Statistical Analysis Plan: J6E-MC-KWAD

A Phase 2b, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of 3 Active Dose Regimens of MORF-057 in Adults with Moderately to Severely Active Ulcerative Colitis

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STATISTICAL ANALYSIS PLAN

A Phase 2b, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of 3 Active Dose Regimens of MORF-057 in Adults with Moderately to Severely Active Ulcerative Colitis (EMERALD-2)

Protocol Number:	MORF-057-202
Study Drug:	MORF-057
Study Phase:	Phase 2b
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Analysis Plan Version:	Version 1.0
Analysis Plan Date:	16 September 2024

APPROVAL OF STATISTICAL ANALYSIS PLAN

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol and all applicable regulatory guidance and guidelines.

AMENDMENT HISTORY

This is the original version. No amendment history.

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ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Explanation
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
AST	Aspartate Transaminase
ATC	Anatomical Therapeutic Chemical
B.I.D.	Twice a Day
BLQ	Below Limit of Quantification
BMI	Body Mass Index
CI	Confidence Intervals
CMH	Cochran-Mantel-Haenszel
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient Of Variation
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOT	End Of Treatment
FAS	Full Analysis Set
HRQoL	Health-Related Quality of Life
hs-CRP	High-Sensitivity C-Reactive Protein
IBDQ	Inflammatory Bowel Disease Questionnaire
IRT	Interactive Response Technology
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
MES	Mayo Endoscopic Score
MCS	Full Mayo Clinic Score
mMCS	Modified Mayo Clinic Score
mRNA	Messenger Ribonucleic Acid
NI	Nancy Histopathology Index
P.O.	By Mouth
PD	Pharmacodynamic(S)
PGA	Physician’s Global Assessment

Abbreviation	Explanation
PK	Pharmacokinetic(S)
PP	Per-Protocol
PT	Preferred Term
Q.D.	Once A Day
Q.D.-E	One A Day (Evening)
Q.D.-M	Once A Day (Morning).
QTcF	QT Interval Corrected Through Use of Fridericia's Formula
RHI	Robarts Histopathology Index
SAE	Serious Adverse Event
SD	Standard Deviation
SFU	Safety Follow-Up
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
UC	Ulcerative Colitis
ULN	Upper Limit of Normal
WHODD	World Health Organization Drug Dictionary

1. INTRODUCTION

This statistical analysis plan (SAP) is designed to outline the statistical analysis methods in evaluating the efficacy and safety of study drug MORF-057 in adult participants with moderately to severely active ulcerative colitis (UC) for Phase 2b study MORF-057-202: A Phase 2b, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of 3 Active Dose Regimens of MORF-057 in Adults with Moderately to Severely Active Ulcerative Colitis (EMERALD-2).

This document has been prepared based on the protocol dated 26Apr2023 and CRF dated 14Jun2024. Details will be described in this analysis plan to ensure summary of tables, figures and listings, and the statistical methodology that will be used, are complete and appropriate to allow valid conclusion regarding the study objectives.

1.1. Study Objectives and Endpoints

The following study objectives (Table 1) will be completed by assessing the associated endpoints in participants with moderately to severely active UC.

Table 1: Study MORF-057-202 Objectives and Endpoints

Objectives	Endpoints
Primary Efficacy	
To evaluate the effects of MORF-057 on clinical remission at Week 12	• Proportion of participants in clinical remission at Week 12 as determined using the Modified Mayo Clinic Score (mMCS). The mMCS is a composite of the following subscores: o Mayo endoscopic subscore (MES) o Mayo Clinic Score (MCS) stool frequency subscore o MCS rectal bleeding subscore
Secondary Efficacy	
To evaluate the effects of MORF-057 on clinical response at Week 12	• Proportion of participants with clinical response at Week 12 as determined using the mMCS
Exploratory Efficacy	•
To evaluate the effects of MORF-057 on clinical remission at Week 52	• Proportion of participants in clinical remission at Week 52 as determined using the mMCS
To evaluate the effects of MORF-057 on clinical response at Week 52	• Proportion of participants with clinical response at Week 52 as determined using the mMCS
To evaluate the effect of MORF-057 on MCS remission at Weeks 12 and 52	• Proportion of participants in MCS remission at Weeks 12 and 52. 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 evaluate the effect of MORF-057 on MCS response at Weeks 12 and 52	• Proportion of participants with MCS response at Weeks 12 and 52
To evaluate the effects of MORF-057 on histologic remission at Weeks 12 and 52	• Proportion of participants in histologic remission at Weeks 12 and 52 as determined using the Robarts Histopathology Index (RHI) Score • Proportion of participants in histologic remission at Weeks 12 and 52 as determined using the Nancy Histopathology Index (NI) • Proportion of participants in histologic remission at Weeks 12 and 52 as determined using the Continuous Geboes Score
To evaluate the effects of MORF-057 on histologic improvement at Weeks 12 and 52	• Proportion of participants with histologic improvement at Weeks 12 and 52 as determined using the RHI
To evaluate the effect of MORF-057 on endoscopic improvement at Weeks 12 and 52	• Proportion of participants with endoscopic improvement at Weeks 12 and 52 as determined using the MES
To evaluate the effects of MORF-057 on endoscopic remission at Weeks 12 and 52	• Proportion of participants in endoscopic remission at Weeks 12 and 52 as determined using the MES
To evaluate the effects of MORF-057 on mucosal healing at Weeks 12 and 52	• Proportion of participants in endoscopic remission as determined using the MES and histologic remission as determined using the RHI at Weeks 12 and 52
To evaluate the effects of MORF-057 on mucosal improvement at Weeks 12 and 52	• Proportion of participants with endoscopic improvement as determined using the MES and a histologic improvement as determined using the RHI at Weeks 12 and 52
To evaluate the effects of MORF-057 on symptomatic response at Weeks 2 and 6	• Proportion of participants with symptomatic response at Weeks 2 and 6 as determined using the Partial mMCS. Partial mMCS is a composite of the following subscores: o MCS stool frequency subscore o MCS rectal bleeding subscore
To evaluate the effects of MORF-057 on Partial MCS response at Week 6	• Proportion of participants with Partial MCS response at Week 6. Partial MCS is a composite of the following subscores: o MCS stool frequency subscore o MCS rectal bleeding subscore o MCS PGA
To determine time to symptomatic response by Week 12	• Time to symptomatic response by Week 12 as determined using the Partial mMCS

Objectives	Endpoints
To assess the effect of MORF-057 on non-endoscopic biomarkers of inflammation at Weeks 12 and 52	• Change from baseline to Weeks 12 and 52 in high-sensitivity C-reactive protein (hs-CRP) levels • Change from baseline to Weeks 12 and 52 in fecal calprotectin levels
To evaluate the effect of MORF-057 on patient-reported outcomes (PROs) at Weeks 12 and 52	• Change from baseline to Weeks 12 and 52 in Inflammatory Bowel Disease Questionnaire (IBDQ) Score
To evaluate the effect of MORF-057 on corticosteroid-free remission at Week 52	• Proportion of participants in corticosteroid-free remission at Week 52, as determined using the mMCS, among the participants who were on a stable dose of corticosteroids at baseline
To characterize the effect of MORF-057 on the need for UC-related hospitalizations and surgeries	• Percentage of participants requiring UC-related hospitalization or surgery at Weeks 12 and 52
To evaluate the long-term histologic and endoscopic effects of MORF-057 at Week 104	• Proportion of participants in histologic remission at Week 104 as determined using the RHI • Proportion of participants in histologic remission at Week 104 as determined using the NI • Proportion of participants in histologic remission at Week 104 as determined using the Continuous Geboes Score • Proportion of participants with histologic improvement at Week 104 as determined using the RHI • Proportion of participants with endoscopic improvement at Week 104 as determined using the MES • Proportion of participants in endoscopic remission at Week 104 as determined using the MES • Proportion of participants in endoscopic remission as determined using the MES and histologic remission as determined using the RHI at Week 104 • Proportion of participants with endoscopic improvement as determined using the MES and a histologic improvement as determined using the RHI at Week 104
Safety	
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
Pharmacokinetics (PK)	

Objectives	Endpoints
To characterize the PK of MORF-057	• MORF-057 concentration in plasma
Exploratory Pharmacodynamics (PD)	
To characterize the PD of MORF-057 in peripheral blood	• α4β7 receptor occupancy in blood over time • α4β1 receptor occupancy in blood over time • Change from baseline over time in blood in CCR9 messenger ribonucleic acid (mRNA) • Change from baseline over time in blood lymphocyte subsets

The definitions of efficacy endpoints are described in the following table.

Table 2: Efficacy Endpoints Definitions

Term	Definition
Clinical remission	Determined using the mMCS: Rectal bleeding subscore of 0; a stool frequency subscore of ≤1; and an MES of ≤1 without friability.
Clinical response	Determined using the mMCS: Decrease from baseline in the mMCS ≥2 points and ≥30% from baseline, plus a decrease in rectal bleeding subscore ≥1 or an absolute rectal bleeding subscore ≤1
MCS remission	MCS ≤2 and no subscore higher than 1
MCS response	Decrease in MCS ≥3 points and ≥30% from baseline, plus a decrease in rectal bleeding score ≥1 or an absolute rectal bleeding score ≤1
Histologic remission by RHI	RHI ≤3 (with 0 for lamina propria neutrophils score and neutrophils in the epithelium score and without ulcers or erosions)
Histologic remission by NI	NI=0
Histologic remission by Continuous Geboes	Continuous Geboes ≤3
Histologic improvement	≥7-point reduction in RHI
Endoscopic improvement	MES ≤1
Endoscopic remission	MES=0
Mucosal healing	MES=0 and RHI ≤3 (with 0 for lamina propria neutrophils score and neutrophils in the epithelium score and without ulcers or erosions)
Mucosal improvement	MES ≤1 and ≥7-point reduction in RHI
Symptomatic response	Decrease in Partial mMCS ≥1 point and ≥30% from baseline, plus a decrease in rectal bleeding subscore ≥1 or an absolute rectal bleeding subscore ≤1
Partial MCS response	Decrease in Partial MCS ≥2 points and ≥30% from baseline, plus a decrease in rectal bleeding subscore ≥1 or an absolute rectal bleeding subscore ≤1

Term	Definition
Time to symptomatic response	Time from randomization date to symptomatic response
Corticosteroid-free remission	Determined only in participants who were receiving corticosteroids on study Day 1. Includes such participants who are both in clinical remission (as determined using the mMCS) at Week 52 and off corticosteroids for ≥8 consecutive weeks prior to Week 52.

Please see details of efficacy assessments in Section 6.3 of this document and Section 8.7 of the study protocol.

1.2. Study Design

This study is a randomized, double-blind, placebo controlled, multicenter, Phase 2b study to evaluate the efficacy and safety of 3 active dose regimens of MORF-057 (as capsule, P.O.) versus matching placebo in study participants with moderately to severely active UC.

Approximately 280 participants will be randomized into the treatment groups in a 1:1:1:1 ratio (i.e., 70 participants per group). The study will enroll participants who are advanced therapy naïve (i.e., have no previous exposure to an advanced therapy treatment for UC) and advanced therapy experienced (excluding vedolizumab), with at least 30% but no more than 40% of advanced therapy experienced participants. Randomization stratification factors will include baseline MES (<3 vs 3) and previous use of advanced therapy treatment (advanced therapy naïve vs advanced therapy experienced). All participants will be enrolled from approximately 150 centers worldwide. For this study, moderately to severely active UC will be defined as having an mMCS of 5 to 9 (inclusive), with an MES ≥2 (confirmed by central reader).

The main part of this Phase 2b study will consist of a Screening Period (up to 6 weeks, consisting of Stage 1 and Stage 2 testing), a Treatment Period (52 weeks, including a 12-week Induction Period and a 40-week Maintenance Period), and a Safety Follow up (SFU) Period (4 weeks).

During the main part of this 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, 18, 24, 32, 42, and 52 [End of Treatment (EOT)]), and an SFU Visit (visit to occur 4 weeks after the last dose of study drug is received, which will be at Week 56 if the full Treatment Period 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).

All participants who complete the 52-week Treatment Period will have the opportunity to continue their treatment in a 52-week Maintenance Extension Period.

During the optional Maintenance Extension, there will be 5 scheduled visits: 4 Treatment Visits (Visits 11 14 at Weeks 65, 78, 91, and 104 [EOT]) and an SFU Visit (visit to occur 4 weeks after the last dose of study drug is received, which will be at Week 108 if the full Maintenance Extension is completed or earlier if treatment is discontinued early).

Participants who do not enroll into the Maintenance Extension must complete the final SFU 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 Maintenance Extension will not complete the SFU Period for the main part of the study; instead, they

will directly enter the Maintenance Extension and complete a separate SFU Period, including the Week 108 Visit (4 weeks after receiving the last dose of MORF-057), for a maximum time on-study of 114 weeks.

An independent Data and Safety Monitoring Board (DSMB) will review participant safety data and monitor scientific integrity throughout the study. Details related to the DSMB will be clearly delineated in the DSMB Charter.

