CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 2a, Open-label, Single-arm Study to Evaluate the Efficacy, Safety, and Tolerability of MORF-057 in Adults with Moderately to Severely Active Ulcerative Colitis **(EMERALD-1)**
Protocol Number:	MORF-057-201
Compound:	MORF-057
Brief Title:	A Phase 2a Study to Evaluate the Efficacy and Safety of MORF-057 in Adults with UC
Indication	Moderately to severely active ulcerative colitis
Study Phase:	2a
Sponsor:	Morphic Therapeutic, Inc. 35 Gatehouse Drive, A2 Waltham, MA 02451, USA
IND Number:	147011
Date of Protocol:	Version 4, 27 July 2023

Confidentiality Statement

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Protocol V1	16 December 2021
Protocol V2	09 February 2022
Protocol V3	01 September 2022
Protocol V4	27 July 2023

Version 4 dated 27 July 2023

Overall Rationale for the Amendment

The overall rationale for the protocol amendment Version 4.0 is to introduce planned analyses of the 52-week Treatment Period for the Main Cohort, and the 12-week Treatment Period for the Exploratory Cohort.

The protocol amendment Version 4.0 is considered Substantial by the Sponsor, in accordance with international regulations.

Version 3 dated 01 September 2022

Overall Rationale for the Amendment

The overall rationale for the protocol amendment Version 3.0 is to add the following major changes:

- Change Open-label Extension to Long-term Extension and add details to Schedule of Assessments, add corresponding objective and endpoints, and update study design/schema
- Clarify and expand the enrollment goal
- Update the indication name
- Add Safety Analysis Population and PK Evaluable Population
- Remove the planned interim analysis for sample size reassessment and accordingly adjust the statistical significance level to be used in the analysis of the primary efficacy endpoint
- Clarify the planned analyses for Induction Period, 52-week Treatment Period, and Long-term Extension
- Revise Inclusion/Exclusion criteria regarding rectal bleeding subscore, body mass index, surgical procedures, tuberculosis testing, exploratory cohort (vedolizumab failures) and vedolizumab levels testing
- Specify timing of blood draws for safety-related laboratory tests
- Add the progressive multifocal leukoencephalopathy (PML) objective list
- Add guidance on overdose reporting

- Add guidance on budesonide tapering
- Remove erythrocyte sedimentation rate test
- Add PML Adjudication Committee responsibilities

The protocol amendment Version 3.0 is considered Substantial by the Sponsor, in accordance with international regulations.

Version 2 dated 09 February 2022

Overall Rationale for the Amendment

The overall rationale for the protocol amendment Version 2.0 is to extend the study treatment period from 12 weeks to 52 weeks (resulting in the addition of 5 new study site visits), to add European study sites, and to add the option of participating in an Open-label Extension study at the end of the current study.

The protocol amendment Version 2.0 is considered Substantial by the Sponsor, in accordance with international regulations.

The changes of the protocol amendment Version 2.0 in comparison to Version 1.0 are summarized in Section 10.10.

Summary of Changes Table

Changes to the protocol as implemented by the protocol amendment Version 4.0 in comparison to Version 3.0 are summarized in the Summary of Changes table below. New text is shown in *italics*, deleted text is shown in ~~strikeout~~, and **bold** text is informational. In addition to the changes provided in the Summary of Changes table, minor editorial changes have been made throughout the protocol.

Version 4.0 vs Version 3.0

Section No. and Name	Description of Change	Brief Rationale
Synopsis - Overall Design Section 4.1. Overall Design	Thus, there will be a total of 30 to 40 participants in the study. ~~because w~~*W*hen the Main Cohort recruits 30 participants, the ~~entire~~ study will be closed ~~to new enrollees~~ *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.*	To clarify that the remaining participants already in screening, when the maximum number of participants have enrolled into the main cohort, will be allowed to complete the process and enroll, if eligible
Synopsis - Statistical Methods; General Considerations Section 9.2.1. General Considerations	*The Main Cohort and Exploratory Cohort will be analyzed separately, unless specified otherwise. Data from participants in the Exploratory Cohort will be analyzed only for exploratory purposes.*	To clarify that the Main Cohort and Exploratory Cohorts will be analyzed separately
Synopsis - Statistical Methods; Analyses for Induction Period, 52-week Treatment Period, and Long-term Extension Section 9.3. Analyses for Induction Period, 52-week Treatment Period, and Long-term Extension	There will be ~~2~~*4* analyses planned: *two*~~one~~ for the 12-week Induction Period*s of the Main and Exploratory Cohorts respectively* (i.e., the period for the primary efficacy endpoint) and the other *two* for the 52-week Treatment Period*s of the Main and Exploratory cohorts respectively* (i.e., the 12-week Induction Period plus the 40-week Maintenance Period and the Safety Follow-up).	Introduction of the Main Cohort 52-week analysis and Exploratory Cohort 12-week analysis
Synopsis - Statistical Methods; Induction Period Analysis Section 9.3. Analyses for Induction Period, 52-week Treatment Period, and Long-term Extension, Induction Period Analysis	The analysis of the Induction Period 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 concentrations and parameters, 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*	To clarify the Main Cohort induction analyses

Section No. and Name	Description of Change	Brief Rationale
	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 th~~is~~*e Induction Period* analys~~i~~*e*s.	
Synopsis - Statistical Methods; 52-week Treatment Period Analysis Section 9.3. Analyses for Induction Period, 52-week Treatment Period, and Long-term Extension, 52-week Treatment Period Analysis	*For the Main Cohort, t*~~T~~he 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. 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* analys~~e~~*i*~~s~~ will formally evaluate all the exploratory endpoints defined by Week 52, PK concentration and parameters, and safety of MORF-057 during the 52-week open-label Treatment Period plus the Safety Follow-up Period. The cumulative data, including those from the Induction Period, will be used in th~~isese~~ analys~~i~~*e*s. *The data from the Main and Exploratory Cohorts may be pooled together in the safety analyses as appropriate* *For the Main Cohort participants, t*~~T~~he 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. 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 participants, the analysis of the 52-week Treatment Period will be performed after all 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* analys~~i~~*e*s *for the Main and Exploratory Cohorts* will formally evaluate all the exploratory endpoints defined by Week 52, PK concentration and parameters, and safety of MORF-057 during the 52-week open-label Treatment Period plus the Safety Follow-up Period. The cumulative data, including those from the Induction Period, will be used in th*ese*~~i~~s analys~~e~~*i*s.	Introduction of Main Cohort 52-week analysis and Exploratory Cohort 12-week analysis

Section No. and Name	Description of Change	Brief Rationale
	The data from the Main and Exploratory Cohorts may be pooled together in the safety analyses as appropriate.	
Section 1.2 Schedule of Assessments (SoA); Tables 1 and 2. Schedule of Activities for the Treatment Period and for the Long-term Extension Section 8.8.1 Physical Examinations	**Schedule of Activities, Table 1, Footnote "r" and Table 2, Footnote "h":** Footnote "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 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. Footnote "h": A targeted physical exam is to be performed at all visits (see 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. Physical examinations will be performed at the timepoints specified in the SoA (Section 1.2). A complete physical exam is required at Screening and Visit 10/EOT, and a targeted exam may be performed at all other required visits. For unscheduled visits, *that involve the Instigator or clinical assessment and not the visits that would be for dispensing study drug or for laboratory draws only,* the choice of whether to perform a complete or targeted physical exam is at the discretion of the Investigator and will depend on the reason for the unscheduled visit. Physical examinations must be performed by an Investigator or a medically qualified designee.	To clarify that a completed or targeted physical exam only needs to be performed for visits that involve the Investigator or clinical assessment visits
Section 1.2. Schedule of Assessments (SoA); Tables 1 and 2. Schedule of Activities for the Treatment Period and for the Long-term Extension Section 8.8.2. Vital Signs	**Schedule of Activities, Table 1, Footnote "s" and Table 2, Footnote "i":** 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.	To clarify that vital signs only need to be performed during clinical assessments
Section 1.2. Schedule of Assessments (SoA); Table 1. Schedule of Activities for the Treatment Period Section 8.10.1. Collection of Blood Samples for MORF-057 Concentration Determination in Plasma	**Schedule of Activities, Table 1, Footnote "w":** PK testing at Visits 2, 3, and 5: Blood sampling will be required before the [redacted] and at 1, 2, 3, 4, and 6 hours after the [redacted]. Blood sampling will be optional at 8, 10, and 12 hours after the [redacted]. The 12-hour [redacted] sample will be collected prior to the second daily dose. Time windows for PK sampling can be found in Section 8.10.1. Each [redacted] sample should be obtained within approximately 30 minutes before the [redacted] is administered ~~and at 12 hours (±1 hour)~~ [redacted]	To clarify that all [redacted] sampling should be collected approximately 30 minutes before [redacted] is administered. Samples do not need to be collected 12 hours after the previous dose.

Section No. and Name	Description of Change	Brief Rationale
	For al[redacted] sampling, the samples should be obtained within approximately 30 minutes before the [redacted] is administered. ~~Furthermore, the samples should be obtained at 12 hours (±1 hour)~~ [redacted]	
Section 1.2. Schedule of Assessments (SoA); Table 1. Schedule of Activities for the Treatment Period	**Schedule of Activities, Table 1, Footnote "ii":** *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.*	To clarify that if a participant received a sigmoidoscopy/coloscopy within 12 weeks of their most recent one, they are not required to repeat it
Section 2.2.2. Clinical Findings	*Study MORF-057-104 was conducted to evaluate the safety, tolerability, PK, PD, and FE of MORF-057 optimized formulation with[redacted] capsules, which were tested at [redacted] of [redacted] mg, [redacted] mg, and [redacted] mg and at [redacted] of [redacted] mg [redacted]. ([redacted] mg/capsule) in healthy participants. MORF-057 [redacted] capsules were demonstrated to be safe and well tolerated, and only mild, non-serious adverse events (AEs) were observed, none of which were related to MORF-057. The [redacted] capsules were rapidly absorbed, with a median T_{max} of approximately 2.5 hours. High levels of target engagement of the $\alpha_4\beta_7$ integrin receptor were observed following [redacted] doses of [redacted] mg MORF-057, with 99% mean $\alpha_4\beta_7$ receptor occupancy observed after 14 days of [redacted] mg [redacted]. dosing. Changes in lymphocyte subsets were consistent with those reported for other integrin pathway inhibitors. Overall, the new MORF-057 [redacted] capsule formulation performed well and thus was recommended for use in the MORF-057 Phase 2 program.*	To add results of Study MORF-057-104
Section 2.3.2. Risks	*Collectively from 4 completed MORF-057 studies conducted in [redacted] subjects, MORF-057 was well tolerated with or without food or in combination with midazolam. There were no deaths or SAEs.*	To summarize all 4 completed MORF-057 studies in healthy subjects

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ABBREVIATIONS

5-ASA	5-aminosalicylates
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate transaminase
AT	Advanced therapy
AUC	Area under the concentration-time curve
AUC_{0-12}	Area under the concentration-time curve from time 0 to 12 hours post-dose
AUC_{0-24}	Area under the concentration-time curve from time 0 to 24 hours post-dose
AUC_{0-inf}	Area under the concentration-time curve from time 0 to infinity
AUC_{0-t}	Area under the concentration-time curve from time 0 to last measurable concentration
AUC_{tau}	Area under the concentration-time curve across the dosing interval
AUC_{last}	Area under the concentration-time curve from time 0 to last data point
[redacted]	[redacted]
BMI	Body mass index
C_{12}	Plasma concentration at 12 hours post-dose
C_{24}	Plasma concentration at 24 hours post-dose
CCR9	C-C chemokine receptor 9
CD	Crohn's disease
CIMS	Central Image Management Solutions
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	Maximum observed plasma concentration
CRF	Case report form
C_{trough}	Trough plasma concentration (measured concentration at the end of a dosing interval, taken before the next dose)
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
CYP3A	Cytochrome P450 3A
CYP3A4	Cytochrome P450 3A4
DNA	Deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture database
ELISA	Enzyme-linked immunosorbent assay
EOT	End of Treatment
FAS	Full Analysis Set
FDA	Food and Drug Administration
FE	Food effect

GCP	Good Clinical Practice
hCG	human chorionic gonadotropin
HIV	Human immunodeficiency virus
hs-CRP	High-sensitivity C-reactive protein
IBD	Inflammatory bowel disease
IC_{50}	Half maximal inhibitory concentration
IC_{90}	90% inhibitory concentration
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IL	Interleukin
IRB	Institutional Review Board
JAK	Janus kinase
LVEF	Left ventricular ejection fraction
MAD	Multiple ascending dose
MCS	Mayo Clinic Score
MDRD	Modification of Diet in Renal Disease
MES	Mayo Endoscopic Score
NI	Nancy Index
NOAEL	No-observed-adverse-effect level
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PGA	Physician's Global Assessment
PI	Principal Investigator
PIMS	Physiological intermolecular modulation spectroscopy
PK	Pharmacokinetics
PML	Progressive multifocal leukoencephalopathy
P.O.	By mouth
PP	Per Protocol (Population)
PPD	Purified protein derivative
PT	Preferred Term
QTcF	QT interval corrected through use of Fridericia's formula
RAMP	Risk Assessment and Minimization Program
RHI	Robarts Histopathology Index
RO	Receptor occupancy
S1P	Sphingosine-1-phosphate
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

SFU	Safety Follow-up
SoA	Schedule of activities
SOC	System Organ Class
SUSAR	Suspected unexpected serious adverse event
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
t_{max}	Time to reach C_{max}. Defined as the first point if multiple maximum values occur
TNF-α	Tumor necrosis factor alpha
UC	Ulcerative colitis
ULN	Upper limit of normal
WBC	White blood cell

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 2a, Open-label, Single-arm Study to Evaluate the Efficacy, Safety, and Tolerability of MORF-057 in Adults with Moderately to Severely Active Ulcerative Colitis **(EMERALD-1)**

Brief Title: A Phase 2a Study to Evaluate the Efficacy and Safety of MORF-057 in Adults with UC

Rationale:

Inflammatory bowel disease (IBD) is a term used to describe 2 idiopathic conditions characterized by chronic inflammation of the gastrointestinal tract: Crohn's disease (CD) and ulcerative colitis (UC). In patients with UC, mucosal inflammation and ulceration occurs in the rectum and can extend proximally to a portion of or to the full colon, resulting in symptoms and signs including the urgency to defecate, fatigue, bloody stool, diarrhea, nausea or loss of appetite, weight loss, fever, and anemia. Initial therapy for moderately to severely active UC generally includes 5-aminosalicylates (5-ASA) and steroids. However, long-term use of steroids has been associated with adverse effects.

Integrins are a family of receptors known to regulate aspects of mucosal inflammation that underlie UC disease progression. Ulcerative colitis is associated with activation of immune cells expressing the integrin $\alpha_4\beta_7$ and trafficking of these cells from the bloodstream into the gut and the surrounding tissue to promote chronic inflammation. Specific inhibition of $\alpha_4\beta_7$ is a validated mechanism for the treatment of IBD, as demonstrated by vedolizumab ([redacted]), a monoclonal antibody administered via intravenous infusion. MORF-057 is a small molecule that is designed to selectively inhibit integrin $\alpha_4\beta_7$ and that is administered orally, thus avoiding the need for periodic therapeutic infusions and the complications associated with this form of drug administration.

A first-in-human Phase 1 study of MORF-057 (MORF-057-101) in healthy study participants has been completed. The study included 3 parts: a [redacted]; up to [redacted] mg) part, a [redacted]; up to [redacted] mg [redacted] part, and a food effect part [redacted] mg [redacted].). MORF-057 was demonstrated to be safe and well tolerated in these healthy study participants across all parts of the study. Mild, non-serious adverse events (AEs) were reported, none of which resulted in study drug discontinuation. Maximum saturation of $\alpha_4\beta_7$ receptor occupancy was observed following [redacted] mg [redacted] dosing in the [redacted] part of the study. MORF-057 also exhibited favorable pharmacokinetics (PK) profiles. The mean plasma trough concentration obtained with [redacted] mg [redacted] was 22 ng/mL. This exposure seen in healthy individuals is expected to be similar in UC patients and will provide levels to achieve adequate efficacy and safety.

The current Phase 2a study (MORF-057-201) aims to evaluate the efficacy, safety, PK, and tolerability of orally administered MORF-057 capsules in study participants with moderately to severely active UC. Data from this study will provide further information to advance the clinical development program of MORF-057 for the treatment of UC.

Objectives and Endpoints:

The following study objectives will be completed by assessing the associated endpoints in participants with moderately to severely active UC.

Objectives	Endpoints
Primary	
To evaluate the effects of MORF-057 on histologic improvement at Week 12	• Change from baseline to Week 12 in the Robarts Histopathology Index (RHI) Score
Secondary	
To assess the safety and tolerability of MORF-057	• Frequencies and proportions for treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), and TEAEs leading to study drug discontinuation
To evaluate the effect of MORF-057 on clinical improvement at Week 12	• Change from baseline to Week 12 in the Modified Mayo Clinic Score (MCS). Modified MCS is a composite of the following subscores: o Mayo endoscopic subscore (MES) o MCS stool frequency subscore o MCS rectal bleeding subscore
To characterize the PK of MORF-057	• MORF-057 concentration in plasma • Plasma PK parameters ($AUC_{0\text{-}12}$, AUC_{tau}, C_{max}, C_{trough}, t_{max}, C_{12})
Exploratory	
To evaluate the effects of MORF-057 on histologic improvement at Weeks 6, 12, and 52	• 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
To evaluate the effect of MORF-057 on clinical improvement at Weeks 6, 12, and 52	• Change from baseline to Weeks 6 and 52 in the Modified MCS. Modified MCS is a composite of the following subscores: o MES o MCS stool frequency subscore o 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: o MES o MCS stool frequency subscore o MCS rectal bleeding subscore o MCS Physician's Global Assessment (PGA)

Objectives	Endpoints
To assess the effect of MORF-057 on non-endoscopic biomarkers of inflammation	• 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
To characterize the pharmacodynamics (PD) of MORF-057 in peripheral blood and mucosal tissue	• $\alpha_4\beta_7$ and $\alpha_4\beta_1$ receptor occupancies 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
To characterize the effect of MORF-057 on 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
To assess the long-term safety of MORF-057 and effects of MORF-057 on hs-CRP and fecal calprotectin levels	• 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

Overall Design:

This study is an open-label, single-arm, multicenter Phase 2a study to evaluate the efficacy, PK, PD, safety, and tolerability of MORF-057 in participants with moderately to severely active UC. The Main Cohort of the study will include [redacted] participants with moderately to severely active UC who have or have not been exposed to biologics therapies and have not previously been treated with vedolizumab. In addition, an Exploratory Cohort will be comprised of a [redacted] participants with moderately to severely active UC who are intolerant to or secondary non-responders (as defined in Section 5.1) to vedolizumab. Thus, there will be a total of [redacted] participants in the study. When the Main Cohort recruits [redacted] participants, 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. All participants will be enrolled from up to 30 centers located in North America and Europe. For this study, moderately to severely active UC will be defined as having a Modified MCS of 5 to 9 (inclusive) with an MES ≥2 (confirmed by central reader). In the Main Cohort, the enrollment goal is for approximately 55% to 75% of the participants to be advanced therapy (AT)-naïve (i.e., to have no previous exposure to a biologic treatment, Janus kinase [JAK] antagonists, or sphingosine-1-phosphate [S1P] receptor agonists for UC).

Participant safety data will be reviewed by an independent Data and Safety Monitoring Board (DSMB). Details related to the DSMB will be clearly delineated in the DSMB Charter.

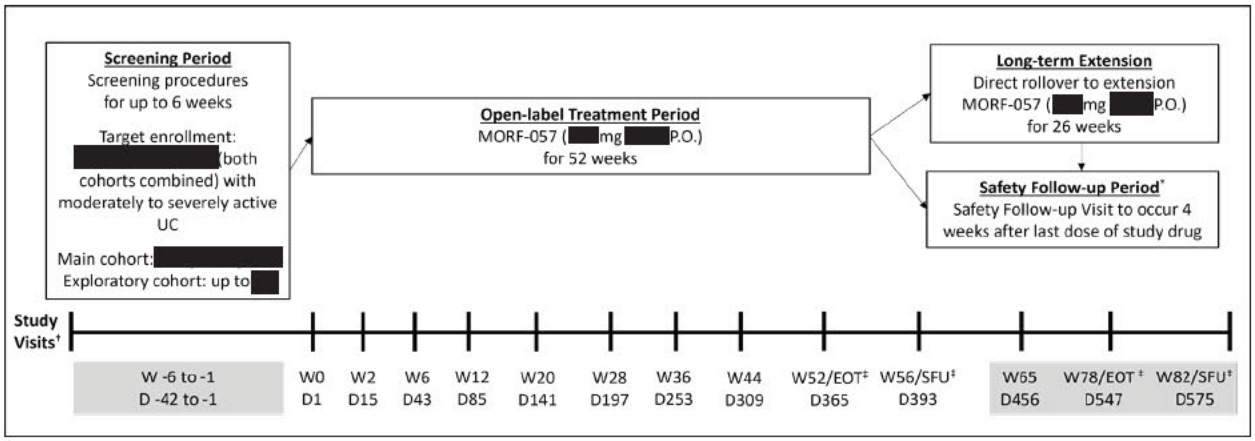
The main part of this Phase 2a study will consist of 3 study periods: a Screening Period (up to 6 weeks), a Treatment Period (52 weeks, including a 12-week Induction Period and a 40-week Maintenance Period), and a Safety Follow-up Period (4 weeks). During the study, there will be approximately 11 scheduled study visits: Screening Visit(s) (Visit 1 at Weeks -6 to -1), multiple Treatment Visits (Visits 2-10 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 [redacted] mg [redacted]. by mouth [P.O.]) 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 and complete a separate Safety Follow-up Period, including the Week 82 Visit (4 weeks after receiving the last dose of MORF-057).

During the optional Long-term Extension, there will be 3 scheduled study visits: 2 Treatment Visits (Visits 11-12 at Weeks 65 and 78), and a Safety Follow-up Visit (4 weeks after the last dose of study drug is received, which will be Visit 13 at 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] P.O.) for the full 26-week extended Treatment Period.

A study schema is provided below.

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.

Main Inclusion Criteria:

Participants are eligible to be included in the study only if all the following criteria apply:

Age

1. 18 to 85 years of age, inclusive, at the time of signing the Informed Consent Form (ICF)

Type of Participant and Disease Characteristics

2. Participant has had signs/symptoms of moderately to severely active UC for at least 3 months prior to Screening, and the diagnosis was confirmed during the Screening Period with the following criteria: a Modified MCS of 5 to 9 (inclusive) with an MES ≥2 (confirmed by central reader)
3. Has an RHI Score of 10 or greater
4. Has evidence of UC extending at least 15 cm from the anal verge
5. Is an AT-naïve participant or a participant who had an inadequate response, loss of response, or intolerance to no more than 3 drugs in 2 classes of the following:
   a. Tumor necrosis factor (TNF-α) antagonists, including infliximab, adalimumab, or golimumab
   b. Interleukin (IL)-12/IL-23 antagonists, including ustekinumab
   c. JAK antagonists, including tofacitinib and upadacitinib
   d. S1P receptor agonists, including ozanimod
   e. Any investigational product with the same mechanism as one of those outlined above (5a through 5d)
   f. Integrin inhibitors, including vedolizumab (participants in the Exploratory Cohort only)

   Note: Participants who have a history of primary non-response to 2 of the classes above will not be eligible. Participants who have received treatment with these agents at sub-therapeutic doses, or durations, should be discussed with the Medical Monitor to assess eligibility.
6. Meets the following washout criteria of prior UC therapy relative to study Day 1:
   a. TNF-α antagonists: at least 8 weeks
   b. IL-12/IL-23 antagonists, including ustekinumab: at least 8 weeks
   c. JAK antagonists, including tofacitinib and upadacitinib: at least 2 weeks
   d. S1P receptor agonists, including ozanimod: at least 4 weeks
7. If the participant has been receiving any of the non-prohibited medications for UC listed below, he/she must discontinue use at least 5 half-lives before study Day 1 or must agree to maintain stable doses of these concomitant medications starting from the time specified below until the end of the Safety Follow-up Period, with the exception of tapering oral corticosteroid dose after 12 weeks of being in the trial.

a. 5-Aminosalicylates (not exceeding 4.8 g per day): at least 2 weeks prior to study Day 1
b. Oral corticosteroids (not exceeding prednisone 30 mg per day, budesonide 9 mg per day, or equivalent): at least 2 weeks prior to study Day 1
c. 6-Mercaptopurine (any stable dose): at least 4 weeks prior to study Day 1
d. Azathioprine (any stable dose): at least 4 weeks prior to study Day 1
e. Methotrexate (any stable dose): for at least 4 weeks prior to study Day 1

8. In the opinion of the Investigator, the participant can fully participate in all aspects of this clinical study

Weight

9. Has a body mass index (BMI) within the range of 18.0 and 40.0 kg/m^2 (inclusive) at Screening

Sex and Contraceptive/Barrier Requirements

10. A participant is eligible to participate if he/she agrees to abide by the guidelines set forth in this protocol regarding contraception requirements (see full contraception guidelines in Section 10.5):

a. A male participant is eligible to participate if he agrees to the following during the study Treatment Period and for at least 28 days after receiving the last dose of MORF-057:

- Abstains from heterosexual intercourse as his preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agrees to remain abstinent

OR

- Agrees to use contraception/barrier methods as detailed below:
  - Agrees to use a male condom, with female partner use of an additional highly effective contraceptive method with a failure rate of <1% per year (as described in Section 10.5.2) when having sexual intercourse with a woman of childbearing potential who is not currently pregnant
  - Agrees to use a male condom when engaging in any activity that allows for passage of ejaculate to another person

b. A female participant is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies:

- Is a woman of non-childbearing potential (as defined in Section 10.5.1)

OR

- Is a woman of childbearing potential (as defined in Section 10.5.1) and agrees to use a contraceptive method that is highly effective with a failure rate of <1% per year (as described in Section 10.5.2) during the study Treatment Period and for at least 28 days after receiving the last dose of MORF-057

Note: Women who use any oral hormonal contraception must use an additional physical barrier method (Section 10.5.2).

