Protocol: 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

NCT05611671

Approval Date: 27-Mar-2025

Clinical Study Protocol

Protocol Title:	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
Compound:	MORF-057
Brief Title:	A Phase 2b Study to Evaluate MORF-057 in Adults with Moderately to Severely Active UC
Indication	Moderately to severely active ulcerative colitis
Study Phase:	2b
Sponsor:	Morphic Therapeutic, Inc. (A Wholly Owned Subsidiary of Eli Lilly and Company) 35 Gatehouse Drive, A2 Waltham, MA 02451, USA
IND Number:	147011
UTN Number:	U1111-1283-7075
EU CT Number:	2022-500953-17-00
Protocol Version:	Version 3.0, 26 March 2025

Protocol Version: Version 3.0, 26 March 2025

Sponsor Signatory:

PPD

27-Mar-2025 | 8:19 AM PDT

PPD

Date

Head of Morphic Clinical Development
Morphic Therapeutic, Inc. (A Wholly Owned Subsidiary of Eli Lilly and Company)

Protocol Amendment Summary of Changes

DOCUMENT HISTORY	
Document	**Date**
Protocol V1.0	01 June 2022
Protocol V2.0	26 April 2023
Protocol V2.1 (EU)	26 April 2023
Protocol V3.0	26 March 2025

Version 3.0 dated 26 March 2025

Overall Rationale for the Amendment

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

- To merge Global Protocol Version 2.0 and European Union Protocol Version 2.1
- To revise to the most up to date development program information
- To clarify and revise the name of the extension period
- To revise the dose for the Long-Term Extension Period
- To add the Dose Switch Follow-up 1 and 2
- To revise the definition for the End of Study
- To add an optional exploratory fecal calprotectin sample
- To revise the study schema
- To revise the contraception requirements

Summary of Changes Table

This protocol amendment merges the 2 previous protocol versions: Protocol Version 2.0 (applicable globally in countries outside of the European Union [EU]) and Version 2.1 (applicable only in the EU). Additional changes have also been incorporated into this Version 3.0, which is now applicable globally.

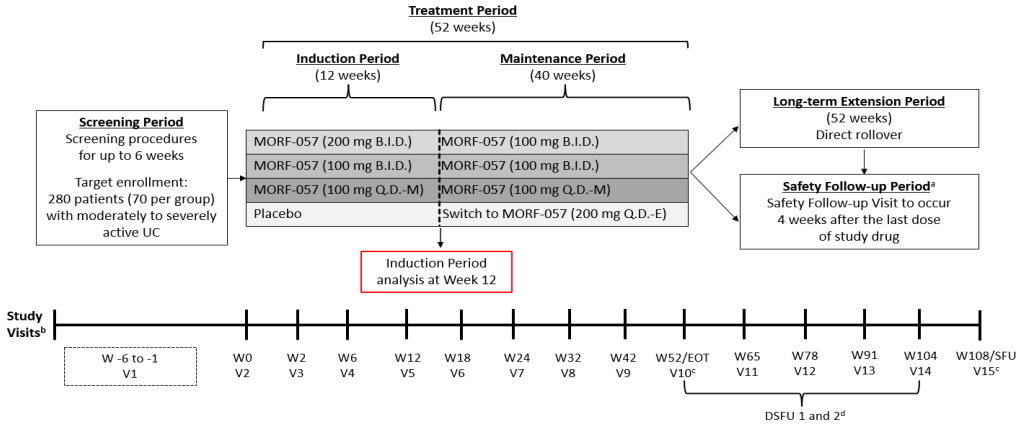
This protocol amendment is considered Substantial by the Sponsor, according to the criteria specified in the EU Clinical Trials Regulation 536/2014. Changes to the protocol as implemented by this amendment are summarized in the Summary of Changes table below. New text is shown in *italics*, deleted text is shown in ~~strikeout~~, and **bold** text is informational. In addition to the changes provided in the Summary of Changes table, minor editorial changes have been made throughout the protocol.

Section No. and Name	Description of Change	Brief Rationale
Global change	**Add "(A Wholly Owned Subsidiary of Eli Lilly and Company)" after Morphic Therapeutic, Inc.**	To update Sponsor name
Global change	**"Maintenance Extension" and "Extension" was changed to "Long-Term Extension" or "LTE" throughout the Protocol.**	To clarify and revise the names of the extension period
Global change	**The Long-Term Extension Period End of Treatment Visit was changed to Long-Term Extension End of Treatment throughout Protocol.**	To clarify the extension period End of Treatment Visit
Global change	**LTE was replaced with LTE Period.**	To be consistent
Global change	**Changed CYP3A4 to CYP3A throughout document.**	To clarify for consistency
Abbreviations	~~CYP3A4 Cytochrome P450 3A4~~ *DDI Drug-drug interaction* *DSFU Dose Switch Follow-up* *EU European Union* *IB Investigator's Brochure* *LTE Long-Term Extension*	To update the abbreviations used throughout the protocol
1.1. Synopsis-Rationale:	*Relevant data from all non-clinical and clinical studies in the MORF-057 development program are provided in the current Investigator's Brochure.* ~~A first in human Phase 1 study of MORF-057 (MORF-057-101) in healthy study participants has been completed. The study included 3 parts: a single ascending dose ([SAD] up to 400 mg) part, a multiple ascending dose ([MAD] up to 100 mg twice a day [B.I.D.] for 14 days) part, and a food effect ([FE] fixed dose of 100 mg B.I.D.) part. MORF-057 was demonstrated to be safe and well tolerated in these healthy study participants across all parts of the study. MORF-057 also exhibited favorable pharmacokinetics (PK) profiles. The observed exposure in healthy individuals is expected to be similar in patients with UC and to provide the receptor occupancy at these exposures that may translate to intended efficacy and safety outcomes. The 100 mg B.I.D. regimen in participants with UC is being~~	To revise to the most up to date development program information

Section No. and Name	Description of Change	Brief Rationale
	~~evaluated in an ongoing open label, single arm, Phase 2 study (MORF-057-201) to provide safety, PK, pharmacodynamics (PD), and preliminary efficacy data to inform further development of MORF-057 in patients with UC.~~ ~~A Phase 1 study (CCI) was conducted in healthy participants to investigate the safety, tolerability, PK, and PD of single and multiple doses of MORF-057 immediate-release (IR) capsules. The single (25 mg, 200 mg, and 100 mg [with and without food]) and multiple (200 mg B.I.D. for 14 days) dosing of MORF-057 IR capsules was demonstrated to be safe and well tolerated. The new MORF-057 IR capsule formulation was selected to be used in future studies. Data from this study and the MORF-057-101 study were primarily used for selecting the doses and dosing regimens for this current Phase 2b study (MORF-057-202).~~	
1.1. Synopsis – Overall Design: 4.1. Overall Design	During the optional *LTE Period*, there will be *up to* ~~5~~*7* scheduled visits: 4 Treatment Visits (Visits 11-14 at Weeks 65, 78, 91, and 104 [*Long-Term Extension (LTE)* EOT]), *2 Dose Switch Follow-ups (DSFUs; these 2 visits will only occur if participant consents to dose switch),* 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 *LTE Period* is completed or earlier if treatment is discontinued early). *Due to the changes in Version 3.0 of this protocol, all participants who choose to continue their treatment in the LTE Period will be asked to re-consent to the LTE Period dose switch to 200 mg twice a day (B.I.D.). The dose switch will occur at Visit 10 or at a scheduled visit in the LTE Period (Visit 11, 12, or 13). If the participant does not consent to the dose switch, they will be allowed to remain on their current LTE Period dose and schedule; they will not need to attend DSFUs 1 or 2. Participants in the LTE Period who consent to the dose switch will have a scheduled DSFU 1 at 4 weeks after the dose switch, and then DSFU 2 will be 4 weeks after DSFU 1. The participant will then attend the next scheduled visit (Visit 11, 12, 13, or 14) per the Schedule of Activities (SoA). A participant cannot switch their dose after Visit 13. An SFU Visit will occur 4 weeks after the last dose of study drug is received, which will be at Week 108 if the full LTE Period is completed or earlier if treatment is discontinued early.* Participants who do not enroll into the *LTE Period* ~~must~~*will* 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 the main part of the study *(*a maximum time on study of 62 weeks*)*. Participants who choose to continue in the *LTE Period* will not complete the SFU ~~Period~~*Visit* for the main part of the study; instead, they will directly enter the *LTE Period* and complete a separate SFU ~~Period~~*Visit*~~, including the Week 108 Visit~~ (4 weeks after receiving the last dose of MORF-057 *in the LTE Period*), for a maximum time on study of 114 weeks.	To revise the dose, the number of visits, and add Dose Switch Follow-ups for the Long-Term Extension Period In the Induction Period analysis for this study, a dose-response was observed between the 3 active doses, and 200 mg B.I.D. was the clinically most active dose. Changing the dose for the Long-Term Extension Period from 100 mg B.I.D. to 200 mg B.I.D. will provide current study participants with an opportunity to receive a higher dose that may be more clinically active. Based on all available clinical data, this change is not expected to increase the risk of any potential safety effects.

<table>
<tr><th>Section No. and Name</th><th>Description of Change</th><th>Brief Rationale</th></tr>
<tr><td>1.1. Synopsis – Study Treatment:

4.1. Overall Design</td><td>All participants who choose to continue in the LTE Period will continue receiving the same MORF-057 regimen they had during the Maintenance Period for up to an additional 52 weeks. However, at Visit 10 or at a scheduled visit in the LTE Period (Visit 11, 12, or 13), if the participant consents, the MORF-057 dose for the LTE Period will be switched to 200 mg B.I.D. If the participant does not consent to the dose switch, they will be allowed to remain on their current LTE Period dose and schedule. The dosing regimens for the 4 treatment groups during the study are shown below.
<table>
<tr><th></th><th>Induction Period (12 Weeks)</th><th>Maintenance Period (40 Weeks)/ LTE Period (52 Weeks)</th><th>LTE Period (52 Weeks)*</th></tr>
<tr><td>Group 1</td><td>MORF-057 (200 mg B.I.D.)</td><td>MORF-057 (100 mg B.I.D.)</td><td>MORF-057 (200 mg B.I.D.)</td></tr>
<tr><td>Group 2</td><td>MORF-057 (100 mg B.I.D.)</td><td>MORF-057 (100 mg B.I.D.)</td><td>MORF-057 (200 mg B.I.D.)</td></tr>
<tr><td>Group 3</td><td>MORF-057 (100 mg Q.D.-M)</td><td>MORF-057 (100 mg Q.D.-M)</td><td>MORF-057 (200 mg B.I.D.)</td></tr>
<tr><td>Group 4</td><td>Placebo</td><td>MORF-057 (200 mg Q.D.-E)</td><td>MORF-057 (200 mg B.I.D.)</td></tr>
</table>
Abbreviations: B.I.D., twice a day; LTE, Long-Term Extension; Q.D. E, once a day (evening); Q.D. M, once a day (morning).
* Relevant for participants who consent to the dose switch in the LTE Period. For those that do not consent to the dose switch in the LTE Period, they will remain on their current LTE Period dose.</td><td>In the Induction Period analysis for this study, a dose-response was observed between the 3 active doses, and 200 mg B.I.D. was the clinically most active dose. Changing the dose for the Long-Term Extension Period from 100 mg B.I.D. to 200 mg B.I.D. will provide current study participants with an opportunity to receive a higher dose that may be more clinically active. Based on all available clinical data, this change is not expected to increase the risk of any potential safety effects.</td></tr>
<tr><td>1.1. Synopsis – Study Treatment:</td><td>The study drug will be supplied as ~~IR~~immediate release capsules for oral administration (MORF-057 100 mg capsule or placebo). Refer to the main protocol for additional treatment details. ~~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.” Each participant will be instructed to take 4 capsules per day during the Induction Period and 3 capsules per day during the Maintenance Period/Maintenance Extension Period.~~</td><td>To clarify the number of capsules to be taken per day during the Long-Term Extension Period</td></tr>
</table>

Section No. and Name	Description of Change	Brief Rationale
1.1. Synopsis – Study Schema: 4.1. Overall Design	 Abbreviations: B.I.D., twice a day; *DSFU, Dose Switch Follow-up;* 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. *a*~~*~~ The SFU Visit ~~at Week 56~~ will not be performed *at Week 56* for participants who enter the *LTE* Period. *b*‡ The assessments to be performed at each visit and the acceptable time windows for each visit are provided in the Schedule of Activities. *c*‡ 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. *d At Visit 10 or at a scheduled visit in the LTE Period (Visit 11, 12, or 13), all participants will be asked to re-consent to switch their dose to 200 mg B.I.D. Participants who do not consent to the dose switch will remain on their current LTE Period dose. The DSFU 1 will occur 4 weeks after the dose switch, and DSFU 2 will occur 4 weeks after DSFU 1. Participants who do not consent to the dose switch will not need to attend DSFUs 1 or 2.*	To revise the dose, the number of visits, and add Dose Switch Follow-ups for the Long-Term Extension Period

Section No. and Name	Description of Change	Brief Rationale
1.1. Synopsis –Main Inclusion Criteria: 5.1. Inclusion Criteria	**"oral aminosalicylates" was in Version 2.0 but not in Version 2.1, which has been combined in Version 3.0.** Type of Participant and Disease Characteristics #4 4. Demonstrated an inadequate response, loss of response, or intolerance to at least one of the following treatments (including *oral aminosalicylates*,* corticosteroids, immunosuppressants, and/or advanced therapies for UC) in the opinion of the Investigator, as defined below: *a. Oral aminosalicylates (e.g., mesalamine, sulfasalazine, olsalazine, or balsalazide)* • *Signs and symptoms of persistently active disease during a current or prior course of at least 4 weeks of treatment with ≥2.0 g/day mesalamine, 4 g/day sulfasalazine, 1 g/day olsalazine, or 6.75 g/day balsalazide* **Note: Inadequate response, loss of response, or intolerance to oral aminosalicylates does not apply to this Inclusion Criterion in European Union (EU) countries.* *d.* Advanced therapies for UC (e.g., biologic agents, Janus kinase [JAK] antagonists, or sphingosine 1 phosphate [S1P] receptor agonists) Note: Participants who have received a prior advanced therapy agent for up to 1 year and did not have a documented non-response may be enrolled; however, the participants must have discontinued the advanced therapy agent for reasons other than inadequate response or intolerance (e.g., change of insurance, well controlled disease) and must meet the criteria for inadequate response, loss of response, or intolerance to *aminosalicylates,* corticosteroids, and/or immunosuppressants, as defined above.	To combine Protocol Amendment Version 2.0 and Version 2.1 to Version 3.0
1.1. Synopsis –Main Inclusion Criteria: 5.1. Inclusion Criteria	**"8-week" was in Version 2.0 and "12-week" was in Version 2.1, which have been combined in Version 3.0.** Type of Participant and Disease Characteristics #4 ~~b.~~*c.* Immunosuppressants (e.g., azathioprine, 6-mercaptopurine, or methotrexate) • Signs and symptoms of persistently active disease despite a history of at least one *8**-week regimen of oral azathioprine (≥1.5 mg/kg/day), 6-mercaptopurine (≥1 mg/kg/day or a documented 6-thioguanine nucleotide level of 230-450 pmol/8 × 108 red blood cell count or higher on the current dosing regimen), injectable methotrexate (≥12.5 mg/week subcutaneous [SC] or intramuscular) **Note: A history of signs and symptoms of persistently active disease despite a history of at least one 12-week regimen of immunosuppressants is required in EU countries.*	To combine Protocol Amendment Version 2.0 and Version 2.1 to Version 3.0

Section No. and Name	Description of Change	Brief Rationale
1.1. Synopsis –Main Inclusion Criteria: 5.1. Inclusion Criteria	**"4 weeks" was in Version 2.0 and "12 weeks" was in Version 2.1, which have been combined in Version 3.0.** Type of Participant and Disease Characteristics #6 a. Oral 5-Aminosalicylates (not exceeding 4.8 g per day): at least 2 weeks prior to study Day 1 b. Oral corticosteroids (not exceeding prednisone 30 mg/day, budesonide 9 mg/day, beclomethasone dipropionate 5 mg/day, methylprednisolone 24 mg/day, or equivalent): at least 2 weeks prior to study Day 1 c. 6-Mercaptopurine (any stable dose): at least 4 weeks* prior to study Day 1 d. Azathioprine (any stable dose): at least 4 weeks* prior to study Day 1 *e.* Methotrexate (any stable dose): for at least 4 weeks* prior to study Day 1 **Note: Participants must be on any stable dose of 6-mercaptopurine, azathioprine, or methotrexate for at least 12 weeks prior to study Day 1 in EU countries.*	To combine Protocol Amendment Version 2.0 and Version 2.1 to Version 3.0
1.1. Synopsis –Main Inclusion Criteria: 5.1. Inclusion Criteria	Type of Participant and Disease Characteristics #7 7. If the participant has had UC for over 7 years, he/she must have had a full colonoscopy in the last 2 years or must agree to have a full colonoscopy (rather than sigmoidoscopy) with appropriate*, per local guidelines,* colon cancer surveillance biopsies at Screening	To clarify inclusion criteria
1.1. Synopsis –Main Inclusion Criteria: 5.1. Inclusion Criteria	Sex and Contraceptive/Barrier Requirements #10 b. A female participant is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies: • Is a woman of non-childbearing potential (as defined in Section 10.5.1) OR • Is a woman of childbearing potential (as defined in Section 10.5.1) and agrees to use a contraceptive method that is highly effective with a failure rate of <1% per year (as described in Section 10.5.2) during the study Treatment Period and for at least 28 days after receiving the last dose of MORF-057 *Note: For contraception requirements on or after Protocol Amendment Version 3.0, see Section 10.5.2.2.*	To revise the contraception requirements for study participants who receive the increased dose of MORF-057 (200 mg B.I.D.) during the Long-Term Extension Period
1.1. Synopsis –Exclusion Criteria: 5.1. Exclusion Criteria	6. Has positive findings on a *Subjective P*~~p~~rogressive *M*~~m~~ultifocal *L*~~l~~eukoencephalopathy (PML) ~~subjective~~ symptom checklist during Screening or prior to the administration of the first dose of study drug on study Day 1 6. Has positive findings on a *Subjective* PML ~~subjective~~ symptom checklist during Screening or prior to the administration of the first dose of study drug on study Day 1	Administrative change

<table>
<tr><th>Section No. and Name</th><th>Description of Change</th><th>Brief Rationale</th></tr>
<tr><td>1.1. Synopsis –Statistical Methods:
9.3. Analyses for Induction Period, 52-week Treatment Period, and LTE Period</td><td>Analyses for Induction Period, 52-week Treatment Period, and LTE Period
The details of the analyses will be described in the SAP. ~~The results for the main part of the study will be reported in the Clinical Study Report.~~ Additional analysis of the optional 52-week LTE Period for the participants enrolled into the LTE Period will also be performed as appropriate. ~~The results for the LTE Period will be reported in a Clinical Study Report Addendum.~~</td><td>To clarify the analyses for each period</td></tr>
<tr><td>1.1. Synopsis –Statistical Methods:
9.3. Analyses for Induction Period, 52-week Treatment Period, and LTE Period</td><td>52-week Treatment Period Analysis
The analysis of the 52-week Treatment Period 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 LTE Period) or discontinued from the study ~~before~~during the 52-~~Week~~week ~~assessments~~Treatment Period.
52-week LTE Period Analysis
The analysis of the LTE Period will be performed after all the participants enrolled into the LTE Period have completed the 52-week LTE Period and the Safety Follow-up Period or discontinued the study ~~before~~during the ~~Week 104 assessment~~LTE Period. The analysis will evaluate the long-term safety of MORF-057 and selected efficacy endpoints at Week 104 as appropriate during the LTE Period plus the Safety Follow-up Period.</td><td>To clarify the Long-Term Extension Period Analysis</td></tr>
<tr><td>1.2. Schedule of Activities (SoA)</td><td>The SoA for the Treatment Period is provided in Table 1. The SoA for the LTE Period* is provided in Table 2.</td><td>To reflect the changes in the Long-Term Extension Period due to changes in the dosing regimen</td></tr>
<tr><td>1.2. Schedule of Activities (SoA)</td><td>Table 1. Schedule of Activities for the Treatment Period
<table>
<tr><td>Visit</td><td>1</td><td>5</td><td>7</td><td>10/EOT</td></tr>
<tr><td></td><td>Stage 1</td><td>Stage 2</td><td></td><td>Stage 2</td></tr>
<tr><td>Future Research (Optional)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Fecal sample for fecal calprotectin[hh]</td><td></td><td></td><td></td><td>X</td></tr>
<tr><td>Efficacy Assessments</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Fecal sample for fecal calprotectin</td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
</table>
hh Participation in future research sample collection is optional. Fecal samples for fecal calprotectin will be collected at the same visits as the fecal calprotectin efficacy assessments (Visit 10/EOT). Fecal samples may be collected at any time on the day prior to the scheduled visit day.</td><td>To reflect the addition of an optional exploratory fecal calprotectin sample</td></tr>
<tr><td>1.2. Schedule of Activities (SoA)</td><td>Added Footnote ‘hh,’ which reordered the footnotes afterwards.</td><td>Administrative</td></tr>
<tr><td>1.2. Schedule of Activities (SoA)</td><td>Table 1 Footnote
Abbreviations: AE, adverse event; B.I.D., twice a day; C. diff., Clostridiodes difficile; ECG, electrocardiogram; EOT, End of Treatment; HIV, human immunodeficiency virus; hs-CRP, high</td><td>Administrative</td></tr>
</table>

Section No. and Name	Description of Change	Brief Rationale
	sensitivity C reactive protein; IBDQ, Inflammatory Bowel Disease Questionnaire; ICF, Informed Consent Form; IGRA, interferon gamma release assay; *LTE, Long-Term Extension;* MCS, Mayo Clinic Score; MES, Mayo Endoscopic Subscore; NI, Nancy Histopathology Index; PD, pharmacodynamics; PK, pharmacokinetics; PML, progressive multifocal leukoencephalopathy; RHI, Robarts Histopathology Index; RNA, ribonucleic acid; RO, receptor occupancy; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SCR, Screening; SFU, Safety Follow-up; TB, tuberculosis; UNS, unscheduled.	
1.2. Schedule of Activities (SoA)	**Table 1 Footnote** d Visit 10 is split into Stage 1 and Stage 2 to clarify the timing of the endoscopy procedure. The endoscopy procedure at Visit 10 Stage 1 should be performed *on or within 7 days* before the Visit 10 Stage 2 in clinic assessments have been completed. ~~kkll For t~~*T*he Visit 10/EOT *Stage 1* endoscopy procedure *should occur on or within*~~, there is a window of +~~7 days ~~from~~*before* the actual *Stage 2* visit date.	To clarify the timing of endoscopy at Visit 10
1.2. Schedule of Activities (SoA)	**Table 1 Footnote** n Participant Diaries are to be completed daily by the participant at home and brought to each study visit for review by study personnel. *Participant Diaries should not be completed after the participant has finished their participation in the study at the SFU Visit.* See Section 8.5 for the required contents of the Participant Diaries.	To clarify the Participant Diary should not be completed after the participant exits the study
1.2. Schedule of Activities (SoA)	**Table 1 Footnote** r Participants will be provided the option to participate in the *LTE* Period. Participants who want to continue in the *LTE Period* will be required to provide informed consent. *Due to the changes in Version 3.0 of this protocol, all participants who choose to continue their treatment in the LTE Period will be asked to re-consent to the LTE Period dose to 200 mg B.I.D. The dose switch will occur at Visit 10 or at a scheduled visit in the LTE Period (Visit 11, 12, or 13).*	To reflect the changes to the Long-Term Extension Period
1.2. Schedule of Activities (SoA)	**Table 1 Footnote** ~~sstt~~ Site staff will contact the participants, by phone or other ~~forms~~*means*, on the next business day after the Visit 5 clinic visit is complete to confirm the participants are using the new supply of study drugs for the Maintenance Period. Record the date and time of the participant's first Maintenance Period dose.	To clarify language
1.2. Schedule of Activities (SoA)	**Added DSFU 1 and 2 columns to Table 2 along with their respective activities. Only these changes are shown here and not the whole table. Addition of 'a' and 'b' footnotes reordered footnotes afterwards.** Table 2. Schedule of Activities for the *LTE* Period*	To reflect the changes to the Long-Term Extension Period, and to clarify that participants do not need to record study drug administration details in their Participant Diaries

	Study Procedure	*Dose Switch Follow-up 1* [a]	*Dose Switch Follow-up 2* [b]	*LTE* Period*				Safety Follow-up	UNS [~~a~~c]	during the LTE Period
	Visit	*DSFU 1*	*DSFU 2*	11	12	13	14/*LTE* EOT [~~b~~d, ~~e~~e]	SFU [~~d~~f, eg]		
	Week	*4 weeks after the dose switch*	*4 weeks after DSFU 1*	65	78	91	104	108		
	Study Day			456± 7	547± 7	638± 7	729±7	757+7 [~~f~~h]		
	Informed consent			*X* *	*X* *	*X* *				
	Fill out Participant Diary (daily rectal bleeding, stool frequency~~, study drug administration~~) [~~g~~i]	*X*	*X*							
	Participant Diary completion and compliance review	*X*	*X*							
	Pregnancy test [~~h~~j]	*X*	*X*							
	Safety Assessments									
	Concomitant medications	*X*	*X*							
	Physical exam [~~i~~l]	*X*	*X*							
	Vital signs [~~k~~m]	*X*	*X*							
	PML checklist [~~l~~n]	*X*	*X*							
	Hematology and coagulation	*X*	*X*							

Section No. and Name	Description of Change	Brief Rationale
	<table><tr><td>Serum chemistry</td><td>X</td><td>X</td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Urinalysis</td><td>X</td><td>X</td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>AE/SAE assessment ~~mo~~, ~~np~~</td><td>X</td><td>X</td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Study Drug</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Study drug accountability</td><td>X</td><td>X</td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Confirm switch of study drug [t]</td><td>X</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr></table> Abbreviations: AE, adverse event; *B.I.D., twice a day; DSFU, Dose Switch Follow-up; ICF, Informed Consent Form; LTE, Long-Term Extension; LTE* EOT, *Long-Term Extension* End of Treatment; MES, Mayo Endoscopic Subscore; NI, Nancy Histopathology Index; PML, progressive multifocal leukoencephalopathy; RHI, Robarts Histopathology Index; SAE, serious adverse event; SFU, Safety Follow-up; UNS, unscheduled. ** Note: Due to the changes in Version 3.0 of this protocol, all participants who choose to continue their treatment in the LTE Period will be asked to re-consent to the LTE Period dose switch to 200 mg B.I.D. The dose switch will occur at Visit 10 or at a scheduled visit in the LTE Period (Visit 11, 12, or 13). For example, a participant who has already completed Visit 11 at the time that Protocol Version 3.0 is active will complete the dose switch at Visit 12 (Week 78). Then, the DSFU 1 will be completed 4 weeks later (Week 82), and the DSFU 2 will be 4 weeks after DSFU 1 (Week 86). Then, the participant will resume regular visits with the next visit at Visit 13 (Week 91) through the end of the study. If the participant does not consent to the dose switch, they will remain on their current LTE Period dose and schedule and will not need to attend DSFUs 1 or 2.* *a The DSFU 1 will occur 4 weeks after the dose switch.* *b The DSFU 2 will occur 4 weeks after the DSFU 1.* *t Site staff will contact the participants who consented, by phone or other means, on the next business day after the dose switch in the LTE Period to confirm the participants have switched to the new dose (200 mg B.I.D.) of study drug correctly. Record the date and time of the participant's first dose of the new dose (200 mg B.I.D.) in the source documents.*	
1.2. Schedule of Activities (SoA)	**Table 2 Footnote** ~~b~~*d* Visit 14 is split into Stage 1 and Stage 2 to clarify the timing of the endoscopy procedure. The endoscopy procedure at Visit 14 Stage 1 should be performed *on or within 7 days* before the Visit 14 Stage 2 in clinic assessments have been completed.	To clarify the timing of endoscopy at Visit 14

Section No. and Name	Description of Change	Brief Rationale
	~~p~~*r* Endoscopy is required at Visit 14/*LTE* EOT Stage 1 unless it was performed within 6 months of the *LTE* EOT Visit. *The Visit 14/LTE EOT Stage 1 endoscopy procedure should occur on or within 7 days before the actual Stage 2 visit date.* ~~There is a window of +7 days for the endoscopy procedure from the actual visit date.~~	
2.1. Study Rationale	It is currently being developed as an oral therapy for UC because vedolizumab, which has the same mechanism of action, has demonstrated efficacy in patients with UC who have moderately to severely active disease. *Relevant data from all non-clinical and clinical studies in the MORF-057 development program are provided in the current Investigator's Brochure (IB).* ~~A first in human Phase 1 MORF-057 study (MORF-057-101) in healthy study participants has been completed. The study included 3 parts: a single ascending dose ([SAD] up to 400 mg) part, a multiple ascending dose ([MAD] up to 100 mg twice a day [B.I.D.] for 14 days) part, and a food effect ([FE] fixed dose of 100 mg B.I.D.) part. MORF-057 was demonstrated to be safe and well tolerated in these healthy study participants across all parts of the study. MORF-057 also exhibited favorable pharmacokinetics (PK) profiles. The observed exposure in healthy individuals is expected to be similar in patients with UC and to provide the receptor occupancy at these exposures that may translate to intended efficacy and safety outcomes. The 100 mg B.I.D. regimen in participants with UC is being evaluated in an ongoing open label, single arm, Phase 2 study (MORF-057-201) to provide safety, PK, pharmacodynamics (PD), and preliminary efficacy data to inform further development of MORF-057 in patients with UC.~~ ~~A Phase 1 study ([redacted]) was conducted in healthy participants to investigate the safety, tolerability, PK, and PD of single and multiple doses of MORF-057 immediate-release (IR) capsules. The single (25 mg, 200 mg, and 100 mg [with and without food]) and multiple (200 mg B.I.D. for 14 days) dosing of MORF-057 IR capsules was demonstrated to be safe and well tolerated. The new MORF-057 IR capsule formulation was selected to be used in future studies. Data from this study and the MORF-057-101 study were primarily used for selecting the doses and dosing regimens for this current Phase 2b study (MORF-057-202).~~	To revise to the most up to date development program information
2.2.1. Non-clinical Findings	~~MORF-057 has a moderate blood clearance with a terminal half-life of less than 3 hours in mice, rats, dogs, and monkeys. Absorption following oral administration was rapid with a Tmax of up to 2 hours. Moderate bioavailability was observed in rats and dogs, but low bioavailability was observed in mice and cynomolgus monkeys. The binding of MORF-057 to plasma proteins was high across species and was not different from the in vitro assessment in human plasma.~~ *MORF-057 has been characterized in Good Laboratory Practice-compliant toxicity and safety studies. MORF-057 had no effect on respiration, neurobehavior, or cardiovascular function, and had no genotoxicity or phototoxicity potential. Potential toxicity risks based on non-clinical data include effects to the stomach, liver, hematopoietic system, and embryo-fetal development.* *See the current MORF-057 IB for additional details.* ~~In 3-month oral repeat dose toxicity studies in Sprague Dawley rats and beagle dogs, the no observed adverse effect levels (NOAELs) were 450 mg/kg/day in male and female rats, and 300 mg/kg/day in male and female dogs.~~	To revise to the most up to date development program information

