EMERALD

STATISTICAL ANALYSIS PLAN

Protocol Title:	**A Phase 2a, Open-label, Single-arm Study to Evaluate the Efficacy, Safety, and Tolerability of MORF-057 in Adults with Moderate to Severe Ulcerative Colitis (EMERALD-1)**
Protocol Number:	MORF-057-201
Phase:	Phase 2a
Sponsor:	Morphic Therapeutic, Inc. 35 Gatehouse Drive, A2 Waltham, MA 02451 United States

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Approval of Statistical Analysis Plan for Study MORF-057-201

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2. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Only abbreviations and terms relevant to the statistical analysis plan (SAP) are repeated herein. The reader is referred to the protocol for the complete and comprehensive list of abbreviations and definitions of terms for the study.

Abbreviation or specialist term	Explanation
ADaM	Analysis Data Model
Adj R^2	adjusted coefficient of determination
AE	adverse event
AI_{AUC}	accumulation index based upon AUC_{tau} (AUC_{tau}/AUC_{0-12})
AI_{Cmax}	accumulation index based upon $C_{max,ss}$ ($C_{max,ss}/C_{max}$)
ALT	alanine transaminase
AST	aspartate transaminase
ATC	Anatomical Therapeutic Chemical
AUC	area under the concentration-time curve
AUC_{0-12}	area under the plasma concentration-time curve from time zero (0) to 12 hours post-dose
AUC_{0-inf}	area under the plasma concentration-time curve from time 0 extrapolated to infinity
AUC_{0-t}	area under the plasma concentration-time curve from time 0 to the last measured concentration post-dose
AUC_{tau}	area under the plasma concentration-time curve across the dosing interval (t = [redacted])
[redacted]	[redacted]
BLQ	below the limit of quantification
BMI	body mass index
C_{12}	plasma concentration at 12 hours post-dose
C_{ave}	average plasma concentration based on [redacted]
CCR9	C-C chemokine receptor 9
CD	Crohn's Disease
C. diff	Clostridium difficile
CDISC	Clinical Data Interchange Standards Consortium
C_{last}	last temporal measured plasma concentration post-dose
CL/F	apparent total body clearance after single dose oral administration
CL_{ss}/F	apparent total body clearance at steady state after oral administration

Abbreviation or specialist term	Explanation
C_{max}	maximum observed plasma concentration post-dose
$C_{max,ss}$	maximum observed plasma concentration post-dose at steady state
CRF	case report form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	trough plasma concentrations obtained at the end of the dosing interval (12 hours post-dose)
CV	coefficient of variation
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
EOT	end of treatment
FAS	Full Analysis Set
hs-CRP	high sensitivity C reactive protein
ICF	Informed Consent Form
ICH	International Council for Harmonization
IRT	Inventory and Resupply Technology
$Lambda_z$ (λ_z)	apparent first-order terminal elimination phase rate constant
LOCF	last observation carried forward
$\lambda_{z,f}$	apparent functional first-order elimination phase rate constant
LLOQ	lower limit of quantification
LS	lymphocyte subsets
MCS	Mayo Clinic Score
MedDRA	Medical Dictionary for Regulatory Activities
MES	Mayo Endoscopic Subscore
mRNA	messenger ribonucleic acid
NCA	non-compartmental analysis
NI	Nancy Index
PD	pharmacodynamics
PGA	Physician's Global Assessment
PIMS	physiological intermolecular modulation spectroscopy
PK	pharmacokinetics

Abbreviation or specialist term	Explanation
PML	progressive multifocal leukoencephalopathy
PO	by mouth
PP	Per Protocol
PT	Preferred Term
QTcF	QT interval corrected using Fridericia's formula
RHI	Robarts Histopathology Index
RNA	ribonucleic acid
RO	receptor occupancy
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus
SCR	screening
SD	standard deviation
SDTM	Study Data Tabulation Model
SFU	safety follow-up
SoA	schedule of activity
SOC	system organ class
$t_{1/2}$	apparent first-order terminal elimination half-life
$t_{1/2,f}$	apparent functional first-order elimination half-life
TB	tuberculosis
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TFL	tables, figures, and listings
t_{last}	time of last measured concentration post-dose
t_{max}	time of maximum observed plasma concentration post-dose
$t_{max,ss}$	time of maximum observed plasma concentration post-dose at steady state
UC	ulcerative colitis
ULN	upper limit of normal
UNS	unscheduled
V_z/F	apparent volume of distribution during terminal phase after single dose oral administration or at steady state after oral administration
WHODRUG	World Health Organization Drug Dictionary

3. INTRODUCTION

3.1. Preface

This document presents a statistical analysis plan (SAP) for Morphic Therapeutic's Study MORF-057-201 (A phase 2a, open-label, single arm, multicenter study to evaluate the efficacy, pharmacokinetics [PK], pharmacodynamics [PD], safety and tolerability of MORF-057 in adults with moderate or severe Ulcerative Colitis [UC] [EMERALD-1]).

Reference materials for SAP version 1.0 (dated 17MAY2022) includes the protocol amendment version 2 (dated 09FEB2022) and eCRF dated 25MAR2022. Reference materials for SAP version 2.0 (dated 20DEC2022) includes the protocol amendment version 3 (dated 01SEP2022). Reference material for this SAP amendment (SAP version 3.0) includes the protocol version 4 (dated 27JUL2023).

3.2. Scope of Analyses

This SAP is to describe the statistical analysis methods and data presentation for all planned analyses. Results from the analyses specified in this SAP will be included in the final clinical study report (CSR) for Study MORF-057-201, and may also be utilized for regulatory submissions, manuscripts, or other clinical development activities.

Ad-hoc, post-hoc exploratory analyses not identified in this SAP may be performed to further examine the study data. These analyses will be clearly described, in the final CSR if relevant. Additional analyses not prospectively identified in this SAP may also be completed for publications, regulatory or other inquiries. These analyses, if performed, may not be reported in the CSR, and will be reported in a separate document appropriately.

3.3. Summary of Statistical Analysis Changes to the Protocol

The following changes to the protocol amendment version 2 (dated 09FEB2022) have been made in the SAP version 1.0 (dated 17MAY2022):

- Definition of analysis populations (Full Analysis Set [FAS], Per Protocol [PP] set, PK population, PK evaluable population, PD population) are modified by including the participants from both Main Cohort and Exploratory Cohort in Section 7.1.
- It is further clarified in Section 7.1 that Safety Analysis Population will be used for the safety analysis, instead of using the FAS, even though they are the same.
- It is clarified in Section 7.1 that the PP Set includes all participants in the FAS who do not have a major protocol deviation relevant to the primary and secondary efficacy endpoints analysis.
- Additional exploratory analyses are added in Section 9.4.1 for the following variables:
  - Proportion of participants in clinical remission and clinical response at Weeks 12 and 52 as determined using the Modified Mayo Clinic Score (MCS),

  - Proportion of participants in MCS remission and MCS response at Weeks 12 and 52
  - Proportion of participants with endoscopic improvement and endoscopic remission at Weeks 12 and 52
  - Proportion of participants with histologic remission at Weeks 12 and 52 as determined using the Robarts Histopathology Index (RHI) score.

3.4. Summary of Changes to the Statistical Analysis Plan

The following major changes to the SAP version 1.0 (dated 17MAY2022) have been made in the SAP version 2.0 (dated 20DEC2022):

- Following the protocol amendment version 3 (dated 01SEP2022)
  - The planned interim analysis for sample size reassessment is removed. Accordingly, the statistical significance level to be used in the final analysis of the primary efficacy endpoint is adjusted to 0.05 (two-sided).
  - The analysis for Long-term Extension is added.
- Corticosteroid use at baseline (yes/no) is added in the summary of baseline UC disease history.
- Proportion of participants with NI score ≤1 at Week 12 is added in the exploratory analysis for the consistency with the protocol.
- It is clarified that the summary of safety results will be based on the safety data during the on-Treatment Period, unless specified otherwise.
- The definition of treatment-emergent adverse events is further clarified.
- It is clarified that, for post baseline calculations of stool frequency and rectal bleeding subscores, the visit date or the date of Endoscopy procedure, whichever comes first, will be used as the reference date.

The following major changes to the SAP version 2.0 (dated 20DEC2022) have been made in this SAP version 3.0:

- Following the protocol amendment version 4 (dated 27JUL2023)
  - The analysis of the Induction Period for the Exploratory Cohort will be performed after all the participants in the Exploratory Cohort have completed the 12-week Induction Period (i.e., completed the Week 12 visit) or discontinued the study before the Week 12 assessment. The analysis of the 52-week Treatment Period for the Main Cohort will be performed after all the participants in the Main Cohort have completed the 52-week Treatment Period (and the Safety Follow-up Period for participants who did not enroll into the optional Long-term Extension) or discontinued from the study before the Week 52 assessment and the Safety Follow-up Period. In the event that the timing of the Induction Period analysis for the Exploratory Cohort aligns closely with the timing of the 52-week Treatment Period analysis for the Main Cohort, both analyses will be combined into one analysis.

- The below baseline summaries were added:
  - The number of advanced therapies received for UC
  - Categorized extent of disease
- The following subgroup factor was added in the subgroup analysis:
  - Baseline MES score (2 vs 3).
- Additional exploratory analyses are added in Section 9.4.1 for the following variables:
  - Proportion of participants with symptomatic remission, proportion of participants with partial MCS response, and proportion of participants with partial MCS remission.
  - Proportion of participants in clinical remission at both Weeks 12 and 52, in clinical remission at Week 12 but not at Week 52, and in clinical remission at Week 52 but not at Week 12, as determined using the Modified MCS based on the central Endoscopy subscore
- The re-allocation rules of early termination visit in Section 7.3.8 were further clarified.
- The calculation of stool frequency subscore and rectal bleeding subscore at study visits with no Endoscopy procedure performed was further clarified in Appendix 1

4. STUDY OBJECTIVES AND ENDPOINTS

4.1. Study Objectives

4.1.1. Primary Objective

- To evaluate the effects of MORF-057 on histologic improvement at Week 12.

4.1.2. Secondary Objectives

- To assess the safety and tolerability of MORF-057.
- To evaluate the effect of MORF-057 on clinical improvement at Week 12.
- To characterize the PK of MORF-057.

4.1.3. Exploratory Objectives

- To evaluate the effect of MORF-057 on histologic improvement at Weeks 6, 12, and 52.
- To evaluate the effect of MORF-057 on clinical improvement at Weeks 6, 12, and 52.
- To assess the effect of MORF-057 on non-endoscopic biomarkers of inflammation.
- To characterize the pharmacodynamics (PD) of MORF-057 in peripheral blood and mucosal tissue.
- To characterize the effect of MORF-057 on microbiome parameters in stool, blood, and mucosal tissue.
- To assess the long-term safety of MORF-057 and effects of MORF-057 on hs-CRP and fecal calprotectin levels

4.2. Study Endpoints

4.2.1. Primary Endpoint

- Change from baseline to Week 12 in the RHI Score.

4.2.2. Secondary Endpoints

- Frequencies and proportions for treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), and TEAEs leading to study drug discontinuation.
- Change from baseline to Week 12 in the Modified MCS. Modified MCS is a composite of the following subscores:
  - Mayo endoscopic subscore (MES).
  - MCS stool frequency subscore.
  - MCS rectal bleeding subscore.

- MORF-057 concentration in plasma
- Plasma PK parameters (AUC_{0-12}, AUC_{tau}, C_{max}, C_{trough}, t_{max}, C_{12}).

4.2.3. Exploratory Endpoints

- Change from baseline to Weeks 6 and 52 in RHI Score.
- Change from baseline to Weeks 6, 12, and 52 in the Nancy Index (NI).
- Change from baseline to Weeks 6, 12, and 52 in the Continuous Geboes Score.
- Change from baseline to Weeks 6 and 52 in the Modified MCS. Modified MCS is a composite of the following subscores:
  - MES.
  - MCS stool frequency subscore.
  - MCS rectal bleeding subscore.
- Change from baseline to Weeks 6, 12, and 52 in the Full MCS. Full MCS is a composite of the following subscores:
  - MES.
  - MCS stool frequency subscore.
  - MCS rectal bleeding subscore.
  - MCS Physician's Global Assessment (PGA).
- Change from baseline to Weeks 2, 6, 12, 20, 28, 36, and 52 in high sensitivity C reactive protein (hs-CRP) levels.
- Change from baseline to Weeks 2, 6, 12, 20, 28, 36, and 52 in fecal calprotectin levels.
- PD of MORF-057 in peripheral blood and mucosal tissue.
  - α4β7 and α4β1 receptor occupancies (RO) in blood over time.
  - Change from baseline over time in blood C-C chemokine receptor 9 (CCR9) mRNA.
  - Change from baseline over time in blood lymphocyte subsets.
  - Blood and mucosal tissue gene and/or protein expression over time.
- Microbiome parameters in stool, blood, and mucosal tissue
  - Microbiome composition in stool and mucosal tissue over time.
  - Changes in microbiome-derived metabolites in stool and blood over time.
  - Metatranscriptomic changes in the stool and mucosal tissue microbiome over time.

