query in the electronic data capture application. The appropriate investigational staff will answer queries sent to the PI. This will be audit trailed by the electronic data capture application meaning that the names of investigational staff, time and date are logged.

11.2.4 Source Documents

The eCRF is essentially considered a data entry form and should not constitute the original (or source) medical records unless otherwise specified. Source documents are all documents used by the PI or hospital that relate to the participant's medical history, that verify the existence of the participant, and that relate to the inclusion and exclusion criteria, and all records covering the participant's participation in the study. They include laboratory notes, memoranda, material dispensing records, participant files etc.

Participant-reported eDiary data are counted as source and will not undergo source data verification by CRO staff. The participant can be source for some data points but that should be stated in the source verification list at study start.

The PI is responsible for maintaining source documents. These will be made available for inspection by the study monitor at each monitoring visit. The PI must submit a completed eCRF for each participant who signed the written ICF. All supportive documentation submitted with the eCRF, such as laboratory or hospital records, should be clearly identified with the study number and the participant number. Any personal information, including participant name, should be removed, or rendered illegible to preserve individual confidentiality.

11.2.5 User Identification

eCRF records will be automatically appended with the identification of the creator, by means of their unique UserID. Specified records will be electronically signed by the PI to document his/her review of the data and acknowledgement that the data are accurate. This will be facilitated by means of the PI's unique UserID and password; date and time stamps will be added automatically at time of electronic signature. If an entry in an eCRF requires change, the correction should be made in accordance with the relevant software procedures.

11.2.6 Audit Trail

All changes will be fully recorded in a protected audit trail, and a reason for the change will be required.

Once all data have been entered, verified and validated, the database will be locked.

11.2.7 Medical Review of Safety Data

All available demographic and safety data (including, but not limited to, cumulative listings of AE and SAE reports, laboratory data, vital signs and physical examinations) will be reviewed in a blinded fashion continuously during the study. The DMC will be informed in case of any relevant findings such as identified safety signals. Based on these ongoing reviews, the DMC may make recommendations and InDex Pharmaceuticals may halt the enrolment, modify the dose level, add, or modify safety procedures or discontinue the study.

11.3 Study Monitoring and Auditing

This study will be monitored at all stages of its development by InDex Pharmaceutical's representative [REDACTED]. Monitoring will include personal visits and telephone communication to assure that the investigation is conducted according to the protocol and to comply with guidelines of ICH-GCP. On-site review of CRFs will include a review of forms for completeness and clarity, and consistency with source documents available for each participant.

Any data recorded directly in the eCRF, for which no other written or electronic record will be maintained in the participant's medical record, will be considered source data and should be signed by the investigator (e.g., results of physical examinations, vital signs, or the study intervention administration procedure). During monitoring visits, the data recorded in the eCRFs, source document, and other study-related records will be compared against each other in order to ensure accurate data that reflect the actual experience of the participant in the study, i.e., source data verification. The Monitoring Plan will state the level of verification. Data points that are entered electronically by participants will be counted as source.

The investigator and appropriate personnel will be periodically requested to attend meetings/trainings organised by the sponsor [REDACTED] to assure acceptable protocol execution. The study may be audited by InDex Pharmaceuticals or inspected by regulatory authorities. If such an audit inspection occurs, the investigator must agree to allow access to required participant records. By signing this protocol, the investigator grants permission to personnel from InDex Pharmaceuticals, its representatives, and appropriate Clinical Research Associates for on-site monitoring of all appropriate study documentation, as well as on-site review of the procedures employed in the eCRF generation, where clinically appropriate.

11.4 Retention of Records

The investigator must arrange for retention of study records at the site. The nature of the records and the duration of the retention period must meet the requirements of the relevant regulatory authorities. In addition, because this is an international study, the retention period must meet the requirements of the most stringent authority. The investigator should take measures to prevent accidental or premature destruction of these documents.

11.5 Use of Study Findings

By signing the study protocol, the investigator agrees to the use of results of the study for the purposes of national and international registration. If necessary, the authorities will be notified of the investigator's name, address, qualifications and extent of involvement. Clinical study

reports covering clinical and biometric aspects of the study will be prepared by InDex Pharmaceuticals or delegate.

12 Ethical Requirements

12.1 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, regulatory requirements, GCP and the ethical principles of the Declaration of Helsinki and Council for International Organisations of Medical Sciences (CIOMS) international. The final study protocol, including any substantial amendments and the final version of the participant information and consent form, will be reviewed and approved by regional IECs and by the regulatory authorities in each country prior to inclusion of participants.