11. For the study Treatment Period and at least 28 days after receiving the last dose of MORF-057, male participants must agree not to donate sperm and female participants must agree not to donate eggs (ova, oocytes).

Informed Consent

12. Capable of giving signed informed consent, as described in Section 10.1.4, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol

Exploratory Cohort Inclusion Criteria:

In addition to meeting Inclusion Criteria 1 through 12, the following criteria must be met for participants to be included in the Exploratory Cohort:

13. Those intolerant to (e.g. infusion-related skin reaction, allergy, or side effects unrelated to $\alpha_4\beta_7$ inhibition) or secondary non-responders* to vedolizumab who have been dosed within the past 5 years with the drug. Up to 5 of the 10 Exploratory Cohort participants may be included based on clinical criteria only. The remaining participants must also meet at least 1 of the following criteria:
    a. Documented vedolizumab levels in blood of ≤10 µg/mL 6 to 8 weeks after their most recent dose or at what is considered clinical trough. If the participant has had vedolizumab levels in blood tested and documented in their medical chart prior to Screening, the test does not need to be repeated.
    b. Non-saturating receptor occupancy of vedolizumab in blood 6 to 8 weeks after their most recent dose
    c. Documented presence of anti-drug antibodies against vedolizumab. If the participant has had a positive anti-drug antibody test that has been documented prior to Screening, the test does not need to be repeated.

    ***Note**: Secondary non-response is defined as having initially responded to Induction therapy and then had recurrence of symptoms after receiving at least 2 of the Maintenance doses, 300 mg every 8 weeks (discontinuation despite clinical benefit does not qualify).
14. The participants should also have received their last dose of vedolizumab at least 6 weeks prior to study Day 1 to allow sufficient washout

Exclusion Criteria:

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

Medical Conditions

1. Diagnosed with indeterminate colitis, microscopic colitis, ischemic colitis, radiation colitis, or CD or has clinical findings suggestive of CD

2. Has current evidence of un-resected colonic dysplasia or un-resected adenomatous colonic polyps or evidence of toxic megacolon, abdominal abscess, symptomatic colonic stricture, fistula, stoma, ileostomy, or colostomy at Screening
3. Currently requires or is anticipated to require surgical intervention for UC during the study or is planning to undergo major surgery during the study period
4. Has had a surgical procedure requiring general anesthesia within 30 days prior to Screening
5. Has a history of any major neurological disorders, including stroke, multiple sclerosis, brain tumor, demyelinating, or neurodegenerative disease. For questions about whether this applies to a specific case, consult with the Medical Monitor.
6. Has positive findings on a subjective neurological screening questionnaire or progressive multifocal leukoencephalopathy (PML) subjective symptom checklist during Screening or prior to the administration of the first dose of study drug on study Day 1
7. Has an active bacterial, viral, or parasitic pathogenic enteric infection, including *Clostridium difficile*; has cytomegalovirus, hepatitis B or C virus, or human immunodeficiency virus (HIV); had an infection requiring hospitalization or intravenous antimicrobial therapy, or an opportunistic infection within 3 months prior to Screening; had any infection requiring oral antimicrobial therapy within 2 weeks prior to Screening; or has a history of more than 1 episode of herpes zoster or any episode of disseminated herpes zoster infection
8. Has a positive diagnostic tuberculosis (TB) test at Screening (defined as a positive [redacted] test). If the participant has had a confirmed negative [redacted] or other Interferon Gamma Release Assay test within 90 days prior to Screening, the test does not need to be repeated. In cases where the [redacted] test result is indeterminate, the participant may have the test repeated once, and if the second test is negative, the participant will be eligible. In the event the second test also has an indeterminate result or [redacted] is unavailable, the Investigator has the option to perform a purified protein derivative (PPD) skin test. If the PPD reaction is <5 mm, then the participant is eligible. If the reaction is ≥5 mm or PPD testing is not done, the participant is not eligible. An exception can be made for participants with a history of latent TB who are currently receiving treatment for latent TB per local standard care, who will initiate treatment for latent TB before the first dose of study drug, or who have documentation of completing appropriate treatment for latent TB within 2 years prior to study Day 1.
9. Tests positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) during the Screening Period. Participants who test positive for SARS-CoV-2 can undergo retesting throughout the Screening Period. Testing to be performed according to site-specific testing procedures and country-specific requirements.

10. Had any vaccination (including live virus vaccinations) within 3 weeks prior to study Day 1. **Note:** For vaccinations requiring a series of doses, the last in the series should be completed by 3 weeks prior to study Day 1 (e.g., SARS-CoV-2 two-shot vaccination series).
11. Has a concurrent, clinically significant, serious, unstable comorbidity (such as uncontrolled cardiovascular, pulmonary, hepatic, renal, gastrointestinal, genitourinary, hematological, coagulation, immunological, endocrine/metabolic, or other medical disorder) that, in the judgement of the Investigator, would compromise compliance with the protocol, interfere with interpretation of the study results, or pre-dispose participants to safety risks
12. Has a known primary or secondary immunodeficiency
13. Has a history of myocardial infarction, unstable angina, transient ischemic attack, decompensated heart failure requiring hospitalization, congestive heart failure (New York Heart Association Class 3 or 4), uncontrolled arrhythmias, cardiac revascularization, uncontrolled hypertension, or uncontrolled diabetes within 6 months of Screening
14. Has a history of left ventricular ejection fraction (LVEF) <50%
15. Has a clinically significant abnormal electrocardiogram (ECG) at Screening, including a QT interval corrected through use of Fridericia's formula (QTcF) ≥450 ms for males and ≥470 ms for females
16. Abnormal hematology (hemoglobin level, white blood cell [WBC] count, or platelet count) or coagulation results at Screening, as evidenced by the ranges provided below:*
    a. Hemoglobin level <8.0 g/dL
    b. Absolute WBC count $<3.0 \times 10^9$/L
    c. Absolute lymphocyte count $<0.5 \times 10^9$/L
    d. Absolute lymphocyte count >5.0 x 10^9/L
    e. Absolute neutrophil count $<1.2 \times 10^9$/L
    f. Platelet count $<100 \times 10^9$/L or $>1000 \times 10^9$/L
    g. International normalized ratio >1.5
17. Clinically significant abnormal urinalysis results, as deemed by the Investigator or designee
18. Abnormal organ function at Screening, as evidenced by the following:*
    a. Alanine aminotransferase or aspartate aminotransferase >2.5 × upper limit of normal (ULN)
    b. Chronic kidney disease stages 4 and 5, defined as having a glomerular filtration rate <30 mL/min/1.73m2 as calculated using the Modification of Diet in Renal Disease (MDRD) equation, receiving dialysis, or being listed for or has received a renal transplant

c. Total bilirubin ≥1.5 × ULN

***Note**: Repeat testing should be done at the discretion of the Investigator. Consult with the Medical Monitor as needed.

19. History of active malignancy in the 5 years preceding study Day 1, except in cases of basal cell skin cancer, squamous cell skin cancer, or other in-situ malignancies that have been excised and resolved and the participant was deemed clear of cancer after appropriate follow-up. Participants with a history of malignancy or those at high risk for malignancy may only be enrolled after a consultation with the Medical Monitor.

Prior/Concomitant Therapy

20. Treatment with cyclosporine, mycophenolate, tacrolimus, or sirolimus within 30 days or 5 half-lives (whichever is shorter) prior to study Day 1
21. Any previous treatment with vedolizumab or other integrin inhibitors (except participants for the Exploratory Cohort)
22. Experiencing toxicities from prior therapy with Grade >1 within 1 week prior to first dose of study drug
23. Fecal microbiota transplantation within 3 months prior to Screening
24. If treatment with a moderate-to-strong cytochrome P450 3A4 (CYP3A4) inducer or inhibitor was received, a washout period of at least 30 days or 5 half-lives (whichever is shorter) is required prior to study Day 1. See Section 6.7.2 for a list of moderate-to-strong P450 inducers and inhibitors.
25. If treatment with a moderate-to-strong organic anion transporter polypeptide-1B inhibitor was received, a washout period of at least 14 days or 5 half-lives (whichever is shorter) is required prior to study Day 1. See Section 6.7.2 for a list of moderate-to-strong organic anion transporter polypeptide-1B inhibitors.

Prior/Concurrent Clinical Study Experience

26. Concurrent participation in any other interventional study
27. Received any investigational therapy within 30 days or 5 half-lives (whichever is longer) prior to study Day 1
28. Previous exposure to MORF-057 and/or a known hypersensitivity to drugs with a similar mechanism to MORF-057

Other Exclusions

29. Females who are pregnant or lactating or who are planning on becoming pregnant during the course of the study
30. Current or recent history of alcohol dependence or illicit drug use that, in the opinion of the Investigator, may interfere with the participant's ability to comply with the study procedures

31. Mental or legal incapacitation or a history of clinically significant psychiatric disorders at the time of the Screening Visit that would impact the ability to participate in the trial according to the Investigator
32. Unable to attend study visits or comply with procedures

Study Intervention:

MORF-057 is a small molecule therapy that selectively inhibits the $\alpha_4\beta_7$ integrin. This investigational product will be supplied as [redacted] capsules for oral administration. The study drug dosage will be [redacted] mg [redacted]. P.O. for the full 52-week Treatment Period. Each MORF-057 dose will be administered as [redacted]-mg capsules with or without food.

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, with the exception of the morning doses for Visits 2-10, which will be administered during the study visits after pre-dose blood samples have been drawn (see details in the Schedule of Activities). Participants will be instructed to record all details about the doses administered at home in the Participant Diary.

Participants who enroll into the Long-term Extension will continue the study drug dosage ([redacted] mg [redacted] P.O.) for the 26-week extended Treatment Period. Each MORF-057 dose will be administered as four 25-mg capsules with or without food. Through the Long-term Extension, MORF-057 will continue to be self-administered at home, with the exception of the morning doses for Visits 11-12, which will be administered during the study visits after pre-dose blood samples have been drawn (see details in the Schedule of Activities). Participants will be instructed to record all details about the doses administered at home in the Participant Diary.

Statistical Methods:

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. Data will be summarized/analyzed at scheduled visits unless stated otherwise. A significance level of 0.025 one-sided (0.05 two-sided) will be used for the primary efficacy endpoint. No hypothesis testing will be performed for the secondary and exploratory efficacy endpoints. No hypothesis testing will be performed on safety data. The Main Cohort and Exploratory Cohort will be analyzed separately, unless specified otherwise. Data from participants in the Exploratory Cohort will be analyzed only for exploratory purposes.

Sample Size Determination

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 28 participants with >80% power. A drop-out rate of 5% would lead to a total of 30 participants being enrolled in the Main Cohort. A maximum of 10 additional participants may be enrolled in the Exploratory Cohort, giving a total of 30 to 40 enrolled participants in the study.

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 the purpose of 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 Periods of the Main and Exploratory Cohorts respectively (i.e., the period for the primary efficacy endpoint) and the other two for the 52-week Treatment Periods of the Main and Exploratory cohorts respectively (i.e., the 12-week Induction Period plus the 40-week Maintenance Period and the Safety Follow-up). Additional analysis of the optional Long-term Extension Period for the participants enrolled into the Long-term Extension will be performed as appropriate.

Induction Period Analysis

The analysis of the Induction Period 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 concentrations and parameters, 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 the Induction Period analyses.

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 not enrolling into the optional Long-term Extension Period) or discontinued 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 endpoints defined by Week 52, PK concentration and parameters, and safety of MORF-057 during the 52-week open-label Treatment Period plus the Safety Follow-up Period. The cumulative data,

including those from the Induction Period, will be used in these analyses. 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.

Analysis Populations

The Full Analysis Set (FAS) is defined as all enrolled participants in the Main Cohort and Exploratory Cohort who took at least one dose of study medication. The FAS will be used for efficacy analyses.

The Per Protocol (PP) Population is defined as all participants in the FAS who do not have any major protocol deviations relevant to the primary and secondary efficacy endpoint analysis. All decisions to exclude participants from the PP set will be made prior to the database lock of the study. The PP Population will be used for sensitivity analysis of the primary efficacy endpoint and maybe other selected efficacy endpoints as appropriate.

The Safety Analysis Population is defined as all participants in both the Main Cohort and Exploratory Cohort who received at least 1 dose of study medication. The Safety Analysis Population will be used for safety analysis.

The PK Population is defined as all participants in the FAS who have 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.

The 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 not violate the protocol in a way that may invalidate or bias the results, and must have the reliable data for the overall PK summaries. The criteria that the data must meet for the inclusion of a participant in this population will be specified in the study SAP.

The PD Population is defined as all participants in the FAS who have at least 1 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.

Primary Endpoint

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 data for the primary efficacy endpoint will be assessed for normality. If the data are normally distributed, then a one-sample t-test will be used for the analysis. If the data are not normally distributed, then a signed rank test will be used. If there are a large number of participants excluded from the Per Protocol Population due to major protocol deviations, then a sensitivity analysis of the primary efficacy endpoint will be performed using the Per Protocol Population. In addition, the proportion of participants in the FAS with a change from

baseline to Week 12 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.

Secondary Endpoints

The continuous secondary efficacy endpoint (change from baseline to Week 12 in Modified MCS) will be analyzed similarly to the primary efficacy endpoint using the FAS. No hypothesis testing will be performed for the secondary efficacy endpoint.

The Safety Analysis Population will be used for the summarization of all safety data. Adverse events will be coded using the current Medical Dictionary of Regulatory Activities by System Organ Class (SOC) and Preferred Term (PT), classified from verbatim terms. A TEAE is defined as an AE that occurs between administration of the first dose of study drug and 7 days after the last dose of study drug. TEAEs and TESAEs will be summarized using frequencies and proportions; summaries will be provided for overall and according to SOC and PT. TEAEs leading to study drug discontinuation will be summarized or listed, as appropriate. Summaries of TEAEs will also be presented by severity and relationship (see Section 10.4.3). The duration of TEAEs will be determined and included in listings, along with the action taken and outcome.

The plasma PK parameters $AUC_{0\text{-}12}$, AUC_{tau}, C_{max}, C_{trough}, t_{max}, and C_{12} will be estimated by non-compartmental analysis using the PK Population. PK/PD analyses will be conducted as deemed appropriate and may be reported separately from the Clinical Study Report.

Exploratory Endpoints

The continuous exploratory efficacy endpoints (change from baseline to Weeks 6 and 52 in RHI Score and Modified MCS; change from baseline to Weeks 6, 12, and 52 in NI, Continuous Geboes Score, and Full MCS; and change from baseline to Weeks 2, 6, 12, 20, 28, 36, and 52 in hs-CRP and fecal calprotectin levels) will be analyzed similarly to the primary efficacy endpoint using the FAS. No hypothesis testing will be performed for the exploratory efficacy endpoints. In addition, the proportion of participants with NI score ≤1 at Week 12 will be provided.

The exploratory PD endpoints ($\alpha_4\beta_7$ and $\alpha_4\beta_1$ receptor occupancies over time and change from baseline over time in blood CCR9 mRNA) will be summarized descriptively. Additional 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. The PD Population will be used for the summarization and analysis of these exploratory endpoints.

Other Safety Assessments

Other safety data will include safety laboratory parameters, vital signs, and ECG findings. These data will be summarized with descriptive statistics by absolute values and change from baseline using the Safety Analysis Population. The incidence of laboratory abnormalities will be summarized. Worst shift in grade and changes from baseline to Weeks 6, 12, and 52 of the laboratory analytes will be reported. Physical examination findings that are recorded as AEs will be included in those data presentations.

Data and Safety Monitoring:

A DSMB has been appointed to this study. The DSMB is a group of independent clinicians/scientists who are appointed to monitor the safety and scientific integrity of a human research intervention, and to make recommendations to the Sponsor regarding the modification, continuance, or stopping of a study based on assessments of safety. Additionally, a separate PML Adjudication Committee will oversee a PML Risk Assessment and Minimization Program (RAMP) to monitor all participants for PML. The composition, responsibilities, and meeting schedules of the DSMB and the PML Adjudication Committee will be described in separate charters.

1.2. Schedule of Activities (SoA)

The SoA for the Treatment Period is provided in Table 1. The SoA for the Long-term Extension is provided in Table 2.

Table 1. Schedule of Activities 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	

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]**	
Serum test for follicle-stimulating hormone [o]	X											
Dispense stool collection kit [p]	X	X	X	X	X	X	X	X	X	X [p]		
Discuss participation and informed consent in Long-term Extension [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 [u]	X	X	X	X	X	X	X	X	X	X	X	X [b]
Serum chemistry [u]	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 [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 Physician's Global Assessment	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 sample for fecal calprotectin test	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	X [kk]		
Study drug administration on site [ll]		X	X	X	X	X	X	X	X	X [mm]		

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 Long-term Extension 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. Participants who choose to enroll into the Long-term Extension after Visit 10/EOT will complete a Safety Follow-up Visit at Week 82.

[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. Participants who test positive for SARS-CoV-2 can undergo retesting throughout the Screening Period.

[j] [redacted] TB test. If the participant has had a confirmed negative [redacted] or other Interferon Gamma Release Assay test within 90 days prior to Screening, the test does not need to be repeated. 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] Participants being considered for the Exploratory Cohort will require testing for vedolizumab blood levels, RO of vedolizumab, and anti-drug antibodies against vedolizumab. If the participant has had vedolizumab levels in blood or presence of anti-drug antibodies against vedolizumab tested and documented in their medical chart prior to Screening, the test does not need to be repeated.

[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 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. Stool collection kits will be dispensed at Visit 10 only for participants continuing in the Long-term Extension.

[q] Participants will be provided the option to participate in the Long-term Extension. Participants who want to continue in the Long-term Extension will sign a separate ICF.

[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 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] Blood samples for hematology, coagulation, and serum chemistry assessments will be collected before the [redacted] on Visits 2-10.

[v] Record adverse events from the time the ICF is signed. 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 before the [redacted] and at 1, 2, 3, 4, and 6 hours after the AM dose. Blood sampling will be optional at 8, 10, and 12 hours [redacted]. The 12-hour [redacted] sample will be collected prior to the second daily dose. Time windows for PK sampling can be found in Section 8.10.1. Each [redacted] sample should be obtained within approximately 30 minutes before the [redacted] is administered.

[x] PK testing at Visits 4, 6, 7, 8, and 9: Blood sampling will be required before the [redacted] and at 1 and 3 hours [redacted]. Time windows for PK sampling can be found in Section 8.10.1. Each [redacted] should be obtained within approximately 30 minutes [redacted] is administered and at 12 hours (±1 hour) after [redacted]

[y] PK testing at Visit 10/EOT: Blood sampling will be required [redacted]. The sample should be obtained within approximately 30 minutes [redacted] is administered and at 12 hours (±1 hour) after the [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: The blood samples for RO testing collected [redacted] are required. The 12-hour [redacted] dose samples for RO testing are optional. The 12-hour [redacted] sample will be collected prior to the second daily dose. RO sampling to occur at the corresponding PK sampling time.

[bb] Blood samples for immunophenotyping (lymphocyte subsets analysis) will be collected before the [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 before the [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 before the [redacted] on Visits 2-10. Blood pharmacogenomics sample will be collected before the [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), histopathology, 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] At Visit 10/EOT, the study drug will be dispensed only for participants continuing treatment in the Long-term Extension.

[ll] [redacted] required on site for all visits. For Visits 2, 3, and 5, if optional PK/RO sampling will be performed at 8-12 hours [redacted], the [redacted] must not be taken until PK/RO sampling is complete for that day.

[mm] 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 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 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.
[i] 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.
[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 before the [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 before the [redacted] on Visits 11-12.

2. INTRODUCTION

2.1. Study Rationale

Inflammatory bowel disease (IBD) is a term used to describe 2 idiopathic conditions characterized by chronic inflammation of the gastrointestinal tract: Crohn's disease (CD) and ulcerative colitis (UC). In patients with UC, mucosal inflammation and ulceration occurs in the rectum and can extend proximally to a portion of or to the full colon, resulting in symptoms and signs such as urgency to defecate, fatigue, bloody stool, diarrhea, nausea or loss of appetite, weight loss, fever, and anemia.

Initial therapy for UC generally includes the anti-inflammatory drugs 5-aminosalicylates (5-ASA) and steroids. Immunomodulators (e.g., methotrexate, azathioprine, and 6-mercaptopurine) may subsequently be used to maintain remission and avoid long-term steroid use. However, these treatments often fail to control the disease long-term, particularly in patients with moderately to severely active UC, and both the steroids and the immunomodulators can produce significant side effects.

The introduction of biologic agents has improved the therapeutic options for patients with moderately to severely active UC. Approved biologics include tumor necrosis factor alpha (TNF-α) antagonists (infliximab, adalimumab, certolizumab, and golimumab), the anti-$\alpha_4\beta_7$ integrin monoclonal antibody vedolizumab ([redacted]), and the anti-interleukin 12/23 monoclonal antibody ustekinumab (Stelara®). Another therapeutic option recently approved for the treatment of UC is Janus kinase (JAK) inhibitors, such as the small molecule tofacitinib (Xeljanz®). Despite this increase in therapeutic options for the treatment of UC, the percentage of patients with moderately to severely active UC who do not respond to induction therapy is still substantial, and the durability of response is low. For example, in Phase 3 studies in patients with moderately to severely active UC, adalimumab treatment achieved clinical remission at 8 weeks in 18.5% of patients and maintained remission in 8.5% at 52 weeks ([redacted] package insert). Thus, there remains an unmet need for more effective therapies for UC.

The pathogenesis of IBD is associated with activation of immune cells and their trafficking into the gut and the surrounding tissue to promote chronic inflammation. The integrin $\alpha_4\beta_7$ is required by immune cells to facilitate trafficking from the bloodstream to mucosal tissues, including the gut. This is achieved through binding of the $\alpha_4\beta_7$ integrin on immune cells to its cognate ligand, MAdCAM-1, expressed on the endothelial vessels within close proximity to mucosal tissues. Importantly, the $\alpha_4\beta_7$ integrin is employed by immune cells in the pathogenesis of IBD; therefore, inhibiting $\alpha_4\beta_7$ blocks the entry of immune cells into mucosal tissue, thereby alleviating the inflammation associated with IBD in many patients. Thus, the $\alpha_4\beta_7$ integrin is an ideal therapeutic target for selectively blocking inflammation of the gastrointestinal tract while minimizing effects in other organs (Fedyk, 2012). Inhibition of $\alpha_4\beta_7$ is a validated mechanism for the treatment of IBD, as demonstrated by vedolizumab ([redacted]), a monoclonal antibody administered via intravenous infusion.

MORF-057 is a small molecule designed to selectively inhibit integrin $\alpha_4\beta_7$. It is currently being developed as an oral therapy for UC because vedolizumab, which has the same mechanism of action, has shown more favorable responses in UC patients with moderately to severely active

disease than in CD patients. The development program for MORF-057 may be expanded to include CD patients in the future.

A first-in-human Phase 1 MORF-057 study (MORF-057-101) in healthy study participants has been completed. The study included 3 parts: a [redacted] up to [redacted] mg) part, a [redacted] up to [redacted] mg [redacted] part, and a food effect (FE; [redacted] of [redacted] mg [redacted]) part. MORF-057 was demonstrated to be safe and well tolerated in these healthy study participants across all parts of the study. Mild, non-serious adverse events (AEs) were reported, none of which resulted in study drug discontinuation. Maximum saturation of $\alpha_4\beta_7$ receptor occupancy was observed following [redacted] mg [redacted] dosing in the [redacted] part of the study. MORF-057 also exhibited favorable pharmacokinetics (PK) profiles. The mean plasma trough concentration obtained with [redacted] mg [redacted] was 22 ng/mL. This exposure seen in healthy individuals is expected to be similar in UC patients and will provide levels to achieve adequate efficacy and safety.

The current Phase 2a study (MORF-057-201) aims to evaluate the efficacy, safety, PK, and tolerability of orally administered MORF-057 capsules in adults with moderately to severely active UC. Data from this study will provide further information to advance the clinical development program of MORF-057 for the treatment of UC.