- Long-term Extension
  - Frequencies and proportions for TEAEs, TESAEs, and TEAEs leading to study drug discontinuation through Week 82
  - Change from baseline to Week 65 and Week 78 in hs-CRP levels
  - Change from baseline to Week 65 and Week 78 in fecal calprotectin levels

5. STUDY METHODS

5.1. General Study Design and Plan

The main part of this Phase 2a study will consist of three study periods: a Screening Period (up to 6 weeks), a Treatment Period (52 weeks, including a 12-week Induction Period and a 40-week Maintenance Period), and a Safety Follow-up Period (4 weeks).

During the study, there will be approximately 11 scheduled study visits: Screening Visit(s) (Visit 1 at Weeks -6 to -1), multiple Treatment Visits (Visits 2 to 10 at Weeks 0, 2, 6, 12, 20, 28, 36, 44, and 52), and a Safety Follow-up Visit (visit to occur 4 weeks after the last dose of study drug is received, which will be Visit 11 at Week 56 if the full study is completed or earlier if treatment is discontinued early).

Study Day 1 represents the first day of the Treatment Period (i.e., when the participant will receive the first dose of study drug). Participants will receive the same MORF-057 dosage ([redacted] mg [redacted] by mouth [PO]) for the full 52-week Treatment Period.

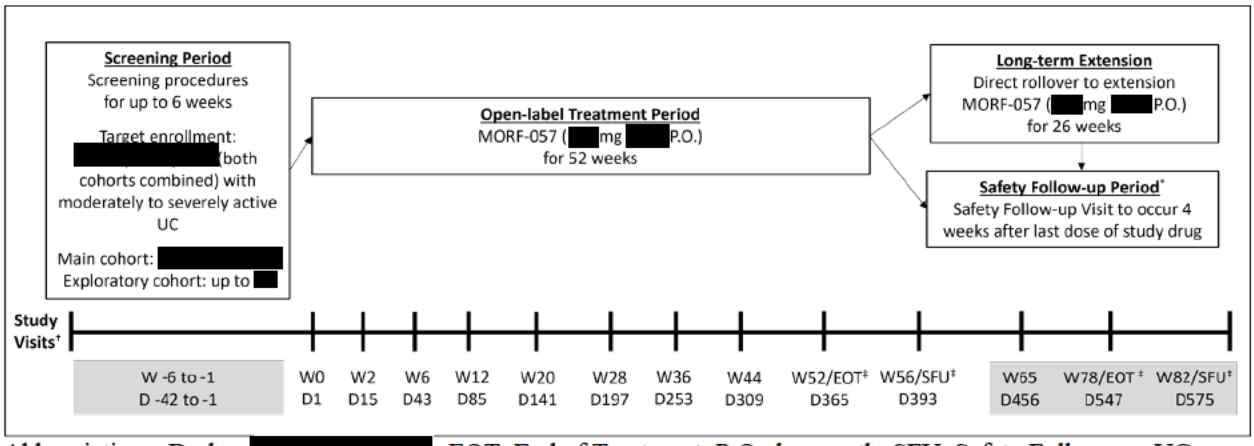
All participants who complete the open-label Treatment Period will have the opportunity to continue their treatment in an optional 26-week Long-term Extension after completing the Week 52 assessments. Participants who do not enroll into the Long-term Extension must complete the final Safety Follow-up Period for the main part of the study, including the Week 56 Visit (4 weeks after receiving the last dose of MORF-057), for a maximum time on study of 62 weeks.

Participants who choose to continue in the Long-term Extension will not complete the Safety Follow-up Period for the main part of the study; instead, they will directly enter the Long-term Extension.

During the optional Long-term Extension, there will be 3 scheduled study visits: 2 Treatment Visits (Visits 10 to 11 at Weeks 52 and 65), and an End of Treatment Visit (Visit 12 at Week 78). A Safety Follow-up Visit (4 weeks after the last dose of study drug is received), will be Visit 13 (Week 82) if the full Long-term Extension is completed or earlier if treatment is discontinued before completing the study. Participants will continue to receive the same MORF-057 dosage ([redacted] mg [redacted] PO) for the full 26-week extended Treatment Period.

A study schema is provided below.

Figure 1 Study Schema



Abbreviations: D, day; [redacted]; EOT, End of Treatment; P.O., by mouth; SFU, Safety Follow-up; UC, Ulcerative Colitis W, week.

* The Safety Follow-up Visit at Week 56 will not be performed for participants who enter the Long-term Extension. Participants who continue in the Long-term Extension will complete a Safety Follow-up Visit at Week 82.

† The assessments to be performed at each visit and the acceptable time windows for each visit are provided in the Schedule of Activities.

‡ In cases where the participant withdraws early from the study treatment, the EOT and SFU Visit assessments may be performed earlier than the timepoints shown here.

The Main Cohort of the study will include approximately [redacted] with moderately to severely active UC who have or have not been exposed to biologic therapies and have not previously been treated with vedolizumab. In addition, an Exploratory Cohort will comprise a maximum of ten additional participants with moderately to severely active UC who are intolerant to or secondary non-responders to vedolizumab. Thus, there will be a total of [redacted] in the study. When the Main Cohort recruits [redacted], the study will be closed for any new screening in the main cohort and the remaining participants already in screening will be allowed to complete the process and enroll, if eligible.

The first dose of MORF-057 will be administered in the clinic on Study Day 1 under the supervision of study personnel. All subsequent doses will be self-administered at home, apart from the [redacted] for Visits 2 to 10, which will be administered during the study visits after pre-dose blood samples have been drawn (see details in the Schedule of Activities Table 1). Participants will be instructed to record all details about the doses administered at home in the Participant Diary. Study drug accountability (number of capsules dispensed and returned) will be recorded in the Inventory and Resupply Technology (IRT) system.

The other procedures performed in this study are listed in the Schedule of Activity (Table 1 and Table 2).

Table 1: Schedule of Activity (SOA) for the Treatment Period

Study Procedure	SCR [a]	Treatment Period									Safety Follow-up	UNS [b]
Visit	1	2	3	4	5	6	7	8	9	10/EOT [c]	11/SFU [d, e]	UNS
Week	-6 to -1	0	2	6	12	20	28	36	44	52	56	
Study Day	-42 to -1	1	15±3	43±3	85±3	141±7	197±7	253±7	309±7	365±7	393+7 [f]	
Informed consent [g]	X											
Demographics	X											
Medical and surgical history	X	X										
Assess inclusion/exclusion criteria	X											
Confirm inclusion/exclusion criteria		X										
Enrollment [h]		X										
SARS-CoV-2 Screening [i]	X											
Test for TB [j]	X											
Fecal sampling and cell culture for *C. diff.* and enteric pathogens, including ova and parasite testing	X											
Testing for HIV antibody, hepatitis B surface antigen, and hepatitis C virus antibody	X											
Cytomegalovirus test [k]	X											
Serum alcohol screen	X											
Urine drug screen	X											
Exploratory Cohort eligibility testing [l]	X											
Review Participant Diary instructions	X											
Fill out Participant Diary (daily rectal bleeding, stool frequency, study drug administration) [m]	X	X	X	X	X	X	X	X	X	X	X	
Collect/review Participant Diary compliance	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy test [n]	X	X	X	X	X	X	X	X	X	X	X	
Serum test for follicle-stimulating hormone [o]	X											
Dispense stool collection kit [p]	X	X	X	X	X	X	X	X	X			

Study Procedure	SCR [a]	Treatment Period									Safety Follow-up	UNS [b]
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10/EOT [c]**	**11/SFU [d, e]**	**UNS**
Week	**-6 to -1**	**0**	**2**	**6**	**12**	**20**	**28**	**36**	**44**	**52**	**56**	
Study Day	**-42 to -1**	**1**	**15±3**	**43±3**	**85±3**	**141±7**	**197±7**	**253±7**	**309±7**	**365±7**	**393+7 [f]**	
Discuss participation in Open-label Extension study [q]									X	X		
Safety Assessments												
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X			X	X					X		
Physical exam [r]	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs [s]	X	X	X	X	X	X	X	X	X	X	X	X
PML checklist [t]	X	X	X	X	X	X	X	X	X	X	X	
Hematology and coagulation	X	X	X	X	X	X	X	X	X	X	X	X [b]
Serum chemistry	X	X	X	X	X	X	X	X	X	X	X	X [b]
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X [b]
AE/SAE assessment [u, v]	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetic Assessment												
Plasma sample for PK analysis		X [w]	X [w]	X [x]	X [w]	X [x]	X [x]	X [x]	X [x]	X [y]		
Pharmacodynamics Biomarkers												
Fecal sample for microbiome analyses		X	X	X	X	X	X	X	X	X		
Blood sample for microbiome-derived metabolite analysis [z]		X	X	X	X	X	X	X	X	X		
Whole blood sample for RO [aa]		X	X		X							
Whole blood sample for immunophenotyping [bb]		X	X	X	X	X	X	X	X	X		
Blood sample for PIMS [cc]		X			X							
PAXgene RNA blood sample for gene expression [dd]		X	X	X	X	X	X	X	X	X		
Blood sample for protein biomarkers [ee]		X	X	X	X	X	X	X	X	X		
Future Biomarker Research												
Blood PD sample collection for future analysis [ff]		X	X	X	X	X	X	X	X	X		
Blood pharmacogenomics sample collection for future analysis [ff]		X										

Study Procedure	SCR [a]	Treatment Period									Safety Follow-up	UNS [b]
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10/EOT [c]**	**11/SFU [d, e]**	**UNS**
Week	**-6 to -1**	**0**	**2**	**6**	**12**	**20**	**28**	**36**	**44**	**52**	**56**	
Study Day	**-42 to -1**	**1**	**15±3**	**43±3**	**85±3**	**141±7**	**197±7**	**253±7**	**309±7**	**365±7**	**393+7 [f]**	
Efficacy Assessments												
Sigmoidoscopy with biopsy [gg]	X			X [hh]	X					X [ii]		
MCS PGA	X	X	X	X	X	X	X	X	X	X		
MCS rectal bleeding subscore	X	X	X	X	X	X	X	X	X	X		
MCS stool frequency subscore	X	X	X	X	X	X	X	X	X	X		
Locally and centrally read MES	X			X	X					X		
Centrally read RHI Score, Continuous Geboes Score, and NI	X			X	X					X		
Serum for hs-CRP test [jj]	X	X	X	X	X	X	X	X		X		
Fecal calprotectin	X		X	X	X	X	X	X		X		
Study Drug												
Study drug accountability			X	X	X	X	X	X	X	X		
Dispense study drug		X	X	X	X	X	X	X	X			
Study drug administration on site [kk]		X	X	X	X	X	X	X	X	X [ll]		

Abbreviations: AE, adverse event; *C. diff., Clostridium difficile*; ECG, electrocardiogram; EOT, end of treatment; hs-CRP, high sensitivity C reactive protein; MCS, Mayo Clinic Score; MES, Mayo Endoscopic Subscore; NI, Nancy Index; PD, pharmacodynamics; PIMS, physiological intermolecular modulation spectroscopy; PK, pharmacokinetics; PML, progressive multifocal leukoencephalopathy; RHI, Robarts Histopathology Index; RNA, ribonucleic acid; RO, receptor occupancy; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SCR, Screening; SFU, Safety Follow-up; TB, tuberculosis; UNS, unscheduled.

a Once informed consent is obtained, listed procedures may be performed at any time during the Screening Period.

b Clinically relevant laboratory testing or re-testing (e.g., hematology, coagulation, serum chemistry, or urinalysis) may be performed at unscheduled visits. No specific tests are required for unscheduled visits. Results of any study procedures performed at an unscheduled visit will be recorded and collected for the study.

