CLINICAL STUDY PROTOCOL

Protocol Number: NX-13-201

FDA IND Number: 144838

EU CT # 2022-503005-38-00

A Randomized, Double-Blind, Placebo-Controlled, Multiple Dose, Multicenter Phase 2 Induction Study with Long-Term Extension to Evaluate the Clinical Activity and Safety of Oral NX-13 in Participants with Moderate to Severe Ulcerative Colitis

Protocol Amendment 2.0	**16 July 2023**
Protocol Amendment 1.1	14 February 2023
Protocol Amendment 1	03 February 2023 (not implemented)
Protocol Version 1.0	(Original protocol, not implemented)
Sponsor:	Landos Biopharma, Inc. PO Box 11239 Blacksburg VA 24062 USA
Clinical Research Organization:	ICON

PROTOCOL APPROVAL PAGE

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Protocol Amendment 2.0

16 July 2023

July 16, 2023

[redacted]
[redacted], Landos Biopharma, Inc.

Date

INVESTIGATOR AGREEMENT

A Randomized, Double-Blind, Placebo-Controlled, Multiple Dose, Multicenter Phase 2 Induction Study with Long-Term Extension to Evaluate the Clinical Activity and Safety of Oral NX-13 in Participants with Moderate to Severe Ulcerative Colitis

I have read the protocol and agree that it contains all necessary details for carrying out this trial.

I undertake to conduct this trial within the time designated.

I understand that all information concerning the investigational product supplied to me by the sponsor in connection with this trial and not previously published is considered confidential information.

The information includes the clinical protocol, the case report form, technical methodology, and basic scientific data provided in the Investigator's Brochure. I agree that documents and other data pertinent to this trial are the property of the sponsor.

Furthermore, I understand that any changes in the protocol must be approved in writing by the sponsor.

By my signature below, I hereby attest that I have read, understood, and agree to abide by all conditions, instructions, and restrictions contained in the above protocol.

Investigator:

_____ _____ _____

Date

Telephone Number of Investigational Site:

_____

_____

_____

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PROTOCOL SYNOPSIS

Title

A Randomized, Double-Blind, Placebo-Controlled, Multiple Dose, Multicenter Phase 2 Induction Study with Long-Term Extension to Evaluate the Clinical Activity and Safety of Oral NX-13 in Participants with Moderate to Severe Ulcerative Colitis

Objectives and Endpoints

OBJECTIVE	ENDPOINT
Primary Objective – Overall Study	**Primary Endpoint – Overall Study**
To assess the clinical activity of oral NX-13 vs placebo	Change from baseline in Modified Mayo Score (MMS) at Week 12
Secondary Objectives – Overall Study	**Secondary Endpoints – Overall Study**
Safety and tolerability	• Proportion of participants with TEAEs in induction period • Proportion of participants with SAEs in induction period • Change from baseline in clinical laboratory results, vital signs, and ECGs over time in induction period
Clinical remission	Proportion of participants with MMS ≤2 at Week 12
Clinical response	Proportion of participants with ≥2 points and ≥30% decrease from baseline in MMS with ≥1 point decrease in rectal bleeding subscore RBS or RBS ≤1 at Week 12
Endoscopic response	Proportion of participants with endoscopic subscore ES ≤1 at Week 12
Endoscopic remission	Proportion of participants with endoscopic subscore ES = 0 at Week 12
Endoscopic-histologic mucosal improvement	Proportion of participants with ES ≤1 and Geboes score <2.0 at Week 12
Symptomatic remission	Proportion of participants with RBS = 0 and (i) stool frequency subscore SFS = 0 or (ii) SFS = 1 with baseline SFS ≥2, at Week 12
Exploratory Objectives – Induction (Week 12)	**Exploratory Endpoints – Induction (Week 12)**
[redacted]	• Change from baseline in SFS over time in induction period • Change from baseline in RBS over time in induction period • Change from baseline in Robarts Histopathology Index (RHI) at Week 12
	• Change from baseline in IBDQ total score and domain subscores over time in induction period

[redacted]	• Change from baseline in FACIT-F scores over time in induction period • Shifts from baseline in Rectal Urgency scores over time in induction period • Change from baseline in Abdominal Pain Scores over time in induction period
	NX-13 plasma concentration
	Change from baseline in FCP, CRP, tissue [redacted], cytokines, and gene expression (qPCR) over time in induction period
Exploratory Objectives – LTE (Week 52)	**Exploratory Endpoints – LTE (Week 52)**
[redacted]	

Abbreviations: CRP = C-reactive protein; ECG = electrocardiogram; ES = endoscopic subscore; FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue; FCP = fecal calprotectin; [redacted]; IBDQ = Inflammatory Bowel Disease Questionnaire; LTE = long-term extension; MMS = Modified Mayo Score; qPCR = quantitative polymerase chain reaction; [redacted]; RBS = rectal bleeding subscore; RHI = Robarts Histology Index; SAE = serious adverse event; SFS = stool frequency subscore; TEAE = treatment-emergent adverse event

Study Design

This is a randomized, double-blind, placebo-controlled, multiple dose exploratory Phase 2 induction study with a long-term extension (LTE) period in participants with moderate to severe ulcerative colitis (UC).

Participants will have endoscopically documented UC for at least 3 months prior to screening, with moderate to severe activity defined as Modified Mayo Score (MMS) ≥ 5, including endoscopic score (ES) ≥ 2, rectal bleeding subscore (RBS) ≥ 1, and stool frequency subscore (SFS) ≥ 1. They must have failed, had an inadequate response to, or been intolerant of at least one prior therapy including conventional therapy (5-ASA with systemic glucocorticosteroids/ glucocorticoids, systemic glucocorticosteroids/glucocorticoids alone, or thiopurines), biologic therapy (including monoclonal antibodies against tumor necrosis factor [TNF], integrin, or anti IL-12/23 (p19 or p40 subunits) (e.g., ustekinumab)), and/or advanced therapy (JAK inhibitor, S1P receptor modulator), but not have failed more than 2 classes of biologic therapy.

The screening period may take up to 42 days. After all other screening assessments have supported eligibility, and at least 5 days but not more than 14 days prior to randomization, participants will undergo an endoscopy (colonoscopy or flexible sigmoidoscopy [FS]) as appropriate with biopsies. Approximately 80 participants from the United States and rest of world will be randomized 2:2:1 to receive NX-13 250 mg, NX-13 750 mg, or placebo administered orally once per day during the 12-week induction period. Randomization will be stratified within each treatment arm by prior exposure to biologics or advanced therapies for UC.

After completion of the induction period and Week 12 endoscopy, participants may continue in the 40-week LTE period. Participants who were randomized to NX-13 250 mg or NX-13 750 mg during the induction period will continue to receive the same blinded investigational product (IP) during the LTE. Participants who were randomized to placebo during the induction period will be randomized 1:1 to receive blinded NX-13 at 250 mg or 750 mg once daily.

As an exploratory study, it will be deemed successful if the primary endpoint for the active treatment at 12 weeks is superior to placebo with a 1-tailed p value < 0.05 (2-tailed value ≤ 0.10).

Study Population

The study will enroll approximately 80 participants with moderate to severe active UC, who meet all of the following criteria:

Inclusion Criteria

1. 18 to 75 years of age at time of informed consent
2. Able to give informed consent, attend, and comply with study visits and e-diaries

3. Diagnosed with UC ≥ 3 months prior to screening. The diagnosis of UC must be confirmed by endoscopic and histologic evidence. The endoscopy and histology report should be present in source documents; however, if not available, the screening endoscopy and histology report may serve as such.
4. Received a surveillance colonoscopy (performed according to local standard) within 12 months prior to the planned randomization date to rule out dysplasia in individuals with pancolitis > 8 years duration or individuals with left sided colitis > 12 years duration. Individuals without a surveillance colonoscopy within the prior 12 months will have a colonoscopy at screening (i.e., in place of the screening proctosigmoidoscopy). Any adenomatous polyps must be removed according to routine practice prior to the study participant's first dose of investigational product.
5. Moderate to severe disease activity, characterized by all of the following (see Section 7.3.1 for details):
    - MMS ≥ 5
      defined as follows:
    - ES ≥ 2 within 14 days prior to randomization
    - RBS ≥ 1
6. An inadequate response to, loss of response to, or intolerance of at least 1 of the following therapies, as defined below (see Section 12.9 for details):

    Conventional therapy classes:

    - Oral 5-ASA compounds plus systemic glucocorticosteroids/glucocorticoids
    - Systemic glucocorticosteroids/glucocorticoids
    - Thiopurines

    Biologic therapy classes:

    - Anti-TNF monoclonal antibodies or biosimilars
    - Anti-integrin monoclonal antibodies
    - Anti-IL-12/23 monoclonal antibodies

    Advanced therapy classes:

    - JAK inhibitors
    - S1P receptor modulators
7. Eligible male participants must either:
    - Be surgically sterile (i.e., vasectomy) for ≥ 3 months (≥ 90 days) before screening; or
    - Agree to the following, from the time of randomization until at least 30 days after last dose of investigational product:
        - Agree to use a condom with spermicide when sexually active with a female partner who was not using a highly effective method of birth control
        - Agree not to participate in a conception process (i.e., active attempt to impregnate, sperm donation, or in vitro fertilization)
8. Eligible female participants must be:

- Nonpregnant, evidenced by a urine dipstick pregnancy test within 24 hours prior to randomization, and
- Nonlactating

9. Eligible female participants of non-childbearing potential must be surgically sterile or postmenopausal (defined as ≥ 1 year without menses).
    - Women must be surgically sterile for at least 6 months before screening as confirmed by medical history. Surgical procedures are tubal ligation performed laparoscopically, hysterectomy, and/or bilateral oophorectomy; or other procedures if sponsor agrees.
    - A postmenopausal state is defined as no menses for ≥ 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy.
10. Women of childbearing potential (WOCBP) must:
    - Agree to use birth control methods that are considered highly effective:
        - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, transdermal
        - Progestogen-only hormonal contraception associated with inhibition of ovulation: oral, injectable, implantable
        - Intrauterine device (IUD)
        - Intrauterine hormone-releasing system (IUS)
        - Bilateral tubal occlusion
        - Vasectomized partner
        - Sexual abstinence

      Note: Contraceptive measures such as Plan B (used after unprotected sex) are not considered highly effective methods of contraception for this study
    - Agree not to participate in a conception process (i.e., active attempt to become pregnant, egg donation, in vitro fertilization) for at least 30 days after the last dose of investigational product

Exclusion Criteria

1. Severe extensive colitis as evidenced by:
    - Physician judgment that the participant is likely to require hospitalization for medical care or surgical intervention of any kind for UC (e.g., colectomy) within the 12 weeks after randomization
    - Current evidence of fulminant colitis, toxic megacolon or recent history (within 6 months prior to screening) of toxic megacolon, or bowel perforation
2. Diagnosis of Crohn's disease (CD) or indeterminate colitis, or the presence or history of a fistula consistent with CD
3. Inadequate response to an induction course of more than 2 classes of biologics (e.g., TNF alpha, integrin or IL-12/23) approved for UC

4. Diagnosis of microscopic colitis, ischemic colitis, or radiation colitis
5. History of active bacterial, viral, fungal, or mycobacterial infectious colitis requiring oral antibiotic/anti-infective treatment within 4 weeks prior to screening.
6. Infection requiring hospitalization or intravenous (IV) antimicrobial therapy within 8 weeks prior to screening
7. Presence of indefinite dysplasia or UC-associated dysplasia on colonoscopy or FS, or a history of UC-associated dysplasia
8. History of colectomy (total or subtotal), ileoanal pouch, Kock pouch, or ileostomy; or is planning bowel surgery
9. History of spontaneous gastrointestinal (GI) perforation (other than appendicitis or mechanical injury), diverticulitis, or at significantly increased risk of GI perforation per the investigator's judgment
10. Hospitalization for exacerbation of UC requiring IV steroids (i.e., UC flare) within 12 weeks prior to screening (a single dose of IV steroids is acceptable)
11. Treatment with cyclosporine, tacrolimus, sirolimus, methotrexate, or mycophenolate mofetil within 4 weeks prior to screening.
12. Thiopurine washout is required to be completed within 6 weeks prior to screening.
13. Treatment with a biologic agent (e.g., infliximab, vedolizumab) within 6 weeks or 5 elimination half-lives (whichever is less) prior to screening. For anti-IL-12/23 (p19 or p40 subunits) (e.g., ustekinumab) a total of 12 weeks (6 weeks prior to screening and 6 weeks of screening) or 5 elimination half-lives (whichever is less) of washout.
14. Treatment with an advanced oral UC therapy (e.g., JAK inhibitor, S1P modulator) within 4 weeks prior to screening
15. Treatment with IV glucocorticosteroids/glucocorticoids, rectal glucocorticosteroids/ glucocorticoids, rectal or topical 5-ASA, or enema within 2 weeks prior to screening
16. Treatment with oral prednisone at a daily dose of > 20 mg (or equivalent) or active oral glucocorticosteroids/ glucocorticoids , e.g., budesonide at a daily dose of > 9 mg or equivalent, within 30 days prior to screening. If receiving systemically active oral glucocorticosteroids/ glucocorticoids , must be on a stable dose for at least 14 days prior to screening.
17. Confirmed or suspected infection of the intestinal tract, including positive Clostridioides difficile stool test at screening
18. Have acute or chronic hepatitis B infection or test positive for hepatitis B virus (HBV) at screening
19. Have current hepatitis C infection or test positive for hepatitis C virus (HCV) at screening
20. Have known infection with human immunodeficiency virus as confirmed by medical history
21. Live virus vaccination within 4 weeks prior to randomization (Note: no currently available vaccine for SARS-CoV-2 is a live virus vaccine)
22. Fecal microbial transplantation within 30 days prior to screening
23. Known primary or secondary immunodeficiency

24. Previously received stem cell transplantation
25. Has been a previous recipient of an organ transplant, which requires continued immunosuppression
26. Any surgical procedure requiring general anesthesia within 4 weeks prior to randomization, or planned elective surgery during the study
27. History of malignant neoplasms or carcinoma within 5 years prior to screening (except basal cell and in situ squamous cell carcinomas of the skin that have been fully excised and resolved)
28. Requirement for regular dosing of strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, clarithromycin) or inducers (e.g., rifampin, phenytoin, carbamazepine) or CYP2C19 inhibitors (e.g., fluconazole, fluoxetine, fluvoxamine, ticlopidine) or inducers (e.g., rifampin)
29. Current or recent history of alcohol dependence or recreational drug use that, in the opinion of the investigator, may interfere with the individual's ability to comply with the study procedures
30. Mental or legal incapacitation at the time of screening or a history of clinically significant psychiatric disorders that would impact the individual's ability to participate in the study, according to the investigator
31. Any concurrent clinically significant medical condition that, in the judgment of the investigator, may pose an unacceptable risk to the participant, including any known hypersensitivity to the drug product or any of its excipients
32. Participants with evidence of active or latent infection with Mycobacterium tuberculosis (TB) or participants with this history who have not completed a generally accepted full course of treatment (with completion of this treatment at least 6 months prior to start of screening) are excluded. All other participants must have either the Mantoux (purified protein derivative [PPD]) tuberculin skin test or interferon gamma release assay (IGRA) performed. See Section 12.7 for details
33. Unable to comply with study activities (e.g., swallow 3 whole tablets per day without crushing, breaking, or chewing)
34. Concurrent participation in any other investigational study, or individuals who have received any investigational therapy within 4 weeks or 5 elimination half-lives (whichever is longer) prior to screening
35. Women who are pregnant, breastfeeding, or contemplating pregnancy, from the time of informed consent until at least 30 days after the last dose of investigational product.
36. Estimated absolute glomerular filtration rate of < 30 mL/minute
37. Liver transaminases (ALT, AST) > 1.5× ULN at screening
38. Total bilirubin > 1.5× ULN at screening, or > 2.0× ULN for individuals with Gilbert's syndrome
39. Hemoglobin < 9g/dL (< 5.6 mmol/L) at screening
40. Individuals who are investigational site staff members or relatives of those site staff members or are Sponsor or CRO employees directly involved in the conduct of the study

Screening blood tests with an abnormal result may be repeated once, if deemed appropriate by the investigator. The retest should be performed within 7 days after the original test, and results must be available within the 42-day screening period.

