CONFIDENTIAL

NCT 03178669

CLINICAL STUDY PROTOCOL

(including synopsis)

Protocol Title:	A Randomised Dose-Optimisation Study to Evaluate the Efficacy and Safety of Cobitolimod in Moderate to Severe Active Ulcerative Colitis Patients
Protocol Number:	CSUC-01/16
EudraCT Number:	2016-004217-26
Phase:	IIb
Study Sponsor:	InDex Pharmaceuticals AB
Protocol Version:	1.1
Version Date:	19JAN2017

Dataprotection

STATEMENT OF COMPLIANCE

This study will be conducted in accordance with this Clinical Study Protocol, CSUC-01/16 version 1.1, dated 19JAN2017 and also 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).
- European Clinical Trial and Food and Drug Administration Directives
- Respective local laws and regulations.
- Regulatory requirements for reporting of serious adverse events

_____ DATE:_____

[redacted]

_____ DATE:_____

[redacted]

SIGNATURE PAGE

The signature below constitutes that I have read and agreed to protocol. CSUC-01/16 version 1.1, dated 19JAN2017. I am aware of my responsibilities as an investigator under Good Clinical Practice (GCP), Helsinki Declaration, European Clinical Trials Directives, Food Drug Administration (FDA) and local regulations (as applicable) and the study protocol.

I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff who will be involved in the study.

Investigator´s Signature: _____ Date: _____

Name (print): _____

KEY ROLES AND CONTACT INFORMATION

COORDINATING INVESTIGATOR	Dataprotection [redacted]
PROJECT MANAGER	[redacted]
STUDY SPONSOR	[redacted]
SPONSORS CLINICAL TRIAL MANAGER	[redacted]
STUDY MEDICAL MONITOR	[redacted]
STUDY MEDICAL ADVISOR	[redacted]

STATISTICIAN	[redacted]
DATA MANAGEMENT	
SAFETY HANDLING	
CLINICAL LABORATORY	

TABLE OF CONTENTS

Tables in Text

Figures in Text

LIST OF ABBREVIATIONS

5-ASA	5-Aminosalicylic Acid
6-MP	6-Mercaptopurine
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
AZA	Azathiopurine
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CAI	Clinical Activity Index
CPK	Creatine Phosphokinase
CRO	Contract Research Organisation
CRP	C-reactive Protein
CSUC	Clinical Study Ulcerative Colitis
CU-UC	Compassionate Use Ulcerative Colitis
DNA	Deoxyribonucleic Acid
DSMB	Data Safety Monitoring Board
ECCO	European Crohn´s and Colitis Organisation
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EC	Ethics Committee
EU	European Union
FAS	Full Analysis Set
GCS	Glucocorticosteroids
GGT	Gamma-Glutamyl Transpeptidase
HR	Heart Rate
IBDQ	Inflammatory Bowel Disease Questionnaire
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IL-10	Interleukin 10
ITT	Intention-to-Treat
IV	Intravenous

IVRS	Interactive Voice Response System
LFT	Liver Function Test
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	No Observed Adverse Effect Level
NSAID	Non-Steroidal Anti-inflammatory Drugs
NRI	Non Responder Imputation
PI	Principal Investigator
PGA	Physicians Global Assessment
PPS	Per Protocol Analysis Set
PRO	Patient Reported Outcome
PT	Prothrombin Time
QOL	Quality of Life
RBC	Red Blood Cells
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SOP	Standard Operating Procedures
SP	Sulphasalazine
SUSAR	Suspected Unexpected Serious Adverse Reaction
TPMT	Thiopurine Methyltransferase
TNFα	Tumour Necrosis Factor Alpha
UC	Ulcerative Colitis
US	United States
WBC	White Blood Cells

Clinical Study Synopsis
CSUC-01/16

SYNOPSIS

Name of the Sponsor/Company: InDex Pharmaceuticals AB
Name of Active Ingredient/Product: Cobitolimod (earlier named Kappaproct®) and/or DIMS0150, (deoxyribonucleic acid-based immunomodulatory sequence 0150)
STUDY CODE: CSUC-01/16
A Randomised Dose Optimisation Study to Evaluate the Efficacy and Safety of Cobitolimod in Moderate to Severe Active Ulcerative Colitis Patients
INVESTIGATOR(S): TBD
STUDY CENTRE(S): Approximately 90 European sites will participate in the study.
PHASE OF DEVELOPMENT: Phase IIb
STUDY OBJECTIVES: **Primary Objective** To evaluate the efficacy of cobitolimod treatment at different dose levels and frequencies compared to placebo with regard to clinical remission 6 weeks after first treatment, in patients with moderate to severe active ulcerative colitis (UC). **Secondary Objectives** • To evaluate the safety and tolerability of cobitolimod. • To evaluate the efficacy of cobitolimod treatment compared to placebo in clinical remission, clinical response and clinical symptoms. • To evaluate the efficacy of cobitolimod treatment compared to placebo in endoscopic and histological remission and response. • To evaluate the effect of cobitolimod on quality of life (QOL).
STUDY DESIGN: This phase IIb study is a randomised, double-blind, dose-optimisation study, of cobitolimod compared to placebo. The study population will be patients with moderate to severe active UC who are no longer responding adequately, to conventional therapies. Active left sided UC patients with a Modified Mayo score (excluding the friability at grade 1

for the endoscopic sub score) of 6-12, with an endoscopic sub score ≥2 and no other individual sub score <1, who are at least 18 years of age will be eligible for enrolment.

In total, 215 eligible patients will be randomly assigned in a 1:1:1:1:1 allocation to receive rectal doses of cobitolimod 31 mg, cobitolimod 125 mg, cobitolimod 250 mg, at Week 0 and 3 (in total two doses of active drug) and placebo at Week 1 and 2, cobitolimod 125 mg at Week 0, 1, 2, 3 (in total four doses of active drug) or placebo at Week 0, 1, 2, 3. Randomisation will be stratified for the following categories of patients: concomitant use of glucocorticoidsteroid (GCS) treatment (Yes/No) and previously treated with tumour necrosis factor alpha (TNF-α) inhibitors (Yes/No).

Study treatment will be administered rectally using an enema.

The screening period will have two screening visits. At the first screening visit 1a a written informed consent will be obtained before any other study procedure is done. Patients will be assigned a patient identification number and enrolment procedures will commence. At the second screening visit 1b, a full colonoscopy will be performed.

Visits will be performed at Day -14, Day-7, Day -4, Week 0 and Week 1, 2, 3, 6, 10.

Evaluation and follow-up of patients will be performed at all visits. If the patient's disease deteriorates or does not improve, it is the investigator´s responsibility to judge if an alternative treatment is needed.

SELECTION OF PATIENTS:

Inclusion Criteria

Patients must meet all of the following inclusion criteria to be randomised in the study:

1. Male or female ≥ 18 years of age
2. Established diagnosis of UC, with minimum time from diagnosis of ⩾3 months
3. Moderately to severely active left sided UC (disease should extend 15 cm or more above the anal verge and not beyond the splenic flexure) determined by a Modified Mayo score (excluding the friability at grade 1 for the endoscopic sub score) of 6 to 12 with an endoscopic sub score ⩾2 assessed by central reading of endoscopy performed at screening visit 1b, and no other individual sub score <1
4. Current oral 5-ASA/SP use or a history of oral 5-ASA/SP use
5. Current GCS use or history of GCS dependency, refractory, or intolerance, including no GCS treatment due to earlier side-effects (only one of the GCS criteria have to be fulfilled, see definition in European Crohn´s and Colitis organisation (ECCO) guidelines)
6. Demonstrated an inadequate response, loss of response, or intolerance to **at least one** of the following agents:

- Immunomodulators, e.g. cyclosporine, methotrexate, AZA/6-MP, tacrolimus
  - For example,signs and symptoms of persistently active disease despite previous treatment with at least one 8 week regimen of oral AZA (≥1.5 mg/kg) or 6-MP (≥0.75 mg/kg) or lower doses prompted by intolerance or thiopurine methyltransferase (TPMT) deficiency *or*
  - For example, previous intolerance (including, but not limited to, nausea/vomiting, abdominal pain, pancreatitis, liver function test (LFT) abnormalities, lymphopenia, TPMT genetic mutation, infection) to at least one immunomodulator
- TNF-α inhibitors and/or anti-integrins:
  - Signs and symptoms of persistently active disease despite previous treatment with at least one induction regimen with 2 doses at least 2 weeks apart (or doses as recommended according to the current labels) of for e.g.:
    - Infliximab 5 mg/kg (intravenous (IV)) *or*
    - Golimumab 200/100 mg (subcutaneous (SC)) *or*
    - Adalimumab 160/80 mg (SC) *or*
    - Vedolizumab 300 mg (IV) *or*
  - History of intolerance (including but not limited to infusion-related reaction, demyelination, congestive heart failure, infection)

Recurrence of symptoms during maintenance dosing with any of the above medications following prior clinical benefit, (secondary failure) [discontinuation despite clinical benefit does not qualify]

7. Allowed to receive a therapeutic dose of following UC drugs during the study:

   a) Oral GCS therapy (≤20 mg prednisone or equivalent/daily) providing that the dose has been stable for 2 weeks prior to visit 1a
   b) Oral MMX Budesonide therapy (9mg/daily) initiated at least 8 weeks before visit 1 a.
   c) Oral 5-ASA/SP compounds, providing that the dose has been stable for 2 weeks prior to visit 1a and initiated at least 8 weeks before visit 1a
   d) AZA/6-MP providing that the dose has been stable for 8 weeks prior to visit 1b and been initiated at least 3 months before visit 1a

8. Ability to understand the treatment, willingness to comply with all study requirements and ability to provide informed consent

Exclusion Criteria

Patients presenting with any of the following will not be included in the study:

1. Suspicion of differential diagnosis such as; Crohn's enterocolitis, ischaemic colitis, radiation colitis, indeterminate colitis, infectious colitis, diverticular disease, associated colitis, microscopic colitis, massive pseudopolyposis or non-passable stenosis

2. Acute fulminant UC and/or signs of systemic toxicity
3. UC limited to the rectum (disease which extend <15 cm above the anal verge)
4. History of malignancy, except for:
    - Treated (cured) basal cell or squamous cell in situ carcinoma
    - Treated (cured) cervical intraepithelial neoplasia or carcinoma in situ of the cervix with no evidence of recurrence within the previous 5 years prior to the screening visit 1a
5. History or presence of any clinically significant disorder that, in opinion of the investigator, could impact on patient's possibility to adhere to the protocol and protocol procedures or would confound the study result or compromise patient safety
6. Concomitant treatment with cyclosporine, methotrexate, tacrolimus, TNF-α inhibitors, anti-integrins or similar immunosuppressants and immunomodulators at enrolment. Any prior treatment with such drugs must have been discontinued at least 8 weeks prior to visit 1a *or* have non-measurable serum concentration levels
7. Treatment with rectal GCS, 5-ASA/SP or tacrolimus within 2 Weeks before visit 1b
8. Long term treatment with antibiotics or non-steroidal anti-inflammatory drugs (NSAIDs) within two weeks prior to visit 1a (one short treatment regime for antibiotics and occasional use of NSAIDS are allowed)
9. Serious active infection
10. Gastrointestinal infections including positive Clostridium difficile stool assay
11. Currently receiving parenteral nutrition or blood transfusions
12. Females who are lactating or have a positive serum pregnancy test during the screening period
13. Women of childbearing potential not using reliable contraceptive methods (reliable methods are barrier protection, hormonal contraception, intra-uterine device or abstinence) throughout the duration of the study
14. 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
15. Previous exposure to cobitolimod

PLANNED TRIAL SIZE:

Given that the purpose of this trial is to determine whether cobitolimod is efficient and therefore whether to proceed with further development, there is only one outcome of interest, superiority of one or more of the experimental arms to the control (placebo). In this scenario,

a one-sided testing framework is appropriate.

Further phase III trials will be required to confirm the efficacy, and thus the standard type I error rate control at the 0.05 level is not strictly necessary. The assumption is that a one-sided test of the null hypothesis, that there is no difference in the primary endpoint between each active treatment arm and control (placebo), with a false-positive (type I error) rate of 0.10 is appropriate. The use of this higher type I error and of a low type II error of 0.10 gives to the trial high statistical power to detect a clinically meaningful effect while maintaining an acceptable sample size.

Assuming

- a 10 % remission rate for the placebo
- a type I error of 0.10
- a 35 % remission rate for the active cobitolimod treatment
- a power of 90 %
- a one-tailed test for differences between proportions

Thirty-five (35) patients per group are needed.

To allow for 10-20 % dropout rate the sample size is decided to 43 patient per treatment group and 215 patients in total.

Allocating 43 patients per treatment arm will also satisfy a power goal of 80 % using a two-sided test at the 0.05 type I error rate.

