Statistical Analysis Plan (SAP)

Protocol 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
Protocol Version No./Date:	Protocol Amendment 2/16-Jul-2023
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1.0 Approvals

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(NOTE: Electronic Signatures should only be used if all parties have the ability to eSign.)

2.0 Change History

Version/Date	Change Log
1.0/ 24Mar2024	• SAP v1.0 Created
1.1/ 25Jun2024	• Update population set definition to include “All Screened Subjects” and “LTE Entered Set” • Updated the period 1 and period 2 definition, update period 1 from Screening • Updated text from Drug Administration to Drug Exposure for under section “Dates of First and Last Dose of Study Drug” • Updated the text to handle tie for the mode in rectal urgency score. • Updated the FACIT-T calculation algorithm and appendix per FACIT-Fatigue Subscale Scoring Guidelines • Included details on finding the date of prep for endoscopy, during endoscopy and after endoscopy when calculating the MMS • Update the AE collection up to 21 days from 14 days after the date and time of last dose of study drug • Added the detail on finding prior exposure to biologic use based on CRF page under demographic section • Updated how to determine height and weight under demographic section • Update section 8.4 o week 48 end date as 351 o update analysis visit to match the table shell o include map of EOT to week 12 or week 52 • Added EOT to Geboes score and RHI score collection • Update the demographic section on stratification variable “prior exposure to biologics or advanced therapies for UC.” • Update windowing section for each different parameter per discussion with LND • Update Estimand sections on variable of interest from “change from baseline in Rectal Urgency” to “shift from baseline in Rectal urgency” • Remove the weekly average calculation for “rectal urgency” and only keep ‘mode’ • Remove change from baseline in rectal urgency for appendix 1 • Update rounding for “average abdominal pain score” to 1 decimal place • Update the Geboes numeric scoring to section 8.7.3.1 and appendix 5 • Add the new section of delayed outcomes, • Update change from protocol section, • Update appendix 1 with delayed endpoints. • Update prior/current medication information relative to the screening. • Updated section 8.7.3.5.1 for glucocorticosteroids/glucocorticoids use at study entry and at week 52 • Updated section 10.8.4.1 to report QTcF as part of PCS findings.

Version/Date	Change Log
	• Added text for prior UC medication • Updated the in section 7.5.2 actual treatment definition when subjects received different kit assignment. • Update section 7.5.2.3 Per-Protocol Set definition
1.2/15Jul2024	• Removed Per-Protocol Set definition and relevant analysis using Per-Protocol Set • Updated the approach of handling intercurrent events of subjects take the prohibited medication for the estimands with respect to primary and secondary endpoints • Added and updated secondary endpoints based on AbbVie definition • Added subgroup analyses for the primary and secondary endpoints • Added proposed listings of patients who potentially used prohibited medications for the blinded data review meeting
1.3/16Aug2024	• RHI Grade 5 range and example for are updated • New endpoints are added to section 'Change from protocol', Estimand and Appendix • Updated the terminology for efficacy endpoints during the LTE period per AbbVie's request • Prohibited medication identification is added under 'prior and concomitant medication' • '21 days' is removed from section 8.3 period end dates as it is applicable to safety analyses and is defined in the corresponding sections. • Summaries of exposure adjusted event rate are added under AE section • Some subgroup identification of coded term are added to Appendix • Potential drug-induced liver injury (DILI) criteria are updated • ICH categories of protocol deviations are added to section 10.6 and appendix • Bar plots and forest plots are added
1.4/27Aug2024	• Update change from protocol section • Update the definition for Glucocorticoid-free remission • Updated the intercurrent event of UC-related prohibited medications, included uc-related prohibited medication to analysis window section • Added the section "efficacy assessment and derivation" section prior to endpoints section • Update the analysis windowing section to map the MMS dates to clinical visit dates • Update total person-year in days including 21 days • Update the appendix 1 including all the newly added endpoints and time points • Align all the stratification name as "prior biologics or advanced therapies" • Update the lab shift table summary • Update the definition for subgroup "For prior exposure to anti-TNF

Version/Date	Change Log
	• Move the actual treatment information under SAP section treatment group • Move the LTE summary to the SAP section LTE efficacy analyses • Update the safety follow-up in SAP section time points and visit windowing • Update the interim analysis section • Update clinical response per partial MMS at week 4 definition
1.5/17Sep2024	• Subgroup of prior failure to anti-TNF added to demographic and baseline section • Lab shift table text is updated • UC prohibited medication identification section is updated • Updated the appendix section to make it more readable • LTE endpoints section is updated to include all the specific endpoints • Clinical response per MMS at LTE baseline is updated to include missing/subjects with ICE • SAS proc freq code is updated per AbbVie request • All death is removed from the TEAE overall summary
2.0/20Sep2024	• Update the change from protocol section • Add 'baseline abdominal pain' and 'baseline rectal urgency'to baseline section • Update the appendix 1 • Update to a more generic version of the MedDRA • Update period 1 definition including LTE not treated subjects
2.1/19Nov2024	• Update the text derivation and summary of abdominal pain and rectal urgency • Update the subgroup text specifying the ATC4CD • Removing duplicate text "duration of UC" under demographic section
2.1/26Nov2024	• Updated the derivation of total exposure time in days to use days rather than years of exposure. In addition, 21 days is added only for subject who did not continue to LTE period
2.1/03Dec2024	• Forest plots will display the LS mean difference (continuous endpoints) or unadjusted risk difference (binary endpoints) between NX-13 and placebo
2.2/18Dec2024	• Add subgroup of 'use of baseline Immunosuppressant' under section demographic and baseline characteristics • Removed "total expected number of doses" in section 10.5.1. When a subject does not return the container, then this dispensation event will be excluded in the calculation for the total number of doses taken and total compliance
2.2/20Dec2024	• Update the subgroup analysis. Due to small count of the subgroups, the fixed factor of prior exposure to biologics or advanced therapies for UC based on CRF CM data will be removed in the subgroup ANCOVA model for the primary efficacy endpoint. Likewise, these stratification factors will

Version/Date	Change Log
	not be controlled and a chi-square test will be performed in the subgroup analysis for all secondary endpoints in the Induction Period • Clarify that rectal urgency score, instead of abdominal pain, will be analyzed based on the mode, where the mode of rectal urgency score will be derived following the same algorithm of selecting the records to calculate average of abdominal pain • Updated FCP unit
2.3/09Jan2024	• Specified level for number of prior use of biologics and number of prior failure of biologics or advanced therapies • Specified level for median UC disease duration • Updated the adjusted risk difference sample code • Updated some appendix 1 exploratory endpoints • Updated baseline definition • Modified the interim analysis section

3.0 Table of Contents

4.0 Purpose

The Statistical Analysis Plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under AbbVie/Landos Biopharma Protocol NX-13-201.

5.0 Scope

The SAP outlines the following:

- Study Objectives
- Study Design
- Study Estimands
- Applicable Study Definitions
- Statistical Methods

6.0 Introduction

This SAP describes the statistical methodology and analyses to be conducted for the protocol entitled "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."

This SAP should be read in conjunction with the study protocol and case report form (CRF). Any further changes to the protocol or CRF may necessitate updates to the SAP and need to be described in the Clinical Study Report (CSR).

6.1 Changes from Protocol

CCI

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7.0 Study Design

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

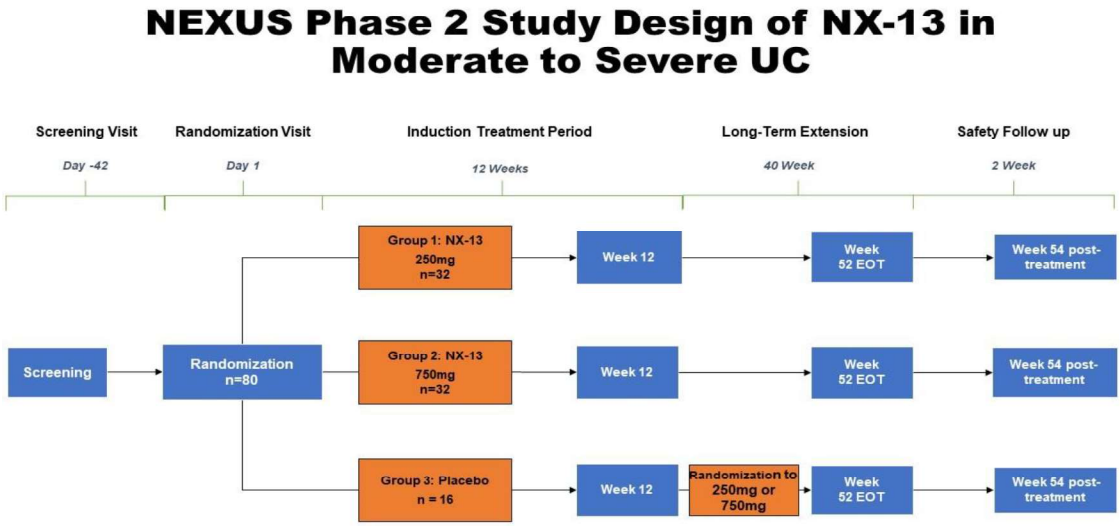
Participants will have endoscopically documented UC for at least 3 months prior to screening, with moderate to severe activity defined as Modified Mayo Score (MMS) ≥ 5, including endoscopic score (ES) ≥ 2, rectal bleeding subscore (RBS) ≥ 1, and stool frequency subscore (SFS) ≥ 1. They must have failed, had an inadequate response to, or been intolerant of at least one prior therapy including conventional therapy (5-ASA with systemic glucocorticoids / glucocorticoids, systemic glucocorticosteroids/ glucocorticoids alone, or thiopurines), biologic therapy (including monoclonal antibodies against tumor necrosis factor [TNF, integrin, or 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.

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.

Figure 1 Study Design Schematic



7.1 Sample Size Considerations

The primary endpoint is the change from baseline (CFB) in MMS at Week 12 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%. The resulting 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.

7.2 Randomization

After informed consent has been obtained, all participants will receive a participant identification number assigned by the ICON 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 biologics or advanced therapies for UC (Yes/ No), with the biologics or advanced therapies-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.

7.3 Types of Planned Analysis

There will be one planned interim analysis when all randomized participants either complete the induction period or discontinue the study. The purpose of the interim analysis is to compare the induction period data of NX-13 with placebo. Please refer to SAP section Interim Analysis for further details. This is the primary and final efficacy analysis for the placebo-controlled induction period.

The final analysis will be performed when all subjects complete the treatment period and all follow-up visits or discontinue from the study.

7.4 Objectives

7.4.1 Induction Period

7.4.1.1 Primary Objectives (Induction Period)

- Assess the clinical activity of oral NX-13 compared with placebo with respect to the primary efficacy endpoint of change from baseline in MMS at Week 12

7.4.1.2 Secondary Objectives (Induction Period)

- Evaluate the safety and tolerability of oral NX-13 compared with placebo over a 12-week treatment period
- Evaluate the effect of oral NX-13 compared with placebo with respect to each secondary efficacy endpoint according to SAP Section Secondary Endpoints

7.4.1.3 Exploratory Objectives (Induction Period)

- Evaluate the effect of oral NX-13 compared with placebo with respect to each exploratory efficacy endpoint in the induction period according to SAP Section Exploratory Efficacy Endpoints in Induction Period
- Evaluate the effect of oral NX-13 on pharmacokinetics over time in induction period
- Evaluate the effect of oral NX-13 on biomarker response over time in induction period

7.4.2 LTE Period

7.4.2.1 Exploratory Objectives (LTE Period)

- Evaluate the effect of oral NX-13 with respect to each exploratory efficacy endpoint over a 40-week LTE period according to SAP Section Exploratory Efficacy Endpoints in the LTE Period
- Evaluate the safety and tolerability of oral NX-13 over a 40-week LTE period
- Evaluate NX-13 plasma concentration over a 40-week LTE period
- Evaluate the effect of oral NX-13 on biomarker response over a 40-week LTE period

7.5 Estimands

7.5.1 Estimand Attributes

Objectives	Estimands
Primary	Primary estimand
• To assess the clinical activity of oral NX-13 vs placebo with respect to the primary efficacy endpoint of change from Baseline in MMS at Week 12	• Treatment of interest: NX-13 • Population of interest: subjects with moderate to severe active UC • Variable/endpoint of interest: change from baseline in MMS at Week 12 • Potential intercurrent events: subjects take UC-related prohibited medication • Strategy to address intercurrent events: using a hypothetical strategy, where subjects who take prohibited medication will be handled using a

	return-to-baseline (RTB) approach for MMS at visit on or after the intercurrent event of prohibited medication use. • A sensitivity analysis will be conducted using a treatment policy strategy where data will be analyzed as observed regardless of the intercurrent event of UC-related prohibited medication use • Population level summary: difference in mean change from baseline between NX-13 and Placebo
Secondary	Estimands