Participants may be rescreened once for eligibility determination.

Investigational Product Dosage and Administration

NX-13 will be supplied as 250 mg tablets for once daily oral administration.

Participants will be randomized to receive NX-13 250 mg, NX-13 750 mg, or matching placebo in a double-blind fashion during the induction period. Participants who enter the LTE period will receive NX-13 250 mg or NX-13 750 mg in a blinded fashion.

Prohibited Therapies During the Study That Require Washout Prior to Screening

The following biologic therapies require completion of at least 6 weeks of washout prior to informed consent (first day of screening), or the participant must have no active drug detected at start of screening as determined by therapeutic drug monitoring.

- TNF antagonists
- Anti-integrin therapy
- Anti-IL-12/23 (p19 or p40 subunits) therapy (e.g., ustekinumab) a total of 12 weeks (6 weeks prior to screening and 6 weeks of screening) or 5 elimination half-lives (whichever is less) of washout.

Note: for eligibility, subjects previously treated with biologics may not have had inadequate response to a full course of induction with more than 2 classes of these agents.

The following small molecule agents require completion of at least 4 weeks of washout prior to informed consent (first day of screening):

- Oral JAK inhibitors
- S1P modulators

Statistical Methods

A Statistical Analysis Plan (SAP) will be developed and finalized prior to the unblinding of treatment allocation codes. It will describe in detail the assumptions and methods of analysis. As this is an exploratory study, a 1-sided test has been chosen, with alpha = 0.05.The target sample size is 71 participants. Assuming a 10% drop out rate during induction, approximately 80 participants with moderate to severe UC are planned to be enrolled. The primary endpoint is change from baseline (CFB) in mean MMS for NX-13 compared to placebo. The sample size assumes that the CFB in the MMS for the placebo group will be -1.75, for the active group will be -2.65, and the delta will be 0.9. The one-tailed alpha is set at 0.05, and the power is 80%.

Eligible participants will be randomized in a double-blind fashion to one of 3 treatment arms in a 2:2:1 ratio to receive NX-13 250 mg (n=32), NX-13 750 mg (n=32), or matching placebo (n=16). Randomization will be stratified within each treatment arm by prior exposure to biologic therapy for UC, with the biologic therapy-exposed population limited to approximately 50% of the total sample size. All participants who are randomized to NX-13 250 mg or NX-13 750 mg during the induction period will continue to receive the same blinded investigational

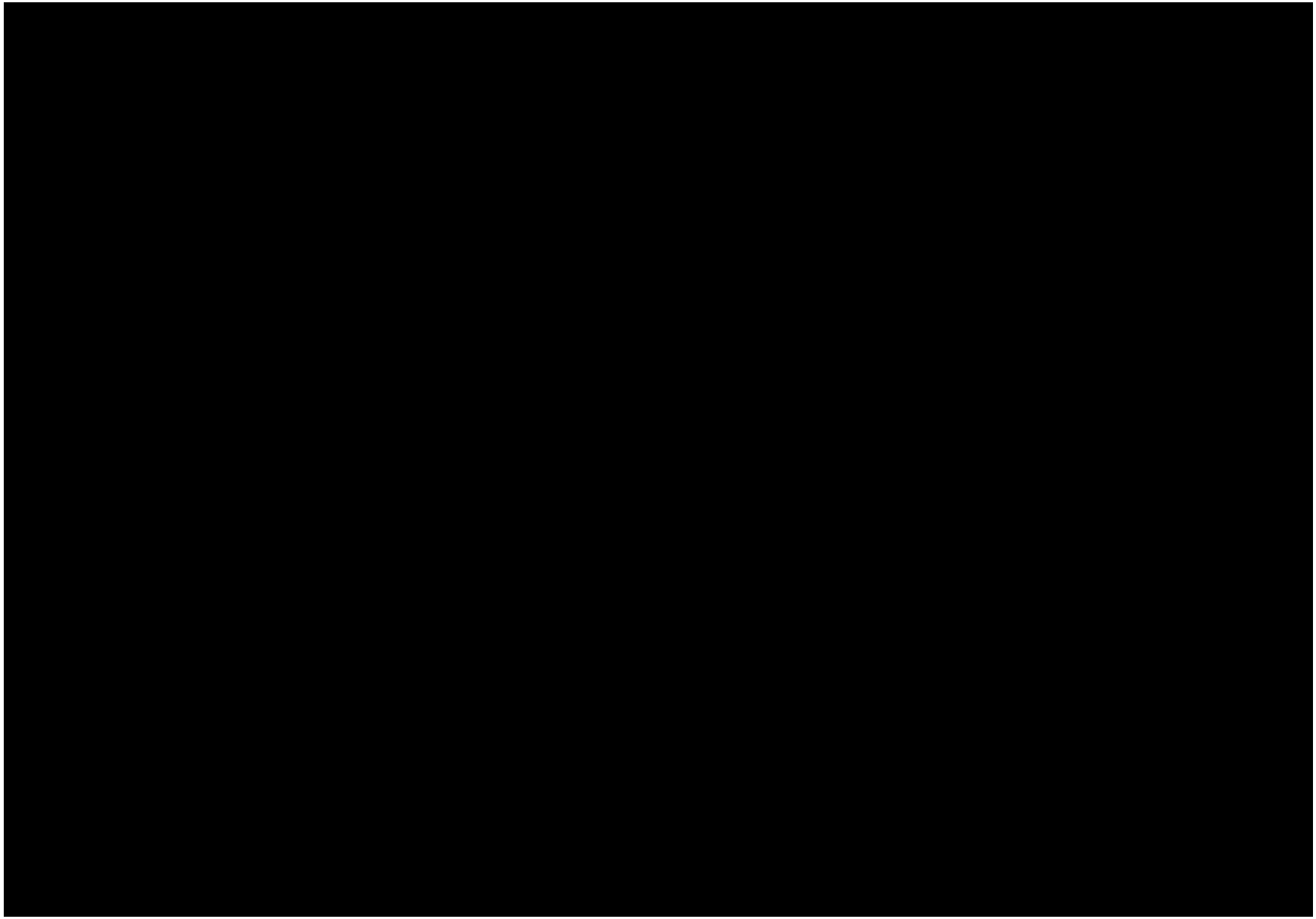
product for the 40-week LTE period. Participants who are randomized to placebo during the induction period will be randomized to receive a blinded NX-13 dose of 250 mg or 750 mg per day during the LTE.

Efficacy analyses will be performed on the ITT analysis set and will be comprised of ANCOVA on the primary endpoint and CMH chi-square tests on the secondary endpoints. Exploratory efficacy endpoints will be analyzed descriptively. Safety analyses will be performed on the SAF analysis set and will be descriptive. PK analyses will be performed on the PK analysis set.

An interim analysis will be performed after all participants complete the induction period.

TIME AND EVENTS SCHEDULE: 12-Week Induction Period

Study Procedure	Screening	Randomization	Treatment			Safety Follow-up	Unscheduled
Visit	**1** [a]	**2** [b]	**3**	**4**	**5** [c, d]	**(W2PT)** [e]	**UNS** [d, f]
Week	**S**	**0**	**4**	**8**	**12/EOT/ Assess** [g]	**W2PT**	
Study Day	**-42 to 0**	**1**	**29 ±4**	**57 ±4**	**85 ±7**	**(+14 to 21)**	
Informed consent	X						
Assess inclusion/exclusion	X				(X) [g]		
Confirm inclusion/exclusion		X					
Demographics	X						
Medical/surgical history, medication history [h]	X						
Full physical exam [i]	X				X		
Targeted physical exam [j]		X		X		(X)	X
Weight, height [k]	X	X			X		
Vital signs [l]	X	X	X	X	X	(X)	X
[redacted]							



[redacted]

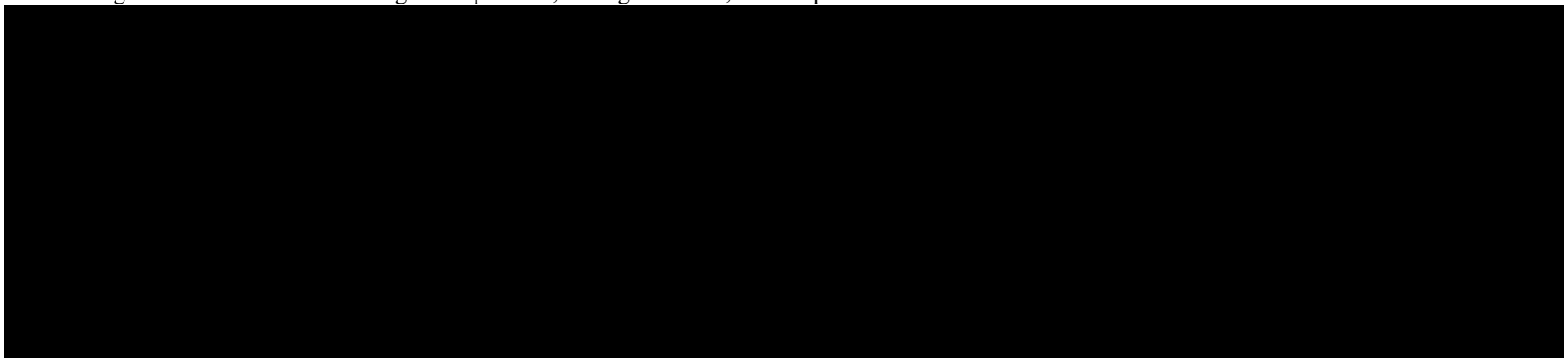
h Includes general medical/surgical history and prior medication history as well as UC-specific medical history and UC medication history.
i Evaluation of all body systems except rectal and genital examinations.
j Evaluation to address any abnormalities reported previously plus any new abnormalities including body areas reported as adverse events or changes in disease activity.
k Height will be recorded at screening only.
l Vital signs will be recorded for sitting blood pressure, resting heart rate, and temperature.

[redacted]

TIME AND EVENTS SCHEDULE: 40-Week Extension Period

Study Procedure	Long-Term Extension Period					Safety Follow-up	Unscheduled
Visit [a]	**6**	**7**	**8**	**9**	**10/EOT** [b, c]	**11** [d]	**UNS** [c, e]
Week [a]	**18**	**24**	**32**	**48**	**52**	**W2PT**	
Study Day [a]	**127 ±7**	**169 ±7**	**225 ±7**	**337 ±7**	**365 ±7**	**(+14 to 21)**	
Full physical exam [f]					X		
Targeted physical exam [g]	X	X	X	X		X	X
Weight		X			X		
Vital signs [h]	X	X	X	X	X	X	X

f Evaluation of all body systems except rectal and genital examinations.
g Evaluation to address any abnormalities reported previously plus any new abnormalities including body areas reported as adverse events or changes in disease activity.
h Vital signs will be recorded for sitting blood pressure, resting heart rate, and temperature.



STUDY ACTIVITIES

Induction Period: Visit 1 (Screening Visit)

The screening visit begins when the informed consent form has been signed and ends immediately before randomization. The screening endoscopy is the last activity of the screening period and must take place within 14 days prior to randomization.

During the screening period the following activities will occur:

- Informed consent
  No study activity may occur prior to obtaining informed consent
- Assess inclusion/exclusion
- Demographics
- Medical/surgical history
- Prior medication history
- UC history
- UC medication history
- Full physical exam
- Weight, height
- Vital signs

[redacted]

Induction Period: Visit 2 (Randomization, first dose) within 14 days after endoscopy

[redacted]

During the randomization visit the following activities will occur:

- Confirm inclusion/exclusion
- Targeted physical exam
- Weight
- Vital signs

[redacted]

Induction Period: Visit 3 (Week 4)

[redacted]

During Visit 3 the following activities will occur:

- Vital signs

[redacted]

Induction Period: Visit 4 (Week 8)

During Visit 4 the following activities will occur:

- Targeted physical exam
- Vital signs

[redacted]

[redacted]

Induction Period: Visit 5 or End of Treatment (Week 12: last induction visit or if investigational product use is discontinued early)

[redacted]

During Visit 5 the following activities will occur:

- Assess inclusion/exclusion for LTE portion of study
- Full physical exam
- Weight
- Vital signs

[redacted]

Induction Period: Safety Follow Up

This visit will take place 14-21 days after either early termination or the Week 12 visit for participants who will not continue into the LTE portion of the study.

During the Safety Follow-up Visit, the following activities will occur:

- Targeted physical exam
- Vital signs

LTE Period: Visit 6 (Week 18)

During Visit 6 the following activities will occur:

- Targeted physical exam
- Vital signs

[redacted]

LTE Period: Visit 7 (Week 24)

[redacted]

During Visit 7 the following activities will occur:

- Targeted physical exam
- Weight
- Vital signs

[redacted]

[redacted]

LTE Period: Visit 8 (Week 32)

During Visit 8 the following activities will occur:

- Targeted physical exam
- Vital signs

[redacted]

LTE Period: Visit 9 (Week 48)

[redacted]

During Visit 9 the following activities will occur:

- Targeted physical exam
- Vital signs

[redacted]

LTE Period: Visit 10 or End of Treatment (Week 52: last LTE visit or if investigational product use is discontinued early)

[redacted]

During Visit 10 the following activities will occur:

- Full physical exam
- Weight
- Vital signs

[redacted]

LTE Period: Safety follow-up (14-21 days after last study visit)

This visit will take place 14-21 days after either early termination or the Week 52 visit.

During the Safety Follow-up Visit, the following activities will occur:

- Targeted physical exam
- Vital signs

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
5-ASA	5-aminosalicylic acid
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
Anti-HBc Ab	Anti-hepatitis B core antibody
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
CD	Crohn's disease
CFB	Change from baseline
CIMS	Central Image Management Solutions
CRO	Contract research organization
CRP	C-reactive protein
DR	Delayed-release
ECG	Electrocardiogram
eCRF	Electronic case report form
EOS	End of study
EOT	End of treatment
ES	Endoscopic score
FACIT-F	Functional Assessment of Chronic Illness Therapy – Fatigue
FCP	Fecal calprotectin
FS	Flexible sigmoidoscopy
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GI	Gastrointestinal
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HRQOL	Health-related quality of life
hsCRP	High-sensitivity C-reactive protein
IB	Investigator's Brochure
IBD	Inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICH	International Council for Harmonisation
IEC	Independent ethics committee
IGRA	Interferon gamma release assay
IHC	Immunohistochemical
INR	International normalized ratio
IP	Investigational product

Abbreviation	Definition
IR	Immediate-release
IRB	Institutional review board
IRT	Interactive response technology
ITT	Intent-to-treat
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous(ly)
LTE	Long-term extension
MedDRA	Medical Dictionary for Regulatory Activities
MMS	Modified Mayo Score
MTD	Maximum tolerated dose
[redacted]	
NOAEL	No-observed-adverse-effect level
NRS-11	11-point numeric rating scale
NSAID	Nonsteroidal anti-inflammatory drug
PK	Pharmacokinetic(s)
PP	Per-protocol
PPD	Purified protein derivative
PRO	Patient reported outcome
PT	Prothrombin time
QTcF	Fridericia's corrected QT interval
RBC	Red blood cell
RBS	Rectal bleeding subscore
RHI	Robarts Histopathology Index
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SD	Standard deviation
SFS	Stool frequency subscore
SOC	System Organ Class
SUSAR	Suspected unexpected serious adverse reaction
TB	tuberculosis
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
Th	T helper
TNF-α	Tumor necrosis factor alpha
Treg	T regulatory
TST	Tuberculin skin test

Abbreviation	Definition
UC	Ulcerative colitis
ULN	Upper limit of normal
WOCBP	Woman/women of childbearing potential

1 INTRODUCTION

Inflammatory bowel disease (IBD) is an autoimmune disease of the gastrointestinal (GI) tract with unknown etiology that encompasses 2 primary clinical manifestations: ulcerative colitis (UC) and Crohn's disease (CD). IBD affects over 1.5 million people in North America and 2.5 million in Europe, with a growing global spread and a prevalence of 0.5% of the population in most impacted regions.[1, 2]

UC manifests through complex interactions between the gut microbiome, dysregulated immune responses, genetic mutations, diet, and other environmental factors. As a result, the precise stimulus for the initiation of disease may differ widely among patients with UC. Current therapies have limited efficacy and significant side effects including systemic immunosuppression, increased incidence of opportunistic and rare infections, and increased risk for lymphoma.[3]

An unmet clinical need remains because UC and UC symptoms are not well managed pharmacologically with current drugs.[4] One new approach involves immunometabolism, which has emerged as a major mechanism central to adaptive and innate immune regulation. Metabolic pathways are closely tied to cell signaling and differentiation which leads different subsets of immune cells to adopt unique metabolic programs specific to their state and environment.[5]

[redacted] is a novel target, located on mitochondria, that can reduce inflammation.[6] [redacted] are part of the pattern recognition network that identifies damage, pathogens, or homeostatic altering patterns in the body (eg, from infectious agents) and, as a crucial component of the innate immune system trigger the initial response. Many [redacted] are positive regulatory agents that increase inflammatory signaling networks. In contrast, [redacted] belongs to a small group of negative regulatory [redacted] that are believed to decrease an overactive immune response.[7] [redacted] is linked to IBD through immunometabolic regulation of $CD4_+$ T cells. [redacted] deletion has been shown to worsen the progression of IBD in mice, which suggests that [redacted] activation could improve the disease.