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

INVESTIGATIONAL THERAPY AND TREATMENT DURATION:

During the treatment period of the study, cobitolimod 31 mg, 125 mg or 250 mg or placebo will be given in two doses, at Week 0 and Week 3 and placebo will be given at Week 1 and Week 2 or cobitolimod 125 mg every week (Week 0, 1, 2, and 3). To ensure the study remains blinded, all patients will be treated Week 0, 1, 2, and 3 with either cobitolimod or placebo. The drug will be administered by study personnel using an enema.

The primary endpoint will be assessed after 6 weeks. Safety evaluation and disease

monitoring will be performed at each visit after the first dose.

REFERENCE THERAPY:

Placebo is a rectal solution where the ingredient is water, identically packed and administered as cobitolimod.

CONCOMITANT THERAPY:

The patients may be receiving a therapeutic dose of the following concomitant therapies: oral GCS (≤ 20 mg prednisone or equivalent/day), if stable dose for at least 2 weeks prior to screening visit 1a, and/or oral MMX Budesonide (9mg/day) if stable dose for at least 8 weeks prior screening visit 1a, and/or oral 5-ASA and/or SP, if stable dose for at least 2 weeks prior

screening visit 1a. The 5-ASA/SP treatment should have been initiated at least 8 weeks before screening
visit 1a.
The patient may also receive AZA/6-MP, if stable dose for at least 8 weeks prior to screening visit 1b. The treatment should have been initiated at least 3 months before visit 1a.
The patient shall stay on same dose of allowed UC treatment up to end of study (Week 10) except for the GCS that can start to be tapered off at Week 6, if the patient is in remission.

During the study, concomitant treatment with biologics (such as TNF-α inhibitors and anti-integrins), cyclosporine, methorexate, tacrolimus, or similar immunomodulatory/ immunosuppressant drugs is not allowed, and should have been stopped (due to documented lack of efficacy, side effects or other reasons,) at least 8 weeks prior to visit 1a or have non-measurable serum concentration levels.

OUTCOME MEASUREMENTS:

Primary Efficacy Endpoint

Proportion of patients with clinical remission at Week 6, defined by Modified Mayo sub scores, i) rectal bleeding of 0, ii) stool frequency of 0 or 1 (with at least one point decrease from Baseline, Week 0), and iii) endoscopy score of 0 or 1 (excluding friability).

Secondary Exploratory Endpoints

- Proportion of patients with symptomatic remission at Week 6, defined by the Mayo sub scores, i) rectal bleeding of 0, ii) stool frequency of 0 or 1 (with at least one point decrease from Baseline, Week 0), (patient reported outcome) [PRO2]
- Proportion of patients with absence of rectal bleeding at Week 6, defined by the Mayo sub score rectal bleeding of 0
- Proportion of patients with normal or enhanced stool frequency at Week 6, defined by the Mayo sub score stool frequency of 0 or 1 (with at least one point decrease from Baseline, Week 0)
- Proportion of patients with endoscopic remission at Week 6, defined by the Modified Mayo endoscopic sub score of 0 or 1 (excluding friability)
- Proportion of patients with histological remission at Week 6, defined by the Nancy histological index of grade 0 or 1
- Proportion of patients with complete histological remission at Week 6, defined by the Nancy histological index grade of 0
- Proportion of patients with histological response at Week 6, defined by the Nancy histological index score of ≤2 (if 2 then with at least one point decrease from Baseline, Week 0)
- Proportion of patients with endoscopic and histological remission at Week 6

- Proportion of patients with symptomatic remission at Week 4, defined by the Mayo sub scores, i) rectal bleeding of 0, ii) stool frequency of 0 or 1 (with at least one point decrease from Baseline, Week 0), (patient reported outcome) [PRO2]
- Proportion of patients with absence of rectal bleeding at Week 4, defined by the Mayo sub score rectal bleeding of 0
- Proportion of patients with normal or enhanced stool frequency at Week 4, defined by the Mayo sub score stool frequency of 0 or 1 (with at least one point decrease from Baseline, Week 0)
- Proportion of patients with modified clinical remission at Week 6, defined by the Modified Mayo score ≤ 2 and sub scores, i) rectal bleeding of 0, ii) stool frequency of 0 or 1 (with at least one point decrease from Baseline, Week 0), iii) endoscopy score of 0 or 1 (excluding friability) and iiii) physician´s global assessment (PGA) of 0 or 1
- Proportion of patients with durable symptomatic remission, defined by the Mayo sub scores, i) rectal bleeding of 0, ii) stool frequency of 0 or 1 (with at least one point decrease from Baseline, Week 0) [PRO2] at both Week 6 and Week 10
- Proportion of patients with clinical response at Week 6, defined as clinical remission or a three point and ≥30 % decrease from Baseline, Week 0 in the sum of the Modified Mayo score, i) rectal bleeding, ii) stool frequency and iii) endoscopy score (excluding friability), iiii) physicians global assessment (PGA)
- Proportion of patients with a defecation urgency score of 0 or a decrease of at least one point in defecation urgency at Week 6 compared to Baseline, Week 0
- Mean change in faecal calprotectin at Week 1, 2, 3, and 6 compared to Baseline, Week 0
- Mean change in steroid dosage for patients in remission at Week 6 to Week 10
- Mean change in each of the inflammatory bowel disease questionnaire (IBDQ) sub domains at Week 6 compared to Baseline, Week 0

Safety Endpoints

- Incidence of adverse events (AEs)
- Incidence of serious adverse events (SAEs)
- Vital signs
- Electrocardiogram (ECG)
- Physical Examination
- Laboratory Findings

STATISTICAL METHODS:

Planned Interim Analysis:

No formal statistically based interim analysis will be performed. However, the safety data will

be reviewed periodically during the conduct of the study by the independent data safety monitoring board (DSMB). The objective of the DSMB data review is safety.

Study Population:

The full analysis set (FAS), will be based on the intention-to-treat (ITT) principles, which consists of all randomised patients who meet the inclusion criteria (as assessed by the investigator on the inclusion/exclusion criteria form), and receive at least one dose of the study drug (active or placebo).

The per protocol set (PPS) is defined as FAS patients who do not have important protocol deviations considered to have a major effect on the primary efficacy endpoint, and have completed the Modified Mayo sub scores assessment at Week 0 and Week 6.

Safety population: all patients included in the study and treated with at least one dose of study drug.

Planned Analysis:

The analysis of the primary endpoint is conducted on the FAS and PPS.

The primary analysis of the primary endpoint will be performed using the Cochran Mantel Haenzel test adjusting for randomisation strata GCS use/non use and TNF-α prior use/non use at Baseline, Week 0.

The primary endpoint will be proportion of patients with clinical remission at Week 6 tested using an overall type I error rate of 0.10 using a one-sided test.

The p-value for testing the null hypotheses must be less than 0.10 to be considered to have met the primary objective.

The primary efficacy endpoint will also be tested using the same approach as described above but with the use of an overall type I error rate of 0.05 using a two-sided test.

There will be no adjustment for multiplicity as all results will be regarded as exploratory. If a statistically significant difference among cobitolimod groups compared to placebo will exist, an analysis in terms of fractional polynomial for analysis of binary data will be applied to explore the dose-response relationship.

SAFETY:

Safety data will be evaluated using descriptive statistics.

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

Data Safety Monitoring Board

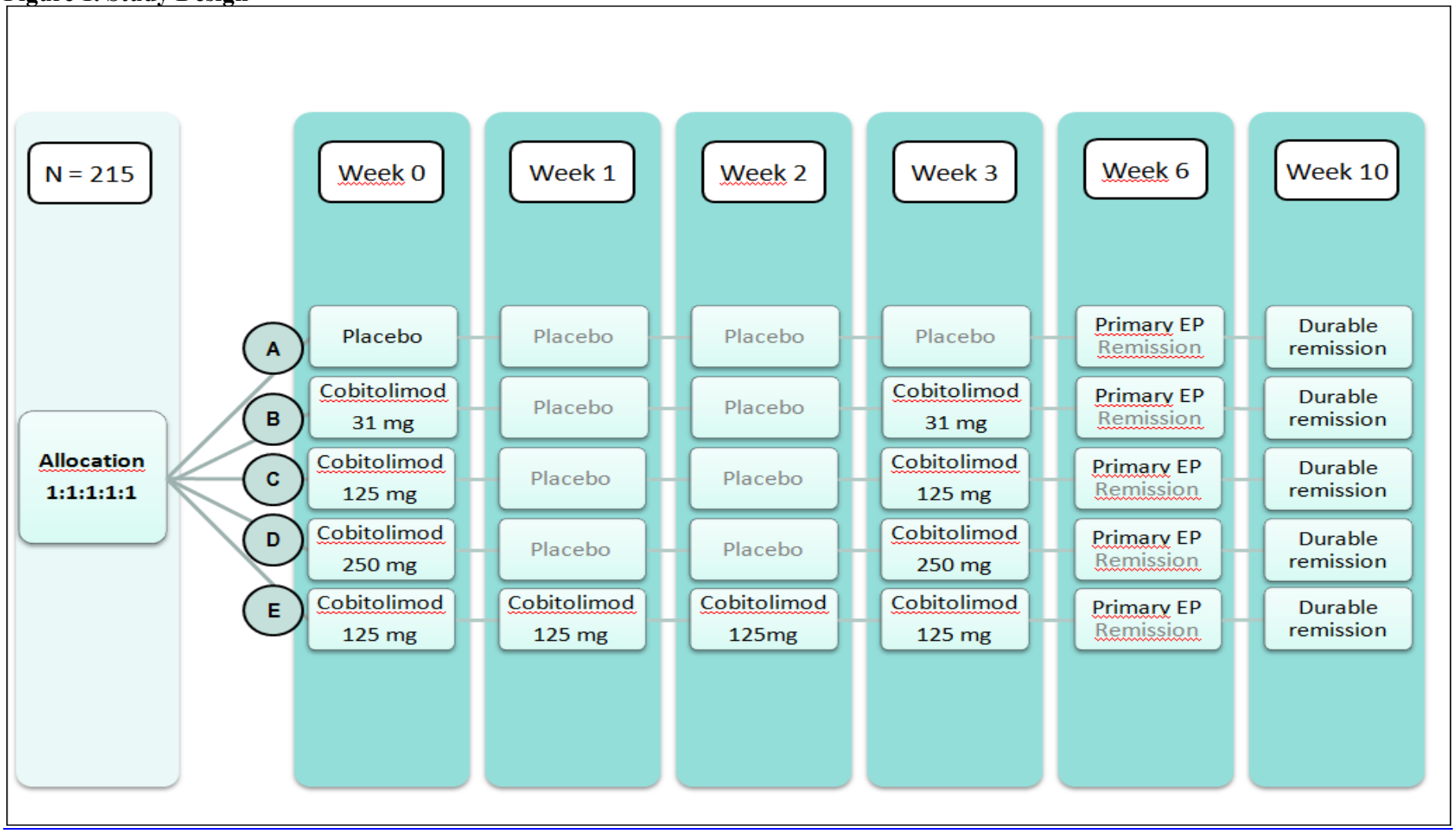
DSMB will monitor the study for patient safety data.