• To evaluate the safety and tolerability of oral NX-13 compared with placebo over a 12-week treatment period	• Treatment of interest: NX-13
	• Population of interest: subjects with moderate to severe active UC
	• Variable/endpoint of interest:
	  ○ TEAEs during induction period
	  ○ SAEs during induction period
	• Potential intercurrent events: not applicable
	• Strategy to address intercurrent events: not applicable
	• Population level summary: descriptive summary of proportions

	• Treatment of interest: NX-13
	• Population of interest: subjects with moderate to severe active UC
	• Variable/endpoint of interest:
	  ○ change from baseline in clinical laboratory results during induction period
	  ○ change from baseline in vital signs during induction period
	  ○ change from baseline in ECGs during induction period
	• Potential intercurrent events: not applicable
	• Strategy to address intercurrent events: not applicable
	• Population level summary: descriptive summary of change from baseline

• To evaluate the effect of oral NX-13 compared with placebo with respect to each secondary efficacy endpoint	• Treatment of interest: NX-13 • Population of interest: subjects with moderate to severe active UC

	• Variable/endpoint of interest: each secondary efficacy endpoint as defined in SAP Section Secondary Endpoints • Potential intercurrent events: subjects take UC-related prohibited medication • Strategy to address intercurrent events: using a composite strategy, where subjects who take prohibited medication will be counted as a non-responder to that secondary efficacy endpoint at visit on or after the intercurrent event of UC-related prohibited medication use. • A sensitivity analysis will be conducted using a treatment policy strategy where data will be analyzed as observed regardless of the intercurrent event of UC-related prohibited medication use • Population level summary: difference in proportion between NX-13 and Placebo
Exploratory - Induction	
• To evaluate the effect of oral NX-13 compared with placebo with respect to each binary exploratory efficacy endpoint in the induction period	• Treatment of interest: NX-13 • Population of interest: subjects with moderate to severe active UC • Variable/endpoint of interest: Each binary exploratory efficacy endpoint in induction period as defined in SAP Section Exploratory Efficacy Endpoints in Induction Period • Potential intercurrent events: subjects take UC-related prohibited medication • Strategy to address intercurrent events: using a composite strategy, where subjects who take UC-related prohibited medication will be counted as a non-responder to that endpoint at visit on or after the intercurrent event of UC-related prohibited medication use. • Population level summary: descriptive summary of proportion of subjects achieving the corresponding endpoint
• To evaluate the effect of oral NX-13 compared with placebo with respect to each continuous exploratory efficacy endpoint in the induction period	• Treatment of interest: NX-13 • Population of interest: subjects with moderate to severe active UC • Variable/endpoint of interest:

	Each continuous exploratory efficacy endpoint in induction period as defined in SAP Section Exploratory Efficacy Endpoints in Induction Period • Potential intercurrent events: subjects take UC-related prohibited medication • Strategy to address intercurrent events: using a hypothetical strategy, where subjects who take prohibited medication will be handled using a return-to-baseline (RTB) approach for the corresponding endpoint at visit on or after the intercurrent event of UC-related prohibited medication use. • Population level summary: descriptive summary of mean change from baseline

• To evaluate the effect of oral NX-13 on biomarker response over time in induction period	• Treatment of interest: NX-13
	• Population of interest: subjects with moderate to severe active UC
	• Variable/endpoint of interest:
	  ○ change from baseline in FCP during induction period
	  ○ change from baseline in CRP during induction period
	• Potential intercurrent events: not applicable
	• Strategy to address intercurrent events: not applicable
	• Population level summary: descriptive summary of change from baseline

Exploratory - LTE	Endpoints
• To evaluate the effect of oral NX-13 with respect to each binary exploratory efficacy endpoint in the LTE period	• Treatment of interest: NX-13 • Population of interest: subjects with moderate to severe active UC • Variable/endpoint of interest: each binary exploratory efficacy endpoint in LTE period as defined in SAP Section Exploratory Efficacy Endpoints in the LTE Period • Potential intercurrent events: subjects take UC-related prohibited medication • Strategy to address intercurrent events: treatment policy strategy where data will be analyzed as observed regardless of the intercurrent event of UC-related prohibited medication use

	• Population level summary: proportion of subjects achieving the corresponding endpoint
• To evaluate the effect of oral NX-13 with respect to each continuous exploratory efficacy endpoint in the LTE period	• Treatment of interest: NX-13 • Population of interest: subjects with moderate to severe active UC • Variable/endpoint of interest: each continuous exploratory efficacy endpoint in LTE period as defined in SAP Section Exploratory Efficacy Endpoints in the LTE Period • Potential intercurrent events: subjects take UC-related prohibited medication • Strategy to address intercurrent events: treatment policy strategy where data will be analyzed as observed regardless of the intercurrent event of UC-related prohibited medication use • Population level summary: descriptive summary of mean change from baseline

• To evaluate the safety and tolerability of oral NX-13 over a 40-week LTE period	• Treatment of interest: NX-13
	• Population of interest: subjects with moderate to severe active UC
	• Variable/endpoint of interest:
	  ○ TEAEs during the LTE period
	  ○ SAEs during the LTE period
	• Potential intercurrent events: not applicable
	• Strategy to address intercurrent events: not applicable
	• Population level summary: descriptive summary of proportions

	• Treatment of interest: NX-13
	• Population of interest: subjects with moderate to severe active UC
	• Variable/endpoint of interest:
	  ○ change from Week 12 in clinical laboratory results over LTE period
	  ○ change from Week 12 in vital signs over LTE period
	  ○ change from Week 12 in ECGs over LTE period
	• Potential intercurrent events: not applicable

	• Strategy to address intercurrent events: not applicable • Population level summary: descriptive Summary of change from Induction baseline and from LTE baseline

• To evaluate the effect of oral NX-13 on biomarker response over a 40-week LTE period	• Treatment of interest: NX-13
	• Population of interest: subjects with moderate to severe active UC
	• Variable/endpoint of interest:
	  ○ change from Week 12 in FCP during LTE period
	  ○ change from Week 12 in CRP during LTE period
	• Potential intercurrent events: not applicable
	• Strategy to address intercurrent events: not applicable
	• Population level summary: descriptive summary of change from Induction baseline and from LTE baseline

7.5.2 Population Sets

7.5.2.1 All Screened Subjects and LTE Entered Subjects

All screened subjects consist of all subjects who signed the informed consent form and are screened for participation in this study.

LTE entered subjects consist of all participants who are either re-randomized to the LTE period or continuing enrolment into the LTE period.

7.5.2.2 Intent-to-Treat Analysis Set and LTE Intent-to-Treat Analysis Set

All randomized participants who receive at least 1 dose of investigational product in the induction period 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 all induction efficacy analyses.

The LTE intent-to-treat analysis set (ITT) consists of all subjects who are enrolled or re-randomized into the LTE period and receive at least 1 dose of investigational product in the LTE period. Subjects will be summarized according to the randomized/assigned treatment group in the LTE period. The LTE ITT analysis set will be used for all LTE efficacy analyses.

7.5.2.3 Safety Analysis Set (SAF) and LTE Safety Analysis Set

All participants who receive at least 1 dose of investigational product in the induction period will be included in the safety analysis set (SAF), and all participants who receive at least 1 dose of investigational product in the LTE will be included in the LTE SAF. Safety analyses will be performed according to the most frequent treatment received per period, despite any differences to the intended randomized/assigned treatment.

8.0 Conventions and Derivations

8.1 Treatment Groups

The outputs for induction and long-term extension period will be labeled as follows:

For induction period:

For efficacy and safety analyses the induction treatment is of interest:

NX-13 250mg: subjects randomized/received NX-13 250mg in induction period.

NX-13 750mg: subjects randomized/received NX-13 750mg in induction period.

Pooled NX-13: subjects randomized/received either NX-13 250 mg or 750 mg in induction period.

Placebo: subjects randomized/received placebo in induction period.

Total: subjects randomized/ received either NX-13 250mg, 750mg or Placebo in induction period.

Total will not be presented for efficacy analyses.

For **long-term extension period**:

For efficacy analyses, the treatment sequence from induction to LTE is of interest:

NX-13 250mg/ NX-13 250mg: subjects randomized/received NX-13 250mg in induction and LTE period.

NX-13 750mg/ NX-13 750mg: subjects randomized/received NX-13 750mg in induction and LTE period.

Placebo/ NX-13 250mg: subjects randomized/received placebo in induction and switched to NX-13 250mg in LTE period.

Placebo/ NX-13 750mg: subjects randomized/received placebo in induction and switched to NX-13 750mg in LTE period.

Pooled NX-13: subjects randomized/received either NX-13 250mg or 750mg in LTE period.

For safety analyses, the LTE treatment is of interest:

Pooled NX-13 250mg: subjects received NX-13 250mg in LTE period.

Pooled NX-13 750mg: subjects received NX-13 750mg in LTE period

Pooled NX-13: subjects received either NX-13 250mg/ 750mg in LTE period

Actual Treatment for safety analyses:

If subjects received a kit of treatment different than the randomized kit, the actual treatment will be based on the most frequent treatment received in each period.

8.2 Baseline and Change from Baseline

Unless otherwise stated, baseline is defined as the last non-missing measurement on or prior to the date of first dose of randomized study drug.

The LTE baseline is defined as the Week 12 or the last available measurement prior to the first dose of LTE treatment.

Change from baseline at any post-baseline time point is defined as:

$$\text{Change from baseline} = \text{Observed value at post dose timepoint} - \text{Observed value at baseline}$$

$$\text{Percentage change from baseline} = \frac{\text{Observed value at post dose timepoint} - \text{Observed value at baseline}}{\text{Observed value at baseline}} * 100$$

The "percentage change from baseline" will be set to 0 if both "observed value at post dose timepoint" and "observed value at baseline" are 0.

8.3 Study Periods

Period 1 (Induction period) = Screening to Week 12 visit date, including safety follow-up visit for those who do not enter LTE or for those who do enter LTE but do not receive any LTE dose.

Period 2 (LTE period) = End of Week 12 visit date + 1 to Week 52, including LTE safety follow-up visit.

8.4 Time Points and Analysis Visit Windows

Study day 1 is defined as the date of first study drug administration. The analysis visit windows with target day and analysis visit window range are shown in **Table 1**. If more than one visit occurs within an analysis visit window then the visit that is closest to target date should be used for analysis. For the efficacy data, if there are multiple visits which are equidistant from the nominal day, use the one after the nominal day for analysis. For the safety data, if more than one visit occurs and dates are equidistant to the target date then the safety data with worst results will be used for analysis. Data collected after last dose will not be assigned to analysis visit windows and will always be shown as "Follow-up".

For identifying the worst results, check the absolute distance from the results to the lower normal limit if they are lower than the center value (average of lower normal limit and upper normal limit) or to the upper normal limit if they are greater than the center value. The value with greater distance is the worst result.

Table 1 Study Visits

Fecal Calprotectin (FCP)

FCP assessments are collected at Baseline, Week 4, Week 8, Week 12, Week 24, and Week 52.

Analysis Visit	Analysis Target Window	Analysis Window Range
Baseline	1	≤ Day 1
Week 4	29	Day 2 – Day 43
Week 8	57	Day 44 – Day 71
Week 12	85	Day 72 – last induction dose*
LTE baseline	85	Day 2 – last induction dose
Week 24	169	1st LTE dose – Day 267
Week 52	365	≥ Day 268

*The upper bound does not apply to subjects who prematurely discontinued study drug during the induction period and stayed in the study for downstream safety and efficacy assessments.

IBDQ and FACIT-F

IBDQ and FACIT-F assessments are collected at Baseline, Week 12, Week 24, and Week 52.

Analysis Visit	Analysis Target Window	Analysis Window Range
Baseline	1	≤ Day 1
Week 12	85	Day 2 – last induction dose*

LTE baseline	85	Day 2 – last induction dose
Week 24	169	1st LTE dose – Day 267
Week 52	365	≥ Day 268

*The upper bound does not apply to subjects who prematurely discontinued study drug during the induction period and stayed in the study for downstream safety and efficacy assessments.

C-reactive protein (CRP), Endoscopic Score, MMS, Geboes Score, RHI
CRP, Endoscopic Score, MMS, Geboes Score, RHI assessments are collected and assessed at Baseline, Week 12 and Week 52.
MMS includes 3 components SFS, RBS and ES. SFS and RBS are linked to ES data by CRF visit and MMS is presented based on the analysis visit windowing applied to SFS/RBS date according to the visit.