Enrolled participants will be randomized to a treatment group to receive active MORF-057 or placebo. Participants initially randomized into an active MORF-057 treatment group will receive an active treatment (according to study period and group assignment) for the full 52-week Treatment Period. Participants initially randomized into the placebo group will be switched to an active MORF-057 regimen (200 mg once a day – evening [Q.D.E]) after they complete the Induction Period and the Week 12 assessments. After participants complete the full 52-week Treatment Period, they will have the option to enter an additional 52-week Maintenance Extension Period. All participants who choose to continue in the Maintenance Extension will continue receiving the same MORF-057 regimen they had during the Maintenance Period for up to an additional 52 weeks. The dosing regimens for the 4 treatment groups during the study are shown below.

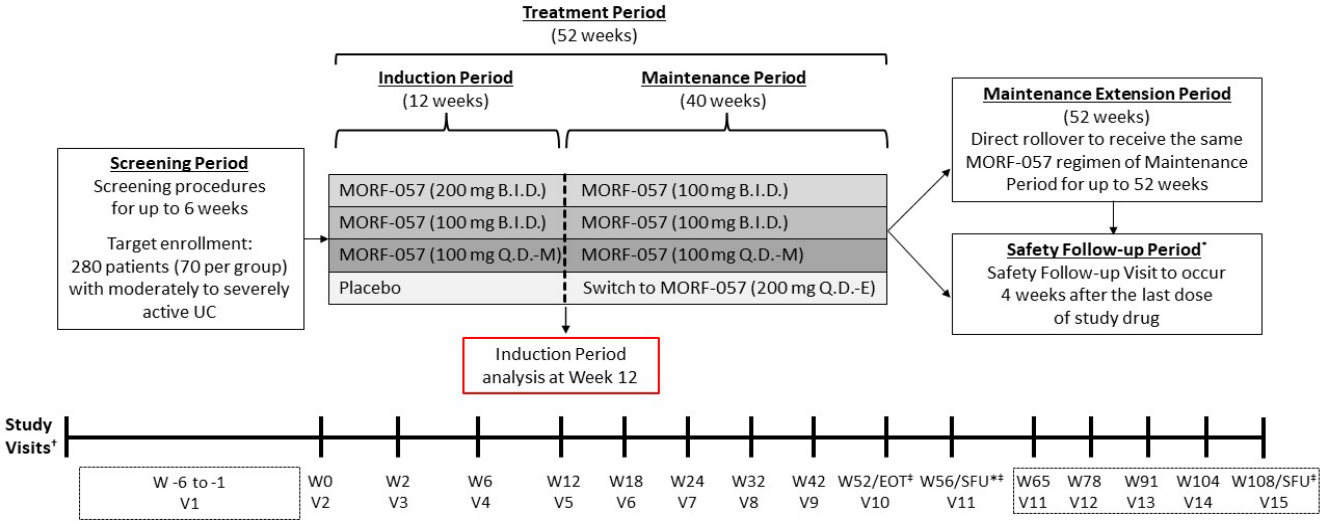
Table 3: Study Dose Regimens

	Induction Period (12 Weeks)	**Maintenance Period (40 Weeks)/ Maintenance Extension Period (52 Weeks)**
Group 1	MORF 057 (200 mg B.I.D.)	MORF 057 (100 mg B.I.D.)
Group 2	MORF 057 (100 mg B.I.D.)	MORF 057 (100 mg B.I.D.)
Group 3	MORF 057 (100 mg Q.D. M)	MORF 057 (100 mg Q.D. M)
Group 4	Placebo	MORF 057 (200 mg Q.D. E)

B.I.D.: twice a day; Q.D. E: once a day (evening); Q.D. M: once a day (morning).

A study schema is provided in Figure 1.

Figure 1: Study Schema



B.I.D.: twice a day; EOT: End of Treatment; Q.D. E: once a day (evening); Q.D. M: once a day (morning); SFU: Safety Follow up; UC: ulcerative colitis; V: visit; W: week.

* The SFU Visit at Week 56 will not be performed for participants who enter the Maintenance Extension Period.

† 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.

A participant is considered to have completed the study if he/she has completed the Screening and 52-week Treatment Periods of the main part of the study and attended the SFU Visit OR has completed the Week 52/EOT Visit and has been enrolled into the Maintenance Extension Period.

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.

1.3. Sample Size and Power

The sample size was determined based on the primary endpoint of clinical remission at Week 12 by using the Chi-Squared Test to compare two proportions. A sample size of 70 participants per group (giving a total of 280) will provide 80% power to detect a difference of 15% in the clinical remission rate between MORF-057 and placebo, based on the use of a two-sided test at the alpha=0.10 level of significance. The calculation is based upon an assumed placebo remission rate of 7%.

1.4. Randomization and Blinding

1.4.1. Randomization

An interactive response technology (IRT) will be used to centrally randomize all participants into 1 of the 4 treatment groups (see Table 3 for dosing regimens). The randomization code will be maintained by the IRT provider. Randomization will be stratified by baseline MES (<3 vs 3) and previous use of advanced therapy treatment (advanced therapy naïve vs advanced therapy experienced). Participants

initially randomized into the placebo group will be switched to an active MORF 057 regimen (200 mg Q.D. E) after they complete the Induction Period and the scheduled assessments at Week 12 (including endoscopy).

Study treatment will be dispensed at the study visits as summarized in the Schedule of Activities (SoA) in Section 1.2 of the study protocol.

1.4.2. Blinding

This is a double-blind study in which the Sponsor, participants, site staff, site pharmacy, Investigators, and outcome assessors will be blinded to the study treatment through Week 12. The double-blind will be maintained by using identical study drug bottles and labels for MORF-057 and placebo. The placebo will have an identical appearance to that of the MORF-057 capsules. Participants will receive their study drug supplies in "morning bottles" and "evening bottles." Each participant will receive the same number of "morning bottles" and "evening bottles" according to the respective study period (Induction or Maintenance/Maintenance Extension). In the morning, participants should take 1 capsule from EACH "morning bottle." In the evening, participants should take 1 capsule from EACH "evening bottle." After all participants have completed the Induction Period and scheduled assessments at the Week 12 Visit, the Induction Period analyses will be performed. After the database lock for the Induction Period analyses, the analysis results will be unblinded at the population level. However, the access to treatment assignment for individual participants will be limited to only the necessary persons from the Sponsor and the external vendors that will generate the unblinded analysis results and perform the validation. All other Sponsor personnel, the project study team, site Investigator, site staff, and study participants will remain blinded to the individual treatment assignments through the end of the study. The details of measures taken to maintain integrity of blinded data was described in the study blinding plan.

The IRT will be programmed with blind breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Sponsor prior to unblinding a participant's treatment assignment, unless this could delay emergency treatment for the participant. If a participant's treatment assignment is unblinded, the Sponsor must be notified within 24 hours of this occurrence. The date and reason for the unblinding must be recorded in the participant's medical records and IRT. If a participant's treatment is unblinded, the participant will be withdrawn from the study.

Sponsor safety staff or designee may unblind the treatment assignment for any participant in case the SAE meets the requirement for expedited reporting (e.g., is a suspected unexpected serious adverse reaction [SUSAR]). If the report requires expedited reporting to one or more regulatory agencies, a copy of the report, identifying the participant's treatment assignment, will be sent to the regulatory agency in accordance with local regulations and/or Sponsor policy. All other Sponsor staff, as well as the Investigators and study participants, will remain blinded to study assignments until database lock.

1.5. Planned Analysis

The Treatment Period (i.e., 52 weeks) in the main part of the study includes the 12-week Induction Period and the 40-week Maintenance Period, see Section 1.2. The Induction Period includes the placebo group as a comparator, while all the participants will receive an active MORF-057 treatment during the 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 for the main part of the study: one for the 12-week Induction Period (i.e., the period for the primary efficacy endpoint) and one for the 52-week Treatment Period (i.e., the 12-week Induction Period plus the 40-week Maintenance Period).

Additionally, at the end of the optional Extension Period, another analysis will be performed for the 104-week Total Treatment Period, which includes the main part of the study and the 52-week Maintenance extension period.

1.5.1. Induction Period Analysis

The Induction Period Analysis will be performed after all the participants have completed the Week 12 assessments or discontinued the study before the Week 12 assessments. The analysis will formally evaluate the primary and secondary efficacy endpoints, all the exploratory efficacy endpoints defined by Week 12, and safety of MORF057 vs placebo during the 12-week Induction Period. The PK and PD data during the 12-week Induction Period will also be summarized.

The 12-week Induction Period is defined as the time from the date of randomization to the Induction Period Last Dose date recorded on the Study Period Transition electronic case report form (eCRF) for participants continuing to the Maintenance Period, or the study end date (i.e., the date of the last visit including the SFU visit or last scheduled procedure) for participants who have discontinued the study before entering the Maintenance Period.

If participants continue to the Maintenance Period, they should complete all the Visit 5 (Week 12) assessments before starting their maintenance treatment according to the protocol. However, a small number of participants were observed to deviate from the protocol by starting their maintenance treatment shortly before completing all the Visit 5 (Week 12) assessments. In such cases, all efficacy assessments, clinical laboratory tests, vital signs and electrocardiogram (ECG) collected at Visit 5 (Week 12) will still be included in the analyses for the 12-week Induction Period, even if they are measured after the participants start their maintenance dose. The PK and PD samples collected at Visit 5 (Week 12) for these participants will be handled in the Induction Period Analysis according to the rules specified in Section 2.7 and Section 2.8. Any adverse events that occur after the date of last induction treatment dose will not be included in the Induction Period Analysis. If both the last induction treatment dose and the first maintenance treatment dose occur on the same day, any adverse events reported on that day will be considered for the Maintenance Period and not included in the Induction Period Analysis, unless there is evidence to confirm that the events occurred before the administration of the maintenance treatment.

1.5.2. 52-week Treatment Period Analysis

The 52-week Treatment Period Analysis will be performed after all the participants have completed the Week 52 assessments (and Safety Follow-up Period for participants not rolling over into the Maintenance Extension Period) or discontinued from the study before the Week 52 assessments. The analysis will formally evaluate the efficacy (including all the exploratory efficacy endpoints defined by Week 52), PK, PD, and safety of MORF-057 during the 52-week Treatment Period.

The 52-week Treatment Period is the 12-week Induction Period plus the 40-week Maintenance Period. The 40-week Maintenance Period is defined as the time from the Maintenance Period First Dose date recorded on the Study Period Transition eCRF page to the date of last treatment recorded on the EOT eCRF page for the main part of the study for participants rolling over to the Extension Period, or to the

study end date (i.e., the date of the last visit including the SFU visit or last procedure) for participants not entering the Extension Period or who discontinued the study early.

Participants initially randomized into an active MORF-057 treatment group (i.e., Group 1, Group 2, and Group 3 in Table 3), will receive an active MORF-057 treatment (according to study period and group assignment) for the full 52-week Treatment Period. The cumulative data, including those from the Induction Period, will be used for these groups in the 52-week Treatment Period Analysis. For participants initially randomized into the placebo group during the Induction Period and subsequently switched to an active MORF 057 treatment (i.e., 200 mg Q.D.-E) during the Maintenance Period (i.e., Group 4 in Table 3), only the data collected during the 40-week Maintenance Period will be included in the 52-week Treatment Period Analysis to assess the effect of MORF-057 treatment, unless otherwise specified. Participants who are randomized into the placebo group during the Induction Period and have discontinued the study treatment before entering the Maintenance Period will not be included in this analysis.

In addition, when the Induction Period analysis is performed, an exploratory analysis for the 52-week Treatment Period may also be conducted for the subgroup of participants who have either completed their Week 52 assessments or discontinued the study by the time the last randomized participant completes their Visit 5 (Week 12) assessments.

1.5.3. 104-week Total Treatment Period Analysis

The 104-week Total Treatment Period Analysis will be performed after all the participants enrolled into the Maintenance Extension have completed the Visit 14 (Week 104) assessments and the Safety Follow up Period or discontinued the study. The analysis will evaluate the exploratory efficacy endpoints at Week 104 as appropriate and the long-term safety of MORF 057 during the 104-week Total Treatment Period.

The 104-week Total Treatment Period consists of the 52-week Treatment Period (see Section 1.5.2) and the 52-week Extension Period (see Section 1.5.3). The 52-week Extension Period is defined as the time from the day after the last day of the 40-week Maintenance Period up to the date of the last visit including the SFU visit or last scheduled procedure during the Extension Period.

Similarly to the 52-week Treatment Period Analysis, in the 104-week Total Treatment Period analysis, for participants initially randomized into an active MORF-057 treatment group, the cumulative data during the 104-week Total Treatment Period, including those from the Induction Period and Maintenance Period, will be used. For participants initially randomized into the placebo group during the Induction Period and subsequently switched to an active MORF-057 treatment during the Maintenance and Extension Periods, only the data during the Maintenance and Extension Periods will be included in this analysis to assess the effect of MORF-57 treatment, unless otherwise specified.

1.6. Changes From Planned Analysis in the Protocol

Additional analyses are added in Section 4.8.3.1 and Section 4.8.3.4 for the following variables:

- Symptomatic response and Partial MCS response at Week 12 and Week 52
- Symptomatic remission at Weeks 2, 6, 12 and 52
- Time to symptomatic remission by Week 12

- Change from baseline to Week 12 in the mMCS score
- Clinical remission, clinical response, and Corticosteroid-free remission at Week 104

1.7. Changes From the Previous Version of SAP

Not applicable.