2.2. Background

Inhibition of $\alpha_4\beta_7$ integrin is an important therapeutic goal for the treatment of moderately to severely active UC that has been clinically validated with the monoclonal antibody vedolizumab [redacted]). MORF-057 is an orally administered small molecule designed to selectively inhibit integrin $\alpha_4\beta_7$. It prevents MAdCAM-1 from binding to the $\alpha_4\beta_7$ integrin via a competitive mechanism (Yu, 2012). There are several potential clinical advantages of using MORF-057 (an orally administered drug) for the treatment of UC over vedolizumab (a drug administered via intravenous infusion), which uses the same mechanism of action. These advantages include a flexible dosing regimen and minimal safety concerns regarding immunogenicity and serious infusion reactions, requiring less clinical visits and therefore reducing patient and healthcare provider burden. MORF-057 has the potential to be an effective and safe oral $\alpha_4\beta_7$ integrin inhibitor that would be an important addition to the therapeutic armamentarium for UC.

A detailed description of the chemistry, pharmacology, efficacy, and safety of MORF-057 is provided in the current Investigator's Brochure. Important non-clinical and clinical study results are summarized below.

2.2.1. Non-clinical Findings

Non-clinical studies have demonstrated that MORF-057 is highly selective for $\alpha_4\beta_7$ over other integrins by a range of [redacted] to [redacted]. In addition, in a monkey gut homing model, MORF-057 blocked gut homing of $\alpha_4\beta_7$-positive T cells into lymphoid tissue, as measured by frequency of lymphocytes in tissue and in circulating blood as biomarkers, suggesting MORF-057 can inhibit an established and important mechanism involved in the pathogenesis of IBD.

MORF-057 has a moderate blood clearance with a terminal half-life of less than 3 hours in mice, rats, dogs, and monkeys. Absorption following oral administration was rapid with a t_{max} of up to 2 hours. Moderate bioavailability was observed in rats and dogs, but low bioavailability was

observed in mice and cynomolgus monkeys. The binding of MORF-057 to plasma proteins was high across species and was not different from the in vitro assessment in human plasma.

In a 6-month oral repeat-dose study of MORF-057 in Sprague Dawley rats, significant, reversible increases in circulating white blood cells (WBCs), lymphocytes, eosinophils, and large unstained cells were seen at the high dose of 450 mg/kg/day due to the pharmacological action of MORF-057. Non-adverse changes in cellularity in the spleen were observed at the high dose of 450 mg/kg/day, which were attributed to the pharmacological activity of MORF-057. The no-observed-adverse-effect level (NOAEL) in this study was 50 mg/kg/day in male and female rats. The adverse changes in rats after 6 months of dosing were degeneration/regeneration of chief cells in the glandular stomach at 125 or 450 mg/kg/day, which appeared to be partially reversible by 4 weeks post-dose.

In a 9-month oral repeat-dose study in beagle dogs, the NOAEL was 300 mg/kg/day, the highest dose tested. Non-adverse hepatobiliary changes were observed in several dogs that received 300 mg/kg/day of MORF-057; these changes correlated with increases in alanine transaminase (ALT) and alkaline phosphatase (ALP) measured in the same dogs. There were no adverse histopathological changes in dogs after 9 months of dosing. The degeneration/regeneration of chief cells in the glandular stomach observed in rats after 6 months of dosing was not noted in the beagle dogs at any dose up to 300 mg/kg/day, even though C_{max} values were 10-fold higher and AUC_{last} values were up to 20-fold higher in dogs compared to rats.

For a human dose of [redacted] mg [redacted] the safety margin for MORF-057 in rats, the most sensitive toxicology species, is 6.5-8.7. The safety margins compared to dogs is 161 to 177 fold.

MORF-057 had no effects on fertility in male or female Sprague Dawley rats, no effect on early embryonic development in female rats, and no effects on embryo-fetal development in Sprague Dawley rats or white New Zealand rabbits.

2.2.2. Clinical Findings

MORF-057 has been evaluated in a first-in-human study (MORF-057-101). This study included [redacted], FE, and [redacted] assessments in healthy study participants. Overall, MORF-057 was well tolerated at all doses in the [redacted], FE, and [redacted] cohorts with no safety signals identified. All treatment-emergent adverse events (TEAEs) reported during the study were mild to moderate in severity and resolved within the safety reporting period; none required study drug discontinuation. Following [redacted] between [redacted] mg and [redacted] mg and [redacted] between [redacted] mg [redacted] and [redacted] mg [redacted]., MORF-057 was rapidly absorbed, and systemic exposure increased with an increase in dose in a generally proportional manner. No clinically relevant FE was demonstrated, indicating MORF-057 can be dosed without regard to timing of food intake. In the [redacted] and [redacted] cohorts, mean $\alpha_4\beta_7$ receptor occupancy increased with dose and study day, achieving saturation (>99%) in certain individuals in each cohort above [redacted] mg, particularly in all study participants in the [redacted] mg [redacted]. [redacted] cohort. The variability of $\alpha_4\beta_7$ receptor occupancy following [redacted] and [redacted] between [redacted] mg [redacted]. and [redacted] mg [redacted]. tended to decrease with an increase in dose and decreased after repeated [redacted] [redacted] from Day 1 to Day 14. In contrast, $\alpha_4\beta_1$ receptor occupancy was below the lower limit of quantification at all doses in the SAD and MAD cohorts. Preliminary analyses of changes in lymphocyte subsets and C-C chemokine receptor 9 (CCR9) transcripts over time in the MAD cohort were consistent with those reported with other integrin pathway inhibitors, including vedolizumab. Overall, the results of this Phase 1 study demonstrated

favorable PK/pharmacodynamics (PD) and safety profiles, supporting further clinical development of MORF-057.

Clinical drug-drug interaction studies (Studies MORF-057-102 and MORF-057-103) evaluating the inhibitory and inductive potential of MORF-057 on cytochrome P450 3A (CYP3A) in healthy participants have been completed. MORF-057 did not have an effect on midazolam PK following a single dose, whereas it was identified as a weak inducer of cytochrome P450 3A4 (CYP3A4) with a 33% decrease of midazolam AUC (a weak inducer is defined as ≥20% and <50% decrease in AUC of a sensitive substrate) following [redacted] at [redacted] mg [redacted] (Study MORF-057-102). The midazolam drug-drug interaction results were consistent with the in vitro cytochrome P450 (CYP) inhibition and induction data indicating that, at the clinical exposure of [redacted] mg [redacted]. dose, MORF-057 has the potential to be a weak CYP3A4 inducer with minimal inhibition of major CYPs. Co-administration of ethinyl estradiol/levonorgestrel with MORF-057 (Study MORF-057-103), compared with administration of ethinyl estradiol/levonorgestrel alone, did not substantially alter ethinyl estradiol or levonorgestrel exposure (AUCs and C_{max}). The 90% confidence intervals of the geometric mean ratios for ethinyl estradiol AUC_{0-24}, C_{max}, and C_{24} were contained within the 80.00% to 125.00% no-effect range with the exception of the lower limits of AUC_{0-t} and AUC_{0-inf}. The 90% confidence intervals of the geometric mean ratios for levonorgestrel AUCs and C_{24} were contained within the 80.00% to 125.00% no-effect range with the exception of the lower limit of C_{max}. An overall marginal decrease in PK parameters was observed.

Study MORF-057-104 was conducted to evaluate the safety, tolerability, PK, PD, and FE of MORF-057 optimized formulation with [redacted] capsules, which were tested at [redacted] of [redacted] mg, [redacted] mg, and [redacted] mg and at [redacted] of [redacted] mg [redacted] ([redacted] mg/capsule) in healthy participants. MORF-057 [redacted] capsules were demonstrated to be safe and well tolerated, and only mild, non-serious adverse events (AEs) were observed, none of which were related to MORF-057. The [redacted] capsules were rapidly absorbed, with a median T_{max} of approximately 2.5 hours. High levels of target engagement of the $\alpha_4\beta_7$ integrin receptor were observed following [redacted] doses of [redacted] mg MORF-057, with 99% mean $\alpha_4\beta_7$ receptor occupancy observed after 14 days of [redacted] mg [redacted]. dosing. Changes in lymphocyte subsets were consistent with those reported for other integrin pathway inhibitors. Overall, the new MORF-057 [redacted] capsule formulation performed well and thus was recommended for use in the MORF-057 Phase 2 program.

2.3. Benefit/Risk Assessment

Detailed information about the known and expected benefits and risks and reasonably expected AEs of MORF-057 may be found in the current Investigator's Brochure.

2.3.1. Benefits

MORF-057 inhibits $\alpha_4\beta_7$ integrin binding to MAdCAM-1, which is the same mechanism used by the marketed drug vedolizumab. Studies of vedolizumab have shown this to be an effective mechanism for treating patients with UC (Feagan, 2013). Therefore, MORF-057 may benefit patients with moderately to severely active UC whose disease has progressed or has been unresponsive to currently approved standard of care agents. In addition, there are several potential clinical advantages of using MORF-057 (an orally administered drug) for the treatment of UC over vedolizumab (a drug administered via intravenous infusion). These include the following:

- Oral drugs are preferred by patients and healthcare providers over injectables. Beyond the fear of needles, the requirement for frequent infusion center visits is a substantial burden, particularly for younger patients with UC who have active professional and family lives.
- Oral formulation allows for flexible dosing regimen. An oral drug that is rapidly cleared upon cessation of dosing may be desirable for treating physicians in clinical situations such as pregnancy, during serious infections, and in the peri-operative period. Additionally, an oral drug is more easily titrated to clinical effect and may be used in fixed-dose combinations with other oral agents. The long half-life of vedolizumab means that it cannot be removed rapidly.
- As with all therapeutic proteins, there is the potential for immunogenicity with vedolizumab. During the Phase 3 trials, 4% of patients developed anti-vedolizumab antibodies, 59% of which were neutralizing antibodies that reduced plasma levels of the treatment antibody [redacted] package insert).
- Serious infusion reactions, including anaphylaxis, have been reported with vedolizumab.

2.3.2. Risks

Overall, based on the available data for MORF-057, the risk to study participants is expected to be minimal.

Collectively from 4 completed MORF-057 studies conducted in [redacted], MORF-057 was well tolerated with or without food or in combination with midazolam. There were no deaths or SAEs.

In a 6-month toxicology study in Sprague Dawley rats and a 9-month toxicology study in beagle dogs, the NOAEL values were 50 mg/kg/day for rats and 300 mg/kg/day for dogs (Section 2.2.1).

Safety precautions that will be taken during the study are listed below:

- Safety assessments and monitoring will be performed throughout the study, including evaluating the incidence of TEAEs, as well as abnormalities in clinical laboratory values, vital signs, and 12-lead ECGs.
- A Data and Safety Monitoring Board (DSMB) has been appointed to this study. The DSMB will monitor the safety of the participants and the scientific integrity of the study.
- Natalizumab, a monoclonal antibody that inhibits both $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrins, has been associated with PML, a serious brain infection. Data from human whole blood ex vivo assay suggests that MORF-057 has significant selectivity (~700 fold at IC_{90}) for binding integrin $\alpha_4\beta_7$ over integrin $\alpha_4\beta_1$. However, out of an abundance of caution, all participants enrolled in this study will be monitored for PML through the use of a PML Risk Assessment and Minimization program (RAMP).
- Non-clinical Good Laboratory Practice studies in rats and rabbits showed that MORF-057 has no effects on fertility, early embryonic development, or embryo-fetal

development. The available non-clinical data suggest that exposure to clinical-strength doses of MORF-057 does not present a risk to the mother or fetus. Additional studies evaluating the effects of MORF-057 on pre- and post-natal development have not been conducted and the safety profile of MORF-057 in women who are pregnant or lactating is not available; therefore, inclusion/exclusion criteria (see Section 5) and safety monitoring regarding contraception and pregnancy have been included to mitigate the potential relevant risks.

Safety criteria for study drug discontinuation are outlined in Section 7.

The Sponsor will immediately notify the Investigator if any additional safety or toxicology information becomes available during the study.

2.3.3. Overall Benefit Risk Conclusion

Considering the measures taken to minimize risk to the participants in this study and given that the potential risks identified in association with MORF-057 can be readily monitored during the study, the participants are not being exposed to undue risk, and the potential risks are justified by the anticipated benefits that may eventually be afforded to patients with moderately to severely active UC.

3. Objectives and Endpoints

The following study objectives will be completed by assessing the associated endpoints in participants with moderately to severely active UC.

Objectives	Endpoints
Primary	
To evaluate the effects of MORF-057 on histologic improvement at Week 12	• Change from baseline to Week 12 in the Robarts Histopathology Index (RHI) Score
Secondary	
To assess the safety and tolerability of MORF-057	• Frequencies and proportions for TEAEs, treatment-emergent serious adverse events (TESAEs), and TEAEs leading to study drug discontinuation
To evaluate the effect of MORF-057 on clinical improvement at Week 12	• Change from baseline to Week 12 in the Modified Mayo Clinic Score (MCS). Modified MCS is a composite of the following subscores: o Mayo endoscopic subscore (MES) o MCS stool frequency subscore o MCS rectal bleeding subscore
To characterize the PK of MORF-057	• MORF-057 concentration in plasma • Plasma PK parameters ($AUC_{0\text{-}12}$, AUC_{tau}, C_{max}, C_{trough}, t_{max}, C_{12})
Exploratory	
To evaluate the effects of MORF-057 on histologic improvement at Weeks 6, 12, and 52	• 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

Objectives	Endpoints
To evaluate the effect of MORF-057 on clinical improvement at Weeks 6, 12, and 52	• Change from baseline to Weeks 6 and 52 in the Modified MCS. Modified MCS is a composite of the following subscores: o MES o MCS stool frequency subscore o 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: o MES o MCS stool frequency subscore o MCS rectal bleeding subscore o MCS Physician's Global Assessment (PGA)
To assess the effect of MORF-057 on non-endoscopic biomarkers of inflammation	• 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
To characterize the PD of MORF-057 in peripheral blood and mucosal tissue	• $\alpha_4\beta_7$ and $\alpha_4\beta_1$ receptor occupancies in blood over time • Change from baseline over time in blood CCR9 mRNA • Change from baseline over time in blood lymphocyte subsets • Blood and mucosal tissue gene and/or protein expression over time
To characterize the effect of MORF-057 on 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
To assess the long-term safety of MORF-057 and effects of MORF-057 on hs-CRP and fecal calprotectin levels	• 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

4. STUDY DESIGN

4.1. Overall Design

This study is an open-label, single-arm, multicenter Phase 2a study to evaluate the efficacy, PK, PD, safety, and tolerability of MORF-057 in participants with moderately to severely active UC. The Main Cohort of the study will include approximately [redacted] with moderately to severely active UC who have or have not been exposed to biologics therapies and have not previously been treated with vedolizumab. In addition, an Exploratory Cohort will be comprised of a maximum of 10 additional participants with moderately to severely active UC who are intolerant to or secondary non-responders (as defined in Section 5.1) 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. All participants will be enrolled from up to 30 centers located in North America and Europe. For this study, moderately to severely active UC will be defined as having a Modified MCS of 5 to 9 (inclusive) with an MES ≥2 (confirmed by central reader). In the Main Cohort, the enrollment goal is for approximately 55% to 75% of the participants to be advanced therapy (AT)naïve (i.e., to have no previous- exposure to a biologic treatment, JAK antagonists, or sphingosine-1-phosphate [S1P] receptor agonists for UC).

Participant safety data will be reviewed by an independent DSMB. Details related to the DSMB will be clearly delineated in the DSMB Charter.

The main part of this Phase 2a study will consist of 3 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 2-10 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 [P.O.]) for the full 52-week Treatment Period.

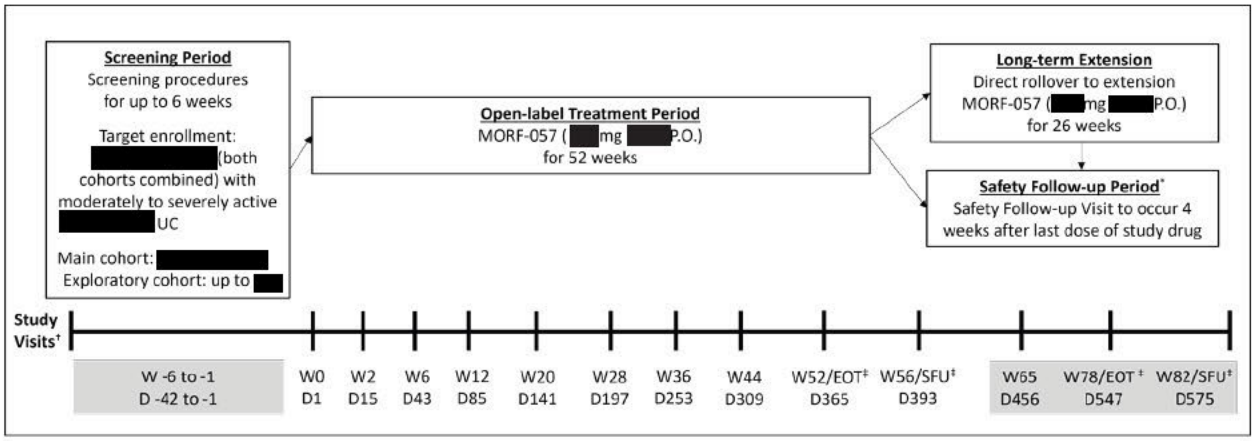
All participants who complete the open-label Treatment Period will have the opportunity to continue their treatment in an optional 26-week Long-term Extension after completing the Week 52 assessments. Participants who do not enroll into the Long-term Extension must complete the final Safety Follow-up 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 and complete a separate Safety Follow-up Period, including the Week 82 Visit (4 weeks after receiving the last dose of MORF-057).

During the optional Long-term Extension, there will be 3 scheduled study visits: 2 Treatment Visits (Visits 11-12 at Weeks 65 and 78), and a Safety Follow-up Visit (4 weeks after the last dose of study drug is received, which will be Visit 13 at 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] P.O.) for the full 26-week extended Treatment Period.

A study schema is provided in Figure 1.

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 objectives and endpoints for the study are provided in Section 3.

4.2. Scientific Rationale for Study Design

This open-label, [redacted], multicenter Phase 2a study was designed to assess the efficacy of MORF-057 ([redacted] mg [redacted] P.O.) in participants with moderately to severely active UC when administered for 52 weeks (including a 12-week Induction Period plus a 40-week Maintenance Period). This design simulates assessment of treatment goals for UC in clinical practice, wherein participants are evaluated for induction of remission, followed by assessment of maintenance of remission over a longer period of time (usually assessed over 52 weeks of continuous treatment in clinical studies). The 52-week study will be followed by an optional 26-week Long-term Extension. This extension will provide further access to the study drug to the participants and further efficacy and safety data up to 78 weeks of exposure.

A [redacted] study design was selected to obtain preliminary evidence of the efficacy of MORF-057 over time in participants with UC. A placebo control design was not chosen for this preliminary efficacy study because sustained and clinically meaningful spontaneous improvement in patients with moderately to severely active UC is rare. The open-label study design provides an early readout of safety and efficacy to inform further development of MORF-057 in the Phase 2 clinical program.

Histology plays a critical role in diagnosing UC and monitoring disease progression. Robarts Histopathology Index is a validated and reliable tool that is commonly used to evaluate the histological response of a treatment in patients with UC. Therefore, the RHI was selected as the primary efficacy endpoint of this study.

Study entry criteria were carefully selected to reflect an adult population consistent with the moderately to severely active UC population likely to be treated with MORF-057 in clinical practice.

4.3. Justification for Dose

A dosing regimen of [redacted] mg [redacted] has been selected for the current study. In study MORF-057-101, which included SAD and MAD assessments in healthy adults, maximum saturation of $\alpha_4\beta_7$ receptor occupancy was observed following [redacted] mg [redacted] dosing in the [redacted] part of the study. MORF-057 exhibited favorable PK profiles with only mild, non-serious AEs reported that did not result in study drug discontinuation. The mean plasma trough concentration obtained with [redacted] mg [redacted] was 22 ng/mL. This exposure seen in healthy individuals is expected to be similar in UC patients and will provide levels to achieve adequate efficacy and safety.

MORF-057 is designed specifically to inhibit $\alpha_4\beta_7$, which is involved in the trafficking of immune cells to sites of inflammation in the intestinal mucosa but exhibits low inhibition of all other integrins, including $\alpha_4\beta_1$. Integrin $\alpha_4\beta_1$ regulates immune cell trafficking to many non-mucosal tissue sites including skin, lung, and the central nervous system (von Andrian, 2000). In human whole blood ex vivo studies, the selectivity ratio of IC_{50} and IC_{90} values with respect to $\alpha_4\beta_7$ and $\alpha_4\beta_1$ for MORF-057 are [redacted] and [redacted], respectively. The MORF-057 dose selected for the current study is anticipated to cause minimal to no $\alpha_4\beta_1$ inhibition in humans, and $\alpha_4\beta_7$ and $\alpha_4\beta_1$ receptor occupancies in blood will be assessed as an exploratory endpoint.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed the Screening and 52-week Treatment Periods of the study and attended the Safety Follow-up Visit OR has completed the Week 52/EOT Visit and has been enrolled into the Long-term Extension.

The end of the study is defined as the date of the last visit of the last participant in the main part of the study or last scheduled procedure shown in the schedule of activities (SoA) for the last participant in the main part of the study globally.

The results for the Long-term Extension may be reported in a Clinical Study Report Addendum.

5. STUDY POPULATION

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

5.1. Inclusion Criteria

Main Inclusion Criteria:

Participants are eligible to be included in the study only if all the following criteria apply:

Age

1. 18 to 85 years of age, inclusive, at the time of signing the Informed Consent Form (ICF)

Type of Participant and Disease Characteristics

2. Participant has had signs/symptoms of moderately to severely active UC for at least 3 months prior to Screening, and the diagnosis was confirmed during the Screening Period with the following criteria: a Modified MCS of 5 to 9 (inclusive) with an MES ≥2 (confirmed by central reader)
3. Has an RHI Score of 10 or greater
4. Has evidence of UC extending at least 15 cm from the anal verge
5. Is an AT-naïve participant or a participant who had an inadequate response, loss of response, or intolerance to no more than 3 drugs in 2 classes of the following:
   a. TNF-α antagonists, including infliximab, adalimumab, or golimumab
   b. Interleukin (IL)-12/IL-23 antagonists, including ustekinumab
   c. JAK antagonists, including tofacitinib and upadacitinib
   d. S1P receptor agonists, including ozanimod
   e. Any investigational product with the same mechanism as one of those outlined above (5a through 5d)
   f. Integrin inhibitors, including vedolizumab (participants in the Exploratory Cohort only)

   Note: Participants who have a history of primary non-response to 2 of the classes above will not be eligible. Participants who have received treatment with these agents at sub-therapeutic doses, or durations, should be discussed with the Medical Monitor to assess eligibility.
6. Meets the following washout criteria of prior UC therapy relative to study Day 1:
   a. TNF-α antagonists: at least 8 weeks
   b. IL-12/IL-23 antagonists, including ustekinumab: at least 8 weeks
   c. JAK antagonists, including tofacitinib and upadacitinib: at least 2 weeks
   d. S1P receptor agonists, including ozanimod: at least 4 weeks
7. If the participant has been receiving any of the non-prohibited medications for UC listed below, he/she must discontinue use at least 5 half-lives before study Day 1 or must agree to maintain stable doses of these concomitant medications starting from

the time specified below until the end of the Safety Follow-up Period, with the exception of tapering oral corticosteroid dose after 12 weeks of being in the trial.

a. 5-Aminosalicylates (not exceeding 4.8 g per day): at least 2 weeks prior to study Day 1
b. Oral corticosteroids (not exceeding prednisone 30 mg per day, budesonide 9 mg per day, or equivalent): at least 2 weeks prior to study Day 1
c. 6-Mercaptopurine (any stable dose): at least 4 weeks prior to study Day 1
d. Azathioprine (any stable dose): at least 4 weeks prior to study Day 1
e. Methotrexate (any stable dose): for at least 4 weeks prior to study Day 1

8. In the opinion of the Investigator, the participant can fully participate in all aspects of this clinical study

Weight

9. Has a body mass index (BMI) within the range of 18.0 and 40.0 kg/m^2 (inclusive) at Screening

Sex and Contraceptive/Barrier Requirements

10. A participant is eligible to participate if he/she agrees to abide by the guidelines set forth in this protocol regarding contraception requirements (see full contraception guidelines in Section 10.5):

a. A male participant is eligible to participate if he agrees to the following during the study Treatment Period and for at least 28 days after receiving the last dose of MORF-057:

- Abstains from heterosexual intercourse as his preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agrees to remain abstinent

OR

- Agrees to use contraception/barrier methods as detailed below:
  - Agrees to use a male condom, with female partner use of an additional highly effective contraceptive method with a failure rate of <1% per year (as described in Section 10.5.2) when having sexual intercourse with a woman of childbearing potential who is not currently pregnant
  - Agrees to use a male condom when engaging in any activity that allows for passage of ejaculate to another person

b. A female participant is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies:

- Is a woman of non-childbearing potential (as defined in Section 10.5.1)

OR

- Is a woman of childbearing potential (as defined in Section 10.5.1) and agrees to use a contraceptive method that is highly effective with a failure rate of <1% per year (as described in Section 10.5.2) during the study

Treatment Period and for at least 28 days after receiving the last dose of MORF-057

Note: Women who use any oral hormonal contraception must use an additional physical barrier method (Section 10.5.2).