Section No. and Name	Description of Change	Brief Rationale
	~~In a 6-month oral repeat dose study of MORF-057 in Sprague Dawley rats, significant, reversible increases in circulating white blood cells (WBCs), lymphocytes, eosinophils, and large unstained cells were seen at the high dose of 450 mg/kg/day due to the pharmacological action of MORF-057. Non-adverse changes in cellularity in the spleen were observed at the high dose of 450 mg/kg/day, which were attributed to the pharmacological activity of MORF-057. The NOAEL in this study was 50 mg/kg/day in male and female rats. The adverse changes in rats after 6 months of dosing were degeneration/regeneration of chief cells in the glandular stomach at 125 or 450 mg/kg/day, which appeared to be partially reversible by 4 weeks post-dose.~~ ~~In a 9-month oral repeat dose study in beagle dogs, the NOAEL was 300 mg/kg/day, the highest dose tested. Non-adverse hepatobiliary changes were observed in several dogs that received 300 mg/kg/day of MORF-057; these changes correlated with increases in alanine transaminase (ALT) and alkaline phosphatase (ALP) measured in the same dogs. There were no adverse histopathological changes in dogs after 9 months of dosing. The degeneration/regeneration of chief cells in the glandular stomach observed in rats after 6 months of dosing was not noted in the beagle dogs at any dose up to 300 mg/kg/day, even though Cmax values were 10-fold higher and area under the concentration-time curve (AUC)last values were up to 20-fold higher in dogs compared to rats.~~ ~~For a human dose of 200 mg B.I.D. for 3 months, the safety margin for MORF-057 in rats, the most sensitive toxicology species, is 47.1-65.8-fold. For a human dose of 100 mg B.I.D., the safety margins are 101.5-141.8-fold for 3 months of dosing and 6.5-8.7-fold for chronic dosing. The safety margins compared to dogs is 121.4-136.9-fold for a human dose of 200 mg B.I.D. for 3 months and 161-177-fold for a human dose of 100 mg B.I.D.~~ ~~MORF-057 had no effects on fertility in male or female Sprague Dawley rats, no effect on early embryonic development in female rats, and no effects on embryo-fetal development in Sprague Dawley rats or white New Zealand rabbits.~~ *For human doses of 100 or 200 mg twice a day (B.I.D.), the calculated safety margin based on the no observed adverse effect levels (NOAELs) for the gastric changes identified in the 26-week study (50 mg/kg/day) is 8.2-fold or 4.1-fold, respectively. Likewise, the exposure multiple based on the NOAEL observed in dogs in the 39-week study (300 mg/kg/day) is 190.2-fold or 95.6-fold for the 100 or 200 mg B.I.D. doses, respectively. The exposure margin based on a dose (60 mg/kg) that caused non-adverse minimal elevations of liver transaminases (alanine transaminase [ALT] 1.24 x) in dogs dosed for 39 weeks is approximately 20-fold for the 100 mg B.I.D. and 10-fold for the 200 mg B.I.D. doses. The safety margin based on the embryo-fetal NOAEL in rabbits (50 mg/kg/day) is 0.8-fold or 1.6-fold for the 100 or 200 mg B.I.D. doses, respectively (refer to Section 4 of the current IB for details).*	
2.2.2. Clinical Findings	~~MORF-057 has been evaluated in a first-in-human study (MORF-057-101). This study included SAD, FE, and MAD assessments in healthy study participants. Overall, MORF-057 was well tolerated at all doses in the SAD, FE, and MAD cohorts with no safety signals identified. All treatment-emergent adverse events (TEAEs) reported during the study were mild to moderate in severity and resolved within the safety reporting period; none required study drug discontinuation. Following single doses between 25 mg and 400 mg and multiple doses between 25 mg B.I.D. and 100 mg B.I.D., MORF-057~~	To revise to the most up to date development program information

Section No. and Name	Description of Change	Brief Rationale
	~~was rapidly absorbed, and systemic exposure increased with an increase in dose in a generally proportional manner. No clinically relevant FE was demonstrated, indicating MORF-057 can be dosed without regard to timing of food intake. In the SAD and MAD cohorts, mean α4β7 receptor occupancy increased with dose and study day, achieving saturation (>99%) in certain individuals in each cohort above 25 mg, particularly in all study participants in the 100 mg B.I.D. MAD cohort. The variability of α4β7 receptor occupancy following single and multiple doses between 25 mg B.I.D. and 100 mg B.I.D. tended to decrease with an increase in dose and decreased after repeated B.I.D. doses from Day 1 to Day 14. In contrast, α4β1 receptor occupancy was below the lower limit of quantification at all doses in the SAD and MAD cohorts. Preliminary analyses of changes in lymphocyte subsets and C-C chemokine receptor 9 (CCR9) transcripts over time in the MAD cohort were consistent with those reported with other integrin pathway inhibitors, including vedolizumab. Overall, the results of this Phase 1 study demonstrated favorable PK/PD and safety profiles, supporting further clinical development of MORF-057.~~ ~~Clinical drug-drug interaction studies (Studies MORF-057-102 and MORF-057-103) evaluating the inhibitory and inductive potential of MORF-057 on cytochrome P450 3A (CYP3A) in healthy participants have been completed. MORF-057 did not have an effect on midazolam PK following a single dose, whereas it was identified as a weak inducer of cytochrome P450 3A4 (CYP3A4) with a 33% decrease of midazolam AUC (a weak inducer is defined as ≥20% and <50% decrease in AUC of a sensitive substrate) following multiple daily doses at 100 mg B.I.D. for 14 days (Study MORF-057-102). The midazolam drug-drug interaction results were consistent with the in vitro cytochrome P450 (CYP) inhibition and induction data indicating that, at the clinical exposure of 100 mg B.I.D. dose, MORF-057 has the potential to be a weak CYP3A4 inducer with minimal inhibition of major CYPs. Co-administration of ethinyl estradiol/levonorgestrel with MORF-057 (Study MORF-057-103), compared with administration of ethinyl estradiol/levonorgestrel alone, did not substantially alter ethinyl estradiol or levonorgestrel exposure (AUCs and Cmax). The 90% confidence intervals (CIs) of the geometric mean ratios for ethinyl estradiol AUC0-24, Cmax, and C24 were contained within the 80.00% to 125.00% no-effect range with the exception of the lower limits of AUC0-t and AUC0-inf. The 90% CIs of the geometric mean ratios for levonorgestrel AUCs and C24 were contained within the 80.00% to 125.00% no-effect range with the exception of the lower limit of Cmax. An overall marginal decrease in PK parameters of hormonal contraceptives was observed.~~ ~~Study CCI was conducted to evaluate the safety, tolerability, PK, PD, and FE of MORF-057 optimized formulation with IR capsules, which were tested at single doses of 25 mg, 100 mg, and 200 mg and at multiple doses of 200 mg B.I.D. (100 mg/capsule) in healthy participants. MORF-057 IR capsules were demonstrated to be safe and well tolerated, and only mild, non-serious adverse events (AEs) were observed, none of which were related to MORF-057. The IR capsules were rapidly absorbed, with a median Tmax of approximately 2.5 hours. High levels of target engagement of the α4β7 integrin receptor were observed following single and multiple B.I.D. doses of 200 mg MORF-057, with 99% mean α4β7 receptor occupancy observed after 14 days of 200 mg B.I.D. dosing. Changes in lymphocyte subsets were consistent with those reported for other integrin pathway inhibitors. Overall,~~	

Section No. and Name	Description of Change	Brief Rationale
	~~the new MORF-057 IR capsule formulation performed well and thus was recommended for use in the MORF-057 Phase 2 program.~~ *Collectively from 7 Phase 1 MORF-057 studies conducted in healthy participants (N=171 who received MORF-057 across all 7 studies), MORF-057 was well tolerated. There were no deaths or serious adverse events (SAEs).* *Drug-drug interactions (DDI) were also evaluated in the Phase 1 clinical program. At a dose of 100 mg B.I.D., MORF-057 is a weak inducer of cytochrome P450 3A (CYP3A). Although other doses have not been assessed for CYP3A induction, higher doses likely carry the risk of greater induction. MORF-057 is also a substrate of hepatic transporters organic anion transporting polypeptide (OATP) 1B1/3 and a sensitive substrate of CYP3A.* *Safety data are also available from the completed 52-week Treatment Period in the open-label Phase 2a study, MORF-057-201 (N=39) and from the 12-week Induction Period in this ongoing placebo-controlled Phase 2b study, MORF-057-202 (N=280). Overall, the treatment with MORF-057 was well tolerated in participants with moderately to severely active UC.* • *No death occurred in any of the completed or ongoing studies.* • *In the Phase 2b study, 5 participants who received either MORF-057 or placebo reported at least 1 serious treatment-emergent adverse event (TEAE), all in Study MORF-057-202. The Investigator considered that none of these serious TEAEs were related to the study drug.* • *In the Phase 2 studies, a total of 11 participants discontinued the study treatment due to TEAEs, with 6 MORF-057 treated participants in Study MORF-057-201 and 5 participants who received either MORF-057 or placebo in Study MORF-057-202.* • *The most frequently reported TEAEs in participants receiving MORF-057 at any dose in the Phase 2 studies included ulcerative colitis, anemia, nasopharyngitis, and headache.* • *No cases of Progressive Multifocal Leukoencephalopathy (PML) were reported in any of the completed or ongoing studies.* *The observed safety profile was consistent with the class safety profile for α4β7 integrin inhibitors.* *No safety signals have been identified in any of the MORF-057 clinical studies.* *The clinical efficacy of MORF-057 has been evaluated in UC patients in the open label Study MORF-057-201. In this study, a statistically significant decrease in Robarts Histopathology Index (RHI) Score from baseline to Week 12 was achieved, as well as a reduced modified Mayo Clinic Score (mMCS) from baseline. Additionally, a 25.7% remission rate was demonstrated based on mMCS.* *In the 12-week Induction Period analysis for this ongoing placebo-controlled Phase 2b study, MORF-057-202, the primary and secondary objectives of clinical remission and clinical response, respectively, were not achieved. A dose-response was observed between the 3 active doses, and 200 mg B.I.D. was the clinically most active dose.* *Refer to the current IB for details on the clinical studies conducted to date.*	

Section No. and Name	Description of Change	Brief Rationale
2.3.2.1. Risks of MORF-057	*Potential toxicity risks based on MORF-057 non-clinical data include effects to the stomach, liver, hematopoietic system, and embryo-fetal development. The gastric, hepatic, and hematopoietic findings demonstrated partial or complete reversibility and are generally clinically monitorable.* *Phase 1 DDI studies indicate that MORF-057 is a weak inducer of CYP3A. Sensitive CYP3A substrates for which small decreases in exposure can result in an unacceptable decrease in efficacy should be used with caution. In particular, systemic hormonal contraception should not be considered reliable and should not be used for the purpose of contraception.* *Based on available clinical data from both completed and ongoing studies, there are no anticipated risks of particular severity that require monitoring beyond the routine monitoring typically associated with integrin receptor antagonists or other immunomodulatory products in human studies.* ~~In healthy study participants (Study MORF-057-101), MORF-057 was well tolerated at all doses in the SAD, MAD, and FE cohorts with no safety signals identified. All TEAEs reported during the study were mild to moderate in severity and resolved within the safety reporting period; none required study drug discontinuation. In a 6-month toxicology study in Sprague Dawley rats and a 9-month toxicology study in beagle dogs, the NOAEL values were 50 mg/kg/day for rats and 300 mg/kg/day for dogs (Section 2.2.1).~~ Safety precautions that will be taken during the study are listed below: • ~~Progressive multifocal leukoencephalopathy (~~PML~~)~~ is a fatal opportunistic infection of the central nervous system and has been associated with systemic immunosuppressants, including integrin receptor antagonists (e.g., natalizumab and vedolizumab). • ~~Non-clinical Good Laboratory Practice studies in rats and rabbits showed that MORF-057 has no effects on fertility, early embryonic development, or embryo-fetal development. The available non-clinical data suggest that exposure to clinical strength doses of MORF-057 does not present a risk to the mother or fetus. Additional studies evaluating the effects of MORF-057 on pre- and post-natal development have not been conducted and the safety profile of MORF-057 in women who are pregnant or lactating is not available; therefore, inclusion/exclusion criteria (see Section 5) and safety monitoring regarding contraception and pregnancy have been included to mitigate the potential relevant risks.~~ • *Potential toxicity risks of MORF-057 based on non-clinical data include effects to embryo-fetal development. There is no clinical experience with MORF-057 in pregnant and breastfeeding women and therefore, the potential effects of MORF-057 use during pregnancy and lactation are not known. Women who are breastfeeding or pregnant are excluded from this study. Women of childbearing potential (WOCBP) and men who participate in this study must agree to avoid pregnancy and will be instructed on contraception requirements while they are in this study (see Section 10.5).* • *Clinical studies have demonstrated that MORF-057 is a weak inducer of CYP3A, a substrate of hepatic transporters OATP1B1/3, and a sensitive substrate of CYP3A. Inhibitors of OATP1B1/3 or inhibitors/inducers of CYP3A can alter exposures of MORF-057 and their use is prohibited in this study (see Section 6.7.3).*	To revise to the most up to date development program information

<table>
<tr><th>Section No. and Name</th><th>Description of Change</th><th>Brief Rationale</th></tr>
<tr><td>4.4. End of Study Definition</td><td>~~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 LTE Period.~~ A participant is considered to have completed the study if he/she has completed the Screening Period and 52-week Treatment Period of the main part of the study and attended the SFU Visit OR has been enrolled into the LTE Period, completed the Week 104/LTE EOT Visit and attended the SFU Visit.
The end of the study is defined as the date of the last visit or last scheduled procedure for the last participant in the study globally. This may occur during the main part of the study, or in the optional LTE Period, depending on that participant's choice whether or not to continue in the LTE Period.</td><td>To revise the End of Study definition</td></tr>
<tr><td>6.1. Study Treatment Description</td><td>A description of each study treatment type is provided in Table 3, and a description of each treatment group is provided in Table 4. ~~More detailed information about MORF-057 and placebo can be found in the Pharmacy Manual.~~ Refer to Section 8.3 for study drug administration instructions.
More detailed information about MORF-057 and placebo can be found in the Pharmacy Manual.
MORF-057 and placebo capsules will be manufactured, quality control tested, and released in accordance with Good Manufacturing Practice.</td><td>To clarify text</td></tr>
<tr><td>6.1. Study Treatment Description</td><td>Table 4. Treatment Groups
<table>
<tr><td>Group title</td><td>Group 1</td><td>Group 2</td><td>Group 3</td><td>Group 4</td></tr>
<tr><td>Type</td><td>• Induction: Experimental
Maintenance/LTE Period: Experimental</td><td>• Induction: Experimental
Maintenance/LTE Period: Experimental</td><td>• Induction: Experimental
Maintenance/LTE Period: Experimental</td><td>• Induction: Placebo
Maintenance/LTE Period: Experimental</td></tr>
<tr><td>Induction Period dosing regimen
(12 Weeks)</td><td><u>MORF-057</u>
(200 mg B.I.D.)
Total dose/day: 400 mg</td><td><u>MORF-057</u>
(100 mg B.I.D.)
Total dose/day: 200 mg

<u>~~Placebo~~</u></td><td><u>MORF-057</u>
(100 mg Q.D.-M)
Total dose/day: 100 mg

<u>~~Placebo~~</u></td><td><u>Placebo</u></td></tr>
</table></td><td>To revise the dose for the Long-Term Extension Period

In the Induction Period analysis for this study, a dose-response was observed between the 3 active doses, and 200 mg B.I.D. was the clinically most active dose. Changing the dose for the Long-Term Extension Period from 100 mg B.I.D. to 200 mg B.I.D. will provide current study participants with an opportunity to receive a higher dose that may be more clinically active. Based on all available clinical data, this change is not expected</td></tr>
</table>

Section No. and Name	Description of Change					Brief Rationale
	Maintenance Period dosing regimen (40 Weeks)/ *LTE* Period dosing regimen (52 Weeks)	MORF-057 (100 mg B.I.D.) Total dose/day: 200 mg ~~Placebo~~	MORF-057 (100 mg B.I.D.) Total dose/day: 200 mg ~~Placebo~~	MORF-057 (100 mg Q.D.-M) Total dose/day: 100 mg ~~Placebo~~	MORF-057 (200 mg Q.D.-E) Total dose/day: 200 mg ~~Placebo~~	to increase the risk of any potential safety effects.
	Instructions for administration	Take 1 capsule from EACH bottle for the respective dosing time (morning or evening). *Each bottle contains 30 capsules of either MORF-057 or placebo.*	Take 1 capsule from EACH bottle for the respective dosing time (morning or evening). *Each bottle contains 30 capsules of either MORF-057 or placebo.*	Take 1 capsule from EACH bottle for the respective dosing time (morning or evening). *Each bottle contains 30 capsules of either MORF-057 or placebo.*	Take 1 capsule from EACH bottle for the respective dosing time (morning or evening). *Each bottle contains 30 capsules of either MORF-057 or placebo.*	
	*LTE Period (52 Weeks)**	*MORF-057 (200 mg B.I.D.) Total dose/day: 400 mg*	*MORF-057 (200 mg B.I.D.) Total dose/day: 400 mg*	*MORF-057 (200 mg B.I.D.) Total dose/day: 400 mg*	*MORF-057 (200 mg B.I.D.) Total dose/day: 400 mg*	

<table>
<tr><th>Section No. and Name</th><th>Description of Change</th><th>Brief Rationale</th></tr>
<tr><td></td><td>
<table>
<tr><td>Instructions for administration</td><td>Bottles will contain 30 (thirty) MORF-057 100 mg capsules. Take 2 capsules in the morning and 2 capsules in the evening.</td><td>Bottles will contain 30 (thirty) MORF-057 100 mg capsules. Take 2 capsules in the morning and 2 capsules in the evening.</td><td>Bottles will contain 30 (thirty) MORF-057 100 mg capsules. Take 2 capsules in the morning and 2 capsules in the evening.</td><td>Bottles will contain 30 (thirty) MORF-057 100 mg capsules. Take 2 capsules in the morning and 2 capsules in the evening.</td></tr>
</table>
Abbreviations: B.I.D., twice a day; LTE, Long-Term Extension; Q.D.-E, once a day (evening); Q.D.-M, once a day (morning).
* Relevant for participants who consent to the dose switch in the LTE Period. For those that do not consent to the dose switch in the LTE Period, they will remain on their current LTE Period dose.
</td><td></td></tr>
<tr><td>6.3.1. Randomization</td><td>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). All participants who consent will be switched to a new MORF-057 dose in the LTE Period.</td><td>To clarify treatment assignment due to the dose switch for the Long-Term Extension Period</td></tr>
<tr><td>6.3.2. Blinding</td><td>Each participant will receive the same number of “morning bottles” and “evening bottles” according to the respective study period (Induction or Maintenance/LTE Period prior to dose switch). In the morning, participants should take 1 capsule from EACH “morning bottle.” In the evening, participants should take 1 capsule from EACH “evening bottle.” In the LTE Period after the dose switch, bottles will contain 30 (thirty) MORF-057 100 mg capsules. Participants who consent will take 2 capsules in the morning and 2 capsules in the evening. Those that do not consent to the dose switch will remain on their current LTE Period dose.
All other Sponsor personnel, the project study team, site Investigator, site staff, and study participants will remain blinded to the individual treatment assignments in the Induction and Maintenance/LTE Period through the end of the study including the LTE Period.</td><td>To clarify blinding procedures relative to the study period</td></tr>
<tr><td>6.3.2. Blinding</td><td>Sponsor ~~safety~~Pharmacovigilance staff ~~or designee may~~will unblind ~~the~~all SAE reports in the safety database~~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])~~.</td><td>To reflect the new process due to the transfer of pharmacovigilance responsibilities to Eli Lilly and Company</td></tr>
</table>

<table>
<tr><th>Section No. and Name</th><th>Description of Change</th><th>Brief Rationale</th></tr>
<tr><td>6.4. Study Treatment Compliance</td><td>The site staff will contact participants, by phone or other ~~forms~~means, on the next business day after the Visit 5 clinic visit to confirm the participants have switched from the Induction Period study drug to the new Maintenance Period study drug bottles. In addition, the site staff will contact the participants who consented, by phone or other means, on the next business day after the dose switch in the LTE Period to confirm the participants have switched to the new dose (200 mg B.I.D.) of study drug correctly. Record the date and time of the participant's first dose of the new dose (200 mg B.I.D.) in the source documents.</td><td>To clarify the process to confirm participants' treatment compliance following the dose switch for the Long-Term Extension Period</td></tr>
<tr><td>6.4. Study Treatment Compliance</td><td>When participants self-administer the study drug at home, compliance with prescribed treatment regimen will be assessed at each visit. Participants will be instructed to record all details about the study drug administered at home in the Participant Diary during the Induction and Maintenance Periods.</td><td>To clarify that participants do not need to record study drug administration details in their Participant Diaries during the LTE Period</td></tr>
<tr><td>6.6. Overdose</td><td>An overdose is defined as any timepoint where the study participant took more pills than directed or took pills from a different bottle than directed (if the total daily number of capsules consumed could exceed the maximum total daily number of capsules possible per protocol [4 total capsules/day]).</td><td>To clarify overdose definition</td></tr>
<tr><td>7.1.1. Permanent Discontinuation</td><td>The participant has confirmed PML
The participant has abnormal liver function results and re-testing results indicate clinically significant abnormalities, as detailed in Table 12
Repeated or significant N~~n~~on-compliance with study treatment (see Section 6.4) or study procedures to the extent that continued participation would pose an unacceptable risk to the participant, as determined by the Investigator</td><td>To revise permanent discontinuation reasons</td></tr>
<tr><td>7.1.2. Dose Interruptions and Re-challenge</td><td>7.1.2. Dose Interruption~~s~~ and Re-challenge
Situations requiring study drug interruption and the potential for re-challenge are presented in Table 7.
Decisions regarding dose interruptions and re-challenges will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.
Table 7. Study Drug Interruption and Re-challenge Guidelines
<table>
<tr><th>Clinical Situation/Event</th><th>Study Drug Interruption</th><th>Re-Challenge</th></tr>
<tr><td>Possible drug-induced liver damage</td><td>Requirements are outlined in Table 12</td><td>Requirements are outlined in Table 12</td></tr>
<tr><td>PML Screening</td><td>Requirements for study drug interruption after positive Subjective PML questionnaire are outlined in Section 8.8.5</td><td>Requirements for re-challenge are dependent on PML being definitively ruled out as outlined in algorithm within the PML Reference Guide</td></tr>
<tr><td>Serious Adverse Event</td><td>Investigator and Sponsor Medical Monitor may interrupt</td><td>Re-challenge decision will be made in each clinical situation in</td></tr>
</table></td><td>To clarify and consolidate dose interruptions and re-challenges</td></tr>
</table>

Section No. and Name	Description of Change	Brief Rationale
	<table><tr><td></td><td>*study drug administration if deemed necessary*</td><td>*consultation with Investigator and Sponsor Medical Monitor*</td></tr></table> *Abbreviations: PML, progressive multifocal leukoencephalopathy.* ~~.Guidance regarding dose interruptions for possible drug-induced liver injury (i.e., Hy's law cases) can be found in Table 11.~~ ~~7.1.3. Re-challenge~~ ~~Re-challenge may be allowed at the discretion of the Investigator and Medical Monitor.~~	
7.1.2. Dose Interruption and Re-challenge	**Addition of Table 7 required reordering of Tables.**	To reflect the addition of Table 7
8.1.1. Prior Medications	Study sites should make every effort to ~~collect~~*document a participant's* prior UC medications.	To clarify text
8.3.1. Dosing Instructions	*Induction Period* For the Induction Period, each 30-day study drug supply will consist of 2 cartons (1 for morning and 1 for evening). Inside each carton, there will be 2 corresponding bottles of study drug. Thus, an Induction Period 30-day study drug supply will consist of the following bottles: morning bottle #1, morning bottle #2, evening bottle #1, and evening bottle #2. *Each participant will be instructed to take 4 capsules per day, 1 from each bottle, during the Induction Period.* *Maintenance Period/LTE Period (all participants including those who do not consent to the dose switch in the LTE Period)* For the Maintenance Period/*LTE* Period, each 30-day study drug supply will consist of 1 carton. Inside the single carton, there will be 3 bottles of study drug: morning bottle, evening bottle #1, and evening bottle #2. In the morning, participants should take 1 capsule from ~~EACH~~*the* "morning bottle." In the evening, participants should take 1 capsule from EACH "evening bottle." Each participant will be instructed to take ~~4 capsules per day during the Induction Period and~~ 3 capsules per day during the Maintenance Period/*LTE* Period *(no dose switch)*. It is important to note that the bottles may contain capsules with either MORF-057 100 mg or placebo. Thus, the study drug must be taken exactly as directed in the Pharmacy Manual. *LTE Period (for participants who re-consent to the dose switch in the LTE Period)* *All participants will be asked to re-consent to switch their dose to 200 mg B.I.D. The dose switch will occur at Visit 10 or at a scheduled visit in the LTE Period (Visit 11, 12, or 13). If a participant does not consent to the dose switch, they will be allowed to stay on their current LTE Period dose as described above. During the LTE Period, all participants will receive their study drug supplies as bottles containing 30 (thirty) MORF-057 100 mg capsules. Participants should take 2 capsules in the morning and 2 capsules in the evening.* Participants will take the assigned study drug ~~(MORF-057 or placebo [see Section 6.1])~~ with water twice daily. The study drug can be taken with or without food. No *unplanned* dose adjustments will be allowed.	To revise the dose for the Long-Term Extension Period based on the completed Induction Period analysis where a dose-response was observed between the 3 active doses, and 200 mg B.I.D. was the most clinically active dose

Section No. and Name	Description of Change	Brief Rationale
8.5. Participant Diary	*Participant Diaries should not be completed after the participant has finished their participation in the study at the SFU Visit.* Diary entries will include study drug administration details *in the Induction and Maintenance Periods*, along with daily rectal bleeding, and stool frequency information (the 2 patient reported outcome measures of the Full and mMCS, see Section 8.7.3).	To clarify the Participant Diary should not be completed after the participant exits the study, and to clarify that participants do not need to record study drug administration details in their Participant Diaries during the LTE Period
8.6. Stool Collection	Stool samples will be required for pathogen/parasite testing, to assess fecal calprotectin levels, and for future ~~microbiome~~ research *(if participant consents; see Section 8.12)*.	To reflect the addition of an optional exploratory fecal calprotectin sample
8.7.1. Endoscopy with Biopsy	Endoscopy will be performed at Screening (Visit 1) and during Stage 1 of Visits 5, 10/EOT, and 14/*LTE* EOT.	To reflect the change in the Long-Term Extension Period End of Treatment name
8.7.1. Endoscopy with Biopsy	Table ~~8~~*9*. Instructions for Endoscopic Biopsies Visit 14/ (Week 104 or *LTE* EOT) Abbreviations: EOT, End of Treatment; *LTE EOT, Long-Term Extension End of Treatment*.	To reflect the change in the Long-Term Extension Period End of Treatment name
8.8.1. Physical Examinations	Physical examinations will be performed at the timepoints specified in the SoA (Section 1.2). A complete physical exam is required at Screening, Visit 10/EOT, and Visit 14/*LTE* EOT; and a targeted exam may be performed at all other required visits.	To reflect the change in the Long-Term Extension Period End of Treatment name
8.8.4. Clinical Safety Laboratory Tests	All protocol-required laboratory tests, as defined in Section 10.3, must be conducted in accordance with the Laboratory Manual. In case of abnormal liver function test results, Investigators should follow the instructions in ~~Table 11 (Hy's law cases table)~~ *Table 12* for re-testing and follow-up procedures.	Administrative
8.8.5. Progressive Multifocal Leukoencephalopathy	The Subjective PML Checklist will be administered to participants during Screening ~~to exclude individuals with a positive response from enrolling into the study~~. The Subjective PML Checklist (Section 10.2) will also be completed at study visits according to the schedule in the SoA (Section 1.2). If the results of the questionnaire are suggestive of signs and symptoms of PML, ~~the~~*hold any further doses of study drug and notify the Medical Monitor. The* participant will undergo Objective PML Checklist testing (Section 10.2), a full neurological exam by a neurologist, and, if indicated, additional testing. *Study drug may not be resumed until PML has been definitively ruled out.*	To clarify PML monitoring

Section No. and Name	Description of Change	Brief Rationale
	A participant with confirmed PML will be excluded from the study or will permanently discontinue study drug and will be withdrawn from the study (see Section 7.1.1).	
8.9. Adverse Events and Other Safety Reporting	Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally ~~authorized~~*acceptable* representative).	To reflect current ICH guidelines
8.9.4. Regulatory Reporting Requirements for SAEs, SUSARs, and Periodic Reports	~~Morphic Therapeutic~~*The Sponsor* or a designee is responsible for notifying the relevant regulators (including the authorities in the European Economic Area (EEA) via EudraVigilance and the IRBs/IECs) and the Investigator sites within the specified timeframes of all SUSARs, as applicable per local requirements. ~~Morphic Therapeutic~~*The Sponsor* will make the determination whether the event is unexpected. **The following sentence is in Protocol Amendment Version 2.0 but not in Version 2.1 and is added to Version 3.0.** *It is the Principal Investigator's responsibility to notify the IRB/IEC according to the relevant regulatory timelines of ~~all~~ SUSARs of which the Investigator is notified by ~~Morphic Therapeutic~~the Sponsor that occur at his or her site, if appropriate.*	To clarify reporting requirements
8.12. Future Research	If consent is provided by the participant, blood, stool, and colonic tissue samples will be collected and may be used for ~~further~~*future* PD, pharmacogenomics, microbiome-related research, *fecal calprotectin assessment,* and future research. If consent is provided by the participant, the remaining blood and colonic tissue samples from the study-required procedures may also be used for future research, including future PK research.	To reflect the addition of an optional exploratory fecal calprotectin sample and clarify sample collection for future research
8.13. Potential Adjustments due to COVID-19 or Other Global Issues	8.13. Potential Adjustments due to ~~COVID-19~~*Pandemics* or Other Global Issues Adjustments to the planned study procedures might be necessary due to ~~the ongoing~~ ~~COVID-19~~ pandemic *events* and/or newly identified global issues.	To revise for any pandemic
10.1.1. Regulatory and Ethical Considerations	**IRB/IEC information was in Protocol Amendment Version 2.0 but not Version 2.1, and "Member States Concerned" was in Version 2.1 but not Version 2.0. Both are now in Version 3.0.** The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to~~,~~ *an IRB/IEC or to the Member States Concerned and* reviewed~~,~~ and approved by the *IRB/IEC or Member States Concerned, as applicable,* before the study is initiated. Any amendments to the protocol will require *IRB/IEC or Member States Concerned, as applicable,* approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants. Protocols and any substantial amendments to the protocol will require *Member States Concerned or health authority*, *as applicable,* approval prior to initiation, in line with country-specific requirements. The Investigator will be responsible for the following:	To combine Protocol Amendment Version 2.0 and Version 2.1 to Version 3.0

Section No. and Name	Description of Change	Brief Rationale
	• *Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC, as applicable* • *Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures, as applicable* • Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the *IRB/IEC or Member States Concerned, as applicable,* European Union Clinical Trials Regulation 536/2014 for clinical studies, and all other applicable local regulations	
10.1.4. Informed Consent Process	**IRB/IEC information was in Protocol Amendment Version 2.0 but not Version 2.1, and "Member States Concerned" was in Version 2.1 but not Version 2.0. Both are now in Version 3.0.** The Investigator or his/her representative will explain the nature of the study, including the risks and benefits, to each participant or his/her legally ~~authorized~~*acceptable* representative, if applicable, and answer all questions regarding the study. Participants must be informed that their participation is voluntary. Each participant or his/her legally ~~authorized~~*acceptable* representative, if applicable, will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, *Member States Concerned/*~~and~~ the IRB/IEC or study center. A copy of the ICF(s) must be provided to the participant or his/her legally ~~authorized~~*acceptable* representative, if applicable.	To reflect current ICH guidelines and combine Protocol Amendment Version 2.0 and Version 2.1 to Version 3.0
10.1.4. Informed Consent Process	Additional Consents The main ICF will contain separate sections for the following additional consents: • Optional collection of blood, colonic tissue, and stool samples for future PD, microbiome-related analyses, *fecal calprotectin assessment,* and future research.~~, and~~ *If consent is provided,* use of the remaining blood and colonic tissue samples from the study-required procedures *may also be used* for future research, including future PK research (see Sections 8.7.1, 8.10, 8.12, and the SoA in Section 1.2).	To reflect the addition of an optional exploratory fecal calprotectin sample
10.1.4. Informed Consent Process	Additional ICFs will be provided to participants or their partners for review and signature, as needed: • ~~Pregnant Partner~~*Pregnancy Follow-up* (see Section 8.9.5)	To revise the name of the consent form
10.1.5. Data Protection	**IRB/IEC information was in Protocol Amendment Version 2.0 but not Version 2.1, and "Member States Concerned" was in Version 2.1 but not Version 2.0. Both are now in Version 3.0.** In particular, the participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate *IRB/IEC members or Member States Concerned members, as applicable,* and by inspectors from regulatory authorities.	To combine Protocol Amendment Version 2.0 and Version 2.1 to Version 3.0
10.1.9. Data Quality Assurance	**IRB/IEC information was in Protocol Amendment Version 2.0 but not Version 2.1 and is now in Version 3.0.**	To combine Protocol Amendment Version

Section No. and Name	Description of Change	Brief Rationale
	The Investigator must permit study-related monitoring, audits, *IRB/IEC review (if applicable)*, and regulatory agency inspections and provide direct access to source data documents.	2.0 and Version 2.1 to Version 3.0
10.1.9. Data Quality Assurance	**The following paragraph was kept from Protocol Amendment Version 2.1 and not edited as is in Version 2.0.** The contents of the electronic Trial Master File pertaining to the conduct of this study must be retained by the Sponsor and the Investigator for at least 25 years after study completion unless local regulations, institutional policies, or by an agreement with the Sponsor require a longer retention period. However, the medical files of participants shall be archived in accordance with national law. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.	To combine Protocol Amendment Version 2.0 and Version 2.1 to Version 3.0
10.1.9. Data Quality Assurance	Please reference *the current version of* ICH E6 ~~(R2) Section 8~~ for the minimum list of essential documents required for the conduct of a clinical trial.	To reflect current ICH guidelines
10.1.11.2. Study/Site Termination	**IRB/IEC information was in Protocol Amendment Version 2.0 but not Version 2.1, and "Member States Concerned" was in Version 2.1 but not Version 2.0. Both are now in Version 3.0.** Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to: ~~For study termination:~~ ~~• Discontinuation of further study drug development~~ ~~For site termination:~~ • Failure of the Investigator to comply with the protocol, the requirements of the *Member States Concerned or IRB/IEC, as applicable,* or local health authorities, the Sponsor's procedures, or GCP guidelines • Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator • Total number of participants enrolled earlier than expected *Reasons for study termination include, but are not limited to:* • *Recommendation of the DSMB based on the ongoing review of safety* • *If a positive benefit/risk ratio is no longer observed, based on DSMB review of unblinded data* • *Discontinuation of further study drug development* If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the *Member States Concerned~~,~~ and/or the IRBs/IECs, as applicable,* the regulatory authorities, and any CROs used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements.	To combine Protocol Amendment Version 2.0 and Version 2.1 to Version 3.0 and clarify study/site termination
10.2. Appendix 2: Progressive Multifocal Leukoencephalopathy Checklists	Objective PML Checklist – To be completed for ~~patients~~*participants* with positive subjective finding **Table Footnotes** × If objective test corroborates the reported symptom, refer the participant for a Neurology consult. Otherwise, please follow up with the participant one week after the *O~~o~~*bjective *C~~c~~*hecklist was administered to ensure symptoms are not recurring.	Administrative

Section No. and Name	Description of Change	Brief Rationale
	× Please notify your Clinical Research Associate and ~~Morphic Therapeutic~~*the Sponsor* of any positive *O*~~o~~bjective *C*~~c~~hecklist findings.	
10.3. Appendix 3: Clinical Laboratory Tests	**IRB/IEC information was in Protocol Amendment Version 2.0 but not Version 2.1, and "Member States Concerned" was in Version 2.1 but not Version 2.0. Both are now in Version 3.0.** **Table 11 Footnotes** a Local urine testing will be standard for the protocol unless serum testing is required by local regulation or *Member States Concerned or IRB/IEC, as applicable*.	To combine Protocol Amendment Version 2.0 and Version 2.1 to Version 3.0
10.3. Appendix 3: Clinical Laboratory Tests	Table ~~1~~*12*. Abnormal Liver Function Results: Re-testing and Follow-up Procedures Next steps: • Discuss with Medical Monitor regarding resumption of IMP** **Table 12 Footnotes** *** Resumption of the study drug can be considered only in consultation with the Medical Monitor and only if the liver test results returned to near baseline and if a self-limited non-study drug etiology is identified. Otherwise, the study drug should be permanently discontinued.*	To clarify follow-up procedures for abnormal liver function results
10.4.2. Definition of SAE	c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been admitted *to the hospital for inpatient care, regardless of the length of stay*~~(usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting~~.	To clarify the definition of SAE
10.4.4. Reporting of SAEs	• SAEs will be reported to *Lilly Global Patient Safety by email* CCI [redacted] *(email address will be defined in a study-specific safety reporting plan)*.	To update SAE reporting email due to the transfer of pharmacovigilance responsibilities to Eli Lilly and Company
10.5.2. Contraception Guidance for Female Study Participants	10.5.2. Contraception Guidance *for Female Study Participants* *10.5.2.1. Female Study Participants Who Do Not Consent to Dose Switch in LTE Period* *Note: This is relevant for participants who do not consent to the dose switch in the LTE Period. For contraception requirements for those who do consent to the dose switch in the LTE Period, see Section 10.5.2.2.* *10.5.2.2. Female Study Participants Who Do Consent to Dose Switch in LTE Period* *Note: This is relevant for participants who do consent to the dose switch to 200 mg B.I.D. in the LTE Period. For contraception requirements for those who do not consent to the dose switch in the LTE Period, see Section 10.5.2.1.* *For participants that are currently using systemic (e.g., oral, implantable) hormonal contraception but have consented to the MORF-057 dose switch:*	To revise the contraception requirements for participants who consent to the increased study drug dose in the LTE Period

<table>
<tr><th>Section No. and Name</th><th>Description of Change</th><th>Brief Rationale</th></tr>
<tr><td></td><td>

They must change to new contraception by the time of DSFU 2 (8 weeks after the dose switch) or as soon as possible.
All participants must remain abstinent until new contraception is in place.