Analysis Visit	Analysis Target Window	Analysis Window Range
Baseline	1	≤ Day 1
Week 12	85	Day 2 – last induction dose*
LTE baseline	85	Day 2 – last induction dose
Week 52	365	≥ 1st LTE dose

*The upper bound does not apply to subjects who prematurely discontinued study drug during the induction period and stayed in the study for downstream safety and efficacy assessments.

Daily Diary and UC-related Prohibited Medications: Rectal Urgency, Abdominal Pain, Stool Frequency, Rectal Bleeding, and partial MMS

Diary assessments are collected at Baseline, Week 4, Week 8, Week 12, Week 18, Week 24, Week 32, Week 48 and Week 52. Daily assessments prior to a planned visit based on date were linked to that planned visit. The planned visit date is then used to apply windowing.
Partial MMS includes 2 components, SFS and RBS, and is presented based on the analysis visit windowing applied to SFS/RBS date according to the visit.
Concomitant UC-related prohibited medications up to Week 12, analysis visits will be assigned based on analysis visit window below.

Analysis Visit	Analysis Target Day	Analysis Window Range
Baseline	1	≤ Day 1
Week 4	29	Day 2 – Day 43
Week 8	57	Day 44 – Day 71
Week 12	85	Day 72 – last induction dose*
LTE baseline	85	Day 2 – last induction dose
Week 18	127	1st dose of LTE – Day 148
Week 24	169	Day 149 – Day 197
Week 32	225	Day 198 – Day 281
Week 48	337	Day 282 – Day 351

Week 52	365	≥ Day 352

*The upper bound does not apply to subjects who prematurely discontinued study drug during the induction period and stayed in the study for downstream safety and efficacy assessments.

Safety Table Windowing

Safety follow-up will be based on the scheduled clinical visit "safety follow-up".

Hematology, Chemistry

Hematology and Chemistry assessments are collected at Baseline, Week 4, Week 8, Week 12, Week 18, Week 24, Week 48 and Week 52, Safety follow-up.

Analysis Visit	Analysis Target Day	Analysis Window Range
Baseline	1	≤ Day 1
Week 4	29	Day 2 – Day 43
Week 8	57	Day 44 – Day 71
Week 12	85	Day 72 – last induction dose*
LTE baseline	85	Day 2 – last induction dose
Week 18	127	1st dose of LTE – Day 148
Week 24	169	Day 149 – Day 253
Week 48	337	Day 254 – Day 351
Week 52	365	≥ Day 352 (excluding safety follow-up)

*The upper bound does not apply to subjects who prematurely discontinued study drug during the induction period and stayed in the study for downstream safety and efficacy assessments.

Urinalysis

Urinalysis assessments are collected at Baseline, Week 8, Week 12, Week 18, Week 24, Week 48 and Week 52, Safety follow-up.

Analysis Visit	Analysis Target Day	Analysis Window Range
Baseline	1	≤ Day 1
Week 8	57	Day 2– Day 71
Week 12	85	Day 72 – last induction dose*
LTE baseline	85	Day 2 – last induction dose
Week 18	127	1st dose of LTE – Day 148
Week 24	169	Day 149 – Day 253
Week 48	337	Day 254 – Day 351
Week 52	365	≥ Day 352 (excluding safety follow-up)

*The upper bound does not apply to subjects who prematurely discontinued study drug during the induction period and stayed in the study for downstream safety and efficacy assessments.

Weight, ECG
Weight and ECG assessments are collected at Baseline, Week 12, Week 24, and Week 52.

Analysis Visit	Analysis Target Day	Analysis Window Range
Baseline	1	≤ Day 1
Week 12	85	Day 2 – last induction dose*
LTE baseline	85	Day 2 – last induction dose
Week 24	169	1st LTE dose – Day 267
Week 52	365	≥ Day 268

*The upper bound does not apply to subjects who prematurely discontinued study drug during the induction period and stayed in the study for downstream safety and efficacy assessments.

Vital Signs
Vital Signs assessments are collected at Baseline, Week 4, Week 8, Week 12, Week 18, Week 24, Week 32, Week 48 and Week 52, Safety follow-up.

Analysis Visit	Analysis Target Day	Analysis Window Range
Baseline	1	≤ Day 1
Week 4	29	Day 2 – Day 43
Week 8	57	Day 44 – Day 71
Week 12	85	Day 72 – last induction dose*
LTE baseline	85	Day 2 – last induction dose
Week 18	127	1st dose of LTE – Day 148
Week 24	169	Day 149 – Day 197
Week 32	225	Day 198 – Day 281
Week 48	337	Day 282 – Day 351
Week 52	365	≥ 352 (excluding safety follow-up)

*The upper bound does not apply to subjects who prematurely discontinued study drug during the induction period and stayed in the study for downstream safety and efficacy assessments.

8.5 Dates of First and Last Dose of Study Drug

Subjects are dispensed study treatment at each visit, starting with Day 1 (Week 0) and at each subsequent visit.

Date of first dose of study drug:

- The date of first dose of study drug will be the first dose date recorded on the Dose Exposure (Visit 2) page of the CRF.
- The date of first dose of study drug in the LTE will be the last dose date on the Dose Exposure (Visit 5) page of the CRF + 1.

Date of last dose of study drug:

- Date of last dose of study drug will be the date collected on the End of Treatment page of the CRF. If date of last dose of study drug is not available and subject is lost to follow-up based on End of Treatment CRF page then use the latest date where a dose is recorded.

- The date of the last dose of study drug in the induction period will be the date of the last dose of study drug on Dose Exposure (Visit 5).

8.6 Imputation of Partial Dates

Missing or partial dates will only be imputed to determine the timing of AEs or concomitant medications in relation to study drug dosing and death date. The original, non-imputed, dates will be retained in the clinical trial database and will be included in subject listings that accompany the CSR. Please refer to Appendix 2: Imputation Rules for Partial or Missing Dates.

8.7 Efficacy Assessment and Derivation

8.7.1 Modified Mayo Score (MMS)

MMS includes 3 components: SFS, RBS, and ES. SFS and RBS are taken from the participant e-diary where each subject will record their RBS and SFS on a daily basis. ES is taken from the central reader. Total score ranges from 0 to 9, with higher scores indicating more severe disease activity. The 3 components and scores are described in **Table 2**:

Table 2 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)	

8.7.2 Modified Mayo Score Calculation

The SF and RB will be collected in the e-diary during the 14 days prior to the visit.

Initially the focus will be on the diary data within 7 days prior to the visit. Diary entries obtained during preparation for an endoscopy, the day of an endoscopy, or the day after an endoscopy will be excluded from MMS calculation.

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(3) If there is not enough usable diary data within 7 days prior to the visit, data from the 14-day diary will be used, applying step 1 and step 2.

(4) ES is taken directly from the central reader.

(5) Total MMS will be calculated based on the sum of each subscore for end of induction period (visit 5) and end of long term extension period (visit 10). Total MMS = average stool frequency subscore + average rectal bleeding subscore + endoscopy subscore.

The total MMS will be missing if any subscores are missing. Examples of subscore calculations are shown in **Table 3**.

Table 3 RBS or SFS Subscore Calculation Example

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8.7.3 Geboes and Robarts Histopathology Index Scoring Calculation

The Geboes scores and Robarts Histopathology Index scores are collected at baseline, end of induction period (visit 5/EOT), and end of LTE period (visit 10/EOT). The Geboes scoring system is a stepwise ordinal grading system for histological assessment of disease severity in UC. The Geboes score includes 7 histological items (Grade 0 – Grade 5) summed to a continuous variable, ranging from 0 to 22. Each of these seven subscoring items is evaluated individually on a scale from 0 to 3 except for the surface epithelia injury, which is evaluated on a scale from 0 to 4. Please refer to Appendix 5: Geboes Scoring System. Higher Geboes scores indicate more severe disease. The sum will be missing if any individual grade is missing.

The Robarts Histopathology Index (RHI) score is used to assess the disease severity. The RHI is defined as the sum of four weighted items from Geboes: Grade 1: lamina propria chronic inflammation; Grade 2B: lamina propria neutrophils; Grade 3: epithelial neutrophils; Grade 5: surface epithelial injury. The weights are provided as Robarts Multiplier in Appendix 6: Robart Histopathology Index. Higher RHI scores indicate more severe disease. The total score will be calculated based on the non-missing Geboes grades. The sum will be considered as missing if any Geboes grade is missing. Please refer to the following example:

RHI Score = Geboes Grade 1 Score + 2 * Geboes Grade 2B Score + 3 * Geboes Grade 3 Score + 5 * Geboes Grade 5 Score

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8.7.4 Inflammatory Bowel Disease Questionnaire (IBDQ) Scoring

The Inflammatory Bowel Disease Questionnaire (IBDQ-32) is a disease-specific health-related quality of life (HRQOL) instrument for patients with IBD. IBDQ-32 is collected at baseline, end of induction period (visit 5/EOT), and end of LTE period (visit 10/EOT). 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 of 32 to 224 (with higher scores indicating better HRQOL). IBDQ-32 items are provided in Appendix 7: Domains of the 32-Item Inflammatory Bowel Disease Questionnaire (IBDQ-32). If subjects are missing one out of 32 items, then the affected IBDQ domain score and IBDQ total score will be missing.

8.7.5 Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) Scoring

The Functional Assessment of Chronic Illness Therapy (FACIT) instrument is a comprehensive compilation of questions that measure HRQOL in patients with chronic illnesses. FACIT-F is collected at baseline, end of induction period (visit 5/EOT), and end of LTE period (visit 10/EOT). The tool comprises 13 questions. The responses are each recorded on a 5-point Likert scale. Scores range from 0 to 52, with lower scores

representing greater fatigue. The FACIT-F items are provided in Appendix 8: Functional Assessment of Chronic Illness Therapy – Fatigue.

At least 7 out of 13 questions must be answered to calculate the FACIT-F score. If less than 7 questions are answered, the FACIT-F score will be missing. The detailed guidelines for calculating the FACIT-F, following the FACIT-Fatigue Subscale Scoring Guidelines, are outlined below:

Instructions:

1. Record answers in "item response" column. If missing, mark with an X
2. Perform reversals as indicated and sum individual items to obtain a score.
3. Multiply the sum of the item scores by the number of items in the subscale, then divide by the number of items answered. This produces the subscale score.
4. The higher the score, the better the quality of life.

Subscale	Item Code	Reverse item?		Item Response	Item Score
FATIGUE SUBSCALE	HI7	4	-	_____	=_____
	HI12	4	-	_____	=_____
	An1	4	-	_____	=_____
	An2	4	-	_____	=_____
Score range: 0-52	An3	4	-	_____	=_____
	An4	4	-	_____	=_____
	An5	0	+	_____	=_____
	An7	0	+	_____	=_____
	An8	4	-	_____	=_____
	An12	4	-	_____	=_____
	An14	4	-	_____	=_____
	An15	4	-	_____	=_____
	An16	4	-	_____	=_____

Sum individual item scores: _____
Multiply by 13: _____
Divide by number of items answered:_____
=Fatigue Subscale score

8.7.6 Rectal Urgency and Abdominal Pain Questionnaire Scoring

The Rectal Urgency and Abdominal Pain Questionnaire describes the subject's key symptoms with moderate to severe rectal urgency and abdominal pain within a 24-hour recall period. Subjects record their rectal urgency and abdominal pain in the e-diary on a daily basis. The rectal urgency is recorded on a 5-point scale. Abdominal pain is recorded on a 11-point rating scale. The details are provided in Appendix 3: Rectal Urgency and Abdominal Pain Questionnaire. Diary entries obtained during preparation for an endoscopy, the day of an endoscopy, or the day after an endoscopy will be excluded from average rectal urgency calculation and mode of rectal urgency score.

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8.7.7 Glucocorticoid-free Remission

One additional exploratory endpoint will also be analyzed as the proportion of subjects achieving glucocorticoid-free remission at Week 52, which is defined as subjects with clinical remission per MMS (MMS ≤ 2 with RBS = 0, SFS ≤ 1 and not greater than baseline, and endoscopy score ≤ 1) at Week 52 and with no glucocorticosteroids/glucocorticoids (CS) use at Week 52 among subjects with CS use at baseline.

CS use at baseline:

- 'Yes' if subjects had medication (started before and ongoing at 1st induction dose), under CRF CM page Category for Medication: Corticosteroids.
- Otherwise “No”.

CS use at Week 52:

- At Week 52, it is defined as a 90 day period on or prior to the MMS analysis date.
- 'Yes' if subjects taking any CS during the 90 day period on or prior to the MMS analysis date, under CM page Category for Medication: Corticosteroids.
- “No” if subjects not taking any CS during the 90 day period on or prior to the MMS analysis date, under CM page Category for Medication: Corticosteroids.