2. DEFINITIONS AND DATA HANDLING CONVENTIONS

2.1. Definition of Baseline

2.1.1. Baseline for Safety Analysis

Induction Period Analysis

For safety variables in the Induction Period Analysis, baseline is defined as the last non-missing assessment prior to the first dose of study drug (MORF-057 or placebo).

52-week Treatment Period Analysis and 104-week Total Treatment Period Analysis

For safety variables in the 52-week Treatment Period Analysis and 104-week Total Treatment Period Analysis, baseline is defined as:

- The last non-missing assessment prior to the first dose of study drug, for participants initially randomized into an active MORF-057 treatment group.
- The last non-missing assessment prior to the first dose of maintenance treatment, for participants initially randomized into the placebo group and subsequently switched to an active MORF-057 treatment during the Maintenance/Extension Period.

2.1.2. Baseline for Efficacy Analysis

Induction Period Analysis

For the efficacy endpoints in the Induction Period Analysis, baseline value is defined as the last non-missing assessment prior to randomization.

52-week Treatment Period Analysis and 104-week Total Treatment Period Analysis

For efficacy variables in the 52-week Treatment Period Analysis and 104-week Total Treatment Period Analysis, baseline is defined as:

- The last non-missing assessment prior to randomization, for participants who are initially randomized into an active MORF-057 treatment group.
- The last non-missing assessment prior to the first dose of maintenance treatment, for participants initially randomized into the placebo group and subsequently switched to an active MORF-057 treatment during the Maintenance/Extension Period.

2.2. Definitions of Study Days

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

The following conventions will be used to calculate study day for reporting purposes:

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

Unless otherwise specified, study days for participants initially randomized into an active MORF-057 treatment group will be calculated relative to the date of the first dose in the Induction Period. However, for participants initially randomized into the placebo group, study days will be calculated separately for the Induction Period, the Maintenance and Extension Treatment Periods. During the Induction Period, study days for this group will be calculated relative to the first dose date of the induction treatment. During the Maintenance and Extension Periods, study days for this group will be calculated relative to the first dose date of the maintenance treatment recorded on the Study Period Transition eCRF page. For participants in this group who have discontinued the study before entering the Maintenance Period, no study days will be calculated for the Maintenance and Extension Period.

2.3. Mapping Rules for Early Treatment Termination and Unscheduled Visits

If a participant discontinued from study drug prematurely, they will be encouraged to complete the end of treatment (EOT) Visit at the time of study drug discontinuation and the Safety Follow-up Visit (visit to occur 4 weeks after the last dose of study drug is received). In the analyses, the efficacy and safety parameters measured at the EOT Visit will be re-allocated according to the following rules:

- If the assessment date for a given parameter at the EOT Visit is closer to the previous scheduled study visit date (the scheduled study visits are the general visits specified in the Schedule of Activities in Section 1.2 of the study protocol) and this parameter is scheduled to be measured at that visit but there is no measurement, the EOT Visit for this parameter will be re-allocated to the previous scheduled study visit. This re-allocation will not apply if the EOT visit falls within the Maintenance Period and the previously scheduled study visit occurs during the Induction Period.
- If the assessment date for a given parameter at the EOT Visit is closer to the next scheduled study visit date and this parameter is scheduled to be measured at that visit but there is no measurement, the EOT Visit for this parameter will be re-allocated to the next scheduled study visit. This re-allocation will not apply if the EOT visit falls within the Induction Period and the next scheduled study visit occurs during the Maintenance Period.
- Otherwise, the EOT visit will remain unassigned to a nominal visit.

The above re-allocation of the EOT Visit will be performed for each efficacy and safety parameter based on its individual scheduled visits in the protocol. Please see Section 1.2 of the study protocol for the scheduled visits for each parameter to be measured.

In addition, any clinical laboratory parameters, vital signs, and ECG measured at the unscheduled visits will be re-allocated according to the same rules above.

2.4. Missing Data

Unless otherwise specified, there will be no substitutions made to accommodate missing data points, and the observed cases, without imputation, will be used for the analyses.

2.4.1. Handing of Partial Dates on UC Diagnosis Dates

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

- If month and year are present but day is missing, then the day will be set to the first day of the month.

- If year is present but not month and day, month and day will be set to January 1st.

2.4.2. Handling of Partial Dates for Adverse Events or Concomitant Medications

When determining the treatment emergent adverse events (TEAEs) or concomitant medications, partial dates will be handled as follows:

Start Dates

- If the year is unknown, then the date will not be imputed and will be assigned a missing value.
- If the month is unknown, then:
  - If the year matches the first dose date year, then impute the month and day of the first dose date.
  - Otherwise, assign 'January.'
- If the day is unknown, then:
  - If the month and year match the first dose date month and year, then impute the day of the first dose date.
  - Otherwise, assign the first day of the month.

Stop Dates

- If the year is unknown, then the date will not be imputed and will be assigned a missing value.
- If the month is unknown, then assign 'December.'
- If the day is unknown, then assign the last day of the month.
- If the imputed date is after end of study date, then end of study date will be used.

2.4.3. Handing of Missing Data in Efficacy Analysis

For analysis of primary and secondary efficacy endpoints and other binary exploratory efficacy endpoints, missing endpoint data will be imputed using a nonresponder imputation (NRI) method, unless otherwise specified. Participants will be considered nonresponders for the NRI analysis if they have missing clinical efficacy data at a time point of interest.

For continuous exploratory efficacy endpoints expressed as change from baseline at Week 12, the primary analysis will use the analysis of covariance (ANCOVA) model for comparing MORF-057 group with the placebo group. Participants who have missing baseline value or the value at Week 12 will be excluded from the analysis. The details are described in Section 4.8.3.

2.5. Coding Dictionary for Adverse Event, Medical History and Medications

All adverse events and medical history will be coded by system organ class (SOC) and preferred term (PT) using the most recent version of Medical Dictionary for Regulation Affairs (MedDRA) available at time of database lock.

The severity of adverse events will be graded by Terminology Criteria for Adverse Events (CTCAE 5.0 or later).

All medications will be coded using the most recent version of World Health Organization Drug Dictionary (WHODD) available at time of database lock.

2.6. Pooling of Study Centers

Unless otherwise specified, data from all study centers will be pooled for analysis.

2.7. Handling Rules for PK Concentration

2.7.1. Below limit of quantification (BLQ)

- BLQ at pre-dose will be set to zero for the calculation of the mean concentration for Visit 2 (Day 1 only). BLQs at pre-dose for all other subsequent dosing days or before the last quantifiable measurement will be imputed as lower limit of quantification (LLOQ).
- Mean concentrations at any individual time point will only be calculated if at least half of the participants have valid values (i.e., quantifiable, and not missing) at this time point.
- In cases where a mean value is not calculated, due to the above criterion not being met, the mean value will be set to missing.

2.7.2. Other Handling Rules

- Previous Evening Dose:
  - For participants who are randomized to Group 1 (200 mg BID for Induction Period and 100 mg BID for Maintenance/Extension Periods) and Group 2 (100 mg BID for both Induction and Maintenance/Extension Periods), if the previous evening dose was not taken, the pre-AM dose PK sample collected at the PK visit (except at visit 2) is considered invalid. However, all post-dosing PK samples remain valid.
- Morning dosing time:
  - If morning dosing time is not reported, then all pre-AM dose and post-dosing PK samples are invalid.
  - If morning dosing time is available, and any post-dose PK samples are collected more than 30 minutes outside the specified timepoint (i.e., PK sample collection time relative to morning dose > 30 mins), then the post-dose PK samples collected at that timepoint are considered invalid. For instance, for PK sample at 1hr after the AM dose, if the actual sample collection time relative to the AM dose is outside the window of 1hr (± 30min), this PK sample will be considered as invalid.
- At Visit 5 (Week 12), if participants deviate from the protocol and start their maintenance treatment before completing the collection of all PK samples, the following rules will be used to handle the PK samples at this visit:
  - For participants randomized to Group 1 (200 mg BID for the Induction Period and 100 mg BID for the Maintenance/Extension Periods), any PK samples collected after the first

maintenance dose will be considered invalid. However, PK samples collected before the first maintenance dose remain valid.

- For participants randomized to Group 2 (100 mg BID for both Induction and Maintenance/Extension Periods) or Group 3 (100 mg QD-M for both Induction and Maintenance/Extension Periods), all PK samples will be considered valid, regardless of whether they are collected before or after the first maintenance dose.

All PK samples considered invalid and PK samples collected at early termination End of Treatment (EOT) visit will not be included in the PK summary but provided in the listings.

2.8. Handling Rules for PD Data

For α4β7 and α4β1 receptor occupancies, and relative CCR9 mRNA expression which are collected at Visit 5 (Week 12),

- If participants are randomized into Group 2 (MORF-057 100 mg B.I.D. – MORF-057 100 mg B.I.D) or Group 3 (MORF-057 100 mg Q.D.-M – MORF-057 100 mg Q.D.-M), all data collected at Visit 5 (Week 12) will be considered as valid and included in the table summary for the Induction Period analysis.
- If participants are randomized to Group 1 (MORF-057 200 mg B.I.D. – MORF-057 100 mg B.I.D.) or Group 4 (Placebo – MORF-057 200 mg Q.D.-E), any data collected after the first maintenance dose will be considered as invalid and not be included in the table summary but provided in the listings.

3. ANALYSIS POPULATIONS AND APPLICATIONS

3.1. Full Analysis Set (FAS)

The Full Analysis Set (FAS) includes all randomized participants who received at least one dose of study drug (MORF-057 or Placebo).

The FAS population will be used as the primary analysis population for all efficacy endpoints. Participants will be analyzed according to the treatment group they were randomized into.

3.2. Per Protocol (PP) Population

The Per Protocol (PP) Population is defined as all participants in the FAS Population who did not have any major protocol deviations related to the primary or secondary efficacy endpoint analyses.

All decisions to exclude participants for the PP Population will be made prior to the unblinding of the study. The PP Population may be used for sensitivity efficacy analyses of, at a minimum, the primary efficacy endpoint.

Participants in the PP population will be analyzed according to the randomized treatment group.

3.3. Safety Population

The Safety Population includes all participants who receive at least one dose of study drug (MORF-057 or Placebo).

The safety analysis population will be used for safety analysis. Participants will be analyzed according to the actual treatment received (see Section 6.2 for details). Randomized participants will be excluded from the safety analysis population only if there is documented evidence that participants have not taken any of study drugs (MORF-057 or placebo).

In addition,

- If a participant randomized to the placebo group receives MORF-057 by mistake during the 12-week Induction Period, his/her data for the Induction Period analysis will be included in the MORF-057 dose group in which he/she was treated for the longest duration.
- If a participant randomized to a MORF-057 dose group receives a different MORF-057 dose by mistake during the 12-week Induction Period, his/her data for the Induction Period analysis will be included in the MORF-057 dose group in which he/she was treated for the longest duration.
- If any participants receive a MORF-057 dose different from the one expected in the protocol by mistake during the Maintenance Period/Maintenance Extension Period, their actual maintenance dose group will be based on the MORF-057 dose in which they were treated with the longest duration.

3.4. Pharmacokinetic (PK) Population

The PK Population includes all randomized participants who received at least one dose of study drug and had at least one measurable PK concentration.

The PK Population will be used for PK data analysis.

3.5. Pharmacodynamic (PD) Population

The PD Population is defined as all randomized participants who received at least one dose of study drug and had at least one measurable post-dose PD measurement and its corresponding pre-dose PD measurement for, at minimum, one of the PD biomarkers.

The PD population will be used for the summarization of PD endpoints.

3.6. Application of Analysis Populations

Participants' demographics, baseline characteristics, UC disease history, study drug exposure and compliance, safety and efficacy endpoints will be summarized for the following populations.

Table 4: Application of Analysis Populations

Type	FAS	Safety Population	PP Population
Demographic and baseline characteristics	X		X
Medical history	X		
UC disease history	X		X
Protocol deviations	X		
Prior and concomitant medications	X		
Extent of treatment exposure and compliance		X	
Primary efficacy endpoint analysis	X		X
Secondary efficacy endpoints analysis	X		X
Exploratory efficacy endpoint analysis	X		
Subgroup analysis for • Primary efficacy endpoints • Secondary efficacy endpoints	X		
Safety Analysis (TEAEs, lab, vital sign, and ECG)		X	

FAS: Full Analysis Set; PP: Per-Protocol.

4. STATISTICAL ANALYSIS

All analyses described in this plan are considered as a prior analysis in that they have been defined prior to database lock. Any additional analysis performed after database lock will be considered as post hoc analysis and may be described as exploratory analyses in the clinical study report (CSR) as needed.

All summaries and statistical analyses will be performed using SAS v9.4 or later.

Continuous variables will be summarized with number of participants (n), mean, standard deviation (SD), median, first quantile (Q1), third quantile (Q3), minimum (min) and maximum (max). In addition, coefficient of variation (CV%) and geometric mean with CV% will be reported for summary of serum concentration and PD parameters.