Landos Biopharma, Inc. (Landos) has developed NX-13 [redacted], a novel oral, gut-selective small molecule with low systemic absorption that activates [redacted] for treatment of IBD. Activation of [redacted] by NX-13 has been shown to decrease disease severity in animal models of IBD via immunometabolic effects that promote oxidative phosphorylation while decreasing the activity of NF-κB and reducing oxidative stress. In preclinical models, a reduction in colonic lesions and overall disease severity was seen at a dose as low as 1 mg/kg, indicating a high potential for further development as an investigational new drug for UC.[8, 9, 10]

1.1 Background

UC broadly involves defects within both the epithelial barrier and mucosal immune system. In UC, epithelial cells commonly produce lower levels of mucin and form a more permeable barrier layer.[11] These 2 factors result in greater infiltration of and exposure to intestinal bacteria and other microbes. In response, epithelial and immune cells have increased uptake and recognition of antigens, causing a self-perpetuating loop of altered gut microflora, increasing inflammation, and damage to the colonic epithelium.[12] Importantly, many genes involved in

antigen uptake and recognition, such as major histocompatibility complexes, toll-like receptors, and [redacted], are common genetic risk factors for UC.[13, 14, 15]

Immunologically, the balance between inflammatory and anti-inflammatory cell types is skewed in patients with UC. This is most apparent within CD4+ T helper (Th) cells, in which pro-inflammatory Th1, Th2, and Th17 cells are elevated at the expense of anti-inflammatory T regulatory (Treg) cells.[16] [redacted] κB activity [redacted] Safety studies with NX-13 demonstrated a lack of toxicity up to a tested limit dose of 1,000 mg/kg in rats and 500 mg/kg in dogs.

Additional information is provided in the Investigator's Brochure (IB).

1.2 Clinical Experience

Two double-blind, randomized, placebo-controlled studies have evaluated oral formulations of NX-13. The first, Study NX-13-1a, was a single ascending dose/multiple ascending dose study in 56 healthy volunteers, and the second, Study NX-13-1b, was a safety, efficacy and pharmacokinetic study in 38 participants with ulcerative colitis. Results are summarized below.

Study NX-13-1a

Study NX-13-1a consisted of single oral NX-13 dosing up to and including 4000 mg, and multiple doses (daily for 7 consecutive days) up to and including 4000 mg, or placebo, administered to 56 healthy adult volunteers. No serious adverse events (SAEs) were reported in either portion of this study.

[redacted]

[redacted]

Study NX-13-1b

Study NX-13-1b was a 28-day randomized, double-blind study that evaluated the safety, tolerability, and PK of orally administered NX-13 in adult patients with active UC. Two immediate-release (IR) doses (250 mg and 500 mg) and one delayed-release (DR) 500-mg dose were assessed and compared with placebo. The 38 participants were randomly assigned to each arm: 11 to each drug group and 5 to placebo.

[redacted]

1.3 Rationale for Study

Due to the involvement of microbial and dietary factors in the onset and progression of UC, many pattern-recognition receptors have been implicated in the pathogenesis of UC. Unlike many of its family members, [redacted] has neither well-characterized and prominent genetic mutations nor inflammatory effects. Out of the known human [redacted], 3 are categorized as negative regulatory [redacted], of which [redacted] is one. While [redacted] interacts with many of the same downstream signaling elements as other [redacted], [redacted] serves to control and mitigate

these responses rather than activate them. This includes control of ROS and NF-κB signaling, leading to a downstream decrease in tumor necrosis factor alpha (TNF-α), interleukin-6, and interferon-γ production and a lessening of mucosal inflammation. Mechanistically, the activation of [redacted] could have a 3-fold benefit in UC with the ability to modulate epithelial integrity, host-microbiome interactions, and mucosal immune responses. As such, NX-13 could be a potent improvement on current therapeutics for UC.

There is an unmet clinical need in UC for safer and more effective therapeutics. Currently, the treatment paradigm for UC is a complex based approach through a series of broadly immunosuppressive agents. The starting therapy for UC is 5-aminosalicylic acid (5-ASA) or a derivative. There is a therapeutic gap for patients with moderate disease that are not controlled with 5-ASA. Patients who fail to respond to 5-ASA may sometimes become dependent on the use of glucocorticosteroids/glucocorticoids to combat flares.[17] Steroid-sparing alternatives are needed in the therapeutic progression in UC. The current treatment paradigm leads directly into biologic-based therapies, which are largely restricted to moderate to severe cases and are associated with their own side effects.[17, 18] Still, less than half of patients respond to biologics and over one-third of responders will fail to maintain remission 1 year after starting biologics.[19]

NX-13 is being developed by Landos to fulfill a significant and unmet clinical need to better manage UC with safer and more effective oral therapies.

1.3.1 Justification for Route of Administration

NX-13 is an orally active molecule based on preclinical studies in multiple animal models of IBD. When dosed orally, NX-13 has very limited systemic absorption, and animal models have confirmed its topical gut activity. To maximize convenience for study participants and based on the preclinical PK and efficacy studies, an oral route of administration will be used.

1.3.2 Justification for Dose Selection

The 2 doses to be used in this study were selected based on data from the completed Phase 1a studies, NX-13-1A and NX-13-1B. There were no dose limiting toxicities observed in the single dose portion of NX-13-1a at doses up to 4000 mg. The repeat dosing portion established the dose-limiting toxicity as Grade 1 and 2 dizziness that was only observed at increased frequency over placebo in the 4000 mg/day repeat dose. Thus, the maximum tolerated dose (MTD) for repeat administration is 2000 mg. The Phase 1b study showed some clinical benefit at a daily dose of 250 mg, with no step up at 500 mg, while plasma concentrations for the 2 doses tested did not separate, suggesting that a higher dose should be tested.

A placebo control is justified in this proof-of-concept study for several reasons. A placebo control enables the clearest means of identification of a treatment effect using the fewest participants. By use of a biased coin randomization, placebo will only be administered to 20% of study participants. There are clear instructions for termination in the event of a clinically significant increase in disease severity. In general, fewer than half of patients with IBD experience remission with any active treatment, and this fraction is lower in those who have failed a prior line of therapy. Several active treatments are permitted as concomitant therapy, provided that they were part of ongoing therapy. No active treatment will be discontinued after entry into the study (unless clinically indicated) except for glucocorticosteroids/glucocorticoids

which should be tapered after the induction period. All participants will be informed of the use of placebo and the available alternative therapies.

1.3.3 Justification for Duration of Treatment

Nonclinical experience with NX-13 includes 6-month rat and 9-month dog toxicology studies conducted under Good Laboratory Practices. In both of these studies the no-observed-adverse-effect level (NOAEL) was the highest dose studied as no drug-related toxicity was observed in clinical, laboratory, or histopathological assessments. Previous clinical experience in normal healthy volunteers with NX-13 demonstrated no differences in plasma concentration or adverse event (AE) profile between single- and 7-day dosing up to the repeat dose MTD of 2000 mg/day, suggesting limited potential for accumulation of investigational product or cumulative toxicities. Clinical experience in patients with active UC extends to 4 weeks with no SAEs or clustering or differences in AE profile between active dose and placebo groups, and no evidence of drug accumulation. Clinical activity of NX-13 was assessed as change from baseline in the Total Mayo Score at 28 days. Baseline score ranged from 7.0 to 8.6 on the 12-point scale. Placebo-treated participants had a mean change from baseline (CFB) of -1.0 (1.41) compared with patients in the 250 mg IR, 500 mg IR, and 500 mg DR groups who had mean CFB values of -3.4 (2.01), -3.0 (2.71), and -2.1 (3.30), respectively. The standard approach to development of drugs to treat UC consists of an induction period ranging from 6 to 16 weeks, and a maintenance period that extends total exposure to approximately 52 weeks. Endoscopy is needed to document improvement in the MMS. To minimize the frequency of this invasive test while maximizing the likelihood of detecting a meaningful change, a 12-week time point was selected to evaluate induction. Since pivotal trials require evidence of effectiveness in maintenance, a long-term extension (LTE) period will evaluate safety and efficacy of NX-13 in participants over a total of 52 weeks. An endoscopy at that time point will permit an assessment of long-term efficacy.

1.4 Risk-Benefit Statement

Structural characteristics of NX-13 have not suggested homology with any genetically encoded human biological molecule. There is no known suggestion of off-target activity based on receptor screening, and in particular no expectation of immune system adverse effects at the proposed doses. Genotoxicity studies in vitro with NX-13 did not identify mutagenicity potential. Preclinical studies have not suggested species specificity for any pharmacodynamic effect.

Cardiovascular, central nervous system and respiratory safety pharmacology studies in intact animals have suggested no organ specific toxicities. The results of the program of nonclinical safety pharmacology and toxicity studies conducted in rats and dogs with NX-13 suggest that the drug has no specific target organ toxicities. Any such effects will be carefully monitored in humans, should they occur.

Studies in healthy volunteers for up to 4000 mg/day for up to 1 week have shown that the MTD is 2000 mg/day with dose limiting toxicities consisting of Grade 1 and 2 dizziness, nausea, visual impairment and decrease in attention, all of which resolved with cessation of treatment. Participants with UC were treated for up to 28 days with up to 500 mg/day of NX-13 which was safe, well tolerated, and associated with improvement in indices of disease activity.

Additional information about the expected benefits and risks of NX-13 can be found in the IB. The IB is the reference for the most current risk: benefit information.

As noted above, any risk associated with placebo treatment has been mitigated in the study design.

2 STUDY OBJECTIVES AND ENDPOINTS

OBJECTIVE	ENDPOINT
Primary Objective – Overall Study	**Primary Endpoint – Overall Study**
To assess the clinical activity of oral NX-13 vs placebo	Change from baseline in Modified Mayo Score (MMS) at Week 12
Secondary Objectives – Overall Study	**Secondary Endpoints – Overall Study**
Safety and tolerability	• Proportion of participants with TEAEs in induction period • Proportion of participants with SAEs in induction period • Change from baseline in clinical laboratory results, vital signs, and ECGs over time in induction period
Clinical remission	Proportion of participants with MMS ≤2 at Week 12
Clinical response	Proportion of participants with ≥2 points and ≥30% decrease from baseline in MMS with ≥1 point decrease in rectal bleeding subscore RBS or RBS ≤1 at Week 12
Endoscopic response	Proportion of participants with endoscopic subscore ES ≤1 at Week 12
Endoscopic remission	Proportion of participants with endoscopic subscore ES = 0 at Week 12
Endoscopic-histologic mucosal improvement	Proportion of participants with ES ≤1 and Geboes score <2.0 at Week 12
Symptomatic remission	Proportion of participants with RBS = 0 and (i) stool frequency sub ore SFS = 0 or (ii) SFS = 1 with baseline SFS ≥2, at Week 12
[redacted]	**Exploratory Endpoints – Induction (Week 12)**
	• Change from baseline in SFS over time in induction period • Change from baseline in RBS over time in induction period • Change from baseline in Robarts Histopathology Index (RHI) at Week 12
	• Change from baseline in IBDQ total score and domain subscores over time in induction period • Change from baseline in FACIT-F scores over time in induction period

[redacted]	• Shifts from baseline in Rectal Urgency scores over time in induction period • Change from baseline in Abdominal Pain scores over time in induction period
	NX-13 plasma concentration
	Change from baseline in FCP, CRP, tissue [redacted], cytokines, and gene expression (qPCR) over time in induction period
Exploratory Objectives – LTE (Week 52)	**Exploratory Endpoints – LTE (Week 52)**
[redacted]	

Abbreviations: CRP = C-reactive protein; ECG = electrocardiogram; ES = endoscopic subscore; FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue; FCP = fecal calprotectin; [redacted]; IBDQ = Inflammatory Bowel Disease Questionnaire; LTE = long-term extension; MMS = Modified Mayo Score; qPCR = quantitative polymerase chain reaction; [redacted]; RBS = rectal bleeding subscore; RHI = Robarts Histology Index; SAE = serious adverse event; SFS = stool frequency subscore; TEAE = treatment-emergent adverse event

3 STUDY DESIGN

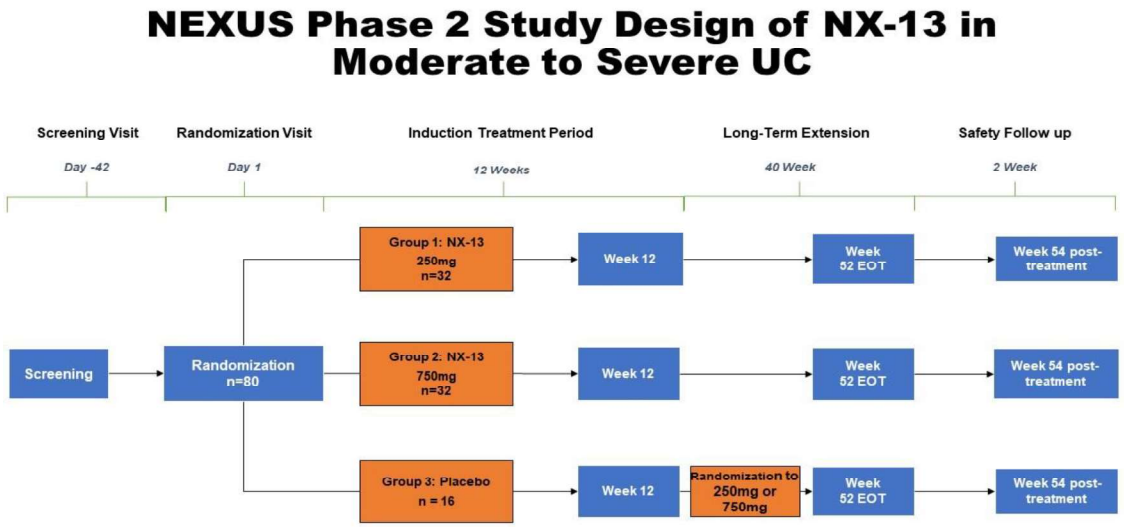
3.1 Overall Design

This is a randomized, double-blind, placebo-controlled, multiple dose exploratory Phase 2 induction study with LTE period to evaluate the clinical activity and safety of oral NX-13 in participants with moderate to severe UC.

Participants will have endoscopically documented UC for at least 3 months prior to screening, with moderate to severe activity defined as MMS ≥ 5, including endoscopic score (ES) ≥ 2, rectal bleeding subscore (RBS) ≥ 1, and stool frequency subscore (SFS) ≥ 1. They must have failed, had an inadequate response to, or been intolerant of at least one prior therapy including conventional therapy (5-ASA with glucocorticosteroids/glucocorticoids, glucocorticosteroids/glucocorticoids alone, or thiopurines), biologic therapy (including monoclonal antibodies against TNF, integrin, or anti IL-12/23 (p19 or p40 subunits) (e.g., ustekinumab)), and/or advanced therapy (JAK inhibitor, S1P receptor modulator), but not have failed more than 2 classes of biologic therapy. The study includes a screening period of up to 6 weeks, a 12-week induction period, a 40-week LTE period, and 2-week safety follow-up period (Figure 1). The maximum duration for study participation is 60 weeks.