c If participant discontinues early from the study Treatment Period, perform the visit 10/EOT procedures and schedule Visit 11/SFU for 28 days (+7 days) after the participant takes the last dose of study drug (unless consent is withdrawn).

d Participants who will not enroll into the Open-label Extension Study will complete the Safety Follow-up Visit, which should be performed 28 days (+7 days) after the participant takes the last dose of study drug. Eligible participants who choose to enroll into the Open-label Extension Study after Visit 10/EOT will not attend the Safety Follow-up Visit.

e If participant discontinues early from the Study Treatment Period, perform the visit 11/SFU procedures 28 days (+7 days) after the participant takes the last dose of study drug (unless consent is withdrawn).

f The Safety Follow-up Visit is to occur 28 days (+7) after the last dose of study drug is received. If the EOT Visit occurs before Day 365, the day for the Safety Follow-up Visit can be adjusted according to the date of last study drug dose.

g Informed consent process can begin prior to the start of the Screening window. For example, this can be done if washout from medications is required.

h Enrollment may occur at any point within a 42-day window of when all Screening procedures have been completed and all results required to assess eligibility are available. Enrollment will usually occur the same day as first dosing, but if dosing the same day is not feasible, then enrollment will be considered Day -1 and first dose will be considered Day 1.

i SARS-CoV-2 test will be performed during the Screening Period according to site-specific procedures and country-specific requirements.

j [redacted] TB test. In cases where the [redacted] test is indeterminate, the participant may have the test repeated once and if their second test is negative, they will be eligible. In the event a second test is also indeterminate or [redacted] is unavailable, the Investigator has the option to perform a purified protein derivative skin test.

k Cytomegalovirus will be tested with biopsy sample collected at Screening.
l Patients being considered for the Exploratory Cohort will require testing for vedolizumab blood levels, RO of vedolizumab, and anti-drug antibodies against vedolizumab.
m Participant Diaries are to be completed at the end of each day by the participant at home and brought to each study visit for review by study personnel. See Protocol Section 8.5 for the required contents of the Participant Diaries.
n Only required for women of childbearing potential. A serum test should be used at Screening, and a urine test should be used throughout rest of study. On Day 1, a urine test must be completed, and results reviewed prior to start of the study drug.
o Serum test for follicle-stimulating hormone level to be performed only for female participants of non-childbearing potential who are not surgically sterile.
p Stool collection kits are to be dispensed to participants at the visits indicated. The participant should use this kit to collect one sample at home within 24 hours before the next site visit. The sample should be frozen immediately and brought to the clinic on the day of the site visit. **Note:** Sample is to be collected prior to bowel preparation for Visits 4, 5, and 10/EOT.
q Eligible participants should be provided the option to participate in the Open-label Extension Study.
r A complete physical exam is to be performed at Screening and Visit 10/EOT, and a targeted exam may be performed at all other required visits (see Protocol Section 8.8.1 for descriptions). For unscheduled visits, that involve the Investigator or clinical assessment and not the visits that would be for dispensing study drug or for laboratory draws only, the type of exam will be at the Investigator's discretion and determined based on the reason for the visit.
s Vital signs to be recorded at all visits that involve the Investigator or clinical assessment visits and not the visits that would be for dispensing study drug or for laboratory draws only. These will include blood pressure, heart rate, respiratory rate, and temperature.
t If the results of the questionnaire are suggestive of PML, a full neurological exam and, if indicated, additional testing are to be performed.
u Record adverse events from the time the ICF is signed.
v Participants are to be contacted by phone as needed to monitor the status of the event.
w PK testing at Visits 2, 3, and 5: Blood sampling will be required [redacted] and at [redacted]. Blood sampling will be optional at [redacted]. The [redacted] sample will be collected prior to the [redacted] dose. Time windows for PK sampling can be found in Protocol Section 8.10.1. Each [redacted] sample should be obtained within [redacted] is administered and at [redacted].
x PK testing at Visits 4, 6, 7, 8, and 9: Blood sampling will be required [redacted] and at [redacted]. Time windows for PK sampling can be found in Protocol Section 8.10.1. Each [redacted] sample should be obtained within [redacted] is administered.
y PK testing at Visit 10/EOT: Blood sampling will be required [redacted]. The sample should be obtained within [redacted] is administered and at [redacted].
z Blood samples for microbiome-derived metabolite analysis will be collected [redacted] on Visits 2-10. Microbiome sampling to occur at the corresponding PK sampling time.
aa RO testing at Visit 2, 3, and 5: Blood sampling will be required [redacted]. Blood sampling will be optional at [redacted] The [redacted] sample will be collected prior to the [redacted]. RO sampling to occur at the corresponding PK sampling time.
bb Blood samples for immunophenotyping (lymphocyte subsets analysis) will be collected [redacted] on Visits 2-10. Collection time at Visits 3-10 must be consistent with baseline (Visit 2) collection ±2 hours. Immunophenotype sampling to occur at the corresponding PK sampling time.
cc Blood samples for PIMS analysis will be collected [redacted] on Visits 2 and 5. PIMS sampling to occur at the corresponding PK sampling time.
dd PAXgene RNA blood samples (for CCR9 analysis) will be collected [redacted] on Visit 2-10. Collection time at Visits 3-10 must be consistent with baseline (Visit 2) collection ±2 hours. PAXgene sampling to occur at the corresponding PK sampling time.
ee Blood samples for protein biomarkers will be collected [redacted] on Visits 2-10. Protein biomarker sampling to occur at the corresponding PK sampling time.
ff Participation in future biomarker research sample collection is optional. Blood PD samples will be collected [redacted] on Visits 2-10. Blood pharmacogenomics sample will be collected [redacted] on Visit 2. PD and pharmacogenomics sampling to occur at the corresponding PK sampling time.
gg Full colonoscopy is optional at any timepoint if the Investigator deems it necessary. The Screening Endoscopy procedure should be scheduled at least 16 days prior to the planned start of the study drug (Day 1) to allow for central reading. Colonic mucosa biopsies will be collected for cytomegalovirus testing (Screening only), microbiome, spatial transcriptomics/proteomics, and gene expression analyses.
hh The Visit 4 Endoscopy is optional.
ii For the visit 10/EOT Endoscopy procedure, there is a window of ±7 days from the actual visit date. For participants who discontinue treatment before Week 6, a repeat sigmoidoscopy will be performed any time after MORF-057 dosing Day 14. For participants who discontinue treatment after Week 6, a repeat sigmoidoscopy will be performed

any time if the optional Week 6 sigmoidoscopy was not exercised. If the Week 6 optional sigmoidoscopy was exercised, a repeat sigmoidoscopy will be performed after the 28th day post Week 6 sigmoidoscopy. Participants who complete a sigmoidoscopy/colonoscopy within 12 weeks of the EOT visit are not required to repeat the procedure. If the procedure was performed further than 12 weeks, please consult the Sponsor Medical Monitor.

jj Blood samples for hs-CRP analysis will be collected [redacted] on Visits 2-8 and Visit 10.

kk [redacted] required on site for all visits. For Visits 2, 3, and 5, if optional PK/RO sampling will be performed at [redacted] must not be taken until PK/RO sampling is complete for that day.

ll At Visit 10/EOT, participants will only receive an [redacted] will be provided.

Table 2: Schedule of Activities for the Long-term Extension

Study Procedure	Long-term Extension		Safety Follow-up	UNS [a]
Visit	**11**	**12/EOT [b]**	**13/SFU [c, d]**	**UNS**
Week	**65**	**78**	**82**	
Study Day	**456±7**	**547±7**	**575+7 [f]**	
Fill out Participant Diary (daily rectal bleeding, stool frequency, study drug administration) [e]	X	X	X	
Collect/review Participant Diary compliance	X	X	X	
Pregnancy test [f]	X	X	X	
Dispense stool collection kit [g]	X			
Safety Assessments				
Concomitant medications	X	X	X	X
Physical exam [h]	X	X	X	X
Vital signs [i]	X	X	X	X
PML checklist [j]	X	X	X	
Hematology and coagulation [k]	X	X	X	X [a]
Serum chemistry [k]	X	X	X	X [a]
Urinalysis	X	X	X	X [a]
AE/SAE assessment [l, m]	X	X	X	X
Efficacy Assessments				
Serum for hs-CRP test [n]	X	X		
Fecal sample for fecal calprotectin test	X	X		
Study Drug				
Study drug accountability	X	X		
Dispense study drug	X			

Abbreviations: AE, adverse event; EOT, end of treatment; hs-CRP, high-sensitivity C-reactive protein; ICF, informed consent form; PML, progressive multifocal leukoencephalopathy; SAE, serious adverse event; SFU, Safety Follow-up; UNS, unscheduled.

[a] Clinically relevant laboratory testing or re-testing (e.g., hematology, coagulation, serum chemistry, or urinalysis) may be performed at unscheduled visits. No specific tests are required for unscheduled visits. Results of any study procedures performed at an unscheduled visit will be recorded and collected for the study.

[b] If participant discontinues early from the Long-term Extension, perform the visit 12/EOT procedures and schedule Visit 13/SFU for 28 days (+7 days) after the participant takes the last dose of study drug (unless consent is withdrawn).

[c] All participants enrolled in the Long-term Extension will complete the SFU (Visit 13 at Week 82), which should be performed 28 days (+7 days) after the participant takes the last dose of study drug.

[d] If participant discontinues early from the Long-term Extension, perform the visit 13/SFU procedures 28 days (+7 days) after the participant takes the last dose of study drug (unless consent is withdrawn).

[e] Participant Diaries are to be completed at the end of each day by the participant at home and brought to each study visit for review by study personnel. See Section Protocol Section 8.5 for the required contents of the Participant Diaries.

[f] Only required for women of childbearing potential. A urine test should be used throughout the Long-term Extension.

[g] Stool collection kits are to be dispensed to participants at the visits indicated. The participant should use this kit to collect one sample at home within 24 hours before the next site visit. The sample should be frozen immediately and brought to the clinic on the day of the site visit.
[h] A targeted physical exam is to be performed at all visits (see Protocol Section 8.8.1 for descriptions). For unscheduled visits, the type of exam will be at the Investigator's discretion and determined based on the reason for the visit.
[i] Vital signs to be recorded at all visits. These will include blood pressure, heart rate, respiratory rate, and temperature.
[j] If the results of the questionnaire are suggestive of PML, a full neurological exam and, if indicated, additional testing are to be performed.
[k] Blood samples for hematology, coagulation, and serum chemistry assessments will be collected [redacted] on Visits 11-12.
[l] Record adverse events from the time the ICF for the Long-term Extension is signed.
[m] Participants are to be contacted by phone as needed to monitor the status of the event.
[n] Blood samples for hs-CRP analysis will be collected [redacted] on Visits 11-12.

5.2. Randomization and Blinding

Not applicable.

6. SAMPLE SIZE

The sample size for this study is based on the number of participants needed for the Main Cohort. Assuming a one-sided alpha at 0.025 for the final analysis, a standard deviation of 12, and a one sample t-test, a mean treatment effect of ≥ 7-point reduction in RHI can be detected using [redacted] with > 80% power. A dropout rate of 5% would lead to a total of [redacted] being enrolled in the Main Cohort. A maximum of [redacted] may be enrolled in the Exploratory Cohort, giving a total of [redacted] in the study.

7. GENERAL CONSIDERATIONS

Descriptive statistics will be reported for all primary, secondary, and exploratory data. Categorical parameters will be reported using frequency and proportions, whereas continuous parameters will be reported using mean, standard deviation, median, minimum, and maximum unless otherwise specified. Data will be summarized/analyzed separately for the Main Cohort and Exploratory Cohort at scheduled visits unless stated otherwise. Data from participants in the Exploratory Cohort will be analyzed only for exploratory purposes.

No hypothesis testing will be performed for the secondary and exploratory efficacy endpoints. No hypothesis testing will be performed on safety data.

7.1. Analysis Populations

There will be six (6) analysis populations defined for this study.

7.1.1. Full Analysis Set (FAS)

The FAS includes all enrolled participants in both the Main Cohort and Exploratory Cohort who received at least one dose of study drug. The FAS will be used for efficacy analyses.