Unless otherwise specified, mean, geometric mean, median, Q1 and Q3 will be reported to one more decimal than the raw data. The standard deviation (SD) will be reported to two more decimals than the raw data. CV% will be reported to 1 decimal and min and max will be reported as raw data. The confidence interval will be reported using the same number of decimals as the raw data.

Categorical variables will be tabulated by number of participants (n) with percentage (%) of the total number of participants for a given category of the analysis population. Participants with missing data are not included in calculations of percentages, except in the primary analyses of binary efficacy variables using the NRI method as specified in Section 4.8, or unless otherwise specified. Percentage will be reported to one decimal place. The confidence interval (CI) for the proportion will be calculated using the normal approximation approach when reported, unless otherwise specified.

Unless otherwise specified, the data for the Induction Period Analysis (see Section 1.5.1) will be presented by MORF-057 dose groups during the Induction Period and placebo, i.e.,

- 200 mg B.I.D.
- 100 mg B.I.D.
- 100 mg Q.D.-M
- Placebo

For the 52-week Treatment Period Analysis (see Section 1.5.2), the cumulative data, including the data from both the Induction and Maintenance Periods, will be used for participants initially randomized into an active MORF-057 treatment group and presented by treatment groups denoted by induction MORF-057 dose followed by maintenance MORF-057 dose, i.e.,

- 200 mg B.I.D. - 100 mg B.I.D.
- 100 mg B.I.D. – 100 mg B.I.D
- 100 mg Q.D.-M – 100 mg Q.D.-M.

For participants initially randomized into the placebo group during the Induction Period and subsequently switched to MORF-057 treatment (i.e., 200 mg Q.D.-E) during the Maintenance Period, unless otherwise specified, only the data collected during the Maintenance Period will be used in the 52-week Treatment Period Analysis to evaluate the effect of MORF-057 200 mg Q.D.-E. The data will be presented in the treatment group denoted by 200 mg Q.D.-E.

The data for the 104-week Total Treatment Period Analysis (see Section 1.5.3) will be presented by treatment groups similar to the 52-week Treatment Period Analysis described above, unless otherwise specified. All data during the 104-week Total Treatment Period will be used in the analysis for participants initially randomized to an active MORF-057 treatment group, and only the data during the Maintenance and Extension Periods will be used for participants initially randomized to placebo and subsequently switched to MORF-057 for maintenance treatment.

Unless otherwise specified, only scheduled visits including re-allocated visits (EOT or unscheduled visits, as described in Section 2.3) will be included in all by-visit analyses of efficacy and safety data. For the group of participants initially randomized to placebo and subsequently switched to MORF-057 for maintenance treatment, only the visits after Visit 5 (week 12) will be included in the by-visit analyses for the 52-week Treatment Period Analysis and the 104-week Total Treatment Period Analysis.

Data that are not summarized will be listed only. All data will be listed as collected for all randomized participants and will be ordered by randomized treatment group and visit if applicable.

4.1. Participants' Disposition

Participants' disposition will be summarized by the number and percentage for the following categories:

- Participants screened
- Screen failures
- Participants randomized
- Completed the 12-week Induction Period
- Discontinued the treatment during the 12-week Induction Period and reasons for treatment discontinuation
- Completed the 52-week Treatment Period (Induction Period plus Maintenance Period)
- Discontinued the treatment during the 52-week Treatment Period and reasons for treatment discontinuation.
- Discontinued the treatment during the 40-week Maintenance Period and reasons for treatment discontinuation.
- Discontinued the main part of study and reasons for study discontinuation
- Completed the 52-week Treatment Period but not enrolled into the Maintenance Extension Period.
- Enrolled into the Maintenance Extension Period
  - Completed the Maintenance Extension Treatment
  - Discontinued the treatment during the Maintenance Extension Period and reasons for treatment discontinuation
  - Completed the Maintenance Extension Period
  - Discontinued study during Maintenance Extension Period and reasons for study discontinuation

- Discontinued the treatment during main part of study or Maintenance Extension Period and reasons for treatment discontinuation
- Discontinued study during main part of study or Maintenance Extension Period and reasons for study discontinuation

For the screened and screen failure, percentages will be calculated using the number of screened participants as the denominator. For all other categories of participants, data will be presented by randomized treatment group, with percentages calculated using the number of randomized participants within each treatment group as the denominator unless otherwise specified. Reasons for screen failures will be summarized. A separate listing of screen failures will also be provided.

Completion of study treatment period is defined as follows:

- A participant is considered to have completed 12-week induction Period if they have completed the Visit 5 (Week 12). If a participant attends Visit 5 (Week 12) but decides to discontinue the treatment, making Visit 5 (Week 12) the EOT visit, they will still be considered to have completed the 12-week Induction Period if they have been on the treatment for at least 84 days.
- A participant is considered to have completed 52-Week Treatment Period if their treatment status is completed treatment reported on EOT eCRF page for the main part of the study.
- A participant is considered to have completed Maintenance Extension Treatment Period if their treatment status is completed treatment reported on EOT eCRF page for Extension Period.

In addition, the number and percentage of participants in each analysis population, including FAS, PP population, safety population, PK population, and PD population, will be summarized in a table by number of participants based on the randomized population.

4.2. Demographic and Baseline Characteristics

The participants' demographic and baseline characteristics will be summarized by treatment group and overall for FAS including:

- Age at screening (years), calculated as integer of (informed consent date – birthdate)/365.25 if not reported
- Age category (< 65, ≥ 65)
- Sex
- Ethnicity
- Race
- Height at baseline (cm)
- Weight at baseline (kg)
- Body mass index (BMI) (kg/m^2)
- Country

- Substance use
  - Tobacco use
  - Alcohol use

The demographic and baseline characteristics will also be summarized by treatment group and overall for the following subgroups:

- Prior use of advanced therapy treatment (naïve vs experienced)
- Baseline MES score (<3 or 3)
- Baseline mMCS score (≤ 7 or > 7)

4.3. Baseline Ulcerative Colitis Disease History

The participants' baseline ulcerative colitis (UC) disease history will be summarized by randomized treatment group and overall for FAS including:

- Age at UC diagnosis (years) calculated as (year of UC diagnosis – year of birthday).
- Years since UC diagnosis, calculated as integer of (informed consent date – UC initial diagnosis date)/365.25 (see Section 2.4.1 for partial date handling rules).
- Previous use of advanced therapy for UC (naïve vs experienced)
  - Advanced therapies for UC will be identified using the following approach: First, a preliminary search will be conducted using Anatomical Therapeutic Chemical (ATC) level 4 codes, including L04AA, L04AB, L04AC, L04AE, L04AF, and L03AX. Two clinicians will then independently perform a thorough, blinded manual review of all prior UC medications, including those identified in the preliminary search, to identify the advanced therapies. Special attention will be given to the drugs lacking ATC level 4 codes, such as investigational drugs. Any discrepancies between the two clinicians will be resolved through reconciliation. The final list of advanced therapies for UC will be determined during the blinded data review and documented before the database lock and unblinding of treatment. Participants who previously received blinded treatment in an advanced therapy trial will be considered as advanced therapy-experienced.
- Number of advanced therapies for UC disease by category (1, 2, ≥3)
- Corticosteroid use at baseline (yes/no)
  - Corticosteroids for UC will be identified using the following approach: First, a preliminary search will be conducted using ATC level 4 codes, including A07EA, A01AC, and H02AB. Two clinicians will then independently perform a thorough, blinded manual review of all prior medications, including those identified in the preliminary search, to identify corticosteroid use for UC. Any discrepancies between the two clinicians will be resolved through reconciliation. The final list of corticosteroids for UC will be determined during the blinded data review and documented before the database lock and unblinding of treatment.
- Corticosteroid dose used at baseline

- Immunomodulator use at baseline
  - Immunomodulators will be identified by searching ATC level 4 codes, including L04AX and L01BB, along with thorough blinded manual review of medications by the clinical team. All immunomodulators will be determined during blinded data review and documented before the database lock and unblinding of treatment.
- Central modified Mayo Clinical Score (mMCS) at baseline
- Central modified Mayo Clinical Score (mMCS) at baseline by category
  - mMCS <= 7
  - mMCS > 7
- Central Full Mayo Clinical Score (MCS) at baseline
- Partial MCS at baseline
- Mayo component scores at baseline
  - Stool frequency (see Section 6.1 for calculation)
  - Rectal bleeding (see Section 6.1 for calculation)
  - Physician's global assessment
  - Central endoscopy subscore
- RHI Score at baseline
- Family history of UC (yes/no)
- Family history of Crohn's Disease (yes/no)
- Previously been in remission from UC (yes/no)
- Extent of disease (cm) and by category
  - Proctosigmoiditis: 0 <= Extent of Disease <=30
  - Left sided colitis: 30 < Extent of Disease <=50
  - Extensive colitis: Extent of Disease > 50

The baseline UC disease history will also be summarized by treatment group and overall for the following subgroups:

- Prior use of advanced therapy treatment (naïve vs experienced)
- Baseline MES score (<3 or 3)
- Baseline mMCS score (≤ 7 or > 7)

4.4. Medical History

Medical history will be coded by system organ class (SOC) and preferred term (PT) using the most recent version of Medical Dictionary for Regulation Affairs (MedDRA) available at time of database lock.

The number and percentage of participants experiencing any medical history will be tabulated by SOC and PT by randomized treatment group and overall for Full Analysis Population.

If a SOC or PT is reported more than once for a participant, the participant will be counted only once for that term.

4.5. Prior and Concomitant Medications

All medications will be coded using Anatomical Therapeutic Chemical (ATC) classification based on the most recent version of the World Health Organization Drug Dictionary (WHO-DD) available at time of database lock.

Prior medications are defined as any medications that start prior to the first dose of study drug (MORF-057 or placebo).

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

The number and percentage of participants who have taken prior medications for UC disease, general prior medications excluding medications for UC disease or concomitant medications will be summarized by ATC level 4 and preferred term for each randomized treatment group and overall for FAS. A participant will be counted only once for the medications taken more than once.

Concomitant medications will be summarized for the Induction Period, the 52-week Treatment Period, and the 104-week Total Treatment Period.

The summary of concomitant medications for the Induction Period will only include concomitant medications that occurred on or before the last dose of induction period treatment.

The summary of concomitant medications for the 52-week Treatment Period will include the concomitant medications taken during the 52-week Treatment Period for participants initially randomized into an active MORF-057 treatment group and include only the concomitant medications taken during the Maintenance Period for participants initially randomized into the placebo group and subsequential switched to the MORF-057 treatment during the Maintenance Period.

The summary of concomitant medications for the 104-week Total Treatment Period will include the concomitant medications taken during the 104-week Total Treatment Period for participants initially randomized into an active MORF-057 treatment group, and include only the concomitant medications taken during the Maintenance and Extension Periods for participants initially randomized into the placebo group and subsequential switched to the MORF-057 treatment during the Maintenance and Extension Periods.

Concomitant medications for the Maintenance Period will include the concomitant medications taken during the Maintenance Period, as well as the concomitant medications starting before the Maintenance Period and continuing through the first day of the Maintenance Period or missing stopping date. Concomitant medications for the Extension Period will include the concomitant medications taken during the Extension Period, as well as the concomitant medications starting before the Extension Period and continuing through the first day of the Extension Period or missing stopping date. If the last dose date of induction treatment and the first dose date of maintenance treatment occurs on the same day and

a concomitant medication stops on that day, this medication will be considered as the concomitant medication for the Induction Period but not for the Maintenance Period.

4.6. Extent of Treatment Exposure and Compliance

The treatment exposure and compliance will be summarized separately for following treatment periods using Safety Population:

- 12-week Induction Period
- 52-week Treatment Period
- 104-week Total Treatment Period

4.6.1. Treatment Exposure

The extent of treatment exposure will be assessed by the duration of treatment exposure, which will be defined as the total number of days a participant is exposed to any study drug during the treatment period, regardless of unplanned intermittent discontinuations.

4.6.1.1. Treatment Exposure for the Induction Treatment Period

For the 12-week Induction Period, the duration of treatment exposure will be summarized by actual treatment groups (200 mg B.I.D., 100 mg B.I.D., 100 mg Q.D.-M, and Placebo) and calculated as:

- Days = last dose date of Induction Treatment – first dose date of induction treatment + 1

For the 12-Week Induction Period, the last dose date will be the Induction Period Last Dose Date recorded on the Study Period Transition eCRF page, or the last dose date as recorded on the EOT eCRF page for the main part of the study if the participant has discontinued the treatment prematurely before entering the Maintenance Period.

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

- 1 to 42 days
- 43 to 84 days
- > 84 days

4.6.1.2. Treatment Exposure for the 52-week Treatment Period

For participants who are randomized to an active MORF-057 treatment group (Group1, Group 2 and Group 3 in Table 3) and have received at least one dose of MORF-057, the cumulative treatment exposure to MORF 057 during the 52-week Treatment Period, including the exposure during the Induction Period, will be summarized by treatment groups based on the actual MORF-057 dose received during the induction period. The duration of treatment exposure for 52-week Treatment Period will be calculated as:

- Days = last dose date on 52-week Treatment – first dose date of induction treatment + 1

The last dose date on 52-week Treatment will be the date of last treatment recorded on the EOT eCRF page for the main part of the study (i.e., 52-week Treatment Period).