11. For the study Treatment Period and at least 28 days after receiving the last dose of MORF-057, male participants must agree not to donate sperm and female participants must agree not to donate eggs (ova, oocytes).

Informed Consent

12. Capable of giving signed informed consent, as described in Section 10.1.4, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol

Exploratory Cohort Inclusion Criteria:

In addition to meeting Inclusion Criteria 1 through 12, the following criteria must be met for participants to be included in the Exploratory Cohort:

13. Those intolerant to (e.g. infusion-related skin reaction, allergy, or side effects unrelated to $\alpha_4\beta_7$ inhibition) or secondary non-responders* to vedolizumab who have been dosed within the past 5 years with the drug. Up to 5 of the 10 Exploratory Cohort participants may be included based on clinical criteria only. The remaining participants must also meet at least 1 of the following criteria:
    a. Documented vedolizumab levels in blood of ≤10 µg/mL 6 to 8 weeks after their most recent dose or at what is considered clinical trough. If the participant has had vedolizumab levels in blood tested and documented in their medical chart prior to Screening, the test does not need to be repeated.
    b. Non-saturating receptor occupancy of vedolizumab in blood 6 to 8 weeks after their most recent dose
    c. Documented presence of anti-drug antibodies against vedolizumab. If the participant has had a positive anti-drug antibody test that has been documented prior to Screening, the test does not need to be repeated.

    ***Note**: Secondary non-response is defined as having initially responded to Induction therapy and then had recurrence of symptoms after receiving at least 2 of the Maintenance doses, 300 mg every 8 weeks (discontinuation despite clinical benefit does not qualify).

14. The participants should also have received their last dose of vedolizumab at least 6 weeks prior to study Day 1 to allow sufficient washout

5.2. Exclusion Criteria

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

Medical Conditions

1. Diagnosed with indeterminate colitis, microscopic colitis, ischemic colitis, radiation colitis, or CD or has clinical findings suggestive of CD
2. Has current evidence of un-resected colonic dysplasia or un-resected adenomatous colonic polyps or evidence of toxic megacolon, abdominal abscess, symptomatic colonic stricture, fistula, stoma, ileostomy, or colostomy at Screening
3. Currently requires or is anticipated to require surgical intervention for UC during the study or is planning to undergo major surgery during the study period
4. Has had a surgical procedure requiring general anesthesia within 30 days prior to Screening
5. Has a history of any major neurological disorders, including stroke, multiple sclerosis, brain tumor, demyelinating, or neurodegenerative disease. For questions about whether this applies to a specific case, consult with the Medical Monitor.
6. Has positive findings on a subjective neurological screening questionnaire or PML subjective symptom checklist during Screening or prior to the administration of the first dose of study drug on study Day 1
7. Has an active bacterial, viral, or parasitic pathogenic enteric infection, including *Clostridium difficile*; has cytomegalovirus, hepatitis B or C virus, or human immunodeficiency virus (HIV); had an infection requiring hospitalization or intravenous antimicrobial therapy, or an opportunistic infection within 3 months prior to Screening; had any infection requiring oral antimicrobial therapy within 2 weeks prior to Screening; or has a history of more than 1 episode of herpes zoster or any episode of disseminated herpes zoster infection
8. Has a positive diagnostic tuberculosis (TB) test at Screening (defined as a positive [redacted] test). If the participant has had a confirmed negative [redacted] or other Interferon Gamma Release Assay test within 90 days prior to Screening, the test does not need to be repeated. In cases where the [redacted] test result is indeterminate, the participant may have the test repeated once, and if the second test is negative, the participant will be eligible. In the event the second test also has an indeterminate result or [redacted] is unavailable, the Investigator has the option to perform a purified protein derivative (PPD) skin test. If the PPD reaction is <5 mm, then the participant is eligible. If the reaction is ≥5 mm or PPD testing is not done, the participant is not eligible. An exception can be made for participants with a history of latent TB who are currently receiving treatment for latent TB per local standard care, who will initiate treatment for latent TB before the first dose of study drug, or who have documentation of completing appropriate treatment for latent TB within 2 years prior to study Day 1.

9. Tests positive for Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) during the Screening Period. Participants who test positive for SARS-CoV-2 can undergo retesting throughout the Screening Period. Testing to be performed according to site-specific testing procedures and country-specific requirements.
10. Had any vaccination (including live virus vaccinations) within 3 weeks prior to study Day 1. **Note:** For vaccinations requiring a series of doses, the last in the series should be completed by 3 weeks prior to study Day 1 (e.g., SARS-CoV-2 two-shot vaccination series).
11. Has a concurrent, clinically significant, serious, unstable comorbidity (such as uncontrolled cardiovascular, pulmonary, hepatic, renal, gastrointestinal, genitourinary, hematological, coagulation, immunological, endocrine/metabolic, or other medical disorder) that, in the judgement of the Investigator, would compromise compliance with the protocol, interfere with interpretation of the study results, or pre-dispose participants to safety risks
12. Has a known primary or secondary immunodeficiency
13. Has a history of myocardial infarction, unstable angina, transient ischemic attack, decompensated heart failure requiring hospitalization, congestive heart failure (New York Heart Association Class 3 or 4), uncontrolled arrhythmias, cardiac revascularization, uncontrolled hypertension, or uncontrolled diabetes within 6 months of Screening
14. Has a history of left ventricular ejection fraction (LVEF) <50%
15. Has a clinically significant abnormal ECG at Screening, including a QT interval corrected through use of Fridericia's formula (QTcF) ≥450 ms for males and ≥470 ms for females
16. Abnormal hematology (hemoglobin level, WBC count, or platelet count) or coagulation results at Screening, as evidenced by the ranges provided below:*
    a. Hemoglobin level <8.0 g/dL
    b. Absolute WBC count $<3.0 \times 10^9$/L
    c. Absolute lymphocyte count $<0.5 \times 10^9$/L
    d. Absolute lymphocyte count >5.0 x 10^9/L
    e. Absolute neutrophil count $<1.2 \times 10^9$/L
    f. Platelet count $<100 \times 10^9$/L or $>1000 \times 10^9$/L
    g. International normalized ratio >1.5
17. Clinically significant abnormal urinalysis results, as deemed by the Investigator or designee
18. Abnormal organ function at Screening, as evidenced by the following:*
    a. Alanine aminotransferase or aspartate aminotransferase >2.5 × upper limit of normal (ULN)

b. Chronic kidney disease stages 4 and 5, defined as having a glomerular filtration rate <30 mL/min/1.73m^2 as calculated using the Modification of Diet in Renal Disease (MDRD) equation, receiving dialysis, or being listed for or has received a renal transplant

c. Total bilirubin ≥1.5 × ULN

***Note**: Repeat testing should be done at the discretion of the Investigator. Consult with the Medical Monitor as needed.

19. History of active malignancy in the 5 years preceding study Day 1, except in cases of basal cell skin cancer, squamous cell skin cancer, or other in-situ malignancies that have been excised and resolved and the participant was deemed clear of cancer after appropriate follow-up. Participants with a history of malignancy or those at high risk for malignancy may only be enrolled after a consultation with the Medical Monitor.

Prior/Concomitant Therapy

20. Treatment with cyclosporine, mycophenolate, tacrolimus, or sirolimus within 30 days or 5 half-lives (whichever is shorter) prior to study Day 1
21. Any previous treatment with vedolizumab or other integrin inhibitors (except participants for the Exploratory Cohort)
22. Experiencing toxicities from prior therapy with Grade >1 within 1 week prior to first dose of study drug
23. Fecal microbiota transplantation within 3 months prior to Screening
24. If treatment with a moderate-to-strong CYP3A4 inducer or inhibitor was received, a washout period of at least 30 days or 5 half-lives (whichever is shorter) is required prior to study Day 1. See Section 6.7.2 for a list of moderate-to-strong P450 inducers and inhibitors.
25. If treatment with a moderate-to-strong organic anion transporter polypeptide-1B inhibitor was received, a washout period of at least 14 days or 5 half-lives (whichever is shorter) is required prior to study Day 1. See Section 6.7.2 for a list of moderate-to-strong organic anion transporter polypeptide-1B inhibitors.

Prior/Concurrent Clinical Study Experience

26. Concurrent participation in any other interventional study
27. Received any investigational therapy within 30 days or 5 half-lives (whichever is longer) prior to study Day 1
28. Previous exposure to MORF-057 and/or a known hypersensitivity to drugs with a similar mechanism to MORF-057

Other Exclusions

29. Females who are pregnant or lactating or who are planning on becoming pregnant during the course of the study

30. Current or recent history of alcohol dependence or illicit drug use that, in the opinion of the Investigator, may interfere with the participant's ability to comply with the study procedures
31. Mental or legal incapacitation or a history of clinically significant psychiatric disorders at the time of the Screening Visit that would impact the ability to participate in the trial according to the Investigator
32. Unable to attend study visits or comply with procedures

5.3. Lifestyle Considerations

The following dietary and lifestyle restrictions are recommended:

- Refrain from consuming grapefruit, grapefruit juice, starfruit, limes, and bitter oranges.
- Refrain from excessive caffeine consumption, defined as ≥800 mg/day. For each scheduled study visit, participants should refrain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) before the [redacted] dose until after all study assessments and blood collections have been completed for that visit.
- For each scheduled study visit, participants should refrain from consuming alcohol before the [redacted] dose until after all study assessments and blood collections have been completed for that visit.
- Refrain from the use of cannabidiol and tetrahydrocannabinol.

5.4. Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs).

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened based on discussion and agreement between the Investigator and the Sponsor Medical Monitor. Re-screened participants should be assigned a new participant number for every screening/re-screening event.

6. STUDY TREATMENT

6.1. Study Treatment Description

A description of the study drug is provided in Table 3. More detailed information about the study drug can be found in the Pharmacy Manual.

Refer to Section 8.3 for study drug administration instructions.

MORF-057 capsules will be manufactured, quality control tested, and released in accordance with Good Manufacturing Practice.

Table 3. Study Intervention

Study drug	MORF-057
Type	Small molecule drug
Dose formulation	[redacted] capsule (Swedish orange capsule size 4)
Unit dose strength	[redacted] mg/capsule
Route of Administration	Oral
Dosage	[redacted] mg [redacted]
Use	Experimental
IMP/NIMP	IMP
Sourcing	Provided by Sponsor
Packaging and Labeling	Capsules are packaged in a high-density polyethylene bottle containing an oxygen absorber canister and coil and closed with a child-resistant cap equipped with a heat-sealed foil liner. Each bottle will be labeled as per country requirements.
Storage	Capsules must be stored at 20°C to 25°C (68°F to 77°F). Excursions are permitted from 15°C to 30°C (59°F to 86°F).

Abbreviations: [redacted]., [redacted] IMP, investigational medicinal product; NIMP, non-investigational medicinal product.

6.2. Preparation, Handling, Storage, and Accountability

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study drug received, and any discrepancies are reported and resolved before use of the study drug.

Only participants enrolled in the study may receive MORF-057, and only authorized site staff may supply or administer MORF-057. All MORF-057 supplies must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study drug accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation,

and final disposition records). All unused study drug for all participants should be maintained until review by a study monitor during site visits and at the time of database lock.

All unused MORF-057 capsules remaining at the completion of the study will either be returned to the Sponsor or destroyed at the investigational site per Sponsor instruction. It is the responsibility of the Investigator to ensure that the Sponsor has provided written authorization prior to return or destruction of study drug. Study drug return/destruction will be documented in the site files. No unused study drug may be disposed until fully accounted for by the study monitor.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label, single-arm study; therefore, randomization and blinding will not be used.

Enrollment will be conducted using interactive response technology.

6.4. Study Treatment Compliance

When participants are dosed at the site, they will receive the study drug directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study drug and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

When participants self-administer the study drug at home, compliance with prescribed dosage will be assessed at each visit. Participants will be instructed to record all details about the doses administered at home in the Participant Diary. Participants will also be advised to bring any remaining study drug supply to each site visit. Compliance will be assessed by reviewing the Participant Diary entries and counting returned capsules during the site visits; the findings will be documented in the source documents and relevant form. Deviation(s) from the prescribed dosage regimen should be recorded.

A record of the quantity of MORF-057 dispensed to and administered by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions, will also be recorded.

6.5. Continued Access to Study Intervention after the End of the Study

All participants will have the opportunity to enroll into a separate Long-term Extension after completing the Week 52 assessments. Participants who are willing to enroll into the Long-term Extension will skip the Safety Follow-up Visit at Week 56 and directly enter the Long-term Extension. Participants enrolled into the Long-term Extension will complete the Safety Follow-up Visit at Week 82.

Participants who do not enroll in the Long-term Extension will no longer have access to the study drug after they complete the 52-week Treatment Period. Participants who continue in the Long-term Extension will no longer have access to the study drug after they complete the 26-week extended Treatment Period.

6.6. Treatment of Overdose

There are no data available on the effects of acute or chronic overdosage with MORF-057.

For this study, any total daily dose of MORF-057 greater than 200 mg will be considered an overdose.

In the event of an overdose, the Investigator/treating physician should:

- Contact the Medical Monitor within 24 hours
- Evaluate the participant to determine, in consultation with the Medical Monitor, whether study drug should be interrupted or discontinued
- Closely monitor the participant for any AEs/SAEs and/or laboratory abnormalities
- Document the quantity of the excess dose as well as the duration of the overdose
- Enter the overdose information into the electronic data capture database (EDC) within 24 hours of notification

6.7. Concomitant Therapy

Any medications (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) or vaccines that the participant receives from the time of Screening through the Safety Follow-up Visit must be recorded in the electronic case report form (eCRF) along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose, frequency, and route of administration

Any medication given for a study-related AE should be recorded from the time of informed consent.

6.7.1. Allowed Medications for the Treatment of Ulcerative Colitis

The following list of concomitant medications for UC will be allowed during the study:

- 5-Aminosalicylates (not exceeding 4.8 g per day)
- Oral corticosteroids (not exceeding prednisone 30 mg per day, budesonide 9 mg per day, or equivalent)
- 6-Mercaptopurine (any stable dose)
- Azathioprine (any stable dose)
- Methotrexate (any stable dose)

Although these medications are allowed, participants should not start or stop any of these medications during the study. Furthermore, participants must maintain stable doses of these concomitant medications throughout the study until the end of the Safety Followup- Period, with the exception of tapering oral corticosteroid dose after 12 weeks of being in the trial. See Inclusion Criterion 3 (Section 5.1) for screening r-elated requirements for these medications.

If any other medications need to be started due to worsening of UC symptoms, the Medical Monitor should be contacted.

6.7.1.1. Tapering of Oral Corticosteroids

If medically appropriate to initiate a taper of oral corticosteroids (e.g., at least 1 month of stable clinical improvement approximating baseline status), the following steroid tapering schedules should be used, unless medically contraindicated after discussion with the Medical Monitor.

Participants receiving prednisone at the time of enrollment should maintain their current dose regimen during the Induction Period. After completion of the Week 12 visit, participants are allowed to completely taper off prednisone by reducing dose at 5 mg per week until daily dose reaches 10 mg per day, then further reducing dose at 2.5 mg per week until prednisone is completely tapered off.

Participants receiving budesonide at the time of enrollment should maintain their current dose regimen during the Induction Period. After completion of the Week 12 visit, participants are allowed to completely taper off budesonide by reducing dose at 3 mg per day for every 2 weeks until budesonide is completely tapered off. Participants receiving budesonide MMX (1 tablet, 9 mg) can reduce dosage by taking 6 mg budesonide (2 tablets, 3 mg each) daily for two weeks, followed by 3 mg budesonide (1 tablet, 3 mg) daily for two weeks to complete the tapering process.

However, during the taper, if participants experience clinical worsening of UC, increasing the dose back up to the dose used at trial entry (but not higher) is permitted. Participants are advised to resume the taper within 2 to 4 weeks.

6.7.2. Prohibited Medications

The following concomitant medications/therapies are prohibited for the entire duration of the study, including Safety Follow-up:

- Treatments for UC other than those listed in Section 6.7.1 (including TNF-α antagonists, integrin antagonists, IL-12/IL-23 antagonists, JAK antagonists, and S1P receptor agonists)
- Receipt of a live virus vaccine from 3 weeks prior to study Day 1 until 28 days after the last dose of study drug
- **Note:** Non-live vaccines, including those for SARS-CoV-2, should not be administered between 3 weeks prior to study Day 1 and the Week 12 assessments. After the Week 12 assessments, such vaccines can be administered according to local vaccination standards. Per Exclusion Criterion 10, if the participant has started a vaccination series before Day 1, the last in the series should be completed by 3 weeks prior to Day 1 (Section 5.1).
- Moderate-to-strong CYP3A inhibitor or inducer (see Table 4)
- Moderate-to-strong organic anion transporter polypeptide-1B inhibitor (see Table 4)
- Cyclosporine, mycophenolate, tacrolimus, or sirolimus
- Nonsteroidal anti-inflammatory drugs (NSAIDs) including but not limited to ibuprofen, naproxen, indomethacin, and celecoxib. However, participants may take aspirin for secondary prevention of cardiovascular event at a dose not exceeding 100 mg per day.

- Any investigational therapy

Table 4. Examples of Drugs Potentially Altering Exposures to MORF-057[#]

CYP3A Inhibitors (Moderate to Strong)			
Aprepitant	Indinavir	Telithromycin	Mifepristone*
Ceritinib	Itraconazole	Tucatinib	Norfloxacin*
Clarithromycin	Ketoconazole	Verapamil	Norfluoxetine*
Crizotinib	Mibefradil	Voriconazole	Regorafenib*
Diltiazem	Nefazodone	Amiodarone*	Telaprevir*
Erythromycin	Nelfinavir	Boceprevir*	
Fluconazole	Ribociclib	Ciprofloxacin*	
Grapefruit juice	Ritonavir	Delavirdine*	
Idelalisib	Saquinavir	Fluvoxamine*	
CYP3A Inducers			
Barbiturates	Elagolix	Modafinil	Pioglitazone
Brigatinib	Enzalutamide	Nevirapine	Rifabutin
Carbamazepine	Eslicarbazepine	Oritavancin	Rifampin
Clobazam	Glucocorticoids	Oxcarbazepine	St. John's wort
Dabrafenib	Letermovir	Phenobarbital	Telotristat
Efavirenz	Lorlatinib	Phenytoin	Troglitazone
OATP1B1/3 Inhibitors			
Atazanavir and ritonavir	Cyclosporine	Gemfibrozil	Rifampin (single dose)
Clarithromycin	Erythromycin	Lopinavir and ritonavir	Simeprevir

[#] This is not an exhaustive list CYP3A inhibitors/inducers or OATP1B1 inhibitors.
* Time-dependent inhibitors
Sources: (Flockhart, 2021) (US FDA, 2020)

6.7.3. Prohibited Procedures

The following concomitant procedures are prohibited during the study:

- Major elective surgery
- Immunoadsorption columns
- Intravenous immunoglobulin or plasmapheresis
- Blood donations during the study and for 28 days after the last dose of study drug

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Treatment

7.1.1. Permanent Discontinuation

In rare instances, it may be necessary for a participant to permanently discontinue the study drug. If the study drug is permanently discontinued, the participant should remain in the study to be evaluated for the 4-week Safety Follow-up Visit. See the SoA (Section 1.2) for the assessments to be performed at the time of study drug discontinuation (End of Treatment Visit) and follow-up for any further evaluations that need to be completed.

A participant's study treatment may be discontinued if any of the following occur during the study:

- Use of disallowed medications and/or procedures as defined in Sections 6.7.2 and 6.7.3
- Severe uncontrolled infection
- Lack of efficacy defined as:
  - Determined by the Investigator that the participant is not benefiting from the investigational treatment and/or continued participation would pose an unacceptable risk to the participant
  - Administration of a rescue medication (a new medication or increase in dose of a baseline medication to treat new or unresolved UC symptoms). Anti-diarrheals for control of chronic diarrhea are not considered rescue medication.
  - Requirement for abdominal surgery due to complications from UC
- Pregnancy or planned pregnancy (see Section 8.9.5)
- Non-compliance with study treatment (see Section 6.4)
- Sponsor or the Investigator deems it is necessary for the participant

If a participant who does not meet the enrollment criteria is inadvertently enrolled, that participant must be discontinued from the study drug, and the Sponsor or Sponsor designee must be contacted. An exception may be granted in rare circumstances for which there is a compelling safety reason to allow the participant to continue. In these rare cases, the Investigator must obtain documented approval from the Sponsor or Sponsor's designee to allow the participant to continue in the study.

The reason for discontinuation of the study drug will be recorded in the clinical records and the participant's eCRF.

7.1.2. Temporary Discontinuation

Decisions regarding dose interruptions will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

7.1.3. Re-challenge

Re-challenge may be allowed at the discretion of the Investigator and Medical Monitor.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, or compliance reasons. This is expected to be uncommon.

The participant should be encouraged to complete the End of Treatment Visit (Visit 10 in the main part of the study, or Visit 12 in the Long-term Extension) at the time of study drug discontinuation and the Safety Follow-up Visit (Visit 11 in the main part of the study, or Visit 13 in the Long-term Extension) at 28 days (+7) after the last dose of study drug. See the SoA (Section 1.2) for details regarding the data to be collected at the End of Treatment and Safety Follow-up Visits.

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

Participants who withdraw or are withdrawn from the study will not be replaced.

Closure/termination of specific study centers or of the study as a whole are handled as described in Section 10.1.11.2.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's clinical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Section 1.2). Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study drug.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a Screening Log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Repeat or unscheduled blood samples may be taken for safety reasons or for technical issues with the samples.

Maximum volume of blood to be obtained over the duration of the study will not exceed local regulation requirements.

8.1. Medical History

The participant's demographics and medical and surgical history are to be recorded at Screening. In addition, the participant's medication history should be collected for at least 12 months prior to Day 1.

All prior advanced therapies for the treatment of UC (e.g., antagonists to TNF-α, JAK, or IL-12/IL-23; S1P receptor agonists; integrin inhibitors [Exploratory Cohort only]; or other new investigational treatments) with the reason for discontinuation are to be collected for participants where possible.

8.2. Screening-specific Tests

8.2.1. Pathogen Screening

8.2.1.1. Tuberculosis

All participants will complete TB screening to determine eligibility. See Exclusion Criterion 8 (Section 5.2) and the SoA (Section 1.2) for details regarding testing requirements.

8.2.1.2. SARS-CoV-2

All participants will complete SARS-CoV-2 screening to determine eligibility. See Exclusion Criterion 9 (Section 5.2) and the SoA (Section 1.2) for details regarding testing requirements.

8.2.1.3. C. difficile and Enteric Pathogens

All participants will complete *C. difficile* and enteric pathogen screening (including ova and parasite testing) to determine eligibility. See Exclusion Criterion 7 (Section 5.2) and the SoA (Section 1.2) for details regarding testing requirements.

8.2.1.4. Cytomegalovirus

All participants will complete cytomegalovirus screening to determine eligibility. See Exclusion Criterion 7 (Section 5.2) and the SoA (Section 1.2) for details regarding testing requirements.

8.2.1.5. HIV, Hepatitis B, and Hepatitis C

All participants will complete the following screening tests to determine eligibility: HIV antibody, hepatitis B surface antigen, and hepatitis C virus antibody. See Exclusion Criterion 7 (Section 5.2) and the SoA (Section 1.2) for details regarding testing requirements.

8.2.2. Drug/Alcohol Screening

All participants will complete a serum alcohol screen and a urine drug screen to determine eligibility. See Exclusion Criterion 30 (Section 5.2) and the SoA (Section 1.2) for details regarding testing requirements.

8.2.3. Exploratory Cohort Screening Tests

All participants being considered for the Exploratory Cohort must undergo a specific panel of blood tests to determine eligibility (see Inclusion Criteria 13 and 14 [Section 5.1] and the SoA [Section 1.2]). The specific tests are described below:

- Vedolizumab blood levels 6 to 8 weeks after their most recent dose or at what is considered clinical trough. (If the participant has had vedolizumab levels in blood tested and documented in their medical chart prior to Screening, the test does not need to be repeated.)
- Receptor occupancy of vedolizumab in blood 6 to 8 weeks after their most recent dose
- Anti-vedolizumab antibody testing (If the participant has had a positive anti-drug antibody test that has been documented prior to Screening, the test does not need to be repeated.)

8.3. Study Drug Administration

8.3.1. Dosing Instructions

Participants will swallow [redacted] mg capsules of MORF-057 with water [redacted]. MORF-057 can be taken with or without food. No dose adjustments will be allowed.