Table 1. Schedule of Activities

Study Procedures	Screening		Randomisation		Treatment Period			Primary Endpoint/ Early discontinuation	Follow Up
	Visit 1a	Visit 1b	Visit 2a (Phone)	Visit 2b	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
	Day -14	Day-7 to -10	Day -4 to -7	Week 0 Day 0	Week 1 Day 7 +/- 3 days	Week 2 Day 14 +/- 3 days	Week 3 Day 21 +/- 3 days	Week 6 Day 42 +/- 3 days	Week 10 Day 70 +/- 7 days
Informed Consent	X								
Demographics[1]	X								
Review incl/excl criteria	X	X	X						
Tobacco Use	X							X	
Medical History[2]	X								
Ulcerative Colitis History[2]	X								
Prior Therapies[19]	X								
Vital Signs[3]	X			X	X	X	X	X	X
Physical Examination[4]	X			X	X	X	X	X	X
Laboratory:									
Haematology[5]	X			X	X	X	X	X	X
Blood Chemistry[6]	X			X	X	X	X	X	X
Lipid profile[7]	X							X	
Urinanalysis[8]	X			X				X	
Stool Culture/microscopy[9]	X								
Pregnancy Test[10]	X			X	X	X	X	X	
Biomarkers[11]	X			X	X	X	X	X	X
Future Biomedical Research	X			X	X	X	X	X	X
ECG[12]	X			X				X	
Endoscopy:									
-Full colonoscopy+biopsy[13]		X							
-Flex sigmoidoscopy+ biopsy[13]								X	
eDiary instructions[14]	X								
Assessments:									
eDiary compliance[14]		X		X	X	X	X	X	X
PGA[15]		X	(X)					X	X
IBDQ[16]				X			X	X	
Urgency of defecation				X	X	X	X	X	X
Adverse Event (AE)[17]		X	X	X	X	X	X	X	X
Extraintestinal Manifestation[18]				X				X	X
Concomitant Medication[19]				X	X	X	X	X	X
Randomisation[20]			X						
Study Drug administration[21]				X	X	X	X		
Leakage Measure[22]				X	X	X	X		

1. Date of birth, gender, race, height (cm), weight (kg).
2. Medical History (including UC history) is to include the entire screening period, until just prior to the first dose of study drug with exception of AEs related to study procedures.
3. Blood pressure and heart rate at every visit (except visit 1b and 2a), body temperature, height and weight only at Visit 2b.
4. 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 drug and thereafter as an AE.
5. Haemoglobin, haematocrit, platelet count, RBC, WBC, platelets, neutrophil, eosinophil, basophil, lymphocyte, and monocytes count. Fibrinogen, APTT and PT (including INR) in non-fasting samples.
6. Albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), amylase, blood urea nitrogen (BUN), calcium, chloride, creatine phosphokinase (CPK), creatinine, gamma glutamyl transferase (GGT), glucose, phosphorus, potassium, sodium,total bilirubin, total protein, uric acid, in non-fasting samples.
7. Total cholesterol and triglyceride, in non-fasting samples.
8. Blood, glucose, ketones, leucocytes, nitrite, protein, pH.
9. Stool culture of Clostridium difficile Toxin B, Shigella, Campylobacter, Yersinia and Salmonella, as well as ova and parasites.
10. Only for females of childbearing potential; Serum pregnancy test at screening visit 1a and then dip-stick tests at all other occasions.
11. Serum CRP and faecal calprotectin.
12. A 12 lead ECG will be done at screening visit 1a and visit 6. On visit 2b, ECG will be taken before study drug administration and 30 minutes after treatment.
13. A full colonoscopy will be required at visit 1b, and flexible sigmoidoscopy at primary endpoint, visit 6. Videos will be sent for central reading and biopsies collected for histopathological grading according the Nancy score and future biomedical research (if consented). 3 biopsies should be taken from each bowel segment investigated (see protocol section 7.7; separate instructions are provided).
14. Patient will be prompted to fill in the e-dairy on a daily basis. Patient should be instructed how to use the eDiary at visit 1a and if needed on all visits.
15. PGA will be assessed at visit 1b (if not eDiary data are available then at visit 2a) and at visit 6 and 7
16. IBDQ should be filled in before administration of study drug.
17. The patients will be questioned about AEs at each clinic visit. Only AEs related to study specific procedures at screening visit will be recorded at Visit 1a, 1b and 2b.
18. There will be questions regarding Extra Intestinal Manifestation disease/symptoms at visit 2b, visit 6 and visit 7.
19. All concomitant medication taken should be reported at each visit. UC treatment should be reported up to 3 years before screening visit. For UC treatment dose and start and stop date will be reported for the last treatment period.
20. Inclusion/exclusion criteria will be reviewed at several occasions during the screening period up to randomisation e g when the results of the safety laboratory and stool culture analyses have been obtained. When central reading result has been obtained a telephone contact visit will be done to ensure patient is still willing to participate and that all inclusion and exclusion criteria still are fulfilled. Randomisation procedure will then commence and patient will be scheduled for the first treatment visit.
21. The study drug solution will be administered by the physician using a rectal enema. The exact time for start of the administration will be recorded in the eCRF.
22. Any leakage of study drug should be recorded in the eCRF.

Figure 1. Study Design



Clinical Study Protocol

CSUC-01/16

1. INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

1.1. The Disease

Ulcerative colitis (UC) is a disease characterized by chronic inflammation of the rectal and colonic mucosa, affecting the innermost lining in the first stage. The disease is recurrent, with both active 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 [1]. Symptoms of active UC include progressive loose stools with blood and increased frequency of bowel movements. Active mucosal inflammation is diagnosed by endoscopy.

The stools contain pus, mucous and blood and are often associated with abdominal cramping with urgency to evacuate (tenesmi). Diarrhoea may have an insidious onset or, more rarely, start quite suddenly. In severe cases the symptoms may include fever and general malaise. In severe stages, deep inflammation of the bowel wall may develop with abdominal tenderness, tachycardia, fever and risk of bowel perforation. Furthermore, patients with UC may suffer extra intestinal manifestations such as arthralgia and arthritis, erythema nodosum, pyoderma gangrenosum and inflammation in the eyes. In the case of remission or inactive UC, patients are usually free of bowel symptoms. The extent of inflamed and damaged mucosa differs among patients with UC. UC that affects only the rectum is termed ulcerative proctitis. The condition is referred as distal colitis when inflammatory changes are present in the left side of the colon up to the splenic flexure. In extensive UC the transverse colon is also affected, and pancolitis designates a disease involving the entire colon.

Active mucosal inflammation is diagnosed by endoscopy and is characterized by a loss of vascular patterning, oedema, petechia, spontaneous bleeding and fibrinous exudates. The endoscopic picture is that of continuous inflammation, starting in the rectum and extending proximally to a variable extent into the colon. Biopsies obtained at endoscopy and subjected to histological examination help to diagnose the condition. Infectious causes, including Clostridium difficile, Campylobacter, Salmonella and Shigella, may mimic UC and should be excluded by stool cultures.

The medical management of UC is divided into treatment of active disease and maintenance of remission. The treatment of patients with active UC aims to reduce inflammation and promote colon healing and mucosal recovery. In the majority of cases the disease may be controlled with conventional drugs including sulphasalazine (SP), 5-aminosalicylic acid (5-ASA) [2] and glucocorticosteroids (GCS) [3]. Distal disease, limited to the rectum and the recto-sigmoid area, is usually brought into remission using rectal formulations. When the extent is more proximal and/or the symptoms more severe, oral GCS is also needed. GCS are generally used to treat disease flare-ups and are not recommended for maintenance of remission since there are significant side effects in long-term use (immunodeficiency, adrenal insufficiency, hyperglycemia, hypothalamic pituitary adrenal axis suppression, steroid-induced osteoporosis: reduced bone density, weight gain, muscle break down) and the possible development of steroid dependent disease. Glucocorticoid drugs act non-selectively, so in the long run they may impair many healthy anabolic processes. As a result, maintenance treatment with systemic GCS is not advised [4]. New formulations of GCS have been developed with the aim of limiting systemic activity and reducing GCS adverse events (AEs) for patients who become refractory to GCS and suffer from severe or moderately severe attacks of UC The addition of immunomodulatory agents such as AZA/6-MP and

cyclosporine are sometimes used as rescue therapies and last resort before surgery. However, immunomodulators are slow-acting and the induction of remission in these patients is often temporary [5].

Treatment options for UC have rapidly expanded over the past 10 years and now include multiple biologic agents in addition to prior medication options [6]. Three tumour necrosis factor alpha (TNF-α) inhibitors currently approved for the treatment of moderate to severe UC are infliximab, adalimumab, and golimumab. These agents bind TNF-α, neutralize its activity, and prevent it from binding to its receptor. Infliximab and adalimumab have also been shown to induce apoptosis of activated T cells and macrophages. All three TNF-α inhibitors carry potential risks associated with their use, and should be avoided in patients with uncontrolled infections, advanced heart failure, neurologic conditions and in patients with a history of malignancy, due to a potential risk of accelerating the growth of a tumour. Other potential adverse effects of TNF-α inhibitor therapy include acute infusion reactions and serious infusion reactions, including anaphylaxis, convulsions, and hypotension. Injection site reactions and rare anaphylactic reactions can also occur with subcutaneously (SC) administered TNF-α inhibitor agents. Other possible adverse effects include neutropenia, hepatotoxicity, serum sickness, leukocytoclastic vasculitis, rash including psoriasiform rash, and induction of autoimmunity. Approximately 50% of patients receiving infliximab develop antinuclear antibodies after 2 years. Serious infections occur in 2–4% of patients treated with TNF-α inhibitors [6].

All three TNF-α inhibitor agent have been shown to be effective in inducing and maintaining clinical response and remission in patients with UC, with fairly comparable safety profiles. Regardless of the TNF-α inhibitor agent chosen, combination therapy with azathioprine is likely more effective for inducing remission than TNF-α inhibitor monotherapy. However, there are still up to 50% of patients receiving TNF-α inhibitor agent who fail to respond to induction dosing, and even more patients who lose response to the TNF-α inhibitor agent over time [6]. Vedolizumab, an α4β7 integrin inhibitor was recently approved for the treatment of UC. In the GEMINI 1 trial, vedolizumab was found to be more effective than placebo for inducing and maintaining clinical response, clinical remission, and mucosal healing [7]. In theory, because of the unique location of the α4β7 integrin on lymphocytes homing to the gut, it may be expected that vedolizumab will have a reduced risk of systemic infections and malignancy compared with systemically acting agents. In the GEMINI 1 trial, there was no increased risk of infection, serious adverse reaction, or malignancy in patients receiving vedolizumab.

UC patients who are chronically active and treatment refractory poses a serious medical challenge and often the only remaining course of action is colectomy. A total colectomy is a potentially curative option in severe UC, but is a life-changing operation that entails risks as complications, such as pouch failure, pelvic sepsis, infertility in women, and nocturnal faecal soiling, may follow. Therefore, surgery is usually reserved for patients with severe refractory disease, surgical emergencies, or patients with colorectal dysplasia or cancer.

1.2. Cobitolimod

Cobitolimod is a modified single strand deoxyribonucleic acid (DNA)-based synthetic oligodeoxyribonucleotide [redacted] The immune system is the key mediator of the

changes of UC. The mucosa of the colon and rectum of patients with UC contains active immune cells, which produce damage to the tissue. Cobitolimod will be administered in the region of inflammation, which places the drug in close contact with a high number of intended target cells, ensuring that the drug will reach an area rich in TLR9 expressing cells. The activation of these cells by cobitolimod induces various cytokines, such as type I interferons and interleukin 10 (IL-10) which are believed to be important factors for the clinical effect of cobitolimod.

1.3. Non-Clinical Experience

A range of non-clinical safety studies have been conducted with cobitolimod according to good laboratory practice.

A 13-week, repeat dose toxicity study in rats examining the effects of repeated intravenous (IV), and subcutaneous (SC) administration of cobitolimod showed that the drug was well tolerated with no mortality and no treatment related clinical signs observed. Increases in white blood cell counts (WBC) and spleen weights were observed at doses of 100 mg/kg. However, recovery was seen in both parameters. Subcutaneous administration was associated with minimal or mild subcutaneous inflammation and reddening at the injection site at necropsy. No clinical adverse effects were recorded [8].

A 13-week, repeat dose toxicity study in rats of repeated rectal administration of cobitolimod showed equally low toxicity. Pathology examinations revealed no necropsy or histology findings related to repeated administration of cobitolimod. The no observed adverse effect level (NOAEL) in this study was determined to be 33 mg/kg/day. [9].

A 19 day, repeat dose toxicity study in cynomolgus monkey, with a 4-week recovery period after repeated IV infusion or SC administration of 100 mg/kg cobitolimod showed no treatment related adverse effects on any of the parameters analyzed. The animals were dosed on 6 occasions during the test period. Studies investigating the toxicokinetics showed no evidence of drug accumulation after dosing. There was a transient presence of cobitolimod in plasma shortly after administration, with higher levels shown after intravenous infusion compared to subcutaneous administration. The NOAEL was considered to be 100 mg/kg/day. [10].

A fertility and early embryonic development study as well as an embryo-foetal development study in the rat, dosed by subcutaneous and rectal routes, showed no adverse effect of cobitolimod on mating behaviour, fertility, early embryonic development, pregnancy or on conseptus development from implantation to the closure of the hard palate, following exposure during the period of organogenesis (Day 6 to 16 of gestation).

The *in vivo* genotoxic potential of cobitolimod has been evaluated in a micronucleus test (GLP) in bone marrow erythrocytes of young male and female CD-1 mice (after 0 h and 24 h intravenous dosing followed by sampling at 48 h). No micronucleus induction was detected.

1.4. Clinical Experience

Four clinical trials have been performed with, cobitolimod. Along with the named patient use programme a total of 249 Inflammatory Bowel Disease patients have received at least one dose of cobitolimod to date. The most evaluated dose is 31.2 mg (15,6 mg/mL, in a 2 mL concentrate, diluted in 50 mL sterile water). This dose was rounded to 30 mg in the studies.

1.4.1. Pilot Study, HICS-9801

Cobitolimod was first assessed for clinical efficacy and safety in an explorative placebo-controlled, double-blind study in steroid resistant or steroid dependent patients with active distal UC or distal Crohn´s disease and concomitant steroid treatment.

Eleven patients were randomised to receive either a single rectal dose of cobitolimod (3 mg or 30 mg) or placebo.

Clinical and endoscopic evaluation at Week 1 showed a response rate of >70% in the treatment group and of 25% in the placebo group [11].

1.4.2. Phase II Dose Finding Study, CSUC-01/02

This was a double-blind, randomised, placebo-controlled, single-dose, multicentre, dose finding study of cobitolimod in 151 mild to moderately active UC patients.