For participants who are initially randomized into the placebo group and subsequently switched to MORF-057 200 mg Q.D. -E for maintenance treatment, the summary of treatment exposure for the 52-week Treatment Period will include only the exposure to MORF-057 during the Maintenance Period. The duration of exposure will be based on the number of days they received MORF-057 during the Maintenance Period, which will be calculated as:

- Days = last dose date on 52-week Treatment – first dose date of maintenance treatment + 1

The last dose date on 52-week Treatment will be the date of last treatment recorded on the EOT eCRF page for the main part of the study. The first dose date of maintenance treatment will be the Maintenance Period First Dose date recorded on the Study Period Transition eCRF page.

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

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

4.6.1.3. Treatment Exposure for the 104-week Total Treatment Period

The treatment exposure over the 104-week Total Treatment Period will be summarized similarly to the summaries for 52-week Treatment Period described in Section 4.6.1.2.

For participants who are initially randomized into an active MORF-057 treatment group and have received MORF-057 during the Induction Period, the cumulative treatment exposure to MORF 057 during Total Treatment Period, including the exposure during the Induction Period, will be summarized, and the duration of treatment exposure for the Total Treatment Period will be calculated as

- Days = last dose date on Extension Period – first dose date of Induction Treatment + 1

Where the last dose date on Extension Period will be the date of last treatment recorded on the EOT eCRF page for Extension Period.

For participants initially randomized to the placebo group and subsequently switched to MORF-057 200 mg Q.D. -E for maintenance treatment, the summary of treatment exposure for the Total Treatment Period will include only the exposure to MORF-057 during the Maintenance and Extension Periods. The duration of exposure will be based on the number of days they received MORF-057 during the Maintenance and Extension Periods, which will be calculated as:

- Days = last dose date on Extension Period – first dose date of maintenance treatment + 1

The last dose date on Extension Period will be the date of last treatment recorded on the EOT eCRF page for the Extension Period. The first dose date of maintenance treatment will be the Maintenance Period First Dose date recorded on the Study Period Transition eCRF page.

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

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

4.6.2. Compliance

Compliance is calculated using the formula below.

- Compliance rate (%) = (Total number of capsules consumed)/(Total number of capsules expected) x100%

The total number of capsules expected is calculated as duration of treatment (days) x number of expected capsules per day.

4.6.2.1. Overall Compliance

Overall compliance is calculated based on the number of capsules consumed and expected, regardless of whether the capsules contain MORF-057 or placebo. Each participant is expected to take 4 capsules per day (2 capsules in the morning and 2 capsules in the evening) during the Induction Period and 3 capsules per day (1 capsule in the morning and 2 capsules in the evening) during the Maintenance Period/Maintenance Extension Period.

4.6.2.2. Compliance with MORF-057

For participants initially randomized into an active MORF-057 treatment group (i.e., Group1, Group 2, and Group 3 in Table 3), the compliance with MORF-057 will be calculated based on the number of capsules of MORF-057 consumed and expected.

For participants initially randomized to placebo for induction treatment and subsequently switched to MORF-057 200 mg Q.D. -E for maintenance treatment(i.e., Group 4 in Table 3), the compliance with MORF-057 will be calculated only for the Maintenance Period/Maintenance Extension Period based on the number of capsules of MORF-057 consumed and expected when they switched their study drug to MORF057.

In this study, MORF-057 was administered in the form of 100 mg capsules. The numbers of capsules of MORF-057 expected per day for each treatment group are listed in Table 5 below.

Table 5: Number of Capsules of MORF-057 Expected per Day

Treatment Groups	12-Week Induction Period		Maintenance (40 weeks) and Optional Extension Period (52 weeks)	
	Dosage	Number of MORF-057 Capsules Expected per Day	Dosage	Number of MORF-057 Capsules Expected per Day
Group 1	200 mg B.I.D.	4	100 mg B.I.D.	2
Group 2	100 mg B.I.D.	2	100 mg B.I.D.	2
Group 3	100 mg Q.D. -M	1	100 mg Q.D. -M	1
Group 4	Placebo	0	200 mg Q.D. -E	2

B.I.D.: twice a day; Q.D.-E: once a day (evening); Q.D.-M: once a day (morning).

If the last dose date of induction treatment and the first dose date of maintenance treatment occurs on the same day, the number of capsules of MORF-057 expected on that day will be based on the number of capsules expected for the induction treatment in the morning and the number of capsules expected for the maintenance treatment in the evening. according to treatment group assignment.

4.6.2.3. Summary of Compliance

Compliance will be summarized separately for the 12-week Induction Period, the 52-week Treatment Period, and the 104-week Total Treatment Period, similarly to the summaries for treatment exposure as described in Section 4.6.1.

The compliance rate will be summarized using continuous descriptive statistics and summarized categorically by counts and percentage for each of the following categories:

- < 50%
- 50-59%
- 60-69%
- 70- 79%
- 80-100%
- >100%
- < 80%
- >120%

4.7. Protocol Deviations

All protocol deviations will be reviewed, assessed, and finalized prior to database lock. Classification of deviations as major or minor protocol deviations, and decisions regarding exclusion of participants and/or participants' data from the statistical analyses, will be decided before the database lock.

The number and percentage of participants with major deviations will be summarized by type of deviations based on FAS for the 12-week Induction Period, the 52-week Treatment Period, and the 104-week Total Treatment Period, as defined in Section 1.5.

Any major protocol deviations occurred up to Visit 5 (Week 12) will be included in the summary for the 12-week Induction Period.

4.8. Efficacy Analysis

Unless otherwise specified, all efficacy endpoints will be analyzed based on the FAS.

In the analyses stratified by the randomization stratification factors (baseline MES [<3 vs 3] and previous use of advanced therapy treatment [advanced therapy-naïve vs advanced therapy-experienced]), any participant who was randomized under the wrong stratum by mistakes will be analyzed according to the actual stratum the participant belongs to, unless otherwise specified.

The 12-week Induction Period Analysis will include the primary efficacy endpoint, secondary efficacy endpoint, and all exploratory efficacy endpoint defined by Week 12, comparing MORF-057 versus placebo. As specified in Section 1.5, if participants start their maintenance treatment before completing the efficacy assessment at Visit 5 (Week 12) due to a protocol deviation, the efficacy data collected at Visit 5 (Week 12) will still be included in the analyses for the 12-week Induction Period, even if they are measured after the participants start their maintenance dose..

The 52-week Treatment Period Analysis will include all exploratory efficacy endpoints defined at Week 52, and the 104-week Total Treatment Period Analysis will include all exploratory efficacy endpoints defined at Week 104. All those exploratory endpoints will be summarized descriptively by treatment groups.

In the analyses for the 52-week Treatment Period and the 104-week Total Treatment Period, for participants randomized to the treatment group with placebo as the induction treatment and MORF-057 200 mg Q.D.-E as the maintenance treatment, they will be presented in the treatment group denoted by 200mg Q.D.-E. Summaries for this group will be based on the participants randomized to the placebo group during the Induction Period who have subsequently continued to the Maintenance Period. The denominator for calculating the proportions for this group will be the number of participants continuing to the Maintenance Period, unless otherwise specified. In all by-visit summaries and plots, only visits after Visit 5 (Week 12) will be presented for this group.

4.8.1. Primary Efficacy Endpoint Analysis

The primary efficacy endpoint is proportion of participants in clinical remission at Week 12 as determined by mMCS: rectal bleeding subscore of 0; a stool frequency subscore of ≤1; and an MES of ≤1 without friability.

The calculation of rectal bleeding subscore and stool frequency subscore is described in Section 6.1.

The statistical hypotheses for the primary efficacy endpoint are:

- Null hypothesis (H0): The proportion of participants in clinical remission at Week 12 is the same between the MORF-057 and placebo groups.
- Alternative hypothesis (Ha): The proportion of participants in clinical remission at Week 12 is different between the MORF-057 and placebo groups.

4.8.1.1. Primary Efficacy Analysis

The clinical remission rate at Week 12 will be analyzed for FAS using a two-sided Cochran-Mantel-Haenszel (CMH) test at 10% level of significance, stratified by randomization stratification factors (baseline MES [<3 vs 3] and previous use of advanced therapy treatment [advanced therapy-naïve vs advanced therapy-experienced]), for comparison of each MORF-057 dose group with the placebo group. The p-values will be provided. The point estimates of risk difference between groups with both 95% and 90% confidence intervals (CIs) will also be computed based on the stratified risk difference using the Cochran-Mantel-Haenszel (CMH) weights (see the method in Section 6.5). All participants with missing data for determination of endpoint status will be considered as a nonresponder by using the NRI method.

The study will be considered as a success if at least one MORF-057 dose achieves the statistical significance at the specified significant level after the multiplicity adjustment as specified in Section 4.8.6.

4.8.1.2. Sensitivity Analysis for Primary Efficacy Endpoint

The following sensitivity analyses will be performed:

- Repeat the primary efficacy analysis as described in Section 4.8.1.1 based on the PP Population.
- Compare the combined MORF-057 200 BID and 100 BID dose group with the placebo group based on the FAS.

Furthermore, if there is any discrepancy between the randomization stratum reported in the IRT and the actual stratum the participant belongs to, a sensitivity analysis for the primary endpoint will be performed using CMH method stratified by the randomization stratum reported in the IRT based on the FAS. Any discrepancies between the randomization stratum reported in IRT and the actual stratum will be summarized.

A summary of proportion of clinical remitters with stool frequency subscore 0 as well as 1 will be provided based on the FAS.

4.8.2. Secondary Efficacy Endpoint Analysis

The secondary endpoint for this study is the proportion of participants with clinical response at Week 12 as determined using the mMCS: decrease from baseline in the mMCS ≥2 points and ≥30% from baseline, plus a decrease in rectal bleeding subscore ≥1 or an absolute rectal bleeding subscore ≤1.

The clinical response rate will be analyzed based on FAS using CMH method stratified by randomization stratification factors (baseline MES [<3 vs 3] and previous use of advanced therapy treatment [advanced therapy-naïve vs advanced therapy-experienced]) for comparison of each MORF-057 dose group with the placebo group, similar to the primary analysis performed for the primary endpoint. The p values will be provided. The point estimates of risk difference between groups, along with both 90% and 95% CIs will be computed based on the stratified risk difference using the Cochran-Mantel-Haenszel (CMH) weights. All participants with missing data for determination of endpoint status will be considered as a non responder in the analysis by using the NRI method.

Sensitivity analysis will be performed by repeating the secondary efficacy analysis using the PP Population. Additionally, another sensitivity analysis will compare the combined MORF-057 200 BID and 100 BID dose groups with the placebo group for FAS.

Furthermore, if there is any discrepancy between the randomization stratum reported in the IRT and the actual stratum the participant belongs to, a sensitivity analysis for the secondary endpoint will be performed using CMH method stratified by the randomization stratum reported in the IRT based on FAS.

4.8.3. Exploratory Efficacy Endpoints Analysis

All exploratory efficacy endpoints will be summarized using the FAS, unless otherwise specified.

4.8.3.1. Proportion-Based Exploratory Efficacy Endpoints

The proportion-based exploratory efficacy endpoints are listed in Table 6 (see the definitions of endpoints in Table 2 and the details of efficacy assessments in Section 6.3).

Table 6: Proportion-Based Exploratory Efficacy Endpoints

Rate	Week2	Week 6	Week 12	Week 52	Week 104
Clinical remission				X	
Clinical response				X	
MCS remission			X	X	
MCS response			X	X	
Histologic remission by RHI			X	X	X
Histologic remission by NI			X	X	X
Histologic remission by Continuous Geboes			X	X	X
Histologic improvement by RHI			X	X	X
Endoscopic improvement			X	X	X
Endoscopic remission			X	X	X
Mucosal healing (endoscopic remission and histologic remission as determined using the RHI)			X	X	X
Mucosal improvement (endoscopic improvement and histologic improvement as determined using the RHI)			X	X	X
Symptomatic response	X	X			
Partial MCS response		X			
Corticosteroid-free remission				X	
Need for UC-related hospitalizations and surgeries			X	X	

Induction Period Analysis

The proportion-based exploratory endpoints (see for definition in Table 2) at Week 12, as outlined in Table 6, will be included in the Induction Period Analysis and analyzed using CMH method stratified by randomization stratification factors for comparison of each MORF-057 dose group with the placebo group, similar to the primary efficacy analysis as described in Section 4.8.1.1. The p-value will be calculated for exploratory use. The point estimates of risk difference between MORF-057 and placebo groups with 95% CI will be computed based on the stratified risk difference using the Cochran-Mantel-Haenszel (CMH) weights. All participants with missing data for determination of endpoint status will be considered as a non responder in the analysis by using the NRI method. Additionally, all these exploratory endpoints will also be summarized with the proportions and 95% CI for each treatment group by previous use of advanced therapy for UC (naïve vs experienced), by baseline MES score (<3 vs 3), and by baseline mMCS score (≤ 7 or > 7).