8.3.2. Missed Dose Instructions

MORF-057 capsules should be taken at approximately the same time every day in the [redacted] and in the [redacted]. The interval between doses should be as close to 12 hours as possible. Participants should be instructed that if they forget to take a dose, they can take the dose within [redacted] of the [redacted]; otherwise, they should take their next dose at the regular time on the following day. Participants who vomit a capsule should be instructed not to take another capsule at that dosing time, but to take the next scheduled dose at the regular time. Participants will record their daily dose in the Participant Diary. Missed doses that occur at any time during a week prior to PK sampling should be recorded in the eCRF. Participants should be instructed to

contact the Investigator if they miss more than 2 consecutive doses; in such cases, the Investigator should consult with the Medical Monitor regarding any actions required.

8.4. Virtual/Hybrid Visits

To allow participants to remain in the study to continue to be evaluated, a virtual or hybrid visit may be considered only for participants who are not able to participate in an on-site visit. Some visit assessments and procedures may be performed virtually or off-site with the permission of the Investigator and Sponsor in accordance with all national, state, and local laws or regulations of the pertinent regulatory authorities. Examples of assessments or procedures that may be conducted virtually, if allowed by local law and regulation, include safety assessments as applicable (e.g., AE/SAE assessments), review of Participant Diary compliance, and collection of samples for pregnancy testing and/or central laboratory assessments.

Regardless of how a study visit and its associated procedures are conducted, all study procedures should be performed by qualified study site staff or qualified individuals as delegated by the Investigator.

8.5. Participant Diary

Participants will be asked to capture study data in their Participant Diary. Entries will begin on the first day of Screening after diary training is completed and will continue through the Safety Follow-up Visit. Diary entries will include study drug administration details and daily rectal bleeding and stool frequency information (the 2 patient-reported outcome measures of the Full and Modified MCS, see Section 8.7.3). Diaries are to be completed daily by the participant. The Participant's Diary will be reviewed by study site staff to ensure the participant is compliant with diary entries through EDC and during each study visit at the times noted in the SoA (Section 1.2).

Detailed descriptions regarding Participant Diary recordings can be found in the Patient Guide.

8.6. Stool Collection

Stool samples will be required to assess fecal calprotectin levels, microbiome composition in stool, microbiome-derived metabolites in stool, and meta-transcriptomic changes in stool microbiome. Samples for these tests should be collected on site, if possible, according to the respective schedules shown in the SoA (Section 1.2).

In addition, stool collection kits are to be dispensed to participants at the visits indicated in the SoA. 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 of the main Treatment Period. These samples will be used as back-ups if the participant is unable to provide a fresh sample during the respective site visit.

See the Laboratory Manual for additional details about stool collection procedures.

8.7. Efficacy Assessments

8.7.1. Endoscopy with Biopsy

Endoscopy will be performed at Screening (Visit 1) and Visits 4 (optional), 5, and 10/EOTFlexible sigmoidoscopy with colonoscopy scope is the suggested procedure, but full colonoscopy is optional at any timepoint if the Investigator deems it necessary. During these procedures, colonic mucosa biopsies will be collected for cytomegalovirus testing (Screening only), histopathology, spatial transcriptomics/proteomics, microbiome, and gene expression analyses. A total of 12 biopsies will be collected during each endoscopy procedure. To ensure quality data and standardization, the same endoscopist should be used throughout the study wherever possible. A detailed image review charter from the central reading laboratory will outline the endoscopic procedures, video recordings, and equipment.

For each participant, a video recording of the entire endoscopic procedure will be performed using an acceptable storage medium.

The original location (colonic segment) of biopsy specimens acquired at Screening must be clearly indicated. Detailed instructions for endoscopic biopsies (e.g., anatomic site, normal or inflamed mucosa) can be found in the Central Image Management Solutions (CIMS) Biopsy Quick Reference Card.

Biopsy specimen transfer, processing, slide preparation, and digitization of slides for histopathologic scoring procedures will be detailed in the Image Review Charter. Histopathology results will not be made available to study sites, except for the RHI Score at Screening, which will be required for determining study eligibility.

Biopsy samples will be processed by a central laboratory. The histologic endpoints (i.e., 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). However, treatment decisions will be made by the treating Investigator.

Processing, transfer, and storage of biopsy specimens for PD biomarker analysis will be described in the Laboratory Manual.

8.7.2. Histologic Scores

Histological improvement will be assessed with the RHI Score, NI, and Continuous Geboes Score. These are each described in detail in Section 10.6.

RHI Score

The RHI Score is determined by evaluating 4 histologic items: chronic inflammatory infiltrate score, lamina propria neutrophils score, neutrophils in epithelium score, and erosion or ulceration score.

Nancy Index

The NI is determined by evaluating 3 histological items: ulceration, acute inflammatory cells infiltrate, and chronic inflammatory infiltrate.

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).

8.7.3. Mayo Clinic Score

The Full MCS and Modified MCS will be used to assess clinical improvement. The Full MCS is a composite of the following subscores: MES, MCS stool frequency subscore, MCS rectal bleeding subscore, and the Physician's Global Assessment. 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 the SoA (Section 1.2).

Mayo endoscopic subscore: Endoscopy will be used to visualize the mucosa to enable calculation of the MES. The MES reports the worst appearance of the mucosa as visualized by flexible sigmoidoscopy or colonoscopy on a 4-point scale (see Section 10.7).

Rectal bleeding subscore: The rectal bleeding subscore is a patient-reported measure. This item reports the most severe amount of blood passed per rectum for a given day on a 4-point scale (see Section 10.7). The participant will record this in their Participant Diary daily.

Stool frequency subscore: The stool frequency subscore is a patient-reported measure. This item reports the number of stools in a 24-hour period, relative to the normal number of stools for that participant in the same period on a 4-point scale (see Section 10.7). A stool is defined as a trip to the toilet when the participant has either a bowel movement, passage of blood alone, passage of blood and mucus, or passage of mucus only. The total number of stools passed in a 24-hour period will be recorded by the participant in their Participant Diary daily. The reference "normal" stool frequency for that participant will be recorded on the first day of the Screening visit and is the number of stools in a 24-hour period when the participant is in remission. If the participant has never achieved remission, the reported stool frequency before initial onset of signs and symptoms of UC will be used as the reference stool frequency.

Physician's Global Assessment: The PGA is a physician-reported measure that summarizes the Investigator's assessment of the participant's UC disease activity on a 4-point scale (see Section 10.7). The Investigator will record the PGA in the site tablet or other relevant device or system at the specified study visits.

8.7.4. Non-endoscopic Biomarkers of Inflammation

8.7.4.1. High-sensitivity C-reactive Protein

Blood will be collected for measurement of CRP according to the schedule specified in the SoA (Section 1.2). C-reactive protein is an acute-phase protein that is expressed in response to inflammation. It will be assessed using an hs-CRP test.

8.7.4.2. Fecal Calprotectin

Stool samples will be collected for measurement of fecal calprotectin according to the schedule specified in the SoA (Section 1.2). Fecal calprotectin levels correlate with the number of neutrophils in the gut and thus are used as a biomarker of intestinal inflammation.

8.8. Safety Assessments

8.8.1. Physical Examinations

Physical examinations will be performed at the timepoints specified in the SoA (Section 1.2). A complete physical exam is required at Screening and Visit 10/EOT, and a targeted exam may be performed at all other required visits. 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 choice of whether to perform a complete or targeted physical exam is at the discretion of the Investigator and will depend on the reason for the unscheduled visit. Physical examinations must be performed by an Investigator or a medically qualified designee.

Complete physical examinations include the following body systems: general appearance, skin, head, ears, eyes, nose, throat, neck, lungs, heart, abdomen, musculoskeletal, extremities, and neurological. At Screening, this exam will also include height and weight to calculate BMI.

Targeted physical examinations include the following: abdominal examination, assessment of any new symptoms or observations, and follow-up of any previously identified clinically abnormalities and examination of related body systems.

8.8.2. Vital Signs

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.

The following guidelines should be followed during the measurement of blood pressure:

- The participant's arm should be bare and supported at heart level.
- An appropriately sized cuff (cuff bladder encircling at least 80% of the arm) should be used.
- The participant's legs should not be crossed during the evaluation.

Blood pressure and pulse measurements should be preceded by at least 10 minutes of rest for the participant in a quiet setting without distractions.

Vital signs are to be taken before blood collection for laboratory tests.

8.8.3. Electrocardiograms

Single 12-lead ECGs will be performed at the timepoints specified in the SoA (Section 1.2). Measurements will include PR, QRS, QT, and QTcF.

Single 12-lead ECGs will be obtained after the participant has rested for at least 10 minutes in the supine position; this rest period can be combined with the required vital signs rest period.

Repeat ECGs will be permitted as necessary due to poor quality and/or by Investigator discretion.

8.8.4. Clinical Safety Laboratory Tests

Blood/urine samples will be collected for safety laboratory testing (serum chemistry, hematology, coagulation, and urinalysis) at the timepoints specified in the SoA (Section 1.2). Blood samples will be collected before the [redacted] on Visits 2-10 of the main Treatment Period and before the [redacted] on Visits 11-12 of the Long-term Extension. See Section 10.3 for a listing of laboratory analytes to be collected. Repeat/unscheduled samples may be collected at the Investigator's discretion.

The Investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study drug should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.

If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.

All protocol-required laboratory tests, as defined in Section 10.3, must be conducted in accordance with the Laboratory Manual.

If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (e.g., SAE or AE or dose modification), then the results must be recorded.

8.8.5. Progressive Multifocal Leukoencephalopathy

The Subjective PML Checklist will be administered to participants during Screening to exclude individuals with a positive response from enrolling into the study. The Subjective PML Checklist (Section 10.2) will also be completed according to the schedule in the SoA (Section 1.2). If the results of the questionnaire are suggestive of PML, the participant will undergo Objective PML Checklist testing (Section 10.2), a full neurological exam by a neurologist, and, if indicated, additional testing.

8.8.6. Pregnancy/Menopause Testing

Pregnancy testing will be required for women of childbearing potential. A serum β human chorionic gonadotropin (hCG) pregnancy test will be performed at Screening. A urine hCG pregnancy test will be performed at all subsequent visits. On Day 1, a urine test must be completed and results reviewed prior to start of the study drug.

A serum test for follicle-stimulating hormone level will be performed at Screening only for female participants of non-childbearing potential who are not surgically sterile.

8.9. Adverse Events and Other Safety Reporting

The definitions of AEs and SAEs can be found in Section 10.4.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious and considered related to the study drug or study procedures. For each AE, the Investigator will evaluate and report the onset (date and time), resolution (date and time), severity, causality, action taken, serious outcomes (if applicable), and whether or not it caused the participant to discontinue the study.

The method of recording, evaluating, and assessing causality and study drug relationship of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.4.

8.9.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the signing of the ICF until the Safety Follow-up Visit at the timepoints specified in the SoA (Section 1.2).

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.4.4. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study drug or study participation, the Investigator must promptly notify the Sponsor.

8.9.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Participants should be instructed to report any AEs that they experience to the Investigator. Beginning at the time of first dose, Investigators should make an assessment for AEs at each visit and record the event on the appropriate AE eCRF. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.9.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.4.3.

8.9.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and Investigators.

An Investigator who receives an Investigator Safety Report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate, according to local requirements.

Investigator Safety Reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary. The term SUSAR refers to an AE that occurs in a participant and which is assessed by the Sponsor and/or Investigator as being unexpected (i.e., not listed in the Investigator's Brochure or not listed at the specificity or severity that has been observed), serious, and as having a reasonable possibility of a causal relationship with the study drug (i.e., related to the study drug per causality assessment in Section 10.4.3). Reports of these reactions are subject to expedited submission to regulatory authorities.

Morphic Therapeutic or designee is responsible for notifying the relevant regulatory authorities and Investigator sites within the specified timeframes of all SUSARs. Morphic Therapeutic will make the determination whether the event is unexpected. It is the PI's responsibility to notify the IRB/IEC according to the relevant regulatory timelines of all SUSARs of which the Investigator is notified by Morphic Therapeutic that occur at his or her site.

Morphic Therapeutic or designee will report all relevant information about SUSARs that are fatal or life-threatening as soon as possible to the US Food and Drug Administration (FDA), and, in any case, no later than 7 days after knowledge by the Sponsor of such a case. Relevant follow-up information will subsequently be communicated within an additional 8 days.

Morphic Therapeutic or designee will report all other SUSARs to the FDA as soon as possible but within 15 days of Morphic Therapeutics' first knowledge of the event.

The Sponsor will also report any additional expedited safety reports required in accordance with the timelines outlined in country-specific legislation.

Morphic Therapeutic will also inform all Investigators as required per local regulation.

The requirements above refer to the requirements relating to investigational medicinal product.

8.9.5. Pregnancy

Details of all pregnancies in female participants and female partners of male participants will be collected from the start of the study Treatment Period until 28 days after the last dose of study drug is received.

If a pregnancy is reported in a female participant or female partner of a male participant, the Investigator should follow the procedures outlined below:

Female participant who becomes pregnant

If a pregnancy is reported in a female study participant, the study drug should be discontinued immediately and the participant should then complete the End of Treatment and Safety Follow-up Visits. Pregnancy information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of the participant's pregnancy. The participant will then undergo pregnancy follow-up to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the study participant and the neonate, and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Male participant with a partner who becomes pregnant

The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours. The female partner will then undergo pregnancy follow-up to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the mother and the neonate, and the information will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure. The male study participant may continue taking the study drug.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) will also be considered SAEs and will be reported as such.

Any post-study pregnancy-related SAE considered reasonably related to the study drug by the Investigator will be reported to the Sponsor as described in Section 8.9.4. While the Investigator is not obligated to actively seek this information in former study participants/pregnant female partners, he or she may learn of an SAE through spontaneous reporting.

8.9.6. Adverse Events of Special Interest

There are no adverse events of special interest for this study.

8.10. Pharmacokinetics

8.10.1. 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 the SoA (Section 1.2).

Additional detailed instructions for the blood collection, processing, storage, and shipment to the bioanalytical laboratory will be detailed in the Laboratory Manual. The actual date and time (24-hour clock time) of each sample will be recorded, along with the date and time of study drug administration.

The sampling windows for the PK assessment are provided in Table 5.

Table 5. Pharmacokinetics Sampling Windows

Visit	Collection timepoints and associated windows
2, 3, and 5	Required: Before [redacted] and at 1hr(±15min), 2hr(±15min), 3hr(±30min), 4hr(±1hr), and 6hr(±1hr) after [redacted] *Optional: 8hr(±1hr), 10hr(±1hr), and 12hr(-1hr)* after* [redacted]
4, 6, 7, 8, and 9	Required: Before [redacted] and at 1hr(±15min) and 3hr(±1hr) after [redacted]
10	Required: Before [redacted]

* 12-hou[redacted] sample to be collected prior to the[redacted]

For all [redacted] sampling, the samples should be obtained within approximately 30 minutes before the [redacted] is administered.

8.10.2. Determination of Drug Concentration and PK Parameters

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

PK Parameter	Description
AUC_{0-12}	Area under the concentration-time curve from time 0 to 12 hours post-dose
AUC_{tau}	Area under the concentration-time curve across the dosing interval
C_{max}	Maximum observed plasma concentration
C_{trough}	Trough plasma concentration (measured concentration at the end of a dosing interval, taken before the next dose)
t_{max}	Time to reach C_{max}. Defined as the first point if multiple maximum values occur
C_{12}	Plasma concentration at 12 hours post-dose

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

8.11. Pharmacodynamics

Details on the handling and processing of PD samples (blood, stool, and mucosal tissue) are outlined in the Laboratory Manual.

8.11.1. Receptor Occupancy

Whole blood samples for receptor occupancy assays will be collected according to the schedule specified in the SoA (Section 1.2). The following receptor occupancy assays will be performed:

- A pharmacologically relevant receptor occupancy assay that assesses drug inhibition of $\alpha_4\beta_7$ integrin binding to its natural ligand MAdCAM-1
- Receptor occupancy assay that evaluates drug inhibition of the off-target integrin $\alpha_4\beta_1$. To evaluate inhibition of $\alpha_4\beta_1$ integrin binding, an exploratory receptor occupancy assay using its ligand, LDV peptide fragment of fibronectin, will be used.

8.11.2. CCR9 mRNA

Blood samples will be collected in PAXgene RNA tubes to assess changes of transcript levels of CCR9.

8.11.3. Lymphocyte Subsets

Blood samples for immunophenotyping will be collected according to the schedule specified in the SoA (Section 1.2). Lymphocyte subsets assessed may include $\alpha_4\beta_7$-high effector memory and central memory T-cells and B-cells. Additional subsets may be analyzed, as well.

8.11.4. Gene and/or Protein Expression

Gene and/or protein expression will be assessed in blood and mucosal tissues.

Mucosal tissues for this analysis will be collected at the time of endoscopy.

Blood samples for protein biomarkers will be collected according to the schedule specified in the SoA (Section 1.2).

8.11.5. Microbiome Analyses

Microbiome composition will be assessed in stool and mucosal tissue samples. Microbiome-derived metabolites will be measured in stool and blood samples. Metatranscriptomic changes over time in the stool and mucosal tissue microbiome will also be examined.

Mucosal tissues for metatranscriptomic and microbiome composition analyses will be collected at the time of endoscopy.

Stool samples for microbiome composition, metabolite, and metatranscriptomic analyses will be collected according to the schedule specified in the SoA (Section 1.2).

Blood samples for microbiome-derived metabolite analysis will be collected according to the schedule specified in the SoA (Section 1.2).

8.11.6. Physiological Intermolecular Modulation Spectroscopy

Blood samples for physiological intermolecular modulation spectroscopy (PIMS) will be collected according to the schedule specified in the SoA (Section 1.2).

8.12. Future Pharmacodynamics and Pharmacogenomics Research

With participants' consent, blood samples will be collected and used for further PD and pharmacogenomics research by Morphic Therapeutics to contribute to the understanding of UC or related diseases, to the development of related or new treatments, or to the development of new research methods. Participation in this collection of samples for future research is optional. Samples for future research will be collected according to the schedule specified in the SoA (Section 1.2). Samples may be stored for a maximum of 15 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the Sponsor.

8.13. Potential Adjustments Due to COVID-19

Adjustments to the planned study procedures might be necessary due to the ongoing COVID-19 pandemic. Any such specific measures will be detailed in the respective ancillary documents, such as site-facing and patient-facing documents.

9. STATISTICAL CONSIDERATIONS

The Statistical Analysis Plan (SAP) will be finalized prior to the first participant dosed and may be amended as needed due to a protocol amendment. It will include a more technical and detailed description of the data summarization and analysis described in this section. Any change from the planned statistical analyses specified in the protocol will be fully described in the SAP and Clinical Study Report.

9.1. Analysis Sets

The following analysis sets will be used for the study analyses:

Full Analysis Set (FAS) is defined as all enrolled participants in the Main Cohort and Exploratory Cohort who took at least 1 dose of study medication. The FAS will be used for efficacy analyses.

Per Protocol (PP) Population is defined as all participants in the FAS who do not have any major protocol deviations relevant to the primary and secondary efficacy endpoint analysis. All decisions to exclude participants from the PP set will be made prior to the database lock of the study. The PP Population will be used for sensitivity analysis of the primary efficacy endpoint and maybe other selected efficacy endpoints as appropriate.

Safety Analysis Population is defined as all participants in both the Main Cohort and Exploratory Cohort who received at least 1 dose of study medication. The Safety Analysis Population will be used for safety analysis.

PK Population is defined as all participants in the FAS who have 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.

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 not violate the protocol in a way that may invalidate or bias the results, and must have the reliable data for the overall PK summaries. The criteria that the data must meet for the inclusion of a participant in this population will be specified in the study SAP.

PD Population is defined as all participants in the FAS who have at least 1 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.

9.2. Statistical Analyses

9.2.1. 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. Data will be summarized/analyzed at scheduled visits unless stated otherwise. A significance level of 0.025 one-sided (0.05 two-sided) will be used for the primary efficacy endpoint. No hypothesis testing will be performed for the secondary and exploratory efficacy endpoints. No hypothesis testing will be performed on safety data. The Main Cohort and Exploratory Cohort will be analyzed separately,

unless specified otherwise. Data from participants in the Exploratory Cohort will be analyzed only for exploratory purposes.

9.2.2. Primary Endpoint

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 data for the primary efficacy endpoint will be assessed for normality. If the data are normally distributed, then a one-sample t-test will be used for the analysis. If the data are not normally distributed, then a signed rank test will be used. If there are a large number of participants excluded from the Per Protocol Population due to major protocol deviations, then a sensitivity analysis of the primary efficacy endpoint will be performed using the Per Protocol Population. In addition, the proportion of participants in the FAS with a change from baseline to Week 12 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.

9.2.3. Secondary Endpoints

The continuous secondary efficacy endpoint (change from baseline to Week 12 in Modified MCS) will be analyzed similarly to the primary efficacy endpoint using the FAS. No hypothesis testing will be performed for the secondary efficacy endpoint.

The Safety Analysis Population will be used for the summarization of all safety data. Adverse events will be coded using the current Medical Dictionary of Regulatory Activities by System Organ Class (SOC) and Preferred Term (PT), classified from verbatim terms. A TEAE is defined as an AE that occurs between administration of the first dose of study drug and 7 days after the last dose of study drug. TEAEs and TESAEs will be summarized using frequencies and proportions; summaries will be provided for overall and according to SOC and PT. TEAEs leading to study drug discontinuation will be summarized or listed, as appropriate. Summaries of TEAEs will also be presented by severity and relationship (see Section 10.4.3). The duration of TEAEs will be determined and included in listings, along with the action taken and outcome.

The plasma PK parameters $AUC_{0\text{-}12}$, AUC_{tau}, C_{max}, C_{trough}, t_{max}, and C_{12} will be estimated by non-compartmental analysis using the PK Population. PK/PD analyses will be conducted as deemed appropriate and may be reported separately from the Clinical Study Report.

9.2.4. Exploratory Endpoints

The continuous exploratory efficacy endpoints (change from baseline to Weeks 6 and 52 in RHI Score and Modified MCS; change from baseline to Weeks 6, 12, and 52 in NI, Continuous Geboes Score, and Full MCS; and change from baseline to Weeks 2, 6, 12, 20, 28, 36, and 52 in hs-CRP and fecal calprotectin levels) will be analyzed similarly to the primary efficacy endpoint using the FAS. No hypothesis testing will be performed for the exploratory efficacy endpoints. In addition, the proportion of participants with NI score ≤1 at Week 12 will be provided.

The exploratory PD endpoints ($\alpha_4\beta_7$ and $\alpha_4\beta_1$ receptor occupancies over time and change from baseline over time in blood CCR9 mRNA) will be summarized descriptively. Additional 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. The PD Population will be used for the summarization and analysis of these exploratory endpoints.

9.2.5. Other Safety Analyses

Other safety data will include safety laboratory parameters, vital signs, and ECG findings. These data will be summarized with descriptive statistics by absolute values and change from baseline using the Safety Analysis Population. The incidence of laboratory abnormalities will be summarized. Worst shift in grade and changes from baseline to Weeks 6, 12, and 52 of the laboratory analytes will be reported. Physical examination findings that are recorded as AEs will be included in those data presentations.

Participant safety data will be reviewed by an independent DSMB. Additional details related to the DSMB are included in Section 10.1.6 and will be clearly delineated in the DSMB Charter.

9.3. 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 the purpose of 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 Periods of the Main and Exploratory Cohorts respectively (i.e., the period for the primary efficacy endpoint) and the other two for the 52-week Treatment Periods of the Main and Exploratory Cohorts respectively (i.e., the 12-week Induction Period plus the 40-week Maintenance Period and the Safety Follow-up). Additional analysis of the optional Long-term Extension Period for the participants enrolled into the Long-term Extension will be performed as appropriate.

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 concentrations and parameters, 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 the Induction Period analyses.

52-week Treatment Period Analysis

For the Main Cohort participants, the analysis of the 52-week Treatment Period will be performed after all 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. 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 participants, the analysis of the 52-week Treatment Period will be performed after all 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 for the Main and Exploratory Cohorts will formally evaluate all the exploratory endpoints defined by Week 52, PK concentration and parameters, and safety of MORF-057 during the 52-week open-label Treatment Period plus the Safety Follow-up Period. The cumulative data, including those from the Induction Period, will be used in these analyses.

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.

9.4. Sample Size Determination

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 28 participants with >80% power. A dropout rate of 5% would lead to a total of 30 participants being enrolled in the Main Cohort. -A maximum of 10 additional participants may be enrolled in the Exploratory Cohort, giving a total of 30 to 40 enrolled participants in the study.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European Clinical Trials Directive 2001/20/EC or European regulation 536/2014 for clinical studies (as applicable), and all other applicable local regulations

After reading the protocol, each Investigator will sign the Investigator's Agreement page (Section 10.9). The study will not start at any study center at which the Investigator has not signed the protocol.

10.1.2. Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial

certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Insurance

The Sponsor has obtained liability insurance, which covers this study as required by local law and/or national regulations and/or ICH guidelines, whichever is applicable. The terms of the insurance will be kept in the study files.

10.1.4. Informed Consent Process

The Investigator or his/her representative will explain the nature of the study, including the risks and benefits, to each participant or his/her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Each participant or his/her legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participant or his/her legally authorized representative.