WOCBP and WONCBP may participate in this trial.
WOCBP who are completely abstinent as their preferred and usual lifestyle, or exclusively engage in sexual relations with other individual(s) who are assigned female at birth, as their preferred and usual lifestyle must follow the rules in this table.
<table>
<tr><th>Must…</th><th>Must not…</th></tr>
<tr><td>agree to either remain abstinent or exclusively engage in sexual relations with other individual(s) who are assigned female at birth, and not plan a pregnancy during the study</td><td>

use periodic abstinence methods

calendar
ovulation
symptothermal, or
post-ovulation

declare abstinence just for the duration of a trial, or
use the withdrawal method

</td></tr>
</table>
WOCBP who are NOT completely abstinent as their preferred and usual lifestyle, or who do NOT exclusively engage in sexual relations with other individual(s) who are assigned female at birth, as their preferred and usual lifestyle, must follow the rules in this table.
<table>
<tr><th>Must…</th></tr>
<tr><td>Agree to use 1 highly effective method of contraception together with a barrier method of contraception (see below). Note: During this study, systemic hormonal contraception is not considered effective or highly effective and therefore is not permitted as a means of contraception.

Barrier method of contraception includes condoms (male or female) with or without a spermicidal agent, diaphragm, or cervical cap with spermicide.</td></tr>
</table>
</td><td></td></tr>
</table>

<table>
<tr><th>Section No. and Name</th><th>Description of Change</th><th>Brief Rationale</th></tr>
<tr><td></td><td>
These methods of contraception must be used during the study and for at least 28 days after the last dose of the study intervention.

Examples of different methods of contraception:
Note: Participants who switch to 200 mg B.I.D. cannot use oral or systemic hormonal contraception as an effective method.
<table>
<tr><th>Methods</th><th>Examples</th></tr>
<tr><td>Highly effective contraception (less than 1% failure rate)</td><td>
• Fallopian tubal sterilization methods other than bilateral salpingectomy (laparoscopic bipolar electrocoagulation, plastic ring application on the uterine tubes, fallopian tube ligation, hysteroscopic sterilization). Note: Bilateral salpingectomy is indicative of permanent sterilization. Please see the WONCBP definition above.
• Total abstinence
• Sexual relationships exclusively between individuals who are assigned the same sex at birth
• Vasectomy – for individuals assigned male at birth in clinical trials and for the partner of an individual assigned female at birth (if only sexual partner)
• Fallopian tube implants (if confirmed by hysterosalpingogram), or
• Intrauterine devices (IUD) with or without hormone-releasing system
</td></tr>
<tr><td>Effective contraception</td><td>
• Penile condom with or without spermicide
• Vaginal condom with or without spermicide
• Diaphragm with spermicide
</td></tr>
</table>
</td><td></td></tr>
</table>

Section No. and Name	Description of Change		Brief Rationale
		• *Cervical sponge with spermicide, or* • *Cervical cap with spermicide* *Note: Penile and vaginal condoms should not be used in combination.*	
	Ineffective methods of contraception whether used alone or in any combination	• *Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation (listed below)* –*oral* –*intravaginal* –*transdermal* –*injectable* • *Progestogen-only hormone contraception associated with inhibition of ovulation* –*oral* –*injectable* –*implantable* • *Spermicide alone* • *Periodic abstinence* • *Fertility awareness (calendar method, temperature method, cervical mucus, or symptothermal)* • *Withdrawal* • *Postcoital douche, or* • *Lactational amenorrhea* • *Ablation (endometrial or uterine) is not considered a form of contraception*	

<table>
<tr><th>Section No. and Name</th><th>Description of Change</th><th>Brief Rationale</th></tr>
<tr><td></td><td>Abbreviations: IUD, intrauterine device; WONCBP, woman of non-childbearing potential.</td><td></td></tr>
<tr><td>10.5.3. Contraception Guidance for Male Study Participants</td><td>10.5.3. Contraception Guidance for Male Study Participants
<table>
<tr><th>Participant Population</th><th>Contraception Guidance</th></tr>
<tr><td>All male study participants…</td><td>should refrain from sperm donation for the duration of the study and for at least 14 days after the last dose of the study intervention.</td></tr>
<tr><td>Male study participants with partner(s) who are WOCBP [a]…</td><td>must
remain abstinent (if this is their preferred and usual lifestyle), or
use condoms and at least 1 additional effective method of contraception (see “Examples of different methods of contraception” table) for the duration of the study and for at least 28 days after the last dose of the study intervention.</td></tr>
<tr><td>Male study participants with partner(s) who are pregnant [a]…</td><td>must
remain abstinent (if this is their preferred and usual lifestyle), or
use condoms for the duration of the study and for at least 28 days after the last dose of the study intervention.</td></tr>
<tr><td>Male study participants who exclusively engage in sexual relations with other individual(s) who are</td><td>are not required to use contraception.</td></tr>
</table></td><td>To revise the contraception requirements for participants who consent to the increased study drug dose in the LTE Period</td></tr>
</table>

<table>
<tr><th>Section No. and Name</th><th>Description of Change</th><th>Brief Rationale</th></tr>
<tr><td></td><td>
<table>
<tr><td>assigned male at birth, as their preferred and usual lifestyle…</td><td></td></tr>
</table>
Abbreviations: WOCBP, woman of childbearing potential.
a Male study participants who have undergone orchiectomy but not penectomy must use condoms during sex, but the partner who is WOCBP is not required to use an additional form of contraception. Male study participants who have undergone orchiectomy and penectomy are not required to use condoms.
Examples of different methods of contraception [a]:
<table>
<tr><th>Methods</th><th>Examples</th></tr>
<tr><td>Highly effective contraception (less than 1% failure rate)</td><td>
• Fallopian tubal sterilization methods other than bilateral salpingectomy (laparoscopic bipolar electrocoagulation, plastic ring application on the uterine tubes, fallopian tube ligation, hysteroscopic sterilization). Note: Bilateral salpingectomy is indicative of permanent sterilization. Please see the WONCBP definition above.
• Combined (estrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation (listed below)
–oral
–intravaginal
–transdermal
–injectable
• Progestogen-only hormonal contraception associated with inhibition of ovulation
–oral
–injectable
–implantable
</td></tr>
</table>
</td><td></td></tr>
</table>

Section No. and Name	Description of Change		Brief Rationale
		• *Total abstinence* • *Sexual relationships exclusively between individuals who are assigned the same sex at birth* • *Vasectomy – for individuals assigned male at birth in clinical trials and for the partner of an individual assigned female at birth (if only sexual partner)* • *Fallopian tube implants (if confirmed by hysterosalpingogram), or* • *Intrauterine devices (IUD) with or without hormone-releasing system*	
	Effective contraception	• *Progestogen-only hormonal contraception, where inhibition of ovulation is not the primary mode of action* • *Penile condom with or without spermicide* • *Vaginal condom with or without spermicide* • *Diaphragm with spermicide* • *Cervical sponge with spermicide* • *Cervical cap with spermicide* *Note: Penile and vaginal condoms should not be used in combination.*	
	Ineffective methods of contraception whether used alone or in any combination	• *Spermicide alone* • *Periodic abstinence* • *Fertility awareness (calendar method, temperature method, cervical mucus, or symptothermal)* • *Withdrawal* • *Postcoital douche, or*	

Section No. and Name	Description of Change	Brief Rationale
	• *Lactational amenorrhea* *Abbreviations: IUD, intrauterine device; WONCBP, woman of non-childbearing potential.* *a Ablation (endometrial or uterine) is not considered a form of contraception.*	
10.9. Appendix 9: Genetics	**IRB/IEC information was in Protocol Amendment Version 2.0 but not Version 2.1, and "Member States Concerned" was in Version 2.1 but not Version 2.0. Both are now in Version 3.0.** • Genetic variation may impact a participant's response to the study drug, susceptibility to, and severity and progression of disease. Variable response to study treatment may be due to genetic determinants that impact treatment absorption, distribution, metabolism, and excretion; mechanism of action of the treatment; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and *IRB/IEC or Member States Concerned* allow, *as applicable,* blood samples will be collected for DNA analysis from consenting participants.	To combine Protocol Amendment Version 2.0 and Version 2.1 to Version 3.0
10.11. Appendix 11: Changes to This Protocol in Previous Amendments	**Added Appendix 11 showing changes made in previous Protocol Amendment Version 2.0 and 2.1.**	Administrative

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Abbreviations

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AUC	Area under the concentration-time curve
AUC_{0-24}	Area under the concentration-time curve from time 0 to 24 hours post-dose
AUC_{0-inf}	Area under the concentration-time curve from time 0 to infinity
AUC_{0-t}	Area under the concentration-time curve from time 0 to last measurable concentration
AUC_{last}	Area under the concentration-time curve from time 0 to last data point
B.I.D.	Twice a day
BMI	Body mass index
C_{24}	Plasma concentration at 24 hours post-dose
CCR9	C-C chemokine receptor 9
C. difficile	*Clostridiodes difficile*
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	Maximum observed plasma concentration
CMH	Cochran-Mantel-Haenszel
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
C_{trough}	Trough plasma concentration (measured concentration at the end of a dosing interval, taken before the next dose)
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
CYP3A	Cytochrome P450 3A
DDI	Drug-drug interaction
DNA	Deoxyribonucleic acid
DSFU	Dose Switch Follow-up
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EEA	European Economic Area
EOT	End of Treatment
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FE	Food effect
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
hCG	human chorionic gonadotropin
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life

HRT	Hormonal replacement therapy
hs-CRP	High-sensitivity C-reactive protein
IB	Investigator's Brochure
IBD	Inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
IC_{50}	Half maximal inhibitory concentration
IC_{90}	90% of maximal inhibitory concentration
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IGRA	Interferon gamma release assay
IL	Interleukin
IR	Immediate-release
IRB	Institutional Review Board
IRT	Interactive Response Technology
JAK	Janus kinase
LTE	Long-Term Extension
LTE EOT	Long-Term Extension End of Treatment
LVEF	Left ventricular ejection fraction
MAD	Multiple ascending dose
MCS	Full Mayo Clinic Score
MedDRA	Medical Dictionary of Regulatory Activities
MES	Mayo Endoscopic Score
mMCS	Modified Mayo Clinic Score
mRNA	Messenger ribonucleic acid
NI	Nancy Histopathology Index
NOAEL	No-observed-adverse-effect level
PD	Pharmacodynamics
PGA	Physician's Global Assessment
PK	Pharmacokinetics
PML	Progressive multifocal leukoencephalopathy
P.O.	By mouth
PP	Per Protocol
PPD	Purified protein derivative
PRO	Patient-reported outcome
PT	Preferred Term
Q.D.	Once a day
Q.D. -E	Once a day (evening)
Q.D. -M	Once a day (morning)
QTcF	QT interval corrected through use of Fridericia's formula
RAMP	Risk Assessment and Minimization Program
RHI	Robarts Histopathology Index
S1P	Sphingosine-1-phosphate
SAD	Single ascending dose

SAE	Serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SC	Subcutaneous
SFU	Safety Follow-up
SoA	Schedule of Activities
SOC	System Organ Class
SUSAR	Suspected unexpected serious adverse event
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
T_{max}	Time to reach C_{max}. Defined as the first point if multiple maximum values occur
TNF-α	Tumor necrosis factor alpha
UC	Ulcerative colitis
ULN	Upper limit of normal
WBC	White blood cell
WOCBP	Woman of Childbearing Potential
WONCBP	Woman of Non-childbearing Potential

1. Protocol Summary

1.1. Synopsis

Protocol Title: 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)**

Brief Title: A Phase 2b Study to Evaluate MORF-057 in Adults with Moderately to Severely Active UC

Rationale:

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

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

Relevant data from all non-clinical and clinical studies in the MORF-057 development program are provided in the current Investigator's Brochure.

The current Phase 2b study (MORF-057-202) aims to evaluate the efficacy and safety of 3 active dose regimens of MORF-057 (as capsule, by mouth [P.O.]) versus placebo in study participants with moderately to severely active UC. Data from this study will provide further information to advance the clinical development program of MORF-057 for the treatment of UC.

Objectives and Endpoints:

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

Objectives	Endpoints
Primary 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

Objectives	Endpoints
	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)
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)

Objectives	Endpoints
	• 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 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

Objectives	Endpoints
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 treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), and TEAEs leading to study drug discontinuation
Pharmacokinetics (PK)	
To characterize the PK of MORF-057	• MORF-057 concentration in plasma

Objectives	Endpoints
Exploratory Pharmacodynamics (PD)	
To characterize the PD of MORF-057 in peripheral blood	• $\alpha_4\beta_7$ receptor occupancy in blood over time • $\alpha_4\beta_1$ receptor occupancy in blood over time • Change from baseline over time in blood C-C chemokine receptor 9 (CCR9) messenger ribonucleic acid (mRNA) • Change from baseline over time in blood lymphocyte subsets

Efficacy Analysis Definitions
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 ≤2 (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
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 ≥12 consecutive weeks prior to Week 52.

Overall 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 4 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 Long-Term Extension (LTE) Period.

During the optional LTE Period, there will be up to 7 scheduled visits: 4 Treatment Visits (Visits 11-14 at Weeks 65, 78, 91, and 104 [Long-Term Extension (LTE) EOT]), 2 Dose Switch Follow-ups (DSFUs; these 2 visits will only occur if participant consents to dose switch), 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 LTE Period is completed or earlier if treatment is discontinued early).

Due to the changes in Version 3.0 of this protocol, all participants who choose to continue their treatment in the LTE Period will be asked to re-consent to the LTE Period dose switch to 200 mg twice a day (B.I.D.). The dose switch will occur at Visit 10 or at a scheduled visit in the LTE Period (Visit 11, 12, or 13). If the participant does not consent to the dose switch, they will be allowed to remain on their current LTE Period dose and schedule; they will not need to attend DSFUs 1 or 2. Participants in the LTE Period who consent to the dose switch will have a scheduled DSFU 1 at 4 weeks after the dose switch, and then DSFU 2 will be 4 weeks after DSFU 1. The participant will then attend the next scheduled visit (Visit 11, 12, 13, or 14) per the Schedule of Activities (SoA). A participant cannot switch their dose after Visit 13. An SFU Visit will occur 4 weeks after the last dose of study drug is received, which will be at Week 108 if the full LTE Period is completed or earlier if treatment is discontinued early.

Participants who do not enroll into the LTE Period will complete the final SFU Visit (4 weeks after receiving the last dose of MORF-057) for the main part of the study (a maximum time

on-study of 62 weeks). Participants who choose to continue in the LTE Period will not complete the SFU Visit for the main part of the study; instead, they will directly enter the LTE Period and complete a separate SFU Visit (4 weeks after receiving the last dose of MORF-057 in the LTE Period), 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.

Study Treatment:

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 LTE Period. All participants who choose to continue in the LTE Period will continue receiving the same MORF-057 regimen they had during the Maintenance Period for up to an additional 52 weeks. However, at Visit 10 or at a scheduled visit in the LTE Period (Visit 11, 12, or 13), if the participant consents, the MORF-057 dose for the LTE Period will be switched to 200 mg B.I.D. If the participant does not consent to the dose switch, they will be allowed to remain on their current LTE Period dose and schedule. The dosing regimens for the 4 treatment groups during the study are shown below.

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

Abbreviations: B.I.D., twice a day; LTE, Long-Term Extension; Q.D.-E, once a day (evening); Q.D.-M, once a day (morning).
* Relevant for participants who consent to the dose switch in the LTE Period. For those that do not consent to the dose switch in the LTE Period, they will remain on their current LTE Period dose.

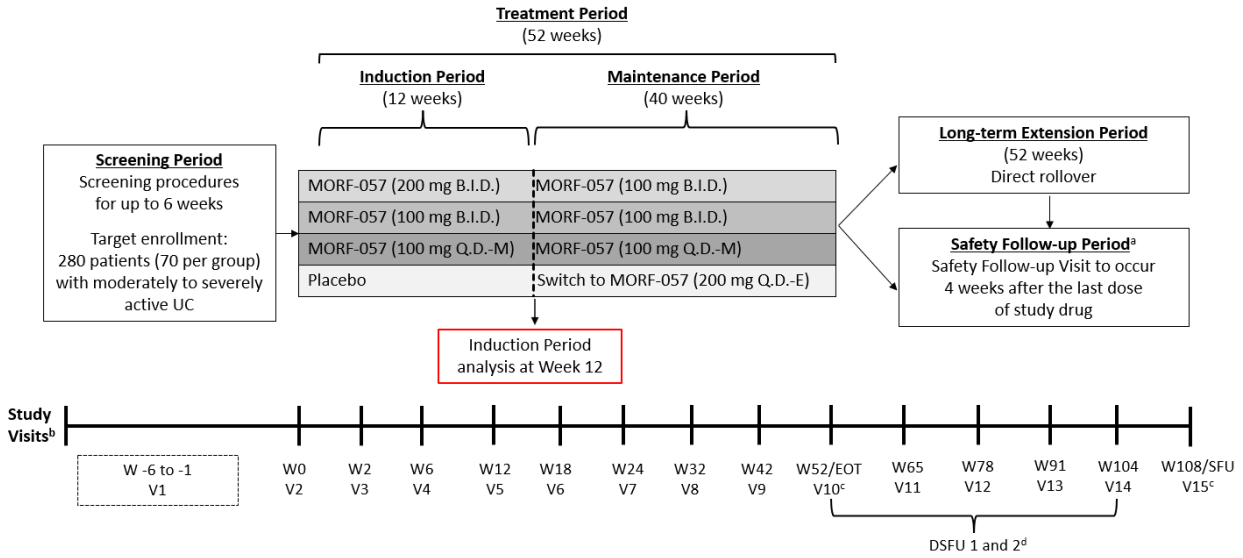
The study drug will be supplied as immediate-release capsules for oral administration (MORF-057 100 mg capsule or placebo). Refer to the main protocol for additional treatment details.

The first dose of the study drug will be administered in the clinic on study Day 1 under the supervision of study personnel. All subsequent doses will be self-administered at home, with the exception of the morning doses for Visits 2-10, which will be administered during the study visits

after pre-dose blood samples have been drawn (see details in the SoA). Participants will be instructed to record all details about the doses administered at home in the Participant Diary.

A study schema is provided below.

Study Schema:



Abbreviations: B.I.D., twice a day; DSFU, Dose Switch Follow-up; 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.

a The SFU Visit will not be performed at Week 56 for participants who enter the LTE Period.

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

c 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.

d At Visit 10 or at a scheduled visit in the LTE Period (Visit 11, 12, or 13), all participants will be asked to re-consent to switch their dose to 200 mg B.I.D. Participants who do not consent to the dose switch will remain on their current LTE Period dose. The DSFU 1 will occur 4 weeks after the dose switch, and DSFU 2 will occur 4 weeks after DSFU 1. Participants who do not consent to the dose switch will not need to attend DSFUs 1 or 2.

Main Inclusion Criteria:

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

Age

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

Type of Participant and Disease Characteristics

2. Participant has had diagnosis of UC supported by signs/symptoms, endoscopy, and histology for at least 3 months prior to Screening. Moderately to severely active UC was determined during the Screening Period with the following criteria: an mMCS of 5 to 9 (inclusive), with an MES ≥2 (confirmed by central reader)
3. Has evidence of UC extending at least 15 cm from the anal verge

4. Demonstrated an inadequate response, loss of response, or intolerance to at least one of the following treatments (including oral aminosalicylates*, corticosteroids, immunosuppressants, and/or advanced therapies for UC) in the opinion of the Investigator, as defined below:

    a. Oral aminosalicylates (e.g., mesalamine, sulfasalazine, olsalazine, or balsalazide)

        - Signs and symptoms of persistently active disease during a current or prior course of at least 4 weeks of treatment with ≥2.0 g/day mesalamine, 4 g/day sulfasalazine, 1 g/day olsalazine, or 6.75 g/day balsalazide

    ***Note:** Inadequate response, loss of response, or intolerance to oral aminosalicylates does not apply to this Inclusion Criterion in European Union (EU) countries.

    b. Corticosteroids

        - Signs and symptoms of persistently active disease despite a history of at least one induction regimen that included a dose equivalent to prednisone ≥30 mg/day orally for at least 3 weeks or intravenously for 1 week

        OR

        - Unable to taper corticosteroids to below a dose equivalent to prednisone 10 mg daily orally without recurrent active disease

        OR

        - Signs and symptoms of persistently active disease during or after a course of at least 4 weeks of treatment with 9 mg/day budesonide or 5 mg/day beclomethasone

        OR

        - Unable to taper oral budesonide below 6 mg/day without recurrent active disease

        OR

        - History of intolerance to corticosteroids (including, but not limited to, Cushing's syndrome, osteopenia/osteoporosis, hyperglycemia, insomnia, or infection)

    c. Immunosuppressants (e.g., azathioprine, 6-mercaptopurine, or methotrexate)

        - Signs and symptoms of persistently active disease despite a history of at least one 8*-week regimen of oral azathioprine (≥1.5 mg/kg/day), 6-mercaptopurine (≥1 mg/kg/day or a documented 6-thioguanine nucleotide level of 230-450 pmol/8 × 108 red blood cell count or higher on the current dosing regimen), injectable methotrexate (≥12.5 mg/week subcutaneous [SC] or intramuscular)

            ***Note:** A history of signs and symptoms of persistently active disease despite a history of at least one 12-week regimen of immunosuppressants is required in EU countries.

        OR

- History of intolerance to at least one immunosuppressant (including, but not limited to, nausea/vomiting, abdominal pain, pancreatitis, liver enzyme abnormalities, lymphopenia, or infection)

Note: Oral methotrexate use is allowed during the study; however, prior or current use of oral methotrexate is not sufficient for inclusion into the study unless the participant was previously treated with aminosalicylates, corticosteroids, or immunosuppressants (azathioprine or 6-mercaptopurine) and had an inadequate response, loss of response, or intolerance to the therapy as defined above.

d. Advanced therapies for UC (e.g., biologic agents, Janus kinase [JAK] antagonists, or sphingosine-1-phosphate [S1P] receptor agonists)

- Primary non-response – Signs and symptoms of persistently active disease despite a history of any of the following:
    - At least one 6-week induction regimen of infliximab (5-10 mg/kg intravenously at 0, 2, and 6 weeks)
    - At least one 4-week induction regimen of adalimumab (one 160 mg SC dose followed by one 80 mg SC dose [or one 80 mg SC dose in countries where this dosing regimen is allowed followed by one 40 mg SC dose] at 2 weeks or earlier)
    - At least one 2-week induction regimen of golimumab (one 200 mg SC dose followed by one 100 mg SC dose at least 2 weeks apart)
    - At least one induction regimen of ustekinumab (single intravenous weight-based infusion of 260 mg [<55 kg body weight], 390 mg [55-85 kg body weight], or 520 mg [>85 kg body weight])
    - A history of completed Induction regimen according to prescribing information for JAK antagonists or S1P receptor agonists

OR

- Secondary non-response – Initially responded to Induction therapy and then had recurrence of symptoms after receiving at least 2 of the Maintenance doses specified below (discontinuation despite clinical benefit does not qualify):
    - Infliximab: ≥5 mg/kg
    - Adalimumab: 40 mg every week or every other week
    - Golimumab: 100 mg injection at Week 6 and every 4 weeks
    - Ustekinumab: 90 mg SC dose 8 weeks after the initial intravenous dose, then every 8-12 weeks thereafter or more frequently

OR

- History of intolerance to at least one advanced therapy agent (including, but not limited to, infusion-related reaction, demyelination, congestive heart failure, or infection)

Note: Participants who have received a prior advanced therapy agent for up to 1 year and did not have a documented non-response may be enrolled; however, the participants must have discontinued the advanced therapy agent for reasons other

than inadequate response or intolerance (e.g., change of insurance, well-controlled disease) and must meet the criteria for inadequate response, loss of response, or intolerance to aminosalicylates, corticosteroids, and/or immunosuppressants, as defined above.

Note: Participant cannot have had inadequate response, loss of response, or intolerance to more than 3 drugs in 2 classes of the following advanced therapies:

a. Tumor necrosis factor alpha (TNF-α) antagonists, including infliximab, adalimumab, or golimumab
b. Interleukin (IL)-12/IL-23 antagonists, including ustekinumab
c. JAK antagonists, including tofacitinib or upadacitinib
d. S1P receptor agonists, including ozanimod
e. Any investigational product with the same mechanism as one of those outlined above (a through d) or a novel mechanism of action

Note: Participants who have a history of primary non-response to 2 or more of the advanced therapy classes above will not be eligible. Participants who have received treatment with these agents at sub-therapeutic doses or durations should be discussed with the Medical Monitor to assess eligibility.

5. Meets the following washout criteria of prior UC therapy relative to study Day 1:

    a. TNF-α antagonists: at least 8 weeks
    b. IL-12/IL-23 antagonists, including ustekinumab: at least 8 weeks
    c. JAK antagonists, including tofacitinib or upadacitinib: at least 1 week
    d. S1P receptor agonists, including ozanimod: at least 4 weeks

    Note: Participants who do not meet the full washout period but have the results of a local drug concentration level performed during the Screening Window deemed by the Medical Monitor to be sub-therapeutic may be eligible for the study earlier than the full washout period.

6. If the participant has been receiving any of the non-prohibited medications for UC listed below, he/she must discontinue use at least 5 half-lives before study Day 1 or must agree to maintain stable doses of these concomitant medications starting from the time specified below until the end of the SFU Period, with the exception of tapering oral corticosteroid dose after 12 weeks of being in the trial.

    a. Oral 5-Aminosalicylates (not exceeding 4.8 g per day): at least 2 weeks prior to study Day 1
    b. Oral corticosteroids (not exceeding prednisone 30 mg/day, budesonide 9 mg/day, beclomethasone dipropionate 5 mg/day, methylprednisolone 24 mg/day, or equivalent): at least 2 weeks prior to study Day 1
    c. 6-Mercaptopurine (any stable dose): at least 4 weeks* prior to study Day 1
    d. Azathioprine (any stable dose): at least 4 weeks* prior to study Day 1
    e. Methotrexate (any stable dose): for at least 4 weeks* prior to study Day 1

    ***Note:** Participants must be on any stable dose of 6-mercaptopurine, azathioprine, or methotrexate for at least 12 weeks prior to study Day 1 in EU countries.

7. If the participant has had UC for over 7 years, he/she must have had a full colonoscopy in the last 2 years or must agree to have a full colonoscopy (rather than sigmoidoscopy) with appropriate, per local guidelines, colon cancer surveillance biopsies at Screening
8. In the opinion of the Investigator, the participant can fully participate in all aspects of this clinical study

Weight

9. Has a body mass index (BMI) ≥18.0 at Screening

Sex and Contraceptive/Barrier Requirements

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

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

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

        OR

        - Agrees to use contraception/barrier methods as detailed below:

            - Agrees to use a male condom, with female partner use of an additional highly effective contraceptive method with a failure rate of <1% per year (as described in Section 10.5.3) when having sexual intercourse with a woman of childbearing potential who is not currently pregnant.

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

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

    OR

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

Note: For contraception requirements on or after Protocol Amendment Version 3.0, see Section 10.5.2.2.

11. For the study Treatment Period and at least 14 days after receiving the last dose of MORF-057, male participants must agree not to donate sperm and female participants must agree not to donate eggs (ova, oocytes).