The proportion of participants with symptomatic response and the proportion of participants with partial MCS response will be summarized by treatment groups at each scheduled visit up to Week 12 inclusive, along with the 95% CI. The point estimates of risk difference between MORF-057 and placebo groups with 95% CI will be computed based on the stratified risk difference using the Cochran-Mantel-Haenszel (CMH) weights. The summaries will use the following two approaches:

- All randomized: at each visit, proportions for each treatment group will be calculated using the total number of participants in the FAS within that group as the denominator, and participants with missing data will be considered as non-responders by using the NRI method. The calculations will include the re-allocated EOT visits (See the re-allocation approach in Section 2.3) at that visit.
- As observed: at each visit, the denominator for calculating the proportions will be the number of participants with non-missing assessment at that visit, without including the re-allocated EOT visits and without using the NRI method.

In addition, the proportion of participants with symptomatic response and partial MCS response will also be summarized by treatment groups at each scheduled visit up to Week 12, along with the 95% CI, using the above two approaches for the following subgroups:

- Prior use of advanced therapy treatment (naïve vs experienced)
- Baseline MES score (<3 vs 3)

Line plots showing the proportion (± 95% CI) at each of the scheduled visits will be provided for each treatment group, both for the overall population and for the above subgroups.

52-week Treatment Period Analysis and 104-week Total Treatment Period Analysis

All proportion-based exploratory efficacy endpoints at Week 52 and Week 104, as outlined in Table 6, will be summarized descriptively by treatment groups. The proportions, along with their corresponding 95% CIs, will be provided for the overall population, by previous use of advanced therapy for UC (naïve vs experienced), by baseline MES score (<3 vs 3), and by baseline mMCS score (≤ 7 or > 7). The denominator for calculating the proportions for each treatment group will be the total number of participants in the FAS within that group, except for the group initially randomized to placebo, which will use the total number of participants continuing to the Maintenance Period as the denominator.

In addition, the proportion of participants with symptomatic response and the proportion of participants with partial MCS response, along with the 95%CI, will be summarized by treatment groups at each

scheduled visit up to Week 52 in the 52-week Treatment Period Analysis and up to Week 104 in the 104-week Total Treatment Period Analysis. The summaries will use the following two approaches:

- All randomized: at each visit, proportions for each treatment group will be calculated using the total number of participants in the FAS within that group as the denominator, except for the group initially randomized to placebo, which will use the number of participants continuing to the Maintenance Period as the denominator. Participants with missing data will be considered as non-responders by using the NRI method. The calculations will include the re-allocated EOT visits (See the re-allocation approach in Section 2.3) at that visit.
- As observed: at each visit, the denominator for calculating the proportions will be the number of participants with non-missing assessment at that visit, without including the re-allocated EOT visits and without using the NRI method.

The above summaries for proportions of participants with symptomatic response and partial MCS response will also be provided for the subgroups by previous use of advanced therapy for UC (naïve vs experienced), and by baseline MES score (<3 vs 3), in both 52-week Treatment Period Analysis and 104-week Total Treatment Period Analysis. Line plots showing the proportion (± 95% CI) at each of the scheduled visits will be provided for each treatment group, both for the overall population and for the subgroups.

4.8.3.2. Continuous Exploratory Efficacy Endpoints

Induction Period Analysis

All the continuous exploratory efficacy endpoints expressed as change from baseline at Week 12 as defined in Section 1.1, including hs-CRP, fecal calprotectin, and IBDQ Score, will be included in the Induction Period Analysis and analyzed in the FAS using an analysis of covariance (ANCOVA) model with treatment and randomization stratification factors as factors and baseline values as a covariate. Any participant who was randomized under the wrong stratum by mistakes will be analyzed according to the actual stratum the participant belongs to. The least-squares means and standard errors with 95% CIs for both changes from baseline in each treatment group and differences between MORF-057 and placebo groups will be provided. P-values will also be calculated for the exploratory use. Participants who do not have the baseline value or the value at Week 12 will be excluded from the analysis.

Additionally, line plots showing mean values (± SE) at baseline and each of the scheduled visits up to Week 12 visit will be presented by treatment groups.

52-week Treatment Period Analysis

For the continuous exploratory efficacy variables, including hs-CRP, fecal calprotectin, and IBDQ Score, summary statistics for baseline value, observed values and changes from baseline at scheduled visits including re-allocated EOT visits (see Section 2.3) up to Week 52 visit will be provided for each treatment group.

Line plots showing mean values (± SE) and mean changes from baseline (±SE) at each of the scheduled visits up to Week 52 visit will also be presented by treatment groups.

4.8.3.3. Time to Events Exploratory Efficacy Endpoint

Time to symptomatic response (see Table 2 for definition) by Week 12 will be analyzed using Cox regression model stratified by randomization stratification factors.

Time to symptomatic response is calculated as the number of days from the randomization date to the earliest visit date recorded in the eCRF page when a participant achieved symptomatic response.

If a participant didn't achieve symptomatic response at any visits by week 12 visit, he/she will be censored as follows:

- Censored at the reference date for calculating stool frequency and rectal bleeding subscores at Week 12 visit (see the determination of reference date in Section 6.1) if he/she completed the 12-week Induction Period.
- Censored at the reference date for calculating stool frequency and rectal bleeding subscores at the last visit (include EOT visit but exclude safety follow-up visit) (see the determination of reference date in Section 6.1) if he/she discontinued treatment during the Induction Treatment period.

The hazard ratios for MORF-057 versus placebo will be provided along with the 95% CIs. The Kaplan-Meier plot will be provided.

4.8.3.4. Additional Exploratory Efficacy Analysis

Additional exploratory analysis will be performed for change from baseline to Week 12 in the mMCS score by using an analysis of covariance (ANCOVA) model with treatment and randomization stratification factors as factors and baseline values as a covariate. Any participant who was randomized under the wrong stratum by mistakes will be analyzed according to the actual stratum the participant belongs to. The least-squares means and standard errors with 95% CIs for both changes from baseline in each treatment group and differences between MORF-057 and placebo groups will be provided. P-values will also be calculated for the exploratory use. Participants who do not have the baseline value or the value at Week 12 will be excluded from the analysis. The change from baseline to Week 12 in the mMCS score will also be summarized descriptively for each treatment group by previous use of advanced therapy for UC (naïve vs experienced), by baseline MES score (<3 vs 3), and by baseline mMCS score (≤ 7 or > 7).

Summary statistics (mean and SD) for baseline value, observed values and changes from baseline at scheduled visits including re-allocated EOT visit (see Section 2.3) will be provided by treatment groups for the following additional continuous exploratory variables on observed cases:

- Stool frequency subscore
- Rectal bleeding subscore
- Partial mMCS

The summaries will be provided both for the overall population and for the subgroups by previous use of advanced therapy for UC (naïve vs experienced) and by baseline MES score (<3 vs 3). The summaries will be provided at each scheduled visit up to Week 12 visit in the Induction Period Analysis, up to Week 52 visit in the 52-week Treatment Period Analysis, and up to Week 104 visit in the 104-week Total Treatment Period Analysis. Line plots showing mean values (± SE) and mean changes from baseline (±SE) at each of the scheduled visits will also be presented by treatment groups, both for the overall population and for the subgroups.

For the histologic variables, i.e., RHI, NI, and continuous Geboes score, descriptive summaries will also be provided by treatment groups for change from baseline at Week 12 in the Induction Period Analysis,

for change from baseline at Week 52 in the 52-week Treatment Period Analysis, and for change from baseline at Week 104 in the 104-week Total Treatment Period Analysis.

Additionally, the proportion and 95% CI will be provided by treatment groups for participants with clinical remission, clinical response, and Corticosteroid-free remission at Week 104.

Symptomatic remission, which is defined as stool frequency subscore = 0 (or = 1 with ≥ 1 point decrease from baseline) and rectal bleeding subscore = 0, will be summarized in the same manner as symptomatic response, as described in Section 4.8.3.1.

4.8.4. Subgroup Analysis for Primary and Secondary Efficacy Endpoints

Subgroup analyses for the primary and secondary efficacy endpoints will be performed for the following baseline factors based on FAS:

- Age (< 65, ≥65)
- Sex (male, female)
- Race (white, non-white)
- Prior use of advanced therapy treatment (naïve vs experienced)
- Baseline MES score (<3 or 3)
- Baseline mMCS score (≤ 7 or > 7)
- Corticosteroid use at baseline (yes/no)
- Immunomodulator use at baseline (yes/no)

The point estimates of risk difference between MORF-057 and placebo groups with 95% CIs will be computed across the subgroups defined for each of the above factors. The computation will be based on the stratified risk difference using the Cochran-Mantel-Haenszel (CMH) weights, following a similar approach as used for the primary and secondary efficacy endpoints in the overall population. The stratification factors include baseline MES (<3 vs 3) and previous use of advanced therapy treatment (naïve vs experienced). In the case that the subgroup factor is identical or similar to a stratification factor (e.g., baseline MES score, and Prior use of advanced therapy treatment), only the stratification factor distinct from the subgroup factor will be used in the calculations.

Forest plots will be provided for subgroup analysis.

4.8.5. Estimands and Intercurrent Events

The estimand corresponding to the primary efficacy endpoint evaluated the difference in the proportion of subjects in clinical remission at Week 12 for each MORF-057 dose versus placebo in the FAS population. For the intercurrent events of premature treatment discontinuation, participants were considered non-responders by using the NRI method. Other binary multiplicity-controlled efficacy endpoints used the same estimand as the primary endpoint.

4.8.6. Multiplicity Adjustments

All statistical inference will be 2 sided at a 0.1 level of significance. To control the overall Type I error rate, a hierarchical testing approach as illustrated in Figure 2 will be applied to the statistical testing of

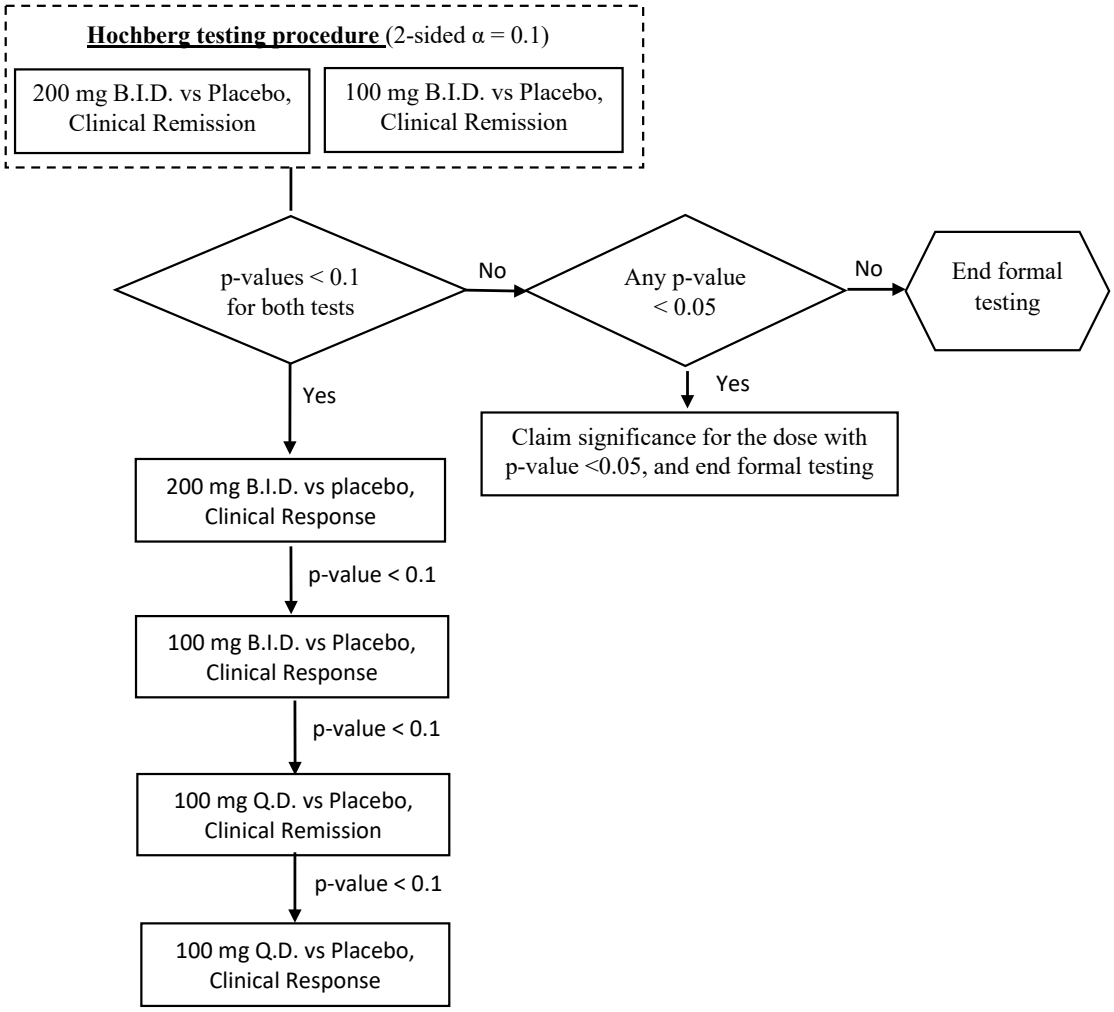
the primary and secondary endpoints for comparisons of each MORF 057 dose group with the placebo group.