7.1.2. Per Protocol (PP) Set

The PP Set includes all participants in the FAS who do not have a major protocol deviation relevant to the primary and secondary efficacy endpoints analysis. All decisions to exclude participants from the PP set will be made prior to the database lock of the study.

The PP Set will be used for sensitivity analysis of the primary efficacy endpoint and maybe also for some other efficacy endpoints as appropriate.

7.1.3. Safety Analysis Population

Includes all participants in both the Main Cohort and Exploratory Cohort who received at least one dose of study drug.

The Safety Analysis Population will be used for safety analysis.

7.1.4. PK Population

The PK Population includes all participants in the FAS and has adequate measurable concentrations to define C_{max} or AUC.

The PK Population will be used in the individual plasma concentration, PK parameter estimation listings, and individual figures. Plasma concentration-time data and PK parameters that are not summarized will be included in the listings and flagged.

7.1.5. PK Evaluable Population

A PK Evaluable Population (a subset of the PK Population) will be used to determine the inclusion of a participant in the overall PK summaries. Participants included in this subset must have data that meet the following criteria:

- Do not have any occurrence of emesis occurring within two times the median t_{max} of MORF-057 on Visits 2, 3, and 5 where non-compartmental analysis (NCA) are to be performed and are deemed to have an impact on the corresponding PK profile. Participants who experience emesis within two times the median t_{max} of MORF-057 on the other visits where sparse PK sampling occurs will be evaluated on a case-by-case basis. All emesis occurrences will be discussed with the Sponsor prior to any decisions for participant exclusions.
- Do not use a concomitant medication which renders the concentration profile unreliable.
- Do not have a quantifiable pre-dose concentration that is greater than 5% of the corresponding C_{max} of Visit 2 Study Day 1; Participants with quantifiable pre-dose concentrations greater than 5% of their corresponding C_{max} at Visit 2 Study Day 1 will be evaluated on a case-by-case basis and discussed with the Sponsor to determine PK data inclusion in summaries.
- Do not violate the protocol (major protocol violation) in a way that may invalidate or bias the results.
- Do not have ≥ 2 consecutive missing plasma concentration values at Visit 2, 3, and 5. This will be evaluated on a case-by-case basis and discussed with the Sponsor to determine the impact of the missing data to the overall PK profile and PK parameter estimation. For all other visits where sparse sampling occurs, all available data will be included in the relevant summaries if all the other above criteria are met.

The PK Evaluable Population will be included in the summaries of plasma concentration-time data (for all visits where PK samples are available), NCA PK parameter estimation (for Visits 2, 3, and 5), and mean concentration-time figures (for all visits where PK samples are available).

7.1.6. PD Population

The PD population is defined as all participants in the FAS who have at least one measurable post-dose PD measurement and its corresponding pre-dose PD measurement for, at minimum, 1 of the PD biomarkers. This population will be used for the summarization of PD (exploratory) endpoints.

7.2. Covariates and Subgroups

7.2.1. Planned Covariates

No covariates are planned to be used in any analyses.

7.2.2. Planned Subgroups

The subgroup analyses for the primary efficacy endpoints will be performed as specified in Section 9.2.3.

7.3. Management of Analysis Data

7.3.1. Unscheduled Visits

Unscheduled visit measurements will not be included in the by visit summaries but will be included in the shift tables (mapped to the nearest post baseline scheduled visit) for safety parameters where the worst/most conservative result will be used.

The determination of baseline values will be based on all measurements from both scheduled and unscheduled visits.

In the sensitivity analysis of the primary efficacy endpoint, the last observation carried forward (LOCF) method will be used. All measurements from both scheduled and unscheduled visits will be used to determine the endpoint value at Week 12.

All visits, scheduled or otherwise, will be provided in data listings.

7.3.2. Missing Data

Unless otherwise specified, there will be no substitutions made to accommodate missing data points. All data recorded on the CRF will be included in data listings that will accompany the CSR.

7.3.2.1. Handling of Missing Date Values

Partial or Missing Dates

For partial UC diagnosis dates, the following imputation methods will be applied:

- If month and year are present but day is missing, then the day will be set to the first day of the month
- If year is present but not month and day, month and day will be set to January 1st

The following conventions will be used to impute missing portions of dates for adverse events (AEs) and concomitant medications, if warranted. Note that the imputed values outlined here may not always provide the most conservative date. In those circumstances, the imputed value may be replaced by a date that will lead to a more conservative analysis.

A. Start Dates

1) If the year is unknown, then the date will not be imputed and will be assigned a missing value.

2) If the month is unknown, then:
    i) If the year matches the first dose date year, then impute the month and day of the first dose date.
    ii) Otherwise, assign 'January.'
3) If the day is unknown, then:
    i) If the month and year match the first dose date month and year, then impute the day of the first dose date.
    ii) Otherwise, assign the first day of the month.

B. Stop Dates
1) If the year is unknown, then the date will not be imputed and will be assigned a missing value.
2) If the month is unknown, then assign 'December.'
3) If the day is unknown, then assign the last day of the month.
4) If imputed date is after end of study date, then end of study date will be used.

7.3.2.2. Imputation Methods

Unless otherwise specified, observed cases, without imputation, will be used for the analyses.

The LOCF method will be used to impute the missing endpoint data at Week 12 for the sensitivity analysis of the primary efficacy endpoint.

7.3.2.2.1. Adverse Events

If the relationship of an AE is missing, it will be summarized as treatment-related.

7.3.3. Handling Rule for PK

7.3.3.1. PK Concentrations

For Visits 2 (Day 1), 3 (Week 2), and 5 (Week 12) only:

Actual sampling time points relative to dosing will be used for the estimation of NCA PK parameters from plasma data. If the actual sampling time is missing, but a valid concentration value has been measured, the concentration value will be flagged, and the nominal time point will be used for the calculation of PK parameters.

In cases of missing pre-dose concentrations for the first dose at Visit 2 (Day 1), the missing concentration will be assumed as zero for the calculation of AUC. In cases of missing pre-dose concentrations at Visit 3 and Visit 5, the C_{trough} or the minimum observed concentration during the dosing interval (if the C_{trough} is missing) will be used as pre-dose concentration values for the calculation of AUC. For all other visits, the missing data will not be imputed.

For all visits with PK samples available:

Actual sampling time points relative to dosing will be reported along with the nominal time point.

7.3.3.2. PK Data Below the Limit of Quantification (BLQ)

The following rules will be used to handle BLQ for the NCA PK parameter calculation (Visits 2, 3, and 5) and individual concentration data (for all visits with PK samples collected):

Plasma concentration values collected at Visits 2, 3, and 5 that are BLQ will be imputed as follows for PK parameter calculation via NCA:

- BLQ values at time points prior to any measurable plasma concentration for the first dose or at time points immediately prior to dosing for multiple doses are imputed as 0 concentration.
- Any other BLQ values are set to missing.
- If two BLQ values occur in succession after t_{max}, the profile is deemed to have terminated at the first BLQ value and any subsequent concentrations are omitted (until the next dosing event occurs) from PK calculations and individual plots.

The following general rules will be applied for the concentration data summaries for all visits (including tabulation and plotting):

- Mean concentrations at any individual time point will only be calculated if at least half of the participants have valid values (i.e., quantifiable, and not missing) at this time point.
- In cases where a mean value is not calculated, due to the above criterion not being met, the mean value will be set to missing for mean plotting purposes.

BLQ will be set to zero for the calculation of these mean values for Visit 1 (Day 1 only). BLQs at pre-dose for all other subsequent dosing days or before the last quantifiable measurement will be imputed as lower limit of quantification (LLOQ).

7.3.4. PD Data

Missing PD data will not be imputed.

7.3.5. Definition of Baseline

Baseline for non-PK measures is defined as the last non-missing measurement before the first dose.

7.3.6. Analysis Day

Analysis day will be calculated from the date of the first dose of study drug. The day of the first dose of study drug will be Day 1, and the day immediately before Day 1 will be Day -1. There will be no Day 0 in this study.

The following conventions will be used to calculate Study Day for reporting purposes:

- Study Day = date of measurement – first dose date +1 if date of measurement is on or after the first dose date.
- Study Day = date of measurement – first dose date if date of measurement is prior to the first dose date.

7.3.7. Analysis Visits

No analysis visit windows will be defined unless otherwise specified, i.e., the nominal visits/time points will be used for all statistical summaries/analyses, except for those defined in Section 7.3.1.

7.3.8. Handling of Early Termination Visit Information

If a participant is terminated early from this study, he/she will be encouraged to complete the EOT Visit at the time of study drug discontinuation and the Safety Follow-up Visit. In summary tables and statistical tests, all efficacy and safety parameters measured at the EOT Visit will be re-allocated according to the following rules:

- If the assessment date for a given parameter at the EOT Visit is closer to the previous scheduled study visit date and this parameter is scheduled to be measured at that visit but there is no measurement, the EOT Visit for this parameter will be re-allocated to the previous scheduled study visit.
- If the assessment date for a given parameter at the EOT Visit is closer to the next scheduled study visit date and this parameter is scheduled to be measured at that visit but there is no measurement, the EOT Visit for this parameter will be re-allocated to the next scheduled study visit.
- Otherwise, the EOT Visit will remain unassigned to a nominal visit.

The above re-allocation of the EOT Visit will be performed for each efficacy and safety parameter based on its individual scheduled visits in the protocol. Please see Table 1 and Table 2 for the scheduled visits for each parameter to be measured.

7.3.9. Pooling of Study Centers

Study centers will be pooled for all analyses, unless otherwise specified.

7.3.10. Coding Conventions for Events and Medications

All adverse events, and medical history will be mapped to the Medical Dictionary for Regulatory Activities (MedDRA) using the version in effect at the time of database lock and Common Terminology Criteria for Adverse Events (CTCAE Version 5.0 or later) systems for reporting (preferred term and body system).

Prior and concomitant medications will be coded using World Health Organization – Drug Dictionary (WHO-DD) based on the version in effect at the time of database lock.

7.3.11. Analysis Software

Data manipulation, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed primarily using SAS (release 9.4 or higher) for Windows. If the use of other software is warranted, the final CSR will detail what software was used and for what purposes.

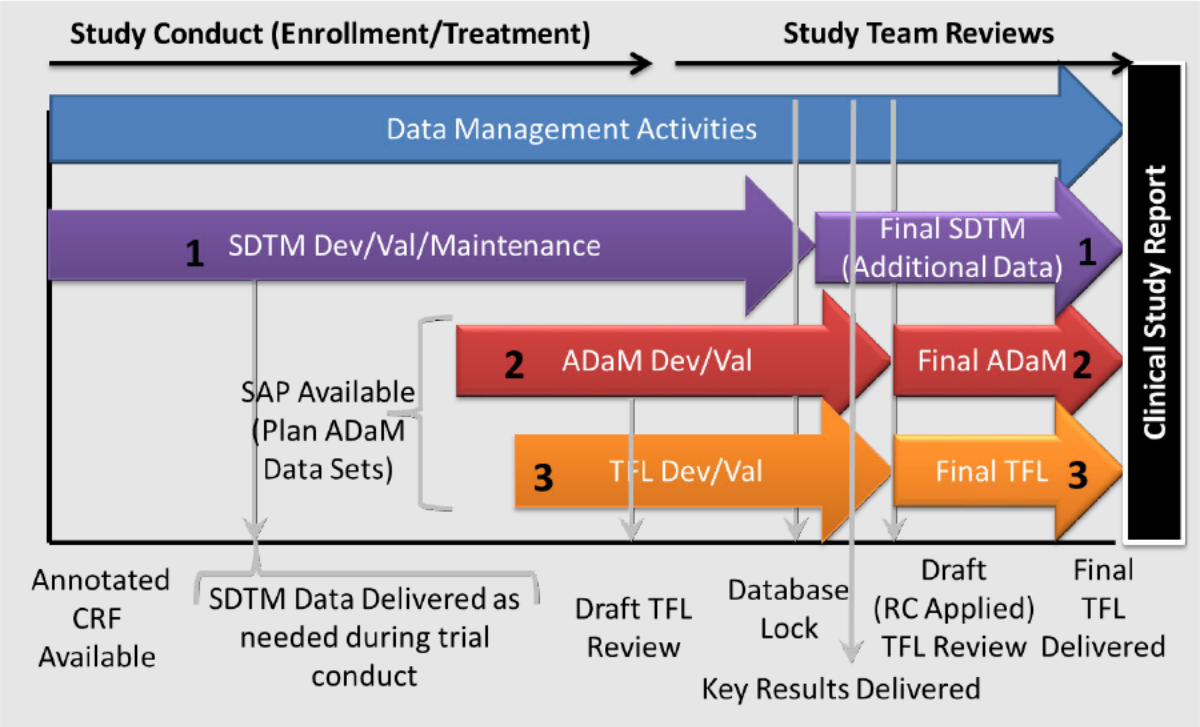
All NCA parameterization will be performed using a validated software, Phoenix® WinNonlin® Version 8.3 (Certara, USA).