As an exploratory study, it will be deemed successful if the primary endpoint for the active treatment at 12 weeks is superior to placebo with a 1-tailed p value < 0.05 (2-tailed value ≤ 0.10).

Figure 1 Study Design Schematic



3.1.1 Screening and Induction Periods

The screening period may take up to 42 days. After all other screening assessments have supported eligibility, and at least 5 days but not more than 14 days prior to randomization, participants will undergo an endoscopy (colonoscopy or flexible sigmoidoscopy [FS]) as appropriate with biopsies. Approximately 80 participants from United States and rest of world will be randomized 2:2:1 to receive NX-13 250 mg, NX-13 750 mg, or placebo administered orally once per day during the 12-week induction period. Randomization will be stratified within each treatment arm by prior exposure to biologics or advanced therapies for UC.

The induction period will extend over a 12-week treatment period (Weeks 1-12) in a double-blind fashion. Participants will receive the first dose of investigational product in the clinic on Day 1 (Visit 2) and receive sufficient investigational product supply to self-administer at home once daily until the next study visit. Participants will return to the clinic approximately every 4 weeks thereafter for study assessments and to receive additional investigational product per the Induction Period Time and Events Schedule.

Participants who are continuing to the LTE and are receiving prednisone at the time of the Week 12 visit must begin to taper their prednisone dose at this visit unless not medically advisable (e.g., their disease activity is too high).

- Prednisone should be tapered one time each week. If the prednisone dose is > 10 mg/day, the dose should be decreased once weekly by 5 mg/day. If the prednisone dose is ≤ 10 mg/day, the dose should be decreased once weekly by 2.5 mg/day.
- If symptoms meet flare criteria during prednisone taper, the dose should be increased back to the original dose until stable, and the taper started again.
- If the second taper fails, then the participant may remain in the study if the stable prednisone dose is ≤10 mg/day. Otherwise, the participant must exit the study.

Participants who have completed the Week 12 visit including the Week 12 endoscopy have the option of entering the LTE period (those participants for whom the benefit/risk is considered favorable by the investigator) or discontinuing from the study after completion of an end of treatment (EOT) visit. Participants who elect not to enter the LTE period will complete a safety follow-up visit 2 weeks after their last dose of investigational product.

3.1.2 LTE Period

The LTE period will extend over a 40-week period (Weeks 13 to 52). Participants who were randomized to NX-13 250 mg or NX-13 750 mg during the induction period will continue to receive the same blinded investigational product during the LTE. Participants who were randomized to placebo during the induction period will be randomized 1:1 to receive blinded NX-13 at 250 mg or 750 mg once daily. Participants will return to the clinic approximately every 6 to 16 weeks thereafter for study assessments and to receive additional investigational product per the Extension Period Time and Events Schedule.

Participants in the LTE who are taking prednisone but were unable to start taper at the Week 12 visit should begin prednisone taper at the Week 18 visit. If it is not medically advisable to begin prednisone taper at the Week 18 visit (e.g., disease activity is too high), and their prednisone dose is > 10 mg/day, the participant must exit the study. If their prednisone dose is ≤ 10 mg/day,

they may remain on the study and, when advisable, begin to taper prednisone. Prednisone tapering details are outlined in Section 3.1.1.

Participants who discontinue the LTE period prior to completion of Week 52 will be asked to complete an EOT visit, including endoscopy with biopsies and blood/urine/stool sample collection. Participants who, in the opinion of the investigator, have a disease relapse will be considered non-responders and exit the study.

All participants who enter the LTE period, regardless of whether they complete the study through Week 52, will complete a safety follow-up visit 2 weeks after their last dose of investigational product.

3.2 Randomization and Blinding

3.2.1 Randomization Procedure

After informed consent has been obtained, all participants will receive a participant identification number assigned by the interactive response technology (IRT). After completion of screening procedures and confirmation of all eligibility requirements, participants will be randomized using the IRT. Eligible participants will be randomized in a double-blind fashion to one of 3 treatment arms in a 2:2:1 ratio to receive NX-13 250 mg (n=32), NX-13 750 mg (n=32), or matching placebo (n=16). Randomization will be stratified within each treatment arm by prior exposure to biologic therapy for UC, with the biologic therapy-exposed population limited to approximately 50% of the total sample size.

Participants who are randomized to NX-13 250 mg or NX-13 750 mg during the induction period will continue to receive the same blinded investigational product for the 40-week LTE period. Participants who are randomized to placebo during the induction period will be randomized to receive a blinded NX-13 dose of 250 mg or 750 mg per day during the LTE.

3.2.2 Blinding

This is a double-blind study.

Blinding will be maintained for the sponsor, contract research organization (CRO), investigators, study personnel, and study participants throughout the entire study. Randomization and investigational product dispensing during the induction period and LTE period will be managed through the IRT.

After completion of the induction period, there will be an appropriate database lock. An unblinded team will be nominated to conduct the primary analysis of unblinded data while a blinded team continues to monitor the study to completion. Additional details will be provided in an unblinding plan.

Personnel responsible for performing PK analysis at the central laboratory will be unblinded to a participant's treatment assignment to identify appropriate samples for analysis. Results of PK analyses will not be shared with any blinded personnel until the entire study is complete and unblinded, except in the case of medical emergency as described in Section 3.2.3.

[redacted] will also be held by the central laboratory until the study is complete and unblinded.

3.2.3 Unblinding Procedure

The investigator and site study personnel must remain blinded to the participant's treatment assignment through the end of the study, except for the unblinded team after completion of induction. Except for the unblinded analysis, the blind should be broken only if the participant experiences a medical emergency and knowledge of the blinded treatment assignment is deemed necessary for further management of the individual.

If unblinding is deemed necessary for the safety of the participant, before breaking the blind, the investigator will contact the medical monitor to discuss the need for the unblinding. The investigator may break the blind independent of the medical monitor if the event is considered an emergency by the investigator and the code break is necessary for the management of the participant. The investigator must inform the medical monitor and/or sponsor, as soon as possible.

Individual code breaks by the investigator will result in withdrawal of the participant from the study. The date and reason for the code break must be documented in the source documents and on the appropriate electronic case report form (eCRF). The sponsor must be informed as soon as possible.

If required for regulatory reporting purposes or if required by local health authorities, the sponsor may unblind treatment assignment for suspected unexpected serious adverse reactions (SUSARs) that are considered by the investigator or sponsor to be related to investigational product (see Section 7.5.3).

4 STUDY PARTICIPANTS

The study is planned to enroll approximately 80 participants with moderate to severe active UC.

Screening blood tests with an abnormal result may be repeated once, if deemed appropriate by the investigator. The retest should be performed within 7 days after the original test, and results must be available within the 42-day screening period.

Participants may be rescreened once for eligibility determination.

4.1 Inclusion Criteria

Participants must meet all of the following criteria for enrollment into the study:

1. 18 to 75 years of age at time of informed consent
2. Able to give informed consent, attend, and comply with study visits and e-diaries
3. Diagnosed with UC ≥ 3 months prior to screening. The diagnosis of UC must be confirmed by endoscopic and histologic evidence. The endoscopy and histology report should be present in source documents; however, if not available, the screening endoscopy and histology report may serve as such.
4. Received a surveillance colonoscopy (performed according to local standard) within 12 months prior to the planned randomization date to rule out dysplasia in individuals with pancolitis > 8 years duration or individuals with left sided colitis > 12 years duration. Individuals without a surveillance colonoscopy within the prior 12 months will have a colonoscopy at screening (i.e., in place of the screening proctosigmoidoscopy).

Any adenomatous polyps must be removed according to routine practice prior to the study participant's first dose of investigational product.

5. Moderate to severe disease activity, characterized by all of the following (see Section 7.3.1 for details):
   - MMS ≥ 5
     defined as follows
   - ES ≥ 2 within 14 days prior to randomization
   - RBS ≥1
6. An inadequate response to, loss of response to, or intolerance of at least 1 of the following therapies, as defined below (see Section 12.9 12.9for details):

   Conventional therapy classes:
   - Oral 5-ASA compounds plus systemic glucocorticosteroids/glucocorticoids
   - Systemic glucocorticosteroids/glucocorticoids
   - Thiopurines

   Biologic therapy classes:
   - Anti-TNF monoclonal antibodies or biosimilars
   - Anti-integrin monoclonal antibodies
   - Anti-IL-12/23 monoclonal antibodies

   Advanced therapy classes:
   - JAK inhibitors
   - S1P receptor modulators
7. Eligible male participants must either:
   - Be surgically sterile (i.e., vasectomy) for ≥ 3 months (≥ 90 days) before screening; or
   - Agree to the following, from the time of randomization until at least 30 days after last dose of investigational product:
     - Agree to use a condom with spermicide when sexually active with a female partner who was not using a highly effective method of birth control
     - Agree not to participate in a conception process (i.e., active attempt to impregnate, sperm donation, or in vitro fertilization)
8. Eligible female participants must be:
   - Nonpregnant, evidenced by a urine dipstick pregnancy test within 24 hours prior to randomization, and
   - Nonlactating
9. Eligible female participants of non-childbearing potential must be surgically sterile or postmenopausal (defined as ≥ 1 year without menses).
   - Women must be surgically sterile for at least 6 months before screening as confirmed by medical history. Surgical procedures are tubal ligation performed laparoscopically, hysterectomy, and/or bilateral oophorectomy; or other procedures if sponsor agrees.

- A postmenopausal state is defined as no menses for ≥ 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy.

10. Women of childbearing potential (WOCBP) must:

- Agree to birth control methods that are considered highly effective:
  - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, transdermal
  - Progestogen-only hormonal contraception associated with inhibition of ovulation: oral, injectable, implantable
  - Intrauterine device (IUD)
  - Intrauterine hormone-releasing system (IUS)
  - Bilateral tubal occlusion
  - Vasectomized partner
  - Sexual abstinence

  Note: Contraceptive measures such as Plan B (used after unprotected sex) are not considered highly effective methods of contraception for this study

- Agree not to participate in a conception process (i.e., active attempt to become pregnant, egg donation, in vitro fertilization) for at least 30 days after the last dose of investigational product

4.2 Exclusion Criteria

Participants who exhibit any of the following conditions are to be excluded from study participation:

1. Severe extensive colitis as evidenced by:
   - Physician judgment that the participant is likely to require hospitalization for medical care or surgical intervention of any kind for UC (e.g., colectomy) within the 12 weeks after randomization
   - Current evidence of fulminant colitis, toxic megacolon or recent history (within 6 months prior to screening) of toxic megacolon, or bowel perforation
2. Diagnosis of CD or indeterminate colitis, or the presence or history of a fistula consistent with CD
3. Inadequate response to an induction course of more than 2 classes of biologics (e.g., TNF alpha, integrin or IL-12/23) approved for UC
4. Diagnosis of microscopic colitis, ischemic colitis, or radiation colitis
5. History of active bacterial, viral, fungal, or mycobacterial infectious colitis requiring oral antibiotic/anti-infective treatment within 4 weeks prior to screening
6. Infection requiring hospitalization or intravenous (IV) antimicrobial therapy within 8 weeks prior to screening
7. Presence of indefinite dysplasia or UC-associated dysplasia on colonoscopy or FS, or a history of UC-associated dysplasia

8. History of colectomy (total or subtotal), ileoanal pouch, Kock pouch, or ileostomy; or is planning bowel surgery
9. History of spontaneous GI perforation (other than appendicitis or mechanical injury), diverticulitis, or at significantly increased risk of GI perforation per the investigator's judgment
10. Hospitalization for exacerbation of UC requiring IV steroids (i.e., UC flare) within 12 weeks prior to screening (a single dose of IV steroids is acceptable)
11. Treatment with cyclosporine, tacrolimus, sirolimus, methotrexate, or mycophenolate mofetil within 4 weeks prior to screening
12. Thiopurine washout is required to be completed within 6 weeks prior to screening.
13. Treatment with a biologic agent (e.g., infliximab, vedolizumab) within 6 weeks or 5 elimination half-lives (whichever is less) prior to screening. For anti-IL-12/23 (p19 or p40 subunits) (e.g., ustekinumab) a total of 12 weeks (6 weeks prior to screening and 6 weeks of screening) or 5 elimination half-lives (whichever is less) of washout
14. Treatment with an advanced oral UC therapy (e.g., JAK inhibitor, S1P modulator) within 4 weeks prior to screening
15. Treatment with IV glucocorticosteroids/glucocorticoids, rectal glucocorticosteroids/glucocorticoids, rectal or topical 5-ASA, or enema within 2 weeks prior to screening
16. Treatment with oral prednisone at a daily dose of > 20 mg (or equivalent) or active oral glucocorticosteroids/ glucocorticoids, e.g., budesonide at a daily dose of > 9 mg or equivalent, within 30 days prior to screening. If receiving systemically active oral g lucocorticosteroids/ glucocorticoids must be on a stable dose for at least 14 days prior to screening.
17. Confirmed or suspected infection of the intestinal tract, including positive Clostridioides difficile stool test at screening
18. Have acute or chronic hepatitis B infection or test positive for hepatitis B virus (HBV) at screening
19. Have current hepatitis C infection or test positive for hepatitis C virus (HCV) at screening
20. Have known infection with human immunodeficiency virus as confirmed by medical history
21. Live virus vaccination within 4 weeks prior to randomization (Note: no currently available vaccine for SARS-CoV-2 is a live virus vaccine)
22. Fecal microbial transplantation within 30 days prior to screening
23. Known primary or secondary immunodeficiency
24. Previously received stem cell transplantation
25. Has been a previous recipient of an organ transplant, which requires continued immunosuppression
26. Any surgical procedure requiring general anesthesia within 4 weeks prior to randomization, or planned elective surgery during the study

27. History of malignant neoplasms or carcinoma within 5 years prior to screening (except basal cell and in situ squamous cell carcinomas of the skin that have been fully excised and resolved)
28. Requirement for regular dosing of strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, clarithromycin) or inducers (e.g., rifampin, phenytoin, carbamazepine) or CYP2C19 inhibitors (e.g., fluconazole, fluoxetine, fluvoxamine, ticlopidine) or inducers (e.g., rifampin)
29. Current or recent history of alcohol dependence or recreational drug use that, in the opinion of the investigator, may interfere with the individual's ability to comply with the study procedures
30. Mental or legal incapacitation at the time of screening or a history of clinically significant psychiatric disorders that would impact the individual's ability to participate in the study, according to the investigator
31. Any concurrent clinically significant medical condition that, in the judgment of the investigator, may pose an unacceptable risk to the participant, including any known hypersensitivity to the drug product or any of its excipients
32. Participants with evidence of active or latent infection with Mycobacterium tuberculosis (TB) or participants with this history who have not completed a generally accepted full course of treatment (with completion of this treatment at least 6 months prior to start of screening) are excluded. All other participants must have either the Mantoux (purified protein derivative [PPD]) tuberculin skin test or interferon gamma release assay (IGRA) performed. See Section 12.7 for details
33. Unable to comply with study activities (e.g., swallow 3 whole tablets per day without crushing, breaking, or chewing)
34. Concurrent participation in any other investigational study, or individuals who have received any investigational therapy within 4 weeks or 5 elimination half-lives (whichever is longer) prior to screening
35. Women who are pregnant, breastfeeding, or contemplating pregnancy, from the time of informed consent until at least 30 days after the last dose of investigational product
36. Estimated absolute glomerular filtration rate of < 30 mL/minute
37. Liver transaminases (alanine transaminase [ALT], aspartate transaminase [AST]) > 1.5× upper limit of normal (ULN) at screening
38. Total bilirubin > 1.5× ULN at screening, or > 2.0× ULN for individuals with Gilbert's syndrome
39. Hemoglobin < 9g/dL (< 5.6 mmol/L) at screening
40. Individuals who are investigational site staff members or relatives of those site staff members or are Sponsor or CRO employees directly involved in the conduct of the study

4.3 Discontinuation/Withdrawal/Stopping Criteria

4.3.1 Early Withdrawal From the Study

If a participant is prematurely withdrawn from the study, the reason for early withdrawal must be documented in the source document and recorded in the eCRF. All EOT procedures that can

be completed will be performed at the time of withdrawal. The participant will be instructed to return all remaining investigational product/supplies. If a participant is withdrawn due to an SAE, the participant will be followed until resolution or stabilization of the event.