Patients were treated with either a single rectal dose of cobitolimod (at 0.3, 3, 30 or 100 mg) or placebo.

The primary endpoint was defined as clinical remission at any time during the 12 Week study period.

The primary endpoint, induction of clinical remission, was defined as a Mayo score equal to zero at any time point. At Week 4 a numerically higher proportion of patients in the 30 mg and 100 mg groups had achieved clinical remission than patients in the lower dose active treatment groups and the placebo group. At Week 4, 16.7% and 20.7% were in clinical remission in the 30 mg and 100 mg groups, respectively, compared to 10.3% in the placebo group, 9.7% in the 0.3 mg group and 3.4% in the 3 mg group. At Week 12, clinical remission was achieved in 9.7%, 13.8%, 30.0%, and 27.6% in the 0.3 mg, 3 mg, 30 mg, and 100 mg group, respectively, as compared to 24.1% in the placebo group. Thus, there was a tendency towards earlier response in the 30 mg and 100 mg groups compared to the other groups, including placebo. There was also a trend, however not statistically significant, of a dose-response relationship for achieving clinical remission among the active treatment groups, but at Week 12 the incidence of clinical remission in the placebo group was nearly equal to that found in the 30 mg and 100 mg groups.

Treatment with cobitolimod was safe and well tolerated.

Adverse drug reactions (ADRs) reported in more than one patients per treatment group were headache in the 0.3 mg, 3 mg and placebo groups, worsening of UC in the 3 mg and placebo groups, and haematuria, proteinuria and pyrexia in the 100 mg group. In the 30 mg group, only single cases of ADRs occurred [12].

1.4.3. Phase II Proof of Concept Study, CSUC-01/06

This study was a multicentre, randomised, placebo-controlled, double-blind, proof of concept study, evaluating clinical response and safety after a single rectal dose of 30 mg cobitolimod or placebo in 34 UC patients with moderate to severe active disease.

Clinical response rates did not show statistically significant differences between cobitolimod and placebo treated patients.

The clinical response at Week 1 was 41.2% in the cobitolimod treated group and 9.1% in the placebo group. Six of the seven patients (85.7%) in the cobitolimod group that showed response at Week 1 were still responders at Week 4, whereas the placebo group patient that

showed response at Week 1 had relapsed by Week 4. In the cobitolimod treated group clinical remission was 11.8 % at Week 1 and 17.7% at Week 4.

None of the patients receiving placebo were in clinical remission at Week 1 or 4. Among the 9 clinical responders at Week 4, four (44.4%) showed concomitant histopathological remission, whereas none of the 4 clinical responders in the placebo group showed histopathological improvement [13].

1.4.4. Named Patient Basis Use of Cobitolimod, CU-UC-01/11

A total of 14 chronic active UC patients who were total treatment failures were treated on a named patient basis with cobitolimod. All patients had a marked reduction in clinical activity index (CAI) scores (Rachemilewitz [14]) within the first week following a single treatment with cobitolimod. Only four patients had a colectomy.

No AEs related to cobitolimod were recorded [15].

1.4.5. Phase III Study, CSUC-01/10

This was a placebo-controlled, double-blind, randomised multi-centre study to assess the efficacy and safety of two doses of cobitolimod as an add-on to current practice in 131 chronic active treatment refractory UC patients with a CAI score ≥9 and an endoscopic score ≥2.

Patients were on a stable tolerable dose of concomitant steroid treatment at inclusion and for the first 12 weeks of treatment.

Patients were treated with 2 rectal doses of cobitolimod (30 mg), or placebo; at Week 0 and at Week 4.

The primary efficacy endpoint of clinical remission at Week 12, defined as a CAI score of ≤4 showed no statistically significant difference between the two treatment groups.

Secondary endpoints showed statistically significant effects in symptomatic remission, (sub scores of blood in stools and number of weekly stools not exceeding 0 or 1, at Week 4 and 8, and in registration remission (CAI score of ≤4 and an endoscopic score of 0 or 1, at Week 4).

The dosing regime was well tolerated. 59.2 % of the patients reported at least one AE (59.8 % in the cobitolimod group and 58.1 % in the placebo group).

Treatment related AEs were reported in 10 (11.5%) patients in the cobitolimod group compared to 4 (9.3%) in the placebo group. A total of 18 (13.8%) patients reported serious adverse events (SAE) across both treatment groups with a greater proportion of patients in the placebo group reporting SAEs than patients in the cobitolimod group: 8 (18.6%) patients and 10 (11.5%) patients, respectively [16].

Overall, data on cobitolimod support a positive benefit- risk assessment for patients with chronic active treatment refractory UC. Cobitolimod is safe and well tolerated and has been shown to be effective at clinical response and remission in patient with chronic active UC, as well as in symptomatic and endoscopic remission in patients with moderate to severe chronic active treatment refractory UC.

1.5. Study Rationale

The doses used in the first clinical testing of cobitolimod in UC patients were extrapolated from previous pre-clinical work and during the study it was demonstrated that both doses (3

mg and 30 mg) were effective. However, due to the limited number of included patients, no certain assessment of which of the two doses was more effective could be made.

The dose finding phase II study considered doses of 0.3 mg, 3 mg, 30 mg and 100 mg and at all dose levels, no statistical significant benefit was noted when compared to placebo. However signs of efficacy were observed at the high dose levels compared to the low dose levels. The study did demonstrate that cobitolimod was well tolerated with no SAEs recorded.

The phase II proof of concept study in UC patients, as well as the named patient basis use patients, again addressed the dose of 30 mg that showed efficacy in the pilot study. This dose has shown beneficial clinical effects and as such, there was no reason to alter this dose level for the treatment of chronic active treatment refractory UC patients in the study to follow.

Thus in the fourth trial patients were treated with two doses of cobitolimod 4 weeks apart. Such patients demonstrated significant improvements in symptomatic remission rates and endoscopic improvement in particular at Week 4 compared to patients receiving placebo.

Non-clinical data suggest that higher doses of cobitolimod could increase its efficacy. Given the good safety profile higher doses will be evaluated. The non-clinical data limits the total dose exposure to 500 mg during one month, and therefore the posology studied will be 31, 125 or 250 mg given twice (at Week 0 and 3) and 125 mg given 4 times (Week 0, 1, 2 and 3), giving a maximum total exposure of 500 mg.

In the clinical studies performed so far a low and infrequent or even just a single dose of cobitolimod has provided remission rates as good as or better than the marketed biologics in moderate to severe UC with a delta of 15-20%. A signal has been seen in all our clinical studies performed demonstrating clinical proof of concept in a meta-analysis.

Cobitolimod will be administered in the left-sided colon, which places the drug in close contact with a high number of intended target cells.

1.6. Potential Risks and Benefits

Cobitolimod has been studied in steroid and treatment refractory UC patients administered as a controlled rectal infusion. The target groups for treatment are patients with chronic active UC in whom previous treatments with conventional drugs, including GCS, have not resulted in adequate response. Results from prior studies indicate a high likelihood of efficacy with cobitolimod in such patients.

Non-clinical safety studies in rodents and cynomolgus monkey have indicated that cobitolimod is well tolerated and no evidence of systemic or local toxicity has been found. Safety assessments from the four placebo-controlled trials with cobitolimod have not indicated any significant toxicity. Administration of cobitolimod is straightforward and drug compliance has been reported as excellent. Overall, cobitolimod has been well tolerated.

The overall data on cobitolimod, as well as extensive clinical experience from similar oligonucleotides, would therefore support a positive benefit risk assessment when administered according to the proposed protocol to chronic active moderate to severe UC patients. For further information, please see the Investigator's brochure.

2. STUDY OBJECTIVES

2.1. Primary Objective

To evaluate the efficacy of cobitolimod treatment at different dose levels and frequencies compared to placebo with regard to clinical remission 6 weeks after first treatment, in patients with moderate to severe active UC.

2.2. Secondary Objective

- To evaluate the safety and tolerability of cobitolimod.
- To evaluate the efficacy of cobitolimod treatment compared to placebo in clinical remission, clinical response and clinical symptoms.
- To evaluate the efficacy of cobitolimod treatment compared to placebo in endoscopic and histological remission and response.
- To evaluate the effect of cobitolimod on quality of life (QOL).

3. STUDY DESIGN AND ENDPOINTS

3.1. Overview

This is a randomised, double blind, placebo-controlled, dose-optimisation, phase IIb study in patients with moderate to severe active left sided UC determined by a Modified Mayo score (excluding the friability at grade 1 for the endoscopic sub score) of 6 to 12 with an endoscopic sub score ≥2 and no other individual sub score <1. Patients who meet all the inclusion criteria and none of the exclusion criteria will be randomised into one of the five treatment arms on a 1:1:1:1:1 ratio and followed for 10 weeks;

- Cobitolimod 31 mg at Week 0 and Week 3, Placebo at Week 1 and 2
- Cobitolimod 125 mg at Week 0 and week 3, Placebo at Week 1 and 2
- Cobitolimod 250 mg at Week 0 and week 3, Placebo at Week 1 and 2
- Cobitolimod 125 mg at Week 0, 1, 2 and 3
- Placebo at Week 0, 1, 2 and 3

Approximately 90 sites in Europe are planned to be enrolled and 215 patients are planned to be randomised. Patient must provide written consent to participate in the study.

A patient will be considered to have completed the study when the assessment at Week 10 has been completed.

A detailed Schedule of Activities is provided in Table 1. A schematic of the study design is provided in Figure 1.

3.2. Study Evaluation Criteria

Endpoints including the Mayo sub scores of blood in stool and stool frequency (patient reported outcome [PRO2]) will be derived using eDiary data. The derivation rules for the primary endpoint are specified under the section 9.5.

3.2.1. Primary Efficacy Endpoint

- Proportion of patients with clinical remission at Week 6, defined by Modified Mayo sub scores; i) rectal bleeding of 0, ii) stool frequency of 0 or 1 (with at least one point decrease from Baseline, Week 0), and iii) endoscopy score of 0 or 1 (excluding friability).

3.2.2. Secondary Exploratory Endpoints

- Proportion of patients with symptomatic remission at Week 6, defined by the Mayo sub scores, i) rectal bleeding of 0, ii) stool frequency of 0 or 1 (with at least one point decrease from Baseline, Week 0), (patient reported outcome) [PRO2]
- Proportion of patients with absence of rectal bleeding at Week 6, defined by the Mayo sub score rectal bleeding of 0
- Proportion of patients with normal or enhanced stool frequency at Week 6, defined by the Mayo sub score stool frequency of 0 or 1 (with at least one point decrease from Baseline, Week 0)
- Proportion of patients with endoscopic remission at Week 6, defined by the Modified Mayo endoscopic sub score of 0 or 1 (excluding friability)
- Proportion of patients with histological remission at Week 6, defined by the Nancy histological index of grade 0 or 1
- Proportion of patients with complete histological remission at Week 6, defined by the Nancy histological index [17,18] grade of 0
- Proportion of patients with histological response at Week 6, defined by the Nancy histological index score of ≤2 (if 2 then with at least one point decrease from Baseline, Week 0)
- Proportion of patients with endoscopic and histological remission at Week 6
- Proportion of patients with symptomatic remission at Week 4, defined by the Mayo sub scores, i) rectal bleeding of 0, ii) stool frequency of 0 or 1 (with at least one point decrease from Baseline, Week 0), (patient reported outcome) [PRO2]
- Proportion of patients with absence of rectal bleeding at Week 4, defined by the Mayo sub score rectal bleeding of 0
- Proportion of patients with normal or enhanced stool frequency at Week 4, defined by the Mayo sub score stool frequency of 0 or 1 (with at least one point decrease from Baseline, Week 0)
- Proportion of patients with modified clinical remission at Week 6, defined by the Modified Mayo score ≤ 2 and sub scores, i) rectal bleeding of 0, ii) stool frequency of 0 or 1 (with at least one point decrease from Baseline, Week 0), iii) endoscopy score of 0 or 1 (excluding friability) and iiii) physician´s global assessment (PGA) of 0 or 1

- Proportion of patients with durable symptomatic remission, defined by the Mayo sub scores, i) rectal bleeding of 0, ii) stool frequency of 0 or 1 (with at least one point decrease from Baseline, Week 0) [PRO2] at both Week 6 and Week 10

- Proportion of patients with clinical response at Week 6, defined as clinical remission or a three point and ≥30 % decrease from Baseline, Week 0 in the sum of the Modified Mayo score, i) rectal bleeding, ii) stool frequency and iii) endoscopy score (excluding friability), iiii) physicians global assessment (PGA)

- Proportion of patients with a defecation urgency score of 0 or a decrease of at least one point in defecation urgency at Week 6 compared to Baseline, Week 0

- Mean change in faecal calprotectin at Week 1, 2, 3, and 6 compared to Baseline, Week 0

- Mean change in steroid dosage for patients in remission at Week 6 to Week 10

- Mean change in each of the inflammatory bowel disease questionnaire (IBDQ) sub domains at Week 6 compared to Baseline, Week 0

3.2.3. Safety Endpoints

- Incidence of AEs
- Incidence of SAEs
- Vital signs
- Electrocardiogram (ECG)
- Physical Examination
- Laboratory Findings

4. STUDY POPULATION

All relevant medical and non-medical conditions should be taken into consideration when deciding whether a particular patient is suitable to participate in this study. Patient eligibility should be reviewed and documented by an appropriately qualified member of the investigator´s study team prior to inclusion in the study. If patient fails to fulfil the inclusion/exclusion criteria, patient can be considered to be re-screened at a later time if eligible.