12.2 Indemnification

InDex Pharmaceuticals indemnification of the investigator and institution during the conduct of this study is addressed in a letter of indemnification provided as a separate document. Other indemnification or insurance will be provided as necessary under local regulations.

With respect to any injury directly or indirectly caused by the study intervention to the participant during this study, InDex Pharmaceuticals assumes liability by law on behalf of the Investigator(s), provided the Investigator/delegate has followed the instructions of InDex Pharmaceuticals in accordance with this protocol and any amendments thereto, that the study intervention administered to the participant in this study has been supplied by InDex Pharmaceuticals and that the Investigator/delegate has generally performed this study in accordance with scientific practice and currently acceptable techniques and know-how.

The participants are covered by insurances held by InDex Pharmaceuticals.

12.3 Sponsor Discontinuation Criteria

InDex Pharmaceuticals reserves the right to discontinue the study at a site or at multiple sites for safety or administrative reasons at any time. In particular, a site that does not recruit at a reasonable rate or is non-compliant with the study protocol or study procedure may be discontinued. Should the study be terminated and/or the site closed for whatever reason, all documentation and study intervention pertaining to the study must be returned to InDex Pharmaceuticals or its representative.

13 Study Committees

13.1 Data Monitoring Committee

Participant safety will be continuously monitored by an independent DMC, composed of representatives from outside of InDex Pharmaceuticals who are experts in their respective disciplines of medicine, statistics and clinical study methodology and conduct. They will review accumulating safety data for safety signal detection in the context of the overall study.

The DMC will together with InDex Pharmaceuticals and [REDACTED] determine the appropriate time frame for reviewing the data during the course of the study and will draw up a DMC charter delineating their guidelines for operating and stopping rules for terminating individual participants, a portion or all of the study prematurely. Based on the reviews the DMC will have the capacity to make recommendations to InDex Pharmaceuticals that might impact the future conduct of the study.

The DMC will also review the interim analysis results from stage 1 of the induction study and form recommendation to the sponsor about the “winning” dose of cobitolimod. Details will be provided in the separate DMC charter and IAP.

In the context of overall participant safety, the DMC will receive online access to all data including a pre-defined safety data package containing a summary update and individual data for selected variables, recruitment rates, number of participants for each visit, dropouts, completeness of eCRFs and data entry and information on AEs and SAEs.

Furthermore, the DMC will be notified of clinically significant abnormal laboratory test values (defined in the DMC charter) of defined variables included in the safety data package.

The DMC will have access to all study data. It may request and will be provided with whatever data it deems necessary or useful to carry out its duties.

14 Publication/Data Sharing Policy

Results from this study are the property of InDex Pharmaceuticals and the data from this study will first be published by InDex Pharmaceuticals. Authors will be decided by InDex Pharmaceuticals. The Investigators will be acknowledged in the publication(s). In the case that individual Investigator(s) wish to publish their own data from this study, InDex Pharmaceuticals will be given not less than 60 days for review and comments for a manuscript and not less than 30 days for an abstract. In case of a difference in opinion, in order to protect their proprietary interests, InDex Pharmaceuticals has the right to delay the submission for an additional 60 days.