4.3.2 Withdrawal Criteria Due to Flare

Participants must withdraw if they meet flare criteria unless the increase in disease activity is due to an infection (e.g., C. difficile) or it occurs during a steroid taper. Flare criteria are as follows:

- An increase in RBS of ≥ 1 point and an increase in ES of ≥ 1 point;
- An increase in RBS of ≥ 2 points and an ES of > 0;
- An increase in SFS of ≥ 2 points and an increase in ES of ≥ 1 point;
- An increase in ES of ≥ 2 points.

Procedures for Suspected Flare During Steroid Taper:

If there is an increase in disease activity (i.e., a persistent increase in RBS by ≥1 point or SFS by ≥2 points for ≥ 7 days) while the participant is undergoing steroid taper, the steroid taper should stop, and the participant should increase the steroid dose to the pre-exacerbation level until stable.

Procedures for Suspected Flare due to Possible Infection:

If there is an increase in disease activity (i.e., a persistent increase in RBS by ≥1 point or SFS by ≥2 points for ≥ 7 days) in a participant who is not undergoing steroid taper, the participant should have testing for infectious agents and, if present, initiation of appropriate treatment. If no infectious agent is present, then the participant should undergo endoscopy with local determination of ES to complete the assessment of flare, if possible.

4.3.3 Withdrawal Criteria Not Due to Flare

A participant may voluntarily withdraw or be withdrawn from the study for reasons including, but not limited to, the following, and after discussion with the investigator and/or the medical monitor:

- Pregnancy
- An AE that compromises the participant's ability to continue study-specific procedures or where it is not considered to be in their best interest to continue to receive investigational product
- At the discretion of the investigator
- Participant choice (withdrawal of consent by participant; investigator will attempt to ascertain reason)
- Protocol violation
- Noncompliance with investigational product
- Noncompliance with diary entries
- A hepatic event or liver test abnormality, where considerations for discontinuation include:

- ALT or AST > 8× ULN
- ALT or AST > 5× ULN for more than 2 weeks
- ALT or AST > 3× ULN and (total bilirubin [TBL] > 2× ULN or international normalized ratio [INR] > 1.5) (consistent with Hy's law criteria)
- ALT or AST > 3× ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)

In the case of an early withdrawal/discontinuation, the participant must be followed for safety assessment for 14 days (2 weeks +7 days) after the last dose of investigational product. The reason for treatment discontinuation will be documented in the eCRF.

4.3.4 Dose Limiting Toxicity

Once a DLT is identified, the subject's study drug will be held until the symptoms resolve. If the symptoms resolve within the below time frames, study drug may be restarted at the initial dose. If symptoms recur, the study drug will be permanently discontinued, and the subject will enter the 2-week follow-up period.

a. CTCAE severity grade 1-2 that does not resolve within one week
b. CTCAE severity grade >3 that does not resolve within 1 day

4.3.5 Clinical Trial Stopping Criteria

The Phase 2 study will be stopped if any of the following conditions are met:

- The incidence or severity of adverse events in this study indicates a potential health hazard to subjects
- Upon request of health authorities

The study may be restarted after appropriate preventative and/or management guidelines have been instituted, and where appropriate, a substantial protocol amendment has been approved by the relevant regulatory authorities and ethics committees, or after informing the relevant regulatory authorities when a substantial protocol amendment is not considered necessary.

4.3.6 Handling of Data and Samples Following Withdrawal From the Study

If a participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a participant withdraws from the study, they may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

5 INVESTIGATIONAL PRODUCT

5.1 Identification and Description

The NX-13 drug substance is a white to off-white solid.

NX-13 will be supplied as 250 mg tablets for once daily oral administration. Placebo will be identical in appearance and size. All tablets will be coated with a white to off-white polymer to

be identical in appearance. Composition of NX-13 and placebo tablets for this study (including list of excipients) is available in the IB.

5.2 Packaging and Labelling

Labelling of the investigational product must conform to all requirements specified by governing regulations.

NX-13 tablets (250 mg) and matching placebo tablets for clinical use will be packaged in blisters with push-through aluminum foil lidding. The final IP label will be coded for blinding as appropriate to the study design and in compliance with the protocol.

Detailed instructions for the supply and labelling dispensing of the investigational product will be described in the study pharmacy manual.

5.3 Supply and Storage

Investigational product will be supplied by the sponsor.

NX-13 and placebo tablets will be stored at room temperature (20°C to 25°C [68°F to 77°F]) with excursions allowed between 15°C and 30°C (59°F to 85°F). Detailed instructions for the storage conditions will accompany the supply shipment to the clinical study sites. The clinical trial supplies must be kept in a secure area at the study site and must be locked when not in use.

Additional storage requirements can be found in the pharmacy manual.

5.4 Dosage and Administration

Participants will be randomized in a double-blind fashion to receive NX-13 250 mg, NX-13 750 mg, or matching placebo during the induction period. Participants who are randomized to NX-13 250 mg or NX-13 750 mg during the induction period will continue to receive the same blinded investigational product for the LTE period. Participants who are randomized to placebo during the induction period will be randomized to receive a blinded NX-13 dose of 250 mg or 750 mg per day during the LTE.

Participants will self-administer investigational product at home once daily, except for specified study visits for PK sample collection where the dose will be taken at the site (see Induction Period Time and Events Schedule and Extension Period Time and Events Schedule for details). Participants will swallow 3 whole tablets (breaking, crushing, or chewing the tablets is prohibited) once per day, with water (if needed), approximately 1 hour before the first meal of the day and whenever possible at the same time each day for consistency.

Participants will receive the first dose of investigational product in the clinic on Day 1 (Visit 2) with appropriate supply to last until the next study visit (see Section 3.1.1 for additional information).

Additional reference information and instructions can be found in the pharmacy manual.

5.5 Compliance

Compliance with investigational product dosing will be monitored by site personnel. If a participant is continually noncompliant with investigational product, the investigator may deem it appropriate to withdraw the participant from the study. Missing doses, overdose (taking a

larger dose than prescribed), abuse (excessive use), and misuse (use in a way other than the intended use) are examples of non-compliance and should be documented.

Participants will receive clear instructions on dosing, handling missing doses, and recording doses. They will be reminded about dosing requirements at each study visit. The investigator will instruct participants who miss a scheduled dose to take it if they have at least 16 hours until their next scheduled dose.

5.6 Investigational Product (IP) Accountability

The investigator is responsible for investigational product accountability at the site and must maintain adequate records of all investigational product received and dispensed. The investigator agrees not to supply investigational product to any person other than participants in this study. All unused and partially used investigational product must be retained at the site until inventoried by the sponsor or designee. Instructions for final disposition of IP will be provided at the completion of the study. No destruction of IP should occur on-site without prior written sponsor approval. All materials containing the investigational product will be disposed in accordance with governing regulations.

6 CONCOMITANT THERAPIES

All medications received by the participant after providing informed consent must be recorded in the eCRF. During study participation, participants will be asked not to take medications that are prohibited at randomization (see Section 4.2).

6.1 Permitted Therapies

The following medications are allowed at study entry, but doses must be stable (i.e., must not be changed) for the duration of the study.

- Oral 5-ASA, not exceeding 4.8 g per day, with stable dose for at least 1 month prior to endoscopy.
- Oral corticosteroid up to a maximum of 20 mg prednisone, 9 mg budesonide, or equivalent, with a stable dose for at least 1 month prior to endoscopy.
- Pain medication (nonsteroidal anti-inflammatory drug [NSAID], including low-dose 81 mg aspirin). Temporary use of opioids must be discussed and approved with the study medical monitor.
- Bile-salt sequestrant (e.g., cholestyramine), if dose is stable for at least 1 month prior to endoscopy
- Antispasmodics, e.g., dicyclomine (Bentyl), Donnatal, Levsinex
- Antibiotics for appropriate infections. The exacerbation of diarrhea on antibiotics is to be followed by a stool culture for C. difficile and if the culture is positive, treatment with vancomycin should be initiated for 14 days.

6.2 Prohibited Therapies

The following prohibited medications must not be used at any time during the study:

- Immunomodulators: azathioprine, 6-MP, methotrexate
- Any investigational or approved biologic therapy for UC (e.g., infliximab, adalimumab, vedolizumab, golimumab, certolizumab, ustekinumab, mirikizumab)
- Any small molecule or approved nonbiologic therapies for UC (e.g., cyclosporine, mycophenolate, tacrolimus, tofacitinib, upadacitinib, ozanimod)
- 5-ASA enemas, glucocorticoid enemas (systemic or topical), rectal suppositories (e.g., 5-ASA and glucocorticoid suppositories are both prohibited)
- Fecal transplant
- Daily use of antidiarrheals, which may affect the patient reported outcome (PRO) of stool frequency (occasional use is allowed)

In addition, administration of live virus vaccine is also prohibited for the duration of study participation and for at least 5 half-lives of NX-13 after the participant's last dose of investigational product.

6.3 Prohibited Therapies That Require Washout Prior to Screening

The following biologic therapies require completion of at least 6 weeks of washout prior to informed consent (first day of screening), or the participant must have no active drug detected at start of screening as determined by therapeutic drug monitoring.

- TNF antagonists
- Anti-integrin therapy
- Anti-IL-12/23 (p19 or p40 subunits) therapy (e.g., ustekinumab) a total of 12 weeks (6 weeks prior to screening and 6 weeks of screening) or 5 elimination half-lives (whichever is less) of washout.

Note: for eligibility subjects previously treated with biologics may not have had an inadequate response to a full course of induction with more than 2 classes of these agents

The following small molecule agents require completion of at least 4 weeks of washout prior to informed consent (first day of screening):

- Oral JAK inhibitors
- S1P modulators

7 STUDY EVALUATIONS

7.1 Study Procedures at Each Scheduled Visit

All study evaluations and procedures with visit windows are provided in the Induction Period Time and Events Schedule and the Extension Period Time and Events Schedule.

Following a screening period of up to 6 weeks (42 days), participants who complete the 12-week induction period, 40-week LTE period, and 2-week safety follow-up will have a maximum duration of study participation of approximately 60 weeks.

7.1.1 Unscheduled Visits

Participants will be instructed to contact the study coordinator/investigator when any significant change in health status occurs. The participant will be asked to return for an unscheduled clinic visit if clinically indicated.

If it is determined that the participant should be withdrawn from the study, the participant will be required to complete the EOT study procedures (see the Induction Period Time and Events Schedule and the Extension Period Time and Events Schedule). The participant will be asked to return for a post-treatment follow-up visit (Section 7.1.2).

7.1.2 Post-Treatment Follow Up

All participants who receive at least one dose of investigational product will be asked to return for a post-treatment follow-up visit, scheduled 2 weeks (+7 days) after their last dose of investigational product. The following study procedures will be performed at this visit:

- Targeted physical exam
- Vital signs
- Laboratory testing
    - Hematology
    - Serum chemistry
    - Urinalysis
    - Urine pregnancy test (WOCBP only)
- Concomitant medications
- Adverse event assessment
- Complete EOS Form

In the case of an early withdrawal/discontinuation, the reason for treatment discontinuation will be documented in the eCRF.

7.1.3 End-of-Study Definition

The End-of-Study for each participant is defined as the end of the post-treatment safety follow-up visit 2 weeks (+7 days) after the last dose of investigational product.

For clinical trials conducted in the EU, a declaration of the end of the clinical trial and early termination, as applicable, will be made according to the procedures outlined in Directive 2001/20/EC, Article 10(c) and for those countries outside the EU, local regulations will be followed. In the US, where applicable, the Investigator will notify the IRB in writing of the study's completion or early termination and send a copy of the notification to Landos. A final Clinical Study Report will be provided to the relevant authorities within 12 months after the end of the study.

7.2 Study Procedure Details

For timing of all study procedures, refer to the Induction Period Time and Events Schedule and the Extension Period Time and Events Schedule.

7.2.1 Informed Consent Procedure

Informed consent must be obtained and documented prior to the participant initiating any study-related procedures. The informed consent process will begin at Visit 1 (including if washout from medications is required). Additional requirements for informed consent are described in Section 9.2.

7.2.2 Demographics and Other Baseline Characteristics

Demographic information will include age, gender, and race/ethnicity as described by the participant.

Weight and height will be recorded at screening. Weight will also be recorded at study visits as specified in the Induction Period Time and Events Schedule and the Extension Period Time and Events Schedule.

A complete medical and surgical history (except for UC) will be recorded. A separate UC history will include date of diagnosis, basis for diagnosis (endoscopy, histology, imaging), maximum extent of disease, prior hospitalizations, prior UC-related surgery, and baseline stool frequency for SF evaluation.

UC medication history will include all prior treatments for UC, start and stop dates, and reasons for discontinuation (primary lack of effect, secondary lack of effect, intolerance, other), and will include investigational as well as approved therapies. Other medication history will include medications relevant to the eligibility criteria and any others that were stopped at or within 3 months prior to signing the informed consent form.

7.2.3 Participant e-Diary

Participants will complete an e-diary daily throughout the study beginning with the first screening visit. Instructions for diary completion will be provided during the screening period and reviewed as needed during the study.

For the 14 days prior to the participant's scheduled date of randomization (i.e., during the screening period), and for the 14 days prior to each study visit during the induction period and LTE period, the participant will record their daily stool number and the rectal bleeding score as defined by the Mayo criteria.

For the entire induction period and LTE period, the participant will enter on a daily basis the time they took their dose of investigational product.

The e-diary will also include the RBS, SFS, and Rectal Urgency and Abdominal Pain Questionnaire (Sections 12.1 and 12.2).

7.2.4 Endoscopy With Biopsy

Participants will undergo endoscopy with biopsies at screening and at the end of induction period treatment, and for those who enter the LTE also at the end of extension period treatment.

The decision to perform a colonoscopy or a FS will be at the discretion of the investigator, except that if the participant has not undergone a full colonoscopy, including biopsies if indicated, in the 12 months prior to screening, then a full colonoscopy, including biopsies if indicated, will be performed. If a full colonoscopy has been performed outside the 12-month

window, the investigator may discuss with the sponsor if the full colonoscopy may be waived for screening.

Clinical sites will follow standard local procedures for endoscopy preparation.

NOTE: The screening endoscopy procedure should be scheduled at least 5 days but not more than 14 days prior to the planned randomization visit to allow for central reading and confirmation of participant eligibility. The EOT endoscopy procedure for the induction period when possible, should use the same modality (i.e., colonoscopy or FS) that was used at screening; exceptions may be made for participants with left-sided disease or proctosigmoiditis, such that those participants should have FS at this visit. The EOT endoscopy procedure for the extension period, when possible, should use the same modality that was used for the induction period. The EOT endoscopy procedures must be done at the time of the EOT visit (or ≤5 days prior to that visit).

Six tissue biopsies will be obtained at screening, and 8 tissue biopsies will be obtained at each of the EOT visits. Tissue biopsies will be obtained from the area with the worst disease 15 to 25 cm from the anal verge. If ulceration is present, the biopsy should be done from the edge of the ulcer. If no ulceration is present, then the biopsy should be done from the most affected area. If mucosa appears normal (e.g., at EOT), then random biopsies should be taken from the area 15 to 25 cm from the anal verge.