The ICF will contain a separate section that addresses the use of samples for optional exploratory research. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the sample storage period (determined based on local country regulations). A separate signature will be required to document a participant's agreement to allow samples to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.

10.1.5. Data Protection

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the ICF.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.6. Data and Safety Monitoring Board

A DSMB has been appointed to this study. The DSMB is a group of independent clinicians/scientists who are appointed to monitor the safety and scientific integrity of a human research intervention, and to make recommendations to the Sponsor regarding the modification, continuance, or stopping of a study based on assessments of safety. The composition, responsibilities, and meeting schedule of the DSMB will be described in a separate DSMB Charter.

10.1.7. PML Adjudication Committee

A PML Adjudication Committee will oversee a PML RAMP to monitor all participants for PML. The composition, responsibilities, and meeting schedules of the PML Adjudication Committee will be described in a separate charter.

10.1.8. Dissemination of Clinical Study Data

The Sponsor will submit a summary of the results of the clinical study to the relevant clinical study databases in a timely manner. As appropriate, this will be accompanied by a summary written in a manner that is understandable to laypersons.

10.1.9. Data Quality Assurance

All participant data relating to the study will be recorded on printed or eCRFs unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the case report form (CRF).

Guidance on completion of CRFs will be provided in the corresponding guidelines.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).

Essential documents for this study should be retained by the Investigator/institution until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These

documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.10. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.11. Study and Site Start and Closure

10.1.11.1. First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants (i.e., when the first site is open).

10.1.11.2. Study/Site Termination

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

For study termination:

- Discontinuation of further study drug development

For site termination:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IRBs/IECs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.12. Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Progressive Multifocal Leukoencephalopathy Checklists

Subjective PML Checklist

Symptoms	"Compared to how you usually feel, have you had a significant change in any of the following?"		If the answer is "Yes", obtain a description of the symptom(s) with examples.	Applicable Objective Test(s): Document results on PML Objective Checklist
	Yes	No		
1. Have you been experiencing any persistent difficulty with your vision, such as loss of vision or double vision? Have you been having trouble with reading?				Test visual fields and ocular motility.
2. Have you been experiencing any persistent difficulty speaking or having your speech understood by others?				Casual observation of speech output for dysarthria or aphasia. Ask patient to name a few objects and repeat a multipart phrase.
3. Have you been experiencing any persistent weakness in an arm or a leg?				Test for pronator drift (Barré maneuver) and/or fixation on arm roll. Assess the ability to hop on either foot; foot and finger tapping. Test symmetric muscle strength.
4. Have you noticed yourself regularly bumping into things or having difficulty writing?				Ask for spontaneous writing sample and observe finger to nose, heel to shin, and tandem gait.
5. Have you regularly been experiencing difficulty understanding others?				Ability to follow serial commands (close your eyes, stick out your

Symptoms	"Compared to how you usually feel, have you had a significant change in any of the following?"		If the answer is "Yes", obtain a description of the symptom(s) with examples.	Applicable Objective Test(s): Document results on PML Objective Checklist
	Yes	No		
				tongue, and touch your left finger to your left ear)
6. Have you had persistent problems with your memory or thinking?				Recall of 3 objects over 1 minute with distraction; ability to follow commands.
7. Have you been experiencing any persistent numbness or other loss of sensation?				Test sensation side to side with pinprick.

PML, progressive multifocal leukoencephalopathy.

Objective PML Checklist – To be completed for patients with positive subjective finding
Perform the objective test(s) that correspond to the subjective checklist finding

Positive Symptom(s)	Applicable Objective Test(s)	Test Result(s)		If test result is abnormal, briefly describe result
		Normal	Abnormal	
1. Difficulty with vision or reading	Test visual field and ocular motility.			
2. Difficulty with speaking	Casual observation of speech output for dysarthria or aphasia. Ask patient to name a few objects and repeat a multipart phrase.			
3. Weakness in an arm or a leg	Test for pronator drift and/or fixation on arm roll. Assess the ability to hop on either foot; foot and finger tapping. Test muscle strength.			
4. Bumping into things or difficulty writing	Ask for spontaneous written sample and observe finger to nose, heel to shin, and tandem gait.			
5. Difficulty understanding others	Ability to follow serial commands (Close your eyes, stick out your tongue, and touch your left finger to your left ear)			
6. Problems with memory or thinking	Recall of 3 objects over 1 minute with distraction; ability to follow commands.			
7. Problems with numbness	Test sensation side to side with pinprick.			

Source: (Parikh, 2018)

× If objective test corroborates the reported symptom, refer the participant for a Neurology consult. Otherwise, please follow-up with the participant one week after the objective checklist was administered to ensure symptoms are not recurring.

× Please notify your CRA and Morphic Therapeutic of any positive objective checklist findings.

10.3. Appendix 3: Clinical Laboratory Tests

The tests detailed in Table 6 will be performed by the central laboratory.

Local laboratory results are only required in the event that the central laboratory results are not available in time for either study treatment administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study treatment decision or response evaluation, the results must be recorded.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Investigators must document their review of each laboratory safety report.

Table 6. Protocol-required Laboratory Tests

Laboratory Tests	Parameters			
Hematology	• Platelet count • RBC count • Hemoglobin • Hematocrit	RBC Indices: • MCV • MCH • % Reticulocytes	WBC count with differential: • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils	
Coagulation	• Prothrombin time • PTT • INR			
Clinical chemistry	• Blood urea nitrogen • Creatinine • Glucose (fasting) • Albumin	• Potassium • Sodium • Calcium • Phosphate	• AST/SGOT • ALT/SGPT • ALP	• Total and direct bilirubin • Total protein
Routine urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)			
Pregnancy testing	• Highly sensitive serum hCG pregnancy test (at Screening and as needed for women of childbearing potential only) • Urine hCG test (at Visits 2-11 in the main Treatment Period and Visits 11-13 of the Long-term Extension for women of childbearing potential only) [a]			
Other screening tests	• SARS-CoV-2 test (test to be determined by site) • Tuberculosis test ([redacted] test, with PPD test as needed) • Biopsy for cytomegalovirus test			

Laboratory Tests	Parameters
	• Fecal sampling and cell culture for *C. difficile* and enteric pathogens, including ova and parasite testing • Serology: HIV antibody, hepatitis B surface antigen, and hepatitis C virus antibody • Follicle-stimulating hormone (at Screening and as needed for women of non-childbearing potential only) • Serum alcohol screen • Urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids, and benzodiazepines) • For exploratory Cohort only: vedolizumab blood levels, receptor occupancy of vedolizumab, and anti-drug antibodies against vedolizumab
Efficacy	• Serum hs-CRP • Fecal calprotectin

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; hCG, human chorionic gonadotropin; HIV, human immunodeficiency virus; hs-CRP, high-sensitivity C-reactive protein; INR, international normalized ratio; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; PPD, purified protein derivative; PTT, partial thromboplastin time; RBC, red blood cell; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase; WBC, white blood cell;

a Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

10.4. Appendix 4: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.4.1. Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with use of the study drug, whether or not considered related to the study drug.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with use of the study drug.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease)
- Exacerbation of a chronic or intermittent pre-existing condition, including an increase in frequency and/or intensity of the condition
- New condition detected or diagnosed after study drug administration even though it may have been present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

10.4.2. Definition of SAE

If an event is not an AE per the definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:

a. Results in death

b. Is life threatening

The term *life threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of intervention dependency or intervention abuse.

10.4.3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The Investigator will then record all relevant AE/SAE information in the eCRF. Each event must be recorded separately.

It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE/SAE eCRF page.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.

The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The severity of an AE will be graded according to the scale below in addition to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. The severity of the AE is determined by the Investigator. The Investigator is encouraged to consult with the Medical Monitor if he/she would like to discuss the case.

Severity will be assessed according to the following scale:

- **Grade 1 (Mild):** Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2 (Moderate):** Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
- **Grade 3 (Severe):** Medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
- **Grade 4 (Life-Threatening):** Life-threatening consequences; urgent intervention indicated.
- **Grade 5 (Death):** Death related to AE.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity, whereas seriousness is defined by the criteria under Section 10.4.2. An AE of severe intensity may not be considered serious.

Assessment of Causality

The Investigator is obligated to assess the relationship between the study drug and the occurrence of each AE/SAE. The Investigator will use clinical judgment to determine the relationship. A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal

relationship. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study drug administration, will be considered and investigated. The Investigator will also consult the Investigator's Brochure and consider known actions or toxicity of the study drug in his/her assessment.

For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor. The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

The causal relationship between the study medication and the AE will be assessed using one of the following categories:

Not Related: An AE is not associated with study medication if:

- Temporal relationship is lacking (e.g., the event did not occur within a reasonable time frame following administration of the study medication).
- Other causative factors more likely explain the event (e.g., a pre-existing condition, other concomitant treatments).
- De-challenge was either not clinically indicated or did not result in clinical improvement.
- AE did not re-occur upon re-challenge (if applicable).

Related: An AE is attributed to the study medication if:

- There is a positive temporal relationship (i.e., the event occurred within a reasonable time frame following administration of study medication).
- The AE is more likely explained by the study drug than by another cause (i.e. the AE shows a pattern consistent with previous knowledge of the study drug or the class of the study drug).
- The event improved on de-challenge and/or re-occurred upon re-challenge (if applicable).

The Sponsor will make the final determination of relatedness of the AE to the study drug, taking into consideration the Investigator's assessment of suspected relatedness. If the relationship between the AE/SAE and the study drug is determined to be "suspected to be related", the event will be considered to be related to the study drug for the purposes of expedited regulatory reporting or determination of stopping rules.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any postmortem findings including histopathology.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.4.4. Reporting of SAEs

SAE Reporting to the Sponsor or designee via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to the Sponsor will be the electronic data collection tool. Event must be reported within 24 hours of the study staff becoming aware.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section). Event must be reported within 24 hours of the study staff becoming aware.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next section) or to the Sponsor or designee by telephone.

SAE Reporting to the Sponsor or Designee via Paper Data Collection Tool (Back-up Option)

- E-mail transmission of the SAE paper data collection tool is the preferred method to transmit this information to the Sponsor or designee.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE data collection tool within the designated reporting timeframes.
- If the electronic system is not available, the SAE paper data collection tool should be signed by the Investigator and emailed to: MorphicSafety@primevigilance.com

10.5. Appendix 5: Contraceptive and Barrier Guidance

10.5.1. Definitions

Woman of Childbearing Potential (WOCBP)

Women in the following categories are considered WOCBP (fertile):

1. Following menarche
2. From the time of menarche until becoming postmenopausal unless permanently sterile (see below)

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle-stimulating hormone (FSH) level in the postmenopausal range (≥30 IU/L) may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement may be required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT at least 6 weeks before study Day 1 to allow confirmation of postmenopausal status before study enrollment.
- Permanent sterilization methods (for the purpose of this study) include:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy
    - For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), Investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- If fertility is unclear (e.g., amenorrhea in athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Woman of Non-childbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

1. Premenopausal female with permanent infertility due to one of the following:
    a. Documented hysterectomy
    b. Documented bilateral salpingectomy
    c. Documented bilateral oophorectomy

d. For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), Investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

2. Postmenopausal female

a. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

i. A high FSH level in the postmenopausal range (≥30 IU/L) may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement may be required.

ii. Females on HRT and whose menopausal status is in doubt must discontinue HRT for at least 6 weeks before study Day 1 to allow confirmation of postmenopausal status before study enrollment.

10.5.2. Contraception Guidance

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of < 1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c] + 1 physical barrier method[d]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c] + 1 physical barrier method[d]
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.* Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Methods[b] That Are User Dependent *Failure rate of < 1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] (listed below) + 1 physical barrier method[d] – oral – intravaginal – transdermal – injectable

• Progestogen-only hormone contraception associated with inhibition of ovulation[c] + 1 physical barrier method[d] – oral – injectable
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. Failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. d. Barrier method of contraception: condoms (male or female) with or without a spermicidal agent, diaphragm or cervical cap with spermicide Note: Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure from friction).

10.6. Appendix 6: Histological Scoring Indices

Robarts Histopathology Index

The RHI is an evaluative index derived from the Geboes Score that was designed to be reproducible and responsive to clinically meaningful change in disease activity in UC over time. It is calculated by evaluating 4 histologic items, each on a scale from 0 to 3. Each item is individually weighted in the RHI formula. The formula is as follows: RHI = (1 × chronic inflammatory infiltrate score) + (2 × lamina propria neutrophils score) + (3 × neutrophils in epithelium score) + (5 × erosion or ulceration score). Thus, the total RHI Score ranges from 0 (no disease activity) to 33 (severe disease activity) (Mosli, 2017).

Nancy Index

The NI is a validated index for assessing histological disease activity in UC. It is determined by evaluating 3 histological items: ulceration, acute inflammatory cells infiltrate, and chronic inflammatory infiltrate. These items are used to define 5 grades of disease activity (Grades 0 to 4). The presence of ulceration on the biopsy specimen corresponds to severely active disease (Grade 4). If there is no ulceration, acute inflammatory cells infiltrate (presence of neutrophils) is assessed. Moderate or severe acute inflammatory cells infiltrate corresponds to moderately active disease (Grade 3), whereas mild acute inflammatory cells infiltrate correspond to mildly active disease (Grade 2). If there is no acute inflammatory cells infiltrate, an assessment of chronic inflammatory infiltrate (presence of lymphocytes and/or plasmacytes and/or eosinophils) is made. A biopsy specimen showing moderate or marked chronic inflammatory infiltrate corresponds to moderate or marked chronic acute inflammatory infiltrate (Grade 1). A biopsy specimen showing mild or no chronic inflammatory infiltrate corresponds to absence of significant histological disease (Grade 0) (Marchal-Bressenot, 2017; Marchal-Bressenot, 2016).

Continuous Geboes Score

The Geboes Score is a stepwise grading system used for the evaluation of microscopic inflammation and histopathologic disease activity in UC. 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) (Geboes, 2000). Each of these grades has 4 to 5 sub-grades. This scoring system has been converted into a continuous scale that is calculated by adding up the numerical values of the different subscores, yielding a final value between 0 and 22.

10.7. Appendix 7: Mayo Clinic Scoring System for Assessment of Ulcerative Colitis Activity

The Mayo Clinic Score ranges from 0 to 12, with higher scores indicating more severe disease. Each subscore is described below.

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 Physician's Global Assessment 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

10.8. Appendix 8: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to the study drug, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact intervention absorption, distribution, metabolism, and excretion; mechanism of action of the intervention; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, blood samples will be collected for DNA analysis from consenting participants.
- DNA samples will be used for research related to MORF-057 or UC and related diseases. They may also be used to develop tests/assays, including diagnostic tests related to MORF-057 and/or interventions of this drug class and UC. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to MORF-057 or study interventions of this class to understand the study disease or related conditions.
- The results of genetic analyses may be reported in the Clinical Study Report or in a separate study summary.
- The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on MORF-057 or study interventions of this class or indication continues but no longer than 15 years or other period as per local requirements.

10.9. Appendix 9: Investigator's Agreement

By signing below, I agree that:

I have read Protocol MORF-057-201 and agree to conduct the study as outlined. Furthermore, I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

10.10. Appendix 10: Summary of Changes Table – Protocol Amendment Version 2.0

Summary of Changes Table

Changes to the protocol as implemented by the protocol amendment Version 2.0 in comparison to Version 1.0 are summarized in the Summary of Changes table below. New text is shown in *italics*, deleted text is shown in ~~strikeout~~, and bold text is informational. In addition to the changes provided in the Summary of Changes table, minor editorial changes have been made throughout the protocol.

Version 2.0 vs Version 1.0

Section No. and Name	Description of Change	Brief Rationale
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)***	To add trial brand name
	"IRB" was changed to "IRB/IEC" throughout the protocol.	To add IECs to the protocol because sites in Europe have been added to the study plan
Abbreviations	*AUC Area under the concentration-time curve* *AUC_{0-24} Area under the concentration-time curve from time 0 to 24 hours post-dose* *AUC_{0-inf} Area under the concentration-time curve from time 0 to infinity* *AUC_{0-t} Area under the concentration-time curve from time 0 to last measurable concentration* *AUC_{last} Area under the concentration-time curve from time 0 to last data point* *C_{24} Plasma concentration at 24 hours post-dose* *CYP Cytochrome P450* *CYP3A Cytochrome P450 3A* *CYP3A4 Cytochrome P450 3A4* *DNA Deoxyribonucleic acid* DSMB Data *and* Safety ~~and~~ Monitoring Board *IEC Independent Ethics Committee* *ESR Erythrocyte sedimentation rate*	To clarify abbreviations
Synopsis - Objectives and Endpoints table, Section 3: Objectives and Endpoints	To evaluate the effects of MORF-057 on histologic improvement at Weeks 6, ~~and~~ 12*, and 52* • Change from baseline to Weeks 6 *and 52* in RHI Score	To add Week 52 endpoints.

Section No. and Name	Description of Change	Brief Rationale
	• Change from baseline to Weeks 6, ~~and~~ 12, *and 52* in the Nancy Index (NI) • Change from baseline to Weeks 6, ~~and~~ 12, *and 52* in the Continuous Geboes Score	
Synopsis - Objectives and Endpoints table, Section 3: Objectives and Endpoints	To evaluate the effect of MORF-057 on clinical improvement at Weeks 6, ~~and~~ 12, *and 52* • Change from baseline to Week*s* 6 *and 52* in the Modified Mayo Clinic Score (MCS). Modified MCS is a composite of the following subscores: o ~~Mayo endoscopic subscore (~~MES~~)~~ o MCS stool frequency subscore o MCS rectal bleeding subscore • Change from baseline to Weeks 6, ~~and~~ 12, *and 52* in the Full MCS. Full MCS is a composite of the following subscores: o MES o MCS stool frequency subscore o MCS rectal bleeding subscore o MCS Physician's Global Assessment (PGA)	To add Week 52 endpoints.
Synopsis - Objectives and Endpoints table, Section 3: Objectives and Endpoints	To assess the effect of MORF-057 on non-endoscopic biomarkers of inflammation • Change from baseline to Weeks 2, 6, ~~and~~ 12, *20, 28, 36, and 52* in high-sensitivity C-reactive protein (hs-CRP) levels • Change from baseline to Weeks 2, 6, ~~and~~ 12, *20, 28, 36, and 52* in fecal calprotectin levels	To add endpoints between Week 12 and Week 52
Synopsis – Overall Design Section 4.1: Overall Design	The Main Cohort of the study will include approximately 30 participants with moderate to severe UC who have *or have not been exposed to biologics therapies and have* not previously been treated with vedolizumab. In addition, an Exploratory Cohort will be comprised of a maximum of 5 additional participants with moderate to severe UC who are secondary non-responder*s* (as defined in Section 5.1) to vedolizumab. Thus, there will be a total of 30 to 35 participants in the study. All participants will be enrolled ~~across approximately 7~~*from up to 30* centers located in ~~the United States~~*North America and Europe*. For this study, moderate to severe UC will be defined as having a ~~Full~~*Modified* MCS ~~between 6 and 12~~*of 5 to 9* (inclusive), with a*n* MES ≥2~~,~~ *(confirmed by central reader) and* a rectal bleeding subscore ≥1~~, and a stool frequency subscore ≥1~~. In the Main Cohort, the enrollment goal is for 45% to 55% of	To clarify/update participation criteria and to extend the study to European countries/sites.

Section No. and Name	Description of Change	Brief Rationale
	the participants to be bio-naïve (i.e., to have no previous exposure to a biologic treatment for UC).	
Synopsis – Overall Design Section 4.1: Overall Design	Participant safety data will be reviewed by an independent Data and Safety Monitoring Board (DSMB). ~~and a Steering Committee periodically throughout the study. The Steering Committee will be comprised of select Sponsor personnel who will periodically review data. The data review will be performed in a controlled manner. In addition~~*Details related to the DSMB will be clearly delineated in the DSMB Charter. Separately,* an *efficacy-based* interim analysis will be performed *by an internal Sponsor Steering Committee* using the initial 5 bio-experienced and initial 5 *bio*-naïve subjects in the Main Cohort who have evaluable baseline and Week 12 primary endpoint data. The purpose of the interim analysis is to assess whether the study remains appropriately powered or if the sample size needs to be revised. ~~An independent statistician (not part of the study team) will be responsible for providing the relevant information for the sample size assessment to the Steering Committee.~~ Note that data from participants in the Exploratory Cohort will not be included in the sample size assessment that is performed at the interim analysis. Details related to the ~~DSMB, the Steering Committee, and the~~ interim analysis will be ~~clearly delineated~~*outlined* in the ~~DSMB Charter.~~ *Statistical Analysis Plan (SAP).*	To clarify details regarding the use of a DSMB and a Steering Committee
Synopsis – Overall Design Section 4.1: Overall Design	This Phase 2a study will consist of 3 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 ~~6~~*11* scheduled study visits: Screening Visit(s) (Visit 1 at Weeks -6 to -1), multiple Treatment Visits (Visits 2-~~5~~*10* at Weeks 0, 2, 6, ~~and~~ 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 ~~6~~*11* at Week~~16~~*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 [P.O.]) for the full ~~12~~*52*-week Treatment Period.	To revise the visit schedule to accommodate the extended treatment period (now 52 weeks instead of 12 weeks)
Synopsis – Overall Design Section 4.1: Overall Design	~~Non-clinical chronic toxicology studies in animals are currently ongoing. Depending on the results of those studies, the Sponsor may amend the protocol to extend the treatment duration from 12 weeks to 52 weeks. Participants may be given the option to continue receiving study treatment for the current study (MORF-057-201) after Week 12 until Week 52.~~	To explain the new option to join an Open-label Extension study at the end of the current study

Section No. and Name	Description of Change	Brief Rationale
	~~Participants who choose this option will not complete the Safety Follow-up Period until the end of the full 52-week Treatment Period. A revised Informed Consent Form (ICF) will be provided to participants to explain the additional procedures necessary for those who want to continue in the study beyond the initial 12-week Treatment Period. Maximum time on study for participants who choose to complete only the initial 12-week Treatment Period will be 22 weeks, whereas that for participants who choose to complete the full 52-week Treatment Period (if option is later provided) will be 62 weeks.~~ *Eligible participants will have the opportunity to enroll in a separate Open-label Extension study after completing the Week 52 assessments. Participants who are eligible and willing to enroll into the Open-label Extension study will not complete the Safety Follow-up Period for the current study; instead, they will directly enter the Open-label Extension study. Participants who do not enroll into the separate Open-label Extension study must complete the final Safety Follow-up Period for the current 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.*	
Synopsis – Overall Design Section 4.1: Overall Design	**A new study schema was provided. The new schema shows that the treatment period has been extended from 12 weeks to 52 weeks and when the associated new visits will occur. The schema also shows the new option to join an Open-label Extension study at the end of the current study.**	To reflect changes in the study design
Synopsis – Inclusion Criteria Section 5.1: Inclusion Criteria	2. Patient has had signs/symptoms of moderate to severe UC for at least 3 months prior to Screening, and the diagnosis was confirmed during the Screening Period with the following criteria: a ~~Full~~*Modified* MCS of ~~6~~*5* to ~~12~~*9* (inclusive), with an MES ≥2 (confirmed by central reader)~~,~~ *and* a rectal bleeding subscore ≥1~~, and a stool frequency subscore ≥1~~ 5. Is ~~an advanced therapy~~*a bio*-naïve patient or a patient who had an inadequate response, loss of response, or intolerance to no more than 3 drugs in 2 classes of the following	To clarify the inclusion criteria
Synopsis – Exclusion Criteria Section 5.2: Exclusion Criteria	10. Had any vaccination (including live virus vaccinations) within 3 weeks prior to study Day 1. Note: For vaccinations requiring a series of doses, the last in the series should be completed by 3 weeks prior to study Day 1 (e.g., SARS-CoV-2 *two-shot* vaccination series). 18b. Chronic kidney disease stages 4 and 5, defined as having a glomerular filtration rate <30 mL/min/1.73m^2 as calculated using the Modification of	To clarify the exclusion criteria