8.8 Efficacy Endpoints

8.8.1 Primary Efficacy Endpoint:

The primary endpoint is defined as change from baseline in Modified Mayo Score (MMS) at Week 12.

8.8.2 Secondary Efficacy Endpoints

1. Proportion of subjects achieving **clinical remission per MMS** at Week 12.

   Clinical remission per MMS is defined as achieving MMS ≤2, with RBS = 0, SFS ≤ 1 and not greater than baseline, and endoscopy score ≤ 1.

2. Proportion of subjects achieving **MMS ≤ 2** at Week 12.

   Please refer to SAP Section Modified Mayo Score Calculation

3. Proportion of subjects achieving **RHI ≤ 3** at Week 12.

   Please refer to SAP Section Geboes and Robarts Histopathology Index Scoring Calculation

4. Proportion of subjects achieving **clinical response per MMS** at Week 12.

   Clinical response per MMS is defined as: ≥ 2 points and ≥30 % decrease from baseline in MMS with ≥ 1 point decrease in RBS or RBS ≤ 1. Please refer to SAP Modified Mayo Score Calculation

5. Proportion of subjects achieving **endoscopic response** at Week 12.

   Endoscopic response is defined as findings of endoscopy score ≤ 1.

6. Proportion of subjects achieving **endoscopic remission** at Week 12.

   Endoscopic remission is defined as findings of endoscopy score = 0.

7. Proportion of subjects achieving **endoscopic-histologic mucosal improvement** at Week 12.

Endoscopic-histologic Mucosal Improvement is defined as findings of endoscopy score ≤ 1 and Geboes score < 2.0. Geboes Scoring is defined in SAP section Geboes and Robarts Histopathology Index Scoring Calculation .

8. Proportion of subjects achieving **histologic endoscopic mucosal improvement (HEMI)** at Week 12.

HEMI is defined as endoscopy score ≤ 1 and Geboes score ≤ 3.1

9. Proportion of subjects achieving **histologic endoscopic mucosal remission (HEMR)** at Week 12.

HEMR is defined as endoscopy score = 0 and Geboes score < 2.0.

10. Proportion of subjects achieving **symptomatic remission** at Week 12.

Symptomatic remission is defined as RBS = 0 and (i) SFS = 0, or (ii) SFS = 1 with baseline SFS ≥ 2.

11. Proportion of subjects achieving **clinical response per partial MMS** at Week 4.

Clinical response per partial MMS is defined as ≥ 1 points and ≥ 30% decrease from baseline in partial MMS (total score of RBS and SFS) with ≥ 1 point decrease in RBS or RBS ≤ 1

12. Proportion of subjects achieving **abdominal pain = 0** at Week 12.

Please refer to SAP Section Rectal Urgency and Abdominal Pain Questionnaire Scoring for abdominal pain calculation.

13. Proportion of subjects achieving **rectal urgency = 0** at Week 12.

Please refer to Section Rectal Urgency and Abdominal Pain Questionnaire Scoring for rectal urgency calculation.

8.8.3 Exploratory Efficacy Endpoints in Induction Period

Secondary endpoints 10 to 13 will also be analyzed at each visit where the variable is collected during the induction period (i.e., Week 4, 8, and 12, when applicable) to explore the efficacy over time. The number and percentage of subjects achieving clinical outcomes (endpoints 10 to 13) will also be shown as bar plots by visit during the induction period.

Other exploratory efficacy endpoints to be analyzed for the Induction Period are as follows:

Continuous exploratory endpoints:

- Change from baseline SFS (SAP Section Modified Mayo Score Calculation)
- Change from baseline RBS (SAP Section Modified Mayo Score Calculation)
- Change from baseline RHI (SAP Section Rectal Urgency and Abdominal Pain Questionnaire Scoring)
- Change from baseline ES
- Change from baseline IBDQ (including total and domain score) (SAP Section Inflammatory Bowel Disease Questionnaire (IBDQ) Scoring)

- Change from baseline FACIT-F (SAP Section Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) Scoring)

  Change from baseline abdominal pain score (SAP Section Rectal Urgency and Abdominal Pain Questionnaire Scoring for rectal urgency calculation)

- Change from baseline FCP and CRP

Ordinal exploratory endpoints:

- Shift from baseline in rectal urgency score (SAP Section Rectal Urgency and Abdominal Pain Questionnaire Scoring for rectal urgency calculation)

8.8.4 Exploratory Efficacy Endpoints in the LTE Period

Continuous exploratory endpoints:

- Change from LTE baseline MMS (SAP Section Modified Mayo Score Calculation)
- Change from baseline MMS (SAP Section Modified Mayo Score Calculation)
- Change from LTE baseline SFS (SAP Section Modified Mayo Score Calculation)
- Change from baseline SFS (SAP Section Modified Mayo Score Calculation)
- Change from LTE baseline RBS (SAP Section Modified Mayo Score Calculation)
- Change from baseline RBS (SAP Section Modified Mayo Score Calculation)
- Change from LTE baseline RHI (SAP Section Rectal Urgency and Abdominal Pain Questionnaire Scoring)
- Change from baseline RHI (SAP Section Rectal Urgency and Abdominal Pain Questionnaire Scoring)
- Change from LTE baseline ES
- Change from baseline ES
- Change from LTE baseline IBDQ (including total and domain score) (SAP Section Inflammatory Bowel Disease Questionnaire (IBDQ) Scoring)
- Change from baseline IBDQ (including total and domain score) (SAP Section Inflammatory Bowel Disease Questionnaire (IBDQ) Scoring)
- Change from LTE baseline FACIT-F (SAP Section Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) Scoring)
- Change from baseline FACIT-F (SAP Section Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) Scoring)
- Change from LTE baseline abdominal pain score (SAP Section Rectal Urgency and Abdominal Pain Questionnaire Scoring for rectal urgency calculation)
- Change from baseline abdominal pain score (SAP Section Rectal Urgency and Abdominal Pain Questionnaire Scoring for rectal urgency calculation)
- Change from LTE baseline FCP and CRP
- Change from baseline FCP and CRP

Ordinal exploratory endpoints:

- Shift from LTE baseline in rectal urgency score (SAP Section Rectal Urgency and Abdominal Pain Questionnaire Scoring for rectal urgency calculation)

- Shift from baseline in rectal urgency score (SAP Section Rectal Urgency and Abdominal Pain Questionnaire Scoring for rectal urgency calculation)

Binary exploratory endpoints:

- Proportion of subjects with clinical remission per MMS at week 52
- Proportion of subjects with MMS ≤ 2 at Week 52
- Proportion of subjects with RHI ≤ 3 at Week 52
- Proportion of subjects with clinical response per MMS at Week 52
- Proportion of subjects with endoscopic response at Week 52
- Proportion of subjects with endoscopic remission at Week 52
- Proportion of subjects with endoscopic-histologic mucosal improvement at Week 52
- Proportion of subjects with histologic endoscopic mucosal improvement at Week 52
- Proportion of subjects with histologic endoscopic mucosal remission at Week 52
- Proportion of subjects with symptomatic remission at each scheduled visit during LTE period
- Proportion of subjects with clinical response per partial MMS at each scheduled visit during LTE period
- Proportion of subjects with abdominal pain = 0 at each scheduled visit during LTE period
- Proportion of subjects with rectal urgency = 0 at each scheduled visit during LTE period
- Proportion of subjects with glucocorticoid-free remission at Week 52 (SAP section Glucocorticoid-free Remission)

9.0 Interim Analysis

An interim analysis will be performed when all randomized participants either complete the induction period or discontinue the study.

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10.0 Statistical Methods

10.1 General Consideration

Quantitative displays will be summarized using descriptive statistics. The number of subjects, mean, standard deviation, median, minimum, and maximum will be provided. Decimal precision will be based on the mean value. The median contains the same number of decimal places as the mean, the standard deviation contains one more decimal place, and the minimum and maximum contain one less decimal place. The mean will typically have one more decimal place than the raw values, but if necessary, decimal precision for the mean will be provided in the table specifications.

Categorical variables will be summarized using counts and percentages. Percentages will be rounded to one decimal place, except 100% will be displayed without any decimal places and percentages will not be displayed for zero counts.

All analyses will use SAS version 9.4, or higher.

The treatment sequence will be presented as sub-headers in all listings, when applicable. Tables and figures will be presented following the treatment groups described in the SAP section Treatment Groups.

10.2 Subjects Population Sets

Subjects' assignments to population sets defined in SAP Section Population Sets will be summarized for all screened subjects during induction period. The population set table will be repeated during the LTE period for subjects who opted to participate in the LTE period. Summaries will be presented by treatment and overall. A by-subject listing of population set assignments will also be provided for all randomized subjects.

10.3 Subject Disposition

For induction period, subject disposition table will be summarized for all screened subjects.

- Number and percentage of subjects non-randomized and the reasons for non-randomization
- Number and percentage of subjects randomized and treated
- Number and percentage of subjects who completed induction treatment
- Number and percentage of subjects who discontinued induction treatment and reasons for treatment discontinuation
- Number and percentage of subjects who completed induction period
    - Data is based on CRF form "End of 12-Week Induction Period"
- Number and percentage of subjects who did not complete induction period and reasons for study discontinuation
- Number and percentage of subjects who completed induction period and did not continue into LTE period
- Number and percentage of subjects who continue into LTE period

For LTE period, subject disposition will be tabulated for subjects who opted to participate in the LTE period.

- Number of subjects entered/re-randomized
- Number and percentage of subjects treated
- Number and percentage of subjects who completed LTE treatment
- Number and percentage of subjects who discontinued LTE treatment and reasons for treatment discontinuation
- Number and percentage of subjects who completed LTE period
- Number and percentage of subjects who did not complete LTE period and reasons for study discontinuation

Listings will be provided for induction/LTE treatment completion and discontinuation as well as study completion and discontinuation data using the randomized set. An additional eligibility assessment listing will be presented based on screened subjects. Randomization details as well as mis-stratified subjects will also be listed based on randomized subjects.

A tabulation of the number and percentage of subjects enrolled at each country will be presented.

10.4 Demographic and Baseline Characteristics

Subject demographics will be summarized descriptively by treatment using the ITT population set. In addition, baseline characteristics of UC history will be summarized by treatment group. Data will also be provided in a listing.

Demographics:

- Age at Informed Consent (in years)
- Age Group (18 -64 Years, 65 Years and Above)
- Gender (Female, Male)
- Race (American Indian or Alaska Native, Black or African American, White, Native Hawaiian or Other Pacific Islander, Asian, Other, Not Reported, Unknown)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown)
- Baseline weight: Taken from randomization visit, and if not present then take from the screening visit
- Baseline height: Taken from the screening visit
- Baseline BMI: derived as baseline weight (kg) / (screening height (cm) /100)^2

Baseline ulcerative colitis characteristics:

- Duration of UC (in years): Informed Consent (IC) Date – UC diagnosis date / 365.25. If either date is partially missing, apply the following derivation methods:

Observed	Missing	Derivation
D, M, Y		(Date of IC - Date of UC Diagnosis)/365.25
M, Y	D	[Year(Date of IC) – Year(Date of UC Diagnosis)] + [Month (Date of IC) – Month(Date of UC Diagnosis)]/12
Y	D and M	Year (Date of IC) – Year (Date of UC Diagnosis)

- Basis for Diagnosis (Endoscopy, Histology, Imaging)
- Maximum extent of disease (endoscopy) (Only the rectum, Left sided colitis, Entire colon)
- Prior hospitalization for UC (Yes, No)
- Number of Hospitalizations for UC in last 12 months
- Prior UC related surgery (Yes, No)
- Number of UC related surgeries
- Baseline stool frequency for 24 hours
- Baseline MMS
- Baseline MMS (<=7, >7)
- Baseline SFS
- Baseline RBS
- Baseline endoscopic score (0,1,2,3)

- Baseline RHI
- Baseline Geboes score
- Baseline abdominal pain
- Baseline rectal urgency
- Baseline use of concomitant glucocorticoids (Yes, No)
- Stratification variable: prior exposure to biologics or advanced therapies for UC
    - Prior use of biologics or advanced therapies (Yes, No) based on IRT data
    - Prior exposure to biologics or advanced therapies (Yes, No) based on Prior/Concomitant CRF page:
        - Refer to SAP section Prior and Concomitant Medications to find prior medication: medication started before the first induction dose.
        - Prior exposure to biologics or advanced therapies for UC use will be categorized as 'Yes' if subjects had any prior medication, with the response to the question 'Category for Medication: Biologic or Advanced Therapies' and 'Primary Reason Medication was Discontinued: Inadequate Response, Intolerance, Loss of Response, or Other.
        - Otherwise, prior exposure to biologics or advanced therapies for UC will be categorized as 'No' for all randomized subjects.
- Prior failure to biologics or advanced therapies (Yes, No) based on Prior/Concomitant CRF page:
        - Refer to SAP section Prior and Concomitant Medications to find prior medication: medication started before the first induction dose.
        - Prior failure to biologics or advanced therapies for UC use will be categorized as 'Yes' if subjects had any prior medication, with the response to the question 'Category for Medication: Biologic or Advanced Therapies' and 'Primary Reason Medication was Discontinued: Inadequate Response, Intolerance, or Loss of Response.
        - Otherwise, prior failure to biologics or advanced therapies for UC will be categorized as 'No' for all randomized subjects.
- Use of baseline Immunosuppressant (Yes, No)
- Prior exposure to anti-TNF (Yes, No)
- Prior failure to anti-TNF (Yes, No)
- Median UC disease duration (years) (≤ Median, > Median)
- Baseline CRP (mg/L) (≤5, >5)
- Baseline FCP (ug/g) (≤250, >250)
- Number of prior use of biologics or advanced therapies (0, 1, 2, 3, 4, ⩾5.)
- Number of prior failure of biologics or advanced therapies (0, 1, 2, 3, 4, ⩾5.)