Biopsies will be obtained as follows at each of the 3 study time points (i.e., screening, induction EOT, extension EOT) unless otherwise noted:

- 2 biopsies will be obtained for protein [redacted] expression
- 2 biopsies will be placed in formalin for histopathology and immunohistochemical (IHC) analysis (including [redacted])
- 2 biopsies will be stored in a cryovial with RNA*Later* Stabilization Solution buffer for RNA gene expression, including [redacted] (Section 7.3.8)
- 2 biopsies will be obtained for measurement of NX-13 in colonic tissue (collected at EOT visits only, not screening)

Samples will be processed at the study sites, and then shipped to the central laboratory(ies). Sample processing, handling, and shipping information will be defined in the central laboratory manual and biopsy instruction card.

The endoscopy procedure will be recorded using Central Image Management Solutions (CIMS). Detailed instructions for setting up equipment, capturing, and transmitting endoscopic videos will be provided in a study-specific CIMS manual.

The endoscopy procedure will be recorded using vendor provided equipment, including laptop, cables and recording device. Detailed instructions for setting up equipment, capturing, and transmitting endoscopic videos will be provided in a study-specific imaging manual.

The sites will calculate the MMS using the Central reader ES score. Endoscopy videos and histopathology images will be scored by qualified, independent, blinded central readers (see Section 7.2.5).

7.2.5 Central Reader Training, Scoring, and Blinding

Study central readers will be trained in the use of the imaging eCRF for assessment of endoscopy and lab eCRF for histopathology (qualified gastroenterologists and pathologists, respectively). Standardized training materials will be provided to central readers.

Central readers will enter scores in a study database. Central reader scores will be the primary scores for confirming eligibility and for data analyses.

7.3 Efficacy Evaluations

7.3.1 Modified Mayo Score

The MMS will include the centrally read ES, and the RBS and SFS from the participant e-diary (Section 12.3).

The ES assesses endoscopic disease activity on a 4-point scale (range, 0-3 points), from normal or inactive disease to severe disease activity.

RBS and SFS will be determined from data collected during the 7 days prior to the visit and will include the average of 3 consecutive days, or if 3 are not available, then 4 non consecutive days will be averaged. Values obtained during preparation for an endoscopy, the day of an endoscopy, or the day after an endoscopy will not be considered. If an endoscopy has been performed during the 7 days prior to a visit and appropriate data are not available, data from the prior week will be accepted using the same algorithm. If inadequate data collection has occurred during the week prior to the visit, then the collection period may be increased to a 2-week period, and the participant is educated in proper data collection.

Component	**Score**
Stool Frequency	
Normal number of stools for this participant	0
1 to 2 stools more than normal	1
3 to 4 stools more than normal	2
5 or more stools than normal	3
Rectal Bleeding	
No blood seen	0
Streaks of blood with stool less than half the time	1
Obvious blood (more than just streaks) or streaks of blood with stool most of the time	2
Blood alone passes	3
Findings on Endoscopy	
Normal or inactive disease	0
Mild disease (erythema, decreased vascular pattern, **no friability**)	1
Moderate disease (marked erythema, absent vascular pattern, friability, erosions)	2
Severe (spontaneous bleeding, ulceration)	3
Total Score (0-9)	

7.3.2 Inflammatory Bowel Disease Questionnaire

The Inflammatory Bowel Disease Questionnaire (IBDQ-32) is a disease-specific health-related quality of life (HRQOL) instrument for patients with IBD. The IBDQ-32 covers 4 dimensions: bowel symptoms (10 items), systemic symptoms (5 items), emotional function (12 items), and social function (5 items). Items are scored on a 7-point Likert scale and summed for a total global score in the range 32 to 224 (with higher scores indicating better HRQOL). The IBDQ has been designed to be self-administered and completed in 5 minutes.

7.3.3 Rectal Urgency and Abdominal Pain Questionnaire

The Rectal Urgency and Abdominal Pain Questionnaire was developed following regulatory guidance for PROs. The questionnaire consists of 2 items, each with a 24-hour recall period, that describe the key symptoms experienced by patients with moderate to severe rectal urgency and abdominal pain (Section 12.2).

Rectal urgency is scored (for the prior 24 hours) as the number of bowel movements with urgency ("events") as shown below, with urgency defined as the need to rush to the toilet to avoid an accident.[20]

Rectal Urgency Score	Number of Events
0	2 or fewer events
2.5	3 to 5 events
5.0	6 to 8 events
7.5	9 to 11 events
10	12 or more events

Abdominal pain is scored on an 11-point numeric rating scale (NRS-11), using the raw score with no conversion.

7.3.4 Functional Assessment of Chronic Illness Therapy – Fatigue

The Functional Assessment of Chronic Illness Therapy (FACIT) instrument is a comprehensive compilation of questions that measure health-related quality of life in patients with chronic illnesses. The FACIT-fatigue (FACIT-F) is a subscale of the general questionnaire, the FACIT-G. It was developed to assess fatigue associated with anemia with item content established by combined expert and patient input. The FACIT-F fatigue scale is a reliable and valid instrument to measure fatigue in patients with CD and UC.[21] A difference of 3 to 4 units is considered a minimal clinically important difference.

The tool comprises 13 questions (Section 12.4), the responses to which are each recorded on a 5-point Likert scale. Scores range from 0 to 52, with lower scores representing greater fatigue. It can be completed quickly and is easily scored and interpreted.

7.3.5 Geboes Score

The Geboes scoring system is a stepwise ordinal grading system for histological assessment of disease severity in UC.[22] The scoring system progressively grades disease severity by assessing

7 histological items and grading histological change as grade 0 (structural change only), 1 (chronic cell infiltrations), 2A (lamina propria neutrophils), 2B (lamina propria eosinophils), 3 (neutrophils in the epithelium), 4 (crypt destruction), and 5 (erosion or ulceration).

Each of the grades is subdivided into subgrades, based upon the severity of tissue abnormalities or the extent of cell infiltration (Section 12.5). Subgrades are assessed from the worst area of the biopsy. The continuous Geboes score is the sum of each subgrade score, and this is the score that will be used in this study. Higher Geboes scores are indicative of more severe disease activity.

7.3.6 Robarts Histopathology Index

The Robarts Histopathology Index (RHI) includes four items including; 1: lamina propria chronic inflammation; 2: lamina propria neutrophils; 3: epithelial neutrophils; 4: surface epithelial injury. Each item receives a grade of 1–4; the total score ranges from 0 (no disease activity) to 33 (most severe disease activity). There are different weights for each feature, with the lowest being for chronic inflammation and the highest being for erosion/ulceration (Section 12.6). Histologic Remission is defined as an RHI score ≤ 3.

7.3.7 Pharmacokinetic Assessments

Blood samples will be collected for analysis of NX-13 concentrations in plasma and determination of PK parameters. Samples will be collected prior to dosing in the clinic (trough) and at 1 hour ±30 minutes post dose (peak) at the visits as outlined in the Induction Period Time and Events Schedule and the Extension Period Time and Events Schedule. Participants should fast for at least 1 hour prior to dosing in the clinic and should remain fasting until after the post dose PK sample is collected.

7.3.8 [redacted] and Other Assessments of Disease Activity

[redacted] and other disease activity results will remain blinded to the sponsor, site, and participant throughout the study.

[redacted] samples for measurement of [redacted] should be collected prior to the start of any bowel preparation for endoscopic procedures. Participants will receive instructions and [redacted] sample supplies for collection at home.

[redacted] will be collected and used for [redacted]

[redacted] samples will be collected and used for [redacted]

Samples and data will be stored in accordance with local retention requirements and if used, will be used for specific purposes, to evaluate the effect of NX-13 limited to UC.

7.4 Safety Evaluations

The visits where each of these safety assessments will be performed/recorded are outlined in the Induction Period Time and Events Schedule and the Extension Period Time and Events Schedule.

7.4.1 Adverse Events

All AEs that occur following the signing of the informed consent will be reported on the eCRF. Definitions, documentation, and reporting of AEs are described in detail in Section 7.5.1.

7.4.2 Physical Examination

Height (at the initial visit only) and weight will be recorded.

A complete physical examination includes evaluation of all body systems except rectal and genital examinations.

A targeted physical examination will address any abnormalities reported previously plus any new abnormalities including body areas reported as AEs or changes in disease activity.

7.4.3 Vital Signs

The vital signs to be recorded are sitting blood pressure, resting heart rate, and temperature.

Blood pressure will be recorded with the participant seated, with both feet on the floor, after 3 to 5 minutes of rest. It is preferred that an appropriately sized, automated cuff is used, with 3 readings obtained 1-2 minutes apart, and the average value reported. If an automated cuff is not available, a single auscultatory reading is acceptable.

Resting heart rate can be the value reported by the automated cuff, or a value obtained after 5 minutes of rest.

Temperature should preferably be obtained via tympanic membrane, oral, or temporal artery (skin) thermometer (although other methods are acceptable), and the method recorded.

7.4.4 Clinical Laboratory Tests

Blood, stool and urine samples will be collected and sent to a central laboratory for analysis. The following clinical laboratory tests will be performed:

- Hematology: hematocrit, hemoglobin, mean cell hemoglobin, mean corpuscular volume, red blood cell (RBC) distribution width, RBC count, total and differential white blood cell count, basophils, eosinophils, lymphocytes, neutrophils, monocytes, platelet count
- Serum chemistry: blood urea nitrogen, creatinine, creatine kinase, TBL, AST, ALT, alkaline phosphatase, sodium, potassium, chloride, bicarbonate, calcium, magnesium, inorganic phosphorus, uric acid, total protein, albumin, glucose, gamma glutamyl transferase, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides
- Coagulation: prothrombin time (PT), INR

- Urinalysis: specific gravity, ketones, pH, protein, glucose, blood, nitrite, bilirubin, urobilinogen, leukocytes, microscopic examination. A microscopic urinalysis is only performed if dipstick is positive for leukocyte esterase or blood.
- eGFR, [redacted]

At screening only, serology testing will be performed for HBV (HBsAg and anti-HBc Ab) and HCV (HCV Ab). If HBsAg is negative AND anti-HBc Ab is positive, then reflex PCR for HBV will be performed.

Testing for TB will be performed as described in Section 12.7, using either an IGRA or tuberculin skin test (TST) as appropriate.

In addition to the central laboratory safety tests, WOCBP will have a urine pregnancy test at screening and at all other designated time points.

If a participant experiences elevated ALT or AST > 3× ULN and either TBL level > 2× ULN and/or INR > 1.5, then repeat liver chemistry testing should be performed within 48 to 72 hours or as soon as possible. Upon confirmation of the abnormality, investigational product should be immediately discontinued and retests (ALT, AST, alkaline phosphatase, bilirubin, INR) should be performed weekly until the abnormalities resolve, stabilize, or return to baseline in consultation with the sponsor. If the abnormality persists or worsens, clinical and laboratory monitoring should be continued by the investigator and in consultation with the study medical monitor. If at any time the participant meets withdrawal criteria as described in Section 4.3.2, permanent discontinuation of investigational product should be discussed with the study medical monitor.

7.4.5 Electrocardiograms

Twelve-lead ECGs will be performed using an ECG machine that automatically reports heart rate, PR, QRS, QT, and Fridericia's corrected QT (QTcF) intervals. Where ECG machines cannot or fail to provide automatic reports for QTcF, sites may manually calculate using the standard formula or may use the following web-based calculator for calculation of QTcF:

Mayo Clinic corrected QT interval (QTc) calculator

When using this calculator, QT should be entered in milliseconds and heart rate should be entered in beats/minute. Per Good Clinical Practice (GCP), any calculation (manual or calculator) should be documented as source data. Source data should be signed by the principal investigator or a responsible site representative reviewing ECGs and filed with the participant's study source documents.

Participant should lie in a supine position for 5 minutes prior to performing ECG. Storage and Use of Study Data and Samples.

7.5 Definitions

7.5.1 Adverse Event

An AE is any untoward medical occurrence in a participant or clinical investigation participant that does not necessarily have a causal relationship with the administration of a pharmaceutical

or an investigational product. An AE can therefore be any unfavorable or unintended sign (e.g., including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product. An AE may be a new illness, worsening of a sign or symptom of a condition, or an effect of the investigational product, including the comparator.

Types of events the meet the AE definition include:

- Abnormal laboratory test results or safety assessments (ECG, vital signs) that worsen from baseline and/or are considered clinically significant by the investigator (and are not expected based on the participant's condition).
- New conditions detected or diagnosed after investigational product initiation.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- Signs or symptoms of a possible drug interaction.
- Signs or symptoms of a suspected overdose of any medication. Overdose will not be reported as an AE unless it is an intentional overdose taken with possible suicidal or self-harming intent, which would be reported regardless of sequelae.

Types of events that do not meet the AE definition include:

- Laboratory findings or abnormal safety assessments associated with the participant's underlying UC, unless judged by the investigator to be more severe than expected for the participant's condition.
- Expected UC disease, signs or symptoms, unless more severe than expected for the participant's condition.
- Procedures (medical or surgical procedures such as endoscopy or appendectomy). A condition that leads to a procedure is recorded as an AE.
- Baseline medical conditions that do not worsen.

All AEs that occur after the time of informed consent will be recorded. AEs that occur after administration of the first dose of investigational product (TEAEs) will be reported on the eCRF.

7.5.2 Adverse Drug Reaction

Adverse drug reactions (ADRs) are all noxious and unintended responses to a medicinal product related to any dose. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

7.5.3 Unexpected Adverse Drug Reaction

An unexpected ADR is an ADR, the nature and severity of which is not consistent with the reference safety information as provided in the IB.

7.5.4 Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening, i.e., the participant was at immediate risk of death at the time of the event; it does not include any event that hypothetically might have caused death if it had occurred in a more severe form.
- Requires inpatient hospitalization or prolongation of existing hospitalization. Hospitalizations and/or surgical procedures that are scheduled to occur during the study period, for an illness or disease that existed before participant enrolment in the trial, will not be considered AEs provided the pre-existing condition did not deteriorate (e.g., surgery performed earlier than the planned date).
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event, i.e., an event that may not result in death, be life-threatening, or require hospitalization, but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, convulsions that do not result in inpatient hospitalization, and the development of drug dependency or drug abuse.

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate. In other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Pregnancy in a study participant or the partner of a participant, occurring after randomization, is considered an immediately reportable event (as described in Section 7.7.2).

7.6 Classification

7.6.1 Severity

The severity of AEs will be classified as defined below. The investigator will assess severity for each AE and SAE reported during the study. The assessment will be based on the investigator's clinical judgment, as follows:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated.
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated.
- Grade 4: Serious Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relative

minor medical significance (such as severe headache). This is not the same as "serious," which is based on participant/event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

7.6.2 Assessment of Causality

The relationship of the AE to investigational product will be assessed by the investigator as not related or related as follows:

- **Related**: There is a reasonable possibility that the investigational product caused the AE. Reasonable possibility means that there was evidence to suggest a causal, temporally appropriate relationship between the investigational product and the AE.
- **Not related**: There is not a reasonable possibility that the investigational product caused the AE.

7.7 Procedures for Safety Reporting

All AEs experienced by the participant after signing of the informed consent form until the post-treatment safety follow-up visit will be reported. All AEs must be recorded in the eCRF. For both serious and nonserious AEs, the investigator must determine both the intensity of the event and the relationship of the event to investigational product administration.

All SAEs will be reported to ICON and recorded in the eCRF starting from the time of the signing of the informed consent form up to and including the post-treatment safety follow-up visit.

All SAEs, regardless of the relationship to investigational product, must be reported within 24 hours of site personnel being notified of the occurrence of the event. The investigator (or designee) is required to complete an SAE form and report by email to the Sponsor or designate, as per the study safety manual. SAEs must be reported via eCRF and SAE form.

SAE forms will be provided to each study site. The initial SAE report should include at a minimum: participant number, a narrative description of the event, and an assessment by the investigator of the intensity of the event and relationship of the event to investigational product. The initial SAE report received from the site should be as complete as possible.

A completed SAE form must be reported within 1 working day of awareness of event to:

Contract Research Organization
In Europe, Asia-Pacific, and Africa (EAPA):
ICON Drug Safety Center EAPA
Phone [redacted]
Fax [redacted]
Email MHGSafety@prahs.com

In the Americas:
ICON Drug Safety Center Americas
Phone [redacted]
Fax [redacted]
Email CHOSafety@prahs.com

A complete follow-up SAE report must be submitted when the information, not available at the time of the initial report, becomes available. The sponsor (or designee) may request SAE follow-up information.