15 References

1. Atreya, R., Bloom, S., Scaldaferri, F., Gerardi, V., Admyre, C., Karlsson, A., Knittel, T., Kowalski, J., Lukas, M., Lofberg, R., Nancey, S., Petryka, R., Rydzewska, G., Schnabel, R., Seidler, U., Neurath, M.F., and Hawkey, C. (2016). Clinical Effects of a Topically Applied Toll-like Receptor 9 Agonist in Active Moderate-to-Severe Ulcerative Colitis. *J Crohns Colitis*. 10(11): p. 1294-1302. DOI: 10.1093/ecco-jcc/jjw103.
2. Atreya, R., Peyrin-Biroulet, L., Klymenko, A., Augustyn, M., Bakulin, I., Slankamenac, D., Miheller, P., Gasbarrini, A., Hebuterne, X., Arnesson, K., Knittel, T., Kowalski, J., Neurath, M.F., Sandborn, W.J., Reinisch, W., and group, C.s. (2020). Cobitolimod for moderate-to-severe, left-sided ulcerative colitis (CONDUCT): a phase 2b randomised, double-blind, placebo-controlled, dose-ranging induction trial. *Lancet Gastroenterol Hepatol*. 5(12): p. 1063-1075. DOI: 10.1016/S2468-1253(20)30301-0.
3. Danese, S. and Fiocchi, C. (2011). Ulcerative colitis. *N Engl J Med*, 365(18): p. 1713-25.
4. Gajendran, M., Loganathan, P., Jimenez, G., Catinella, A.P., Ng, N., Umapathy, C., Ziade, N., and Hashash, J.G. (2019). A comprehensive review and update on ulcerative colitis. *Dis Mon*, 65(12): p. 100851.
5. Ungaro, R., Mehandru, S., Allen, P.B., Peyrin-Biroulet, L., and Colombel, J.F. (2017). Ulcerative colitis. *Lancet*, 389(10080): p. 1756-1770.
6. Kobayashi, T., Siegmund, B., Le Berre, C., Wei, S.C., Ferrante, M., Shen, B., Bernstein, C.N., Danese, S., Peyrin-Biroulet, L., and Hibi, T. (2020). Ulcerative colitis. *Nat Rev Dis Primers*, 6(1): p. 74.
7. Sutherland, L.R., Martin, F., Greer, S., Robinson, M., Greenberger, N., Saibil, F., Martin, T., Sparr, J., Prokipchuk, E., and Borgn, L. (1987). 5-Aminosalicylic acid enema in the treatment of ulcerative colitis, proctosigmoiditis and proctitis. *Gastroenterology*, 92: p. 1894-1898.
8. Domenech, E., Manosa, M., and Cabre, E. (2014). An overview of the natural history of inflammatory bowel diseases. *Dig Dis*, 32(4): p. 320-7.
9. Prantera, C. and Marconi, S. (2013). Glucocorticosteroids in the treatment of inflammatory bowel disease and approaches to minimizing systemic activity. *Therap Adv Gastroenterol*, 6(2): p. 137-56.
10. Ford, A.C., Sandborn, W.J., Khan, K.J., Hanauer, S.B., Talley, N.J., and Moayyedi, P. (2011). Efficacy of biological therapies in inflammatory bowel disease: systematic review and meta-analysis. *Am J Gastroenterol*, 106(4): p. 644-59, quiz 660.
11. Troncone, E., Marafini, I., Del Vecchio Blanco, G., Di Grazia, A., and Monteleone, G. (2020). Novel therapeutic options for people with ulcerative colitis: an update on recent developments with Janus Kinase (JAK) inhibitors. *Clin Exp Gastroenterol*, 13: p. 131-139.
12. EMA. (2020). EMA confirms Xeljanz to be used with caution in patients at high risk of blood clots. EMA/92517/2020. E.s.s.c. (PRAC). European Medicines Agency, EMA/92517/2020.
13. FDA. (2019). Safety trial finds risk of blood clots in the lungs and death with higher dose of tofacitinib (Xeljanz, Xeljanz XR) in rheumatoid arthritis patients; FDA to investigate. U.S.F.a.D. Administration. Safety Communications.
14. Devlin, N.J. and Brooks, R. (2017). EQ-5D and the EuroQol Group: Past, Present and Future. *Appl Health Econ Health Policy*, 15(2): p. 127-137.

15. European Quality of Life Group. (2009). Health Questionnaire (EQ-5D-5L). Available from: www.euroqol.org.
16. Levine, J.S. and Burakoff, R. (2011). Extraintestinal manifestations of inflammatory bowel disease. *Gastroenterol Hepatol* (N Y), 7(4): p. 235-41.
17. Ma, C., Sedano, R., Almradi, A., Casteele, N.V., Parker, C.E., Guizzetti, L., Schaeffer, D.F., Riddell, R.H., Pai, R.K., Battat, R., Sands, B.E., Rosty, C., Dubinsky, M.C., Rieder, F., Harpaz, N., Abreu, M.T., Bryant, R.V., Lauwers, G.Y., Kirsch, R., Valasek, M.A., Crowley, E., Sandborn, W.J., Feagan, B.G., Pai, R.K., and Jairath, V. (2021). An International Consensus to Standardize Integration of Histopathology in Ulcerative Colitis Clinical Trials. *Gastroenterology*. 10.1053/j.gastro.2021.02.035. DOI: 10.1053/j.gastro.2021.02.035.
18. Mosli, M.H., Feagan, B.G., Zou, G., Sandborn, W.J., D'Haens, G., Khanna, R., Shackelton, L.M., Walker, C.W., Nelson, S., Vandervoort, M.K., Frisbie, V., Samaan, M.A., Jairath, V., Driman, D.K., Geboes, K., Valasek, M.A., Pai, R.K., Lauwers, G.Y., Riddell, R., Stitt, L.W., and Levesque, B.G. (2017). Development and validation of a histological index for UC. *Gut*, 66(1): p. 50-58.
19. Cheung, W.Y., Garratt, A.M., Russell, I.T., and Williams, J.G. (2000). The UK IBDQ- a British version of the inflammatory bowel disease questionnaire. development and validation. *J Clin Epidemiol*, 53(3): p. 297-306.
20. Irvine, E.J., Feagan, B., Rochon, J., Archambault, A., Fedorak, R.N., Groll, A., Kinnear, D., Saibil, F., and McDonald, J.W. (1994). Quality of life: a valid and reliable measure of therapeutic efficacy in the treatment of inflammatory bowel disease. Canadian Crohn's Relapse Prevention Trial Study Group. *Gastroenterology*, 106(2): p. 287-96.
21. Schroeder, K.W., Tremaine, W.J., and Ilstrup, D.M. (1987). Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med*, 317(26): p. 1625-9.
22. Ayele, B.T., Lipkovich, I., Molenberghs, G., and Mallinckrodt, C.H. (2014). A multiple-imputation-based approach to sensitivity analyses and effectiveness assessments in longitudinal clinical trials. *J Biopharm Stat*, 24(2): p. 211-28.
23. FDA. (2016). Ulcerative colitis: clinical trial endpoints guidance for industry. FDA-2016-D-2319. U.S.D.o.H.a.H. Services. Guidance. Food and Drug Administration (FDA), 15028dft.