Listings of the demographic and baseline characteristics will also be presented.

General medical history consisting of prior medical history (ended prior to screening) and current medical history (ongoing at screening), will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). and tabulated by system organ class (SOC) and preferred term (PT) by treatment group using

the ITT Analysis Set. A listing of medical history will be presented. The actual version of the MedDRA coding dictionary will be noted in the statistical tables and clinical study report.

10.5 Treatments

10.5.1 Extent of Study Drug Exposure

The extent of exposure will be characterized according to the number of subjects exposed, the number of doses taken derived by number of tablets, the duration of exposure derived by dosing date and study drug compliance. Subjects are expected to take 3 tablets once per day. Summary statistics will be provided by treatment for each period using the SAF analysis set, and LTE SAF. All dosing and compliance data will be provided as data listings.

If a subject does not return the container, then this dispensation event will be excluded in the calculation for the total number of doses taken and total compliance.

10.5.1.1 Summary of Dosing

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10.5.1.1 Treatment Duration

Treatment duration (days) = date of last dose – date of first dose + 1.

For duration of exposure in the induction period:

- The last dose of study drug in the induction period will be used for the above calculation

For duration of exposure in the LTE period:

- The date of first dose of study drug in the LTE period will be used for the above calculation

Please refer to SAP Section Dates of First and Last Dose of Study Drug for further details.

10.5.1.2 Compliance

Treatment compliance will be determined from data captured on the Drug Accountability eCRF.

$$\text{Number of expected doses} = \text{date of the last dose} - \text{date of first dose} + 1$$

Treatment compliance will be derived for each period. Compliance is defined as:

$$\text{Percentage Compliance} = \left(\frac{\text{Number of dose taken}}{\text{Number of expected doses}}\right)\text{x}100$$

Compliance for each period will be calculated by sum of doses taken divided by sum of expected doses by treatment group. The number and percentage of subjects with <75%, 75% to 100%, and >100% compliance will be provided by treatment group for each period.

10.5.2 Prior and Concomitant Medications

Prior medications are defined as any medication discontinued prior to the first dose of study treatment. Prior UC and non-UC medications will be summarized separately by treatment. Prior UC medications are identified by a response other than Not Applicable to the question “ONLY FOR UC: Primary Reason Medication was Discontinued” on the Prior/Concomitant CRF page.

Concomitant medications for induction period are defined as any medication

- started on or after the first induction dose and before 1st LTE dose for those who continue in LTE, or

- started on or after the first induction dose and on or before last induction dose for those who don't continue in LTE, or
- prior medication ongoing at the first dose of study medication in induction period.

Concomitant medications for LTE period are defined as any medication

- started on or after the first LTE dose and on or before last LTE dose, or
- prior medication (including concomitant induction medication) ongoing at the first dose of study medication in LTE period.

Medications will be coded using the World Health Organization (WHO) medical dictionary, categorized by Anatomical Therapeutic Chemical (ATC) Classification and summarized by preferred name for the ITT and LTE ITT set. Concomitant medication will be summarized by treatment. A listing of prior and concomitant medications as well as post-study drug discontinuation medications, e.g, starting in safety follow-up period after last dose, will also be presented.

10.5.2.1 Intercurrent Events of UC-Related Prohibited Medication Use

According to protocol section 6, subjects are required to avoid taking prohibited medications at the time of randomization and throughout the study. Only a stable dose of permitted therapy is allowed.

Medications that are considered UC-related prohibited medications include, but not limited to, the ones listed in the SAP section Appendix 11: UC-Related Prohibited Medication. A listing of subjects who take any form of these medications during the induction period will be prepared for the medical team to adjudicate at the blinded data review meeting. Subjects who are deemed to take UC-related prohibited medications which potentially impact the induction efficacy analysis will be identified and finalized at the blinded data review meeting prior to the interim database lock.

The start date of any UC-related prohibited medication use based on medical adjudication will be linked to the relevant clinical visits to determine the occurrence of intercurrent events.

Subjects who take UC-related prohibited medications will be listed and will be summarized in a cumulative manner by visit.

10.6 International Conference on Harmonisation (ICH) Protocol Deviations

All deviations will be identified through medical reviews and by clinical research associates during site monitoring. Subsequently they will be categorized, designated as International Conference on Harmonisation (ICH) deviations potentially impacting efficacy and safety assessments if appropriate, finalized, and agreed with the sponsor prior to interim and final database lock. Please refer to Appendix 10: ICH Protocol Deviation Categories for additional details.

ICH deviations will be tabulated by categories for each period using the ITT Analysis Set, and LTE ITT Analysis Set. All ICH deviations will be listed based on randomized set.

10.7 Efficacy Analyses

ITT analysis set will be used for efficacy analyses. Subject listings for efficacy endpoints will also be produced.

10.7.1 Hypothesis Testing Strategy and Multiplicity

For each statistical comparison, the p-value will be presented. No adjustments will be made for multiplicity.

10.7.2 Primary Estimand

The primary estimand includes 5 attributes defined as following:

- Treatment of interest: NX-13
- Population of interest: subjects with moderate to severe active UC

- Variable/endpoint of interest: **change from baseline in Modified Mayo Score** (MMS) at Week 12
- Strategy to address intercurrent events: using a hypothetical strategy, where subjects who take UC-related prohibited medication will be handled using a return-to-baseline (RTB) approach for MMS at visit on or after the intercurrent event of UC-related prohibited medication use.
- Population level summary: difference in mean change from baseline between NX-13 and Placebo

10.7.2.1 Imputation Methods

Subjects who had the MMS at Week 12 missing will be handled using the RTB approach.

10.7.2.2 Primary Analysis

The primary outcome is the change from baseline in MMS at Week 12. Descriptive statistics will be provided for MMS at baseline, Week 12 and change from baseline at Week 12 by treatment using the ITT Analysis Set.

The clinical question of interest is whether the primary endpoint for pooled NX-13 is superior to placebo at 12 weeks. The null and alternative hypothesis is defined as follows:

$H_o: \mu_t - \mu_p \geq 0$

$H_a: \mu_t - \mu_p < 0$

where μ_t is the mean change from baseline in MMS with NX-13 and μ_p is the mean change from baseline in MMS with placebo. A negative estimate for treatment difference (Active treatment – Placebo) indicates a larger reduction in MMS for NX-13 than for Placebo.

The change from baseline in MMS will be based on analysis of covariance (ANCOVA) model with fixed factor of treatment, prior exposure to biologics or advanced therapies for UC based on CRF CM data, and baseline MMS as covariate.

The least-square mean (LSM) and 90% confidence interval (CI) will be presented for each treatment group. The LSM difference between each NX-13 treatment group and placebo with associated 90% CI will be presented as well as the p-value for the pooled NX-13 vs placebo comparison. Please refer to the following sas code as example:

CCI

[redacted]

10.7.2.3 Sensitivity Analysis

A sensitivity analysis will be conducted based on ITT Analysis Set using a treatment policy strategy where data will be analyzed as observed regardless of the intercurrent event of UC-related prohibited medication use.

10.7.3 Secondary Estimands

The secondary estimands include 5 attributes defined as following:

- Treatment of interest: NX-13
- Population of interest: subjects with moderate to severe active UC
- Variable/endpoint of interest with respect to each secondary endpoint as defined in SAP Section Secondary Endpoints
- Potential intercurrent events: subjects take UC-related prohibited medication
- Strategy to address intercurrent events: using a composite strategy, treating subjects who take UC-related prohibited medication as non-responders (NRs) to the corresponding efficacy outcomes
- Population level summary: difference in proportions between NX-13 and Placebo

10.7.3.1 Imputation Methods

Missing data will be imputed using the non-responder imputation (NRI) approach.

10.7.3.2 Secondary Analysis

Secondary endpoints and relevant clinical assessments/derivations are described in SAP Secondary Endpoints

The clinical question of interest is whether the secondary endpoint for pooled NX-13 is superior to placebo at 12 weeks. The null and alternative hypothesis is defined as follows:

$H_o: P_t - P_p \leq 0$

$H_a: P_t - P_p > 0$

where P_t is the proportion of subjects achieving the secondary endpoint with NX-13 and P_p is the proportion of subjects achieving the secondary endpoint with placebo.

The proportion of subjects achieving each secondary endpoint will be presented by treatment group. Missing data will be considered as NR. Subjects who take UC-related prohibited medication will be counted as non-responders at visits on or after the intercurrent event of UC-related prohibited medication use. The count and percentage of subjects with UC-related prohibited medication use will also be provided.

The unadjusted risk difference (using chisq method) and adjusted (for prior biologics or advanced therapies use) risk difference between each NX-13 treatment group and placebo, as well as the associated 90% CIs will be presented using CMH method. The p-value for the pooled NX-13 vs placebo comparison will be presented. Please refer to the following sas code:

CCI

CCI [redacted]

This applies to all other binary secondary efficacy endpoints, e.g. clinical response, endoscopic response, endoscopic remission, endoscopic-histologic mucosal improvement, symptomatic remission, etc.

10.7.3.3 Sensitivity Analysis

A sensitivity analysis will be conducted based on ITT Analysis Set using a treatment policy strategy where data will be analyzed as observed regardless of the intercurrent event of UC-related prohibited medication use.

10.7.4 Other Exploratory Efficacy Analyses

Of note, secondary endpoints 10 to 13 will also be analyzed at each visit where the variable is collected during the induction period (i.e., Week 4, 8, and 12, when applicable) to explore the efficacy over time, using the same methods to handle missing data and ICEs. The number and percentage of subjects achieving clinical outcomes (endpoints 10 to 13) will be presented in summary tables and bar plots by visit during the induction period.

The continuous endpoints specified in SAP Section Exploratory Efficacy Endpoints in Induction Period will be summarized at each visit where the variable is collected during the induction period, using the same methods to handle missing data and ICEs as for the primary endpoint of change from baseline in MMS at Week 12.

Exploratory efficacy analyses in the induction period will be conducted based on the ITT analysis set.

Similarly, each LTE exploratory endpoint will be analyzed for the LTE period based on the ITT LTE and will also be summarized by subjects' clinical response per MMS at LTE baseline:

- Overall
- Clinical response per MMS at LTE baseline: yes
- Clinical response per MMS at LTE baseline: No
    - If missing clinical response at LTE baseline, it will be considered as no
    - If subjects take UC-related prohibited medication, it will also be considered as no

Clinical response per MMS is defined SAP Section Secondary Endpoints.

The LTE exploratory efficacy endpoints in LTE Period specified in SAP section Exploratory Efficacy Endpoints in the LTE Period will be summarized based on the treatment policy strategy where data is analyzed as observed regardless of the intercurrent event of UC-related prohibited medication use.

Please refer to Appendix 1: Summary of Efficacy Endpoints for the specific method.

10.7.4.1 Continuous Exploratory Analyses

For continuous exploratory endpoints, the summary statistics (including mean, median, standard deviation, minimum, and maximum) will be presented for change from baseline variables. For endpoints during the LTE period, change from LTE baseline will also be presented.

10.7.4.2 Binary Exploratory Analyses

The descriptive summary of numbers and proportions for binary exploratory endpoints will be summarized by treatment group.

10.7.5 Pharmacokinetic (PK) Analyses

Not applicable for SAP.

10.7.6 Biomarkers and Other Assessments of Disease Activity

Post-dosing biomarker results (e.g., FCP, CRP) will be summarized descriptively at each visit along with change from baseline for induction period using ITT analysis set. For the LTE period, change from LTE baseline will also be presented using LTE ITT analysis set.