Pregnancy in a study participant or the partner of a study participant, occurring from after randomization and up to 30 days after last dose of investigational product, is considered an immediately reportable event and must be reported to ICON within 1 working day after the investigator has gained knowledge of the event. Participants who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and discontinue study drug immediately. Participants whose partner has become pregnant or suspects she is pregnant during the study are to report the information to the investigator. Details of the outcome of the pregnancy (e.g., full term delivery, stillbirth, congenital anomaly, miscarriage) will be collected and reported not longer than 1 month after the expected due date.

Any SAE that occurs at any time after completion of the study that the investigator considers to be related to investigational product must be reported to ICON.

7.7.1 Suspected Unexpected Serious Adverse Reactions Reporting

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, including FDA, EU regulatory agencies, investigator, and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted.

An unexpected event is one that is not reported in the IB. Since NX-13 is an investigational medicinal product that has not yet been approved for marketing in any country, the IB in effect during the study will serve as the Reference Safety Information for determining whether an AE is expected or unexpected.

If the event is evaluated as a SUSAR, i.e. unexpected events that are related (reasonable possibility) to NX-13, the Sponsor will submit the SUSAR to the regulatory authorities and the IRB/IEC within 7 calendar days for initial reports of fatal/life-threatening events (with a follow-up report within a further 8 calendar days) and 15 calendar days for all other events, or in accordance with local regulatory requirements, if different. Where there are conflicting evaluations of causal relationship, between the Investigator and the company, the more conservative will be used for reporting purposes. All reporting to regulatory authorities will be by Landos, or through a Landos designated vendor.

If there are SUSARs associated with the use of the investigational product, the appropriate regulatory agency(ies) and all participating investigators will be notified on an expedited basis in accordance with ICH-E2A Guidance for Industry: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, the EU Clinical Trial Regulation 536/2014 and other local regulations. The Investigator must immediately review with the Investigator's site team and retain the documentation in the Investigator Site File. The investigational site also will forward a copy of all expedited reports to his or her IRB and IEC in accordance with national regulations.

It is the responsibility of the investigator to promptly notify the institutional review board (IRB)/independent ethics committee (IEC) of all SUSARs involving risk to human study participants.

7.7.2 Monitoring of Adverse Events and Period of Observation

All AEs should be monitored to determine the outcome or until the investigator considers it medically justifiable to terminate follow-up.

All SAEs should be monitored until resolved or until the SAE is clearly determined to be due to a participant's stable or chronic condition or intercurrent illness(es).

8 STATISTICAL METHODS

Statistical considerations are briefly described below. More details on the analyses and presentation of study results will be provided in the statistical analysis plan (SAP). The SAP will be finalized prior to the unblinding of treatment allocation codes.

8.1 Sample Size Determination

The target sample size is 71 participants. Assuming a 10% drop out rate during induction, approximately 80 participants with moderate to severe UC are planned to be enrolled. The primary endpoint is CFB in mean MMS for NX-13 compared to placebo. The sample size assumes that the CFB in the MMS for the placebo group will be -1.75, for the active group will be -2.65, and the delta will be 0.9. The one-tailed alpha is set at 0.05, and the power is 80%.

8.2 Analysis Populations

8.2.1 Intent-to-Treat Analysis Set

All randomized participants who receive at least 1 dose of investigational product will be included in the intent-to-treat (ITT) analysis set.

In the event of investigational product administration error, analyses on the ITT analysis set will be performed according to the randomized treatment group. The ITT analysis set will be used for the primary endpoint analysis.

8.2.2 Per-Protocol Analysis Set

The per-protocol (PP) analysis set will include all participants who meet enrollment criteria, receive at least one dose of investigational product as required by the protocol, and have no major protocol violations. Major protocol deviations will be defined in the SAP. PP analyses will be performed on the primary endpoint according to the actual treatment received.

8.2.3 Safety Analysis Set

All participants who receive at least 1 dose of investigational product in the induction period will be included in the induction period safety (SAF) analysis set, and all participants who receive at least 1 dose of investigational product in the LTE will be included in the LTE SAF analysis set. Safety analyses will be performed according to the actual treatment received.

8.2.4 [redacted] Analysis Set

[redacted]

8.3 Statistical Analysis

Efficacy analyses will be performed on the ITT analysis set, safety analyses will be performed on the SAF analysis set,[redacted]

Continuous variables will be summarized using the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using counts and percentages.

All data will be included in data listings.

8.3.1 Demographics and Other Baseline Characteristics

Demographics and other baseline characteristics including UC history and UC medication history will be summarized by treatment group using descriptive statistics.

8.3.2 Efficacy Analyses

All efficacy analyses will be performed on the ITT analysis set. The primary endpoint analysis will also be performed on the PP analysis set.

The primary endpoint is the change from baseline in MMS at Week 12. A negative change from baseline corresponds with an improvement in MMS. The superiority of NX-13 compared to placebo will be tested.

The null hypothesis is:

H_0: The difference between NX-13 and placebo in change from baseline in MMS at Week 12 is greater or equal to 0.

The alternative hypothesis is:

H_1: The difference between NX-13 and placebo in change from baseline in MMS at Week 12 is less than 0.

The difference between NX-13 and placebo in the change from baseline in MMS at Week 12 will be analyzed using ANCOVA with treatment and prior exposure to biologic therapy for UC as factors and baseline MMS as a covariate. Statistical significance will be declared if the analysis is significant at the one-sided 5% level (two-sided 10% level). A one-sided test is chosen due to the exploratory nature of the study.

All secondary efficacy endpoints are proportion-based and will be summarized by presenting the point estimate at Week 12 and the 90% confidence interval (CI) for each treatment, as well as the absolute difference in proportions between NX-13 and placebo along with its 90% CI. A CMH chi-square test will be performed stratified by prior exposure to biologic therapy for UC and the adjusted treatment difference will be presented as well as its 90% CI and p-value.

Exploratory efficacy endpoints will be analyzed descriptively. Continuous endpoints will be summarized using descriptive statistics on the change from baseline or change from Week 12, as appropriate. Ordinal data such as the rectal urgency endpoint will be summarized using shifts from baseline or Week 12, as appropriate. Proportion-based endpoints will be summarized using the point estimate and 90% CI as well as the absolute treatment difference and 90% CI. Details of the efficacy analyses will be provided in the SAP.

8.3.3 Safety Analyses

Safety data will be presented by treatment group and time point (if applicable). Analyses over the induction period will be performed on the SAF and analyses over the extension period will be performed on the LTE SAF.

All AEs will be classified according to the Medical Dictionary for Regulatory Activities (MedDRA) dictionary and summarized by system organ class (SOC) and preferred term.

TEAEs will be summarized by the number and percentage of participants experiencing any TEAEs, any severe TEAEs, any treatment-related TEAEs, any SAEs, any treatment-related SAEs, any TEAEs leading to permanent treatment discontinuation, and any TEAEs leading to treatment interruption/dose delay. AEs will also be summarized by severity and relationship to investigational product. If a participant experiences 2 or more AEs for a given preferred term, severity is defined as the severity of the most severe event and relationship to investigational product is the relationship of the most related event.

Vital signs, clinical laboratory results (chemistry, coagulation, hematology, urinalysis) and ECG findings will be summarized continuously (as observed and changes from baseline) and categorically (using shift tables).

8.3.4 [redacted] Analyses

[redacted]

8.3.5 Interim Analysis

An interim analysis will be performed after all participants complete the induction period. Analyses will include demographic and baseline characteristics, efficacy, safety, PK and biomarkers over the induction period. The primary endpoint is measured at Week 12 when participants complete the induction period; there is no impact to the alpha. Further details of the analysis will be provided in the SAP and the unblinding plan.

The results of the interim analyses will not impact the conduct of this trial and participants will continue into the LTE period as planned. The results will be used to prepare for subsequent trials.

8.4 Handling of Missing, Unused, and Spurious Data

For the primary endpoint, missing MMS data will not be imputed. For the proportion-based secondary endpoints, missing data will be imputed as non-responder for analyses.

8.5 Reporting of Deviations to Original Statistical Analysis Plan

All deviations from the original SAP will be reported in the clinical study report.

9 ETHICAL CONSIDERATIONS

The study will be conducted in compliance with the protocol, International Council for Harmonisation GCP (ICH-GCP), and the applicable regulatory requirements.

9.1 Institutional Review Board

All relevant documents for this study will be submitted to an appropriate IRB or IEC for review. A signed and dated letter documenting IRB/IEC approval must be obtained prior to entering study participants at the site. The IRB/IEC must be notified of all subsequent protocol amendments.

9.2 Informed Consent

Prior to any study procedures, it is the responsibility of the investigator to fully inform the participant or legally authorized representative, of all pertinent aspects of the study. Each participant or a legally authorized representative must give written consent prior to the participant's participation in the study. The method of obtaining and documenting the informed consent and the contents of the consent must comply with ICH-GCP and all applicable regulatory requirement(s).

9.3 Confidentiality of Participant Records

All study records containing participant details will identify the participant by the assigned participant identification number. Participant information collected will comply with the requirements for the protection of privacy of individually identifiable health information.

The investigator will grant access to the participant's original medical records, to both monitor(s) and auditor(s) from the sponsor or its designee and to regulatory health authorities, for verification of the data gathered and to audit the data collection process. The participant's confidentiality will be maintained, and the participant's information will be made publicly available to the extent permitted by the applicable laws and regulations.

10 ADMINISTRATIVE REQUIREMENTS

10.1 Protocol Amendments

The sponsor may modify the protocol at any time during the life of the protocol. Protocol amendments will require IRB/IEC approval prior to implementation except when changes to the protocol are required to eliminate immediate hazards to the study participants. The sponsor and IRB/IEC must be notified immediately after such changes have occurred.

10.2 Premature Termination of the Trial

If the investigator or sponsor discovers sufficient reasonable cause for the premature termination of the study, the terminating party will provide written notification documenting the reason for study termination. The appropriate regulatory agencies and IRB/IEC must be notified.

10.3 Completion of Case Report Forms

The investigator and site study personnel will be trained on eCRF completion. The investigator is responsible for all entries in the eCRF for completeness, accuracy, and clarity. The investigator or designee should complete the eCRF as soon as possible after the information is collected. The investigator is responsible to endorse all the information recorded in the eCRF and will provide formal approval of the final submitted data.

10.4 Access to Source Data/Documents

The investigator will permit study related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents.

10.5 Quality Assurance

10.5.1 Onsite Monitoring

The sponsor or its designee will perform onsite monitoring visits periodically during the study. At these visits, the monitor will review study documents to ensure adherence to the study protocol and regulatory requirements, and to review eCRF entries against source documents. Findings from the visit will be discussed with the investigator.

Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate any immediate hazard to study participant. There will be no exemptions from the inclusion or exclusion study criteria. The site should document all protocol deviations in the participant's source documents. In the event of a major deviation, the site should notify the Sponsor or its designee and the IRB/EC as required.

10.5.2 Onsite Audits

The sponsor or its designee may visit the site to conduct an audit of the study in accordance with regulatory guidelines. The audit will require access to all study records and source documents for inspection. Such audits may also be conducted by IRB/IEC or regulatory authorities.

10.5.3 Data Quality Assurance

Study data will be entered in the eCRF by trained study personnel. Data validation edit checks will be defined and implemented. Inconsistent and questionable data detected during data entry or data validation process will be queried. Data clarification forms will be generated, and any discrepancies will be resolved.

10.6 Retention of Study Documents

The investigator must retain all study records for 25 years after the notification of the IRB/IEC regarding the end of the study or according to applicable regulatory requirements, or the length of time required by national or local health authorities, whichever is longer. After that period of time, study records may be destroyed as per local regulations.

If the investigator retires, relocates or withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. The sponsor must be notified in writing if a custodial change occurs.

10.7 Clinical Trial Registration and Disclosure of Results

The sponsor will register this trial on ClinicalTrials.gov before the start of the study and post the results of the clinical trial for public viewing.

10.8 Publication Policy

The sponsor will own all intellectual property and data generated in this project. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter trials only in their entirety. All decisions about publication of the study data will be made by the sponsor. Draft manuscripts, abstracts, and presentations should be developed by the sponsor and circulated to coauthors for review and approval. The sponsor will retain the ownership of the data obtained in this study. Authorship of publications resulting from this study should accurately reflect the contribution of individuals at the sponsor and CRO to the design and implementation of the trial, analysis of the data, and preparation of the manuscript.

10.9 Confidentiality

All confidential information, verbal and written, provided to the investigator by the sponsor will be kept in strict confidence, and restricted to the study personnel involved in conducting the study, except if the information is required by the IRB/IEC or similar committees.

10.10 Financing and Insurance

Financing and insurance will be addressed in a separate agreement with study centers.

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12 APPENDICES

12.1 Appendix 1: Patient-Reported Outcome Diary (Participant e-Diary)

The participant e-diary will capture the PRO scoring for rectal bleeding subscore (RBS) and stool frequency subscore (SFS) daily, as described below. Scoring is required for eligibility in the Induction Phase.

Patient-Reported Outcome Scoring

RBS and SFS scores will be determined from data collected during the 7 days prior to the visit and will include the average of 3 consecutive values, or if 3 are not available, then 4 nonconsecutive days will be averaged. Values obtained during preparation for an endoscopy, the day of an endoscopy, or the day after an endoscopy will not be considered. If an endoscopy has been performed during the 7 days prior to a visit and appropriate data are not available, data from the prior week will be accepted using the same algorithm. If inadequate data collection has occurred during the week prior to the visit, then the collection period may be increased to a 2-week period, and the participant is educated in proper data collection.

Category of Instructions	Specific Instructions to Study Participants
Definition of Stool	Participant will be instructed that a stool is defined as a trip to the toilet when the participant has either a bowel movement, or passes blood alone, blood and mucus, or mucus only Stool frequency will be recorded **daily** in a participant e-diary
Reference Remission Stool Frequency (over 24 hours)	Participant will be asked to identify at the screening visit how many stools he or she had in a 24-hour period when in remission from UC If the participant does not report that he or she has achieved remission, then the participant should be asked to identify the number of stools he or she had per day before initial onset of signs and symptoms of UC – Whether the reference remission stool frequency is based on reported stool frequency when the participant was in remission or reported stool frequency before initial onset of signs and symptoms of UC will be documented. – 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)	Participant will 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 Participant will be instructed to select "No Blood Seen" in the rectal bleeding section if they do not have stool during a given day
Recording of Rectal Bleeding and Stool Frequency Assessments	Participants should be directed to capture their rectal bleeding and stool frequency assessments in event logs or daily diaries* for **14 days** before each visit .

Source: ref 23

12.2 Appendix 2: Rectal Urgency and Abdominal Pain Questionnaire

Rectal Urgency Score:

Rectal Urgency Events are defined as the need to rush to the toilet to have a bowel movement.

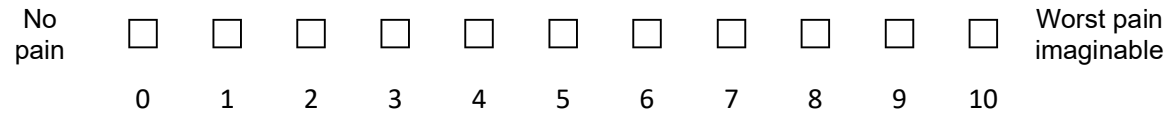
Rectal Urgency Score	Number of Events
0	2 or fewer events
2.5	3 to 5 events
5.0	6 to 8 events
7.5	9 to 11 events
10	12 or more events

During the last calendar day, how many urgent bowel movement events (as defined above) did you have? _____

Rectal Urgency Score: _____

Abdominal Pain Score:

In the past 24-hours, rate your abdominal pain on a scale from 0 (no pain) to 10 (worse imaginable pain).