First, for the primary efficacy endpoint of clinical remission at Week 12, the Hochberg method will be applied to the comparisons of 200 mg B.I.D. with placebo and 100 mg B.I.D. with placebo. If both p values are <0.1, both doses will be declared significant. If one of the p values is ≥ 0.1, the other p value will be tested at a 0.05 significance level and the corresponding dose will be declared significant only if the p value is <0.05. If both p values are ≥0.1, no dose will be declared significant, and no further formal testing will be performed.

If both 200 mg B.I.D. and 100 mg B.I.D. achieved the statistical significance for the primary efficacy endpoint, the fixed sequence method will be used to test the comparison of 100 mg Q.D. with placebo for the primary efficacy endpoint and the comparison of each dose with placebo for the secondary efficacy endpoint of clinical response at Week 12 in a predefined order as specified in Figure 2 below. All tests will be performed at the same significance level alpha=0.1, with the moving to a second test only after a success, i.e., p value <0.1, on the previous test. Further testing stops as soon as one test in the sequence fails to meet significance, i.e., p value ≥0.1.

The testing of the exploratory efficacy endpoints not included in the hierarchical procedure will be used for exploratory purposes only.

Figure 2: Hierarchical Testing Procedure



4.9. Safety Analysis

All safety analyses will be performed based on the safety data collected during the on-treatment period, which is defined as the period from the administration of the first dose of study drug up to 7 days after the last dose of study drug, unless specified otherwise. The safety data will be summarized by treatment groups and the pooled MORF-057 groups based on the Safety Population defined in Section 3.3.

The safety analysis for the Induction Period will include the safety data collected during the 12-week Induction Period (see Section 1.5.1). If participants start their maintenance treatment before completing all safety assessments at Visit 5 (Week 12) due to a protocol deviation, clinical laboratory tests, vital signs and ECG at Week 12 visit will still be included in the 12-week Induction Period Analysis, even if they are measured after the participants start their maintenance dose.

The safety analysis for the 52-week Treatment Period will include cumulative safety data collected during the entire 52-week Treatment Period for the treatment groups randomized to an active MORF-057 dose. For the treatment group initially randomized to placebo and subsequently switched to an

active MORF-057 dose for maintenance treatment, only safety data collected during the 40-week Maintenance Period will be included for the participants in this group who have continued to the Maintenance Period and received MORF-057, as described in Section 1.5.2.

The safety analysis for the 104-week Total Treatment Period will include cumulative safety data collected during the entire 104-week Total Treatment Period for the treatment groups initially randomized to an active MORF-057 dose. For the treatment group initially randomized to placebo and subsequently switched to an active MORF-057 dose for maintenance treatment, only safety data collected during the 40-week Maintenance and 52-week Extension Periods will be included for the participants in this group who have continued to the Maintenance Period and received MORF-057, as described in Section 1.5.3.

In all safety summaries by treatment groups for the 52-week Treatment Period Analysis and the 104-week Total Treatment Period Analysis, participants initially randomized to an active MORF-057 treatment group will be categorized in the treatment group based on their actual MORF-57 dose received during the Induction Period, regardless of the actual maintenance MORF-057 dose. If any participants have their actual MORF-057 dose during the Maintenance/Extension Period different from the maintenance dose planned for the treatment group in which they are included in the analysis, additional summaries or listings may be provided for them as appropriate.

4.9.1. Adverse Events

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary (effective version at the time of database lock) by System Organ Class (SOC) and Preferred Term (PT). Grading of AE will be performed in accordance with CTCAE Version 5.0.

A treatment-emergent AE (TEAE) is defined as an AE that occurs during the period from the administration of the first dose of study drug up to 7 days after the last dose of study drug.

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

The following summary tables will be presented:

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

- Serious TEAE by SOC and PT
- Serious TEAEs by SOC, PT, and maximum Severity
- Serious TEAEs by SOC, PT, and Relationship to Study Drug
- Non-serious TEAEs (PTs with an incidence >5%) by SOC and PT
- TEAEs leading to permanent treatment discontinuation by SOC and PT

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

The TEAE summaries for the 12-week Induction Period will include all TEAEs that occurs before the day of the first maintenance treatment for participants who have continued to the Maintenance Period, and all TEAEs for participants who have discontinued the study treatment before entering the Maintenance Period. If both the last induction treatment dose and the first maintenance treatment dose occur on the same day, any TEAEs reported on that day will be considered for the Maintenance Period and not included in the Induction Period Analysis, unless there is evidence to confirm that the TEAE occurred before the administration of the maintenance treatment.

In the TEAE summaries for the 52-week Treatment Period and the 104-week Total Treatment Period, for participants randomized to the placebo group during the induction period who have subsequently received MORF-057 200 mg Q.D.-E during the Maintenance Period, only the TEAEs that occurs on or after the first day of maintenance treatment dose will be included and presented in the treatment group denoted by 200 mg Q.D.-E. If both the last induction treatment dose and the first maintenance treatment dose occur on the same day, any TEAEs reported on that day will be included in the summaries for this group, unless there is evidence to confirm that the TEAE occurred before the administration of the maintenance treatment. If there are any participants who were randomized to placebo group during the Induction Period and continued to the Maintenance Period but having the actual maintenance treatment different from MORF-057 200 mg Q.D.-E by mistakes, they will not be included in the summaries but presented separately as appropriate.

In addition, the TEAE for the 104-week Total Treatment Period will be summarized based on both the safety population, and the subset of the Safety Population who have continued to the Extension Period.

The following line listings will be provided:

- Listing of all AEs
- Listing of serious TEAE
- Listing of TEAEs leading to withdrawal of study treatment
- Listing of all deaths

4.9.2. Clinical Laboratory Evaluations

Observed results and changes from baseline (see Section 2.1.1) for central clinical laboratory results (hematology, coagulation, chemistry, and urinalysis) will be summarized descriptively for the on-treatment period at the scheduled visits including re-allocated visits (EOT or unscheduled, see Section 2.3).

A shift table from baseline will be used to summarize the number and percentage of participants experiencing laboratory abnormalities at each scheduled visit, as well as for the worst post-baseline values during the on-treatment period for each laboratory parameter. The determination of the worst post-baseline value will use the laboratory results from both scheduled and unscheduled visits.

The following plots will be provided:

- Mean (± SD) and mean change from the baseline (± SD) over scheduled visits for hematology parameters
- Peak alanine transaminase (ALT) or aspartate transaminase (AST) vs. peak total bilirubin post baseline

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

All laboratory data will be presented in a listing. Local laboratory results may be listed separately from central as appropriate, but they will not be summarized with central lab results due to calibration differences.

4.9.3. Vital Signs

Observed and changes from baseline (see Section 2.1.1) for vital signs assessment (weight, BMI, temperature, heart rate, respiratory rate, systolic blood pressure and diastolic blood pressure) will be summarized descriptively for the on-treatment period at the scheduled visit including re-allocated visits (EOT or unscheduled, see Section 2.3).

A shift table from baseline will be provided to summarize abnormalities at each scheduled visit, as well as for the worst post-baseline values during the on-treatment period. The determination of the worst post-baseline value will use the results from both scheduled and unscheduled visits. The abnormalities for vital sign parameters are described in Table 7 below.

Table 7: Vital Sign Abnormal Ranges

Vital Sign	Abnormal - Low	Normal	Abnormal - High
systolic blood pressure (mmHg)	< 90	90 - 140	> 140
diastolic blood pressure (mmHg)	< 60	60 - 90	> 90
heart rate (beats/min)	< 60	60 -100	>100
temperature (0C)	< 36	36 - 38	> 38
respiratory rate (beats/min)	< 12	12 - 18	> 18

All vital sign data by participant ID will be presented in a listing.

4.9.4. ECG

Observed value and changes from baseline for ECG results (heart rate, PR interval, QRS duration, QT interval, and QTcF interval) will be summarized descriptively for the on-treatment period at the scheduled visits including re-allocated visits (EOT or unscheduled).

A shift table from baseline will be provided to summarize abnormalities for QTcF at each scheduled visit, as well as for the worst post-baseline values during the on-treatment period. The determination of the worst post-baseline value will use the results from both scheduled and unscheduled visits. QTcF > 450 ms among male participants and QTcF > 470 ms among female participants will be considered above normal ranges.

Overall interpretation with clinical significance will also be summarized at each scheduled visit.

All ECG data by participant ID will be presented in a listing.

4.10. Pharmacokinetic Analysis

Plasma concentrations of MORF-057 will be summarized by treatment groups at scheduled visit and time using descriptive statistics including number of participants, mean with SD, median, CV% and geometric mean with CV% based on PK Population.

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

The handling rules for values below limit of quantification (BLQ) are described in Section 2.7.1.

The PK analyses for the Induction Period will include the PK data collected during the 12-week Induction Period, see Section 1.5.1. The PK analyses for the 52-week Treatment Period will include the PK data collected during the 52-week Treatment Period, see Section 1.5.2. Additional PK and PK/PD analyses will be conducted as deemed appropriate and may be reported separately from the Clinical Study Report.

4.11. Pharmacodynamic Analysis

Observed values and changes from baseline for α4β7 and α4β1 receptor occupancies will be summarized by treatment groups at scheduled visits using descriptive statistics including number of participants, mean with SD, median, CV% and geometric mean with CV%. The handling rules for PD data are described in Section 2.8.

Plot of mean with SD and boxplot for α4β7 and α4β1 receptor occupancies over scheduled visits will be provided.

The normalized relative expression level of human CCR9 mRNA in blood (relative to the pre-dose baseline) will be calculated at each timepoint using the lab-reported parameter CCR9_IPO8_DeltaCt (i.e., CCR9 Ct – IPO8 Ct), where the relative expression of CCR9 mRNA in blood at a given timepoint relative to pre-dose baseline is calculated using the following formula:

- Relative expression at timepoint x = 2- (CCR9_IPO8_DeltaCt at timepoint x - CCR9_IPO8_DeltaCt at baseline)

The CCR9 mRNA expression will be summarized by treatment groups at each timepoint using descriptive statistics.

The PD analyses for the Induction Period will include the PD data collected during the 12-week Induction Period, see Section 1.5.1. The PD analyses for the 52-week Treatment Period will include the PD data collected during the 52-week Treatment Period, see Section 1.5.2.

Additional analysis of PD endpoints may be described in a biomarker analysis plan separate from the study SAP and reported separately.

5. INTERIM ANALYSIS

The analysis of the 12-week Induction Period will be performed after all the participants have completed the Week 12 assessments or discontinued the study before the Week 12 assessment, as described in Section 1.5.1. The primary and secondary efficacy endpoints will be formally tested only once, specifically at the time of the Induction Period Analysis. When the Induction Period analysis is performed, an exploratory analysis for the 52-week Treatment Period may also be conducted for the subgroup of participants who have either completed their Week 52 assessments or discontinued the study by the time the last randomized participant completes their Week 12 assessments.

An independent DSMB will review participant safety data and monitor scientific integrity throughout the study. Details related to the DSMB will be clearly delineated in the DSMB Charter.

6. APPENDICES

6.1. Calculation of Stool Frequency and Rectal Bleeding Subscores

Stool frequency and rectal bleeding subscores at baseline and post-baseline visits will be calculated based on a reference date determined as follows:

- For baseline, the reference date is the randomization date.
- For post-baseline visits, the reference date is:
  - The earliest of the visit date recorded on eCRF form, the start date of bowel preparation (if performed), or the date of endoscopy procedure, if the endoscopy procedure is performed at the visit.
  - The visit date recorded on the eCRF If no endoscopy procedure is performed at the visit.

The calculation of stool frequency and rectal bleeding subscores will use the 3 most recent consecutive days of completed diary entries (both stool frequency and rectal bleeding data must be non-missing on the same day) within the past 7 days from the reference date. If 3 consecutive days of completed diary entries are not available, then use the 4 most recent nonconsecutive days of completed diary entries within the 7-day period prior to the reference date. If there are fewer than 3 consecutive days or 4 nonconsecutive days of completed diary entries available, then the subscores are set to missing.

In the calculations of stool frequency and rectal bleeding subscores at baseline, diaries collected on the following days within the 7-day period from the reference date will be excluded:

- Days of bowel preparation
- The day of endoscopy + 2 days

Rectal bleeding subscore

The rectal bleeding subscore will be calculated as:

- Take the average of the daily rectal bleeding subscores from the 3 most recent consecutive days or 4 most recent nonconsecutive days if 3 consecutive days of completed diary entries are not available, and then round to the nearest integer (decimal ≥ 0.5 will be rounded to the next highest integer; decimal < 0.5 will be rounded to the current integer).

Stool frequency subscore

The stool frequency subscore will be calculated as:

1. Compute the daily subscore first as below:
   - 0 if (stool frequency from each diary submission – normal number of stools) ≤ 0
   - 1 if (stool frequency from each diary submission – normal number of stools) = 1 or 2
   - 2 if (stool frequency from each diary submission – normal number of stools) = 3 or 4
   - 3 if (stool frequency from each diary submission – normal number of stools) > 4
2. Take the average of the daily stool frequency subscores from the 3 most recent consecutive days or 4 most recent nonconsecutive days if 3 consecutive days of completed diary entries are not

available, and then round to the nearest integer (decimal ≥ 0.5 will be rounded to the next highest integer; decimal < 0.5 will be rounded to the current integer).