4.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be randomised in the study:

1. Male or female ≥ 18 years of age
2. Established diagnosis of UC, with minimum time from diagnosis of ⩾3 months
3. Moderately to severely active left sided UC (disease should extend 15 cm or more above the anal verge and not beyond the splenic flexure) determined by

a Modified Mayo score (excluding the friability at grade 1 for the endoscopic sub score) of 6 to 12 with an endoscopic sub score ⩾2 assessed by central reading of endoscopy performed at screening visit 1b, and no other individual sub score <1

4. Current oral 5-ASA/SP use or a history of oral 5-ASA/SP use

5. Current GCS use or history of GCS dependency, refractory, or intolerance, including no GCS treatment due to earlier side-effects (only one of the GCS criteria have to be fulfilled, see definition in European Crohn´s and Colitis organisation (ECCO) guidelines)

6. Demonstrated an inadequate response, loss of response, or intolerance to **at least one** of the following agents:
   - Immunomodulators, e.g. cyclosporine, methotrexate, AZA/6-MP, tacrolimus
     - For example,signs and symptoms of persistently active disease despite previous treatment with at least one 8 week regimen of oral AZA (≥1.5 mg/kg) or 6-MP (≥0.75 mg/kg) or lower doses prompted by intolerance or thiopurine methyltransferase (TPMT) deficiency *or*
     - For example, previous intolerance (including, but not limited to, nausea/vomiting, abdominal pain, pancreatitis, liver function test (LFT) abnormalities, lymphopenia, TPMT genetic mutation, infection) to at least one immunomodulator
   - TNF-α inhibitors and/or anti-integrins:
     - Signs and symptoms of persistently active disease despite previous treatment with at least one induction regimen with 2 doses at least 2 weeks apart (or doses as recommended according to the current labels) of for e.g.:
       - Infliximab 5 mg/kg (intravenous (IV)) *or*
       - Golimumab 200/100 mg (subcutaneous (SC)) *or*
       - Adalimumab 160/80 mg (SC) *or*
       - Vedolizumab 300 mg (IV) *or*
     - History of intolerance (including but not limited to infusion-related reaction, demyelination, congestive heart failure, infection)

Recurrence of symptoms during maintenance dosing with any of the above medications following prior clinical benefit, (secondary failure) [discontinuation despite clinical benefit does not qualify]

7. Allowed to receive a therapeutic dose of following UC drugs during the study:

   a) Oral GCS therapy (≤20 mg prednisone or equivalent/daily) providing that the dose has been stable for 2 weeks prior to visit 1a
   b) Oral MMX Budesonide therapy (9mg/daily) initiated at least 8 weeks before screening visit 1 a

c) Oral 5-ASA/SP compounds, providing that the dose has been stable for 2 weeks prior to visit 1a and initiated at least 8 weeks before visit 1a
d) AZA/6-MP providing that the dose has been stable for 8 weeks prior to visit 1b and been initiated at least 3 months before visit 1a

8. Ability to understand the treatment, willingness to comply with all study requirements and ability to provide informed consent

4.2. Exclusion Criteria

Patients presenting with any of the following will not be included in the study:

1. Suspicion of differential diagnosis such as; Crohn's enterocolitis, ischaemic colitis, radiation colitis, indeterminate colitis, infectious colitis, diverticular disease, associated colitis, microscopic colitis, massive pseudopolyposis or non-passable stenosis
2. Acute fulminant UC and/or signs of systemic toxicity
3. UC limited to the rectum (disease which extend <15 cm above the anal verge)
4. History of malignancy, except for:
    - Treated (cured) basal cell or squamous cell in situ carcinoma
    - Treated (cured) cervical intraepithelial neoplasia or carcinoma in situ of the cervix with no evidence of recurrence within the previous 5 years prior to the screening visit 1a
5. History or presence of any clinically significant disorder that, in opinion of the investigator, could impact on patient's possibility to adhere to the protocol and protocol procedures or would confound the study result or compromise patient safety
6. Concomitant treatment with cyclosporine, methotrexate, tacrolimus, TNF-α inhibitors, anti-integrins or similar immunosuppressants and immunomodulators at enrolment. Any prior treatment with such drugs must have been discontinued at least 8 weeks prior to visit 1a *or* have non-measurable serum concentration levels
7. Treatment with rectal GCS, 5-ASA/SP or tacrolimus within 2 Weeks before visit 1b
8. Long term treatment with antibiotics or non-steroidal anti-inflammatory drugs (NSAIDs) within two weeks prior to visit 1a (one short treatment regime for antibiotics and occasional use of NSAIDS are allowed)
9. Serious active infection
10. Gastrointestinal infections including positive Clostridium difficile stool assay
11. Currently receiving parenteral nutrition or blood transfusions
12. Females who are lactating or have a positive serum pregnancy test during the screening period

13. Women of childbearing potential not using reliable contraceptive methods (reliable methods are barrier protection, hormonal contraception, intra-uterine device or abstinence) throughout the duration of the study
14. 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
15. Previous exposure to cobitolimod

4.3. Randomisation and Stratification

Patients will be randomised to one of five treatment arms (see section 3.1) on a 1:1:1:1:1 ratio. Randomisation to treatment will be performed at the Randomisation Visit (2a, Phone Call). Randomisation will be stratified for the following factors: concomitant use of GCS treatment (Yes/No) and previous treatment with TNF-α inhibitors (Yes/No). A computer generated randomisation schedule will be used to assign patients to treatment sequences. Treatment assignments will be obtained through the interactive voice response system (IVRS). Information regarding the treatment assignments will be kept securely by [redacted] per its standard operating procedure (SOP).

4.4. Patient participation

A patient will be considered to have completed the study when he or she completes the assessment at Week 10. Patients should be encouraged to complete the study but have the right to make decision regarding the study participation e.g. to discontinue the study drug, but still come on visits or discontinue study drug and not come on further study visits. The patient has no obligation to explain why he/she does not want to continue. The investigator also has the right to stop the patient's treatment in the event of AE, protocol deviations, administrative reasons or other reasons. It is understood by all concerned that an excessive rate of discontinues can render the study un-interpretable. Therefore, unnecessary discontinuation should be avoided.

If a patient decides to not continue with study drug at any time during the study, every effort to complete the early discontinuation examinations (Week 6) should be taken. Irrespective of the reason for not continuing in the study and whenever possible, the patient should be examined. Relevant laboratory test samples should be obtained and all relevant assessments should be completed if applicable.

All SAEs should be followed up until they have returned to baseline status or stabilised.

A final visit in the electronic case report form (eCRF) should be completed for every randomised patient whether the patient completed the study or not. The reason for any early discontinuation should be indicated on this form.

The primary reason for a patient discontinue prematurely should be selected from the following:

AE: Clinical or laboratory events that in the judgment of the investigator, Data Safety Monitoring Board (DSMB) or the Sponsor and in the best interest of the patient constitute grounds for discontinuation. This includes serious and non-serious AE regardless of relation to study drug.

Withdrawal of Consent: If a patient withdraws consent for disclosure of future information at the discontinuation of the study or after completion of the study, no further evaluations

should be performed and no additional data should be collected. The Sponsor may retain and continue to use data collected before patient withdrew his/her consent. The Withdraw Consent reason is only applicable if the patient denies any further contact with site and no further data collection.

Lack of Efficacy/Treatment Failure: Patients experiencing deterioration or no improvement of disease as judged by the investigator, may be discontinued from the study at any time during the study, offered alternative treatment and scored as treatment failures. Treatment failures includes disease worsening, requirement for rescue medication for treatment of UC, requirement for surgical intervention and study drug related AE. Patients may be discontinued for sustained non-response at the discretion of investigator.

Protocol Violation: The patient´s findings, or conduct, fails to meet protocol entry criteria or fails to adhere to the protocol requirements.

Lost to Follow-Up: The patient does not show up for further visits and study personnel can´t reach the patient.

Other: Termination of other reason

4.4.1. Patient Replacement

Randomised patients who discontinued from the study will not be replaced.

4.4.2. Follow-up of early discontinued patients

Patients treated with at least one dose of study treatment should be followed for safety for up to 10 weeks after the first dose.

5. STUDY TREATMENT

5.1. Study Drug

Cobitolimod is a fully synthetic DNA based 19 mer oligodeoxyribonucleotide [redacted]

[redacted]

Placebo is a rectal solution where the ingredient is water. It is tested for microbiological quality and compliant with European Pharmacopoeia (Ph Eur) requirements.

5.2. Study Drug Administration

Cobitolimod and matching placebo will be provided to the study sites by InDex Pharmaceuticals AB or its representative. Cobitolimod is a solution of 0.62 mg/mL (31 mg) and 2.5 mg/mL (125 mg) and 5 mg/mL (250 mg) drug in 50 mL water for injection in single-use siliconised glass vials with rubber stopper and aluminium cap.

The study drug will be administered only to eligible patients under the supervision of the investigator or identified designee(s). Female patients must have a negative urine pregnancy test prior to receiving each dose of study drug.

The study drug will be administered via a rectal enema while patients are in a lying left-sided position. All patients and study personnel will be blinded to study drug assignment for the entire study.

The time for start of the administration will be recorded in the eCRF. After administration the patient will be asked to remain recumbent for 30 minutes and it is allowed to move over to a bed. Any leakage (weight) of study drug will be recorded in the eCRF. The study drug will be administered at visit 2b, 3, 4 and 5. The visit schedule allows for a +/- 3 day deviation from the planned date of visit, and is always calculated from the day of visit 2b. At least three days must pass between visits and thus between the administration of study drug.

5.3. Study Drug Packaging, Labelling, Shipment and Storage

5.3.1. Study Drug Packaging

[redacted] will pack the study drug. Each vial is labelled with content, vial number and study number.

[redacted] will prepare individual patient supplies according to a computer generated randomisation code. The supplies will be packaged in accordance with good manufacturing practice (GMP).

5.3.2. Study Drug Labelling

Each vial will be labelled according to the GMP/good clinical practice (GCP) and the regulatory requirements for the countries participating in the study.

5.3.3. Shipment of Study Drug

Study drug will be delivered to the investigational sites by InDex Pharmaceuticals AB or its representative. The drug will be shipped at room temperature, under controlled conditions.

5.3.4. Storage of Study Drug

The study drug should be stored under controlled conditions at site at 2º - 8ºC. All partially used or unused vials will be retrieved by the sponsor. The investigator should not destroy unused study drug unless the sponsor has provided a written authorisation to do so. The shelf life of the study drug is 36 months at 2º - 8ºC.

5.4. Study Drug Compliance

In accordance with International Conference on Harmonisation (ICH), the investigator and the pharmacy must keep an inventory of all study drug received and administered during the study in the drug 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 vials received and dispensed.

After completion of the study, all unused and returned study drug packs (whether empty or full) should have been destroyed according to approved procedure, the destruction will be documented.

5.5. Blinding and Unblinding

The study is double-blind to study treatments. Blinding is accomplished by giving all study products identical appearance, packaging and labelling and by giving placebo at Week 1 and 2

to the treatment arms which are only given active doses at Week 0 and Week 3. The study will remain blinded until clean file has been declared.

If the treatment assignment must be revealed for the safety of the patient or to treat an AE the investigator may break the blind through IVRS. The IVRS will allow automated emergency unblinding via telephone at any time. Further details of this procedure are described in the separate IVRS manual. Any unblinding must be fully documented. The required information includes date and reason for unblinding as well as the name and the signature of the person who performed the unblinding. If the reason for unblinding is an AE it should be reported on the AE form.

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

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

If a need of unblinding arises when the investigator is unavailable further contact information is provided at the emergency card handed out to the patient at randomisation.

5.6. Overdose

Deliberate or accidental study drug overdose should be treated symptomatically and should be reported as an AE. Definition of overdose is treatment with more than one vial at administration or at other visits than visit 2b, 3, 4 and 5.

5.7. Concomitant Medications

All medications that the patient is prescribed and has taken during the study must be recorded in the eCRF. Any changes need to be reported.