16 Appendices

16.1 Mayo Scoring System for Assessment of Ulcerative Colitis Activity

Grade	Stool frequency ^{a, b}	Rectal Bleeding ^{a, c}	Physician's global assessment ^{a, d}	Colonoscopy/sigmoidoscopy finding ^a
0	Normal number of stools for this participant	No blood seen	Normal or no disease	Normal or inactive disease
1	1 to 2 stools more than normal	Streaks of blood with stool less than half the time	Mild disease	Mild disease (erythema, decreased vascular pattern)
2	3 to 4 stools more than normal	Obvious blood with stool most of the time	Moderate disease	Moderate disease (marked erythema, lack of vascular pattern, friability, erosions)
3	5 or more stools more than normal	Blood alone passed	Severe disease	Severe disease (spontaneous bleeding, ulceration)

^a The 2-component Mayo score (stool frequency and rectal bleeding score) ranges from 0-6. The 3-component Mayo score (endoscopic-, stool frequency- and rectal bleeding score) ranges from 0-9. The 4-component Mayo score (endoscopic-, stool frequency-, rectal bleeding- and PGA score) ranges from 0-12, with higher scores indicating more severe disease.

^b At the screening visit, each participant indicates the number of stools he/she passed in a 24-hour period when in remission or before his/her UC diagnosis, thereby serving as his/her own control to establish the degree of abnormality of the stool frequency.

^c The daily bleeding score represents the most severe bleeding of the day.

^d The PGA acknowledges the 3 other criteria, the participant's daily recall of abdominal discomfort and general sense of well-being, and other observations, such as physical findings and the participant's performance status.

Adapted from: Schroder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med 1987;317(26):1625-9. [21]

16.2 Definitions of Stool Frequency and Rectal Bleeding

Items	Definition
Definition of stool	Participants should be instructed that a stool is defined as a trip to the toilet when the participant has either a bowel movement, or passes blood alone, blood and mucus, or mucus only.
Reference remission stool frequency (over 24 hours)	The participant should be asked to identify at the visit 1a how many stools he or she had in a 24-hour period when in remission from UC. • If the participant does not report that he or she has achieved remission, then the participant should be asked to identify the number of stools he or she had per day before initial onset of signs and symptoms of UC. • Sponsors should record if the reference remission stool frequency is based on reported stool frequency when the participant was in remission or reported stool frequency before initial onset of signs and symptoms of UC. • Both the remission and pre-UC stool frequency should be collected at baseline. This allows exploration of the natural history of pre-diagnosis stool frequency versus remission stool frequency.
Most severe category of rectal bleeding (in a given 24-hour period)	Participants should be instructed to indicate the most severe category that describes the amount of blood they had in their stools for a given day. • Categories of rectal bleeding should be defined as follows: – No blood seen. – Streaks of blood with stool less than half the time. – Obvious blood (more than just streaks) or streaks of blood with stool most of the time. – Blood alone passed. Participants should be instructed to select “No Blood Seen” in the rectal bleeding section if they do not have stool during a given day.