Where the normal number of stools are the values recorded in the UC History eCRF form

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

6.2. Determination of the Actual Treatment Groups for Safety Analysis

Enrolled participants will be randomized into 4 treatment groups (Table 3) and will receive the treatment kits corresponding to the treatment group that they were randomized to, as described in Table 8 below.

During the Induction Period, participants will receive their study drug supplies in Morning Kits and Evening Kits. Each kit includes 2 bottles, each of which contains either MORF-057 or Placebo depending on the kit type. Participants should take 1 capsule from each morning bottle in the morning and take 1 capsule from each evening bottle in the evening for a total of 4 capsules per day.

During the Maintenance Period/Maintenance Extension Period, participants will receive Maintenance Kits with 1 morning bottle and 2 evening bottles. They should take 1 capsule from the morning bottle in the morning and take 1 capsule from each evening bottle in the evening for a total of 3 capsules per day.

Table 8: Treatment Kit Types for Different Treatment Arm

	Induction Period (12 weeks)					**Maintenance Period (40 weeks) + Optional Maintenance Extension Period (52 weeks)**		
	Treatment Description	**AM Kit Type**	**AM kit Bottles**	**PM Kit Type**	**PM Kit Bottles**	**Treatment Description**	**Maintenance Kit Type**	**Kit Bottles**
Group 1	200 mg BID	MORF-057 200 mg Morning Kit of 2 Bottles	2M	MORF-057 200 mg Evening Kit of 2 Bottles	2M	100 mg BID	MORF-057 100 mg BID Maintenance Kit of 3 bottles	AM: 1M PM: 1M1P
Group 2	100 mg BID	MORF-057 100 mg Morning Kit of 2 Bottles	1M1P	MORF-057 100 mg Evening Kit of 2 Bottles	1M1P	100 mg BID	MORF-057 100 mg BID Maintenance Kit of 3 bottles	AM: 1M PM: 1M1P
Group 3	100 mg QD - M	MORF-057 100 mg Morning Kit of 2 Bottles	1M1P	MORF-057 Placebo Evening Kit of 2 Bottles	2P	100 mg QD -M	MORF-057 100 mg QD Maintenance Kit of 3 bottles	AM: 1M PM: 2P
Group 4	Placebo	MORF-057 Placebo Morning Kit of 2 Bottles	2P	MORF-057 Placebo Evening Kit of 2 Bottles	2P	200 mg QD - E	MORF-057 200 mg QD Maintenance Kit of 3 bottles	AM: 1P PM: 2M

BID: twice a day; QD – M: once a day (morning); QD – E: once a day (evening).
Kit Bottles: 2M: 2 bottles containing MORF-057; 1M1P: 1 bottle containing MORF-057 and 1 bottle containing Placebo; 2P: 2 bottles containing Placebo; 1M: 1 bottle containing MORF-057

The actual treatment group that each participant will be included in during the 12-week Induction Period, the 40-week Maintenance Period, and the 52-week Maintenance Extension Period will be determined based on the algorithm described below.

6.2.1. 12-week Induction Period

During the 12-week Induction Period, the actual treatment groups will be derived as:

- **MORF-057 200 mg BID:** If only the MORF-057 200 mg Morning Kit and the MORF-057 200 mg Evening Kit are dispensed and consumed.
- **MORF-057 100 mg QD:** if only the MORF-057 100mg Morning Kit and the MORF-057 Placebo Evening Kit are dispensed and consumed.
- **MORF-057 100 mg BID:** if only the MORF-057 100 mg Morning Kit and the MORF-057 100 mg Evening Kit are dispensed and consumed, and the number of consumed Morning Kits is equal to the number of consumed Evening Kits.
- **Placebo:** If participants received placebo only.

In addition, if a participant randomized to the placebo group receives any dose of MORF-057 by mistake, or if a participant randomized to a MORF-057 dose group receives different MORF-057 dose kits by mistake, he/she will be classified to the MORF-057 dose group in which he/she was treated for the longest duration. In particular,

1. At each visit, the treatment duration of each MORF-057 dose will be calculated as below based on the type of treatment kits dispensed at that visit and the number of consumed capsules of MORF-057 in each dispensed treatment kit.
   - Treatment duration of MORF-057 200mg BID = maximum (the total number of capsules consumed from bottle 1 of MORF-057 200 mg Morning Kit, the total number of capsules consumed from bottle 2 of MORF-057 200 mg Morning Kit, the total number of capsules consumed from bottle 1 of MORF-057 200 mg Evening Kit, the total number of capsules consumed from bottle 2 of MORF-057 200 mg Evening Kit)
   - Treatment duration of MORF-057 100mg BID = minimum (Day_AM100, Day_PM100)
   - Treatment duration of MORF-057 100mg QD = absolute (Day_AM100 - Day_PM100)

   Where,

   - Day_AM100 (the number of days treated with MORF-057 100mg in the morning) = the total number of capsules consumed from the bottle containing MORF-057 of MORF-057 100 mg Morning Kit
   - Day_PM100 (the number of days treated with MORF-057 100mg in the evening) = the total number of capsules consumed from the bottle containing MORF-057 of MORF-057 100 mg Evening Kit
2. The total treatment duration of each MORF-057 dose during the 12-week Induction Period is calculated by summing the treatment durations of that dose across all visits within the period. The actual treatment group assigned to the participant will be the MORF-057 dose group with the longest cumulative duration.

6.2.2. Maintenance Period / Maintenance Extension Period

During the Maintenance Period/Maintenance Extension Period, the actual treatment groups will be derived as:

- MORF-057 100 mg BID: if only the MORF-057 100 mg BID Maintenance Kits are dispensed and consumed.
- MORF-057 100 mg QD: if only the MORF-057 100 mg QD Maintenance Kits are dispensed and consumed.
- MORF-057 200 mg QD: if only the MORF-057 200 mg QD Maintenance Kits are dispensed and consumed.

In addition, if a participant receives the MORF-057 Maintenance kits not corresponding to their scheduled dose arm by mistake, he/she will be classified to the MORF-057 dose group in which he/she was treated for the longest duration. In particular,

1. At each visit, the treatment duration of each MORF-057 dose will be calculated as below based on the type of treatment kits dispensed at that visit and the number of consumed capsules of MORF-057 in each dispensed treatment kit.
   - Treatment duration of MORF-057 200mg QD = minimum (the number of capsules consumed from bottle 2 of MORF-057 200 mg QD Maintenance Kit, the number of capsules consumed from bottle 3 of MORF-057 200 mg QD Maintenance Kit)
   - Treatment duration of MORF-057 100mg BID = minimum (Day_AM100_Maint, Day_PM100_Maint)
   - Treatment duration of MORF-057 100mg QD = absolute (Day_AM100_Maint - Day_PM100_Maint)

   Where,

   - Day_AM100_Maint (the number of days treated with MORF-057 100mg in the morning) = the number of capsules consumed from bottle 1 of MORF-057 100 mg BID Maintenance Kit + the number of capsules consumed from bottle 1 of MORF-057 100 mg QD Maintenance Kit
   - Day_PM100_Maint (the number of days treated with MORF-057 100mg in the evening) = the number of capsules consumed from the evening bottle containing MORF-057 of MORF-057 100 mg BID Maintenance Kit
2. The total treatment duration of each MORF-057 dose during the Maintenance Period/Maintenance Extension Period is calculated by summing the treatment durations of that dose across all visits within the period.. The actual treatment group assigned to the participant for that period will be the MORF-057 dose group with the longest cumulative duration.

6.3. Efficacy Outcomes

6.3.1. MCS, mMCS, Partial MCS and Partial mMCS

The MCS, mMCS, and Partial mMCS are composite of subscores as presented in Table 9:

Table 9: Subscore Components in MCS, mMCS, Patial MCS, and Partial mMCS

Endpoints	MES	Stool Frequency Subscore	Rectal Bleeding Subscore	PGA
MCS	X	X	X	X
mMCS	X	X	X	
Partial MCS		X	X	X
Partial mMCS		X	X	

MES: Mayo Endoscopic Score; MCS: Full Mayo Clinic Score; mMCS: Modified Mayo Clinic Score; PGA: Physician's Global Assessment

The MCS ranges from 0 to 12; the mMCS and partial MCS range from 0 to 9 and the Partial mMCS ranges from 0 to 6. For all 4 of these composite scores, higher scores indicate more severe disease. Each subscore is described below.

Stool frequency: The daily stool frequency score represents each participants' 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
- =5 or more stools more than normal

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

MES: 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 determined 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)

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

- 0=Normal
- 1=Mild disease

- 2=Moderate disease
- 3=Severe disease

6.3.2. Robarts Histopathology Index (RHI) Score

The RHI is an evaluative index derived from the Geboes Score and calculated by evaluating 4 histologic items:

- Chronic inflammatory infiltrate score (0-3)
- Lamina propria neutrophils score (0-3)
- Neutrophils in epithelium score (0-3)
- Erosion or ulceration score (0-3)

Each item is individually weighted in the RHI formula:

- RHI = (1 × chronic inflammatory infiltrate score) + (2 × lamina propria neutrophils Score) + (3 × neutrophils in epithelium score) + (5 × erosion or ulceration score)

Thus, the total score will be ranged from 0 to 33.

6.3.3. Nancy Index (NI)

The NI is determined by evaluating 3 histological items:

- Ulceration (0 or 2)
- Acute inflammatory cells infiltrate (0-3)
- Chronic inflammatory infiltrate (0-4)

An overall grade of NI is 0-4, adjudicated based on the subscores.

6.3.4. 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)
- Erosions or ulcers (Grade 5)

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.

6.3.5. IBDQ Questionnaire

The IBDQ questionnaire is a psychometrically validated participant reported outcome instrument to assess health-related quality of life (HRQoL) in participants with IBD including UC.

The IBDQ consists of 32 items and is grouped into 4 dimensions:

- Bowel function
- Emotional status
- Systemic symptoms
- Social function

Response to each of the questions is graded from 1 to 7, with the overall score ranging from 32 (very poor HRQoL) to 224 (perfect HRQoL). For the total score and each domain, a higher score indicates better quality of life. A score of ≥170 corresponds to clinical remission, and an increase of ≥16 points indicate a clinically meaningful improvement.

6.4. SAS Codes for Primary Efficacy Analysis

Primary SAS Code for Stratified CMH Method

```
proc freq data=adeff;
   table AT_strata * MES_strata *treatment*response/cmh;
run;
```

Where AT_strata is the previous use of advanced therapy treatment (advanced therapy naïve vs advanced therapy experienced), and MES_strata is the baseline MES ((<3 vs 3).

6.5. The Calculation of Stratified Risk Difference Between Two Groups Using the Cochran-Mantel-Haenszel (CMH) Weights

Suppose that participants are randomly assigned into the active group or placebo group, stratified by K factors (K≥2):

Strata	Response	Active Group	Placebo	Total
1	Yes	x_{11}	x_{01}	x_1
	No	n_{11}-x_{11}	n_{01}-x_{01}	n_1-x_1
	Total	n_{11}	n_{01}	n_1
2	Yes	x_{12}	x_{02}	x_2
	No	n_{12}-x_{12}	n_{02}-x_{02}	n_2-x_2
	Total	n_{12}	n_{02}	n_2
…				
K	Yes	x_{1K}	x_{0K}	x_K
	No	n_{1K}-x_{1K}	n_{0K}-x_{0K}	n_K-x_K
	Total	n_{1K}	n_{0K}	n_K

$n_{1j}$is the number of participants randomized to the active group and $x_{1j}$is number of responders in the active group for strata j, and $n_{0j}$is the number of participants randomized to placebo and $x_{0j}$is number of responders in the placebo group for strata j.

The response rate difference $\delta_j = p_{1j} - p_{0j}$ between active group and placebo for strata j is estimated by

$$\hat{\delta}_j = \widehat{p_{1j}} - \widehat{p_{0j}}$$

Where the estimated response rate $\widehat{p_{1j}} = x_{1j}/n_{1j}$ and $\widehat{p_{0j}} = x_{0j}/n_{0j}$.

The overall response rate difference is estimated by the stratified response rate difference using the CMH weights, which is calculated as

$$\widehat{\delta_w} = \sum_{j=1}^{K} w_j \hat{\delta}_j$$

where $w_j = \left(n_{1j}^{-1} + n_{0j}^{-1}\right)^{-1} / \left[\sum_{j=1}^{K}\left(n_{1j}^{-1} + n_{0j}^{-1}\right)^{-1}\right]$ is the weight for stratum j with $\sum_{j=1}^{K} w_j = 1$.

The $100\,(1-\alpha)\%$ confidence interval of the overall response rate difference is given by

$$\widehat{\delta_w} \pm Z_{\alpha/2}\sqrt{\sum_{j=1}^{k} w_j^2 \hat{V}(\hat{\delta}_j)}$$

Where $\hat{V}(\hat{\delta}_j) = \left(\widehat{p_{1j}}(1-\widehat{p_{1j}})/n_{1j}\right) + \left(\widehat{p_{0j}}(1-\widehat{p_{0j}})/n_{0j}\right)$ is the estimated variance of the response rate difference in strata j and $Z_{\alpha/2}$ is the (1-$\alpha/2$) percentile of the standard normal distribution.