The following concomitant UC medications are allowed:

- Oral GCS therapy (≤20 mg prednisone or equivalent/daily) providing that the dose has been stable for 2 weeks prior to visit 1a, and need to be kept stable up to primary endpoint (Week 6). Tapering can start at Week 6 if patients are in remission, see suggested tapering scheme below.
- Oral MMX Budesonide therapy (9mg/daily) initiated at least 8 weeks before screening visit 1 a and need to be kept stable up to primary endpoint (Week 6). Tapering can start at Week 6 if patients are in remission. Tapering per local practice.
- Oral 5-ASA and/or SP compounds, providing that the dose has been stable for 2 weeks prior to visit 1a, and initiated at least 8 weeks before visit 1a. Stable dose up to end of study (Week 10).
- AZA/6-MP providing that the dose has been stable for 8 weeks prior to visit 1b, and been initiated at least 3 months before visit 1a. Stable dose up to end of study (Week 10).

5.8. Prohibited Medications

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

- cyclosporine

- methotrexate
- tacrolimus or similar immunosuppressants/ immunomodulators.
- TNF-α inhibitors
- anti-integrins

Any prior treatment with these drugs must be discontinued at least 8 weeks prior to visit 1a *or* have non-measurable serum concentration levels.

5.9. Oral Corticosteroid Tapering Regimen

Steroid tapering is recommended to start when the patient has reached clinical remission, but earliest at Week 6. Once the decision to initiate steroid tapering is taken based on the investigator's assessment, reduction of the oral steroid dosage following the schedule outlined in the table below is recommended (Table 2). Consideration of the risk of adrenal gland insufficiency is cautioned, especially when the daily dose is lowered to less than 10 mg. For patient who cannot tolerate the corticosteroid taper without recurrence of clinical symptoms the dose may be increased up to original dose. For oral MMX budesonide the tapering schedule should follow the local practice.

Table 2. Schedule of Oral Steroid Dose Reduction given in Mg/Day.

Week	Starting steroid dose		
	20 mg/day	15 mg/day	10 mg/day
6-7	15	10	7.5
7-8	10	7.5	5
8-9	7.5	5	2.5
9-10	5	2.5	0
10-11	2.5	0	0
11-12	0	0	0

Final visit in the study is Week 10, table show titration after study completion as a guide

5.10. Rescue Medications

If a patient requires rescue therapy or dose increase of prior UC treatment, the patient will be discontinued from study drug. Administration of rescue medications constitutes treatment failure. Rescue medications should not be withheld if, in the opinion of the investigator, failure to prescribe them would compromise patient safety. It is on the investigators discretion to decide what treatment is best for the patient.

6. STUDY SCHEDULE

6.1. Visit 1a (Day -14) and 1b (Day -7 to -10) – Screening Visits

The Screening period, will be divided in two separate visits, Visit 1a and 1b.

At the first Screening Visit, 1a the patient will in detail be informed about the study and if agreement to participate, an informed consent form (ICF) will be signed off before any study specific procedures occur (it is accepted that patient sign the ICF before first screening visit, maximum one week ahead and given repeated information at the first screening visit). During

the Screening Visit 1a, procedures to assure the patient´s eligibility for the study participation will be performed. Demographics, (date of birth, gender and race), Vital Signs (blood pressure [BP], heart rate [HR], height, weight, smoking habits), medical history and UC history (including patient´s normal number of stools/day when in remission) will be obtained. A physical examination will also be performed and a 12-lead ECG will be taken.

Non-fasting blood samples will be collected for haematology, blood chemistry including CRP (biomarker), lipid profile analysis and future biomedical research (if consented to). Urine sample will be collected for dipstick analysis (Blood, Glucose, Ketones, Leucocytes, Nitrite, Protein and pH) and if clinically significant microscopy and/or culture. Stool sample for culture, microbiology and biomarker´s will also be collected. Females of childbearing potential will have a serum pregnancy test taken. Concomitant medications will be recorded. Prior UC treatment should be reported up to 3 years before screening visit and will be recorded with used dose; start/stop date and reason why not re-started to ensure inclusion criteria are fulfilled. The last treatment period of each UC drug will be collected. Allowed UC medications will be recorded with start date and dose to ensure stable dose is used during the entire study (GCS up to Week 6). Treatment with cyclosporine, methotrexate, TNF-α inhibitors, anti-integrins, tacrolimus or similar immunomodulatory/immunosuppressant drugs should have been stopped (at least 8 weeks before visit, 1a). These drugs should only have been stopped due to lack of efficacy or intolerable side effects. When laboratory results are available and the patient still is suitable for the study, patient will be informed about preparation for colonoscopy (separate instructions will be provided to the patient) which will be performed at screening visit 1b.

The patient will before leaving the clinic also receive training and instructions how to use an electronic diary (eDiary) for daily entry of data up to the day before the randomisation Visit 2b.

At the second screening visit 1b a full colonoscopy will be performed in order to determine the extent of inflammation. The colonoscopy will be video recorded and send for central reading. During the endoscopy, three biopsy samples will be taken from each bowel segment investigated (ascending colon, transverse colon, descending colon, sigmoid colon, and rectum). These biopsies will be used for central read histopathological evaluation and for future biomedical research (if consented to, if not consented only two biopsies from each segment will be taken).

All inclusion and exclusion criteria will be reviewed at several time points before randomisation.

The interpretation from central reading of colonoscopy videos must be reviewed by the investigator to ensure eligibility prior to randomisation.

Any AEs related to study specific procedures will be recorded at the Randomisation Visit 2b.

PGA assessment should be done at visit 1b after the endoscopy. In case eDiary data are not available (3 days consecutive) the PGA can be done before visit 2a when randomisation occurs.

All obtained information will be reported in the eCRF.

6.2. Visit 2a (Day -4 to-7) and 2b (Week 0) – Randomisation Visits

When the Central reading assessment is available and UC disease is qualifying for the study, the patient will be contacted by phone, Visit 2a, to ensure patient is willing to participate in

the study. If the patient is found to be eligible for study participation, the investigator will follow a central randomisation procedure and obtain a unique number (Patient Identification number) for the patient. If the patient fails to fulfil the inclusion/exclusion criteria, the patient can be re-screened at a later time point. If the re-screening will take place more than 1 month after the first screening visit all procedures need to be re-done, otherwise the s Sponsor/CRO will confirm to site which screening procedures have to be repeated at re-screening in order to ensure that the patient fulfils the criteria for entering the study. If the re-screening is performed more than 1 month after the first screening, patient will receive a new Patient Identification number.

The patient must be scheduled for the Visit 2b/Week 0 visit within 10 days from the performed endoscopy (including the day of endoscopy and first treatment).

At the visit 2b; before study drug administration vital signs (HR, BP and temperature) and physical examination will be performed. Females of childbearing potential will take a dip stick urinary pregnancy test. An ECG will be taken before study drug administration and approximately 30 minutes after treatment, before leaving the clinic.

The patient will be asked to complete an IBDQ questionnaire and extra intestinal manifestations and defecation urgency assessment will be obtained. Non-fasting blood samples will be collected for haematology, blood chemistry including CRP (biomarker) and future biomedical research (if consented to). Urine sample will be collected for dipstick analysis (Blood, Glucose, Ketones, Leucocytes, Nitrite, Protein and pH) and if clinically significant microscopy and/or culture will be send to central laboratory. Stool sample for faecal calprotectin (biomarker) will also be collected. Repeated training and instructions for the patient eDiary handling will be given. It is important to ensure the patient 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 patient will thereafter receive the study drug they were allocated to during the randomisation procedure. The study drug will be administered with a rectal enema. Following study drug administration the patient will be asked to remain recumbent for at least 30 minutes. Any leakage will be measured.

All obtained information will be reported in the eCRF.

6.3. Visit 3 - (Week 1)

This visit should occur on Day 7 (± 3 days). Vital signs (BP and HR) and physical exam will be measured. Non-fasting blood samples will be collected for haematology, blood chemistry including CRP (biomarker) and future biomedical research (if consented to). Stool sample for faecal calprotectin (biomarker) will also be collected. A dipstick urine pregnancy test should be checked. Defecation urgency assessment will be obtained. Repeated instructions for the eDiary handling will be given if necessary. It is important to ensure the patient understands that eDiary data are necessary to evaluate the study. Changes in concomitant medication or new medications should be reported. The patient will be treated with cobitolimod/placebo with a rectal enema. Following drug administration the patient will be asked to remain recumbent for at least 30 minutes. Any leakage will be measured. Patient will be asked if any AE has occurred since last visit.

All obtained information will be reported in the eCRF.

6.4. Visit 4 - (Week 2)

The visit should occur on Day 14 (± 3 days). Vital signs (BP and HR) and physical exam will be measured. Non-fasting blood samples will be collected for haematology, blood chemistry, including CRP (biomarker) and future biomedical research (if consented to). Stool sample for faecal calprotectin (biomarker) will also be collected. A dipstick urine pregnancy test should be checked. Defecation urgency assessment will be obtained. Repeated instructions for the eDiary handling will be given if necessary. It is important to ensure the patient understands that eDiary data are necessary to evaluate the study. Changes in concomitant medication or new medications should be reported. The patient will be treated with cobitolimod/placebo with a rectal enema. Following drug administration the patient will be asked to remain recumbent for at least 30 minutes. Any leakage will be measured. Patient will be asked if any AE has occurred since last visit.

All obtained information will be reported in the eCRF.

6.5. Visit 5 - (Week 3)

The visit should occur on Day 21 (± 3 days). Vital signs (BP and HR) and physical exam will be measured. Non-fasting blood samples will be collected for haematology, blood chemistry including CRP (biomarker) and future biomedical research (if consented to). Stool sample for faecal calprotectin (biomarker) will also be collected. The patient will be asked to complete IBDQ questionnaire and extra intestinal manifestations and defecation urgency assessment will be obtained. Repeated instructions for the eDiary handling will be given if necessary. It is important to ensure the patient understands that eDiary data are necessary to evaluate the study. Changes in concomitant medication or new medications should be reported. The patient will be treated with cobitolimod/placebo with a rectal enema. Following drug administration the patient will be asked to remain recumbent for at least 30 minutes. Any leakage will be measured. Patient will be asked if any AE has occurred since last visit.

All obtained information will be reported in the eCRF.

6.6. Visit 6 - (Week 6) Primary Endpoint or Discontinuation visit

The visit should occur on Day 42 ± 3 days from planned visit schedule (calculated from visit 2b) or if patient decides to not come on further visits perform Week 6 procedures as final visit. Vital signs (BP and HR), tobacco use and physical exam will be measured. Non-fasting blood samples will be collected for haematology, blood chemistry including CRP (biomarker), lipid profile and future biomedical research (if consented to). Urine sample will be collected for dipstick analysis and if clinically significant microscopy and/or culture will be send to central laboratory. Stool sample for faecal calprotectin (biomarker) will also be collected. The patient will be asked to complete IBDQ questionnaire and extra intestinal manifestations and defecation urgency assessment will be obtained. A dip stick urine pregnancy test should be checked. Changes in concomitant medication or new medications should be reported. A flex sigmoidoscopy will be performed and three biopsy samples will be taken from descending colon, sigmoid colon, and rectum (if not consent for future biomedical research only two biopsies from each segment will be taken). The investigator should fill in a PGA. An ECG will be taken. Repeated instructions for the eDiary handling will be given if necessary. It is important to ensure the patient understands that eDiary data are necessary to evaluate the study. Patient will be asked if any AE has occurred since last visit.

All obtained information will be reported in the eCRF.

6.7. Visit 7 – (Week 10)

The visit should occur on Day 70 ± 7 days from planned visit schedule (calculated from visit 2b). Vital signs (BP and HR) and physical exam will be measured. Non-fasting blood samples will be collected for haematology, blood chemistry including CRP (biomarker) and future biomedical research (if consented to). Stool sample for faecal calprotectin (biomarker) will also be collected. The patient will be asked questions regarding extraintestinal manifestations and defecation urgency. The investigator should fill in a PGA. Changes in concomitant medication or new medications should be reported. Patient will be asked if any AE has occurred since last visit.

All obtained information will be reported in the eCRF.

6.8. Unscheduled Visit

An extra visit 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 DSMB can request an extra visit where additional examinations should be conducted and blood sample(s) drawn as agreed with the DSMB.

7. STUDY PROCEDURES

The schedule of activities is provided in Table 1. Study assessments will be performed by the investigator, delegated study personnel or central reader. Patient related events and activities, including specific instructions, procedures, concomitant medications, administration of the study drug; steroid tapering and descriptions of AEs should be recorded in eCRF.

7.1. Central reading

During the endoscopy a video will be recorded (separate instruction will be provided). These videos will be sent to trained central readers for assessment.

7.2. Concomitant Medication

All changes to the prior treatment need to be recorded during the study e. g. stop date or entry of a new treatment.

7.3. Collection of Adverse Event and Serious Adverse Event

Collection of AE will start directly after an Informed Consent is signed. During the screening period only AEs related to study procedure will be reported. Definitions, documentation and reporting of AEs are described in detail in Section 8.

7.4. Demographics

Patient demographics, including sex, age, and race will be collected at the screening visit 1a.