Informed Consent

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

Exclusion Criteria:

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

Medical Conditions

1. Diagnosed with indeterminate colitis, microscopic colitis, ischemic colitis, radiation colitis, or Crohn's disease, or has clinical findings suggestive of Crohn's disease
2. Has current evidence of un-resected colonic dysplasia or un-resected adenomatous colonic polyps or evidence of toxic megacolon, abdominal abscess, symptomatic colonic stricture, fistula, stoma, ileostomy, or colostomy at Screening
3. Currently requires or is anticipated to require surgical intervention for UC during the study
4. Has had a surgical procedure requiring general anesthesia within 30 days prior to Screening or is planning to undergo major surgery during the study period
5. Has a history of any major neurological disorders, including stroke, multiple sclerosis, brain tumor, demyelinating, or neurodegenerative disease. For questions about whether this applies to a specific case, consult with the Medical Monitor.
6. Has positive findings on a Subjective Progressive Multifocal Leukoencephalopathy (PML) symptom checklist during Screening or prior to the administration of the first dose of study drug on study Day 1
7. Has a potentially active bacterial, viral, or parasitic pathogenic enteric infection, including *Clostridiodes difficile (C. difficile)*; has hepatitis B or C virus, or human immunodeficiency virus (HIV); had an infection requiring hospitalization or intravenous antimicrobial therapy, or an opportunistic infection within 3 months prior to Screening; had any infection requiring oral antimicrobial therapy within 2 weeks prior to Screening; or has a history of more than 1 episode of herpes zoster or any episode of disseminated herpes zoster infection
8. Has active tuberculosis (TB), as evidenced by any of the following:
    a. A diagnostic test for TB performed within 30 days prior to Screening or during the Screening Period that is positive, as defined below:
        - A positive interferon gamma release assay (IGRA) test (e.g., [redacted] TB test) or 2 consecutive indeterminate IGRA tests

        OR
        - A purified protein derivative (PPD) skin test ≥5 mm

b. A chest X-ray or imaging per local guidelines within 3 months prior to Screening where active or latent pulmonary TB cannot be excluded

Note: Participants who have tested negative for TB at a certified local lab using an IGRA test within 3 months prior to Screening are not required to repeat this test during the Screening Period if that participant has no clinical signs or symptoms of TB and no known exposures/increased risk factors since the last negative TB test (according to the Investigator's clinical judgement), and the test result is available in the participant's medical record

Note: Participants with a history of latent TB may be enrolled if they complete an assessment for evidence of active TB versus latent TB. Documentation will include a chest X-ray or imaging per local guidelines during the Screening Window and no signs, symptoms, or evidence of ongoing active TB. Participants have had treatment per the local standard of care for a minimum of 2 weeks before the first dose of study drug OR documentation of completing appropriate treatment for latent TB within 2 years before Day 1 of the study. See Section 8.2.2.1 for more details.

9. Has a positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) test result during the Screening Period. Testing for SARS-CoV-2 is required only per local regulations. Participants who have a positive test result can be randomized after a subsequent negative test result during the Screening Period.
10. Had any vaccination (including live virus vaccinations) within 3 weeks prior to study Day 1

    Note: For vaccinations requiring a series of doses, the last in the series should be completed by 3 weeks prior to study Day 1 (e.g., SARS-CoV-2 two-shot vaccination series)
11. Has a concurrent, clinically significant, serious, unstable comorbidity (such as uncontrolled cardiovascular, pulmonary, hepatic, renal, gastrointestinal, genitourinary, hematological, coagulation, immunological, endocrine/metabolic, or other medical disorder) that, in the judgement of the Investigator, would compromise compliance with the protocol, interfere with interpretation of the study results, or pre-dispose participants to safety risks
12. Has a known primary or secondary immunodeficiency
13. Has a history of myocardial infarction, unstable angina, transient ischemic attack, decompensated heart failure requiring hospitalization, congestive heart failure (New York Heart Association Class 3 or 4), uncontrolled arrhythmias, cardiac revascularization, uncontrolled hypertension, or uncontrolled diabetes within 6 months of Screening
14. Has a history of left ventricular ejection fraction (LVEF) <50%
15. Has a clinically significant abnormal electrocardiogram (ECG) at Screening, including a QT interval corrected through use of Fridericia's formula (QTcF) ≥450 ms for males and ≥470 ms for females

16. Abnormal hematology (hemoglobin level, white blood cell [WBC] count, or platelet count) or coagulation results at Screening, as evidenced by the ranges provided below:*

    a. Hemoglobin level <8.0 g/dL
    b. Absolute WBC count $<3.0 \times 10^9$/L
    c. Absolute lymphocyte count $<0.5 \times 10^9$/L
    d. Absolute lymphocyte count >5.5 x 10^9/L
    e. Absolute neutrophil count $<1.2 \times 10^9$/L
    f. Platelet count $<100 \times 10^9$/L or $>1000 \times 10^9$/L
    g. International normalized ratio >1.5. Participants with an international normalized ratio >1.5 due to anticoagulant therapy (e.g., Coumadin) may only be enrolled after a consultation with the Medical Monitor.

17. Clinically significant abnormal urinalysis results, as deemed by the Investigator or designee

18. Abnormal organ function at Screening, as evidenced by the following:*

    a. Alanine aminotransferase or aspartate aminotransferase >2.0 × upper limit of normal (ULN)
    b. Chronic kidney disease stages 4 and 5, defined as having a glomerular filtration rate <30 mL/min/1.73m^2 as calculated using the Modification of Diet in Renal Disease equation, receiving dialysis, or being listed for or has received a renal transplant
    c. Total bilirubin ≥1.5 × ULN

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

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

Prior/Concomitant Therapy

20. Treatment with cyclosporine, mycophenolate, tacrolimus, or sirolimus within 30 days or 5 half-lives (whichever is shorter) prior to study Day 1

21. Any previous treatment with vedolizumab or other licensed or investigational integrin inhibitors

22. Experiencing toxicities from prior therapy with Grade >1 within 1 week prior to first dose of study drug

23. Fecal microbiota transplantation within 3 months prior to Screening

24. Participant needs to continue treatment with a moderate-to-strong cytochrome P450 3A (CYP3A) inducer or inhibitor and, therefore, will be unable to do a washout period of at least

30 days or 5 half-lives (whichever is shorter) prior to study Day 1. See Section 6.7.3 for a list of moderate-to-strong P450 inducers and inhibitors.

25. Participant needs to continue treatment with a moderate-to-strong organic anion transporter polypeptide-1B inhibitor and, therefore, will be unable to do a washout period of at least 14 days or 5 half-lives (whichever is shorter) prior to study Day 1. See Section 6.7.3 for a list of moderate-to-strong organic anion transporter polypeptide-1B inhibitors.

Prior/Concurrent Clinical Study Experience

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

Other Exclusions

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

Statistical Methods:

General Considerations

Descriptive statistics will be reported for all primary, secondary, and exploratory data. Categorical parameters will be reported using frequency and proportions, whereas continuous parameters will be reported using mean, standard deviation, median, minimum, and maximum. Data will be summarized/analyzed at scheduled visits unless stated otherwise.

Sample Size Determination

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%.

Analysis Populations

The **Full Analysis Set (FAS)** will consist of all randomized participants who received at least 1 dose of study drug. 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.

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.

The **Safety Population** will include all participants who received at least 1 dose of the study drug. Participants in this set will be analyzed according to the treatment they actually received. This population will be used for the safety analyses.

The **Pharmacokinetics (PK) Population** is defined as all participants who received at least 1 dose of study drug and had at least 1 measurable PK concentration. The PK Population will be used for the summarization/analysis of PK data.

The **Pharmacodynamics (PD) Population** is defined as all participants who received at least 1 dose of study drug and had at least 1 measurable post-dose PD measurement and its corresponding pre-dose PD measurement for, at minimum, 1 of the PD biomarkers. This population will be used for the summarization of PD (exploratory) endpoints.

Analysis of Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment group and overall.

Efficacy Analyses

All the efficacy analyses will be performed based on the FAS, unless otherwise specified.

<u>Primary Efficacy Endpoint</u>

The primary efficacy endpoint for this study is proportion of participants in clinical remission at Week 12 as determined using the mMCS, which will be evaluated in the FAS.

The primary efficacy endpoint will be analyzed using a two-sided Cochran-Mantel-Haenszel (CMH) test at the 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 and point estimates of risk difference, along with 95% confidence interval (CIs), will be provided. The study will be considered a success if at least one MORF-057 dose achieves the statistical significance at the specified significance level after the multiplicity adjustment. All participants with missing data for determination of endpoint status will be considered as a non-responder in the primary analysis.

The primary analysis will be repeated on the PP Population as a sensitivity analysis. Other sensitivity analyses for the primary efficacy endpoints may also be performed as appropriate. The primary efficacy endpoint will be analyzed for the subgroups defined based on selected categorized

demographic and baseline variables, e.g., age, gender, race, exposure to an advanced therapy treatment for UC (advanced therapy-naïve and advanced therapy-experienced). The details will be described in the Statistical Analysis Plan (SAP).

Secondary Efficacy Endpoint

The secondary endpoint for this study is the proportion of participants with clinical response at Week 12 as determined using the mMCS, which will be evaluated in the FAS.

The secondary endpoint will be analyzed using CMH tests 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 and point estimates of risk difference, along with 95% CIs, will be provided. All participants with missing data for determination of endpoint status will be considered as a non-responder in the analysis.

Exploratory Efficacy Endpoints

All proportion-based exploratory efficacy endpoints at Week 12 as defined in Section 3 (e.g., histologic remission or improvement, endoscopic remission or improvement, mucosal healing or improvement, MCS remission or response, UC-related hospitalization or surgery) will be analyzed in the FAS using CMH tests stratified by randomization stratification factors for comparison of each MORF-057 dose group with the placebo group, similar to the primary analysis performed for the primary efficacy endpoint. The p-values will be calculated for the exploratory use. The point estimates of risk difference, along with 95% CIs, will be provided. All participants with missing data for determination of endpoint status will be considered as a non-responder in the analysis.

All the continuous exploratory efficacy endpoints expressed as change from baseline at Week 12 as defined in Section 3 (e.g., non-endoscopic biomarkers of inflammation, patient-reported outcomes) will be analyzed in the FAS using an analysis of covariance model with treatment and randomization stratification factors as factors and baseline values as a covariate. 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 time-to-event endpoint (time to symptomatic response) will be analyzed using the stratified Cox regression model with treatment group as an independent variable. The stratification factors include the randomization stratification factors.

All exploratory efficacy endpoints at Week 52 will be summarized descriptively by dose regimens. The participants randomized to the placebo arm at the Induction Period and switched to an active MORF-057 dose regimen at the Maintenance Period will be summarized separately for the endpoints at Week 52.

Safety Analyses

The Safety Population will be used for the summarization of all safety data.

Adverse events (AEs) will be coded using the current Medical Dictionary of Regulatory Activities (MedDRA) by System Organ Class (SOC) and Preferred Term (PT), classified from verbatim

terms. A TEAE is defined as an AE that occurs between administration of the first dose of study drug and 7 days after the last dose of study drug. TEAEs and TESAEs will be summarized using frequencies and proportions; summaries will be provided for overall and according to SOC and PT. TEAEs leading to study drug discontinuation will be summarized and listed, as appropriate. Summaries of TEAEs will also be presented by severity and relationship (see Section 10.4.3). The duration of TEAEs will be determined and included in listings, along with the action taken and outcome.

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

The safety analyses will be performed for the 12-week Induction Period, the 52-week Treatment Period, and the 52-week LTE Period plus the Safety Follow-up Period. In the safety analyses for the 12-week Induction Period, the participants initially randomized into the placebo group and switched to an active MORF-057 regimen after the Week 12 assessments will be analyzed as the placebo group. In the safety analyses for the 52-week Treatment Period and 52-week LTE Period, the placebo recipients switched to an active MORF-057 regimen will be analyzed according to the active MORF-057 regimen they received after Week 12, and their data will be presented separately based on only the safety data collected after the start of the MORF-057 dose.

Pharmacokinetics Analyses

PK concentration will be summarized. Additional PK and PK/PD analyses will be conducted as deemed appropriate and may be reported separately from the Clinical Study Report.

Pharmacodynamics Analyses

The exploratory PD endpoints (changes over time in $\alpha_4\beta_7$ and $\alpha_4\beta_1$ receptor occupancies and blood CCR9 mRNA level) will be summarized descriptively. Additional analysis of PD endpoints may be described in a biomarker analysis plan separate from the study SAP and reported separately. The PD Population will be used for the summarization and analysis of PD exploratory endpoints.

Analyses for Induction Period, 52-week Treatment Period, and LTE Period

The Treatment Period in the main part of the study includes the 12-week Induction Period and the 40-week Maintenance Period. For the purpose of statistical analyses, the Induction Period and the Maintenance Period will be treated as 2 independent parts. There will be 2 analyses planned: one for the 12-week Induction Period (i.e., the period for the primary efficacy endpoint) and one for the 52-week Treatment Period (i.e., the 12-week Induction Period plus the 40-week Maintenance Period and Safety Follow-up Period). The details of the analyses will be described in the SAP. Additional analysis of the optional 52-week LTE Period for the participants enrolled into the LTE Period will also be performed as appropriate.

Induction Period 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 assessments. The analysis will formally evaluate the primary and secondary efficacy endpoints, all the

exploratory efficacy endpoints defined by Week 12, and safety of MORF-057 vs placebo during the 12-week Induction Period. The PK and PD data during the 12-week Induction Period will also be summarized.

52-week Treatment Period Analysis

The analysis of the 52-week Treatment Period 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 LTE Period) or discontinued from the study during the 52-week Treatment Period. 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 (and the Safety Follow-up Period for participants not rolling over into the LTE Period). The cumulative data, including those from the Induction Period, will be used in this analysis.

52-week LTE Period Analysis

The analysis of the LTE Period will be performed after all the participants enrolled into the LTE Period have completed the 52-week LTE Period and the Safety Follow-up Period or discontinued the study during the LTE Period. The analysis will evaluate the long-term safety of MORF-057 and selected efficacy endpoints at Week 104 as appropriate during the LTE Period plus the Safety Follow-up Period.

Data and Safety Monitoring:

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

1.2. Schedule of Activities (SoA)

The SoA for the Treatment Period is provided in Table 1. The SoA for the LTE Period* is provided in Table 2.

Table 1. Schedule of Activities for the Treatment Period

Study Procedure	SCR [a]		Treatment Period										Safety Follow-up	UNS [b]
			Induction Period					Maintenance Period						
Visit	**1**		**2**	**3**	**4**	**5 [c]**		**6**	**7**	**8**	**9**	**10/EOT [d, e]**	**SFU [f, g]**	**UNS**
Week	**-6 to -1**		**0**	**2**	**6**	**12**		**18**	**24**	**32**	**42**	**52**	**56**	
Study Day	**-42 to -1**		**1**	**15±3**	**43±3**	**85+5**		**127±7**	**169±7**	**225±7**	**295±7**	**365±7**	**393+7 [h]**	
	Stage 1	**Stage 2**				**Stage 1**	**Stage 2**					**Stage 1**	**Stage 2**	
Informed consent [i]	X													
Demographics	X													
Medical and surgical history	X		X											
Assess inclusion/exclusion criteria	X	X												
Confirm inclusion/exclusion criteria		X	X											
Randomization [j]			X											
SARS-CoV-2 screening [k]	X													
Test for TB [l]	X													
Fecal sampling and cell culture for *C. diff.* and enteric pathogens, including ova and parasite testing	X													
Testing for HIV antibody, hepatitis B surface antigen, and hepatitis C virus antibody	X													
Serum alcohol screen	X													
Urine drug screen	X													
Review of change in substance use [m]							X						X	
Review Participant Diary instructions	X													
Fill out Participant Diary (daily rectal bleeding, stool	X	X	X	X	X		X	X	X	X	X		X	X	

Study Procedure	SCR [a]		Treatment Period										Safety Follow-up	UNS [b]
			Induction Period					Maintenance Period						
Visit	**1**		**2**	**3**	**4**	**5 [c]**		**6**	**7**	**8**	**9**	**10/EOT [d, e]**	**SFU [f, g]**	**UNS**
Week	**-6 to -1**		**0**	**2**	**6**	**12**		**18**	**24**	**32**	**42**	**52**	**56**	
Study Day	**-42 to -1**		**1**	**15±3**	**43±3**	**85+5**		**127±7**	**169±7**	**225±7**	**295±7**	**365±7**	**393+7 [h]**	
	Stage 1	**Stage 2**				**Stage 1**	**Stage 2**					**Stage 1** **Stage 2**		
frequency, study drug administration) [n]														
Participant Diary completion and compliance review		X	X	X	X		X	X	X	X	X	X	X	
Pregnancy test [o]	X		X	X	X		X	X	X	X	X	X	X	X [b]
Serum test for follicle-stimulating hormone [p]	X													
Dispense stool collection kit [q]	X [q]	X			X			X			X			
Discuss participation in LTE Period and informed consent [r]											X	X		
Safety Assessments														
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X X	X	X [b]
12-lead ECG [s]	X		X				X					X		
Physical exam [t]	X		X	X	X		X	X	X	X	X	X	X	X [b]
Vital signs [u]	X		X	X	X		X	X	X	X	X	X	X	X [b]
PML checklist [v]	X		X	X	X		X	X	X	X	X	X	X	
Hematology and coagulation	X		X	X	X		X	X	X	X	X	X	X	X [b]
Serum chemistry	X		X	X	X		X	X	X	X	X	X	X	X [b]
Urinalysis	X		X	X	X		X	X	X	X	X	X	X	X [b]
AE/SAE assessment [w, x]	X	X	X	X	X	X	X	X	X	X	X	X X	X	X [b]
Pharmacokinetic Assessment														
Plasma sample for PK analysis			X [y]	X [y]	X [z]		X [y]	X [z]	X [y]	X [z]	X [z]		X [y]	
Pharmacodynamic Biomarkers														
Whole blood sample for RO [aa]			X	X			X		X				X	
Whole blood sample for immunophenotyping [bb] (country-specific testing)			X	X			X						X	
PAXgene RNA blood sample for gene expression [cc]			X	X			X						X	

Study Procedure	SCR [a]		Treatment Period										Safety Follow-up	UNS [b]
			Induction Period					Maintenance Period						
Visit	**1**		**2**	**3**	**4**	**5 [c]**		**6**	**7**	**8**	**9**	**10/EOT [d, e]**	**SFU [f, g]**	**UNS**
Week	**-6 to -1**		**0**	**2**	**6**	**12**		**18**	**24**	**32**	**42**	**52**	**56**	
Study Day	**-42 to -1**		**1**	**15±3**	**43±3**	**85+5**		**127±7**	**169±7**	**225±7**	**295±7**	**365±7**	**393+7 [h]**	
	Stage 1	**Stage 2**				**Stage 1**	**Stage 2**					**Stage 1** **Stage 2**		
Future Research (Optional)														
Blood PD sample collection [dd]			X	X	X		X	X	X	X	X	X		
Blood pharmacogenomics sample collection [ee]			X											
Blood sample for microbiome-derived metabolite analysis [ff]			X				X					X		
Fecal sample for microbiome analyses [gg]			X				X					X		
Fecal sample for fecal calprotectin [hh]												X		
Efficacy Assessments														
Sigmoidoscopy with biopsy [ii]		X [jj]				X [kk, mm]						X [ll, mm]		
MCS Physician's Global Assessment			X		X		X		X			X		
MCS rectal bleeding subscore	X	X	X	X	X		X	X	X	X	X	X		
MCS stool frequency subscore	X	X	X	X	X		X	X	X	X	X	X		
Centrally read MES		X					X					X		
Centrally read RHI Score, Continuous Geboes Score, and NI		X					X					X		
Serum for hs-CRP test [nn]	X				X		X		X			X		
Fecal sample for fecal calprotectin	X						X		X			X		
IBDQ	X						X					X		
Study Drug														
Study drug accountability				X	X		X	X	X	X	X	X [oo]		
Dispense study drug			X	X	X		X [pp]	X	X	X	X	X [qq]		
Study drug administration on-site [rr]			X	X	X		X [pp]	X	X	X	X	X [ss]		

Study Procedure	SCR [a]		Treatment Period										Safety Follow-up	UNS [b]
			Induction Period					Maintenance Period						
Visit	**1**		**2**	**3**	**4**	**5 [c]**		**6**	**7**	**8**	**9**	**10/EOT [d, e]**	**SFU [f, g]**	**UNS**
Week	**-6 to -1**		**0**	**2**	**6**	**12**		**18**	**24**	**32**	**42**	**52**	**56**	
Study Day	**-42 to -1**		**1**	**15±3**	**43±3**	**85+5**		**127±7**	**169±7**	**225±7**	**295±7**	**365±7**	**393+7 [h]**	
	Stage 1	**Stage 2**				**Stage 1**	**Stage 2**					**Stage 1** **Stage 2**		
Confirm initiation of study drug for the Maintenance Period [tt]							X							

Abbreviations: AE, adverse event; B.I.D., twice a day; *C. diff., Clostridiodes difficile*; ECG, electrocardiogram; EOT, End of Treatment; HIV, human immunodeficiency virus; hs-CRP, high-sensitivity C-reactive protein; IBDQ, Inflammatory Bowel Disease Questionnaire; ICF, Informed Consent Form; IGRA, interferon gamma release assay; LTE, Long-Term Extension; MCS, Mayo Clinic Score; MES, Mayo Endoscopic Subscore; NI, Nancy Histopathology Index; PD, pharmacodynamics; PK, pharmacokinetics; PML, progressive multifocal leukoencephalopathy; RHI, Robarts Histopathology Index; RNA, ribonucleic acid; RO, receptor occupancy; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SCR, Screening; SFU, Safety Follow-up; TB, tuberculosis; UNS, unscheduled.

a Once informed consent is obtained, the procedures listed for Stage 1 of Screening should be performed. Stage 1 will be approximately 2 weeks long and should include the collection of Participant Diary information for 7 days. At the end of Stage 1, the Investigator should use the information collected in the Participant Diary to assess the severity of UC. If the participant is consistently having 3 or more stools per day than normal, often with visible blood, then he/she should proceed to Stage 2 of Screening (including endoscopy). If the participant's stool frequency and rectal bleeding symptoms are milder than what is described, Stage 2 of Screening should not be pursued.

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

c Visit 5 is split into Stage 1 and Stage 2 to clarify the timing of the endoscopy procedure. The endoscopy procedure at Visit 5 Stage 1 should be performed before the Visit 5 Stage 2 in-clinic assessments have been completed.

d Visit 10 is split into Stage 1 and Stage 2 to clarify the timing of the endoscopy procedure. The endoscopy procedure at Visit 10 Stage 1 should be performed on or within 7 days before the Visit 10 Stage 2 in-clinic assessments have been completed.

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

f Participants not participating in the LTE Period will complete the SFU Visit, which should be performed 28 days (+7 days) after the participant takes the last dose of study drug. Eligible participants who choose to participate in the LTE Period after Visit 10 will complete a separate SFU Visit at Week 108 (Table 2).

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

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

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

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

k Testing for SARS-CoV-2 is required only per local regulations. Participants who have a positive test result will be excluded from randomization until a subsequent test result is negative.

l Participants who have tested negative for TB at a certified local lab using an interferon gamma release assay (IGRA) test (e.g., [redacted] TB test) within 3 months prior to Screening are not required to repeat this test during the Screening Period if that participant has no clinical signs or symptoms of TB and no known exposures/increased risk factors since the last negative TB test (according to the Investigator's clinical judgement). In cases where the IGRA test is indeterminate, the participant may have the test repeated once, and if their second test is negative, they will be eligible. The purified protein derivative skin test should be performed when the IGRA test is not possible or if both tests are required by local guidelines.

m Collect information on the participant's change in substance use (e.g., alcohol, tobacco, and drugs).

n Participant Diaries are to be completed daily by the participant at home and brought to each study visit for review by study personnel. Participant Diaries should not be completed after the participant has finished their participation in the study at the SFU Visit. See Section 8.5 for the required contents of the Participant Diaries.

o Only required for women of childbearing potential. A serum test should be used at Screening, and a urine test should be used throughout rest of study. On Day 1, a urine test must be completed and results reviewed prior to start of the study drug.

p Serum test for follicle-stimulating hormone level to be performed only for female participants of non-childbearing potential.

q Stool collection kits are to be dispensed to participants at the visits indicated. The participant should use this kit to collect one sample at home within 24 hours before the next site visit. The sample should be stored as described in the sample collection instructions and brought to the clinic on the day of the site visit. If the participant is unable to produce a stool sample at the Stage 1 Screening Visit, they can collect a sample at home and return it to the site. **Note:** Sample is to be collected prior to bowel preparation for Visits 5 and 10/EOT.

r Participants will be provided the option to participate in the LTE Period. Participants who want to continue in the LTE Period will be required to provide informed consent. Due to the changes in Version 3.0 of this protocol, all participants who choose to continue their treatment in the LTE Period will be asked to re-consent to the LTE Period dose to 200 mg B.I.D. The dose switch will occur at Visit 10 or at a scheduled visit in the LTE Period (Visit 11, 12, or 13).

s ECGs to be performed before the AM dose and 2 hours (±30 minutes) after the AM dose during the Induction and Maintenance Periods. ECGs will be obtained after the participant has rested for at least 10 minutes in the supine position.

t A complete physical exam is to be performed at Screening and Visit 10/EOT, and a targeted exam may be performed at all other required visits (see Section 8.8.1 for descriptions). For unscheduled visits, the type of exam (if necessary to be performed at all) will be at the Investigator's discretion and determined based on the reason for the visit. The Screening exam will include collection of height and weight.

u Vital signs to be recorded at most visits. At unscheduled visits, vital signs are not required and are at the discretion of the Investigator. These will include blood pressure, heart rate, respiratory rate, and temperature. Vital signs are to be taken before blood collection for laboratory tests. Blood pressure and pulse measurements should be preceded by at least 10 minutes of rest for the participant.

v If the results of the questionnaire are suggestive of PML, a full neurological exam and, if indicated, additional testing are to be performed.

w Record adverse events from the time the ICF is signed.

x Participants are to be contacted by phone as needed to monitor the status of the event.

y PK testing at Visits 2, 3, 5, 7, and 10/EOT: Blood samples will be collected before the AM dose and at 1 (±10 min), 2 (±15 min), and 4 (±30 min) hours after the AM dose. For all pre-AM dose sampling, the samples should be obtained before the AM dose is administered. If consent is provided by the participant, these samples may also be used for future PK research studies.

z PK testing at Visits 4, 6, 8, and 9: Blood sample will be collected before the AM dose and 1 hour (±10 min) after the AM dose. For all pre-AM dose sampling, the samples should be obtained before the AM dose is administered. If consent is provided by the participant, these samples may also be used for future PK research studies.

aa RO testing at Visit 2, 3, 5, 7, and 10/EOT: Blood sampling will be required before the AM dose. RO sampling to occur at the corresponding PK sampling time, when applicable.

bb Blood samples for immunophenotyping (lymphocyte subsets analysis) will be collected from a subset of participants (sampling to be country-specific). Samples will be collected before the AM dose on Visits 2, 3, 5, and 10/EOT. Collection time on Visits 3, 5, and 10/EOT must be consistent with baseline (Visit 2) collection ±2 hours.

cc PAXgene RNA blood samples (for CCR9 analysis) will be collected before the AM dose on Visit 2, 3, 5, and 10/EOT. Collection time at Visits 3, 5, and 10/EOT must be consistent with baseline (Visit 2) collection ±2 hours.

dd Participation in future research sample collection is optional. Blood PD samples will be collected before the AM dose on Visits 2-10/EOT.

ee Participation in future research sample collection is optional. Blood pharmacogenomics sample will be collected before the AM dose on Visit 2.

ff Participation in future research sample collection is optional. Blood samples for microbiome-derived metabolite analysis will be collected before the AM dose on Visits 2, 5, and 10/EOT.

gg Participation in future research sample collection is optional. Fecal samples for microbiome analysis will be collected before the AM dose on Visits 2, 5, and 10/EOT. Fecal samples may be collected at any time on the day prior to the scheduled visit day.

hh Participation in future research sample collection is optional. Fecal samples for fecal calprotectin will be collected at the same visits as the fecal calprotectin efficacy assessments (Visit 10/EOT). Fecal samples may be collected at any time on the day prior to the scheduled visit day.

ii Full colonoscopy is optional at any timepoint if the Investigator deems it necessary. However, if the participant has had UC for over 7 years, he/she must undergo a full colonoscopy (rather than sigmoidoscopy) at Screening if a full colonoscopy has not been performed in the last 2 years.

jj During the Screening endoscopy, up to 6 colonic mucosa biopsies will be collected. Two biopsies for the required histopathology must be collected from the worst inflamed area, 15-25 cm from the anus. Record the extent of disease in centimeters from the anal verge. If consent is provided by the participant, 4 additional mucosa biopsies may be collected for the optional future research studies (2 biopsies from the worst inflamed area and 2 from a non-inflamed/least inflamed area). If consent is provided by the participant, any remaining tissue from the required histopathology biopsies may be used for future research studies. See Section 8.7.1 for details on biopsy requirements.

kk The Visit 5 Stage 1 endoscopy procedure should be performed before the in-clinic assessments at Visit 5 Stage 2 have been completed.

ll The Visit 10/EOT Stage 1 endoscopy procedure should occur on or within 7 days before the actual Stage 2 visit date. For participants who discontinue treatment before Week 6, a repeat sigmoidoscopy will be performed any time after MORF-057 dosing Day 14. For participants who discontinue treatment after Week 6, a repeat sigmoidoscopy will be performed any time. Participants who complete the EOT Visit within 2 months after the Week 12 endoscopy are not required to repeat the procedure.

mm Collect up to 6 biopsy samples total (2 for required histopathology and 4 for optional future research studies [if consent is provided by the participant]). If consent is provided by the participant, any remaining tissue from the required histopathology biopsies may be used for future research studies. All biopsies should be collected from the same distance from the anus as collected at the Screening Visit, regardless of the tissue state at the time of the sampling. Record the extent of disease in centimeters from the anal verge. Record the number of centimeters from the anus in which biopsies are collected at all follow-up visits into the Requisition Form.

nn Blood samples for hs-CRP analysis will be collected at Stage 1 Screening and before the AM dose on Visits 4, 5, 7, and 10/EOT.

oo Participants not participating in the LTE Period should return all study drug to the site. No additional dosing should occur after the completion of the EOT Visit.

pp At Visit 5, the Induction Period study drug kits supplied at the previous visit should be used for the AM dose. Please note, a new supply of Maintenance Period study drug kits will be provided at the conclusion of Visit 5. Participants should use the Maintenance Period study drug kits for all future doses after the completion of Visit 5.

qq For participants continuing treatment in the LTE Period, additional study drug will be dispensed at Visit 10.

rr AM dosing required on-site for all visits except the SFU Visit.

ss At Visit 10/EOT, participants not participating in the LTE Period will only receive an AM dose for the day. No PM dose will be provided.

tt Site staff will contact the participants, by phone or other means, on the next business day after the Visit 5 clinic visit is complete to confirm the participants are using the new supply of study drugs for the Maintenance Period. Record the date and time of the participant's first Maintenance Period dose.

Table 2. Schedule of Activities for the LTE Period*

Study Procedure	Dose Switch Follow-up 1 [a]	Dose Switch Follow-up 2 [b]	LTE Period*					Safety Follow-up	UNS [c]
Visit	**DSFU 1**	**DSFU 2**	**11**	**12**	**13**	**14/LTE EOT [d, e]**		**SFU [f, g]**	**UNS**
Week	**4 weeks after the dose switch**	**4 weeks after DSFU 1**	**65**	**78**	**91**	**104**		**108**	
Study Day			**456±7**	**547±7**	**638±7**	**729±7**		**757+7 [h]**	
						Stage 1	**Stage 2**		
Informed consent			X *	X *	X *				
Fill out Participant Diary (daily rectal bleeding, stool frequency) [i]	X	X	X	X	X		X	X	
Participant Diary completion and compliance review	X	X	X	X	X		X	X	
Pregnancy test [j]	X	X	X	X	X		X	X	X [c]
Review of change in substance use [k]							X		
Safety Assessments									
Concomitant medications	X	X	X	X	X	X	X	X	X [c]
Physical exam [l]	X	X	X	X	X		X	X	X [c]
Vital signs [m]	X	X	X	X	X		X	X	X [c]
PML checklist [n]	X	X	X	X	X		X	X	
Hematology and coagulation	X	X	X	X	X		X	X	X [c]
Serum chemistry	X	X	X	X	X		X	X	X [c]
Urinalysis	X	X	X	X	X		X	X	X [c]
AE/SAE assessment [o, p]	X	X	X	X	X	X	X	X	X [c]
Efficacy Assessments									
Sigmoidoscopy with biopsy [q]						X [r]			
Centrally read MES							X		
Centrally read RHI Score, Continuous Geboes Score, and NI							X		
Study Drug									
Study drug accountability	X	X	X	X	X		X [s]		

Study Procedure	Dose Switch Follow-up 1 [a]	Dose Switch Follow-up 2 [b]	LTE Period*					Safety Follow-up	UNS [c]
Visit	**DSFU 1**	**DSFU 2**	**11**	**12**	**13**	**14/LTE EOT [d, e]**		**SFU [f, g]**	**UNS**
Week	**4 weeks after the dose switch**	**4 weeks after DSFU 1**	**65**	**78**	**91**	**104**		**108**	
Study Day			**456±7**	**547±7**	**638±7**	**729±7**		**757+7 [h]**	
						Stage 1	**Stage 2**		
Dispense study drug			X	X	X				
Confirm switch of study drug [t]	X								

Abbreviations: AE, adverse event; B.I.D., twice a day; DSFU, Dose Switch Follow-up; ICF, Informed Consent Form; LTE, Long-Term Extension; LTE EOT, Long-Term Extension End of Treatment; MES, Mayo Endoscopic Subscore; NI, Nancy Histopathology Index; PML, progressive multifocal leukoencephalopathy; RHI, Robarts Histopathology Index; SAE, serious adverse event; SFU, Safety Follow-up; UNS, unscheduled.