7.3.12. Study Data

All study data will be formulated into regulatory compliant data sets to provide transparency, traceability, and integrity of trial analysis results from the collection source. Observed study data will be mapped to the Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) and serve as the source data from the trial. All study analyses will be completed using analysis data sets that are derived from the SDTM and follow the CDISC Analysis Data Model (ADaM) architecture. All planned analyses will be performed using the ADaM data sets developed for this study.

The methods for programming the CDISC SDTM and ADaM data sets are described in Figure 2.

Figure 2: SDTM, ADaM, and TFL Development and Validation



Where:

- Development, Validation, and Maintenance of SDTM Domains
- Development and Validation of ADaM, with input source the appropriate SDTM domains
- Development and Validation of Tables, Figures, and Listings (TFL), with input data source the analysis specific ADaM data sets.

7.4. Planned Study Analyses

7.4.1. Statistical Summaries: Descriptive and Inferential

All p-values will be rounded to and displayed in four decimals. If a p-value less than 0.0001 occurs, it will be shown in tables as <0.0001.

Categorical data will generally be summarized with counts and percentages of participants. The denominator used for the percentage calculation will be clearly defined. Continuous data will generally be summarized with descriptive statistics including n (number of non-missing values), mean, median, standard deviation (SD), 25% and 75% percentile, minimum, and maximum. Arithmetic and geometric means, % coefficient of variation (CV), and % geometric coefficient of variation will also be provided for PK parameters and PD summaries as appropriate. The values of zero will be excluded from the calculation of geometric means and % geometric CV.

Expansion of descriptive table categories within each treatment may occur if such elaborations are thought to be useful.

For the summary statistics of all numerical variables unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported. Data not subject to analysis according to this plan will not appear in any tables or figures but will be included in the data listings as appropriate.

7.4.2. Data Safety Monitoring Board (DSMB)

A DSMB will be monitoring the safety throughout the study. Details about the frequency and content of the reporting will be specified in the DSMB Charter.

7.5. Analyses for Induction Period, 52-week Treatment Period, and Long-term Extension

The study open-label Treatment Period includes 2 parts: the 12-week Induction Period and the 40-week Maintenance Period. For statistical analyses, the Induction Period and the Maintenance Period will be treated as 2 independent parts. There will be 4 analyses planned: two for the 12-week Induction Period of the Main Cohort and Exploratory Cohort respectively (i.e., the period for the primary efficacy endpoint) and the other two for the 52-week Treatment Period of the Main Cohort and Exploratory Cohort respectively (the 12-week Induction Period plus the 40-week Maintenance Period and the Safety Follow-up Period). Additional analysis of the optional Long-term Extension Treatment Period for the participants enrolled into the Long-term Extension will be performed as appropriate.

The analysis of the Induction Period is to evaluate the efficacy and safety during the 12-week Induction Period. The analysis of the 52-week Treatment Period is to use the cumulative combining data from both Induction and Maintenance Periods plus the Safety Follow-up Period.

Induction Period Analysis

The analysis of the Induction Period for the Main Cohort will be performed after all the participants in the Main Cohort have completed the 12-week Induction Period (i.e., completed the Week 12 visit or discontinued the study before the Week 12 assessment). The analysis will formally evaluate the primary and secondary efficacy endpoints, all the exploratory endpoints defined by Week 12, PK concentration and parameters, PD parameters (α4β7 and α4β1 RO, and safety of MORF-057 for the Main Cohort during the 12-week Induction Period.

The analysis of the Induction Period for the Exploratory Cohort will be performed after all the participants in the Exploratory Cohort have completed the 12-week Induction Period (i.e., completed the Week 12 visit) or discontinued the study before the Week 12 assessment. The analysis will evaluate all the efficacy and exploratory endpoints, PK concentrations and parameters, and safety of MORF-057 for the Exploratory Cohort during the 12-week Induction Period. In the event that the timing of the Induction Period analysis for the Exploratory Cohort

aligns closely with the timing of the 52-week Treatment Period analysis for the Main Cohort described below, both analyses will be combined into one analysis.

Only Induction Period data will be used in this analysis. The disposition, demographics and baseline disease characteristics, concomitant medication, and treatment exposure during the Induction Period, will also be presented.

52-week Treatment Period Analysis

For the Main Cohort, the analysis of the 52-week Treatment Period will be performed after all the participants have completed the 52-week open-label Treatment Period (and the Safety Follow-up Period for participants who did not enroll into the optional Long-term Extension) or discontinued from the study before the Week 52 assessment and the Safety Follow-up Period. In the event that the timing of the 52-week Treatment Period analysis for the Main Cohort aligns closely with the timing of the Induction Period analysis for the Exploratory Cohort, both analyses will be combined into one analysis.

For the Exploratory Cohort, the analysis of the 52-week Treatment Period will be performed after all the participants have completed the 52-week open-label Treatment Period (and the Safety Follow-up Period for participants not enrolling into the optional Long-term Extension Period) or discontinued the study before the Week 52 assessment and the Safety Follow-up Period.

The 52-Week Treatment Period analyses will formally evaluate all the exploratory efficacy endpoints defined by Week 52, PK concentration and parameters, PD parameters, and safety of MORF-057 during the 52-week Treatment Period and the Safety Follow-up Period. The cumulative data including those from the Induction Period will be used in these analyses. The analysis will include all the results to report in the CSR.

The data from the Main and Exploratory Cohorts may be pooled together in the safety analyses as appropriate.

Long-term Extension Analysis

The analysis of the Long-term Extension will be performed after all the participants enrolled into the Long-term Extension have completed the 26-week extended Treatment Period and the Safety Follow-up Period or discontinued the study before the Week 78 assessment. The analysis will formally evaluate the safety of MORF-057 and selected efficacy endpoints as appropriate during the Long-term Extension plus the Safety Follow-up Period. The results for the Long-term Extension may be reported in a CSR Addendum.

7.6. Multiple Testing Procedures

There will be no multiplicity adjustment.

8. BASELINE AND EXPOSURE SUMMARIES

Unless otherwise specified, all study data from enrolled participants will be listed. Exploratory Cohort data will be listed in the same listings as the Main Cohort. In the summary tables, the Main Cohort, Exploratory Cohort, and total (Main + Exploratory) will be presented in separate columns of the same tables, unless otherwise specified.

8.1. Subject Disposition

The number and percentage of participants will be summarized for the following categories:

- Participants screened
- Participants screen failed
- Participants enrolled
- Participants completed the 12-week Induction Period
- Participants discontinued the treatment during the 12-week Induction Period and reasons for treatment discontinuation
- Participants completed the 52-week total Treatment Period
- Participants discontinued the treatment during the 52-week total Treatment Period and reasons for treatment discontinuation
- Participants discontinued the study and reasons for study discontinuation
- Participants enrolled into the Long-term Extension
  - Participants completed the Long-term Extension.
  - Participants discontinued the treatment during the Long-term Extension and reasons for treatment discontinuation.

For the screened, and screen failure, percentages will be calculated using the number of screened participants as the denominator. Percentages for all other categories of participants will be calculated using the number of participants enrolled as the denominator. Disposition data will also be presented in a listing.

Additionally, the analysis populations for FAS, PP, PK, PK evaluable, PD, and safety defined in Section 7.1 will be summarized in a table by number of participants on the enrolled population.

Reasons for screen failure will also be summarized.

8.2. Protocol Deviations

Deviations from the protocol will be recorded appropriately. Classification of deviations as major protocol deviations, and decisions regarding exclusion of participants and/or participant data from the statistical analyses, will be decided by the study team before the database lock. All

major protocol deviations will be presented in a summary table by deviation category for FAS as appropriate and is provided in a data listing.

8.3. Demographics and Baseline Disease Characteristics

Demographic data and baseline characteristics (including age (years), age category [< 65, ≥ 65], sex, childbearing potential, ethnicity, race, height (cm), weight (kg) and body mass index (BMI) (kg/m^2), country, substance use) will be summarized descriptively for the FAS and PP populations.

The following baseline UC disease history parameters will be summarized using descriptive statistics based on the FAS and PP populations:

- Age at UC diagnosis (years), calculated as (year of UC diagnosis – year of birthday)
- Years since UC diagnosis, calculated as integer of (informed consent date – UC initial diagnosis date)/365.25
- Previous use of advanced therapy for UC (naïve vs experienced)
- Number of advanced therapies received for UC (1, 2, and ≥3)
- Corticosteroid use at baseline (yes/no)
- Modified MCS at baseline (using the central Endoscopy subscore)
- Modified Mayo Clinic Score at baseline (using the Investigator Endoscopy subscore)
- Full Mayo Clinic Score at baseline (using the central Endoscopy subscore)
- Full Mayo Clinic Score at baseline (using the Investigator Endoscopy subscore)
- Mayo component scores at baseline (stool frequency, rectal bleeding, PGA, Investigator Endoscopy subscore, central Endoscopy subscore)
- Robarts Histopathology Index (RHI) Score at baseline
- Family history of UC (yes/no)
- Family history of Chron's Disease (CD) (yes/no)
- Has participant previously been in remission from UC (yes/no)
- Extent of disease by Endoscopy assessment (cm)
- Categorized extent of disease by Endoscopy assessment (cm)
  - Proctosigmoiditis (0 ≤ extent of disease ≤ 30)
  - Left sided colitis (30 < extent of disease ≤ 50)
  - Extensive colitis (extent of disease > 50)

8.4. Medical History

Medical and surgical history will be coded using the MedDRA Version effective at the time of database lock. Medical history will be summarized by SOC and PT for the Safety Analysis Population.

8.5. Prior and Concomitant Medications

The number and percentages of participants with at least one prior medication will be summarized by Anatomical Therapeutic Chemical (ATC) level 4 and PT using the Safety Analysis Population. Number and percentage of participants with at least one concomitant medication will also be summarized by ATC level 4 and PT.

A concomitant medication is defined as any medication taken between the first dose date and the last dose date (inclusive). A prior medication is defined as any medication that starts prior to the first dose of study drug. Medications still ongoing at first dose date or missing stopping date will be considered as both prior and concomitant medications.

Prior UC medications will be summarized separately in the same manner as other prior and concomitant medications.

8.6. Treatment Exposure and Compliance

For exposure and compliance, Main and Exploratory Cohorts are presented in the same listing and summary tables. In the summary table, total (Main + Exploratory) will also be presented as a column. Study drug ([redacted] mg capsules) will be tracked in the IRT system by pill count of dispensation and return, as well as using a patient diary. The pill count results from IRT will be the primary source of calculating treatment exposure and compliance.

Treatment exposure and compliance will be calculated and summarized for the Safety Analysis Set for the following time periods:

- 12-week Induction Period: Day 1 to Week 12 visit.
- 52-week Treatment Period: the 52-week Open-label Treatment Period (the 12-week Induction Period + the 40-week Maintenance Period).
- 52-week Treatment Period plus Long-term Extension.

8.6.1. Extent of Treatment Exposure

The extent of treatment exposure will be assessed by the duration of treatment exposure, which will be defined as the total number of days a participant is exposed to any study drug, regardless of unplanned intermittent discontinuations. For the time Period defined in Section 8.6, the duration of treatment exposure will be calculated as the total number of days from the first dose date (Study Day 1) to the last dose date in the given time period.

- For the 12-week Induction Period, the last dose date will be Week 12 visit date if the participant has completed Week 12 visit, or to the last dose date as recorded on the EOT eCRF if the participant has discontinued the treatment prematurely before Week 12 visit.
- For the 52-week Treatment Period, the last dose date will be the last dose date as recorded on the EOT eCRF, or to Week 52 visit date if the participants have enrolled into the Long-term Extension.
- For the 52-week Treatment Period plus Long-term Extension, the last dose date will be the last dose date as recorded on the EOT eCRF.