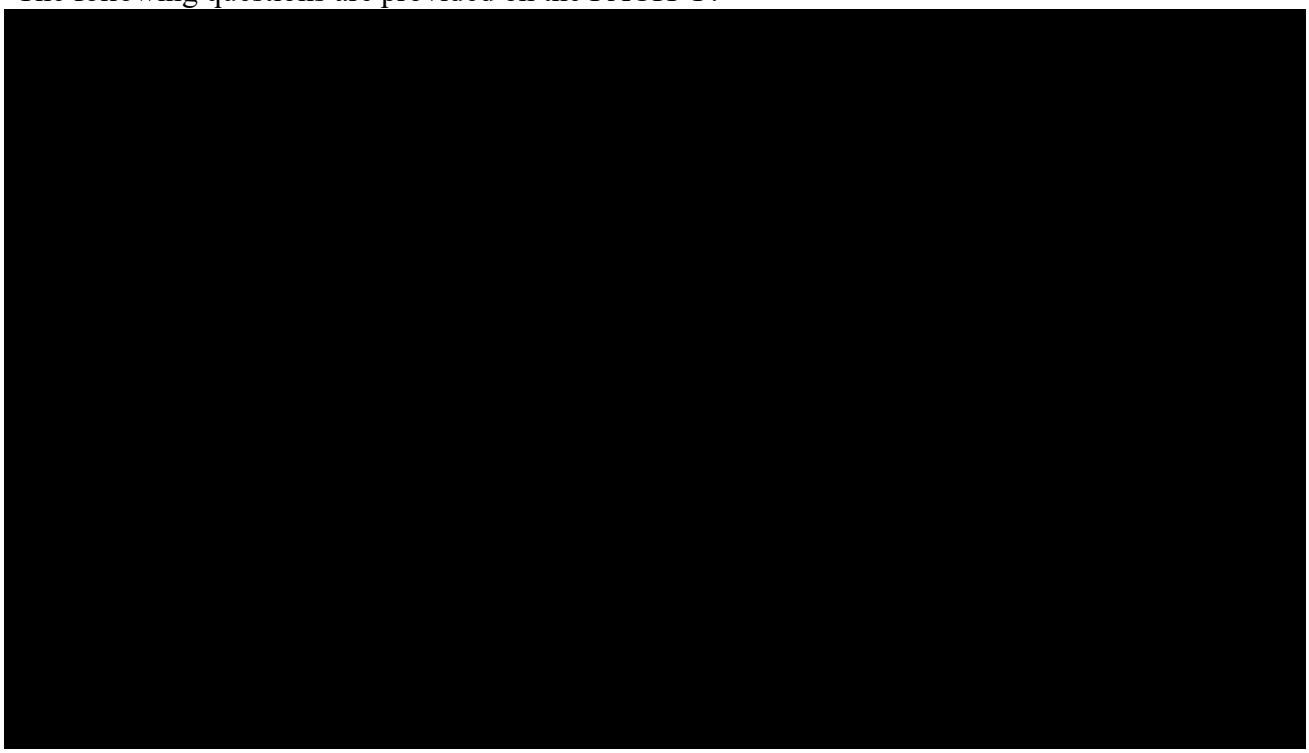
12.3 Appendix 3: Modified Mayo Score

Component	Score
Stool Frequency	
Normal number of stools for this participant	0
1 to 2 stools more than normal	1
3 to 4 stools more than normal	2
5 or more stools than normal	3
Rectal Bleeding	
No blood seen	0
Streaks of blood with stool less than half the time	1
Obvious blood (more than just streaks) or streaks of blood with stool most of the time	2
Blood alone passes	3
Findings on Endoscopy	
Normal or inactive disease	0
Mild disease (erythema, decreased vascular pattern, **no friability**)	1
Moderate disease (marked erythema, absent vascular pattern, friability, erosions)	2
Severe (spontaneous bleeding, ulceration)	3
Total Score (0-9)	

Source: ref 23, ref 24

12.4 Appendix 4: Functional Assessment of Chronic Illness Therapy – Fatigue

The following questions are provided on the FACIT-F:



12.5 Appendix 5: Geboes Scoring System

Grade 0: Structural (architectural change)	
0.0	No abnormality
0.1	Mild abnormality
0.2	Mild or moderate diffuse or multifocal abnormalities
0.3	Severe diffuse or multifocal abnormalities
Grade 1: Chronic inflammatory infiltrate	
1.0	No increase
1.1	Mild but unequivocal increase
1.2	Moderate increase
1.3	Marked increase
Grade 2A: Eosinophils in lamina propria	
2A.0	No increase
2A.1	Mild but unequivocal increase
2A.2	Moderate increase
2A.3	Marked increase
Grade 2B: Neutrophils in lamina propria	
2B.0	None
2B.1	Mild but unequivocal increase
2B.2	Moderate increase
2B.3	Marked increase
Grade 3: Neutrophils in epithelium	
3.0	None
3.1	< 5% crypts involved
3.2	< 50% crypts involved
3.3	> 50% crypts involved
Grade 4: Crypt destruction	
4.0	None
4.1	Probable – local excess of neutrophils in part of crypt
4.2	Probable – marked attenuation
4.3	Unequivocal crypt destruction
Grade 5: Erosion or ulceration	
5.0	No erosion, ulceration, or granulation tissue
5.1	Recovering epithelium + adjacent inflammation
5.2	Probable erosion – focally stripped
5.3	Unequivocal erosion
5.4	Ulcer or granulation tissue

Source: ref 22
Note: Histological remission = continuous Geboes score ≤ 6. Histological response = continuous Geboes score ≤ 12.

12.6 Appendix 6: Robart Histopathology Index

Supplementary Table 1. Scheme for converting Geboes histology scores into Robarts histopathology index (RHI) and Nancy index scores.

Geboes Score		Robarts Criteria	Robarts Multiplier	Nancy Index Criteria
Grade 0*	**Structural (architectural changes)**			
Subgrades				
0.0	No abnormality	–		–
0.1	Mild abnormality	–		–
0.2	Mild or moderate diffuse or multifocal abnormalities	–		–
0.3	Severe diffuse or multifocal abnormalities	–		–
Grade 1	**Chronic inflammatory infiltrate**			
Subgrades				
1.0	No increase	0	1	X
1.1	Mild but unequivocal increase	1		X
1.2	Moderate increase	2		X
1.3	Marked increase	3		X
Grade 2	**Lamina propria neutrophils and eosinophils**			
*2A Eosinophils**				
2A.0	No increase	–		–
2A.1	Mild but unequivocal increase	–		–
2A.2	Moderate increase	–		–
2A.3	Marked increase	–		–
2B Neutrophils				
2B.0	No increase	0	2	X
2B.1	Mild but unequivocal increase	1		X
2B.2	Moderate increase	2		X
2B.3	Marked increase	3		X
Grade 3	**Neutrophils in epithelium**			
Subgrades				
3.0	None	0	3	X
3.1	<5% Crypts involved	1		X
3.2	<50% Crypts involved	2		X
3.3	>50% Crypts involved	3		X
Grade 4*	**Crypt destruction**			
Subgrades				
4.0	None	–		–
4.1	Probable—local excess of neutrophils in part of crypt	–		–
4.2	Probable—marked attenuation	–		–
4.3	Unequivocal crypt destruction	–		–
Grade 5	**Erosion or ulceration**			
Subgrades				
5.0	No erosion, ulceration, orgranulation tissue	0	5	X
5.1	Recovering epithelium + adjacent inflammation	1		X
5.2	Probable erosion, focally stripped	1		X
5.3	Unequivocal erosion	2		X
5.4	Ulcer or granulation tissue	3		X

*Geboes grades 0, 2A, and 4 are not included in the RHI or the Nancy index.

Source: ref 25

12.7 Appendix 7: Detailed Criteria for Exclusion Based on Tuberculosis Testing

Participants with evidence of active or latent infection with Mycobacterium tuberculosis (TB) or participants with this history who have not completed a generally accepted full course of treatment before randomization are excluded. All other participants must have either the Mantoux (purified protein derivative [PPD]) tuberculin skin test or interferon gamma release assay (IGRA) performed.

Participants who have no history of previously diagnosed active or latent tuberculosis are excluded if they have a positive Mantoux (PPD) tuberculin skin test (i.e., ≥ 5 mm induration) or a positive IGRA (the latter to be tested at the central laboratory) during screening or within 12 weeks before randomization.

- An IGRA is strongly recommended for participant with a prior Bacillus Calmette-Guérin (BCG) vaccination but may be used for any participant. Documentation of IGRA product used and the test result must be in the participant's source documentation if performed locally. Acceptable IGRA products include QuantiFERON TB Gold Plus In-Tube Test.
- If the results of the IGRA are indeterminate, the test may be repeated, and if a negative result is obtained, enrollment may proceed. In participants with no history of treated active or latent tuberculosis, a positive test on repeat will exclude the participant.

Participants with a history of active or latent tuberculosis infection must follow instructions outlined below for "Participants with a prior diagnosis of active or latent tuberculosis are excluded unless both of the following criteria are met" in this criterion.

Participants with repeat indeterminate IGRA results, with no prior TB history, may be enrolled after consultation with a pulmonary or infectious disease specialist who determines low risk of infection (i.e., participant would be acceptable for immunosuppressant [e.g., anti-TNF] treatment without additional action). This consultation must be included in source documentation.

Results from a chest x-ray taken within the 3 months before or during screening (Visit 1) must show no abnormalities suggestive of active TB infection as determined by a qualified medical specialist.

Participants with a prior diagnosis of active or latent tuberculosis are excluded unless both of the following criteria are met:

- The participant has previously received an adequate course of treatment for either latent (e.g., 9 months of isoniazid or an acceptable alternative regimen, in a locale where rates of primary multidrug TB resistance are < 5%; participants from regions with higher rates of primary multidrug TB resistance are excluded) or active (acceptable multidrug regimen) TB infection. Evidence of diagnosis and treatment must be included in source documentation. Consultation with a pulmonary or infectious disease specialist to confirm adequate treatment (i.e., participant would be acceptable for immunosuppressant [e.g., anti-TNF] treatment without additional action) must be performed during the screening period. The consultation report must be included in source documentation prior to enrollment.

- A chest x-ray performed within 3 months prior to screening (Visit 1) or during screening (Visit 1) indicates no evidence of active or recurrent disease, and documentation of interpretation by a qualified medical specialist must be included in source documentation.

12.8 Appendix 8: Data Protection in EEA Countries

Landos, as Data Controller, ensures that all processing activities involving personal data performed in the scope of this Study are compliant with, but not limited to, the requirements set by EU General Data Protection Regulation (GDPR 679/2016), its subsequent amendments and any additional national laws on Data Protection, recommendations and guidelines as applicable.

To comply with the applicable rules on the protection of personal data, specifically regarding the implementation of the organizational and technical arrangements aiming to avoid unauthorised access, disclosure, dissemination, alteration or loss of information and processed personal data, Landos has implemented and maintains the following measures:

- restriction and monitoring of physical access to the offices and information processing facilities to employees, personnel and approved visitors;
- ensuring appropriate and restricted user access relevant to the function and type of activity performed in relation to the clinical trial;
- implementing the pseudonymisation and encryption of personal data, as appropriate;
- implementing the ability to ensure the ongoing confidentiality, integrity, availability and resilience of processing systems and services;
- implementing network, application, database security by means of firewalls and antivirus/anti-malware; ensuring detection of malware purposed for unauthorized deletion, blocking, copying of information, disabling security measures and response to such attacks;
- means to restore the availability and access to personal information in a timely manner in the event of a physical or technical incident;
- logging of security events/incidents in information systems;
- implementing procedures that cover reporting, analysis, monitoring and resolution of security incidents;
- ensuring that information systems, computers and software involved in the performance of the services provided in the Study are backed up;
- a process for regularly testing, assessing and evaluating the effectiveness of technical and organisational measures for ensuring the security of the processing;
- implementing procedures to capture within reasonable time-manner any personal data breach occurred;
- implementing procedures and practices for securing destruction of paper documents containing personal data;
- implementing business continuity procedures ensuring that Landos can continue to provide services through operational interruption

All locations, personnel and information systems that are used to perform services for the Study will be covered;

Landos will ensure technical and organizational security measures described above, are regularly reviewed and updated to take into account any evolution on technological developments.

Landos may apply additional specific statutory requirements, where applicable in the national laws, and will implement the necessary security measures even if they are not expressly listed above.

Besides the already above-mentioned technical and organizational measures, Landos, by means of internal measures and imposed contractual clauses to the selected sub-contractors, ensures the confidentiality of records and personal data of subjects.

With exception of the activities in the scope of the on-site monitoring, the name of the patient will neither be asked for, nor recorded by the Landos. An identification number will be allocated to each patient registered in the Study. This number will identify the patient and will be included on all case report forms and corresponding material and data associated with the patient.

Monitors acting on behalf of the Landos will have access to fully identifiable information only in the scope of the on-site monitoring visits, and only for the source data verification mandatory under clinical trial framework, including the ICH-GCP obligations applicable to the conduct of the Study. Staff involved in the performance of this task is bound by any additional stricter confidentiality clauses imposed upon them, as compared to other staff members.

Landos has put in place a functional process of reporting of any data breach occurring at Landos's or its sub-contractor's facilities and premises. In case of the occurrence of any data breach, Landos will immediately apply relevant measures to mitigate the risks to data subjects as appropriate in relation to the specific context of the data breach, taking into account its source, underlying intentions, possibilities of recovery etc… Any data breach presenting risks to the rights and freedoms of data subjects will be reported to the relevant supervisory data protection authority within 72 hours of Landos becoming aware of the data breach. In addition, in case of occurrence of a high-risk breach, data subjects will be informed by Landos (via clinical Study site).

12.9 Appendix 9: Definitions and Details Regarding Eligibility Based on Response to Prior Therapies

Conventional therapy/thiopurines

1. Signs and symptoms of persistently active disease despite a history of at least one 12-week regimen of oral azathioprine (AZA) (≥ 1.5 mg/kg) or 6- mercaptopurine (6-MP) (≥0.75 mg/kg), or methotrexate (MTX) (≥15 mg/week oral, subcutaneous [SC] or intramuscular [IM]) or tacrolimus (documented trough level ≥5 ng/mL), OR
2. The dosage of 6-MP or AZA confirmed to be therapeutic with whole blood thioguanine nucleotide levels > 200 pmol/8 x 10^8 red blood cells, OR
3. History of intolerance to at least one immunomodulator (including but not limited to fever, nausea/vomiting, abdominal pain, pancreatitis, liver function test abnormalities, leukopenia/lymphopenia, thiopurine methyltransferase [TPMT] genetic mutation, infection).

TNFα antagonists or their biosimilars:

1. Signs and symptoms of persistently active disease despite a history of:
   a. At least one 6-week induction regimen of infliximab (≥ 5 mg/kg IV at 0, 2 and 6 weeks), OR
   b. At least one 4-week induction regimen of adalimumab (one 160 mg SC dose followed by one 80 mg SC dose [or one 80 mg SC dose, in countries where this dosing regimen is allowed] followed by one 40 mg SC dose at least 2 weeks apart), OR
   c. At least one 2-week induction regimen of golimumab (one 200 mg SC dose followed by one 100 mg SC dose at least 2 weeks apart), OR
2. Recurrence of symptoms during maintenance dosing following prior clinical benefit, OR
3. History of intolerance (including but not limited to infusion or injection related reaction, demyelination, congestive heart failure, infection).

Note: The medication used to qualify the participant for entry into this category must be approved for the treatment of UC in the country of use, and the participant must have received an adequate course of therapy based on the local guidelines for that therapy.

Inadequate response, loss of response, and intolerance are defined as:

- Inadequate response: Signs and symptoms of persistently active disease despite a history of completing a dosing regimen
- Loss of response: Recurrence of symptoms of active disease during treatment following prior clinical benefit (discontinuation despite clinical benefit does not qualify as having failed or being intolerant to UC biologic therapy).
- Intolerance: Including, but not limited to, infusion- or injection-related reaction, or adverse events that led to a reduction in dose or discontinuation of the medication

Note: To be considered inadequate response, loss of response, or intolerance after treatment with a biologic or a JAK/S1P, the participant must have received an adequate course of therapy based on the local guidelines for that therapy.