* **Note:** Due to the changes in Version 3.0 of this protocol, all participants who choose to continue their treatment in the LTE Period will be asked to re-consent to the LTE Period dose switch to 200 mg B.I.D. The dose switch will occur at Visit 10 or at a scheduled visit in the LTE Period (Visit 11, 12, or 13). For example, a participant who has already completed Visit 11 at the time that Protocol Version 3.0 is active will complete the dose switch at Visit 12 (Week 78). Then, the DSFU 1 will be completed 4 weeks later (Week 82), and the DSFU 2 will be 4 weeks after DSFU 1 (Week 86). Then, the participant will resume regular visits with the next visit at Visit 13 (Week 91) through the end of the study. If the participant does not consent to the dose switch, they will remain on their current LTE Period dose and schedule and will not need to attend DSFUs 1 or 2.

a The DSFU 1 will occur 4 weeks after the dose switch.

b The DSFU 2 will occur 4 weeks after the DSFU 1.

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

d Visit 14 is split into Stage 1 and Stage 2 to clarify the timing of the endoscopy procedure. The endoscopy procedure at Visit 14 Stage 1 should be performed on or within 7 days before the Visit 14 Stage 2 in-clinic assessments have been completed.

e If the participant discontinues early from the LTE Period, perform the LTE EOT procedures and schedule the SFU for 28 days (+7 days) after the participant takes the last dose of study drug (unless consent is withdrawn).

f All participants enrolled in the LTE Period will complete the SFU Visit, which should be performed 28 days (+7 days) after the participant takes the last dose of study drug.

g If the participant discontinues early from the LTE Period, perform the SFU procedures 28 days (+7 days) after the participant takes the last dose of study drug (unless consent is withdrawn).

h The SFU Visit is to occur 28 days (+7 days) after the last dose of study drug is received. If the LTE EOT Visit occurs before Day 729, the day for the SFU Visit can be adjusted according to the date of last study drug dose.
i Participant Diaries are to be completed daily by the participant at home and brought to each study visit for review by study personnel. See Section 8.5 for the required contents of the Participant Diaries.
j Only required for women of childbearing potential. A urine test should be used throughout the LTE Period.
k Collect information on the participant's change in substance use (e.g., alcohol, tobacco, and drugs).
l A complete physical exam is to be performed at Visit 14/LTE EOT, and a targeted exam may be performed at all other required visits (see Section 8.8.1 for descriptions). For unscheduled visits, the type of exam (if necessary to be performed at all) will be at the Investigator's discretion and determined based on the reason for the visit.
m Vital signs to be recorded at most visits. At unscheduled visits, vital signs are not required and are at the discretion of the Investigator. These will include blood pressure, heart rate, respiratory rate, and temperature. Vital signs are to be taken before blood collection for laboratory tests. Blood pressure and pulse measurements should be preceded by at least 10 minutes of rest for the participant.
n If the results of the questionnaire are suggestive of PML, a full neurological exam and, if indicated, additional testing are to be performed.
o Record adverse events from the time the ICF for the LTE Period is signed.
p Participants are to be contacted by phone as needed to monitor the status of the event.
q Full colonoscopy is optional at any timepoint if the Investigator deems it necessary. Collect up to 6 biopsy samples total (2 for required histopathology and 4 for optional future research studies [if consent is provided by the participant]). If consent is provided by the participant, any remaining tissue from the required histopathology biopsies may be used for future research studies. All biopsies should be collected from the same distance from the anus as collected at the Screening Visit, regardless of tissue state at the time of sampling. Record the extent of disease in centimeters from the anal verge. Record the number of centimeters from the anus in which biopsies are collected at all follow-up visits into the Requisition Form.
r Endoscopy is required at Visit 14/LTE EOT Stage 1 unless it was performed within 6 months of the LTE EOT Visit. The Visit 14/LTE EOT Stage 1 endoscopy procedure should occur on or within 7 days before the actual Stage 2 visit date.
s At the LTE EOT Visit, participants should return all study drug to the site. No additional dosing should occur after the completion of the LTE EOT Visit.
t Site staff will contact the participants who consented, by phone or other means, on the next business day after the dose switch in the LTE Period to confirm the participants have switched to the new dose (200 mg B.I.D.) of study drug correctly. Record the date and time of the participant's first dose of the new dose (200 mg B.I.D.) in the source documents.

2. Introduction

2.1. Study Rationale

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

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

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

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

MORF-057 is a small molecule designed to selectively inhibit integrin α4β7. It is currently being developed as an oral therapy for UC because vedolizumab, which has the same mechanism of action, has demonstrated efficacy in patients with UC who have moderately to severely active

disease. Relevant data from all non-clinical and clinical studies in the MORF-057 development program are provided in the current Investigator's Brochure (IB).

The aim of the current MORF-057-202 study is to evaluate the efficacy and safety of 3 active dose regimens of MORF-057 (as capsule, by mouth [P.O.]) versus placebo in study participants with moderately to severely active UC. Data from the MORF-057-202 study will provide further information to advance the clinical development program of MORF-057 for the treatment of UC.

2.2. Background

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

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

2.2.1. Non-clinical Findings

Non-clinical studies have demonstrated that MORF-057 is highly selective for $\alpha_4\beta_7$ over other integrins by a range of >100-fold to 143,000-fold. In addition, in a monkey gut homing model, MORF-057 blocked gut homing of $\alpha_4\beta_7$-positive T-cells into lymphoid tissue, as measured by frequency of lymphocytes in tissue and in circulating blood as biomarkers, suggesting MORF-057 can inhibit an established and important mechanism involved in the pathogenesis of IBD.

MORF-057 has been characterized in Good Laboratory Practice-compliant toxicity and safety studies. MORF-057 had no effect on respiration, neurobehavior, or cardiovascular function, and had no genotoxicity or phototoxicity potential. Potential toxicity risks based on non-clinical data include effects to the stomach, liver, hematopoietic system, and embryo-fetal development.

See the current MORF-057 IB for additional details.

For human doses of 100 or 200 mg twice a day (B.I.D.), the calculated safety margin based on the no observed adverse effect levels (NOAELs) for the gastric changes identified in the 26-week study (50 mg/kg/day) is 8.2 -fold or 4.1-fold, respectively. Likewise, the exposure multiple based on the NOAEL observed in dogs in the 39-week study (300 mg/kg/day) is 190.2-fold or 95.6-fold for the 100 or 200 mg B.I.D. doses, respectively. The exposure margin based on a dose (60 mg/kg) that caused non-adverse minimal elevations of liver transaminases (alanine transaminase [ALT] 1.24 x) in dogs dosed for 39 weeks is approximately 20-fold for the 100 mg B.I.D. and 10-fold for the 200 mg B.I.D. doses. The safety margin based on the embryo-fetal NOAEL in rabbits (50 mg/kg/day) is 0.8-fold or 1.6-fold for the 100 or 200 mg B.I.D. doses, respectively (refer to Section 4 of the current IB for details).

2.2.2. Clinical Findings

Collectively from 7 Phase 1 MORF-057 studies conducted in healthy participants (N=171 who received MORF-057 across all 7 studies), MORF-057 was well tolerated. There were no deaths or serious adverse events (SAEs).

Drug-drug interactions (DDI) were also evaluated in the Phase 1 clinical program. At a dose of 100 mg B.I.D., MORF-057 is a weak inducer of cytochrome P450 3A (CYP3A). Although other doses have not been assessed for CYP3A induction, higher doses likely carry the risk of greater induction. MORF-057 is also a substrate of hepatic transporters organic anion transporting polypeptide (OATP) 1B1/3 and a sensitive substrate of CYP3A.

Safety data are also available from the completed 52-week Treatment Period in the open-label Phase 2a study, MORF-057-201 (N=39) and from the 12-week Induction Period in this ongoing placebo-controlled Phase 2b study, MORF-057-202 (N=280). Overall, the treatment with MORF-057 was well tolerated in participants with moderately to severely active UC.

- No death occurred in any of the completed or ongoing studies.
- In the Phase 2b study, 5 participants who received either MORF-057 or placebo reported at least 1 serious treatment-emergent adverse event (TEAE), all in Study MORF-057-202. The Investigator considered that none of these serious TEAEs were related to the study drug.
- In the Phase 2 studies, a total of 11 participants discontinued the study treatment due to TEAEs, with 6 MORF-057 treated participants in Study MORF-057-201 and 5 participants who received either MORF-057 or placebo in Study MORF-057-202.
- The most frequently reported TEAEs in participants receiving MORF-057 at any dose in the Phase 2 studies included ulcerative colitis, anemia, nasopharyngitis, and headache.
- No cases of Progressive Multifocal Leukoencephalopathy (PML) were reported in any of the completed or ongoing studies.

The observed safety profile was consistent with the class safety profile for α4β7 integrin inhibitors.

No safety signals have been identified in any of the MORF-057 clinical studies.

The clinical efficacy of MORF-057 has been evaluated in UC patients in the open-label Study MORF-057-201. In this study, a statistically significant decrease in Robarts Histopathology Index (RHI) Score from baseline to Week 12 was achieved, as well as a reduced modified Mayo Clinic Score (mMCS) from baseline. Additionally, a 25.7% remission rate was demonstrated based on mMCS.

In the 12-week Induction Period analysis for this ongoing placebo-controlled Phase 2b study, MORF-057-202, the primary and secondary objectives of clinical remission and clinical response, respectively, were not achieved. A dose-response was observed between the 3 active doses, and 200 mg B.I.D. was the clinically most active dose.

Refer to the current IB for details on the clinical studies conducted to date.

2.3. Benefit/Risk Assessment

Detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of MORF-057 may be found in the current IB.

2.3.1. Benefits

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

- Oral drugs are preferred by patients and healthcare providers over injectables. Beyond the fear of needles, the requirement for frequent infusion center visits is a substantial burden, particularly for younger patients with UC who have active professional and family lives.
- Oral formulation allows for flexible dosing regimen. An oral drug that is rapidly cleared upon cessation of dosing may be desirable for treating physicians in clinical situations such as pregnancy, during serious infections, and in the peri-operative period. Additionally, an oral drug is more easily titrated to clinical effect and may be used in fixed-dose combinations with other oral agents.
- Biologics, such as vedolizumab, can act as antigens and induce anti-drug antibodies, which may alter pharmacokinetics (PK)/pharmacodynamics (PD) and impact efficacy. During the Phase 3 trials, 4% of patients developed anti-vedolizumab antibodies, 59% of which were neutralizing antibodies that reduced plasma levels of the treatment antibody ([redacted] package insert). In addition, serious infusion reactions, including anaphylaxis, have been reported with vedolizumab. Oral small molecule drugs avoid safety issues related to intravenous administration and immunogenicity that are often associated with biologics. MORF-057 is an oral small molecule drug that is not immunogenic and does not have intravenous administration-related challenges.

2.3.2. Risks

2.3.2.1. Risks of MORF-057

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

Potential toxicity risks based on MORF-057 non-clinical data include effects to the stomach, liver, hematopoietic system, and embryo-fetal development. The gastric, hepatic, and hematopoietic findings demonstrated partial or complete reversibility and are generally clinically monitorable.

Phase 1 DDI studies indicate that MORF-057 is a weak inducer of CYP3A. Sensitive CYP3A substrates for which small decreases in exposure can result in an unacceptable decrease in efficacy should be used with caution. In particular, systemic hormonal contraception should not be considered reliable and should not be used for the purpose of contraception.

Based on available clinical data from both completed and ongoing studies, there are no anticipated risks of particular severity that require monitoring beyond the routine monitoring typically associated with integrin receptor antagonists or other immunomodulatory products in human studies.

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

- Safety assessments and monitoring will be performed throughout the study, including evaluating the incidence of TEAEs, as well as abnormalities in clinical laboratory values, vital signs, and 12-lead electrocardiograms (ECGs).
- A Data and Safety Monitoring Board (DSMB) has been appointed to this study. The DSMB will monitor the safety of the participants and the scientific integrity of the study.
- PML is a fatal opportunistic infection of the central nervous system and has been associated with systemic immunosuppressants, including integrin receptor antagonists (e.g., natalizumab and vedolizumab). Natalizumab, a monoclonal antibody that inhibits both $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrins, has been associated with PML, a serious brain infection. One case of PML in an [redacted] (vedolizumab)-treated patient with multiple contributory factors has been reported in the post-marketing setting (e.g., human immunodeficiency virus [HIV] infection). Data from human whole blood ex vivo assay suggests that MORF-057 has significant selectivity (~700 fold at IC_{90}) for binding integrin $\alpha_4\beta_7$ over integrin $\alpha_4\beta_1$. However, out of an abundance of caution, all participants enrolled in this study will be monitored for PML through the use of a PML Risk Assessment and Minimization Program (RAMP).
- Potential toxicity risks of MORF-057 based on non-clinical data include effects to embryo-fetal development. There is no clinical experience with MORF-057 in pregnant and breastfeeding women and therefore, the potential effects of MORF-057 use during pregnancy and lactation are not known. Women who are breastfeeding or pregnant are excluded from this study. Women of childbearing potential (WOCBP) and men who participate in this study must agree to avoid pregnancy and will be instructed on contraception requirements while they are in this study (see Section 10.5).
- Clinical studies have demonstrated that MORF-057 is a weak inducer of CYP3A, a substrate of hepatic transporters OATP1B1/3, and a sensitive substrate of CYP3A. Inhibitors of OATP1B1/3 or inhibitors/inducers of CYP3A can alter exposures of MORF-057 and their use is prohibited in this study (see Section 6.7.3).

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

The Sponsor will immediately notify the Investigator of any significant safety or toxicology information during the study.

2.3.2.2. Risk of MORF-057 in Combination with COVID-19 Vaccine

Non-live COVID-19 vaccination is considered a simple concomitant medication within the study. However, the efficacy and safety of non-live vaccines (including non-live COVID-19 vaccines) in subjects receiving MORF-057 is unknown. The individual benefit risk assessment of a vaccine

remains with the Investigator. If the assessment of the Investigator suggests the vaccine to be beneficial, it must be a non-live, replication incompetent vaccine, and be approved or authorized by national health authorities.

2.3.3. Overall Benefit Risk Conclusion

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

3. Objectives and Endpoints

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

Objectives	Endpoints
Primary 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

Objectives	Endpoints
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)
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

Objectives	Endpoints
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
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

Objectives	Endpoints
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)	
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	• $\alpha_4\beta_7$ receptor occupancy in blood over time

Objectives	Endpoints
	• $\alpha_4\beta_1$ receptor occupancy in blood over time • Change from baseline over time in blood CCR9 messenger ribonucleic acid (mRNA) • Change from baseline over time in blood lymphocyte subsets

Efficacy Analysis Definitions
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 ≤2 (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
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 ≥12 consecutive weeks prior to Week 52.

4. Study Design

4.1. Overall 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 Long-Term Extension (LTE) Period.

During the optional LTE Period, there will be up to 7 scheduled visits: 4 Treatment Visits (Visits 11-14 at Weeks 65, 78, 91, and 104 [Long-Term Extension (LTE) EOT]), 2 Dose Switch Follow-ups (DSFUs; these 2 visits will only occur if participant consents to dose switch), 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 LTE Period is completed or earlier if treatment is discontinued early).

Due to the changes in Version 3.0 of this protocol, all participants who choose to continue their treatment in the LTE Period will be asked to re-consent to the LTE Period dose switch to 200 mg B.I.D. The dose switch will occur at Visit 10 or at a scheduled visit in the LTE Period (Visit 11, 12, or 13). If the participant does not consent to the dose switch, they will be allowed to remain on their current LTE Period dose and schedule; they will not need to attend DSFUs 1 or 2. Participants in the LTE Period who consent to the dose switch will have a scheduled DSFU 1 at 4 weeks after the dose switch, and then DSFU 2 will be 4 weeks after DSFU 1. The participant will then attend the next scheduled visit (Visit 11, 12, 13, or 14) per the Schedule of Activities (SoA). A participant cannot switch their dose after Visit 13. An SFU Visit will occur 4 weeks after the last dose of study drug is received, which will be at Week 108 if the full LTE Period is completed or earlier if treatment is discontinued early.

Participants who do not enroll into the LTE Period will complete the final SFU Visit (4 weeks after receiving the last dose of MORF-057) for the main part of the study (a maximum time on-study of 62 weeks). Participants who choose to continue in the LTE Period will not complete the SFU Visit for the main part of the study; instead, they will directly enter the LTE Period and complete a separate SFU Visit (4 weeks after receiving the last dose of MORF-057 in the LTE Period), for a maximum time on-study of 114 weeks.

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.

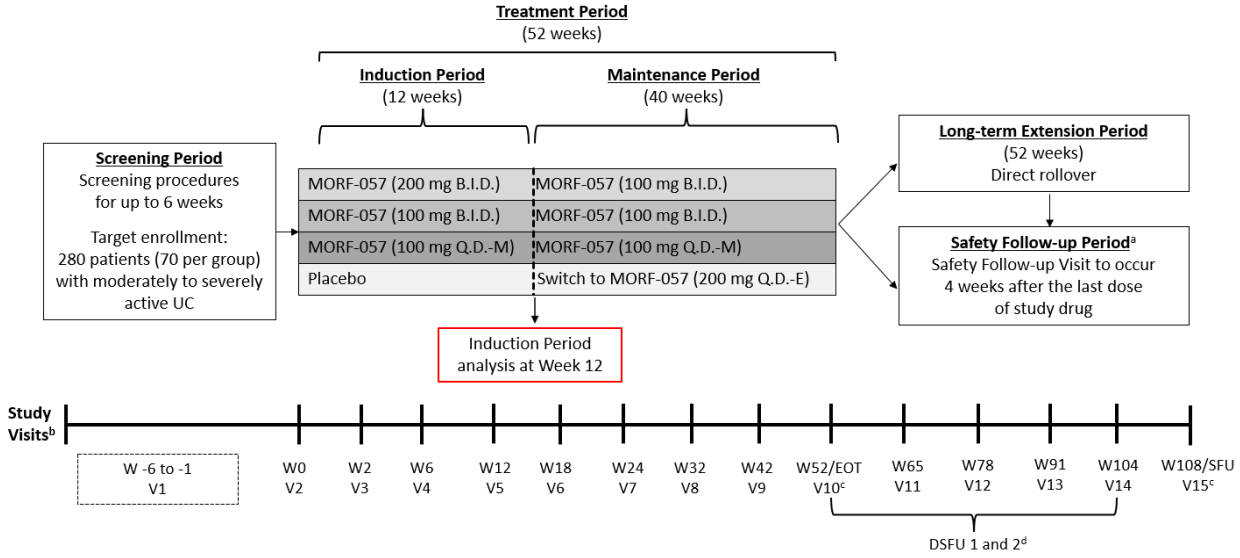
Enrolled participants will be randomized to a treatment group to receive active MORF-057 or placebo. Participants initially randomized into an active MORF-057 treatment group will receive an active treatment (according to study period and group assignment) for the full 52-week Treatment Period. Participants 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 LTE Period. All participants who choose to continue in the LTE Period will continue receiving the same MORF-057 regimen they had during the Maintenance Period for up to an additional 52 weeks. However, at Visit 10 or at a scheduled visit in the LTE Period (Visit 11, 12, or 13), if the participant consents, the MORF-057 dose for the LTE Period will be switched to 200 mg B.I.D. If the participant does not consent to the dose switch, they will be allowed to remain on their current LTE Period dose and schedule. The dosing regimens for the 4 treatment groups during the study are shown below.

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

Abbreviations: B.I.D., twice a day; LTE, Long-Term Extension; Q.D.-E, once a day (evening); Q.D.-M, once a day (morning).
* Relevant for participants who consent to the dose switch in the LTE Period. For those that do not consent to the dose switch in the LTE Period, they will remain on their current LTE Period dose.

A study schema is provided in Figure 1.

Figure 1. Study Schema



Abbreviations: B.I.D. twice a day; DSFU, Dose Switch Follow-up; 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.

a The SFU Visit will not be performed at Week 56 for participants who enter the LTE Period.

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

c 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.

d At Visit 10 or at a scheduled visit in the LTE Period (Visit 11, 12, or 13), all participants will be asked to re-consent to switch their dose to 200 mg B.I.D. Participants who do not consent to the dose switch will remain on their current LTE Period dose. The DSFU 1 will occur 4 weeks after the dose switch, and DSFU 2 will occur 4 weeks after DSFU 1. Participants who do not consent to the dose switch will not need to attend DSFUs 1 or 2.

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

4.2. Scientific Rationale for Study Design

This is a randomized, double-blind, placebo-controlled study. This design will allow for a rigorous evaluation of the safety and efficacy of MORF-057 in participants with moderately to severely active UC.

In the study, 3 active dose regimens of MORF-057 will be compared to placebo for a 12-week Induction Period in order to determine the best overall dosing regimen for future clinical development of MORF-057. This study is the first MORF-057 study with multiple dose arms in UC participants. Multiple B.I.D. doses are being evaluated to compare efficacy, safety, PK parameters, and $\alpha_4\beta_7$ and $\alpha_4\beta_1$ receptor occupancy of MORF-057 B.I.D. administration in UC. An additional Q.D. treatment group is included to compare B.I.D. administration to Q.D. administration. A placebo group is included as a control to compare the efficacy and safety data observed in the active treatment groups to that in a non-active control group. Dose reductions in response to AEs will not be possible due to the double-blind study design; however, study drug interruption will be allowed as deemed necessary by the Investigator and Sponsor Medical Monitor.

In total, the 3 active dose regimens of MORF-057 will be administered for 52 weeks (including a 12-week Induction Period plus a 40-week Maintenance Period). This 52-week design simulates assessment of treatment goals for UC in clinical practice, wherein participants are evaluated for induction of remission, followed by assessment of maintenance of remission over a longer period of time (usually assessed over 52 weeks of continuous treatment in clinical studies). Modern UC clinical trials have Induction Periods lasting 6 to 14 weeks. The 52-week treatment will be followed by an optional 52-week LTE Period. This extension will provide the participants further access to the study drug and collect additional safety and efficacy data up to 104 weeks of exposure.

Participants who are initially randomized to receive placebo will be switched to an active MORF-057 regimen after the 12-week Induction Period. The main purpose for the switch is to collect additional safety data about the active treatment.

The MCS and its derivates are well-established instruments to measure clinical response or remission in patients with UC. The mMCS was chosen for the primary endpoint because it excludes the PGA, a component that the Food and Drug Administration (FDA) and key opinion leaders recommend against using as an endpoint measure to support a marketing application. This recommendation was made because signs and symptoms are best assessed using an outcome instrument that directly reports measurements by patients as opposed to clinicians.

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

Patients were not involved in the design of this study.

4.3. Justification for Dose

The dose regimens selected for this study are provided in Section 4.1.

The selection of dosing regimens was based on the non-clinical and clinical data on mechanism of action of MORF-057, the PK and PD properties, and the safety profile in healthy subjects. In Studies MORF-057-101 and CCI and based on PK-PD modeling, which included PK and PD assessments in healthy adults, separation of exposures was observed/simulated at low (100 mg once a day – morning [Q.D.-M]), mid (100 mg B.I.D.), and high (200 mg B.I.D.) doses, and maximum saturation of α4β7 receptor occupancy was observed following 100 mg B.I.D. and 200 mg B.I.D. doses. It is expected that α4β7 receptor occupancy will be approximately 70% at trough level following 100 mg Q.D.-M dosing. MORF-057 exhibited favorable and near dose-proportional PK across doses with only mild, non-serious AEs reported that did not result in study drug discontinuation. The plasma exposure (AUC), peak (Cmax) and trough (Ctrough) concentrations across selected dosing regimens would help to study dose-response and exposure/concentration response relationships. This exposure was seen in healthy individuals and is expected to be similar in patients with UC to provide levels that would achieve the intended efficacy and safety.

MORF-057 is designed specifically to inhibit α4β7, which is involved in the trafficking of immune cells to sites of inflammation in the intestinal mucosa but exhibits low inhibition of all other integrins, including α4β1. Integrin α4β1 regulates immune cell trafficking to many non-mucosal tissue sites including skin, lung, and the central nervous system (von Andrian 2000). In human whole blood ex vivo studies, the selectivity ratio of IC50 and IC90 values with respect

to α4β7 and α4β1 for MORF-057 are 1:610 and 1:700, respectively. The MORF-057 doses selected for the current study are anticipated to cause minimal to no α4β1 inhibition in humans, and α4β7 and α4β1 receptor occupancies in blood will be assessed as an exploratory endpoint.

The International Council for Harmonisation (ICH)E4 guidelines as well as the Guideline on the development of new medicinal products for the treatment of UC (CHMP/EWP/18463/2006 Rev.1) accept placebo as an acceptable comparator (monotherapy or add-on to established therapy) in clinical trials.

The placebo group serves as a control to evaluate the safety as well as efficacy of MORF-057 in a contemporaneous population.

All participants will be allowed to continue stable background therapy to which either MORF-057 or placebo will be added for 12 weeks.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed the Screening Period and 52-week Treatment Period of the main part of the study and attended the SFU Visit OR has been enrolled into the LTE Period, completed the Week 104/LTE EOT Visit and attended the SFU Visit.

The end of the study is defined as the date of the last visit or last scheduled procedure for the last participant in the study globally. This may occur during the main part of the study, or in the optional LTE Period, depending on that participant's choice whether or not to continue in the LTE Period.

5. Study Population

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

5.1. Inclusion Criteria

Main Inclusion Criteria:

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

Age

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

Type of Participant and Disease Characteristics

2. Participant has had diagnosis of UC supported by signs/symptoms, endoscopy, and histology for at least 3 months prior to Screening. Moderately to severely active UC was determined during the Screening Period with the following criteria: an mMCS of 5 to 9 (inclusive), with an MES ≥2 (confirmed by central reader)
3. Has evidence of UC extending at least 15 cm from the anal verge

4. Demonstrated an inadequate response, loss of response, or intolerance to at least one of the following treatments (including oral aminosalicylates*, corticosteroids, immunosuppressants, and/or advanced therapies for UC) in the opinion of the Investigator, as defined below:

    a. Oral aminosalicylates (e.g., mesalamine, sulfasalazine, olsalazine, or balsalazide)

        - Signs and symptoms of persistently active disease during a current or prior course of at least 4 weeks of treatment with ≥2.0 g/day mesalamine, 4 g/day sulfasalazine, 1 g/day olsalazine, or 6.75 g/day balsalazide

    ***Note:** Inadequate response, loss of response, or intolerance to oral aminosalicylates does not apply to this Inclusion Criterion in European Union (EU) countries.

    b. Corticosteroids

        - Signs and symptoms of persistently active disease despite a history of at least one induction regimen that included a dose equivalent to prednisone ≥30 mg/day orally for at least 3 weeks or intravenously for 1 week

        OR

        - Unable to taper corticosteroids to below a dose equivalent to prednisone 10 mg daily orally without recurrent active disease

        OR

        - Signs and symptoms of persistently active disease during or after a course of at least 4 weeks of treatment with 9 mg/day budesonide or 5 mg/day beclomethasone

        OR

        - Unable to taper oral budesonide below 6 mg/day without recurrent active disease

        OR

        - History of intolerance to corticosteroids (including, but not limited to, Cushing's syndrome, osteopenia/osteoporosis, hyperglycemia, insomnia, or infection)

    c. Immunosuppressants (e.g., azathioprine, 6-mercaptopurine, or methotrexate)

        - Signs and symptoms of persistently active disease despite a history of at least one 8*-week regimen of oral azathioprine (≥1.5 mg/kg/day), 6-mercaptopurine (≥1 mg/kg/day or a documented 6-thioguanine nucleotide level of 230-450 pmol/8 × 10^8 red blood cell count or higher on the current dosing regimen), injectable methotrexate (≥12.5 mg/week subcutaneous [SC] or intramuscular)

            ***Note:** A history of signs and symptoms of persistently active disease despite a history of at least one 12-week regimen of immunosuppressants is required in EU countries.

        OR

- History of intolerance to at least one immunosuppressant (including, but not limited to, nausea/vomiting, abdominal pain, pancreatitis, liver enzyme abnormalities, lymphopenia, or infection)

Note: Oral methotrexate use is allowed during the study; however, prior or current use of oral methotrexate is not sufficient for inclusion into the study unless the participant was previously treated with aminosalicylates, corticosteroids, or immunosuppressants (azathioprine or 6-mercaptopurine) and had an inadequate response, loss of response, or intolerance to the therapy as defined above.

d. Advanced therapies for UC (e.g., biologic agents, JAK antagonists, or sphingosine-1-phosphate [S1P] receptor agonists)

- Primary non-response – Signs and symptoms of persistently active disease despite a history of any of the following:
  - At least one 6-week induction regimen of infliximab (5-10 mg/kg intravenously at 0, 2, and 6 weeks)
  - At least one 4-week induction regimen of adalimumab (one 160 mg SC dose followed by one 80 mg SC dose [or one 80 mg SC dose in countries where this dosing regimen is allowed followed by one 40 mg SC dose] at 2 weeks or earlier)
  - At least one 2-week induction regimen of golimumab (one 200 mg SC dose followed by one 100 mg SC dose at least 2 weeks apart)
  - At least one induction regimen of ustekinumab (single intravenous weight-based infusion of 260 mg [<55 kg body weight], 390 mg [55-85 kg body weight], or 520 mg [>85 kg body weight])
  - A history of completed Induction regimen according to prescribing information for JAK antagonists or S1P receptor agonists

OR

- Secondary non-response – Initially responded to Induction therapy and then had recurrence of symptoms after receiving at least 2 of the Maintenance doses specified below (discontinuation despite clinical benefit does not qualify):
  - Infliximab: ≥5 mg/kg
  - Adalimumab: 40 mg every week or every other week
  - Golimumab: 100 mg injection at Week 6 and every 4 weeks
  - Ustekinumab: 90 mg SC dose 8 weeks after the initial intravenous dose, then every 8-12 weeks thereafter or more frequently

OR

- History of intolerance to at least one advanced therapy agent (including, but not limited to, infusion-related reaction, demyelination, congestive heart failure, or infection)

Note: Participants who have received a prior advanced therapy agent for up to 1 year and did not have a documented non-response may be enrolled; however, the participants must have discontinued the advanced therapy agent for reasons other than inadequate response or intolerance (e.g., change of insurance, well-controlled

disease) and must meet the criteria for inadequate response, loss of response, or intolerance to aminosalicylates, corticosteroids and/or immunosuppressants, as defined above.

Note: Participant cannot have had inadequate response, loss of response, or intolerance to more than 3 drugs in 2 classes of the following advanced therapies:

a. TNF-α antagonists, including infliximab, adalimumab, or golimumab
b. Interleukin (IL)-12/IL-23 antagonists, including ustekinumab
c. JAK antagonists, including tofacitinib or upadacitinib
d. S1P receptor agonists, including ozanimod
e. Any investigational product with the same mechanism as one of those outlined above (a through d) or a novel mechanism of action

Note: Participants who have a history of primary non-response to 2 or more of the advanced therapy classes above will not be eligible. Participants who have received treatment with these agents at sub-therapeutic doses or durations should be discussed with the Medical Monitor to assess eligibility.

5. Meets the following washout criteria of prior UC therapy relative to study Day 1:

    a. TNF-α antagonists: at least 8 weeks
    b. IL-12/IL-23 antagonists, including ustekinumab: at least 8 weeks
    c. JAK antagonists, including tofacitinib or upadacitinib: at least 1 week
    d. S1P receptor agonists, including ozanimod: at least 4 weeks

    Note: Participants who do not meet the full washout period but have the results of a local drug concentration level performed during the Screening Window deemed by the Medical Monitor to be sub-therapeutic may be eligible for the study earlier than the full washout period.

6. If the participant has been receiving any of the non-prohibited medications for UC listed below, he/she must discontinue use at least 5 half-lives before study Day 1 or must agree to maintain stable doses of these concomitant medications starting from the time specified below until the end of the SFU Period, with the exception of tapering oral corticosteroid dose after 12 weeks of being in the trial.

    a. Oral 5-Aminosalicylates (not exceeding 4.8 g per day): at least 2 weeks prior to study Day 1
    b. Oral corticosteroids (not exceeding prednisone 30 mg/day, budesonide 9 mg/day, beclomethasone dipropionate 5 mg/day, methylprednisolone 24 mg/day, or equivalent; see Table 5): at least 2 weeks prior to study Day 1
    c. 6-Mercaptopurine (any stable dose): at least 4 weeks* prior to study Day 1
    d. Azathioprine (any stable dose): at least 4 weeks* prior to study Day 1
    e. Methotrexate (any stable dose): for at least 4 weeks* prior to study Day 1

    ***Note:** Participants must be on any stable dose of 6-mercaptopurine, azathioprine, or methotrexate for at least 12 weeks prior to study Day 1 in EU countries.