Duration of treatment exposure (days) will be summarized using continuous descriptive statistics, and summarized categorically by counts and percentage of participants for each of the following categories and cumulatively according to these categories:

- 1 to 42 days
- 43 to 84 days
- 85 to 182 days
- 183 to 252 days
- 253 to 364 days
- 365 to 546 days
- >546 days

8.6.2. Compliance

Compliance is calculated using the formula below.

$$\text{Compliance rate (\%)} = \frac{Total\ number\ of\ capsules\ consumed}{Total\ number\ of\ capsules\ expected} x100\%$$

Total number of capsules expected = [redacted]

The compliance rate will be summarized using continuous descriptive statistics. The number and percentage of participants in the following compliance rate categories will be reported: < 50%, 50-59%, 60-69%, 70- 79%, 80-100%, > 100%, and < 80%, >120%.

Amount of study drug taken according to pill count based on the IRT and number of days between visits will be listed for reference.

9. EFFICACY ANALYSIS

Unless otherwise specified, all results for enrolled participants in the main and Exploratory Cohort will be listed.

Efficacy will be summarized for the Main Cohort. If the Exploratory Cohort has enough number of participants, data from Exploratory Cohort will also be summarized.

Descriptive statistics will be reported for all primary, secondary, and exploratory data if applicable. No hypothesis testing will be performed for the secondary and exploratory efficacy endpoints.

9.1. Efficacy Variable Overview

Endoscopy will be performed at Screening (Visit 1) and Week 6 (optional), Week 12, Week 52 or EOT visit.

Biopsy samples will be processed by a central laboratory. The histologic endpoints RHI Score, Continuous Geboes Score, and NI will be scored centrally.

The MES will be scored both locally and centrally. If there is a disagreement between the local and central scoring, a second central reader (adjudicator), who will be blinded to knowing if the score is local or central, will select either the local reader or first central reader score to be used as the final score (forced adjudication).

9.1.1. Histologic Scores

Histological improvement will be assessed with the RHI Score, NI, and Continuous Geboes Score

9.1.1.1. Robarts Histopathology Index (RHI) Score

The RHI Score is a weighted sum of 4 histologic items: chronic inflammatory infiltrate score (0-3), lamina propria neutrophils score (0-3), neutrophils in epithelium score (0-3), and erosion or ulceration score (0-3).

Total score will be calculated by an adjudicator. The score ranges from 0 to 33.

9.1.1.2. Nancy Index (NI)

The NI is determined by evaluating 3 histological items: ulceration (0 or 2), acute inflammatory cells infiltrate (0-3), and chronic inflammatory infiltrate (0-4). An overall grade is 0-4, adjudicated based on the subscores.

9.1.1.3. Geboes Score

For the Geboes Score, the microscopic appearance of the mucosa is categorized into 6 grades: structural change only (Grade 0), chronic inflammation (Grade 1), lamina propria neutrophils (Grade 2), neutrophils in epithelium (Grade 3), crypt destruction (Grade 4), and erosions or ulcers (Grade 5).

Each of these grades has 4 to 5 sub-grades. The continuous Geboes Score is calculated by adding up the numerical values of the different subscores, yielding a final value between 0 and 22.

9.1.2. Mayo Clinic Score (MCS) and Mayo Endoscopic Subscore (MES)

The Full MCS (0 to 12) and Modified MCS (0 to 9) will be used to assess clinical improvement. With higher scores indicating more severe disease. The Full MCS is a composite of the following subscores: MES, MCS stool frequency subscore, MCS rectal bleeding subscore, and the PGA.

The Modified MCS is a composite of the following subscores: MES, MCS stool frequency subscore, and MCS rectal bleeding subscore. Each subscore of the Full MCS and Modified MCS is described below; the subscores will be calculated at the timepoints shown in Table 1. Method of calculation is described in Appendix 1.

Stool frequency: Each participant serves as his or her own control to establish the degree of abnormality of the stool frequency.

- 0=Normal number of stools for this participant
- 1=1 to 2 stools more than normal
- 2=3 to 4 stools more than normal
- 3=5 or more stools more than normal

Subscore: 0 to 3

Rectal bleeding: The daily bleeding score represents the most severe bleeding of the day.

- 0=No blood seen
- 1=Streaks of blood with stool less than half the time
- 2=Obvious blood (more than just streaks) or streaks of blood with stool most of the time
- 3=Blood alone passed

Subscore: 0 to 3

Endoscopy: The Endoscopy subscore will be determined both locally and centrally by qualified personnel.

- 0=Normal or inactive disease

- 1=Mild disease (erythema, decreased vascular pattern, no friability)
- 2=Moderate disease (marked erythema, lack of vascular pattern, friability, erosions)
- 3=Severe disease (spontaneous bleeding, ulceration)

Subscore: 0 to 3

Physician's Global Assessment: The PGA acknowledges the 3 other criteria, the participant's daily recollection of abdominal discomfort and general sense of well-being, and other observations, such as physical findings and the participant's performance status.

- 0=Normal
- 1=Mild disease
- 2=Moderate disease
- 3=Severe disease

Subscore: 0 to 3

9.2. Primary Efficacy Endpoint Analysis

The primary efficacy endpoint for this study is change from baseline to Week 12 in RHI Score, which will be tested using the FAS.

The statistical hypotheses for the primary efficacy endpoint are:

- Null hypothesis (H_0): there is no reduction from baseline to Week 12 in RHI Score
- Alternative hypothesis (Ha): the reduction from baseline to Week 12 in RHI Score is larger than zero

9.2.1. Primary Analysis

The data for the primary efficacy endpoint will be assessed for normality using Shapiro-Wilk test. If the data are normally distributed ($p \geq 0.05$), then a two-sided one sample t-test at the alpha = 0.05 will be used for the analysis of the change from baseline in RHI Score (week 12 – baseline). A histogram with a normal bell curve will be produced. If the data are not normally distributed, then a two-sided Wilcoxon signed rank test at the alpha = 0.05 will be used for the analysis. The Wilcoxon signed rank test is to test whether the median of change from baseline deviates from 0 significantly. The p-values will be calculated.

The procedure will be based on the following SAS code sample.

```
proc univariate data=rhi normaltest alpha=0.05;
        var rhi_change_from_baseline;
run;
```

Summary statistics (including n, mean, SD, median, 25th and 75th percentiles, minimum and maximum) will be provided for RHI Score at baseline, Week 12, and change from baseline to Week 12. The 95% CI will be provided for the mean change from baseline assuming that the data are normally distributed.

In the primary analysis, the participants who do not have the RHI Score at the baseline or at Week 12 will be excluded.

9.2.2. Sensitivity Analysis

A sensitivity analysis will be performed to include the participants who have the missing RHI Score at Week 12 by imputing the missing endpoint data at Week 12 using the last available post baseline observation carried forward (LOCF) method. If participants do not have any non-missing post baseline measurement, the missing RHI Score at Week 12 will be imputed using the baseline values.

Sensitivity analysis of the primary efficacy endpoint will also be performed using the PP Population.

9.2.3. Subgroup Analysis

Descriptive analyses will be performed on the primary endpoint across subgroups defined by the following baseline or Screening factors:

- Age group (< 65, ≥ 65)
- Sex (male, female)
- Race (white, non-white)
- Previous use of advanced treatment for UC (naïve vs experienced)
- Corticosteroid use at baseline (yes/no)
- Baseline MES score (2 or 3)

Summary statistics (n, mean, SD, minimum, median, and maximum) using observe cases will be provided for RHI Score at baseline, Week 12, and change from baseline to Week 12 across the subgroups defined by each of the factors above. The 95% CI will be provided for the mean change from baseline assuming that the data are normally distributed

9.2.4. Other Analysis

In addition, the proportion of participants in the FAS with a change from baseline to Week 12 in RHI Score that is at least -7 (that is, a reduction ≥ 7) and the proportion of participants with at least a 50% reduction in RHI Score from baseline to Week 12 will be provided. The 95% CI will also be provided using the normal approximation method.

9.3. Secondary Efficacy Endpoint Analyses

Change from baseline to Week 12 in the Modified MCS (defined in Section 9.1.2) will be analyzed similarly to the primary efficacy endpoint using the FAS. The analysis will be performed for the Modified MCS using the central Endoscopy subscore. Descriptive summary statistics (n, mean, SD, median, 25th and 75th percentiles, minimum, and maximum) will be provided for the Modified MCS at baseline, Week 12, and change from baseline to Week 12. The 95% CI will be provided for the mean change from baseline assuming that the data are normally distributed. Participants who do not have the Modified MCS values at the baseline or at Week 12 will be excluded. No hypothesis testing will be performed for the secondary efficacy endpoint.

Similarly, sensitivity analysis will also be performed for the Modified MCS using the Investigator Endoscopy subscore for FAS.

9.4. Exploratory Efficacy Endpoint Analyses

9.4.1. Clinical Endpoints

The following exploratory efficacy endpoints will be summarized descriptively:

- Change from baseline to Weeks 6 and 52 in RHI Score.
- Change from baseline to Weeks 6, 12, and 52 in the Nancy Index (NI).
- Change from baseline to Weeks 6, 12, and 52 in the Continuous Geboes Score.
- Change from baseline to Weeks 6 and 52 in the Modified MCS.
- Change from baseline to Weeks 6, 12, and 52 in the Full MCS.

The summary will include the number of participants (n), mean, SD, median, 25th and 75th percentiles, minimum, and maximum for baseline values, observed values and observed changes from baseline at scheduled visits (Weeks 6, 12, and 52). The 95% CI will be provided for the mean change from baseline assuming that the data are normally distributed.

Line plots showing mean values (± SD) at each of the scheduled visits of each clinical efficacy endpoints will be presented.

Similarly, the Modified/Full MCS, both the scores using the central Endoscopy subscore and using the Investigator Endoscopy subscore will be summarized.

Additional exploratory summaries will be provided for the following variables, with 95% CI provided using the normal approximation method:

- Proportion of participants in clinical remission and clinical response at Weeks 12 and 52 as determined using the Modified MCS based on the central Endoscopy subscore.
  - Clinical remission is defined as: rectal bleeding subscore of 0; a stool frequency subscore of ≤1; and an MES of ≤1 without friability.

  - Clinical response is defined as: decrease from baseline in the mMCS ≥2 points and ≥30% from baseline, plus a decrease in rectal bleeding subscore ≥1 or an absolute rectal bleeding subscore ≤1.

- Proportion of participants in MCS remission and MCS response at Weeks 12 and 52 based on the central Endoscopy subscore.
  - MCS remission is defined as MCS ≤ 2 and no subscore higher than 1.
  - MCS response is defined as decrease in MCS by ≥3 points and ≥ 30% from baseline, plus a decrease in rectal bleeding score ≥ 1 or an absolute rectal bleeding score ≤ 1.
- Proportion of participants with endoscopic improvement and endoscopic remission at Weeks 12 and 52 as determined using the MES by central reading.
  - Endoscopic improvement is defined as MES ≤ 1.
  - Endoscopic remission is defined as MES = 0.
- Proportion of participants with histologic remission at Weeks 12 and 52 as determined using the RHI Score.
  - Histologic remission by RHI is defined as: RHI ≤ 3 (with 0 for lamina propria neutrophils score and neutrophils in the epithelium score and without ulcers or erosions).
- Proportion of participants with NI score ≤1 at Week 12.
- Proportion of participants in clinical remission at both Weeks 12 and 52, in clinical remission at Week 12 but not at Week 52, and in clinical remission at Week 52 but not at Week 12, as determined using the Modified MCS based on the central Endoscopy subscore.

In the above additional exploratory summaries, participants with missing data at Week 12 or 52 will be considered as non-responders in the corresponding summaries. All the summaries will be provided for the overall group, by previous use of advanced treatment for UC (naïve vs experienced), and by baseline MES score (2 vs 3).

In addition, the proportion of participants with symptomatic remission, the proportion of participants with partial MCS response, the proportion of participants with partial MCS remission will be summarized at each scheduled visit up to Week 52, including the 95% CI. Partial MCS is the sum of stool frequency subscore, rectal bleeding subscore, and PGA. The definitions of symptomatic remission, partial MCS response, and partial MCS remission are:

- Symptomatic remission: stool frequency subscore = 0 (or = 1 with ≥ 1 point decrease from baseline) and rectal bleeding subscore = 0
- Partial MCS response: Decrease in partial MCS ≥2 points and ≥ 30% from baseline, plus a decrease in rectal bleeding subscore ≥1 or an absolute rectal bleeding subscore ≤1.