10.7.7 Subgroup Analysis

Subgroup analysis will be conducted for the primary and secondary endpoints using the same analysis methods previously described (RTB with hypothetical strategy to handle ICE (for continuous endpoints) and NR with composite strategy to handle ICE (for binary endpoints) approaches), unless otherwise specified.

Forest plots will display the LS mean difference (continuous endpoints) or unadjusted risk difference (binary endpoints) between NX-13 and placebo, with a 90% confidence interval, for every subgroup.

The baseline subgroups include:

1) Prior use of biologics or advanced therapies based on CRF data: yes vs no. For this subgroup analysis, biologic/advanced use will not be included in the analysis model.
2) Prior failure of biologics or advanced therapies: yes vs no
    - 'Yes' if subject has medication, under CRF CM page ONLY FOR UC: Primary Reason Medication was Discontinued: inadequate response, loss of response or intolerance
    - 'No' otherwise
3) Use of baseline corticosteroid: yes vs no
    1) 'Yes' if subjects had medication (started before and ongoing at 1st induction dose), under CRF CM page Category for Medication: Corticosteroids.
    2) 'No' otherwise
4) Use of baseline immunosuppressant:
    i) 'Yes', if subject has medication (started before and ongoing at 1st induction dose), among ATC4 coded terms (ATC4CD) from SAP Section Appendix 9: WHO Drug Codes and ATC Coded Terms for Immunosuppressant and anti-TNF: "Coded names for Immunosuppressant"
5) Baseline MMS: ≤7 vs >7
6) Prior exposure to anti-TNF: yes or no
    i) Yes', if subject has medication started before the first induction dose under category "biologics/advanced therapies" among ATC4 coded terms (ATC4CD) from SAP Section Appendix 9: WHO Drug Codes and ATC Coded Terms for Immunosuppressant and anti-TNF:" "Coded names for anti-TNF".
7) Prior failure to anti-TNF: yes or no
    i) Yes', if subject has medication started before the first induction dose under category "biologics/advanced therapies" among ATC4 coded terms(ATC4CD) from SAP Section Appendix 9: WHO Drug Codes and ATC Coded Terms for Immunosuppressant and anti-TNF: "Coded names for anti-TNF" and under the corresponding CRF CM page of such anti-TNF: Primary Reason Medication was Discontinued: inadequate response, loss of response or intolerance.
8) Median UC disease duration (years): ≤x vs >x, x is the median disease duration derived using the ITT population
9) Baseline CRP (mg/L): ≤5 vs >5

10) Baseline FCP (mg/kg): ≤250 vs >250

Due to small count of the subgroups, the fixed factor of prior exposure to biologics or advanced therapies for UC based on CRF CM data will be removed in the subgroup ANCOVA model for the primary efficacy endpoint. Likewise, these stratification factors will not be controlled, and a chi-square test will be performed in the subgroup analysis for all secondary endpoints in the Induction Period.

10.8 Safety Analyses

Safety analyses will be conducted on the SAF and LTE SAF. Safety data including TEAEs, SAEs, clinical laboratory values, vital signs, and ECG findings will be summarized by treatment for each period.

10.8.1 Adverse Events

The collection of adverse event information starts after the time of informed consent. All AEs will be coded to a preferred term (PT) and system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA).

Treatment-emergent adverse events (TEAEs) are defined as AEs that occur after the subject received first dose of study treatment or if a pre-existing condition worsens in severity or becomes serious after receiving the first dose of study treatment until 21 days after the date and time of last dose of study drug.

AE (including deaths) dates will be imputed according to algorithms detailed in SAP Section Imputation of Partial Dates. The imputed date of AE onset will be used to assess whether AEs should be considered as treatment-emergent and included in the safety summaries. The original, partial dates will be included in data listings.

If the relationship is missing for an adverse event, the adverse event will be categorized as related. Severity is assessed using toxicity grades. If the toxicity grade is missing for an event, the event will be categorized as Grade 3 (Severe).

Each TEAE will be assigned to either the induction period or the LTE period based on the AE start date:

- If the start date of the TEAE is prior to the date of first dose in the LTE period then the TEAE will be assigned to the induction period.
- If the start date of the TEAE is on or after the first dose in the LTE period then the TEAE will be assigned to the LTE period.

An overall summary of TEAEs will be presented for each period including the number and percentage of subjects, as well as the number of events, reporting:

- at least one TEAE
- at least one Toxicity Grade 3 or Higher TEAE
- at least one TEAE related to drug
- at least one Toxicity Grade 3 or Higher TEAE related to drug
- TEAE resulting in death
    - Death is defined as adverse events with a toxicity grade of 5 or with an outcome of death.
- at least one serious adverse event (SAE)
- at least one SAE related to drug
- at least one TEAE leading to treatment interruption
- at least one TEAE leading to discontinuation from the treatment
- at least one TEAE leading to discontinuation from the study

This overall summary of TEAEs will also be presented across the induction and LTE periods, among subjects from the SAF who were randomized and received either dose of NX-13 from the beginning of the trial.

TEAEs will be presented by the number and percentage of subjects with each event, categorized by SOC and PT. Summary tables will be reported in decreasing frequency based on the total column. Counting for frequency analysis will be performed by subject and not by AEs, and subjects will only be counted once for recurring AEs within each SOC or PT. However, the number of total AEs per subject, including multiple occurrences of individual AEs, will also be presented.

The summary of TEAEs will be provided for the following:

- TEAEs by SOC and PT
- Related TEAEs by SOC and PT
- Toxicity Grade 3 or Higher TEAE by SOC and PT
- Related Toxicity Grade 3 or Higher TEAE by SOC and PT
- TEAEs resulting in death by SOC and PT
- SAEs by SOC and PT
- Related SAEs by SOC and PT
- TEAEs experienced by > 5% of Subjects by PT
- Non-Serious TEAEs experienced by > 5% of Subjects by PT
- TEAEs Leading to Treatment Interruption by SOC and PT
- TEAEs Leading to Treatment Discontinuation by SOC and PT
- TEAEs Leading to Study Discontinuation by SOC and PT

TEAEs will also be summarized by maximum toxicity grade, including Grade 1 (Mild), Grade 2 (Moderate), Grade 3 (Severe), Grade 4 (Serious), Grade 5 (Death). For each event, subjects are summarized according to the most severe event among the events of that preferred term. A subject who had a mild and a severe event of the same preferred term will be summarized as severe for that event. The following summary will be provided:

- TEAE by SOC, PT and maximum Toxicity Grade

A tabulation of these data, categorized by relationship (Related, Not Related) to the study drug, will be presented. For each event, subjects are summarized according to the relationship among the events of that preferred term reported. A subject who had a related and a non-related event of the same preferred term will be summarized as related for that event. The following summary will be provided:

- TEAE by SOC, PT and Relationship

All adverse events (including TEAE and pre-treatment AE), SAEs and AEs leading to treatment discontinuation will be provided in separate listings. All deaths, whether adverse events with an outcome of death or subjects reporting study discontinuation due to death, will be provided in a listing.

10.8.1.1 Exposure Adjusted Event Rate (EAER)

TEAEs with EAER will be presented for each period. The same summary will also be presented across the induction and LTE periods, among subjects from the SAF who were randomized and received either dose of NX-13 from the beginning of the trial.

Total exposure time in days = sum of exposure days, date of last dose – date of first dose + 1, and for subjects who did not continue to the LTE period, including 21 days after last dose of study drug.

Event rate per 100 person-years of exposure (ER/100 P-Y): 100*365.25*(total number of events)/total exposure time in days.

The descriptive summary will include total number of events, PY of exposure including 21 days after the last dose of study drug, and the event rate per 100 person-years of exposure.

The following EAER summary will be provided:

- Overall Summary of TEAEs
- TEAEs by SOC and PT
- Related TEAEs by SOC and PT
- SAEs by SOC and PT
- TEAEs Leading to Treatment Discontinuation by SOC and PT

10.8.2 Laboratory Data

Clinical laboratory tests consist of hematology, serum chemistry, and urinalysis. Laboratory parameters will be summarized using the International System (SI) of Units. Data will be summarized by visit, and treatment for each period. The following summaries will be provided for each parameter:

- Values at baseline, each visit, and change from baseline values as well as change from LTE baseline for LTE period for continuous parameters.
- For categorical parameters (urinalysis tests), the number and percentage of subjects with each value by visit will be provided.

Grading status e.g. low, normal and high will be used to assess whether the laboratory test results are below, within, or above the reference range. The minimum, maximum and last post-baseline result grading per period for each parameter will be assessed. The following 3 shift tables will be provided for hematology and chemistry laboratory tests, respectively:

- Shift summary of lab results from baseline to the minimum post-baseline result
- Shift summary of lab results from baseline to the maximum post-baseline result
- Shift summary of lab results from baseline to the last post-baseline result

Number and percentage of subjects who meet the potential drug induced liver injury (DILI) criteria per period:

CCI [redacted]

Laboratory data values of the form of “< x” (i.e., below the lower limit of quantification) or > x (i.e., above the upper limit of quantification) will be imputed as “x” but displayed as “< x” or “> x” in the listings.

Listings will be provided for hematology, serum chemistry, coagulation, urinalysis, serology, urine pregnancy, tuberculosis test results and stool samples.

10.8.3 Vital Signs

Vital signs including weight, heart rate, systolic and diastolic blood pressure, and temperature will be summarized by visit, and treatment, for each period. The following summaries will be provided for each parameter:

- Values at baseline, each visit, and change from baseline as well as change from LTE baseline for LTE period;
- Number and percentage of subjects who meet the potential clinically significant criteria:

CCI [redacted]

Vital signs listing, including weight, will be provided using Safety Analysis Set.

10.8.4 ECGs

12-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, the standard formula to calculate QTcF interval = $(\frac{QT}{\frac{1}{RR^3}})$ where RR interval = $\frac{60}{\text{Heart Rate}}$

ECG parameters will be summarized by visit including baseline and change from baseline as well as change from LTE baseline for LTE period, with descriptive statistics by treatment.

Listings will also be provided for ECGs.

10.8.4.1 Potentially Clinically Significant (PCS) ECGs Results

Subjects with PCS ECG will also be summarized by treatment group and split by period if they meet the following criteria:

CCI [redacted]

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[redacted]

10.8.5 Physical Examinations

A listing will be provided for physical examinations using Safety Analysis Set.

11.0 Appendix

Appendix 1: Summary of Efficacy Endpoints

Endpoints	Outcome Measure	Timepoint	Analyses	Analysis Set	Statistical Method	Endpoint/ Analysis[a]
MMS	CFB	Baseline->W12 (Baseline, W12)	Summary of Change from Baseline in MMS	ITT	ANCOVA	Primary/ RTB, AO
	Proportion of MMS ≤ 2	Baseline->W12 (W12)	Summary of MMS ≤ 2	ITT	CMH	Secondary/ NR, AO
	Proportion of subjects with clinical response (≥ 2 points and ≥30 % decreases from baseline in MMS with ≥ 1 point decrease in RBS or RBS ≤ 1)	Baseline->W12 (W12)	Summary of Clinical Response per MMS	ITT	CMH	Secondary/ NR, AO
	Proportion of subjects with clinical remission per MMS (RBS = 0, SFS ≤ 1 and not greater than baseline and ES ≤ 1)	Baseline->W12 (W12)	Summary of clinical remission per MMS	ITT	CMH	Secondary/ NR, AO
	Proportion of subjects with clinical response per partial MMS (≥ 1 points and ≥ 30 % decrease from baseline in partial MMS with ≥ 1 point decrease in RBS or RBS ≤ 1)	Baseline->W4 (W4)	Summary of Clinical Response per Partial MMS	ITT	CMH	Secondary/ NR, AO
		Baseline->W12 (W4, W8. W12)	Summary of Clinical Response per Partial MMS over time	ITT	CMH	Exploratory/ NR
RHI	Proportion of subjects with RHI ≤ 3	Baseline->W12 (W12)	Summary of RHI ≤ 3	ITT	CMH	Secondary/ NR, AO
	CFB	Baseline->W12 (Baseline, W12)	Summary of Change from Baseline in RHI	ITT	Summary Statistics	Exploratory/ RTB
ES	Proportion of subjects with endoscopic response (ES ≤ 1)	Baseline->W12 (W12)	Summary of Endoscopic Response	ITT	CMH	Secondary/ NR, AO
	Proportion of subjects with endoscopic remission (ES = 0)	Baseline->W12 (W12)	Summary of Endoscopic Remission	ITT	CMH	Secondary/ NR, AO