7.5. Electrocardiogram

A 12-lead ECG will be performed and assessed at visit 1a, 2b and 6. At visit 2b the ECG should be taken before study drug administration (after 5 minutes rest) and another ECG approximately 30 minutes after study drug administration. The ECG will be reviewed by the investigator. If abnormalities before first dose of study drug the findings should be reported as medical history. Findings during study should be reported as AEs.

7.6. Eligibility and Evaluation

At visit 1a, the investigator should estimate the patient´s eligibility to the study based on Medical History, UC History and Concomitant therapy. Patient should also be asked about number of daily stool and presence of rectal bleeding. The combined information gives information to decide if patient is eligible for endoscopy.

For assessing eligibility to the study (Mayo score of 6-12) the Modified Mayo score at visit 2a, will be calculated by summarising the visit 1b endoscopy sub score, the PGA assessment and the Mayo sub scores assessed from eDiary at visit 2a.

All components for the assessment of Mayo score have to be collected within 10 days before visit 2b.

7.7. Endoscopy, Biopsy and Histology

A full colonoscopy will be performed with a video endoscope, at the Screening Visit (1b). The endoscope should inspect the whole bowel, up to the Cecum. Three biopsies should be taken from each bowel segment investigated (ascending colon, transverse colon, descending colon, sigmoid colon, and rectum). These biopsies will be used for central read histopathological evaluation (in end of the study) (appendix 15.3) and future biomedical research (if consented to, if not consented only two biopsies from each segment will be taken). There is a centralised assessment and processing of the endoscope videos.

A flexible sigmoidoscopy, performed with a video endoscope will be performed at visit 6. The endoscope should inspect the left-sided colon, up to splenic flexure. Three biopsies should be taken from each bowel segment investigated (descending colon, sigmoid colon, and rectum). The biopsies will be used for central read histopathological evaluation (in end of the study) and future biomedical research (if consented to, if not consented only two biopsies from each segment will be taken). There will be a centralized assessment and processing of the endoscope videos.

Separate instructions for procedure preparations will be provided to the patients.

7.8. Extraintestinal Manifestation Assessment

Patient will be asked questions (appendix 15.4) about specific diseases at visit 2b, visit 6 and visit 7. [20]

7.9. Inflammatory Bowel Disease Questionnaire

IBDQ is a patient questionnaire with 32 questions grouped into four dimensions: bowel, systemic, social, and emotional. The IBDQ will be completed at visit 2b before study drug administration, visit 5 and visit 6 or early termination visit.

7.10. Informed Consent

All patients 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 patient might discontinue and/or withdraw consent from the study at any time and for any reason. All patients will be given the opportunity to ask questions about the study and will be given sufficient time to decide whether to participate in the study or not. Patient's consent will be sought regarding data that will be recorded, collected, processed and might be transferred to the European Union (EU) and non-EU

countries. The data will not identify any person taking part in the study, in accordance with the EU Data Protection Directive (95/46/EU).

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

7.11. Laboratory Procedures

Blood, urine and stool samples will be collected at the time point identified in schedule of activities (Table 1). All samples will be collected in a non-fasting state. The clinical analyses to be performed are listed in Table 3. Unscheduled clinical labs may be obtained at any time during the study to assess any perceived safety concerns.

All females will have a serum pregnancy test at visit 1a and urine dip stick test at visit 2b, 3, 4, 5 and 6; it should be completed prior to each dosing of study drug.

A central laboratory will be used to perform safety tests for haematology and blood chemistry. Central laboratory will also analyse urine (microscopy and/or culture) if the urine dipstick analysis are clinically significant. Safety laboratory reports will show the reference range for each variable and will be reviewed at each visit. 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.

For the purpose of Future Biomedical Research (if consented to), serum and biopsy specimen's may be collected (if not consented no extra samples will be collected) during this clinical trial. The collected specimens may be used for future assay development and to explore and identify biomarkers that enhance the scientific understanding of ulcerative colitis and/or the therapeutic treatment. Such research is for mode of action biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) or development of UC evaluation score and will only be conducted on specimens from appropriately consented subjects.

The signed and interpreted laboratory results will be kept together with the patient's source data as supplemental pages.

Table 3. Clinical Laboratory Analysis.

Haematology	Clinical Chemistry	Urine	Other
Hemoglobin[1]	Albumin[1]	Blood[2]	Faecal Calprotectin[4]
Hematocrit[1]	ALP[1]	Glucose[2]	Stool culture for;
Platelet count[1]	ALT[1]	Ketones[2]	• Clostriudium DifficileToxin B
RBC s[1]	AST[1]	Leucocytes[2]	• Shigella
WBCs[1]	Amylase[1]	Nitrite[2]	• Campylobacter
Platelets[1]	BUN[1]	Protein[2]	• Yersinia
Neutrophils[1]	Calcium[1]	pH[2]	• Salmonella
Eosinophils[1]	Chloride[1]		• Faecal Ova and Parasites
Monocytes[1]	CPK[1]		Urine pregnancy test[3]
Basophils[1]	Creatinin[1]		Pregnancy test[3]
Lymphocytes [1]	CRP[1,4]		Triglycerides[1]
[1]	GGT[1]		Cholesterol[1]
	Glucose[1]		Fibrinogen[1]
	Phosphorus[1]		APTT[1]
	Potassium[1]		PT (including INR)[1]

	Sodium[1] Total Bilirubin [1] Total Protein[1] Uric Acid[1]		Future Biomedical Research[1] Colon biopsies[5]

[1] non-fasting state
[2] dip stick in all cases; microscopy and or/culture if clinically indicated.
[3] for women of childbearing potential
[4] for biomarker assessment
[5] Central read histopathological evaluation.

7.12. Leakage Measure

Weigh the under pad/surface protection sheet before the patient gets on the bed. After the drug has been administered and patient has been lying for 30 minutes weigh the under pad/surface protection again. The outcome will be registered in the eCRF.

7.13. Medical History

A complete medical history will be collected covering information up to the first dose of study drug. Diagnosis/symptoms/signs and the start year 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.

7.14. Mayo Score

- Full Mayo Score

A full Mayo score includes the sub scores; stool frequency, rectal bleeding, endoscopy and PGA.

- Modified Mayo Score

The Modified Mayo Score excludes the friability at grade 1 for the endoscopic sub score.

The Modified Mayo Score excluding friability at grade 1 (appendix 15.1), [21] will be used at visit 2b, to evaluate eligibility to the study.

The sub scores stool frequency and blood in stool will be evaluated during screening period, using eDiary data for the sub scores. The endoscopy sub score will be assessed by using centrally read result from a full colonoscopy (performed within 10 days prior Visit 2b) or sigmoidoscopy (at Visit 6).

- Patient Reported Outcome

PRO2 includes the sub score; stool frequency and rectal bleeding reported daily by the patient and via an eDiary.

7.15. Patient eDiary completion and Review

A Patient eDiary will be used for data collection with regard to patients daily symptoms. The following symptoms will be assessed daily from visit 1a to visit 7.

- Absolute number of stools

- Stool frequency according to the Mayo sub score
- Blood in stool scoring according to the Mayo sub score

eDiary data will be used to calculate the sub scores stool frequency and rectal bleeding (PRO2).

7.16. Physical Examination

A complete physical examination should be performed at each visit 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 clinical significant abnormalities, it should be reported either as medical history (during screening) or as an AE (after first dose).

7.17. Pregnancy Test

Pregnancy tests will be performed on all females of childbearing potential at all visits up to Week 6. Serum pregnancy tests will be carried out at Visit 1a. Pregnancy tests done at Visit 2b, 3, 4, 5 and 6 will be performed with urine dipsticks. If the pregnancy test is positive this is considered as an AE, contact the CRA for further guidance.

7.18. Prior Therapies

The use of any concomitant therapy will be recorded with preferably generic name and start and stop date. For all non-UC therapy the last 8 weeks treatment prior to Screening visit 1a needs to be recorded. For UC treatment such as: GCS, MMX Budesonide, 5-ASA/SP, AZA/6-MP, TNF-α inhibitor, anti-integrins, cyclosporine, tacrolimus or other immunomodulatory/immunosuppressant drugs, generic name, start date and stop date (if applicable) and dose should be recorded unless when treated. Only need to record the last treatment period for each. The reason why these drugs were not restarted when patient relapsed has also to be reported.

7.19. Study Drug Administration

Study drug will be administered via a rectal enema (see separate instructions).

7.20. Tobacco Use

The patient's tobacco history/use will be collected at Visit 1a and Visit 6.

7.21. Ulcerative Colitis History and Assessment

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

Definition of stool
Patients should be instructed that a stool is defined as a trip to the toilet when the patient has either a bowel movement, or passes blood alone, blood and mucus, or mucus only.

Definition of remission reference stool frequency
The patient 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 patient does not report that he or she has achieved remission, then the patient should be asked to identify the number of stools he or she had per day before initial onset of signs and symptoms of UC.

7.22. Urgency of Defecation

Patient will be asked questions (appendix 15.5) [22] about defecation urgency at visit 2b, 3, 4, 5, 6 and 7.

7.23. Vital Signs

Systolic and diastolic BP (mmHg) and HR (beats/min) will be measured in sitting position and after 5 minutes rest at every visit. The use of automated devices for measuring BP and HR are acceptable. Blood pressure and HR should be measured before blood samples are taken. On dosing days, vital signs should be obtained prior to treatment. Body temperature (ºC) will be measured and weight and height will be measured or reported from patient at visit 2b.

8. Adverse Event

Collection of AEs will start directly after the ICF has been signed. During the screening period only AEs related to study procedure will be reported.

Investigators are responsible for recording all AEs observed during the study period (i.e., from the time patient signs the ICF and until the patient has completed the study, (only AEs related to study specific procedures at screening visit will be recorded at Visit 1 and 2 while any other medical finding will be recorded as medical history). Following study drug administration, the patients will be questioned about AEs at each visit to the clinic.

8.1. Adverse Event Definition

An AE is any untoward medical occurrence associated with the use of a drug, whether or not considered drug related. 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 drug, whether or not it is considered to be study drug related. This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of study drug.

8.2. 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 at least a reasonable possibility that the event is related to the product.

8.3. Serious Adverse Event Definition

A SAE is any AE, occurring at any dose and regardless of causality defined as;

- death
- a life-threatening AE (means that the patient was at immediate risk of death as it occurred, does not include if the death may have occurred if a more severe form)
- in-patient 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

8.4. 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 patient, 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, then those changes should be recorded separately (with distinct onset dates).

8.5. Classification of Adverse Events by Relationship to Study Drug

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

8.6. Reporting of Adverse Events

At each visit, the patient will be asked if any new signs or a symptom has occurred since 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 eCRFs. If no AE has occurred during the study period, this should also be recorded in the eCRF.

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

UC is associated with certain characteristic signs and symptoms including diarrhea and rectal bleeding that may be present at Screening Visit and may fluctuate based on individual patient'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 not be collected as an AE. These characteristics of disease activity will be regularly captured.

Exacerbations of disease activity (increase in the daily amount of rectal bleeding beyond the patient´s normal fluctuation, 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

8.7. Reporting of Serious Adverse Events

All SAEs must be reported to the [redacted] Drug Safety Services within 24 hours 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 the following information:

- patient identification
- treatment specification
- AE diagnosis
- time specification for the medical event
- name of the original reporter

Any new information regarding the SAE report should be reported within 24 hours of knowledge. Apart from the information above, this follow-up report should also contain the following information:

- assessment of severity
- assessment of causality

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 drug, Suspected Unexpected Serious Adverse Reactions (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 patients. The appropriate ethics committee (EC) and regulatory authorities, as per local requirements, should be informed by the Sponsor about SAEs associated with the use of the product.

8.8. Follow-up Period after an Adverse Event

If a patient is to discontinue due to an AE, or if an SAE persists at the end of the study treatment period, this should be followed up until the condition has resolved or until the patient is under professional medical care and a potential causality between the study drug and the SAE has been established. An outcome assessment should be performed when an AE persists.

In case of pregnancy during the study the patient 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 also reported to [redacted] via Pregnancy report form.

8.9. Coding of Adverse Events

All AEs will be coded according to medical dictionary for regulatory activities (MedDRA) by [redacted] after the eCRFs have been collected from the study centres.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Analysis Plan

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 a separate Statistical Analysis Plan (SAP). A data display plan (DDP) will also be prepared and included in the SAP. The DDP will describe the layout of the tables and listings to be produced.

9.2. Determination of Trial Size

Given that the purpose of this trial is to determine whether cobitolimod is efficient and therefore whether to proceed with further development, there is only one outcome of interest, superiority of one or more of the experimental arms to the control (placebo). In this scenario, a one-sided testing framework is appropriate.