Section No. and Name	Description of Change	Brief Rationale
	Diet in Renal Disease (MDRD) equation, receiving dialysis, or being listed for *or has received a* renal transplant	
Synopsis – Study Intervention	The study drug dosage will be [redacted] mg [redacted] P.O. for the full ~~12~~*52*-week Treatment Period. Each MORF-057 dose will be administered as [redacted]-mg capsules with or without food. … All subsequent doses will be self-administered at home, with the exception of the [redacted] doses for Visits 2-~~6~~*10*, which will be administered during the study visits after pre-dose blood samples have been drawn (see details in the Schedule of Activities).	To indicate that the treatment period has been extended from 12 weeks to 52 weeks and that additional visits will be required
Synopsis – Statistical Methods – Sample Size Determination	An interim analysis will be performed using the initial 5 bio-experienced and initial 5 *bio*-naïve subjects in the Main Cohort who have evaluable baseline and Week 12 primary endpoint data. At that time, the assumptions regarding the sample size calculation for the primary endpoint (change from baseline to Week 12 in RHI Score) *and drop-out rate* will be re-assessed.	To clarify details regarding the interim analysis
Synopsis – Statistical Methods – Exploratory Endpoints Section 9.2.4: Exploratory Endpoints	The continuous exploratory efficacy endpoints (change from baseline to Week*s* 6 *and 52* in RHI Score and Modified MCS; change from baseline to Weeks 6, ~~and~~ 12, *and 52* in NI, Continuous Geboes Score, and Full MCS; and change from baseline to Weeks 2, 6, ~~and~~ 12, *20, 28, 36, and 52* in hs-CRP and fecal calprotectin levels) will be analyzed similarly to the primary efficacy endpoint using the FAS.	To indicate the additional exploratory analyses associated with the extended treatment period
Synopsis – Statistical Methods – Other Safety Assessments Section 9.2.5: Other Safety Analyses	Worst shift in grade and changes from baseline to Weeks 6*, 12,* and ~~12~~*52* of the laboratory analytes will be reported	To indicate the additional safety analyses associated with the extended treatment period
Synopsis – Data and Safety Monitoring Section 10.1.6: Data and Safety Monitoring Board	**Section 10.1.6 Section heading:** Data *and* Safety ~~and~~ Monitoring Board ~~and Steering Committee~~ A DSMB has been appointed to this study. The DSMB is a group of independent clinicians/scientists who are appointed to monitor the safety and scientific integrity of a human research intervention, and to make recommendations to the Sponsor regarding the modification, continuance, or stopping of a study based on assessments of safety~~or for efficacy based futility. The DSMB and a Steering Committee will review safety data periodically throughout the study. The Steering Committee will be comprised of select Sponsor personnel who will periodically review data. The data review will be performed in a controlled manner~~. The composition, responsibilities, and meeting schedule of the DSMB ~~and the~~	To clarify details regarding the use of a DSMB and a Steering Committee

Section No. and Name	Description of Change	Brief Rationale
	~~Steering Committee~~ will be described in a separate DSMB~~/ Steering Committee~~ Charter.	
Section 1.2: Schedule of Activities	**The Schedule of Activities table was updated. The major changes are listed below.** • **Five new study visits were added due to the extended treatment period, and the associated assessments to be performed at each visit were marked** • **For pharmacokinetics testing at Visits 2, 3, and 5, sampling at 8, 10, and 12 hours after the [redacted] was changed to optional** • **For receptor occupancy testing, required sampling before the [redacted] was added to Visits 3 and 5, and sampling at 12 hours after the [redacted] was changed to optional for Visits 2, 3, and 5** • **The Visit 4 (Week 6) endoscopy was changed from mandatory to optional** • **The row "Discuss possible extension to 52-week Treatment Period (if option is available later)" was changed to "Discuss participation in Open-label Extension study" and the appropriated study visits were marked** • **For the EOT visit, the schedule was changed from administering [redacted] doses to administering only the [redacted] dose will be provided)** • **The footnotes were updated to reflect the changes in the study schedule** • **Footnotes regarding blood sample collection for Pharmacodynamics Biomarkers and Future Biomarker Research were updated to indicate that sampling should occur at the corresponding pharmacokinetics sampling time. Also, in the pharmacokinetics sampling footnotes, a specific window for the [redacted] sampling was added.** • **Footnote regarding study drug administration on site was updated to clarify requirements**	To reflect changes in the study design

Section No. and Name	Description of Change	Brief Rationale
	• **Footnote regarding Exploratory Cohort eligibility testing updated to indicate all 3 tests required (text changed from "and/or" to "and")**	
Section 2.2: Background	There are several potential clinical advantages of using MORF-057 (an orally administered drug) for the treatment of UC over vedolizumab (a drug administered via intravenous infusion), which uses the same mechanism of action. ~~These include the following:~~*These advantages include a flexible dosing regimen and minimal safety concerns regarding immunogenicity and serious infusion reactions, requiring less clinical visits and therefore reducing patient and healthcare provider burden. MORF-057 has the potential to be an effective and safe oral $\alpha_4\beta_7$ integrin inhibitor that would be an important addition to the therapeutic armamentarium for UC.* • ~~Oral drugs are preferred by patients and healthcare providers over injectables. Beyond the fear of needles, the requirement for frequent infusion center visits is a substantial burden, particularly for younger patients with UC who have active professional and family lives.~~ • ~~Oral formulation allows for flexible dosing regimen. An oral drug that is rapidly cleared upon cessation of dosing may be desirable for treating physicians in clinical situations such as pregnancy, during serious infections, and in the peri-operative period. Additionally, an oral drug is more easily titrated to clinical effect and may be used in fixed-dose combinations with other oral agents. The long half-life of vedolizumab means that it cannot be removed rapidly.~~ • ~~As with all therapeutic proteins, there is the potential for immunogenicity with vedolizumab. During the Phase 3 trials, 4% of patients developed anti-vedolizumab antibodies, 59% of which were neutralizing antibodies that reduced plasma levels of the treatment antibody ([redacted] package insert).~~ • ~~Serious infusion reactions, including anaphylaxis, have been reported with vedolizumab.~~ ~~If shown to be safe and effective in patients, MORF-057 could be an important oral therapeutic option for the treatment of moderate to severe UC.~~	To reduce redundancy between Section 2.2 and Section 2.3.1

Section No. and Name	Description of Change	Brief Rationale
Section 2.2.1: Non-clinical Findings	~~In 3-month oral repeat-dose toxicity studies in Sprague Dawley rats and beagle dogs, the no-observed-adverse-effect level (NOAEL) values were 450 mg/kg/day for rats and 300 mg/kg/day for dogs, the highest doses tested in these studies. At the NOAEL dose of 450 mg/kg/day in rats, partially reversible, non-adverse microscopic findings were observed in the liver (mononuclear cell infiltration, periductular), spleen (increased lymphoid cellularity of the periarteriolar lymphoid sheaths, correlating with increased spleen weights), stomach (degeneration/atrophy of chief cells and hyperplasia/hypertrophy of mucous cells), and mesenteric lymph node (increased infiltration of mast cells). These histopathological changes were associated with a spectrum of non-adverse, reversible clinical pathology findings (minimal increases in primarily circulating lymphocytes and eosinophils) at ≥150 mg/kg/day. At the NOAEL dose of 300 mg/kg/day in dogs, minimal, reversible increases in circulating lymphocytes were observed. A 6-month oral repeat dose toxicity study in male and female Sprague Dawley rats and a 9-month oral repeat dose toxicity study in male and female beagle dogs are ongoing.~~ *In a 6-month oral repeat-dose study of MORF-057 in Sprague Dawley rats, significant, reversible increases in circulating white blood cells (WBCs), lymphocytes, eosinophils, and large unstained cells were seen at the high dose of 450 mg/kg/day due to the pharmacological action of MORF-057. Non-adverse changes in cellularity in the spleen were observed at the high dose of 450 mg/kg/day, which were attributed to the pharmacological activity of MORF-057. The no-observed-adverse-effect level (NOAEL) in this study was 50 mg/kg/day in male and female rats. The adverse changes in rats after 6 months of dosing were degeneration/regeneration of chief cells in the glandular stomach at 125 or 450 mg/kg/day, which appeared to be partially reversible by 4 weeks post-dose.* *In a 9-month oral repeat-dose study in beagle dogs, the NOAEL was 300 mg/kg/day, the highest dose tested. Non-adverse hepatobiliary changes were observed in several dogs that received 300 mg/kg/day of MORF-057; these changes correlated with increases in alanine transaminase (ALT) and alkaline phosphatase (ALP) measured in the same dogs. There were no adverse histopathological changes in dogs after 9 months of dosing. The degeneration/regeneration of chief cells in the glandular stomach observed in rats after 6 months of dosing was not noted in the beagle dogs at any dose up to 300 mg/kg/day, even though C_{max}*	To provide the most current non-clinical findings for MORF-057

Section No. and Name	Description of Change	Brief Rationale
	values were 10-fold higher and AUC_{last} values were up to 20-fold higher in dogs compared to rats. *For a human dose of [redacted] mg [redacted]., the safety margin for MORF-057 in rats, the most sensitive toxicology species, is 6.5-8.7. The safety margins compared to dogs is 161 to 177 fold.*	
Section 2.2.2 Clinical Findings	*Clinical drug-drug interaction studies (Studies MORF-057-102 and MORF-057-103) evaluating the inhibitory and inductive potential of MORF-057 on cytochrome P450 3A (CYP3A) in healthy participants have been completed. MORF-057 did not have an effect on midazolam PK following a single dose, whereas it was identified as a weak inducer of cytochrome P450 3A4 (CYP3A4) with a 33% decrease of midazolam AUC (a weak inducer is defined as ≥20% and <50% decrease in AUC of a sensitive substrate) following [redacted] at [redacted] mg [redacted] (Study MORF-057-102). The midazolam drug-drug interaction results were consistent with the in vitro cytochrome P450 (CYP) inhibition and induction data indicating that, at the clinical exposure of [redacted] mg [redacted] dose, MORF-057 has the potential to be a weak CYP3A4 inducer with minimal inhibition of major CYPs. Co-administration of ethinyl estradiol/levonorgestrel with MORF-057 (Study MORF-057-103), compared with administration of ethinyl estradiol/levonorgestrel alone, did not substantially alter ethinyl estradiol or levonorgestrel exposure (AUCs and C_{max}). The 90% confidence intervals of the geometric mean ratios for ethinyl estradiol AUC_{0-24}, C_{max}, and C_{24} were contained within the 80.00% to 125.00% no-effect range with the exception of the lower limits of AUC_{0-t} and AUC_{0-inf}. The 90% confidence intervals of the geometric mean ratios for levonorgestrel AUCs and C_{24} were contained within the 80.00% to 125.00% no-effect range with the exception of the lower limit of C_{max}. An overall marginal decrease in PK parameters was observed.*	To add drug-drug interactions data for MORF-057
Section 2.3.2: Risks	In ~~3~~*a 6*-month toxicology ~~studies~~*study* in Sprague Dawley rats and *a 9-month toxicology study in* beagle dogs, the NOAEL values were ~~450~~*50* mg/kg/day for rats and 300 mg/kg/day for dogs~~, the highest dose tested in those studies~~ (Section 2.2.1).	To provide the most current non-clinical findings for MORF-057
Section 4.2: Scientific Rationale for Study Design	This open-label, single-arm, multicenter Phase 2a study was designed to assess the efficacy of MORF-057 ([redacted] mg [redacted] P.O.) in participants with moderate to severe UC when administered for ~~at least 12 weeks, but the protocol may be amended to extend the treatment duration to~~ 52 weeks ~~if ongoing non-clinical toxicology studies support this plan.~~*(including a 12-week Induction Period plus a 40-week Maintenance Period).*	To indicate that the treatment period has been extended from 12 weeks to 52 weeks

Section No. and Name	Description of Change	Brief Rationale
Section 4.4: End of Study Definition	A participant is considered to have completed the study if he/she has completed all periods of the study and attended the Safety Follow-up Visit *OR has completed the Week 52/EOT Visit and has been enrolled into the Open-label Extension study.*	To indicate participants now have the option to enroll in an Open-label Extension study
Section 6.5: Continues Access to Study Intervention after the End of the Study	~~Non-clinical chronic toxicology studies in animals are currently ongoing. Depending on the results of those studies, the Treatment Period for the current study (MORF-057-201) may be extended to 52 weeks. Thus, although the Treatment Period for this study is currently 12 weeks, participants may have the option later to extend the treatment to 52 weeks. Once a participant completes the study, he/she~~ *Eligible participants will have the opportunity to enroll into a separate Open-label Extension study after Week 52. Participants who have completed the Week 52 assessments and are eligible and willing to enroll into the Open-label Extension study will skip the Safety Follow-up Visit and directly enter the Open-label Extension study.* *Participants who do not enroll in the Open-label Extension study* will no longer have access to the study drug *after they complete the 52-week Treatment Period*.	To specify that the only option to continue receiving MORF-057 after the study is to join the Open-label Extension study
Section 6.7: Concomitant Therapy	~~Paracetamol/Acetaminophen at doses of ≤2 grams/day is permitted for analgesia during the study. Other concomitant medications may be considered on a case-by-case basis by the Investigator in consultation with the Medical Monitor.~~	To clarify which concomitant therapies will be accepted or not
Section 6.7.2: Prohibited Medications	The following concomitant medications/therapies are prohibited for the entire duration of the study, including Safety Follow-up: • Treatments for UC other than those listed in Section 6.7.1 (including TNF antagonists, integrin antagonists, IL-12/IL-23 antagonists, *JAK antagonists,* and S1P receptor agonists) • Receipt of a live virus vaccine from 3 weeks prior to study Day 1 until 28 days after the last dose of study drug. **Note:** Non-live vaccines, including those for SARS-CoV-2, *should not be administered between 3 weeks prior to study Day 1 and the Week 12 assessments. After the Week 12 assessments, such vaccines* can be administered according to local vaccination standards. Per Exclusion Criterion 10, if the participant has started a vaccination series before Day 1, the last in the series should be completed by 3 weeks prior to Day 1 (Section 5.1). ~~After Day 1, the participant can start a vaccination series with a non-live vaccine at any time.~~	To clarify which concomitant therapies will be accepted or not

Section No. and Name	Description of Change	Brief Rationale
	• Moderate-to-strong CYP3A inhibitor or inducer (see Table 4) • Moderate-to-strong organic anion transporter polypeptide-1B inhibitor (see Table 4) • Cyclosporine, mycophenolate, tacrolimus, or sirolimus • *Nonsteroidal anti-inflammatory drugs (NSAIDs) including but not limited to ibuprofen, naproxen, indomethacin, and celecoxib. However, participants may take aspirin for cardio-protection at a dose not exceeding 325 mg per day.* • Any investigational therapy	
Section 7.2: Participant Discontinuation/Withdrawal from the Study	The participant should be encouraged to complete the End of Treatment Visit (Visit ~~5~~*10*) at the time of study drug discontinuation and the Safety Follow-up Visit (Visit ~~6~~*11*) at 28 days (+7) after the last dose of study drug.	To indicate the new visit numbers for the End of Treatment and Safety follow-up visits due to the extended treatment period
Section 8: Study Assessments and Procedures	~~Local endoscopy may be used for baseline assessments in this study if performed within 42 days of study Day 1, consent was obtained from the participant for use in a clinical study, video quality and format is considered adequate for evaluation by centralized reading facility, and biopsy samples are available for central laboratory assessment.~~	To remove the possibility of using local endoscopy performed before study Day 1 for the baseline assessments
Section 8.5: Participant Diary	Diaries are to be completed ~~at the end of each day~~ *daily* by the participant ~~at home and brought to each study visit for review by study personnel~~.	To account for the fact that diary entries may occur multiple times a day
Section 8.6: Stool Collection	Note: Sample is to be collected prior to bowel preparation for Visits 4, *5,* and ~~5~~*10*/EOT.	To indicate the new visit number for the End of Treatment visit due to the extended treatment period
Section 8.7.1: Endoscopy with Biopsy	Endoscopy will be performed at Screening (Visit 1) and Visits 4 *(optional), 5,* and ~~5~~*10*/EOT	To indicate that the Visit 4 endoscopy is now optional and to show the new visit number for the End of Treatment visit due to the extended treatment period
Section 8.8.1: Physical Examinations	A complete physical exam is required at Screening and Visit ~~5~~*10*/EOT, and a targeted exam may be performed at all other required visits.	To indicate the new visit number for the End of Treatment visit due to the extended treatment period
Section 8.10.1 Collection of Blood Samples for MORF-057 Concentration Determination in Plasma	*For all* [redacted] *sampling, the samples should be obtained within approximately 30 minutes before the* [redacted] *is administered. Furthermore, the samples should be obtained at 12 hours (±1 hour) after* [redacted].	To clarify pharmacokinetics sampling window
Section 8.10.2 Determination of Drug Concentration and PK Parameters	The following plasma PK parameters will be calculated for MORF-057 *(as deemed appropriate):*	To account for possible changes in PK analyses resulting from the

Section No. and Name	Description of Change	Brief Rationale
		change to optional testing at certain timepoints
Table 3: Pharmacokinetics Sampling Windows	**Table 3 was updated to reflect the following changes:** • **The pharmacokinetics sampling schedule and associated sampling windows were revised due to the extended treatment period** • **For pharmacokinetics testing at Visits 2, 3, and 5, sampling at 8, 10, and 12 hours after the [redacted] was changed to optional**	To indicate changes in pharmacokinetics sampling
Section 8.11.2: CCR9 mRNA	~~PAXgene RNA blood~~*Blood* samples will be collected *in PAXgene RNA tubes* to assess changes of transcript levels of CCR9.	To clarify the wording regarding CCR9 mRNA sample collection
Section 8.13: Potential Adjustments Due to COVID-19	*Adjustments to the planned study procedures might be necessary due to the ongoing COVID-19 pandemic. Any such specific measures will be detailed in the respective ancillary documents, such as site-facing and patient-facing documents.*	To explain how the potential effects of the COVID-19 pandemic on the study will be addressed
Section 9.3: Interim Analysis	An interim analysis will be performed using the initial 5 bio-experienced and initial 5 *bio*-naïve subjects in the Main Cohort who have evaluable baseline and Week 12 primary endpoint data. At that time, the assumptions regarding the sample size calculation for the primary endpoint (change from baseline to Week 12 in RHI Score) *and drop-out rate* will be re-assessed. ~~An independent statistician (not part of the study team) will be responsible for providing the relevant information for the sample size assessment to the Steering Committee. The Steering Committee will be comprised of select Sponsor personnel who will periodically review data. The data review will be performed in a controlled manner. Note that no data from the participants in the Exploratory Cohort will be included in the re-assessment of the sample size assumptions~~ ~~In addition, participant safety data will be reviewed by an independent DSMB and the Steering Committee periodically throughout the study. Details related to the DSMB, the Steering Committee, and the interim analysis will be clearly delineated in the DSMB Charter.~~*Further details regarding the interim analysis will be outlined in the SAP.*	To clarify details regarding the interim analysis
Section 10.1.4: Informed Consent Process	The ICF will contain a separate section that addresses the use of samples for optional exploratory research. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the *sample* storage period *(determined based on local country regulations)*.	To clarify that the sample storage period for exploratory research is based on local country regulations

Section No. and Name	Description of Change	Brief Rationale
Section 10.4.4: Reporting of SAEs	Contacts for SAE reporting ~~:drugsafety@morphictx.com~~*can be found in the Study Manual*	To update information regarding how to report serious adverse events
Table 4. Protocol-required Laboratory Tests	**"ESR" moved from Coagulation row to Hematology row**	To correctly classify the ESR test
Section 10.7: Appendix 7: Mayo Clinic Scoring System for Assessment of Ulcerative Colitis Activity	**Rectal bleeding:** The daily bleeding score represents the most severe bleeding of the day. … 2=Obvious blood *(more than just streaks) or streaks of blood* with stool most of the time 3=Blood alone ~~passes~~*passed* **Endoscopy:** The endoscopy subscore will be determined both locally and centrally by qualified personnel. … 1=Mild disease (erythema, decreased vascular pattern*, no friability*)	To clarify the Mayo Clinic Scoring System

10.11. Appendix 10: Summary of Changes Table – Protocol Amendment Version 3.0

Summary of Changes Table

Changes to the protocol as implemented by the protocol amendment Version 3.0 in comparison to Version 2.0 are summarized in the Summary of Changes table below. New text is shown in *italics*, deleted text is shown in ~~strikeout~~, and bold text is informational. In addition to the changes provided in the Summary of Changes table, minor editorial changes have been made throughout the protocol.

Version 3.0 vs Version 2.0

Section No. and Name	Description of Change	Brief Rationale
Global change	**'Patients' was changed to 'participants' throughout the Protocol when referring to a study participant.**	Administrative change
Global change	~~TNF~~ *TNF-α*	To correct protein name
Title, Indication, and throughout	**'Moderate to severe ulcerative colitis' was changed to 'moderately to severely active ulcerative colitis' throughout the Protocol.**	To reflect changes in the study indication
Abbreviations	*AT* *Advanced therapy* *CD* *Crohn's disease* *CIMS* *Central Image Management Solutions* *ELISA* *Enzyme-linked immunosorbent assay* ~~ESR Erythrocyte sedimentation rate~~ *PCR* *Polymerase chain reaction*	To update the abbreviations used throughout the protocol

Section No. and Name	Description of Change		Brief Rationale
	PP Per Protocol (Population) TNF-*α* Tumor necrosis factor *alpha*		
Synopsis - Objectives and Endpoints Section 3. Objectives and Endpoints	*To assess the long-term safety of MORF-057 and effects of MORF-057 on hs-CRP and fecal calprotectin levels*	• *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*	To add endpoints corresponding to Long-term Extension
Synopsis - Overall Design Section 4.1: Overall Design	In addition, an Exploratory Cohort will be comprised of a maximum of ~~5~~10 additional participants with ~~moderate~~*moderately* to ~~severe~~*severely active* UC who are *intolerant to or* secondary non-responders (as defined in Section 5.1) to vedolizumab. Thus, there will be a total of 30 to ~~35~~*40* participants in the study *because when the Main Cohort recruits 30 participants, the entire study will be closed to new enrollees*.		To expand the enrollment goal of the Exploratory Cohort: in addition to the enrolling vedolizumab failures using biochemical/lab criteria, another cohort of 5 participants are added whose secondary loss of response to vedolizumab will be defined by clinical criteria only
Synopsis - Overall Design Section 4.1: Overall Design	For this study, ~~moderate~~*moderately* to ~~severe~~*severely active* UC will be defined as having a Modified MCS of 5 to 9 (inclusive) with an MES ≥2 (confirmed by central reader) ~~and a rectal bleeding subscore ≥1.).~~ In the Main Cohort, the enrollment goal is for ~~45~~*approximately 55*% to ~~55~~*75*% of the participants to be ~~bio~~ *advanced therapy (AT)* naïve (i.e., to have no previous exposure to a biologic treatment, *Janus kinase [JAK] antagonists, or sphingosine-1-phosphate [S1P] receptor agonists* for UC).		To clarify inclusion criterion
Synopsis - Overall Design Section 4.1: Overall Design	~~Separately, an efficacy based interim analysis will be performed by an internal Sponsor Steering Committee using the initial 5 bio-experienced and initial 5 bio-naïve subjects in the Main Cohort who have evaluable baseline and Week 12 primary endpoint data. The purpose of the interim analysis is to assess whether the study remains appropriately powered or if the sample size needs to be revised. Note that data from participants in the Exploratory Cohort will not be included in the sample size assessment that is performed at the interim analysis. Details related to the interim analysis will be outlined in the Statistical Analysis Plan (SAP).~~		To remove the planned interim analysis for sample size reassessment
Synopsis - Overall Design Section 4.1: Overall Design	*The main part of this* ~~This~~ Phase 2a study will consist of 3 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).		To clarify the study design

Section No. and Name	Description of Change	Brief Rationale
Synopsis - Overall Design Section 4.1: Overall Design	~~Eligible~~*All* participants *who complete the open-label Treatment Period* will have the opportunity to ~~enroll~~*continue their treatment* in a*n optional* ~~separate Open-label~~ *26-week Long-term* Extension ~~study~~ after completing the Week 52 assessments. ~~Participants who are eligible and willing to enroll into the Open-label Extension study will not complete the Safety Follow-up Period for the current study; instead, they will directly enter the Open-label Extension study.~~ Participants who do not enroll into the ~~separate Open-label~~*Long-term Extension* ~~study~~ must complete the final Safety Follow-up Period for the ~~current~~*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 and complete a separate Safety Follow-up Period, including the Week 82 Visit (4 weeks after receiving the last dose of MORF-057).* *During the optional Long-term Extension, there will be 3 scheduled study visits: 2 Treatment Visits (Visits 11-12 at Weeks 65 and 78), and a Safety Follow-up Visit (4 weeks after the last dose of study drug is received, which will be Visit 13 at 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] P.O.) for the full 26-week extended Treatment Period.* **A new study schema was provided. The new schema shows the expanded enrollment goal in the Exploratory Cohort, change from Open-label Extension Study to Long-term Extension, and the timepoints for the Long-term Extension.** **Study Schema Footnotes:** * The Safety Follow-up Visit at Week 56 will not be performed for participants who enter the ~~Open-label Extension study~~ *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.	To reflect changes in the study design
Synopsis – Main Inclusion Criteria Section 5.1. Inclusion Criteria – Main Inclusion	<u>Type of Participant and Disease Characteristics</u> 2. ~~Patient~~ *Participant* has had signs/symptoms of ~~moderate~~ moderately to ~~severe~~ *severely active* UC for at least 3 months prior to Screening, and the diagnosis was confirmed during the Screening	To clarify inclusion criteria