Endpoints	Outcome Measure	Timepoint	Analyses	Analysis Set	Statistical Method	Endpoint/ Analysis[a]
	CFB	Baseline->W12 (Baseline, W12)	Summary of Change from Baseline in Endoscopy	ITT	Summary Statistics	Exploratory/ RTB
ES + Geboes score	Proportion of subjects with endoscopic-histologic mucosal improvement (ES ≤ 1 and Geboes score < 2.0)	Baseline->W12 (W12)	Summary of Endoscopic-histologic Mucosal Improvement	ITT	CMH	Secondary/ NR, AO
	Proportion of subjects with histologic endoscopic mucosal remission (HEMI) (ES ≤ 1 and Geboes score ≤ 3.1)	Baseline->W12 (W12)	Summary of Histologic Endoscopic Mucosal Remission (HEMI)	ITT	CMH	Secondary/ NR, AO
	Proportion of subjects with histologic endoscopic mucosal remission (HEMR) (ES = 0 and Geboes score < 2.0)	Baseline->W12 (W12)	Summary of Histologic Endoscopic Mucosal remission (HEMR)	ITT	CMH	Secondary/ NR, AO
RBS+SFS	Proportion of subjects with symptomatic remission (RBS = 0, AND SFS = 0, or SFS = 1 for Baseline SFS>=2)	Baseline->W12	Summary of Symptomatic Remission at Week 12	ITT	CMH	Secondary/ NR, AO
		Baseline->W12 (Baseline, W4, W8, W12)	Summary of Symptomatic Remission Over Time	ITT	CMH	Exploratory/ NR
SFS	CFB	Baseline->W12 (Baseline, W4, W8, W12)	Summary of Change from Baseline in SFS	ITT	Summary Statistics	Exploratory/ RTB
RBS	CFB	Baseline->W12 (Baseline, W4, W8, W12)	Summary of Change from Baseline in RBS	ITT	Summary Statistics	Exploratory/ RTB

Endpoints		Outcome Measure	Timepoint	Analyses	Analysis Set	Statistical Method	Endpoint/ Analysis[a]
HRQOL	IBDQ	CFB	Baseline->W12 (Baseline, W12)	Summary of Change from Baseline in IBDQ	ITT	Summary Statistics	Exploratory/ RTB
	FACIT-F	CFB	Baseline->W12 (Baseline, W12)	Summary of Change from Baseline in FACIT-F	ITT	Summary Statistics	Exploratory/ RTB
	Rectal Urgency	Shift from baseline	Baseline->W12 (Baseline, W4, W8, W12)	Summary of Shift from Baseline in Rectal Urgency	ITT	Summary Statistics	Exploratory/ RTB
		Proportion of subjects achieving rectal urgency = 0	Baseline->W12 (W12)	Summary of Rectal Urgency	ITT	CMH	Secondary/ NR, AO
			Baseline->W12 (Baseline, W4, W8, W12)	Summary of Rectal Urgency	ITT	CMH	Exploratory/ NR, AO
	Abdominal Pain	CFB	Baseline->W12 (Baseline, W4, W8, W12)	Summary of Change from Baseline in Abnormal Pain	ITT	Summary Statistics	Exploratory/ RTB
		Proportion of subjects achieving abdominal pain = 0	Baseline->W12 (W12)	Summary of Abdominal Pain	ITT	CMH	Secondary/ NR, AO
			Baseline->W12 (Baseline, W4, W8, W12)	Summary of Abdominal Pain	ITT	CMH	Exploratory / NR
Biomarker Response	FCP	CFB	Baseline->W12 (Baseline, W4, W8, W12)	Summary of Change from Baseline in FCP	ITT	Summary statistics	Exploratory/ RTB

Endpoints		Outcome Measure	Timepoint	Analyses	Analysis Set	Statistical Method	Endpoint/ Analysis[a]
	CRP	CFB	Baseline->W12 (Baseline, W12)	Summary of Change from Baseline in CRP	ITT	Summary statistics	Exploratory/ RTB
MMS		Change from LTE baseline by clinical response per MMS at week 12	W12->W52 (LTE baseline, W52)	Summary of Change from LTE Baseline in MMS	LTE ITT	Summary Statistics	Exploratory/ AO
		CFB by clinical response per MMS at week 12	Baseline->W52 (Baseline, W52)	Summary of Change from Baseline in MMS	LTE ITT	Summary Statistics	Exploratory/ AO
		Proportion of subjects with MMS ≤ 2 at Week 52 by clinical response per MMS at Week 12	W12->W52 (W 52)	Summary of MMS ≤ 2	LTE ITT	Summary Statistics	Exploratory/ AO
		Proportion of subjects with clinical response per MMS at Week 52 by clinical response per MMS at Week 12	W12->W52 (W 52)	Summary of Clinical Response per MMS	LTE ITT	Summary Statistics	Exploratory/ AO
		Proportion of subjects with clinical remission per MMS by clinical response per MMS at Week 12	W12->W52 (W 52)	Summary of Clinical Remission per MMS	LTE ITT	Summary Statistics	Exploratory/ AO
		Proportion of subjects with clinical response per partial MMS (≥ 1 points and ≥ 30 % decrease from baseline in partial MMS with ≥ 1 point decrease in RBS or RBS ≤ 1)	W12->W52 (W18,W24, W32, W48, W52)	Summary of Clinical Response per Partial MMS	ITT	Summary Statistics	Exploratory / AO
		Proportion of subjects with clinical remission and not taking glucocorticoids by clinical response per MMS at Week 12	W52	Summary of Glucocorticoid-Free Remission	LTE ITT	Summary Statistics	Exploratory/ AO
RHI		Proportion of subjects with RHI ≤ 3 by clinical	W12->W52 (W 52)	Summary of RHI ≤ 3	LTE ITT	Summary Statistics	Exploratory/ AO

Endpoints	Outcome Measure	Timepoint	Analyses	Analysis Set	Statistical Method	Endpoint/ Analysis[a]
	response per MMS at Week 12					
	Change from LTE baseline by clinical response per MMS at week 12	W12->W52 (LTE Baseline, W52)	Summary of Change from LTE Baseline in RHI	LTE ITT	Summary Statistics	Exploratory/ AO
	CFB by clinical response per MMS at Week 12	Baseline->W52 (Baseline, W12, W52)	Summary of Change from Baseline in RHI	LTE ITT	Summary Statistics	Exploratory/ AO
ES	Proportion of subjects with endoscopic response (ES ≤ 1) by clinical response per MMS at Week 12	W12->W52 (W 52)	Summary of Endoscopic Response	LTE ITT	Summary Statistics	Exploratory/ AO
	Proportion of subjects with endoscopic remission (ES = 0) by clinical response per MMS at Week 12	W12->W52 (W 52)	Summary of Endoscopic Remission	LTE ITT	Summary Statistics	Exploratory/ AO
	Change from LTE baseline by clinical response per MMS at week 12	W12->W52 (W 52)	Summary of Change from LTE Baseline in ES	LTE ITT	Summary Statistics	Exploratory/ AO
	CFB by clinical response per MMS at Week 12	Baseline->W52 (Baseline, W12, W52)	Summary of Change from Baseline in ES	LTE ITT	Summary Statistics	Exploratory/ AO
ES + Geboes score	Proportion of subjects with endoscopic-histologic mucosal improvement (ES ≤ 1 and Geboes score < 2) by clinical response per MMS at Week 12	W12->W52 (W 52)	Summary of Endoscopic-Histologic Mucosal Improvement	LTE ITT	Summary Statistics	Exploratory/ AO
	Proportion of subjects with histologic endoscopic	W12->W52 (W52)	Summary of HEMI	LTE ITT	Summary Statistics	Exploratory/ AO

Endpoints		Outcome Measure	Timepoint	Analyses	Analysis Set	Statistical Method	Endpoint/ Analysis[a]
		mucosal improvement (HEMI) by clinical response per MMS at Week 12					
		Proportion of subjects achieving histologic endoscopic mucosal remission (HEMR) by clinical response per MMS at Week 12	W12->W52 (W 52)	Summary of HEMR	LTE ITT	Summary Statistics	Exploratory/ AO
SFS + RBS		Proportion of subjects with symptomatic remission (RBS = 0, SFS = 0, or SFS = 1) by clinical response per MMS at Week 12	W12->W52 (LTE baseline, W18, W24, W32, W48, W52)	Summary of Symptomatic Remission	LTE ITT	Summary Statistics	Exploratory/ AO
SFS		Change from LTE baseline by clinical response per MMS at Week 12	W12->W52 (LTE baseline, W18, W24, W32, W48, W52)	Summary of Change from LTE Baseline in SFS	LTE ITT	Summary Statistics	Exploratory/ AO
		CFB by clinical response per MMS at Week 12	Baseline -> W52 (Baseline, W4, W8, W12, W18, W24, W32, W48, W52)	Summary of Change from Baseline in SFS	LTE ITT	Summary Statistics	Exploratory/ AO
RBS		Change from LTE baseline by clinical response per MMS at Week 12	W12->W52 (LTE baseline, W18, W24, W32, W48, W52)	Summary of Change from LTE Baseline in RBS	LTE ITT	Summary Statistics	Exploratory/ AO
		CFB by clinical response per MMS at Week 12	Baseline -> W52 (Baseline, W4, W8, W12, W18, W24, W32, W48, W52)	Summary of Change from Baseline in RBS	LTE ITT	Summary Statistics	Exploratory/ AO
HRQOL	IBDQ	Change from LTE baseline by clinical response per MMS at Week 12	W12->W52 (LTE Baseline, W24, W52)	Summary of Change from LTE Baseline in IBDQ	LTE ITT	Summary statistics	Exploratory/ AO
		CFB by clinical response per MMS at Week 12	Baseline -> W52	Summary of Change from Baseline in IBDQ	LTE ITT	Summary statistics	Exploratory/ AO

Endpoints		Outcome Measure	Timepoint	Analyses	Analysis Set	Statistical Method	Endpoint/ Analysis[a]
			(LTE Baseline, W12, W24, W52)				
	FACIT-F	Change from LTE baseline by clinical response per MMS at Week 12	W12->W52 (LTE Baseline, W24, W52)	Summary of Change from LTE Baseline in FACIT-F	LTE ITT	Summary statistics	Exploratory/ AO
		CFB by clinical response per MMS at Week 12	Baseline -> W52 (LTE Baseline, W12, W24, W52)	Summary of Change from Baseline in FACIT-F	LTE ITT	Summary statistics	Exploratory/ AO
	Rectal Urgency	Shift from LTE baseline by clinical response per MMS at Week 12	W12->W52 (LTE baseline, W18, W24, W32, W48, W52)	Summary of Shift from LTE Baseline in Rectal Urgency	LTE ITT	Summary statistics	Exploratory/ AO
		Shift from baseline by clinical response per MMS at Week 12	Baseline -> W52 (Baseline, W4, W8, W12, W18, W24, W32, W48, W52)	Summary of Shift from Baseline in Rectal Urgency	LTE ITT	Summary statistics	Exploratory/ AO
		Proportion of subjects achieving rectal urgency = 0 by clinical response per MMS at Week 12	W12->W52 (LTE baseline, W18, W24, W32, W48, W52)	Summary of Rectal Urgency	LTE ITT	Summary statistics	Exploratory/ AO
	Abdominal Pain	Change from LTE baseline by clinical response per MMS at Week 12	W12->W52 (LTE baseline, W18, W24, W32, W48, W52)	Summary of Change from LTE Baseline in Abdominal Pain	LTE ITT	Summary statistics	Exploratory/ AO
		CFB by clinical response per MMS at Week 12	Baseline -> W52 (Baseline, W4, W8, W12, W18, W24, W32, W48, W52)	Summary of Change from Baseline in Abdominal Pain	LTE ITT	Summary statistics	Exploratory/ AO
		Proportion of subjects achieving abdominal pain = 0 by clinical response per MMS at Week 12	W12->W52 (LTE baseline, W18, W24, W32, W48, W52)	Summary of Abdominal Pain	LTE ITT	Summary statistics	Exploratory/ AO
Biomarker Response	FCP	Change from LTE baseline by clinical response per MMS at Week 12	W12->W52 (LTE baseline, W24, W52)	Summary of Change from LTE Baseline in FCP	LTE ITT	Summary statistics	Exploratory/ AO

Endpoints		Outcome Measure	Timepoint	Analyses	Analysis Set	Statistical Method	Endpoint/ Analysis[a]
		CFB by clinical response per MMS at Week 12	Baseline -> W52 (Baseline, W4, W8, W12, W24, W52)	Summary of Change from Baseline in FCP	LTE ITT	Summary statistics	Exploratory/ AO
	CRP	Change from LTE baseline by clinical response per MMS at Week 12	W12->W52 (LTE Baseline, W52)	Summary of Change from LTE Baseline in CRP	LTE ITT	Summary statistics	Exploratory/ AO
		CFB by clinical response per MMS at Week 12	Baseline -> W52 (Baseline, W12, W52)	Summary of Change from Baseline in CRP	LTE ITT	Summary statistics	Exploratory/ AO

Note: subgroup analysis will be repeated for the primary and secondary endpoints using primary approach (RTB/NR).
a. AO = as observed; RTB = return to baseline for subjects with ICE/missing endpoints results; NR for binary variable = non-responder with ICE/missing endpoints results

CCI

[redacted]

Appendix 3: Rectal Urgency and Abdominal Pain Questionnaire

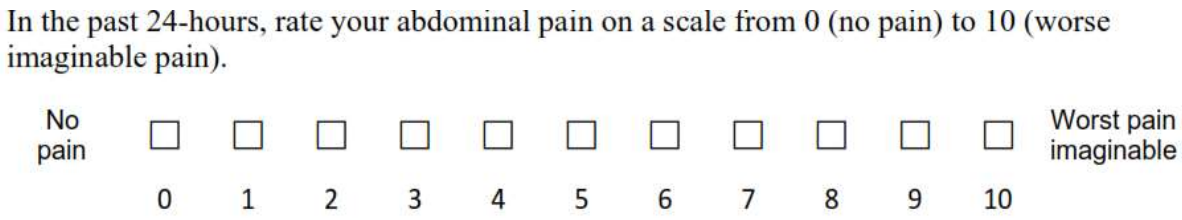
Rectal Urgency Score:

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).