7. If the participant has had UC for over 7 years, he/she must have had a full colonoscopy in the last 2 years or must agree to have a full colonoscopy (rather than sigmoidoscopy) with appropriate, per local guidelines, colon cancer surveillance biopsies at Screening

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

Weight

9. Has a body mass index (BMI) ≥18.0 at Screening

Sex and Contraceptive/Barrier Requirements

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

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

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

        OR

        - Agrees to use contraception/barrier methods as detailed below:
            - Agrees to use a male condom, with female partner use of an additional highly effective contraceptive method with a failure rate of <1% per year (as described in Section 10.5.3) when having sexual intercourse with a woman of childbearing potential who is not currently pregnant.

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

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

        OR

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

    Note: For contraception requirements on or after Protocol Amendment Version 3.0, see Section 10.5.2.2.

11. For the study Treatment Period and at least 14 days after receiving the last dose of MORF-057, male participants must agree not to donate sperm and female participants must agree not to donate eggs (ova, oocytes).

Informed Consent

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

5.2. Exclusion Criteria

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

Medical Conditions

1. Diagnosed with indeterminate colitis, microscopic colitis, ischemic colitis, radiation colitis, or Crohn's disease, or has clinical findings suggestive of Crohn's disease
2. Has current evidence of un-resected colonic dysplasia or un-resected adenomatous colonic polyps or evidence of toxic megacolon, abdominal abscess, symptomatic colonic stricture, fistula, stoma, ileostomy, or colostomy at Screening
3. Currently requires or is anticipated to require surgical intervention for UC during the study
4. Has had a surgical procedure requiring general anesthesia within 30 days prior to Screening or is planning to undergo major surgery during the study period
5. Has a history of any major neurological disorders, including stroke, multiple sclerosis, brain tumor, demyelinating, or neurodegenerative disease. For questions about whether this applies to a specific case, consult with the Medical Monitor.
6. Has positive findings on a Subjective PML symptom checklist during Screening or prior to the administration of the first dose of study drug on study Day 1
7. Has a potentially active bacterial, viral, or parasitic pathogenic enteric infection, including *Clostridiodes difficile (C. difficile)*; has hepatitis B or C virus, or HIV; had an infection requiring hospitalization or intravenous antimicrobial therapy, or an opportunistic infection within 3 months prior to Screening; had any infection requiring oral antimicrobial therapy within 2 weeks prior to Screening; or has a history of more than 1 episode of herpes zoster or any episode of disseminated herpes zoster infection
8. Has active tuberculosis (TB), as evidenced by any of the following:
    a. A diagnostic test for TB performed within 30 days prior to Screening or during the Screening Period that is positive, as defined below:
        - A positive interferon gamma release assay (IGRA) test (e.g., [redacted] TB test) or 2 consecutive indeterminate IGRA tests

        OR
        - A purified protein derivative (PPD) skin test ≥5 mm

    b. A chest X-ray or imaging per local guidelines within 3 months prior to Screening where active or latent pulmonary TB cannot be excluded

Note: Participants who have tested negative for TB at a certified local lab using an IGRA test within 3 months prior to Screening are not required to repeat this test during the Screening Period if that participant has no clinical signs or symptoms of TB and no known

exposures/increased risk factors since the last negative TB test (according to the Investigator's clinical judgement), and the test result is available in the participant's medical record

Note: Participants with a history of latent TB may be enrolled if they complete an assessment for evidence of active TB versus latent TB. Documentation will include a chest X-ray or imaging per local guidelines during the Screening Window and no signs, symptoms, or evidence of ongoing active TB. Participants have had treatment per the local standard of care for a minimum of 2 weeks before the first dose of study drug OR documentation of completing appropriate treatment for latent TB within 2 years before Day 1 of the study. See Section 8.2.2.1 for more details.

9. Has a positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) test result during the Screening Period. Testing for SARS-CoV-2 is required only per local regulations. Participants who have a positive test result can be randomized after a subsequent negative test result during the Screening Period.
10. Had any vaccination (including live virus vaccinations) within 3 weeks prior to study Day 1

    Note: For vaccinations requiring a series of doses, the last in the series should be completed by 3 weeks prior to study Day 1 (e.g., SARS-CoV-2 two-shot vaccination series)
11. Has a concurrent, clinically significant, serious, unstable comorbidity (such as uncontrolled cardiovascular, pulmonary, hepatic, renal, gastrointestinal, genitourinary, hematological, coagulation, immunological, endocrine/metabolic, or other medical disorder) that, in the judgement of the Investigator, would compromise compliance with the protocol, interfere with interpretation of the study results, or pre-dispose participants to safety risks
12. Has a known primary or secondary immunodeficiency
13. Has a history of myocardial infarction, unstable angina, transient ischemic attack, decompensated heart failure requiring hospitalization, congestive heart failure (New York Heart Association Class 3 or 4), uncontrolled arrhythmias, cardiac revascularization, uncontrolled hypertension, or uncontrolled diabetes within 6 months of Screening
14. Has a history of left ventricular ejection fraction (LVEF) <50%
15. Has a clinically significant abnormal ECG at Screening, including a QT interval corrected through use of Fridericia's formula (QTcF) ≥450 ms for males and ≥470 ms for females
16. Abnormal hematology (hemoglobin level, WBC count, or platelet count) or coagulation results at Screening, as evidenced by the ranges provided below:*
    a. Hemoglobin level <8.0 g/dL
    b. Absolute WBC count $<3.0 \times 10^9$/L
    c. Absolute lymphocyte count $<0.5 \times 10^9$/L
    d. Absolute lymphocyte count >5.5 x 10^9/L
    e. Absolute neutrophil count $<1.2 \times 10^9$/L
    f. Platelet count $<100 \times 10^9$/L or $>1000 \times 10^9$/L
    g. International normalized ratio >1.5. Participants with an international normalized ratio >1.5 due to anticoagulant therapy (e.g., Coumadin) may only be enrolled after a consultation with the Medical Monitor.

17. Clinically significant abnormal urinalysis results, as deemed by the Investigator or designee
18. Abnormal organ function at Screening, as evidenced by the following:*
    a. Alanine aminotransferase or aspartate aminotransferase >2.0 × upper limit of normal (ULN)
    b. Chronic kidney disease stages 4 and 5, defined as having a glomerular filtration rate <30 mL/min/1.73m^2 as calculated using the Modification of Diet in Renal Disease equation (National Kidney Foundation), receiving dialysis, or being listed for or has received a renal transplant
    c. Total bilirubin ≥1.5 × ULN

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

Prior/Concomitant Therapy

20. Treatment with cyclosporine, mycophenolate, tacrolimus, or sirolimus within 30 days or 5 half-lives (whichever is shorter) prior to study Day 1
21. Any previous treatment with vedolizumab or other licensed or investigational integrin inhibitors
22. Experiencing toxicities from prior therapy with Grade >1 within 1 week prior to first dose of study drug
23. Fecal microbiota transplantation within 3 months prior to Screening
24. Participant needs to continue treatment with a moderate-to-strong CYP3A inducer or inhibitor and, therefore, will be unable to do a washout period of at least 30 days or 5 half-lives (whichever is shorter) prior to study Day 1. See Section 6.7.3 for a list of moderate-to-strong P450 inducers and inhibitors.
25. Participant needs to continue treatment with a moderate-to-strong organic anion transporter polypeptide-1B inhibitor and, therefore, will be unable to do a washout period of at least 14 days or 5 half-lives (whichever is shorter) prior to study Day 1. See Section 6.7.3 for a list of moderate-to-strong organic anion transporter polypeptide-1B inhibitors.

Prior/Concurrent Clinical Study Experience

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

Other Exclusions

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

5.3. Lifestyle Considerations

No new non-pharmacological therapies should be started during the study period. Information should be collected on the participant's change in substance use (e.g., alcohol, tobacco, and drugs) per the SoA in Section 1.2.

The following dietary and lifestyle restrictions are recommended throughout the duration of the study:

- Refrain from consuming grapefruit, grapefruit juice, starfruit, limes, and bitter oranges.
- Refrain from excessive caffeine consumption, defined as ≥800 mg/day (or >8 cups of brewed coffee per day). For each scheduled study visit, participants should refrain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) before the morning dose until after all study assessments and blood collections have been completed for that visit.
- For each scheduled study visit, participants should refrain from consuming alcohol before the morning dose until after all study assessments and blood collections have been completed for that visit.
- Refrain from the use of cannabidiol and tetrahydrocannabinol.

5.4. Screen Failures

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

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

Note: Participants who are unable to complete all required procedures or assessments within the Screening Window due to technicalities may be eligible to extend their Screening Period up to

2 weeks based on an agreement between the Investigator and the Sponsor Medical Monitor. Screening activities that require repeating will be determined by the Sponsor Medical Monitor and the process outlined in the Monitoring Plan.

Individuals who did not meet the Screening criteria for the MORF-057-201 study may be eligible to be screened for the MORF-057-202 study. The Investigator should discuss such cases with the Sponsor before proceeding.

6. Study Treatment and Concomitant Therapies

6.1. Study Treatment Description

A description of each study treatment type is provided in Table 3, and a description of each treatment group is provided in Table 4. Refer to Section 8.3 for study drug administration instructions.

More detailed information about MORF-057 and placebo can be found in the Pharmacy Manual. MORF-057 and placebo capsules will be manufactured, quality control tested, and released in accordance with Good Manufacturing Practice.

Table 3. Study Treatment

Treatment name	**MORF-057**	**Placebo**
Treatment type	Small molecule drug	Placebo
Dose strength and formulation	100-mg IR capsule (Swedish orange capsule size 0)	0-mg IR capsule (Swedish orange capsule size 0)
Route of administration	Oral	Oral
Dosage regimens	See Table 4	See Table 4
Use	Experimental	Placebo
IMP/NIMP	IMP	IMP
Sourcing	Provided by Sponsor	Provided by Sponsor
Packaging and labeling	30 Capsules are packaged in a high-density polyethylene bottle containing an oxygen absorber canister and coil and closed with a child-resistant cap equipped with a heat-sealed foil liner. Each bottle will be labeled as per country requirements.	30 Capsules are packaged in a high-density polyethylene bottle containing an oxygen absorber canister and coil and closed with a child-resistant cap equipped with a heat-sealed foil liner. Each bottle will be labeled as per country requirements.
Storage	Store according to the country-specific label	Store according to the country-specific label

Abbreviations: IMP, investigational medicinal product; NIMP, non-investigational medicinal product; IR, immediate-release.

Table 4. Treatment Groups

Group title	Group 1	Group 2	Group 3	Group 4
Type	• Induction: Experimental • Maintenance/LTE Period: Experimental	• Induction: Experimental • Maintenance/LTE Period: Experimental	• Induction: Experimental • Maintenance/LTE Period: Experimental	• Induction: Placebo • Maintenance/LTE Period: Experimental
Induction Period dosing regimen (12 Weeks)	MORF-057 (200 mg B.I.D.) Total dose/day: 400 mg	MORF-057 (100 mg B.I.D.) Total dose/day: 200 mg	MORF-057 (100 mg Q.D.-M) Total dose/day: 100 mg	Placebo
Maintenance Period dosing regimen (40 Weeks)/ LTE Period dosing regimen (52 Weeks)	MORF-057 (100 mg B.I.D.) Total dose/day: 200 mg	MORF-057 (100 mg B.I.D.) Total dose/day: 200 mg	MORF-057 (100 mg Q.D.-M) Total dose/day: 100 mg	MORF-057 (200 mg Q.D.-E) Total dose/day: 200 mg
Instructions for administration	Take 1 capsule from EACH bottle for the respective dosing time (morning or evening). Each bottle contains 30 capsules of either MORF-057 or placebo.	Take 1 capsule from EACH bottle for the respective dosing time (morning or evening). Each bottle contains 30 capsules of either MORF-057 or placebo.	Take 1 capsule from EACH bottle for the respective dosing time (morning or evening). Each bottle contains 30 capsules of either MORF-057 or placebo.	Take 1 capsule from EACH bottle for the respective dosing time (morning or evening). Each bottle contains 30 capsules of either MORF-057 or placebo.

Group title	Group 1	Group 2	Group 3	Group 4
LTE Period (52 Weeks)*	MORF-057 (200 mg B.I.D.) Total dose/day: 400 mg	MORF-057 (200 mg B.I.D.) Total dose/day: 400 mg	MORF-057 (200 mg B.I.D.) Total dose/day: 400 mg	MORF-057 (200 mg B.I.D.) Total dose/day: 400 mg
Instructions for administration	Bottles will contain 30 (thirty) MORF-057 100 mg capsules. Take 2 capsules in the morning and 2 capsules in the evening.	Bottles will contain 30 (thirty) MORF-057 100 mg capsules. Take 2 capsules in the morning and 2 capsules in the evening.	Bottles will contain 30 (thirty) MORF-057 100 mg capsules. Take 2 capsules in the morning and 2 capsules in the evening.	Bottles will contain 30 (thirty) MORF-057 100 mg capsules. Take 2 capsules in the morning and 2 capsules in the evening.

Abbreviations: B.I.D., twice a day; LTE, Long-Term Extension; Q.D.-E, once a day (evening); Q.D.-M, once a day (morning).
* Relevant for participants who consent to the dose switch in the LTE Period. For those that do not consent to the dose switch in the LTE Period, they will remain on their current LTE Period dose

6.2. Preparation, Handling, Storage, and Accountability

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

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

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study drug accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records). All unused study drug for all participants should be maintained until review by a study monitor during site visits and at the time of database lock.

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

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Randomization

An interactive response technology (IRT) will be used to centrally randomize all participants into 1 of the 4 treatment groups (see Sections 4.1 and 6.1 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). All participants who consent will be switched to a new MORF-057 dose in the LTE Period.

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

6.3.2. 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 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/LTE Period prior to dose switch). In the morning, participants should take 1 capsule from EACH “morning bottle.” In the evening, participants should take 1 capsule from EACH “evening bottle.” In the LTE Period after the dose switch, bottles will contain 30 (thirty) MORF-057 100 mg capsules. Participants who consent will

take 2 capsules in the morning and 2 capsules in the evening. Those that do not consent to the dose switch will remain on their current LTE Period dose. 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 in the Induction and Maintenance/LTE Period through the end of the study including the LTE Period.

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 Pharmacovigilance staff will unblind all SAE reports in the safety database. If the report requires expedited reporting to one or more regulatory agency, 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.

6.4. Study Treatment Compliance

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

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

The site staff will contact participants, by phone or other means, on the next business day after the Visit 5 clinic visit to confirm the participants have switched from the Induction Period study drug to the new Maintenance Period study drug bottles. In addition, the site staff will contact the participants who consented, by phone or other means, on the next business day after the dose switch in the LTE Period to confirm the participants have switched to the new dose (200 mg B.I.D.) of study drug correctly. Record the date and time of the participant's first dose of the new dose (200 mg B.I.D.) in the source documents.

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

6.5. Continued Access to Study Treatment After the End of the Study

Participants will no longer have access to the study drug after they complete the study.

6.6. Overdose

An overdose is defined as any timepoint where the study participant took more pills than directed or took pills from a different bottle than directed (if the total daily number of capsules consumed could exceed the maximum total daily number of capsules possible per protocol [4 total capsules/day]).

No specific information is available on the treatment of acute or chronic overdosage of MORF-057. In the event of overdose:

- The Investigator will notify the Medical Monitor immediately.
- Evaluate the participant, to determine in collaboration with the Medical Monitor, whether the study drug should be interrupted or discontinued.
- The participant should be observed closely. Appropriate supportive treatment should be provided if clinically indicated.
- Overdose with or without clinical symptoms or abnormal laboratory results should be recorded on the overdose electronic Case Report Form (eCRF) within 24 hours of becoming aware.
- AEs and SAEs associated with overdose will be recorded on the AE eCRF, and SAEs associated with overdose will be reported via the SAE reporting procedure outlined in Section 8.9.

6.7. Concomitant Therapy

6.7.1. Concomitant Medications

Any medications (including over-the-counter or prescription medicines, recreational drugs [e.g., psychoactive drugs like marijuana], vitamins, and/or herbal supplements) or vaccines that the participant receives from the time of ICF signing through the SFU Visit must be recorded in the eCRF along with:

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

Any medication given for an AE should be recorded as such from the time of informed consent.

6.7.2. Allowed Medications for the Treatment of Ulcerative Colitis

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

- Oral 5-aminosalicylates (not exceeding 4.8 g per day)
- Oral corticosteroids (not exceeding prednisone 30 mg per day, budesonide 9 mg per day, beclomethasone dipropionate 5 mg per day, methylprednisolone 24 mg per day, or equivalent; see Table 5)
- 6-Mercaptopurine (any stable dose)
- Azathioprine (any stable dose)
- Methotrexate (any stable dose)

Although these medications are allowed, participants should not start or stop any of these medications during the study. Furthermore, participants must maintain stable doses of all UC-related concomitant medications throughout the study until the end of the SFU Period, with the exception of tapering oral corticosteroid dose after 12 weeks of being in the trial. See Inclusion Criterion 6 (Section 5.1) for Screening-related requirements for these medications, including how long a stable dose must be maintained before study Day 1.

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

Table 5. Corticosteroid Equivalent Doses†

	Equivalent Glucocorticoid Dose (mg)*	Maximum Dose per day for Study (mg)
Short acting		
Hydrocortisone (cortisol)	20	120
Cortisone acetate	25	150
Intermediate acting		
Prednisone	5	30
Prednisolone	5	30
Triamcinolone	4	25
Methylprednisolone	4	24
Long acting		
Dexamethasone	0.75	5
Betamethasone	0.6	5

* Source: Parente 2017
† Other corticosteroids may be used per the medical judgement of the Investigator. Consult the Medical Monitor as needed.

6.7.2.1. Tapering of Oral Corticosteroids

The following corticosteroid tapering schedules should be used, unless medically contraindicated after discussion with the Medical Monitor.

Participants receiving oral corticosteroids at the time of enrollment should maintain their current dose regimen during the Induction Period (first 12 weeks). Upon entering the Maintenance Period, it is strongly recommended that all the participants responding to treatment, as assessed by the Investigator, start tapering their corticosteroid dose OR, in cases where corticosteroids were used as rescue medications (Section 6.7.2.2), tapering must start within 4 weeks after the increase in the corticosteroid therapy, as outlined below:

- Prednisolone (or equivalent) dose should be tapered by 5 mg/day every week until the daily dose reaches 10 mg/day (or prednisone equivalent); then, it should be tapered by 2.5 mg/day every week (or prednisone equivalent) until completely tapered off.
- Budesonide dose should be tapered by 3 mg/day for every 2 weeks until completely tapered off.
- If the participant is on methylprednisolone or beclomethasone, then taper the dose according to the local medical practice.
- If the participant is on corticosteroids as a rescue medication during the Maintenance Period, then taper as suggested above or more quickly if clinically appropriate.

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

6.7.2.2. Rescue Therapies

If during the study a participant's UC condition worsens and requires rescue therapies of changing any UC background medications or initiating a new UC therapy (with the exception of returning the background corticosteroid therapy dose to baseline level), the participant should be withdrawn from the study and appropriate treatment should be given at the discretion of the Investigator. Anti-diarrheals for control of chronic diarrhea and antibiotics for control of infection are not considered rescue medication.

6.7.3. Prohibited Medications

The following concomitant medications/therapies are prohibited for the entire duration of the study, including SFU:

- Treatments for UC other than those listed in Section 6.7.2 (including TNF-α antagonists, integrin antagonists [e.g., vedolizumab], IL-12/IL-23 antagonists, JAK antagonists, and S1P receptor agonists)
- Biologics including, but not limited to, the following list:
    - Etanercept
    - Abatacept
    - Anakinra
    - Rituximab

  - Natalizumab
  - Tocilizumab
  - Efalizumab
  - Ustekinumab
  - Belimumab
  - Golimumab
  - Vedolizumab
  - Infliximab
  - Adalimumab
  - Certolizumab pegol
  - Secukinumab

- Receipt of a live virus vaccine from 3 weeks prior to study Day 1 until 28 days after the last dose of study drug. Live vaccines include but are not limited to the following list:

  - Monovalent live influenza A (H1N1) (intranasal)
  - Seasonal trivalent live influenza (intranasal)
  - Zostavax (herpes zoster, live attenuated)
  - Rotavirus
  - Varicella (chicken pox)
  - Measles-mumps-rubella or measles-mumps-rubella-varicella
  - Oral polio vaccine
  - Smallpox
  - Yellow fever
  - Bacille Calmette-Guérin (BCG)
  - Typhoid (oral)

  Note: Non-live vaccines, including those for SARS-CoV-2, should not be administered between 3 weeks prior to study Day 1 and the Week 12 assessments. After the Week 12 assessments, such vaccines can be administered according to local vaccination standards. Per Exclusion Criterion 10, if the participant has started a vaccination series before Day 1, the last in the series should be completed by 3 weeks prior to Day 1 (Section 5.2).

- Moderate-to-strong CYP3A inhibitor or inducer (see Table 6)
- Moderate-to-strong organic anion transporter polypeptide-1B inhibitor (see Table 6)
- Cyclosporine, mycophenolate, tacrolimus, thalidomide, or sirolimus
- Nonsteroidal anti-inflammatory drugs including but not limited to ibuprofen, naproxen, indomethacin, and celecoxib. (However, participants may take aspirin for cardio-protection at a dose as per local guidelines but not exceeding 325 mg per day.)
- Intravenous corticosteroids
- Rectal 5-aminosalicylates
- Rectal corticosteroids
- Total parenteral nutrition

- Traditional Chinese/Eastern medicines
- Any investigational therapy

Table 6. Examples of Drugs Potentially Altering Exposures to MORF-057[#]

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

[#] This is not an exhaustive list of CYP3A inhibitors/inducers or OATP1B1 inhibitors.
* Time-dependent inhibitors
† Glucocorticoids permitted at the doses indicated in Section 6.7.2
Sources: (Flockhart, 2021) (US FDA, 2020)

6.7.4. Prohibited Procedures

The following concomitant procedures are prohibited during the study:

- Major elective surgery
- Immunoadsorption columns
- Intravenous immunoglobulin or plasmapheresis
- Blood donations during the study and for 28 days after the last dose of study drug
- Donation of sperm or oocytes during the study and for 14 days after the last dose of study drug

7. Discontinuation of Study Treatment and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Treatment

7.1.1. Permanent Discontinuation

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

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

- Use of disallowed medications and/or procedures as defined in Sections 6.7.3 and 6.7.4
- Severe uncontrolled infection
- Changes in ECG considered clinically significant and with reasonable possibility of relationship to study drug
- Lack of efficacy, defined as:
    - Determined by the Investigator that the participant is not benefiting from the investigational treatment and/or continued participation would pose an unacceptable risk to the participant
    - Administration of a rescue medication (a new medication or increase in dose of a baseline medication to treat new or unresolved UC symptoms with the exception of returning the background corticosteroid therapy dose to baseline level). Anti-diarrheals for control of chronic diarrhea and antibiotics for control of infection are not considered rescue medication.
    - Requirement for abdominal surgery due to complications from UC
- Pregnancy or planned pregnancy of the female participant or female partner of a male participant as the participant will be unblinded (see Section 8.9.5)
- The participant has confirmed PML
- The participant has abnormal liver function results and re-testing results indicate clinically significant abnormalities, as detailed in Table 12
- Repeated or significant non-compliance with study treatment (see Section 6.4) or study procedures to the extent that continued participation would pose an unacceptable risk to the participant, as determined by the Investigator
- Sponsor or the Investigator deems it is necessary for the participant
- The participant wishes to voluntarily withdraw from the study (see Section 7.2)
- The participant does not return to the clinic, and attempts to contact the participant are unsuccessful (see Section 7.3)

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

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

7.1.2. Dose Interruption and Re-challenge

Situations requiring study drug interruption and the potential for re-challenge are presented in Table 7. Decisions regarding dose interruptions and re-challenges will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

Table 7. Study Drug Interruption and Re-challenge Guidelines

Clinical Situation/Event	Study Drug Interruption	Re-Challenge
Possible drug-induced liver damage	Requirements are outlined in Table 12	Requirements are outlined in Table 12
PML screening	Requirements for study drug interruption after positive Subjective PML questionnaire are outlined in Section 8.8.5	Requirements for re-challenge are dependent on PML being definitively ruled out as outlined in algorithm within the PML Reference Guide
Serious Adverse Event	Investigator and Sponsor Medical Monitor may interrupt study drug administration if deemed necessary	Re-challenge decision will be made in each clinical situation in consultation with Investigator and Sponsor Medical Monitor

Abbreviations: PML, progressive multifocal leukoencephalopathy.

7.2. Participant Discontinuation/Withdrawal from the Study

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

The participant should be encouraged to complete the EOT Visit at the time of study drug discontinuation and the SFU Visit at 28 days (+7 days) after the last dose of study drug. See the SoA (Section 1.2) for details regarding the data to be collected at the EOT and SFU Visits.

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

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

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

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

7.3. Lost to Follow-up

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

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

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

8. Study Assessments and Procedures

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

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

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

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

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

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

8.1. Medical History

The participant's demographics and complete medical and surgical history, including initial UC diagnosis date and history of UC medication use, will be collected during Screening and recorded in the participant's eCRF.

Study sites should make every effort to collect UC-related medical and surgical history after initial UC diagnosis.

8.1.1. Prior Medications

Study sites should make every effort to document a participant's prior UC medications. All prior treatments for UC, including advanced therapies (e.g., antagonists to TNF-α, JAK, or IL-12/IL-23; S1P receptor agonists; or other new investigational treatments), should be collected and recorded in the eCRF, including dates of start, stop, and dosing regimen changes, along with the reason for discontinuation, where possible.

Information about non-UC therapies and medications received within 1 month prior to Screening will be recorded in the eCRF, including dates of start, stop, and dosing regimen changes.

Non-prohibited UC medications (see Section 6.7.2) started prior to Day 1 that will be continued as concomitant medications during the study must be on a stable regimen, consistent with the requirements in Inclusion Criterion 6 (see Section 5.1).

8.2. Screening-specific Tests

8.2.1. Screening Stages

Once informed consent is obtained, the procedures listed for Stage 1 of Screening should be performed. Stage 1 will be approximately 2 weeks long and should include the collection of Participant Diary information for 7 days. At the end of Stage 1, the Investigator should use the information collected in the Participant Diary to assess the severity of UC. If the participant is consistently having 3 or more stools per day than normal, often with visible blood, then he/she should proceed to Stage 2 of Screening (including endoscopy). If the participant's stool frequency and rectal bleeding symptoms are milder than what is described, Stage 2 of Screening should not be pursued. If the participant has had UC for over 7 years and a full colonoscopy has not been performed in the past 2 years, he/she must undergo a full colonoscopy at Screening (rather than sigmoidoscopy).

8.2.2. Screening for Pathogens and/or Infections

8.2.2.1. Tuberculosis

All participants will complete TB Screening to determine eligibility. Participants with a negative TB test and chest X-ray (or imaging per local guidelines) not suggestive of active TB may be enrolled. Participants with a history of active TB may be enrolled if it has been adequately treated with no evidence of current active TB. Participants with a positive TB test must be assessed for evidence of active TB versus latent TB. Please refer to Table 8 for TB Screening and eligibility details. Exclusion criteria includes those participants with a positive TB diagnostic test performed within 30 days prior to Screening or during the Screening Period (e.g., a positive IGRA test such as a [redacted] TB test, 2 consecutive indeterminate IGRA tests, or a PPD skin test ≥5 mm), and those who had a chest X-ray within 3 months prior to Screening where active or latent pulmonary TB could not be excluded.

The TB Screening tests are diagnostic, and the results should be interpreted with the participant's medical history and exam findings.

The IGRA test should be performed at Screening on all participants, except for those who have had a confirmed negative IGRA test within 3 months prior to Screening. The PPD skin test

should be performed when the IGRA test is not possible or if both tests are required by local guidelines. Test results should be interpreted as shown below:

- For regions that require both IGRA and PPD tests, if either test is positive, the TB test is considered positive.

If the IGRA test is indeterminate, then the Investigator should perform a second IGRA test to rule out a positive test result. If testing remains indeterminate or is positive, then the participant is considered TB positive.

The PPD skin test should be read by a licensed healthcare professional between 48 and 72 hours after administration. A reaction of induration ≥5 mm is considered a positive reaction.

Participants who have tested negative for TB at a certified local lab using an IGRA test within 3 months prior to Screening are not required to repeat this test during the Screening Period if that participant has no clinical signs or symptoms of TB, no known exposures/increased risk factors since the last negative TB test (according to the Investigator's clinical judgement), and the test result is available and adequately documented in the participant's medical record.

Table 8. Summary of Tuberculosis Screening and Eligibility

Test Performed Within 30 Days Prior to Screening or During the Screening Period	**Inclusion**	**Exclusion**
A positive interferon gamma release assay (IGRA) test (e.g., [redacted] TB test)		X
2 consecutive indeterminate IGRA tests		X
A purified protein derivative (PPD) skin test ≥5 mm		X
Test Performed Within 3 Months Prior to Screening	**Inclusion**	**Exclusion**
A chest X-ray within 3 months prior to Screening where active or latent pulmonary TB cannot be excluded		X
A negative test for TB at a certified local lab using an IGRA test (e.g., [redacted] TB test) within 3 months prior to Screening AND • Has no clinical signs or symptoms of TB • No known exposures/increased risk factors since the last negative TB test (according to the Investigator's clinical judgement) • The test result is available and adequately documented in the participant's medical record Note: Re-testing is not required at Screening if all the above criteria are met	X	
History of Latent TB	**Inclusion**	**Exclusion**
Study participants with a positive TB test must be assessed for evidence of active TB versus latent TB. Documentation will include:	X	

• Chest X-ray or imaging per local guidelines during the Screening Window • No signs and symptoms (no evidence of ongoing active TB) • Study participant is being treated per local standard of care for a minimum of 2 weeks before the first dose of study drug OR • Study participant has documentation of completing appropriate treatment for latent TB within 2 years before Day 1 of the study		

Abbreviations: IGRA, interferon gamma release assay; PPD, purified protein derivative; TB, tuberculosis.

See Exclusion Criterion 8 (Section 5.2) and the SoA (Section 1.2) for additional details regarding testing requirements.

8.2.2.2. SARS-CoV-2

Testing for SARS-CoV-2 is required only per local regulations. Participants who have a positive test result will be excluded from randomization until a subsequent test result is negative. See Exclusion Criterion 9 (Section 5.2) and the SoA (Section 1.2) for details regarding testing requirements.

8.2.2.3. *C. difficile* and Enteric Pathogens

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

8.2.2.4. HIV, Hepatitis B, and Hepatitis C

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

8.2.3. Drug/Alcohol Screening

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

8.3. Study Drug Administration

8.3.1. Dosing Instructions

The first dose of the study drug will be administered in the clinic on study Day 1 under the supervision of study personnel. All subsequent doses will be self-administered at home, with the exception of the morning doses for Visits 2-10, which will be administered during the study visits after pre-dose blood samples have been drawn (see details in the SoA, Section 1.2). Participants will be instructed to record all details about the doses administered at home in the Participant Diary.

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/LTE Period).

Induction Period

For the Induction Period, each 30-day study drug supply will consist of 2 cartons (1 for morning and 1 for evening). Inside each carton, there will be 2 corresponding bottles of study drug. Thus, an Induction Period 30-day study drug supply will consist of the following bottles: morning bottle #1, morning bottle #2, evening bottle #1, and evening bottle #2. Each participant will be instructed to take 4 capsules per day, 1 from each bottle, during the Induction Period.

Maintenance Period/LTE Period (all participants including those who do not consent to the dose switch in the LTE Period)

For the Maintenance Period/LTE Period, each 30-day study drug supply will consist of 1 carton. Inside the single carton, there will be 3 bottles of study drug: morning bottle, evening bottle #1, and evening bottle #2. In the morning, participants should take 1 capsule from the "morning bottle." In the evening, participants should take 1 capsule from EACH "evening bottle." Each participant will be instructed to take 3 capsules per day during the Maintenance Period/LTE Period (no dose switch). It is important to note that the bottles may contain capsules with either MORF-057 100 mg or placebo. Thus, the study drug must be taken exactly as directed in the Pharmacy Manual.