- Partial MCS remission: partial MCS ≤ 2 points and no individual subscore >1 point.

The calculations of stool frequency subscore and rectal bleeding subscore at each study visit will follow the approach described in Appendix 1 . The proportions of symptomatic remission, partial MCS response and partial MCS remission will be summarized using the following two approaches:

- All enrolled: at each visit, the proportions will be calculated using the number of all participants in the FAS as the denominator, and participants with missing data will be considered as non-responders.
- As observed: at each visit, the proportions will be calculated using the number of participants with data available at that visit.

In both approaches above, the stool frequency subscore, rectal bleeding subscore, and PGA at the EOT visit will be re-allocated to the closest study visits following the approaches described in section 7.3.8. The summaries will be provided for the overall group, by previous use of advanced treatment for UC (naïve vs experienced), and by baseline MES score (2 vs 3). Line plots showing the proportion (± 95% CI) at each of the scheduled visits will be provided.

Line plots showing mean values (± SD) at each of the scheduled visits will also be provided for 1) stool frequency subscore, 2) rectal bleeding subscore, 3) sum of stool frequency and rectal bleeding subscores.

9.4.2. Other Exploratory Endpoints

Change from baseline to Weeks 2, 6, 12, 20, 28, 36, and 52 in high sensitivity C reactive protein (hs-CRP) levels will be summarized descriptively using mean, SD, median, 25^{th} and 75^{th} percentiles, minimum and maximum. Similarly, fecal calprotectin levels will be summarized in the same manner for the same visits.

Line plots showing mean values (± SD) at each of the scheduled visits will be presented.

Change from baseline to Week 65 and Week 78 in hs-CRP levels and fecal calprotectin levels during Long-term Extension will also be summarized descriptively for the participants who have enrolled into the Long-term Extension.

The exploratory analysis of blood and mucosal tissue gene and/or protein expression over time, microbiome composition in stool and mucosal tissue over time, changes in microbiome-derived metabolites in stool and blood over time, and metatranscriptomic changes in the stool and mucosal tissue microbiome over time will be provided in a biomarker analysis plan separate from the study SAP and reported separately.

10. PHARMACOKINETIC ANALYSES

For PK summary tables, Main and Exploratory Cohorts, as well as total column, will be presented together.

10.1. Collection of Blood Samples for MORF-057 Concentration Determination in Plasma

Blood samples will be collected for measurement of plasma concentrations of MORF-057 according to the schedule specified in Table 3.

The sampling windows for the PK assessment are provided below.

Table 3: Sampling Windows

Visit	Collection timepoints and associated windows
2, 3, and 5	Required: [redacted] *Optional:* [redacted]
4, 6, 7, 8, and 9	Required: [redacted]
10	Required: [redacted]

* [redacted] sample to be collected [redacted].

For all [redacted] sampling, the samples should be obtained within [redacted] is administered.

10.2. General Considerations

Samples for determining the MORF-057 concentration in plasma will be analyzed using appropriate validated bioanalytical methods and may be used in MORF-057 concentration determination investigations. A summary of the bioanalytical methods will be provided in the Laboratory Manual.

The PK Population will be used for the generation of individual concentration-time and PK parameter listings as well as individual figures.

The PK Evaluable Population will be used for the summaries of concentration-time, PK parameters, and mean figures.

Only PK concentration-time data collected at Visits 2, 3, and 5 will be used towards NCA PK parameter estimation. PK parameter estimation via NCA cannot be performed on the sparse PK samples collected for all the other visits. For these visits, the available plasma concentration-time data will be summarized.

Nominal sampling time points relative to dosing will be used for plasma concentration-time summaries and mean figures of plasma concentration-time data. Actual sampling times will be used for individual concentration-time figures, including all recorded concentrations regardless of timing.

All plasma concentration-time data will be reported to the same number of significant figures as displayed in the bioanalytical data.

PK parameters for MORF-057 will be estimated by NCA using the software Phoenix® WinNonlin® Version 8.3 or higher (Certara, USA).

Plasma concentrations at the optional 12 hr post-dose (C_{12} and C_{trough}), $C_{max}/C_{max,ss}$, $t_{max}/t_{max,ss}$, C_{last}, and t_{last} will be obtained directly from experimental observations. If multiple maxima occur at equal concentrations, the first temporal value will be taken as the $C_{max}/C_{max,ss}$ and $t_{max}/t_{max,ss}$. Average plasma concentrations based on BID dosing (C_{ave}) will be calculated as AUC_{tau}/tau, where feasible. If no 12 hr post-dose sample was obtained, C_{12} or C_{trough} will be calculated using one of two methods to allow for the calculation of AUC_{0-12} or AUC_{tau}:

- C_{12} or C_{trough} will be calculated using an extrapolation method via Phoenix WinNonlin standard calculations. If no lambda z is estimated, then
- C_{12} or C_{trough} will be imputed using the available pre-dose concentration for that visit day. Of note, MORF-057 exhibits diurnal variation and trough concentrations from an [redacted] vs a [redacted] do vary. A footnote will be included to indicate that the trough concentrations obtained from a [redacted] will not reflect a true C_{trough} of an [redacted].

All AUCs including AUC_{0-t}, AUC_{tau}, and AUC_{0-12} will be calculated by the linear-up/log-down trapezoidal method, using actual elapsed time values. If the [redacted] or tau time points are not collected, then the AUC_{0-12} and AUC_{tau} will be calculated using an extrapolated concentration via standard WinNonlin calculation methods to report a partial AUC or AUC_{tau}.

In addition, AUC_{0-inf} will be calculated as outlined below following single dose administration (Visit 2; Study Day 1):

$$AUC_{0-inf} = AUC_{0-t} + (C_{last}/\lambda_z),$$

where C_{last} is the last temporal measured plasma concentration post-dose corresponding to t_{last}.

Regression parameters for estimation of λ_z, including the number of time points used, time point range used for the regression (minimum time, maximum time) and adjusted coefficient of determination (adj R^2) will be listed.

The apparent first-order terminal phase elimination half-life, $t_{1/2}$, where determinable, will be calculated as the natural log of 2 divided by the apparent first-order terminal phase elimination rate constant, lambda$_z$ (λ_z). The λ_z will be determined by plotting the concentration-time data on a semi-logarithmic scale and estimated by linear least square regression analysis. The number of

data points included in the regression will be determined by best fit. Visual inspection of the λ_z will also be performed to ensure that a minimum of 3 data points in the terminal phase, excluding C_{max}, is included. The upper and the lower time points, as well as the number of time points used for the λ_z estimation will be reported. For λ_z derived parameters ($t_{1/2}$, $AUC_{0\text{-}inf}$, CL/F, and V_z/F) to be summarized, the adj R^2 value reported in Phoenix®WinNonlin® must be ≥ 0.8.

For time-related PK parameters (t_{max}, $t_{max.ss}$, $t_{1/2}$, and t_{last}) descriptive statistics will include N, arithmetic mean, SD, CV, geometric mean, geometric CV, median, minimum, and maximum.

The $AUC_{\%extrap}$ parameter will be listed and not summarized. This parameter will be reported to one decimal place. The adj-R^2 parameter will be listed and not summarized and will be reported to at least five significant figures.

PK parameters for clearance and volume of distribution following single dose administration will be calculated as follows: $CL/F = Dose/AUC_{0\text{-}inf}$ and $V_z/F = Dose/\lambda_z*AUC_{0\text{-}inf}$

PK parameters for clearance and volume of distribution at steady state following multiple-dose BID administration will be calculated as follows: $CLss/F = Dose/AUC_{tau}$ and $V_z/F = Dose/\lambda_z*AUC_{tau}$, where tau = 12 hours.

For all other PK parameters, descriptive statistics will include n, arithmetic mean, SD, CV, geometric mean, geometric CV, median, minimum, and maximum. These PK parameters will be reported to the same significant figures as displayed in the bioanalytical data, apart from λ_z, which will be reported to at least five significant figures.

For the accumulation indices (AI_{Cmax} and AI_{AUC}), descriptive statistics will include N, arithmetic mean, SD, CV, geometric mean, geometric CV, median, minimum, and maximum. These parameters will be reported to one decimal place.

Figures will be generated to display mean and individual MORF-057 plasma concentration versus time curves on linear and semilogarithmic scales.

Other PK evaluations may be performed for exploratory reasons as needed.

10.3. Pharmacokinetic Analysis

The following plasma PK parameters in Table 4 will be calculated for MORF-057 (as deemed appropriate):

Table 4: Pharmacokinetic Parameters by Visit

PK Parameter	Description
Visit 2 (Study Day 1)	
$AUC_{0\text{-}12}$	Area under the concentration-time curve from time zero (0) to 12 hours post-dose.
$AUC_{0\text{-}t}$	Area under the concentration-time curve from time 0 to the last measured concentration post-dose.

PK Parameter	Description
$AUC_{0\text{-}inf}$	Area under the concentration-time curve from time 0 extrapolated to infinity.
C_{max}	Maximum observed plasma concentration post-dose.
C_{12}	Plasma concentration at 12 hours post-dose.
C_{last}	Last temporal measured plasma concentration post-dose.
t_{last}	Time of the last measurable concentration post-dose.
t_{max}	Time of maximum observed plasma concentration post-dose.
CL/F	Apparent total body clearance after single dose oral administration.
V_z/F	Apparent volume of distribution during terminal phase after single dose (oral administration).
Adj-R^2	Adjusted coefficient of determination.
λ_z	Apparent first-order terminal elimination phase rate constant.
$t_{1/2}$	Apparent first-order terminal elimination half-life.
Visit 3 and Visit 5	
AUC_{tau}	Area under the concentration-time curve across the dosing interval (t = 12 hours; BID).
$C_{max,ss}$	Maximum observed plasma concentration post-dose at steady state.
C_{trough}	Trough plasma concentration (measured concentration at the end of a dosing interval) (12 hours post-dose).
$t_{max,ss}$	Time of maximum observed plasma concentration post-dose at steady state.
CL_{ss}/F	Apparent total body clearance at steady state after oral administration.
V_z/F	Apparent volume of distribution at steady state after oral administration.
Adj-R^2	Adjusted coefficient of determination.
$\lambda_{z,f}$	Apparent functional first-order elimination phase rate constant.
$t_{1/2,f}$	Apparent functional first-order elimination half-life.
AI_{AUC}	Accumulation index based upon AUC_{tau} ($AUC_{tau}/AUC_{0\text{-}12}$). $AUC_{0\text{-}12}$ will be determined using [redacted] on Visit 2 Study Day 1 and AUC_{tau} will be calculated across the dosing interval of [redacted] of Visit 3 and Visit 5, separately.
AI_{Cmax}	Accumulation index based upon $C_{max,ss}$ ($C_{max,ss}/C_{max}$). C_{max} will be determined using [redacted] on Visit 2 Study Day 1 and C_{max} will be calculated across the dosing interval of [redacted] of Visit 3 and Visit 5, separately.
C_{ave}	Average plasma concentration based on [redacted] dosing.

In addition to the parameters above, MORF-057-derived metabolite measurements may be performed as deemed appropriate as an exploratory assessment.

Plasma concentrations of MORF-057 will be listed by visit, participant ID, and timepoint and will be summarized by visit and timepoint using descriptive statistics (n, arithmetic means, standard deviation (SD), CV, median, minimum, maximum, geometric mean, and geometric CV).

PK parameters for MORF-057 (for Visits 2, 3, and 5 only) will be listed by visit and by participant ID and summarized by visit. The arithmetic means (± SD) of plasma concentrations of MORF-057 will be presented graphically on both linear and semilogarithmic scales for each visit. For individual profiles, figures will be presented for each participant with concentration-time profiles on both linear and semi-logarithmic scales for each visit. Concentration values of zero will not be plotted in the semi-logarithmic plots.

PK analyses will be conducted as deemed appropriate and may be reported separately from the CSR.

11. PHARMACODYNAMIC ANALYSES

PD results will be listed and summarized descriptively for the observed values based on the PD population. For summary tables, Main and Exploratory Cohorts will be presented together.

Only RO will be plotted. A line plot will be presented for the mean and SD over nominal time points (Day 1 to Week 52). A box plot will be presented for RO by nominal timepoint (Day 1 to Week 52). Results from RO measurements made from optional blood samples collected at 12h after the AM dose will be analyzed separately from those that are determined from blood samples collected before the AM dose.