Section No. and Name	Description of Change	Brief Rationale
Criteria	Period with the following criteria: a Modified MCS of 5 to 9 (inclusive, with an MES ≥2 (confirmed by central reader) ~~and a rectal bleeding subscore ≥1~~ 5. Is an ~~bio~~ *AT*-naïve participant or a participant who had an inadequate response, loss of response, or intolerance to no more than 3 drugs in 2 classes of the following: 5c. ~~Janus kinase~~ JAK antagonists, including tofacitinib *and upadacitinib* *5f. Integrin inhibitors, including vedolizumab (participants in the Exploratory Cohort only)* 6c. JAK antagonists, including tofacitinib *and upadacitinib*: at least 2 weeks	
Synopsis – Main Inclusion Criteria Section 5.1. Inclusion Criteria – Main Inclusion Criteria	Weight 9. Has a body mass index (BMI) within the range of 18.0 and ~~33~~*40*.0 kg/m^2 (inclusive) at Screening	To change the upper limit on BMI in the inclusion criteria
Synopsis – Exploratory Cohort Inclusion Criteria Section 5.1. Inclusion Criteria	13. ~~Secondary~~ *Those intolerant to (e.g. infusion-related skin reaction, allergy, or side effects unrelated to $\alpha_4\beta_7$ inhibition) or secondary* non-responders* to vedolizumab ~~currently being treated~~ who *have been dosed within the past 5 years* with the drug. *Up to 5 of the 10 Exploratory Cohort participants may be included based on clinical criteria only. The remaining participants must also* ~~display~~ *meet* at least 1 of the following criteria: a. *Documented* vedolizumab levels in blood of ≤10 µg/mL 6 to 8 weeks after their most recent dose *or what is considered clinical trough. If the participant has had vedolizumab levels in blood tested and documented in their medical chart prior to Screening, the test does not need to be repeated.* b. Non-saturating receptor occupancy of vedolizumab in blood 6 to 8 weeks after their most recent dose c. ~~Presence~~ *Documented presence* of anti-drug antibodies against vedolizumab. *If the participant has had a positive anti-drug antibody test that has been documented prior to Screening, the test does not need to be repeated.* **Note: Secondary non-response is defined as having initially responded to Induction therapy and then had recurrence of symptoms after receiving at least 2 of the Maintenance doses, 300 mg every 8 weeks (discontinuation despite clinical benefit does not qualify).*	To clarify inclusion criteria regarding exploratory cohort (vedolizumab failures) and vedolizumab levels testing
Section 1.2. Schedule of Assessments (SoA)	**Schedule of Activities, Table 1, Footnote "l":** *If the participant has had vedolizumab levels in blood or presence of anti-drug antibodies against vedolizumab tested and documented in their medical chart prior to Screening, the test does not need to be repeated.*	

Section No. and Name	Description of Change	Brief Rationale
Section 8.2.3. Exploratory Cohort Screening Tests	• Vedolizumab blood levels 6 to 8 weeks after their most recent dose *or at what is considered clinical trough. (If the participant has had vedolizumab levels in blood tested and documented in their medical chart prior to Screening, the test does not need to be repeated.)* • Receptor occupancy of vedolizumab in blood 6 to 8 weeks after their most recent dose • Anti-vedolizumab antibody testing (*If the participant has had a positive anti-drug antibody test that has been documented prior to Screening, the test does not need to be repeated.)*	
Synopsis - Exclusion Criteria Section 5.2. Exclusion Criteria	Medical Conditions 3. Currently requires or is anticipated to require surgical intervention for UC during the study *or is planning to undergo major surgery during the study period* 4. Has had a surgical procedure requiring general anesthesia within 30 days prior to Screening ~~or is planning to undergo major surgery during the study period~~ 7. Has an active bacterial*, viral,* or parasitic pathogenic enteric infection, including Clostridium difficile; has cytomegalovirus, hepatitis B or C virus, or human immunodeficiency virus (HIV); had an infection requiring hospitalization or intravenous antimicrobial therapy, or an opportunistic infection within 3 months prior to Screening; had any infection requiring oral antimicrobial therapy within 2 weeks prior to Screening; or has a history of more than 1 episode of herpes zoster or any episode of disseminated herpes zoster infection	To clarify exclusion criteria
Synopsis - Exclusion Criteria Section 5.2. Exclusion Criteria Section 1.2. Schedule of Assessments (SoA)	Medical Conditions 8. Has a positive diagnostic tuberculosis (TB) test at Screening (defined as a positive [redacted] test). *If the participant has had a confirmed negative* [redacted] *or other Interferon Gamma Release Assay test within 90 days prior to Screening, the test does not need to be repeated.* **Schedule of Activities, Table 1, Footnote "j":** [redacted] TB test. *If the participant has had a confirmed negative* [redacted] *or other Interferon Gamma Release Assay test within 90 days prior to Screening, the test does not need to be repeated.*	To clarify exclusion criteria regarding tuberculosis testing
Synopsis - Exclusion Criteria Section 5.2. Exclusion Criteria Section 1.2. Schedule of Assessments (SoA)	Medical Conditions 9. Tests positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) during the Screening Period. *Participants who test positive for SARS-CoV-2 can undergo retesting throughout the Screening Period.* Testing to be performed according to site-specific testing procedures and country-specific requirements. **Schedule of Activities, Table 1, Footnote "i":** SARS-CoV-2 test will be performed during the Screening Period according to site-specific procedures and country-specific requirements. *Participants who test positive for SARS-CoV-2 can undergo retesting throughout the Screening Period.*	To clarify exclusion criteria regarding SARS-CoV-2 testing

Section No. and Name	Description of Change	Brief Rationale
Synopsis – Study Intervention	*Participants who enroll into the Long-term Extension will continue the study drug dosage ([redacted] mg [redacted] P.O.) for the 26-week extended Treatment Period. Each MORF-057 dose will be administered as four 25-mg capsules with or without food. Through the Long-term Extension, MORF-057 will continue to be self-administered at home, with the exception of the [redacted] doses for Visits 11-12, which will be administered during the study visits after pre-dose blood samples have been drawn (see details in the Schedule of Activities). Participants will be instructed to record all details about the doses administered at home in the Participant Diary.*	To identify details in the study design of the Long-term Extension
Synopsis – Statistical Methods Section 9.2: Statistical Analysis	General Considerations A significance level of 0.~~0245~~ *025* one-sided (0.~~049~~ *05* two-sided) will be used for the primary efficacy endpoint.	To update statistical methods
Synopsis – Statistical Methods Section 9.4: Sample Size Determination	Sample Size Determination 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.~~0245~~ *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 28 participants with >80% power. A drop out rate of 5% would lead to a total of 30 participants being enrolled in the Main Cohort. A maximum of ~~5~~ *10* additional participants may be enrolled in the Exploratory Cohort, giving a total of 30 to ~~35~~ *40* enrolled participants in the study.	To update statistical methods and to expand the enrollment goal of the Exploratory Cohort: in addition to the enrolling vedolizumab failures using biochemical/lab criteria, another cohort of 5 participants are added whose secondary loss of response to vedolizumab will be defined by clinical criteria only
Synopsis – Statistical Methods *Section 9.3. Analyses for Induction Period, 52-Week Treatment Period, and Long-term Extension*	*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 the purpose of statistical analyses, the Induction Period and the Maintenance Period will be treated as 2 independent parts. There will be 2 analyses planned: one for the 12-week Induction Period (i.e., the period for the primary efficacy endpoint) and the other for the 52-week Treatment Period (i.e., the 12-week Induction Period plus the 40-week Maintenance Period and the Safety Follow-up). Additional analysis of the optional Long-term Extension Period for the participants enrolled into the Long-term Extension will be performed as appropriate.* *Induction Period Analysis* *The analysis of the Induction Period will be performed after all the participants 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*	To clarify the planned analyses

Section No. and Name	Description of Change	Brief Rationale
	endpoints, all the exploratory endpoints defined by Week 12, PK concentrations and parameters, and safety of MORF-057 during the 12-week Induction Period. Only Induction Period data will be used in this analysis. *<u>52-Week Treatment Period Analysis</u>* *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. The analysis will formally evaluate all the exploratory endpoints defined by Week 52, PK concentration and parameters, and safety of MORF-057 during the 52-week open-label Treatment Period plus the Safety Follow-up Period. The cumulative data, including those from the Induction Period, will be used in this analysis.* *<u>Long-term Extension Analysis</u>* *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.*	
Synopsis – Statistical Methods	~~An interim analysis will be performed using the initial 5 bio-experienced and initial 5 bio-naïve subjects in the Main Cohort who have evaluable baseline and Week 12 primary endpoint data. At that time, the assumptions regarding the sample size calculation for the primary endpoint (change from baseline to Week 12 in RHI Score) and drop-out rate will be re-assessed. Note that no data from the participants in the Exploratory Cohort will be included in the re-assessment of the sample size assumptions. As there are no formal defined procedures for adjusting the final analysis significance level in instances of sample size re-assessment, a small adjustment will be made in this study, with alpha = 0.001 two-sided spent at the interim analysis and the final significance level adjusted to alpha = 0.049 two-sided / alpha = 0.0245 one-sided.~~	To remove the planned interim analysis for sample size reassessment and clarify the planned analyses
Section 9.2.5. Other Safety Analyses	9.2.5 Other Safety Analyses Other safety data will include safety laboratory parameters, vital signs, and ECG findings. These data will be summarized with descriptive statistics by absolute values and change from baseline using the ~~FAS~~Safety Analysis Population. The incidence of laboratory abnormalities will be summarized. Worst shift in grade and changes from baseline to Weeks 6, 12, and 52 of the laboratory analytes will be reported. Physical examination findings that are recorded as AEs will be included in those data presentations. *Participant safety data will be reviewed by an independent DSMB. Additional details related to the DSMB are included in Section 10.1.6 and will be clearly delineated in the DSMB Charter.*	

Section No. and Name	Description of Change	Brief Rationale
~~Section 9.3. Interim Analysis~~	~~9.3. Interim Analysis~~ ~~An interim analysis will be performed using the initial 5 bio-experienced and initial 5 bio-naïve subjects in the Main Cohort who have evaluable baseline and Week 12 primary endpoint data. At that time, the assumptions regarding the sample size calculation for the primary endpoint (change from baseline to Week 12 in RHI Score) and drop-out rate will be re-assessed. Further details regarding the interim analysis will be outlined in the SAP.~~	

Section No. and Name	Description of Change	Brief Rationale
Synopsis– Statistical Methods: Analysis Populations Section 9.1 Analysis Sets	The Full Analysis Set (FAS) is defined as all enrolled participants in the Main Cohort *and Exploratory Cohort* who took at least one dose of study medication. The FAS will be used for ~~all~~ efficacy, ~~safety, and biomarker summarizations/~~ analyses. ~~This definition of the FAS is sometimes also known as the Safety Population (note that, as indicated above, the FAS will be used for safety endpoints).~~ The Per Protocol *(PP)* Population is defined as all participants in the FAS who do not have any major protocol deviations *relevant to the primary and secondary efficacy endpoint analysis. All decisions to exclude participants from the PP set will be made prior to the database lock of the study.* The ~~Per Protocol~~*PP* ~~Population~~ ~~may~~will be used for sensitivity ~~efficacy analyses of, at a minimum,~~*analysis of* the primary efficacy endpoint~~.~~ *and maybe other selected efficacy endpoints as appropriate.* *The Safety Analysis Population is defined as all participants in both the Main Cohort and Exploratory Cohort who received at least 1 dose of study medication. The Safety Analysis Population will be used for safety analysis.* The PK Population is defined as all participants in the FAS who have 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.* *The 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 not violate the protocol in a way that may invalidate or bias the results, and must have the reliable data for the overall PK summaries. The criteria that the data must meet for the inclusion of a participant in this population will be specified in the study SAP.* ~~As appropriate, participants in the Exploratory Cohort will also have their data included in summarization and/or analysis of study endpoints.~~	To define the analysis sets of the study
Synopsis– Statistical Methods: Secondary Endpoints Synopsis– Statistical Methods: Other Safety Assessments Section 9.2.3. Secondary Endpoints Section 9.2.5. Other Safety Analyses	~~FAS~~ *Safety Analysis Population*	To add a Safety Analysis Population

Section No. and Name	Description of Change	Brief Rationale
Synopsis– Statistical Methods: Exploratory Endpoints Section 9.2.4. Exploratory Endpoints	~~Details related to the summarization and analysis of the other~~*The* exploratory *PD* endpoints ($\alpha_4\beta_7$ and $\alpha_4\beta_1$ receptor occupancies over time, *and* change from baseline over time in blood CCR9 mRNA~~, change from baseline over time in blood lymphocyte subsets,~~) *will be summarized descriptively. Additional 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*.	To identify how the exploratory PD endpoints will be reported
Synopsis – Data and Safety Monitoring Section 2.3.2 Risks Section 10.1.7 PML Adjudication Committee	*Additionally, a separate PML Adjudication Committee will oversee a PML Risk Assessment and Minimization Program (RAMP) to monitor all participants for PML*. The composition, responsibilities, and meeting schedules of the DSMB *and the PML Adjudication Committee* will be described in ~~a~~ separate ~~charter~~ *charters*. ~~All participants enrolled in this study will be monitored for PML through the use of a PML Risk Assessment and Minimization Program (RAMP), which will be overseen by the DSMB.~~ However, out of an abundance of caution, all participants enrolled in this study will be monitored for PML through the use of a PML Risk Assessment and Minimization program (RAMP)~~, which will be overseen by the DSMB.~~). *Section 10.1.7. PML Adjudication Committee* ~~All participants enrolled in this study will be monitored for PML through the use of a PML Risk Assessment and Minimization Program (RAMP), which will be overseen by the DSMB.~~ *A PML Adjudication Committee will oversee a PML RAMP to monitor all participants for PML. The composition, responsibilities, and meeting schedules of the PML Adjudication Committee will be described in a separate charter.*	To describe the progressive multifocal leukoencephalopathy (PML) Adjudication Committee responsibilities as they relate to the study
Section 1.2. Schedule of Activities (SoA)	**The Schedule of Activities table was updated to change Open-label Extension Study to Long-term Extension, add dispensation of study drug at Visit 10 for participants who want to continue in the Long-term Extension, and add that participants who want to continue in the Long-term Extension will sign a separate ICF.** **Schedule of Activities, Table 1, Footnote "d":** Participants who will not enroll into the ~~Open-label~~*Long-term 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 p~~*P*articipants who choose to enroll into the ~~Open-label~~*Long-term Extension* ~~Study~~ after Visit 10/EOT will ~~not attend the~~*complete a* Safety Follow-up Visit *at Week 82.*	To identify the timeline and describe the details of the Long-term Extension

Section No. and Name	Description of Change	Brief Rationale
	Schedule of Activities, Table 1, Footnote "q": ~~Eligible p~~*P*articipants ~~should~~*will* be provided the option to participate in the ~~Open label~~ *Long-term Extension* ~~study~~. *Participants who want to continue in the Long-term Extension will sign a separate ICF.* **Schedule of Activities, Table 1, Footnote "kk":** *At Visit 10/EOT, the study drug will be dispensed only for participants continuing treatment in the Long-term Extension.* **A new Schedule of Assessments was provided in section 1.2. The new table (Table 2) identifies the timepoints and assessments of the Long-term Extension.**	
Section 1.2. Schedule of Activities (SoA) Section 8.6 Stool Collection	**The Schedule of Activities table was updated to add that stool collection kits will be dispensed at Visit 10 only for participants continuing in the Long-term Extension.** **Schedule of Activities, Table 1, Footnote "p":** *Stool collection kits will be dispensed at Visit 10 only for participants continuing in the Long-term Extension.* Note: Sample is to be collected prior to bowel preparation for Visits 4, 5, and 10/EOT *of the main Treatment Period.*	To add backup stool collection at home for Long-term Extension visits
Section 1.2. Schedule of Activities (SoA) Section 8.8.4. Clinical Safety Laboratory Tests	**Schedule of Activities, Table 1, Footnote "u":** *Blood samples for hematology, coagulation, and serum chemistry assessments will be collected before the* [redacted] *on Visits 2-10.* *Blood samples will be collected before the* [redacted] *on Visits 2-10 of the main Treatment Period and before the* [redacted] *on Visits 11-12 of the Long-term Extension.*	To specify timing of blood draws for safety-related laboratory tests
Section 1.2. Schedule of Activities (SoA)	**Schedule of Activities, Table 1, Footnote "aa":** RO testing at Visit 2, 3, and 5: ~~Blood sampling will be required~~*The blood samples for RO testing collected* before the [redacted]. ~~Blood sampling will be optional at~~ *are required. The* [redacted] *samples for RO testing are optional.* The [redacted] sample will be collected prior to the second daily dose. RO sampling to occur at the corresponding PK sampling time.	To clarify the details of receptor occupancy testing
Section 1.2. Schedule of Activities (SoA)	**Schedule of Activities, Table 1, Footnote "gg":** Colonic mucosa biopsies will be collected for cytomegalovirus testing (Screening only), *histopathology*, microbiome, spatial transcriptomics/proteomics, and gene expression analyses.	To specify the analyses following endoscopy with biopsy
Section 4.2 Scientific Rationale for Study Design	*The 52-week study will be followed by an optional 26-week Long-term Extension. This extension will provide further access to the study drug to the participants and further efficacy and safety data up to 78 weeks of exposure.*	To add rationale for Long-term Extension

Section No. and Name	Description of Change	Brief Rationale
Section 4.4. End of Study Definition	A participant is considered to have completed the study if he/she has completed ~~all periods of the study~~ *the Screening and 52-week Treatment Periods of the study* and attended the Safety Follow-up Visit OR has completed the Week 52/EOT Visit and has been enrolled into the *Long-term Extension* ~~Open-label Extension study~~. The end of the study is defined as the date of the last visit of the last participant in *the main part of* the study or last scheduled procedure shown in the schedule of activities for the last participant in the *main part of the* study globally. *The results for the Long-term Extension may be reported in a Clinical Study Report Addendum.*	To define participant study completion
Section 6.5. Continued Access to Study Intervention after the End of the Study	~~Eligible~~*All* participants will have the opportunity to enroll into a separate ~~Open-label~~ *Long-term* Extension ~~study~~ after ~~Week 52. Participants who have completed~~ completing the Week 52 assessments ~~and~~ *Participants who are* ~~eligible and~~ willing to enroll into the ~~Open-label~~ *Long-term* Extension ~~study~~ will skip the Safety Follow-up Visit *at Week 56* and directly enter the ~~Open-label~~ *Long-term* Extension ~~study~~. *Participants enrolled into the Long-term Extension will complete the Safety Follow-up Visit at Week 82.* Participants who do not enroll in the ~~Open-label~~ *Long-term* Extension ~~study~~ will no longer have access to the study drug after they complete the 52-week Treatment Period. *Participants who continue in the Long-term Extension will no longer have access to the study drug after they complete the 26-week extended Treatment Period.*	To add information on continued access to study intervention in the Long-term Extension
Section 6.6. Treatment of Overdose	• Contact the Medical Monitor ~~immediately~~*within 24 hours* • *Enter the overdose information into the electronic data capture database (EDC) within 24 hours of notification*	To provide guidance on overdose reporting
Section 6.7.1.1. Tapering of Oral Corticosteroids	*Participants receiving budesonide MMX (1 tablet, 9 mg) can reduce dosage by taking 6 mg budesonide (2 tablets, 3 mg each) daily for two weeks, followed by 3 mg budesonide (1 tablet, 3 mg) daily for two weeks to complete the tapering process.*	To add guidance on budesonide tapering
Section 6.7.2 Prohibited Medications	• Nonsteroidal anti-inflammatory drugs (NSAIDs) including but not limited to ibuprofen, naproxen, indomethacin, and celecoxib. However, participants may take aspirin for ~~cardio protection~~ *secondary prevention of cardiovascular event* at a dose not exceeding ~~325~~ *100* mg per day.	To lower the allowed dose of aspirin during the study
Section 7.2. Participant Discontinuation/Withdrawal from the Study	The participant should be encouraged to complete the End of Treatment Visit (Visit 10 *in the main part of the study, or Visit 12 in the Long-term Extension*) at the time of study drug discontinuation and the Safety Follow-up Visit (Visit 11 *in the main part of the study, or Visit 13 in the Long-term Extension*) at 28 days (+7) after the last dose of study drug.	To identify the different End of Treatment Visits in the Main Study and Long-term Extension if a participant discontinues from the study.
Section 8.1. Medical History	All prior advanced therapies for the treatment of UC (e.g., antagonists to TNF-α, JAK, or IL-12/IL-23; S1P receptor agonists; *integrin inhibitors [Exploratory Cohort only]*; or other new investigational treatments) with the reason for discontinuation are to be collected for participants where possible.	To update documentation of medical history

Section No. and Name	Description of Change	Brief Rationale
Section 8.5 Participant Diary	Detailed descriptions regarding Participant Diary recordings can be found in the ~~Study Manual~~*Patient Guide*.	To update the source for Participant Diary instructions
Section 8.7.1. Endoscopy with Biopsy	Detailed instructions for endoscopic biopsies (e.g., anatomic site, normal or inflamed mucosa) can be found in the ~~Study Manual~~ *Central Image Management Solutions (CIMS) Biopsy Quick Reference Card.* Biopsy specimen transfer, processing, slide preparation, and digitization of slides for histopathologic scoring procedures will be detailed ~~in a Histopathology Manual~~*the Image Review Charter.*	To add the Biopsy Quick Reference Card and Image Review Charter
Section 8.7.1. Endoscopy with Biopsy	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). However, treatment decisions will be made by the treating Investigator.	To specify that the adjudicator will be blinded to local vs. central score
Section 8.8.5 Progressive Multifocal Leukoencephalopathy Section 10.2 Appendix 2: Progressive Multifocal Leukoencephalopathy Checklists	~~*The PML checklist will*~~*The Subjective PML Checklist will be administered to participants during Screening to exclude individuals with a positive response from enrolling into the study. The Subjective PML Checklist (Section 10.2) will also be* completed according to the schedule in the SoA (Section 1.2). ~~The checklist is provided in Section 10.2~~. If the results of the questionnaire are suggestive of PML, *the participant will undergo Objective PML Checklist testing (Section 10.2)*, a full neurological exam *by a neurologist*, and, if indicated, additional testing ~~are to be performed~~. **The Objective PML Checklist was added to Appendix 2.**	To include the complete PML checklist in the protocol
Section 9. Statistical Considerations	The Statistical Analysis Plan (SAP) will be finalized prior to the ~~interim analysis~~ *first participant dosed*, *and may be amended as needed due to a protocol amendment.* It will include a more technical and detailed description of the data summarization and analysis described in this section. Any ~~deviation~~ *change* from the planned statistical analyses specified in the protocol will be fully described in the SAP and Clinical Study Report.	To add details about the SAP
Section 9.2.1. General Considerations	A significance level of 0.~~0245~~025 one-sided (0.~~049~~05 two-sided) will be used for the primary efficacy endpoint.	To adjust the statistical significance level to be used in the analysis of the primary efficacy endpoint

<table>
<tr><th>Section No. and Name</th><th>Description of Change</th><th>Brief Rationale</th></tr>
<tr><td>Section 9.4. Sample Size Determination</td><td>~~As there are no formal defined procedures for adjusting the final analysis significance level in instances of sample size re-assessment, a small adjustment will be made in this study, with alpha=0.001 two-sided spent at the interim analysis and the final significance level adjusted to alpha=0.049 two-sided / alpha = 0.0245 one-sided.~~</td><td>To revise the sample sizes needed for this study</td></tr>
<tr><td>Section 10.3. Appendix 3: Clinical Laboratory Tests</td><td>
<table>
<tr><th>Laboratory Tests</th><th colspan="3">Parameters</th></tr>
<tr><td>Hematology</td><td>• Platelet count
• RBC count
• Hemoglobin
• Hematocrit
• ~~ESR~~</td><td><u>RBC Indices</u>:
• MCV
• MCH
• % Reticulocytes</td><td><u>WBC count with differential</u>:
• Neutrophils
• Lymphocytes
• Monocytes
• Eosinophils
• Basophils</td></tr>
<tr><td>Pregnancy testing</td><td colspan="3">• Highly sensitive serum hCG pregnancy test (at Screening and as needed for women of childbearing potential only)
• Urine hCG test (at Visits 2-11 in the main Treatment Period and Visits 11-13 of the Long-term Extension for women of childbearing potential only) [a]</td></tr>
</table>
</td><td>To remove erythrocyte sedimentation rate test and clarify the schedule for pregnancy testing</td></tr>
<tr><td>Section 10.4.4. Appendix 4: Reporting of SAEs</td><td><u>SAE Reporting to the Sponsor or designee via an Electronic Data Collection Tool</u>
~~• Contacts for SAE reporting can be found in the Study Manual~~

<u>SAE Reporting to the Sponsor or Designee via Paper Data Collection Tool (Back-up Option)</u>
• ~~Contacts for SAE reporting can be found in the Study Manual.~~ If the electronic system is not available, the SAE paper data collection tool should be signed by the Investigator and emailed to: [redacted]</td><td>To add details for the reporting of SAEs</td></tr>
<tr><td>Section 10.10. Appendix 10: Summary of Changes Table – Protocol Amendment Version 2.0</td><td>The summary of changes between Protocol Version 1.0 and Version 2.0 was moved to an appendix.</td><td>Administrative change</td></tr>
</table>

Section No. and Name	Description of Change	Brief Rationale
Section 11. References	*Parikh A, Stephens K, Major E, et al. A Programme for Risk Assessment and Minimisation of Progressive Multifocal Leukoencephalopathy Developed for Vedolizumab Clinical Trials. Drug Saf. 2018;41(8):807-16.*	To add a reference

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