LTE Period (for participants who re-consent to the dose switch in the LTE Period)

All participants will be asked to re-consent to switch their dose to 200 mg B.I.D. The dose switch will occur at Visit 10 or at a scheduled visit in the LTE Period (Visit 11, 12, or 13). If a participant does not consent to the dose switch, they will be allowed to stay on their current LTE Period dose as described above. During the LTE Period, all participants will receive their study drug supplies as bottles containing 30 (thirty) MORF-057 100 mg capsules. Participants should take 2 capsules in the morning and 2 capsules in the evening.

Participants will take the assigned study drug with water twice daily. The study drug can be taken with or without food. No unplanned dose adjustments will be allowed. The study drug capsules should be taken at approximately the same time every day in the morning and in the evening. The interval between doses should be as close to 12 hours as possible.

8.3.2. Missed Dose Instructions

Participants should be instructed that if they forget to take a dose, they can take the dose within 6 hours of the normal dosing time; otherwise, they should take their next dose at the regular time. Participants who vomit a capsule should be instructed not to take another capsule at that dosing time, but to take the next scheduled dose at the regular time. Participants should be reminded to complete their Participant Diary accordingly. Participants should be instructed to contact the Investigator if they miss more than 2 consecutive doses; in such cases, the Investigator should consult with the Medical Monitor regarding any actions required.

8.4. Virtual/Hybrid Visits

To allow participants to remain in the study and to continue to be evaluated, a virtual or hybrid visit may be considered only for participants who are not able to participate in an on-site visit. Some visit assessments and procedures may be performed virtually or off-site with the permission of the Investigator and Sponsor in accordance with all national, state, and local laws or regulations of the pertinent regulatory authorities. Examples of assessments or procedures that may be conducted virtually or off-site, if allowed by local law and regulation, include safety assessments

as applicable (e.g., AE/SAE assessments), review of Participant Diary compliance, and collection of samples for pregnancy testing and/or central laboratory assessments.

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

8.5. Participant Diary

Participants will be asked to capture study data in their Participant Diary. Entries will begin on the first day of Screening after diary training is completed and will continue through the SFU Visit. Participant Diaries should not be completed after the participant has finished their participation in the study at the SFU Visit. Diary entries will include study drug administration details in the Induction and Maintenance Periods, along with daily rectal bleeding, and stool frequency information (the 2 patient-reported outcome measures of the Full and mMCS, see Section 8.7.3). Diaries are to be completed daily by the participant. The Participant's Diary will be reviewed by study site staff to ensure the participant is compliant with diary entries through the electronic data capture (EDC) database and during each study visit at the times noted in the SoA (Section 1.2).

Participants who remain chronically non-compliant with diary entries despite intervention and follow-up by the Investigator and site team may be subject to discontinuation as per Section 7.1.

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

8.6. Stool Collection

Stool samples will be required for pathogen/parasite testing, to assess fecal calprotectin levels, and for future research (if participant consents; see Section 8.12). Samples for these tests should be collected on-site, if possible, according to the respective schedules shown in the SoA (Section 1.2).

In addition, stool collection kits are to be dispensed to participants at the visits indicated in the SoA. The participant should use this kit to collect one sample at home within 24 hours before the next site visit. The sample should be stored as described in the sample collection instructions and brought to the clinic on the day of the site visit. If the participant is unable to produce a stool sample at the Stage 1 Screening Visit, they can collect a sample at home and return it to the site. **Note:** Sample is to be collected prior to bowel preparation for Visits 5 and 10/EOT. These samples will be used as back-ups if the participant is unable to provide a fresh sample during the respective site visit.

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

8.7. Efficacy Assessments

8.7.1. Endoscopy with Biopsy

Endoscopy will be performed at Screening (Visit 1) and during Stage 1 of Visits 5, 10/EOT, and 14/LTE EOT. Flexible sigmoidoscopy with colonoscopy scope is the suggested procedure, but full colonoscopy is optional at any timepoint if the Investigator deems it necessary.

During these procedures, colonic mucosa biopsies will be collected for histopathology and optional future research studies. Up to 6 biopsies will be collected during each endoscopy procedure (2 biopsies for the required histopathology and 4 biopsies for the optional future research). The biopsies for future studies will only be collected from the participants who consent to the optional future research. The remaining tissue from the histopathology biopsies may also be used for future research from participants who consent to the optional future research. To ensure quality data and standardization, the same endoscopist should be used throughout the study wherever possible. A detailed image review charter from the central reading laboratory will outline the endoscopic procedures, video recordings, and equipment.

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

Biopsy specimen transfer, processing, slide preparation, and digitization of slides for histopathologic scoring procedures will be detailed within the applicable Laboratory Manual or Histopathology Reference Guide. Histopathology results will not be made available to study sites but will be located within the histopathology laboratory database and added to the electronic Trial Master File after the completion of the trial.

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

The MES will be scored by a central reader. However, treatment decisions post-randomization will be made by the treating Investigator.

For all biopsies in Table 9:

- Record the extent of disease in centimeters from the anal verge
- Record the distance in centimeters from the anus where biopsies are taken into the Requisition Form
- Always review the Laboratory Manual for full instructions related to biopsy sample collection containers, labeling, and storage
- Biopsies for histopathology are the required part of the study
- Optional biopsies are only to be taken in participants who have consented for future research

Table 9. Instructions for Endoscopic Biopsies

Visit 1 (Screening)	<u>Worst inflamed area</u> Take biopsies of the worst inflamed area within 15-25 cm from the anus. • 2 required biopsies for histopathology • 2 optional biopsies for future research <u>Non-inflamed/least inflamed area</u> Take biopsies from a non-inflamed or least inflamed area of the colon. • 2 optional biopsies for future research

Visit 5 (Week 12) Visit 10 (Week 52 or EOT) Visit 14 (Week 104 or LTE EOT)	Take all biopsies at the same distance (cm) from the anus as collected at Visit 1, regardless of tissue state at the time of the sampling. • 2 required biopsies for histopathology • 4 optional biopsies for future research

Abbreviations: EOT, End of Treatment; LTE EOT, Long-Term Extension End of Treatment.

8.7.2. Histologic Scores

Histological improvement will be assessed with the RHI Score, NI, and Continuous Geboes Score. These are each described in detail in Section 10.5.3.

RHI Score

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

Nancy Histopathology Index

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

Geboes Score

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

8.7.3. Mayo Clinic Score

The MCS, mMCS, Partial mMCS, and Partial MCS will be used to assess clinical changes. The MCS is a composite of the following subscores: MES, MCS stool frequency subscore, MCS rectal bleeding subscore, and the PGA. The mMCS is a composite of the following subscores: MES, MCS stool frequency subscore, and MCS rectal bleeding subscore. The Partial mMCS is a composite of the following subscores: MCS stool frequency subscore and MCS rectal bleeding subscore. The Partial MCS is a composite of the following subscores: MCS stool frequency subscore, MCS rectal bleeding subscore, and the PGA. Each subscore of the MCS, mMCS, Partial mMCS, and Partial MCS is described below; the subscores will be calculated at the timepoints shown in the SoA (Section 1.2).

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

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

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

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

8.7.4. Non-endoscopic Biomarkers of Inflammation

8.7.4.1. High-sensitivity C-reactive Protein

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

8.7.4.2. Fecal Calprotectin

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

8.7.5. Inflammatory Bowel Disease Questionnaire

The IBDQ questionnaire is a psychometrically validated patient-reported outcome instrument to assess health-related quality of life (HRQoL) in patients with IBD, including UC (Irvine, 1994).

The IBDQ consists of 32 items, grouped into 4 dimensions: bowel function, emotional status, systemic symptoms, and 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 indicates a clinically meaningful improvement.

The IBDQ (Section 10.8) will be completed by the participant and checked for completeness at the study site as indicated in the SoA (Section 1.2) and will be used in support of the efficacy outcomes. Participants should complete the IBDQ at the clinic before they undergo any procedures or are administered the study drug.

8.8. Safety Assessments

8.8.1. Physical Examinations

Physical examinations will be performed at the timepoints specified in the SoA (Section 1.2). A complete physical exam is required at Screening, Visit 10/EOT, and Visit 14/LTE EOT; and a targeted exam may be performed at all other required visits. For unscheduled visits, the choice of whether to perform a complete or targeted physical exam (if necessary to be performed at all) is at the discretion of the Investigator and will depend on the reason for the unscheduled visit. Physical examinations must be performed by an Investigator or a medically qualified designee.

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

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

8.8.2. Vital Signs

Vital signs to be recorded at most visits as summarized in the SoA (Section 1.2). At unscheduled visits, vital signs are not required and are at the discretion of the Investigator. These will include blood pressure, heart rate, respiratory rate, and temperature.

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

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

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

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

8.8.3. Electrocardiograms

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

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

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

8.8.4. Clinical Safety Laboratory Tests

Blood/urine samples will be collected for safety laboratory testing (serum chemistry, hematology, coagulation, and urinalysis) at the timepoints specified in the SoA (Section 1.2). See Section 10.3

for a listing of laboratory analytes to be collected. Repeat/unscheduled samples may be collected at the Investigator's discretion.

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

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

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

All protocol-required laboratory tests, as defined in Section 10.3, must be conducted in accordance with the Laboratory Manual. In case of abnormal liver function test results, Investigators should follow the instructions in Table 12 for re-testing and follow-up procedures.

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

8.8.5. Progressive Multifocal Leukoencephalopathy

The Subjective PML Checklist will be administered to participants during Screening. The Subjective PML Checklist (Section 10.2) will also be completed at study visits according to the schedule in the SoA (Section 1.2). If the results of the questionnaire are suggestive of signs and symptoms of PML, hold any further doses of study drug and notify the Medical Monitor. The participant will undergo Objective PML Checklist testing (Section 10.2), a full neurological exam by a neurologist, and, if indicated, additional testing. Study drug may not be resumed until PML has been definitively ruled out.

A participant with confirmed PML will be excluded from the study or will permanently discontinue study drug and will be withdrawn from the study (see Section 7.1.1).

8.8.6. Pregnancy/Menopause Testing

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

A serum test for follicle-stimulating hormone (FSH) level will be performed at Screening only for female participants of non-childbearing potential.

Refer to Section 8.9.5 for details regarding pregnancy reporting.

8.8.7. Concomitant Therapies

Any medications and vaccines that participants receive from Screening through the last visit (SoA in Section 1.2) must be recorded in the eCRF (Section 6.7). Refer to Section 6.7.2 for allowed medications and Sections 6.7.3 and 6.7.4 for prohibited medications and procedures, respectively.

8.9. Adverse Events and Other Safety Reporting

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

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

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

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

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

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

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

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

8.9.2. Method of Detecting AEs and SAEs

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

8.9.3. Follow-up of AEs and SAEs

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

8.9.4. Regulatory Reporting Requirements for SAEs, SUSARs, and Periodic Reports

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

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

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

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

The Sponsor or a designee is responsible for notifying the relevant regulators (including the authorities in the European Economic Area (EEA) via EudraVigilance and the IRBs/IECs) and the Investigator sites within the specified timeframes of all SUSARs, as applicable per local requirements. The Sponsor will make the determination whether the event is unexpected. It is the Principal Investigator's responsibility to notify the IRB/IEC according to the relevant regulatory timelines of SUSARs of which the Investigator is notified by the Sponsor that occur at his or her site, if appropriate.

8.9.5. Pregnancy

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

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

Female participant who becomes pregnant

If a pregnancy is reported in a female study participant, the study drug should be discontinued immediately, and the participant should then complete the EOT and SFU Visits. Pregnancy information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of the participant's pregnancy. The participant will then undergo pregnancy follow-up to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the study participant and the neonate, and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination

of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Male participant with a partner who becomes pregnant

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

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

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

8.9.6. Adverse Events of Special Interest

There are no AEs of special interest for this study.

8.10. Pharmacokinetics

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

Blood samples will be collected for measurement of plasma concentrations of MORF-057 and metabolites (if needed) according to the schedule specified in the SoA (Section 1.2). If consent is provided by the participant, these samples may also be used for future PK research studies.

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

The sampling windows for the PK assessment are provided in Table 10.

Table 10. Pharmacokinetics Sampling Windows

Visit	Collection Timepoints and Associated Windows
2, 3, 5, 7, and 10/EOT	Before AM dose and at 1hr (±10 min), 2hr (±15 min), and 4hr (±30 min) after AM dose
4, 6, 8, and 9	Before AM dose and 1 hr (±10 min) after the AM dose

Abbreviations: EOT, End of Treatment; hr, hour; min, minute.

For all pre-AM dose sampling, the samples should be obtained before the AM dose is administered. Participants will be instructed to record all details about the study drug administered at home in the Participant Diary (Section 6.4), especially date/time of previous day morning and evening dosing details and on PK visit days.

8.10.2. Determination of Drug Concentration and PK Parameters

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

This data may be included to perform Population PK analyses.

8.11. Pharmacodynamics

Details on the handling and processing of blood samples for PD analysis are outlined in the Laboratory Manual.

8.11.1. Receptor Occupancy

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

A physiologically relevant receptor occupancy assay will be performed that assesses drug inhibition of $\alpha_4\beta_7$ integrin binding to its natural ligand MAdCAM-1.

To evaluate inhibition of binding to the off-target $\alpha_4\beta_1$ integrin, a receptor occupancy assay using its ligand, LDV peptide fragment of fibronectin, will also be performed.

8.11.2. CCR9 mRNA

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

8.11.3. Lymphocyte Subsets

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

8.12. Future Research

If consent is provided by the participant, blood, stool, and colonic tissue samples will be collected and may be used for future PD, pharmacogenomics, microbiome-related research, fecal calprotectin assessment, and future research. If consent is provided by the participant, the remaining blood and colonic tissue samples from the study-required procedures may also be used for future research, including future PK research. The purpose of future research is to contribute to the understanding of UC or related diseases, to the development of related or new treatments, or to the development of new research methods. Participation in the collection of samples for future research is optional (see Section 10.1.4 for additional consents). Details on the handling and processing of samples for this future research are outlined in the Laboratory Manual. Samples for future research will be collected according to the schedule specified in the SoA (Section 1.2). Samples may be stored for a maximum of 15 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the Sponsor.

8.13. Potential Adjustments due to Pandemics or Other Global Issues

Adjustments to the planned study procedures might be necessary due to pandemic events and/or newly identified global issues. Any such specific measures will be detailed in the respective ancillary documents, such as site-facing and patient-facing documents. Examples are provided below.

- A virtual or hybrid visit may be considered for participants who are not able to participate in an on-site visit (see Section 8.4 for details). If a home study support visit is performed by a study nurse, a courier company will pick up the collected samples (blood/feces) from the participant's home. The nurse will take care of the communications with the courier company and will hand over the samples to the courier.
- Clinical supplies related to the study, including study drug, may be shipped directly to the participant's home in the event the participant cannot visit the study doctor at the clinic to collect the needed study supplies. The courier company used to deliver the supplies will be contracted by the study Sponsor's sub-contractor.

9. Statistical Considerations

The Statistical Analysis Plan (SAP) will be finalized prior to the primary endpoint analysis, and it will include a more technical and detailed description of the data summarization and analysis described in this section. Any change from the planned statistical analyses specified in the protocol will be fully described in the SAP and Clinical Study Report.

9.1. Analysis Sets

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

The **Full Analysis Set (FAS)** will consist of all randomized participants who received at least 1 dose of study drug. 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.

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.

The **Safety Population** will include all participants who received at least 1 dose of the study drug. Participants in this set will be analyzed according to the treatment they actually received. This population will be used for the safety analyses.

The **PK Population** is defined as all participants who received at least 1 dose of study drug and had at least 1 measurable PK concentration. The PK Population will be used for the summarization/analysis of PK data.

The **PD Population** is defined as all participants who received at least 1 dose of study drug and had at least 1 measurable post-dose PD measurement and its corresponding pre-dose PD measurement for, at minimum, 1 of the PD biomarkers. This population will be used for the summarization of PD (exploratory) endpoints.

9.2. Statistical Analyses

9.2.1. General Considerations

Descriptive statistics will be reported for all primary, secondary, and exploratory data. Categorical parameters will be reported using frequency and proportions, whereas continuous parameters will be reported using mean, standard deviation, median, minimum, and maximum. Data will be summarized/analyzed at scheduled visits unless stated otherwise.

9.2.2. Analysis of Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment group and overall.

9.2.3. Efficacy Analyses

All the efficacy analyses will be performed based on the FAS, unless otherwise specified.

9.2.3.1. Primary Efficacy Endpoint

The primary efficacy endpoint for this study is proportion of participants in clinical remission at Week 12 as determined using the mMCS, which will be evaluated in the FAS.

The primary efficacy endpoint will be analyzed using a two-sided Cochran-Mantel-Haenszel (CMH) test at the 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 and point estimates of risk difference, along with 95% CIs, will be provided. The study will be considered a success if at least one MORF-057 dose achieves the statistical significance at the specified significance level after the multiplicity adjustment as

specified in Section 9.2.3.4. All participants with missing data for determination of endpoint status will be considered as a non-responder in the primary analysis.

The primary analysis will be repeated on the PP Population as a sensitivity analysis. Other sensitivity analyses for the primary efficacy endpoints may also be performed as appropriate. The primary efficacy endpoint will be analyzed for the subgroups defined based on selected categorized demographic and baseline variables, e.g., age, gender, race, exposure to an advanced therapy treatment for UC (advanced therapy-naïve and advanced therapy-experienced). The details will be described in the SAP.

9.2.3.2. Secondary Efficacy Endpoints

The secondary endpoint for this study is the proportion of participants with clinical response at Week 12 as determined using the mMCS, which will be evaluated in the FAS.

The secondary endpoint will be analyzed using CMH tests 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 and point estimates of risk difference, along with 95% CIs, will be provided. All participants with missing data for determination of endpoint status will be considered as a non-responder in the analysis.

9.2.3.3. Exploratory Efficacy Endpoints

All proportion-based exploratory efficacy endpoints at Week 12 as defined in Section 3 (e.g., histologic remission or improvement, endoscopic remission or improvement, mucosal healing or improvement, MCS remission or response, UC-related hospitalization or surgery) will be analyzed in the FAS using CMH tests stratified by randomization stratification factors for comparison of each MORF-057 dose group with the placebo group, similar to the primary analysis performed for the primary efficacy endpoint. The p-values will be calculated for the exploratory use. The point estimates of risk difference, along with 95% CIs, will be provided. All participants with missing data for determination of endpoint status will be considered as a non-responder in the analysis.

All the continuous exploratory efficacy endpoints expressed as change from baseline at Week 12 as defined in Section 3 (e.g., non-endoscopic biomarkers of inflammation, PROs) will be analyzed in the FAS using an analysis of covariance model with treatment and randomization stratification factors as factors and baseline values as a covariate. 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 time-to-event endpoint (time to symptomatic response) will be analyzed using the stratified Cox regression model with treatment group as an independent variable. The stratification factors include the randomization stratification factors.

All exploratory efficacy endpoints at Week 52 will be summarized descriptively by dose regimens. The participants randomized to the placebo arm at the Induction Period and switched to an active

MORF-057 dose regimen at the Maintenance Period will be summarized separately for the endpoints at Week 52.

9.2.3.4. Multiplicity Adjustments

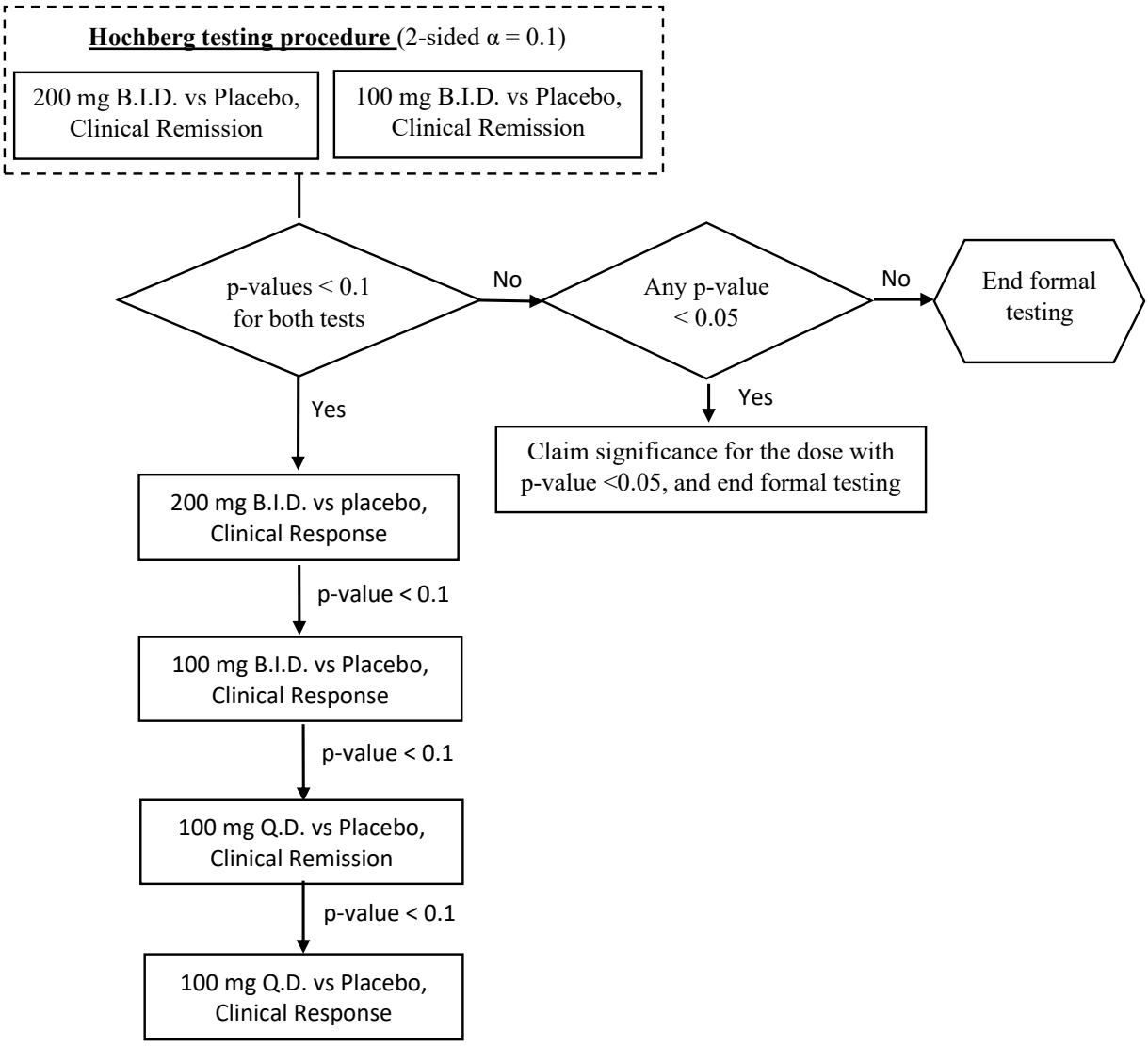
All statistical inference will be 2-sided at a 0.1 level of significance. To control the overall Type I error rate, a hierarchical testing approach as illustrated in Figure 2 will be applied to the statistical testing of the primary and secondary endpoints for comparisons of each MORF-057 dose group 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. The details will be specified in the SAP.

Figure 2. Hierarchical Testing Procedure



9.2.4. Safety Analyses

The Safety Population will be used for the summarization of all safety data.

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

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

The safety analyses will be performed for the 12-week Induction Period, the 52-week Treatment Period, and the 52-week LTE Period plus the Safety Follow-up Period. In the safety analyses for the 12-week Induction Period, the participants initially randomized into the placebo group and switched to an active MORF-057 regimen after the Week 12 assessments will be analyzed as the placebo group. In the safety analyses for the 52-week Treatment Period and 52-week LTE Period, the placebo recipients switched to an active MORF-057 regimen will be analyzed according to the active MORF-057 regimen they received after Week 12, and their data will be presented separately based on only the safety data collected after the start of the MORF-057 dose.

9.2.5. Pharmacokinetics Analyses

PK concentration will be summarized. Additional PK and PK/PD analyses will be conducted as deemed appropriate and may be reported separately from the Clinical Study Report.

9.2.6. Pharmacodynamics Analyses

The exploratory PD endpoints (changes over time in $\alpha_4\beta_7$ and $\alpha_4\beta_1$ receptor occupancies and blood CCR9 mRNA level) will be summarized descriptively. Additional analysis of PD endpoints may be described in a biomarker analysis plan separate from the study SAP and reported separately. The PD Population will be used for the summarization and analysis of PD exploratory endpoints.

9.3. Analyses for Induction Period, 52-week Treatment Period, and LTE Period

The Treatment Period in the main part of the study includes the 12-week Induction Period and the 40-week Maintenance Period. For the purpose of statistical analyses, the Induction Period and the Maintenance Period will be treated as 2 independent parts. There will be 2 analyses planned: one for the 12-week Induction Period (i.e., the period for the primary efficacy endpoint) and one for the 52-week Treatment Period (i.e., the 12-week Induction Period plus the 40-week Maintenance Period and Safety Follow-up Period). The details of the analyses will be described in the SAP. Additional analysis of the optional 52-week LTE Period for the participants enrolled into the LTE Period will also be performed as appropriate.

Induction Period 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 assessments. The analysis will formally evaluate the primary and secondary efficacy endpoints, all the exploratory efficacy endpoints defined by Week 12, and safety of MORF-057 vs placebo during

the 12-week Induction Period. The PK and PD data during the 12-week Induction Period will also be summarized.

52-week Treatment Period Analysis

The analysis of the 52-week Treatment Period 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 LTE Period) or discontinued from the study during the 52-week Treatment Period. 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 (and the Safety Follow-up Period for participants not rolling over into the LTE Period). The cumulative data, including those from the Induction Period, will be used in this analysis.

52-week LTE Period Analysis

The analysis of the LTE Period will be performed after all the participants enrolled into the LTE Period have completed the 52-week LTE Period and the Safety Follow-up Period or discontinued the study during the LTE Period. The analysis will evaluate the long-term safety of MORF-057 and selected efficacy endpoints at Week 104 as appropriate during the LTE Period plus the Safety Follow-up Period.

9.4. Interim Analysis

The analysis of the 12-week Induction Period (Induction Period Analysis) 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 9.3.

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.

9.5. Sample Size Determination

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%.

10. Appendices: Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

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

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines
- Applicable laws and regulations, including European Union Clinical Trials Regulation 536/2014

The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC or to the Member States Concerned and reviewed and approved by the IRB/IEC or Member States Concerned, as applicable, before the study is initiated.

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

Protocols and any substantial amendments to the protocol will require Member States Concerned or health authority, as applicable, approval prior to initiation, in line with country-specific requirements.

The Investigator will be responsible for the following:

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

After reading the protocol, each Investigator will sign the Investigator's Agreement page (Section 10.10). The study will not start at any study center at which the Investigator has not signed the protocol.

The Sponsor will notify the authorities as applicable (in line with country/region requirements) about a serious breach of the regulations or of the version of the protocol applicable at the time of the breach. A 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical trial.

If the Investigator identifies a potential instance of a serious breach, the Sponsor and Contract Research Organization (CRO) should be notified immediately at CCI [redacted] Include any available information at the time of the incident and copies of all documentation, if any, supporting the suspicion.

10.1.2. Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Insurance

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

10.1.4. Informed Consent Process

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

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

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

If a participant or legal representative is unable to read and/or write, an impartial witness should be present during the entire informed consent discussion.

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

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

Additional Consents

The main ICF will contain separate sections for the following additional consents:

- Optional collection of blood, colonic tissue, and stool samples for future PD, microbiome-related analyses, fecal calprotectin assessment, and future research. If consent is provided, use of the remaining blood and colonic tissue samples from the study-required procedures may also be used for future research, including future PK research (see Sections 8.7.1, 8.10, 8.12, and the SoA in Section 1.2).

- Optional blood sampling for future pharmacogenomics analysis, which will involve genetic testing (see Section 8.12, Section 10.9, and the SoA in Section 1.2).

Additional ICFs will be provided to participants or their partners for review and signature, as needed:

- Optional LTE Period (see Section 4.1 and the SoA in Section 1.2)
- Consent to courier deliveries/pick-ups (see Section 8.13)
- Pregnancy Follow-up (see Section 8.9.5)

The Investigator or authorized designee will explain to each participant the objectives of the optional sampling. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the sample storage period (determined based on local country regulations). Signatures will be required to document a participant's agreement to allow the optional samplings. Participants who decline to participate in optional samplings will not be asked to provide signatures.

10.1.5. Data Protection

- Measures must be described that will be implemented to ensure confidentiality of records containing personal data of participants. In particular, the personnel of the site, Sponsor, and vendors (CRO) involved in data processing are bound by obligations of confidentiality and the participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

  The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant. In particular, the participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members or Member States Concerned members, as applicable, and by inspectors from regulatory authorities.

- The contract between Sponsor and study sites specifies the responsibilities of the parties regarding data protection, including handling of data security breaches and respective communication and cooperation of the parties. The process to handle data security breaches, in order to mitigate the possible adverse effects of such breaches to the privacy of study participants, must be described.

- Organizational and technical arrangements that will be implemented to avoid unauthorized access, disclosure, dissemination, alteration, or loss of personal data must be described. In particular, the information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

10.1.6. Data and Safety Monitoring Board

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

10.1.7. PML Adjudication Committee

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

10.1.8. Dissemination of Clinical Study Data

The Sponsor will submit a summary of the results of the clinical study to the relevant clinical study databases (including clinicaltrials.gov and the public domain of the Clinical Trials Information System database at https://euclinicaltrials.eu/home) in a timely manner. As appropriate, this will be accompanied by a summary written in a manner that is understandable to laypersons.

10.1.9. Data Quality Assurance

All participant data relating to the study will be recorded on paper-based Case Report Forms (CRFs) or eCRFs unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for having quality system processes and procedures in place verifying that CRF data entries against source data are accurate and correct. The Investigator is responsible for ensuring source records are maintained in real-time, eCRFs are completed per eCRF Completion Guidelines, and physically or electronically signing the CRF.

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

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

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

The Sponsor or designee is responsible for the data management of this study, including scheduled data audits and verification against original source data/documentation.

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

The contents of the electronic Trial Master File pertaining to the conduct of this study must be retained by the Sponsor and the Investigator for at least 25 years after study completion unless local regulations, institutional policies, or by an agreement with the Sponsor require a longer retention period. However, the medical files of participants shall be archived in accordance with national law. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

Please reference the current version of ICH E6 for the minimum list of essential documents required for the conduct of a clinical trial. Additional documentation may be required by the Sponsor or CRO before, during, and after completion of the trial.

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

10.1.10. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site and digitized copies are maintained in the site section of the electronic Trial Master File.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained by the Investigator and documented in the CRF. The Investigator may need to request previous and current medical records or transfer records as source documents for participants involvement (or enrollment) in this study.

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

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

10.1.11. Study and Site Start and Closure

10.1.11.1. First Act of Recruitment

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

10.1.11.2. Study/Site Termination

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

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

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

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

Reasons for study termination include, but are not limited to:

- Recommendation of the DSMB based on the ongoing review of safety
- If a positive benefit/risk ratio is no longer observed, based on DSMB review of unblinded data
- Discontinuation of further study drug development

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

10.1.12. Publication Policy

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

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

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

10.2. Appendix 2: Progressive Multifocal Leukoencephalopathy Checklists

Subjective PML Checklist

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

PML, progressive multifocal leukoencephalopathy.

Objective PML Checklist – To be completed for participants with positive subjective finding

Perform the objective test(s) that correspond to the subjective checklist finding

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

Source: Parikh 2018

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

× Please notify your Clinical Research Associate and the Sponsor of any positive Objective Checklist findings.

10.3. Appendix 3: Clinical Laboratory Tests

The tests detailed in Table 11 will be performed by the central laboratory.

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

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

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

In case of abnormal liver function test results, Investigators should follow the instructions in Table 12 (Hy's law cases table) for re-testing and follow-up procedures.

Investigators must document their review of each laboratory safety report.

Table 11. Protocol-required Laboratory Tests

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

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

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

a Local urine testing will be standard for the protocol unless serum testing is required by local regulation or Member States Concerned or IRB/IEC, as applicable.