Besides PD biomarkers received directly from the lab, expression of CCR9 mRNA in blood (relative to the pre-dose baseline) will also be calculated at each timepoint and listed. This value is calculated using the lab-reported parameter CCR9_IPO8_DeltaCt, where the expression of CCR9 mRNA in blood at a given timepoint relative to baseline is calculated using the following formula, where baseline is defined separately by period.

Relative expression at timepoint x = $2^{-(\text{CCR9\_IPO8\_DeltaCt at timepoint x - CCR9\_IPO8\_DeltaCt at baseline})}$.

Immunophenotyping results will be listed but analyzed and reported separately from the CSR.

Additional analyses of PD parameters may be specified in a biomarker analysis plan separate from the study SAP and will be reported in a separate document.

12. SAFETY ANALYSES

All safety analyses will be conducted using the Safety Analysis Population, unless specified otherwise. For summary tables, Main and Exploratory Cohorts, as well as total (the pooled Main and Exploratory Cohorts), will be presented as separate columns in the same table if applicable.

The summary of safety results (i.e., adverse events, clinical laboratory, vital signs, and ECG) will be presented based on the safety data during the on-Treatment Period, which is defined as the period from the administration of the first dose of study drug up to 7 days after the last dose of study drug, unless specified otherwise. The listings will include all data. No hypothesis testing will be performed on safety data.

12.1. Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) dictionary (effective version at the time of database lock) will be used for coding AEs. A treatment-emergent AE (TEAE) is defined as an AE that occurs during the period from the administration of the first dose of study drug up to 7 days after the last dose of study drug.

AEs will be classified as related or not related to the study drug by Investigator. If the relationship of an AE is missing/unknown, the AE will be considered study drug related.

The following summary tables will be presented:

- Overall Summary of TEAEs.
  - TEAE
  - Serious TEAE
  - TEAE with grade 3 or worse
  - Treatment-related TEAE
  - Treatment-related serious TEAE
  - TEAE leading to death
  - TEAE leading to permanent treatment discontinuation
- TEAEs by system organ class (SOC) and preferred term (PT).
- TEAEs by SOC, PT, and maximum Severity.
- TEAEs by SOC, PT, and Relationship to Study Drug.
- Serious TEAE by SOC and PT
- Serious TEAEs by SOC, PT, and maximum Severity
- Serious TEAEs by SOC, PT, and Relationship to Study Drug
- Non-serious TEAEs (PTs with an incidence >5%) by SOC and PT

If more than one event occurred with the same PT or SOC for the same participant, the participant will be counted only once for that term.

The following line listings will be provided:

- Listing of serious TEAE including duration.
- Listing of all AEs with a flag for treatment-emergence and variable for duration.
- Listing of TEAEs Leading to Withdrawal of Study Treatment.
- Listing of all deaths.
- Listing of TEAE associated with Overdose

12.2. Clinical Laboratory Evaluations

Observed and changes from baseline for central clinical laboratory results (hematology, coagulation, chemistry, urinalysis) will be summarized descriptively for the on-Treatment Period at all scheduled visits (Baseline, Weeks 2, 6, 12, 20, 28, 36, 44, 52, 65, and 78) for each analysis specified in Section 7.5 as appropriate.

Line plots for the mean (SD) and mean change from the baseline (SD) over nominal time will also be provided for hematology. Peak alanine transaminase (ALT) or aspartate transaminase (AST) vs. peak total bilirubin post baseline will be plotted.

The number of participants ever experienced abnormalities (scheduled and unscheduled) for each lab parameter during on-Treatment Period will be summarized using the shift table for the 12-week Induction Period, 52-week on-Treatment Period, and Long-term Extension.

A listing will be provided for altered liver function test (i.e., patients with any elevated ALT or AST >3 x ULN and associated with an increase in total bilirubin >2 x ULN), including ALT, AST, ALP, and total bilirubin.

A list of abnormal laboratory values will be created separately.

Local laboratory results will be listed separately from central as appropriate, but they will not be summarized with central lab results due to calibration differences.

12.3. Vital Signs

The observed vital sign results (systolic blood pressure, diastolic blood pressure, heart rate, temperature, respiratory rate, weight, and BMI) and change from baseline will be summarized descriptively for the on-Treatment Period at each scheduled visits (Baseline, Weeks 2, 6, 12, 20, 28, 36, 44, 52, 65, and 78) for each analysis specified in Section 7.5 as appropriate

A shift table from baseline of each parameter will also be presented. All vital sign data by participant ID will be presented in a listing.

12.4. ECG

Safety ECG results (PR interval, QRS duration, QT interval, and QTcF interval) will be summarized descriptively for the on-Treatment Period at each scheduled visit (Baseline, Weeks 6, 12 and 52) for the observed value and change from baseline. Overall interpretation along with clinical significance will be summarized.

A shift table of QTcF will be presented for the on-Treatment Period. QTcF > 450 ms among male participants and QTcF > 470 ms among female participants will be considered above normal ranges.

12.5. Physical Examinations

Abnormality in physical exams will be reflected in the medical history and adverse event summaries.

12.6. Endoscopy

Extent of disease, distance from anus where sample of the worst inflammation and non-inflammation are taken in cm, will be listed.

12.7. Other Safety Measures

The PML checklist, COVID-19 test, overdose reports and pregnancy results will be presented in listings only.

No other safety analyses have been prospectively defined. If, however, after study results are reviewed, or Sponsor recommend additional safety parameters or analyses be completed, they will be fully described and documented in the final CSR. The SAP does not need to be amended to complete any other safety measures identified as post-hoc.

13. REPORTING CONVENTIONS

The following reporting conventions will be adopted for the presentation of study data. These conventions will enhance the review process and help to standardize presentation with common notations.

13.1. General Reporting Conventions

- All tables and data listings will be developed in Landscape Orientation in PDF format, unless presented as part of the text in a CSR.
- Figures will be presented in Landscape Orientation, unless presented as part of the text in a CSR.
- Legends will be used for all figures with more than one variable or item displayed.
- Figures will be in presented in color with treatment groups distinguished by different symbols and colors. Lines in figures should be wide enough to view the line after being photocopied.
- Specialized text styles, such as bolding, italics, borders, shading, superscripted and subscripted text will not be used in tables, figures, and data listings unless they add significant value to the table, figure, or data listing.
- Only standard keyboard characters should be used in tables and data listings. Special characters, such as non-printable control characters, printer specific, or font specific characters, will not be used on a table, figure, or data listing. Hexadecimal character representations are allowed (e.g.,μ,α,β).
- All titles will be centered on a page. The ICH numbering convention is to be used for all tables, figures, and data listings.
- All footnotes will be left justified and the bottom of a page. Footnotes must be present on the page where they are first referenced. Footnotes should be used sparingly and must add value to the table, figure, or data listing. If more than four footnote lines are planned, then a cover page may be used to display footnotes.
- Missing values for both numeric and character variables will be presented as blanks in a table or data listing. A zero (0) may be used if appropriate to identify when the frequency of a variable is not observed.
- All date values will be presented as YYYY-MM-DD (e.g., 2013-05-17) ISO 8601 format.
- All observed time values will be presented using a 24-hour clock HH:MM:SS format (e.g., 01:35:45 or 11:26). Seconds should only be reported if they were measured as part of the study, also in ISO 8601 format.
- Time durations will be reported in mixed HHh MMm SSs notation (e.g., 5h 32m, or 27h 52m 31s). The use of decimal notation to present (display) time durations should be avoided (e.g., 0.083h = 5m) unless it is necessary to show the computation of time

differences in a table, figure, or data listing, in which case both notations may be used to display the time duration.

- All tables, figures, and data listings will have the Table, Listing, or Graph status (DRAFT, FINAL), and a date/time stamp on the bottom of each output.
- All analysis programs developed for a table, figure, or data listing display will be self-contained to facilitate transfer of programs to multiple computing environments and transfer to a regulatory agency (if requested).

13.2. Population Summary Conventions

- Population(s) represented on the tables or data listings will be clearly identified in the last title of the Table as "<name of population>" and will be identical in name to that identified in the protocol or SAP.
- Consistent terminology will be used to define and identify a population.
- Sub-population(s) or special population(s) descriptions will provide sufficient detail to ensure comprehension of the population used for analysis in a table or figure.
- Population sizes may be presented for each treatment or dosing category as totals in the column header as (N=xxxx), where appropriate.
- Population sizes shown with summary statistics are the samples sizes (n) of participants with non-missing values.
- All population summaries for categorical variables will include all categories that were planned and for which the participants may have had a response. Percentages corresponding to null categories (cells) will be suppressed.
- All population summaries for continuous variables will include N, mean, SD, minimum, and maximum. Other summaries (e.g., number missing, median, quartiles, 5%, 95% intervals, CV or %CV) may be used as appropriate.
- All percentages are rounded and reported to xx.x%. A percentage of 100% will be reported as 100%. No value of 0% will be reported. Any computation of percent that results in 0% is to be presented as a blank.
- Population summaries that include p-values will report the p-value to four decimal places with a leading zero (0.0001). All p-values reported on default output from statistical software (i.e., SAS® Software version) may be reported at the default level of precision. P-values <0.0001 should be reported as <0.0001 not 0.0000.

APPENDIX 1 MAYO CLINIC SCORE (MCS) CALCULATION

The Full MCS is a composite of four subscores, each ranging from 0-3: MES, stool frequency, rectal bleeding, and the PGA. The Modified MCS is a composite of three subscores: MES, stool frequency, and rectal bleeding.

- The Full MCS is calculated as the sum of the four subscores for MES, stool frequency, rectal bleeding, and the PGA.
- The Modified MCS is calculated as the sum of the three subscores for MES, stool frequency, and rectal bleeding.

MES will be derived based on the answer option for 'Mucosal appearance at Endoscopy' in the MES (Central) eCRF form entered at the scheduled visits. The PGA will be recorded in Physician Global Assessment eCRF form at visits. Participants will complete the stool frequency and rectal bleeding components into their Participant Diary daily. The derivation of stool frequency and rectal bleeding subscores from the diary entries are described below.

Calculation of the stool frequency and rectal bleeding subscores

- For baseline calculation, use 'Visit Date' entered on the visit Date eCRF form for Visit 2 (Week 0) as the reference date. For post baseline calculations at any visits with Endoscopy procedure performed, use 'Visit Date' entered on the visit Date eCRF form or the date of Endoscopy procedure, whichever comes first, as the reference date. For post baseline calculations at any visits with no Endoscopy procedure performed, use 'Visit Date' entered on the visit Date eCRF form as the reference date.
- Take the average of the three most recent consecutive stool frequency/rectal bleeding diary submissions within the past 7 days from the reference date. If three consecutive diary submissions are not available, then use the three most recent diaries within the past 7 days. If there are fewer than three submissions or if the reference date is not available, then the subscores will be set to missing. A diary submission can be considered in the calculation if both stool frequency and rectal bleeding data are available.
- Exclude the following days if Endoscopy procedure is performed: Bowel preparation period, and Endoscopy Start Date to End Date + 3 days. Bowel preparation might not be done always and in that case, do not exclude any days for bowel preparation. Bowel preparation and Endoscopy dates are recorded in the Endoscopy eCRF form.
- Round the average to the nearest integer (Decimal 0.5 and above will be rounded to the next highest integer. Decimal less than.5 will be rounded to the current integer. Example: 1.5 will be rounded to 2 and 1.4 will be rounded to 1).
- For rectal bleeding subscore, take the rounded average number. Calculate the stool frequency subscore as below:
  - 0 if (rounded average number) – normal number of stools ≤ 0

- 1 if (rounded average number) – normal number of stools = 1 or 2
- 2 if (rounded average number) – normal number of stools = 3 or 4
- 3 if (rounded average number) – normal number of stools > 4

Where the normal number of stools are the values recorded in the UC History eCRF form, i.e.,

- The value entered for the question 'On average, when in remission from UC, what was the normal number of stools the subject had in 24 hours?', when 'Has subject previously been in remission from UC?' = 'Yes',
- The value entered for the question 'On average, prior to developing Ulcerative Colitis symptoms or Ulcerative Colitis diagnosis, what was the normal number of stools the subject had in 24 hours?', when 'Has subject previously been in remission from UC?' = 'No'.