Adapted from Ulcerative Colitis Clinical Trial Endpoints, Guidance for Industry, FDA, draft AUG 2016. [23]

16.3 Robarts Histological Index

Chronic inflammatory infiltrate	Lamina propria neutrophils	Neutrophils in epithelium	Erosion or ulceration
0 = No increase	0 = None	0 = None	0 = No erosion, ulceration, or granulation
1 = Mild but unequivocal increase	1 = Mild but unequivocal increase	1 = <5% crypts involved	1 = recovering epithelium + adjacent inflammation
2 = Moderate increase	2 = Moderate increase	2 = <50% crypts involved	2 = unequivocal erosion
3 = Marked increase	3 = Marked increase	3 = >50% crypts involved	3 = ulcer or granulation tissue

Adapted from; Development and validation of a histological index for UC, Mosli et. Al 2017 [\[18\]](#)

16.4 Extraintestinal Manifestations of Inflammatory Bowel Disease

Sites	Extraintestinal manifestations
Musculoskeletal system	• Arthritis; colitic type, ankylosing spondylitis, isolated joint involvement • Hypertrophic osteoarthropathy: clubbing, periostitis • Miscellaneous manifestations: osteoporosis, aseptic necrosis, polymyositis
Dermatologic and oral systems	• Reactive lesions: erythema nodosum, pyoderma gangrenosum, aphthous ulcers, necrotizing vasculitis • Specific lesions: fissures, fistulas, oral Crohn's disease, drug rashes • Nutritional deficiencies: acrodermatitis enteropathica, purpura, glossitis, hair loss, brittle nails • Associated diseases: vitiligo, psoriasis, amyloidosis
Hepatopancreatobiliary system	• Primary sclerosing cholangitis, bile-duct carcinoma • Associated inflammation, autoimmune chronic active hepatitis, pericholangitis, portal fibrosis, cirrhosis, granulomatous disease • Metabolic manifestations: fatty liver, gallstones associated with ileal Crohn's disease
Ocular system	• Uveitis/iritis, episcleritis, scleromalacia, corneal ulcers, retinal vascular disease
Metabolic system	• Growth retardation in children and adolescents, delayed sexual maturation
Renal system	• Calcium oxalate stones

from: *Gastroenterol Hepatol (N Y)*. 2011 Apr; 7(4):235-241. [[16](#)]

16.5 Definitions: Efficacy Endpoints

Evaluation of efficacy endpoints will be done using the following definitions:

Endpoint	Definition
Absence of rectal bleeding	Rectal bleeding score of 0
Clinical remission (by the 3-component Mayo score)	• Rectal bleeding score of 0 and • Stool frequency score of 0 or 1 (with at least one (1) point decrease from I-week 0 if 1 at I-week 0) and • Endoscopic score of 0 or 1 (excluding friability)
Clinical remission, based on the 4-component Mayo score	• Rectal bleeding score of 0 and • Stool frequency score of 0 or 1 (with at least one (1) point decrease from I-week 0 if 1 at I-week 0) and • Endoscopic score of 0 or 1 (excluding friability) and • PGA of 0 or 1 and • Each of all Mayo sub scores ≤ 2
Clinical remission at M-week 45 among those who achieved clinical remission at I-week 6 (by the 3-component Mayo score)	Based on participants with clinical remission (Yes) at I-week 6 in the maintenance study
Clinical response (by the 3-component Mayo score)	Decrease in 3-component Mayo sum score from I - week 0 of at least two (2) points and at least 35% with either a) at least one (1) point decrease in rectal bleeding or b) a rectal bleeding subscore of 0 or 1
Endoscopic improvement	Endoscopic score of 0 or 1
Endoscopic remission	Endoscopic score of 0
50% reduction in faecal calprotectin	A 50% decrease or more in the FCP levels from I - week 0
Histologic remission	• RHI ≤ 3, and • lamina propria neutrophils = 0, and • neutrophils in the epithelium = 0

Histologic improvement	≥ 7 -point RHI decrease from I-week 0
Improvement in IBDQ	≥ 16 -point increase in the IBDQ total score compared to I-week 0
Mucosal healing	Endoscopic improvement and histological remission
Mucosal improvement	Endoscopic improvement and histological improvement
Normalisation of CRP	CRP ≤ 5 mg/L
Normalisation of faecal calprotectin	FCP < 250 mg/kg
Normalisation of IBDQ	IBDQ total score ≥ 170
Normalisation of stool frequency	Stool frequency score of 0 or 1 (with at least one (1) point decrease from I-week 0 if 1 at I-week 0)
Steroid-free remission for at least 8 weeks	Proportion of participants with clinical remission at M-week 45 and steroid-free for at least 8 weeks prior M-week 45.
Symptomatic remission (defined by the 2-component Mayo score)	• Rectal bleeding score of 0 and • Stool frequency score of 0 or 1 (with at least one (1) point decrease from I-week 0 if ≥ 1 at I-week 0)
Time to major UC related events	Number of days from I-week 0 to the day at which the major UC event occurred
Time to loss of response	Number of days from M-week 0 to date at which a loss of response. was confirmed by endoscopy.