Appendix 4: 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)	

Appendix 5: Geboes Scoring System

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

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.

Appendix 7: Domains of the 32-Item Inflammatory Bowel Disease Questionnaire (IBDQ-32)

The questions are grouped into four categories and response options are consistently presented as seven-point scales:

- Bowel symptoms (B),
- Systemic symptoms (S),
- Emotional function (E)
- Social function (SF).

(B) 1. How frequent have your bowel movements been during the last two weeks? Please indicate how frequent your bowel movements have been during the last two weeks:

- 1 BOWEL MOVEMENTS AS OR MORE FREQUENT THAN THEY HAVE EVER BEEN
- 2 EXTREMELY FREQUENT
- 3 VERY FREQUENT
- 4 MODERATE INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
- 5 SOME INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
- 6 SLIGHT INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
- 7 NORMAL, NO INCREASE IN FREQUENCY OF BOWEL MOVEMENTS

For the remaining 31 items, the response options are:

- 1 ALL OF THE TIME
- 2 MOST OF THE TIME
- 3 A GOOD BIT OF THE TIME
- 4 SOME OF THE TIME
- 5 A LITTLE OF THE TIME
- 6 HARDLY ANY OF THE TIME
- 7 NONE OF THE TIME

(S) 2. How often has the feeling of fatigue or of being tired and worn out been a problem for you during the last two weeks?

(E) 3. How often during the last two weeks have you felt frustrated, impatient, or restless?

(SF) 4. How often during the last two weeks have you been unable to attend school or work because of your bowel problem?

(B) 5. How much of the time during the last two weeks have your bowel movements been loose?

(S) 6. How much energy have you had during the last two weeks?

(E) 7. How often during the last two weeks did you feel worried about the possibility of needing to have surgery because of your bowel problem?

(SF) 8. How often during the last two weeks have you had to delay or cancel a social engagement because of your bowel problem?

(B) 9. How often during the last two weeks have you been troubled by cramps in your abdomen?

(S) 10. How often during the last two weeks have you felt generally unwell?

(E) 11. How often during the last two weeks have you been troubled because of fear of not finding a washroom?

(SF) 12. How much difficulty have you had, as a result of your bowel problems, doing leisure or sports activities you would have liked to have done during the last two weeks?

(B) 13. How often during the last two weeks have you been troubled by pain in the abdomen? (S) 14. How often during the last two weeks have you had problems getting a good night's sleep, or been troubled by waking up during the night?

(E) 15. How often during the last two weeks have you felt depressed or discouraged?

(SF) 16. How often during the last two weeks have you had to avoid attending events where there was no washroom close at hand?

(B) 17. Overall, in the last two weeks, how much of a problem have you had with passing large amounts of gas?

(S) 18. Overall, in the last two weeks, how much of a problem have you had maintaining, or getting to, the weight you would like to be at?

(E) 19. Many patients with bowel problems often have worries and anxieties related to their illness. These include worries about getting cancer, worries about never feeling any better, and worries about have a relapse. In general, how often during the last two weeks have you had felt worried or anxious?

(B) 20. How much of the time during the last two weeks have you been troubled by a feeling of abdominal bloating?

(E) 21. How often during the last two weeks have you felt relaxed and free of tension?

(B) 22. How much of the time during the last two weeks have you had a problem with rectal bleeding with your bowel movements?

(E) 23. How much of the time during the last two weeks have you felt embarrassed as a result of your bowel problem?

(B) 24. How much of the time during the last two weeks have you been troubled by a feeling of having to go to the bathroom even though your bowels are empty?

(E) 25. How much of the time during the last two weeks have you felt tearful or upset?

(B) 26. How much of the time during the last two weeks have you been troubled by accidental soiling of your underpants?

(E) 27. How much of the time during the last two weeks have you felt angry as a result of your bowel problem?

(SF) 28. To what extent has your bowel problem limited sexual activity during the last two weeks?

B) 29. How much of the time during the last two weeks have you been troubled by feeling sick to your stomach?

(E) 30. How much of the time during the last two weeks have you felt irritable?

(E) 31. How often during the last two weeks have you felt lack of understanding from others?

(E) 32. How satisfied, happy, or pleased have you been with your personal life during the past two weeks

Appendix 8: Functional Assessment of Chronic Illness Therapy – Fatigue

FACIT Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

Appendix 9: WHO Drug Codes and ATC Coded Terms for Immunosuppressant and anti-TNF

Coded names for Immunosuppressant:

Drug Code: 001138022080 Drug Name: **ACH METHOTREXATE**

WHO ATC

Display 10 15 20 30 50 100 200 500 1000 5000

ATC Code	ATC Level	ATC Text	Official ATC Code	Year,Quarter	Preferred Term	Preferred Term Code
G02CX	4	OTHER GYNECOLOGICALS		20,3	METHOTREXATE SODIUM	001138020019
L01BA	4	FOLIC ACID ANALOGUES	*	85,4	METHOTREXATE SODIUM	001138020019
L04AX	4	OTHER IMMUNOSUPPRESSANTS	*	04,1	METHOTREXATE SODIUM	

WHO ATC
2024MAR01_GLB_B3

Drug Code: 000015010010 Drug Name: **AZATHIOPRINE**

WHO ATC

Display 10 15 20 30 50 100 200 500 1000 5000

ATC Code	ATC Level	ATC Text	Official ATC Code	Year,Quarter	Preferred Term	Preferred Term Code
L04AX	4	OTHER IMMUNOSUPPRESSANTS	*	85,4	AZATHIOPRINE	000015010010

1 - 1

Spread Sheet

WHO ATC
2024MAR01_GLB_B3

Drug Code: 005497010107 Drug Name: **CYCLOSPORINE**

WHO ATC Levels

ATC Code	ATC Level	ATC Text
L	1	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS
L04	2	IMMUNOSUPPRESSANTS
L04A	3	IMMUNOSUPPRESSANTS
L04AD	4	CALCINEURIN INHIBITORS

1 - 4

Drug Code: 012199010120 Drug Name: **TACRO [TACROLIMUS]**

WHO ATC Levels

ATC Code	ATC Level	ATC Text
L	1	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS
L04	2	IMMUNOSUPPRESSANTS
L04A	3	IMMUNOSUPPRESSANTS
L04AD	4	CALCINEURIN INHIBITORS

1 - 4

Drug Code: 000911010445 Drug Name: UNION MERCAPTOPURINE

WHO ATC

Display 10 15 20 30 50 100 200 500 1000 5000

ATC Code	ATC Level	ATC Text	Official ATC Code	Year,Quarter	Preferred Term	Preferred Term Code
L01BB	4	PURINE ANALOGUES	*	85,4	MERCAPTOPURINE	000911010015

1 - 1

WHO ATC
2024MAR01_GLB_B3

Drug Code: 001845010022 Drug Name: THIOGUANINE

WHO ATC

Display 10 15 20 30 50 100 200 500 1000 5000

ATC Code	ATC Level	ATC Text	Official ATC Code	Year,Quarter	Preferred Term	Preferred Term Code
L01BB	4	PURINE ANALOGUES	*	85,4	TIOGUANINE	001845010014

Coded term for anti-TNFs:

Drug Code: 014456010017 Drug Name: **INFLIXIMAB**
WHO ATC

Display 10 15 20 30 50 100 200 500 1000 5000

ATC Code	ATC Level	ATC Text	Official ATC Code	Year,Quarter	Preferred Term	Preferred Term Code
L04AB	4	TUMOR NECROSIS FACTOR ALPHA (TNF-) INHIBITORS	*	99,3	INFLIXIMAB	014456010017

1 - 1

Drug Code: 016129010019 Drug Name: **ADALIMUMAB**
WHO ATC

Display 10 15 20 30 50 100 200 500 1000 5000

ATC Code	ATC Level	ATC Text	Official ATC Code	Year,Quarter	Preferred Term	Preferred Term Code
L04AB	4	TUMOR NECROSIS FACTOR ALPHA (TNF-) INHIBITORS	*	03,2	ADALIMUMAB	016129010019

1 - 1

Drug Code: 062611010018 Drug Name: **GOLIMUMAB**
WHO ATC

Display 10 15 20 30 50 100 200 500 1000 5000

ATC Code	ATC Level	ATC Text	Official ATC Code	Year,Quarter	Preferred Term	Preferred Term Code
L04AB	4	TUMOR NECROSIS FACTOR ALPHA (TNF-) INHIBITORS	*	10,1	GOLIMUMAB	062611010018

1 - 1

Drug Code: 014456090027 Drug Name: **AVSOLA [INFLIXIMAB AXXQ]**
WHO ATC

Display 10 15 20 30 50 100 200 500 1000 5000

ATC Code	ATC Level	ATC Text	Official ATC Code	Year,Quarter	Preferred Term	Preferred Term Code
L04AB	4	TUMOR NECROSIS FACTOR ALPHA (TNF-) INHIBITORS	*	20,1	INFLIXIMAB AXXQ	014456090019

1 - 1

Drug Code: 014456010082 Drug Name: **INFLECTRA [INFLIXIMAB]**
WHO ATC

Display 10 15 20 30 50 100 200 500 1000 5000

ATC Code	ATC Level	ATC Text	Official ATC Code	Year,Quarter	Preferred Term	Preferred Term Code
L04AB	4	TUMOR NECROSIS FACTOR ALPHA (TNF-) INHIBITORS	*	99,3	INFLIXIMAB	014456010017

1 - 1

Drug Code: 016129090011 Drug Name: **ADALIMUMAB BIOSIMILAR 1**
WHO ATC

Display 10 15 20 30 50 100 200 500 1000 5000

ATC Code	ATC Level	ATC Text	Official ATC Code	Year,Quarter	Preferred Term	Preferred Term Code
L04AB	4	TUMOR NECROSIS FACTOR ALPHA (TNF-) INHIBITORS	*	21,3	ADALIMUMAB BIOSIMILAR 1	016129090011

1 - 1

Appendix 10: ICH Protocol Deviation Categories

ICH Deviations
Category 1: Subject entered into the study even though she/he did not satisfy entry criteria
Category 2: Subject who developed withdrawal criteria during the study and were not withdrawn
Category 3: Subject who received wrong treatment or incorrect dose
Category 4: Subject who received excluded or prohibited concomitant treatment

Appendix 11: UC-Related Prohibited Medication

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13.0 Glossary of Abbreviations

Glossary of Abbreviations:	
AE	Adverse Event
AO	As observed
ATC	Anatomic Therapeutic Classification
CRF	Case Report Form
CSR	Clinical Study Report
DILI	Drug Induced Liver Injury
ECG	Electrocardiogram
EOT	End of Treatment
ES	Endoscopic Subscore
FACIT-F	Functional Assessment of Chronic Illness Therapy – Fatigue
FCP	Fecal Calprotectin
HRQOL	Health-related Quality of Life
IBDQ	Inflammatory Bowel Disease Questionnaire

ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IRT	Interactive Response Technology
ITT	Intention-to-treat
LTE	Long-term Extension
MMS	Modified Mayo Score
NR	Non-Responder
PD	Pharmacodynamic
PK	Pharmacokinetic
PP	Per Protocol
QTcF	Fridericia's corrected QT
RBS	Rectal Bleeding Subcore
RHI	Robarts Histopathology Index
RTB	Return-to-Baseline
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SFS	Stool Frequency Subscore
UC	Ulcerative Colitis