Further phase III trials will be required to confirm the efficacy, and thus the standard type I error rate control at the 0.05 level is not strictly necessary. The assumption is that a one-sided test of the null hypothesis that there is no difference in the primary endpoint between each active treatment arm and control (placebo) with a false-positive (type I error) rate of 0.10 is appropriate. The primary endpoint is, no difference between each active treatment arm and control (placebo) with a false-positive (type I error) rate of 0.10 is appropriate. The use of this higher type I error and of a low type II error of 0.10 gives to the trial high statistical power to detect a clinically meaningful effect while maintaining an acceptable sample size.

Assuming

- a 10 % remission rate for the placebo
- a type I error of 0.10
- a 35 % remission rate for the active cobitolimod treatment arm
- a power of 90 %
- a one-tailed test for differences between proportions

Thirty-five (35) patients per group are needed.

To allow for 10-20 % dropout rate the sample size is decided to 43 patient per treatment group and 215 patients in total.

Allocating 43 patients per treatment arm will also satisfy a power goal of 80 % using a two-sided test at the 0.05 type I error rate.

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

9.3. Study Population

9.3.1. Full Analysis Set

The full analysis set (FAS), will be based on the intention-to-treat (ITT) principles, which consists of all randomised patients who meet the inclusion criteria (as assessed by the investigator on the inclusion/exclusion criteria form), and receive at least one dose of the study drug (active or placebo).

9.3.2. Per Protocol Set

The per protocol set (PPS) is defined as FAS patients who do not have important protocol deviations considered to have a major effect on the primary efficacy endpoint, and have completed the Modified Mayo score (excluding friability) assessment at Week 0 and Week 6.

Patients in the PPS are analysed according to their randomised treatment.

9.3.3. Safety Analysis Set

The Safety Analysis Set is defined as all patients randomised in the study and treated with at least one dose of any study drug, i.e. cobitolimod in any dose or Placebo. Safety Analysis Set patients are analysed according to their actual treatment received.

9.4. Patient Demographic and Baseline Characteristics

Baseline values and patient 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, minimum and maximum value. All categorical variables will be summarised in frequency tables.

9.5. Primary Efficacy Endpoint Analysis

Sub scores of blood in stool, stool frequency will be based on the data collected in the eDiary. The measure of stool frequency will be derived calculating the mean daily stool frequency. The measure of blood in stool will be derived calculating the maximum (worst) outcome. Both measures will be derived using the most recent three consecutive days prior to the Week 0 and Week 6 visit, excluding the last two days before these visits.

The rationale for the exclusion of the last two days before the endoscopic procedure is that the preparation for the endoscopy can interfere with the natural clinical course of the symptoms.

A complete description of the derivation rules for the primary endpoint will be described in the SAP.

The analysis of the primary endpoint is conducted on the FAS and PPS.

The primary analysis of the primary endpoint will be performed using the Cochran Mantel Haenzel test adjusting for randomisation strata GCS use/non use and TNF-α prior use/non use at Baseline, Week 0.

The primary endpoint will be proportion of patients with clinical remission at Week 6 tested using an overall type I error rate of 0.10, using a one sided test.

The p-value for testing the null hypotheses must be less than 0.10 to be considered to have met the primary objective.

The primary efficacy endpoint will also be tested using the same approach as described above but with the use of an overall type I error rate of 0.05 using a two-sided test.

There will be no adjustment for multiplicity as all results will be regarded as exploratory. If a statistically significant difference among cobitolimod groups compared to placebo will exist, an analysis in terms of fractional polynomial for analysis of binary data will be applied to explore the dose-response relationship [23].

9.6. Exploratory Efficacy Endpoints Analyses

No multiplicity adjustments are made computing p-values of tests on exploratory variables; reported p-values are nominal. For overall comparison among more than two groups, the null hypothesis is that the proportions are the same in all groups.

The same analysis approach used for the primary efficacy endpoint will be applied to the exploratory efficacy variables referred to as a “Proportion endpoints”.

Continuous endpoints such as mean change from baseline will be evaluated using the ANCOVA, including treatment and stratifying factors as fixed factors and baseline as a covariate in the model.

9.7. Safety Analysis

9.7.1. Analysis of Adverse Events

The number and percentage of patients reporting AEs, and the number of AEs 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 patients experiencing an AE will be compared descriptively between groups.

All patients with AEs will be listed individually with patient number in addition to type of event, start and stop time, duration, seriousness, severity, action taken, relationship to study drug and outcome of AE.

9.7.2. 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.

9.8. Adjustment of Covariates

Baseline values of the parameters to be analysed will be used as covariates in exploratory analyses. In addition, the prior use of TNF-α inhibitor and GCS use will be included as a covariate in exploratory analyses.

9.9. Handling of Dropouts and Missing Data

For the efficacy analyses, missing data will be replaced using the non-responder imputation (NRI). 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. The last-observation-carried-forward will be used as a sensitivity analysis for evaluation of study data. Additional methods for handling missing data will be used and described in the Statistical Analysis Plan (SAP).

9.10. Rules for Excluding Patients from Analysis

Patients will not be excluded from any analyses unless they fall outside a specific definition of the populations described earlier, or unless there is missing data for all endpoints for which an imputation algorithm is not described. Protocol deviations will be described in a separate document for the purposes of defining the Per Protocol Set prior to database lock.

9.11. Procedures for Reporting Deviations from Original Statistical Plan

Any deviations from the original SAP will be described and justified in the final study report.

9.12. Interim Analysis

No formal statistically based interim analysis will be performed. However, the safety data will be reviewed periodically during the conduct of the study by the independent DSMB. The primary objective of the DSMB data review is safety.

10. DATA HANDLING

10.1. Data Handling

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

All source data will be identified at the start of the trial. eDiary data and laboratory data will be considered as source data, all other data will be entered in 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 days of completion of each patient visit, the investigator should agree to have completed and entered data into eCRF for inspection by the clinical monitor.

All of the AEs (whether serious or not) described in the eCRF will be entered in the study database.

The initial notification of SAEs will also be entered in the [redacted] safety database for coding, medical evaluation and notification to the health authorities and independent ethics committees (EC) according to national regulatory requirements.

10.2. 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 information of discrepancies in the process. The database, data entry screens, and program will be designed in accordance with the clinical study protocol.

10.2.1. 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 principal investigator (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 patients.

10.2.2. Entry of Data

All data must be entered in English. The eCRFs should always reflect the latest observations of patients participating in the study. Therefore, the eCRF is to be completed as soon as possible during or after the patient'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.

The patient will fill in eDiary data on a daily basis.

10.2.3. Query Process

The monitor 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 contract research organisation (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, along with 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.

10.2.4. 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 patient's medical history, that verify the existence of the patient, the inclusion and exclusion criteria, and all records covering the patient's participation in the study. They include laboratory notes, memoranda, material dispensing records, patient files etc.

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 patient 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 patient number. Any personal information, including patient name, should be removed or rendered illegible to preserve individual confidentiality.

10.2.5. 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.

10.2.6. 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 has been entered, verified, and validated, the database will be locked.

10.2.7. 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, ECGs, vital signs and physical examinations) will be reviewed in a blinded fashion on an ongoing basis by the [redacted] study medical monitor. The Study Medical Monitor will inform the DSMB in case of any findings. Based on these ongoing reviews, the DSMB may make recommendations and InDex Pharmaceuticals AB may halt the enrolment, modify dose level, add or modify safety procedures or discontinue the study.

10.3. Study Monitoring and Auditing

This study will be monitored at all stages of its development by InDex Pharmaceuticals´ AB representative [redacted] Monitoring will include personal visits and telephone communication to assure that the investigation is conducted according to the protocol and in order 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 patient.

Any data recorded directly in the eCRF, for which no other written or electronic record will be maintained in the patient'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 drug 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 reflects the actual experience of the patient in the study, i.e., source data verification.

Safety Monitors and Clinical Research Associates or assistants may request to witness patient evaluations occurring as part of this protocol. The Investigator and appropriate personnel will be periodically requested to attend meetings/workshops organised by [redacted] to assure acceptable protocol execution. The study may be audited by InDex Pharmaceuticals AB or by regulatory agencies. If such an audit occurs, the investigator must agree to allow access to required patient records. By signing this protocol, the investigator grants permission to personnel from InDex Pharmaceuticals AB, its representatives, and appropriate RAs 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.

10.4. 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 agencies. 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.

10.5. 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 [redacted]

11. ETHICAL REQUIREMENTS

11.1. 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. The final study protocol, including any substantial amendments and the final version of the patient information and consent form, will be reviewed and approved by regional ECs and by the regulatory authorities in each country prior to inclusion of patients.

11.2. Indemnification

InDex Pharmaceuticals AB's 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 drug to the patient during this study, InDex Pharmaceuticals AB assumes liability by law on behalf of the Investigator(s), providing the Investigator/delegate has followed the instructions of InDex

Pharmaceuticals AB in accordance with this protocol and any amendments thereto, that the study drug administered to the patient in this study have been supplied by InDex Pharmaceuticals AB and that the Investigator/delegate have generally performed this study in accordance with scientific practice and currently acceptable techniques and know-how.

The patients are covered by insurances held by InDex Pharmaceuticals AB.

11.3. Sponsor Discontinuation Criteria

InDex Pharmaceuticals AB 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 drug pertaining to the study must be returned to InDex Pharmaceuticals AB or its representative.

12. STUDY COMMITTEES

12.1. Data Safety Monitoring Board

An independent DSMB will evaluate the safety data in the context of the overall trial and the currently existing information about the study drug. The DSMB will be composed of representatives from outside of InDex Pharmaceuticals AB who are experts in their respective disciplines of medicine, statistics and clinical trial methodology and conduct.

The DSMB will together with InDex Pharmaceuticals AB determine the appropriate time frame for reviewing the data during the course of the study, and will draw up a charter delineating their guidelines for operating and stopping rules for terminating individual patients, a portion or all of the trial prematurely.

In the context of overall patient safety, the DSMB 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 patients for each visit, dropouts, completeness of eCRFs and data entry and information on AEs and SAEs.

Furthermore, the DSMB will be notified of abnormal laboratory test values (defined by the laboratory standard reference range for normal) of defined variables included in the safety data package.

The DSMB will have access to all trial data. It may request and will be provided with whatever data it deemed necessary or useful for it to carry out its duties. The data provided will be blinded to treatment group unless specific unblinding is requested by the DSMB.

13. PUBLICATION/DATA SHARING POLICY

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

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15. Appendices

15.1. Mayo Scoring System for Assessment of Ulcerative Colitis Activity[a]

Grade	Stool frequency[b]	Rectal Bleeding[c]	Physician´s global assessment[d]	Colonoscopy/sigmoidoscopy finding
0	Normal number of stools for this patient	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, mild friability)
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 Modified Mayo score (excluded friability at grade 1) ranges from 0-12, with higher scores indicating more severe disease. Partial Mayo score excludes endoscopy.

[b] Each patient serves as his or 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 physicians global assessment acknowledges the 3 other criteria, the patients daily recollection of abdominal discomfort and general sense of well-being, and other observations, such as physical findings and the patient´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

15.2. Definitions of stool frequency and rectal bleeding

Items	Definition
Definition of Stool	Patients should be instructed that a stool is defined as a trip to the toilet when the patient has either a bowel movement, or passes blood alone, blood and mucus, or mucus only
Reference Remission Stool Frequency (over 24 hours)	The patient 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 patient does not report that he or she has achieved remission, then the patient 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 patient 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)	Patients 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 Patients 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.

15.3. Nancy Histological Index

Definitions of grades:

Grade	Definition
0	No or mild disease – No histological significant disease
1	Moderate or marked increase – chronic inflammatory infiltrate with no acute inflammatory infiltrate
2	Mildly active disease - with acute inflammatory cells infiltrate and no ulceration
3	Moderately active disease – with acute inflammatory cells infiltrate and no ulceration
4	Severely active disease – with ulceration

Further clarifications:

Item	**Likert scale anchor points**
Chronic inflammatory infiltrate (defined as the quantity of lymphocytes and plasmacytes in the biopsy specimen)	0 No increase 1 Mild but unequivocal increase 2 Moderate increase 3 Marked increase
Neutrophils in the epithelium	0 None 1 <50% crypt involved 2 >50 % crypt involved
Ulceration (defined as visible epithelial injury and regeneration and/or fibrin and neutrophils and/or tissue granulation)	0 Absent 1 Present
Acute inflammatory cell infiltrate	0 None 1 Mild 2 Moderate 3 Severe
Mucin depletion	0 None 1 Mild 2 Moderate 3 Severe
Neutrophils in lamina propria	0 None 1 Mild 2 Moderate 3 Severe
Basal plasmacytosis	0 None 1 Mild 2 Moderate 3 Severe
Serrated architectural abnormalities (defined as the presence of dilated crypts showing a scalloped lumen)	0 None 1 <5% crypt involved 2 <50% crypt involved 3 >50% crypt involved

15.4. 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

15.5. Urgency of defecation index

Grade	Defecation
0	Continent
1	Hurry
2	Immediately
3	Incontinent

One of the components in the simple clinical colitis activity index (SCCAI).