Table 12. Abnormal Liver Function Results: Re-testing and Follow-up Procedures

<table>
<tr><td colspan="4">Initial Lab Alert</td><td colspan="2"></td></tr>
<tr><td colspan="4">Initial results:
ALT or AST >3 × ULN, BUT <8 × ULN
OR
ALT or AST >3 × ULN, AND bilirubin >2 × ULN

BUT without signs/symptoms of acute liver failure*

Next steps (first approximately 48-72 hours):
• Withhold IMP
• Elicit history
• Physical exam
• Repeat LFT in 48-72 hours, or as soon as practical (central laboratory)
• Check INR</td><td colspan="2">Initial results:
ALT or AST >3 × ULN, with signs/symptoms of acute liver failure*
OR
AST or ALT >8 × ULN, with or without bilirubin increase

Next steps (first approximately 48-72 hours):
• Withhold IMP
• Elicit history
• Physical exam
• Repeat LFT in 48-72 hours, or as soon as practical (central laboratory)
• Check INR</td></tr>
<tr><td colspan="4">Re-test Review</td><td colspan="2">Re-test Review</td></tr>
<tr><td>Re-test results (after approximately 48-72 hours):
ALT or AST
>3 × ULN
AND
bilirubin
>2 × ULN
and/or
INR >1.5

Next steps:
• Discontinue IMP
• Investigate abnormal LFT further
• Early Termination Visit</td><td>Re-test results (after approximately 48-72 hours):
AST or ALT
>5 × ULN

Next steps:
• Continue to withhold IMP
• Repeat in 1-2 weeks. If still >5 × ULN,
• Discontinue IMP
• Investigate abnormal LFT further
• Early Termination Visit</td><td>Re-test results (after approximately 48-72 hours):
AST or ALT
>8 × ULN
OR
ALT or AST
>3 × ULN
with signs/symptoms of acute liver failure*

Next steps:
• Discontinue IMP
• Investigate abnormal LFT further
• Early Termination Visit</td><td>Re-test results (after approximately 48-72 hours):
Improvement

Next steps:
• Discuss with Medical Monitor regarding resumption of IMP**</td><td>Re-test results (after approximately 48-72 hours):
Similar findings as above or with worsening such as bilirubin >2 × ULN or INR >1.5

Next steps:
• Discontinue IMP
• Investigate abnormal LFT further
• Early Termination Visit</td><td>Re-test results (after approximately 48-72 hours):
Improvement

Next steps:
• Discuss with Medical Monitor regarding resumption of IMP**</td></tr>
</table>

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; IMP, investigational medicinal product (MORF-057 or placebo); INR, international normalized ratio; LFT, liver function tests; ULN, upper limit of normal.

*Signs/symptoms of liver failure: fatigue, nausea, right upper quadrant pain and/or tenderness, fever, rash, and eosinophilia.

** Resumption of the study drug can be considered only in consultation with the Medical Monitor and only if the liver test results returned to near baseline and if a self-limited non-study drug etiology is identified. Otherwise, the study drug should be permanently discontinued.

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

10.4.1. Definition of AE

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

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

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition

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

10.4.2. Definition of SAE

An SAE is Defined as any Untoward Medical Occurrence That, at any Dose, Meets one or More of the Criteria Listed Below:

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been admitted to the hospital for inpatient care, regardless of the length of stay. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.

Note: The following are not considered an SAE:

- Scheduled hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline
- Hospitalization for social/convenience considerations
- Scheduled therapy for the target disease of the study, including admissions for colonoscopy or convenience

d. Results in persistent or significant disability/incapacity

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

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

e. Is a congenital anomaly/birth defect

f. Other serious and important medical events:

Medical or scientific judgement should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of intervention dependency or intervention abuse.

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

AE and SAE Recording

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

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

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

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

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

Assessment of Intensity

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

Severity will be assessed according to the following scale:

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

- **Grade 4 (Life-Threatening):** Life-threatening consequences; urgent intervention indicated.
- **Grade 5 (Death):** Death related to AE.

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

Assessment of Causality

The Investigator is obligated to assess the relationship between the study drug and the occurrence of each AE/SAE. The Investigator will use clinical judgement to determine the relationship. A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study drug administration, will be considered and investigated. The Investigator will also consult the Investigator's Brochure and consider known actions or toxicity of the study drug in his/her assessment.

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

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

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

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

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

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

- There is a positive temporal relationship (i.e., the event occurred within a reasonable time frame following administration of study medication).

- The AE is more likely explained by the study drug than by another cause (i.e. the AE shows a pattern consistent with previous knowledge of the study drug or the class of the study drug).
- The event improved on de-challenge and/or re-occurred upon re-challenge (if applicable).

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

Follow-up of AEs and SAEs

- All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).
- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any postmortem findings including histopathology.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.4.4. Reporting of SAEs

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

- The primary mechanism for reporting an SAE to the Sponsor will be the electronic data collection tool. The SAE must be reported within 24 hours of the study staff becoming aware.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section). The SAE must be reported within 24 hours of the study staff becoming aware.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.

- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next section) or to the Sponsor or designee by telephone.
- SAEs will be reported to Lilly Global Patient Safety by email (email address will be defined in a study-specific safety reporting plan).

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

- E-mail transmission of the SAE paper data collection tool is the preferred method to transmit this information to the Sponsor or designee.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE data collection tool within the designated reporting timeframes.
- SAEs will be reported to Lilly Global Patient Safety by email (email address will be defined in a study-specific safety reporting plan).

10.5. Appendix 5: Contraceptive and Barrier Guidance

10.5.1. Definitions

Woman of Childbearing Potential (WOCBP)

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

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

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

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

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

Woman of Non-childbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

1. Premenopausal female with permanent infertility due to one of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

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

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

2. Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range (≥30 IU/L) may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement may be required.
    - Females on HRT and whose menopausal status is in doubt must discontinue HRT for at least 6 weeks before study Day 1 to allow confirmation of postmenopausal status before study enrollment.

10.5.2. Contraception Guidance for Female Study Participants

10.5.2.1. Female Study Participants Who *Do Not* Consent to Dose Switch in LTE Period

Note: This is relevant for participants who **do not** consent to the dose switch in the LTE Period. For contraception requirements for those who **do** consent to the dose switch in the LTE Period, see Section 10.5.2.2.

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

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

10.5.2.2. Female Study Participants Who *Do* Consent to Dose Switch in LTE Period

Note: This is relevant for participants who **do** consent to the dose switch to 200 mg B.I.D. in the LTE Period. For contraception requirements for those who **do not** consent to the dose switch in the LTE Period, see Section 10.5.2.1.

For participants that are currently using systemic (e.g., oral, implantable) hormonal contraception but have consented to the MORF-057 dose switch:

- They must change to new contraception by the time of DSFU 2 (8 weeks after the dose switch) or as soon as possible.
- All participants must remain abstinent until new contraception is in place.

WOCBP and WONCBP may participate in this trial.

WOCBP who are completely abstinent as their preferred and usual lifestyle, or exclusively engage in sexual relations with other individual(s) who are assigned female at birth, as their preferred and usual lifestyle must follow the rules in this table.

Must…	**Must not…**

agree to either remain abstinent or exclusively engage in sexual relations with other individual(s) who are assigned female at birth, and not plan a pregnancy during the study	• use periodic abstinence methods
	  ○ calendar
	  ○ ovulation
	  ○ symptothermal, or
	  ○ post-ovulation
	• declare abstinence just for the duration of a trial, or

Must…	Must not…
	• use the withdrawal method

WOCBP who are NOT completely abstinent as their preferred and usual lifestyle, or who do NOT exclusively engage in sexual relations with other individual(s) who are assigned female at birth, as their preferred and usual lifestyle, must follow the rules in this table.

Must…
Agree to use 1 **highly** effective method of contraception together with a barrier method of contraception (see below). Note: During this study, systemic hormonal contraception is not considered effective or highly effective and therefore is not permitted as a means of contraception. Barrier method of contraception includes condoms (male or female) with or without a spermicidal agent, diaphragm, or cervical cap with spermicide. These methods of contraception must be used during the study and for at least 28 days after the last dose of the study intervention.

Examples of different methods of contraception:

Note: Participants who switch to 200 mg B.I.D. cannot use oral or systemic hormonal contraception as an effective method.

Methods	Examples
Highly effective contraception (less than 1% failure rate)	• Fallopian tubal sterilization methods other than bilateral salpingectomy (laparoscopic bipolar electrocoagulation, plastic ring application on the uterine tubes, fallopian tube ligation, hysteroscopic sterilization). Note: Bilateral salpingectomy is indicative of permanent sterilization. Please see the WONCBP definition above. • Total abstinence • Sexual relationships exclusively between individuals who are assigned the same sex at birth • Vasectomy – for individuals assigned male at birth in clinical trials and for the partner of an individual assigned female at birth (if only sexual partner) • Fallopian tube implants (if confirmed by hysterosalpingogram), or • Intrauterine devices (IUD) with or without hormone-releasing system
Effective contraception	• Penile condom with or without spermicide • Vaginal condom with or without spermicide • Diaphragm with spermicide • Cervical sponge with spermicide, or

Methods	Examples
	• Cervical cap with spermicide Note: Penile and vaginal condoms should not be used in combination.
Ineffective methods of contraception whether used alone or in any combination	• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation (listed below) – oral – intravaginal – transdermal – injectable • Progestogen-only hormone contraception associated with inhibition of ovulation – oral – injectable – implantable • Spermicide alone • Periodic abstinence • Fertility awareness (calendar method, temperature method, cervical mucus, or symptothermal) • Withdrawal • Postcoital douche, or • Lactational amenorrhea • Ablation (endometrial or uterine) is not considered a form of contraception

Abbreviations: IUD, intrauterine device; WONCBP, woman of non-childbearing potential.

10.5.3. Contraception Guidance for Male Study Participants

Participant Population	Contraception Guidance
All male study participants…	should refrain from sperm donation for the duration of the study and for at least 14 days after the last dose of the study intervention.
Male study participants with partner(s) who are WOCBP [a]…	must • remain abstinent (if this is their preferred and usual lifestyle), or • use condoms and at least 1 additional effective method of contraception (see "Examples of different methods of contraception" table) for the duration of the study and for

Participant Population	Contraception Guidance
	at least 28 days after the last dose of the study intervention.
Male study participants with partner(s) who are pregnant [a]...	must • remain abstinent (if this is their preferred and usual lifestyle), or • use condoms for the duration of the study and for at least 28 days after the last dose of the study intervention.
Male study participants who exclusively engage in sexual relations with other individual(s) who are assigned male at birth, as their preferred and usual lifestyle…	are not required to use contraception.

Abbreviations: WOCBP, woman of childbearing potential.
a Male study participants who have undergone orchiectomy but not penectomy must use condoms during sex, but the partner who is WOCBP is not required to use an additional form of contraception. Male study participants who have undergone orchiectomy and penectomy are not required to use condoms.

Examples of different methods of contraception [a]:

Methods	Examples
Highly effective contraception (less than 1% failure rate)	• Fallopian tubal sterilization methods other than bilateral salpingectomy (laparoscopic bipolar electrocoagulation, plastic ring application on the uterine tubes, fallopian tube ligation, hysteroscopic sterilization). Note: Bilateral salpingectomy is indicative of permanent sterilization. Please see the WONCBP definition above. • Combined (estrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation (listed below) – oral – intravaginal – transdermal – injectable • Progestogen-only hormonal contraception associated with inhibition of ovulation – oral – injectable – implantable • Total abstinence • Sexual relationships exclusively between individuals who are assigned the same sex at birth

Methods	Examples
	• Vasectomy – for individuals assigned male at birth in clinical trials and for the partner of an individual assigned female at birth (if only sexual partner) • Fallopian tube implants (if confirmed by hysterosalpingogram), or • Intrauterine devices (IUD) with or without hormone-releasing system
Effective contraception	• Progestogen-only hormonal contraception, where inhibition of ovulation is not the primary mode of action • Penile condom with or without spermicide • Vaginal condom with or without spermicide • Diaphragm with spermicide • Cervical sponge with spermicide • Cervical cap with spermicide Note: Penile and vaginal condoms should not be used in combination.
Ineffective methods of contraception whether used alone or in any combination	• Spermicide alone • Periodic abstinence • Fertility awareness (calendar method, temperature method, cervical mucus, or symptothermal) • Withdrawal • Postcoital douche, or • Lactational amenorrhea

Abbreviations: IUD, intrauterine device; WONCBP, woman of non-childbearing potential.
a Ablation (endometrial or uterine) is not considered a form of contraception.

10.6. Appendix 6: Histological Scoring Indices

Robarts Histopathology Index

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

Nancy Histopathology Index

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

Continuous Geboes Score

The Geboes Score is a stepwise grading system used for the evaluation of microscopic inflammation and histopathologic disease activity in UC. The microscopic appearance of the mucosa is categorized into 6 grades: structural change only (Grade 0); chronic inflammation (Grade 1); lamina propria neutrophils (Grade 2); neutrophils in epithelium (Grade 3); crypt destruction (Grade 4); and erosions or ulcers (Grade 5) (Geboes, 2000). Each of these grades has 4 to 5 sub-grades. This scoring system has been converted into a continuous scale that is calculated by adding up the numerical values of the different subscores, yielding a final value between 0 and 22.

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

The MCS, mMCS, and Partial mMCS will be used to assess clinical changes. The MCS is a composite of the following subscores: MES, MCS stool frequency subscore, MCS rectal bleeding subscore, and the PGA. The mMCS is a composite of the following subscores: MES, MCS stool frequency subscore, and MCS rectal bleeding subscore. The Partial mMCS is a composite of the following subscores: MCS stool frequency subscore and MCS rectal bleeding subscore.

The MCS ranges from 0 to 12, the mMCS ranges from 0 to 9, and the Partial mMCS ranges from 0 to 6. For all 3 of these composite scores, higher scores indicate more severe disease. Each subscore is described below.

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

0=Normal number of stools for this participant

1=1 to 2 stools more than normal

2=3 to 4 stools more than normal

3=5 or more stools more than normal

Subscore: 0 to 3

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

0=No blood seen

1=Streaks of blood with stool less than half the time

2=Obvious blood (more than just streaks) or streaks of blood with stool most of the time

3=Blood alone passed

Subscore: 0 to 3

Endoscopy: The endoscopy subscore will be determined centrally by qualified personnel.

0=Normal or inactive disease

1=Mild disease (erythema, decreased vascular pattern, no friability)

2=Moderate disease (marked erythema, lack of vascular pattern, friability, erosions)

3=Severe disease (spontaneous bleeding, ulceration)

Subscore: 0 to 3

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

0=Normal

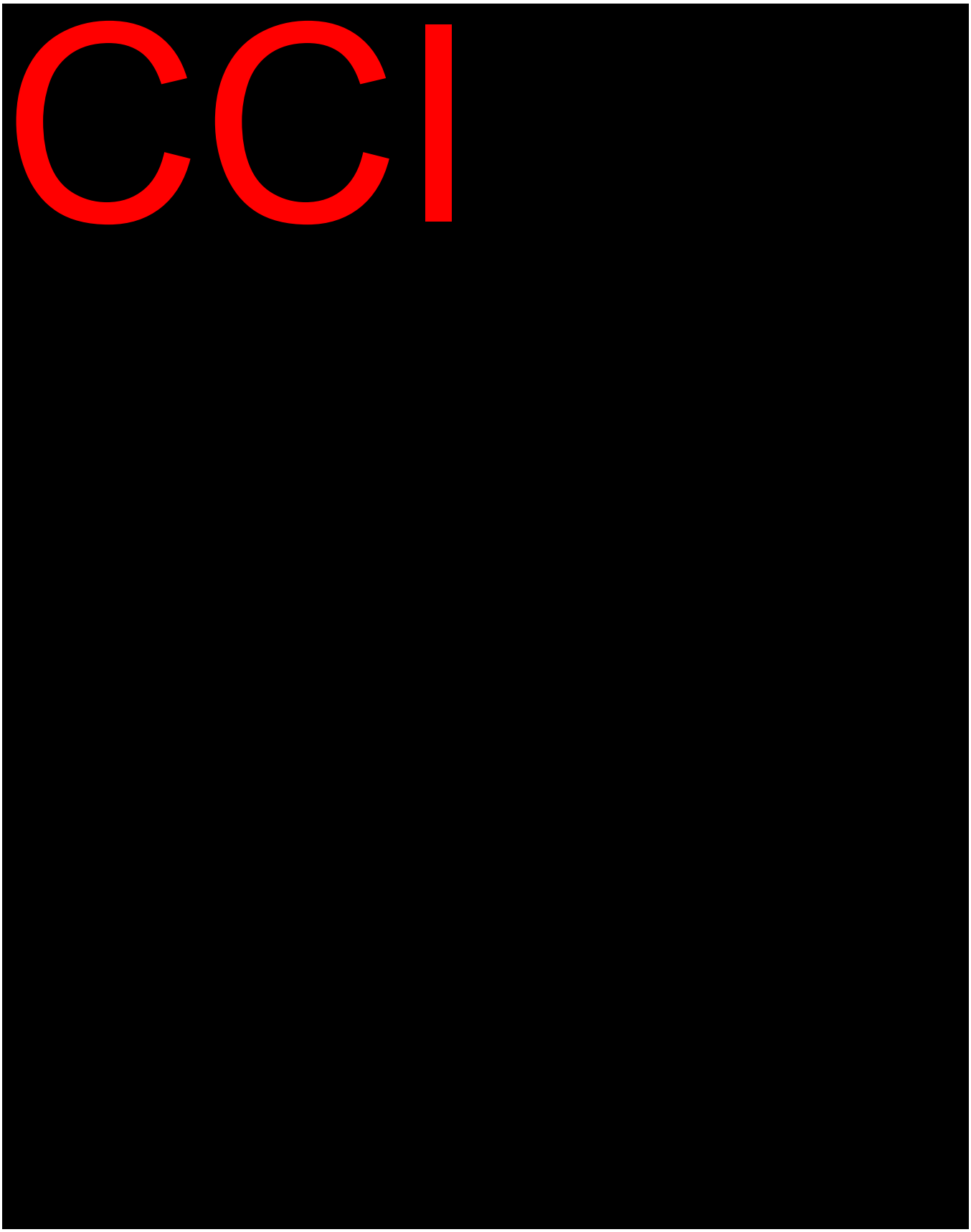
1=Mild disease

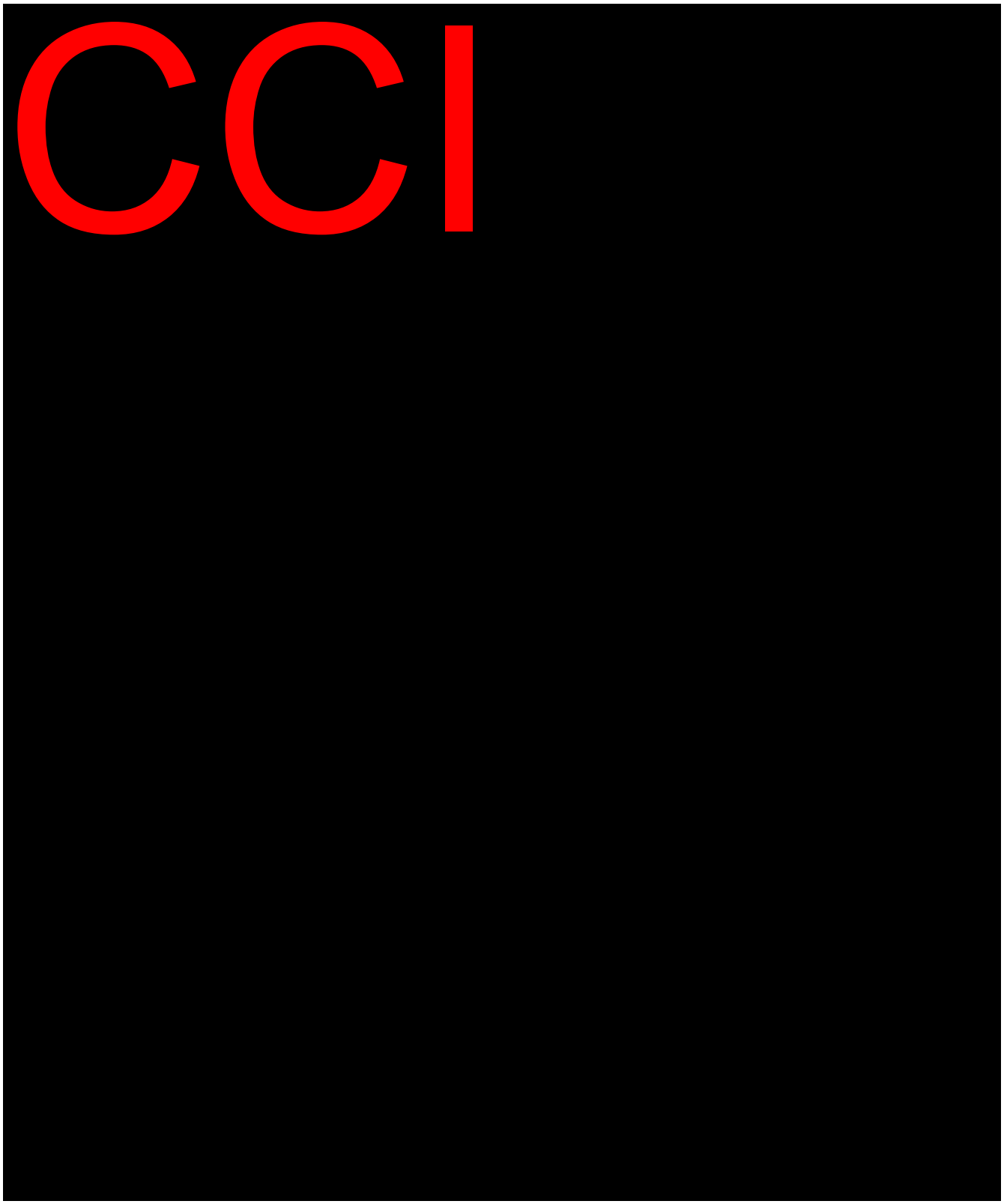
2=Moderate disease

3=Severe disease

Subscore: 0 to 3

10.8. Appendix 8: Inflammatory Bowel Disease Questionnaire (IBDQ)

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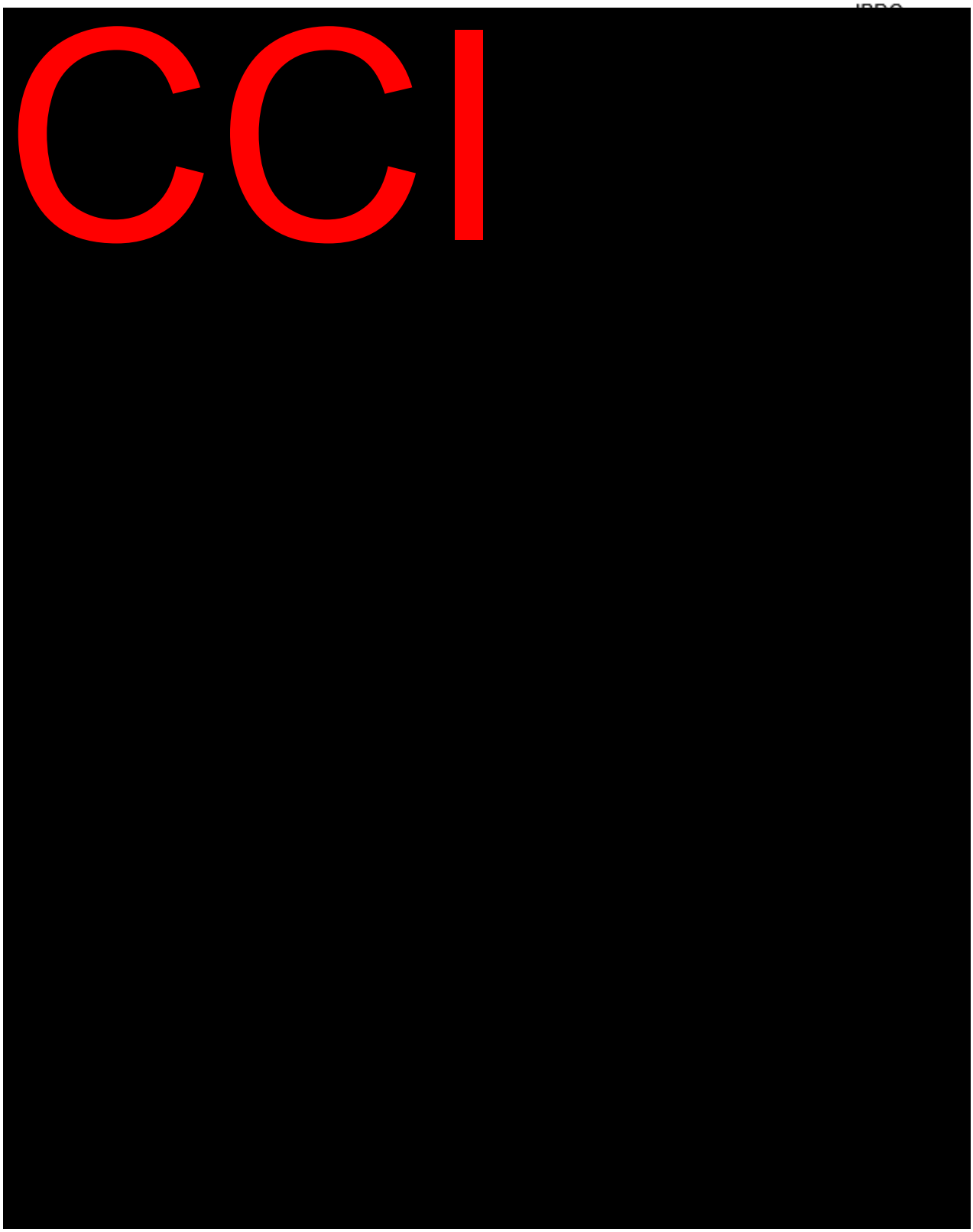
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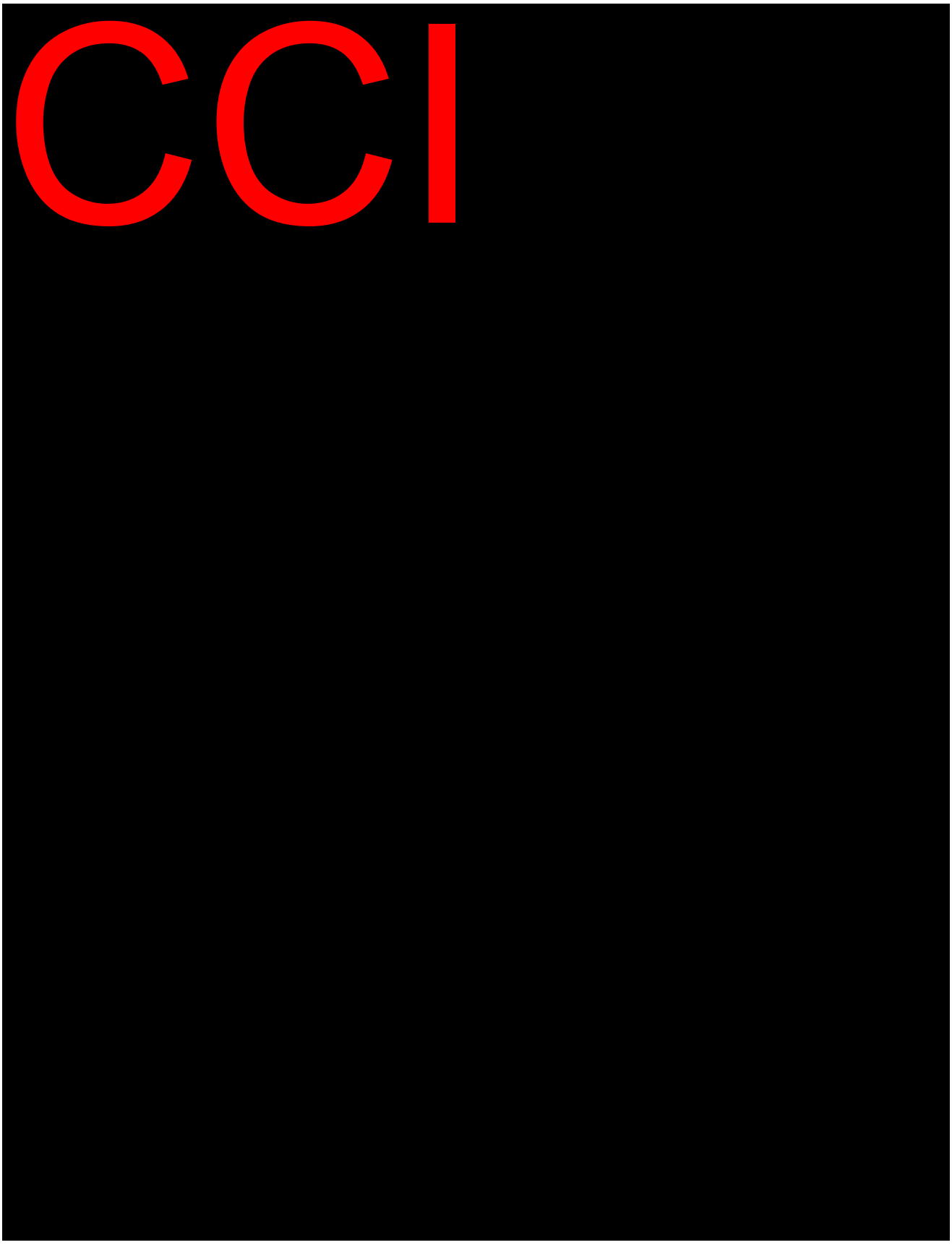
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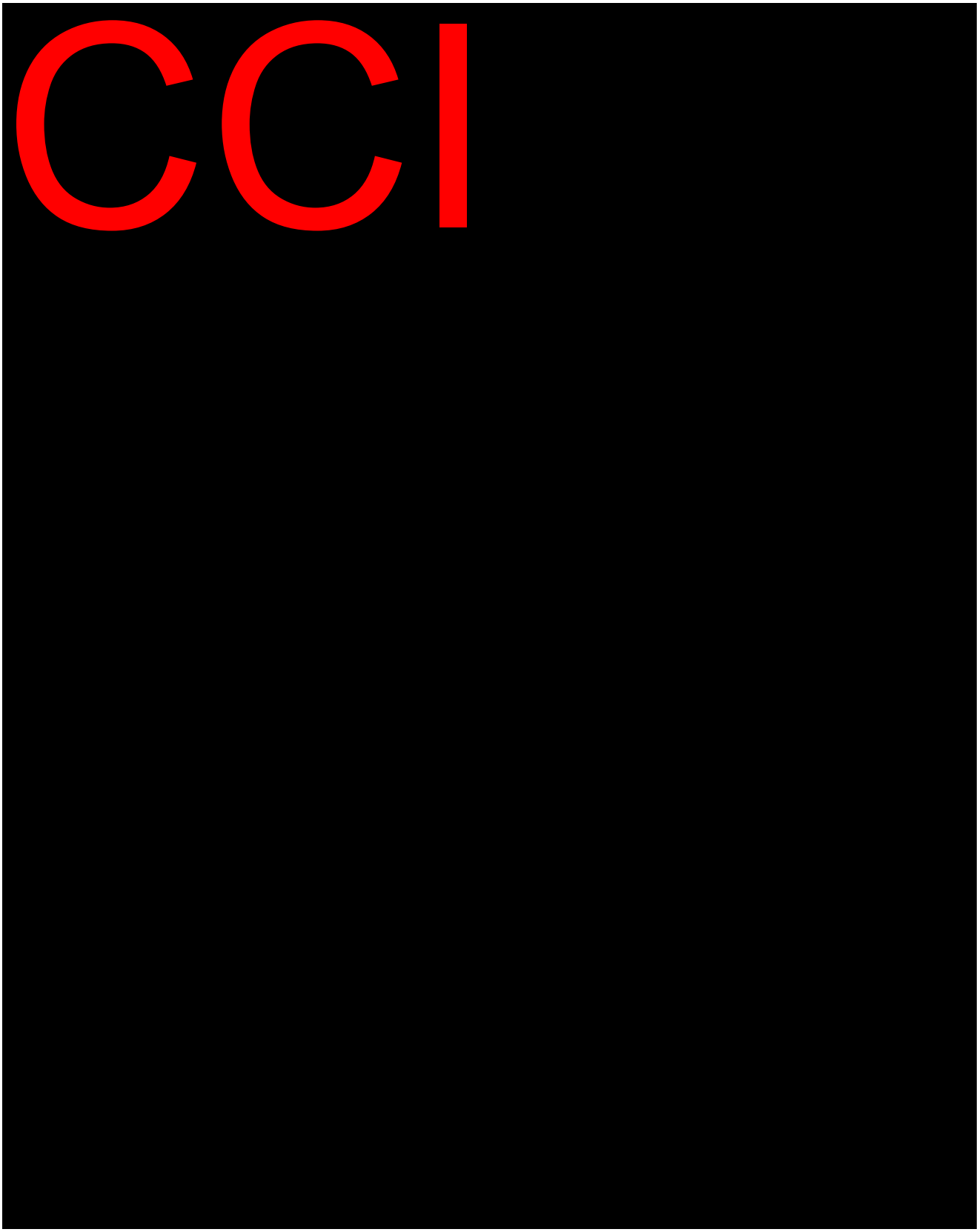
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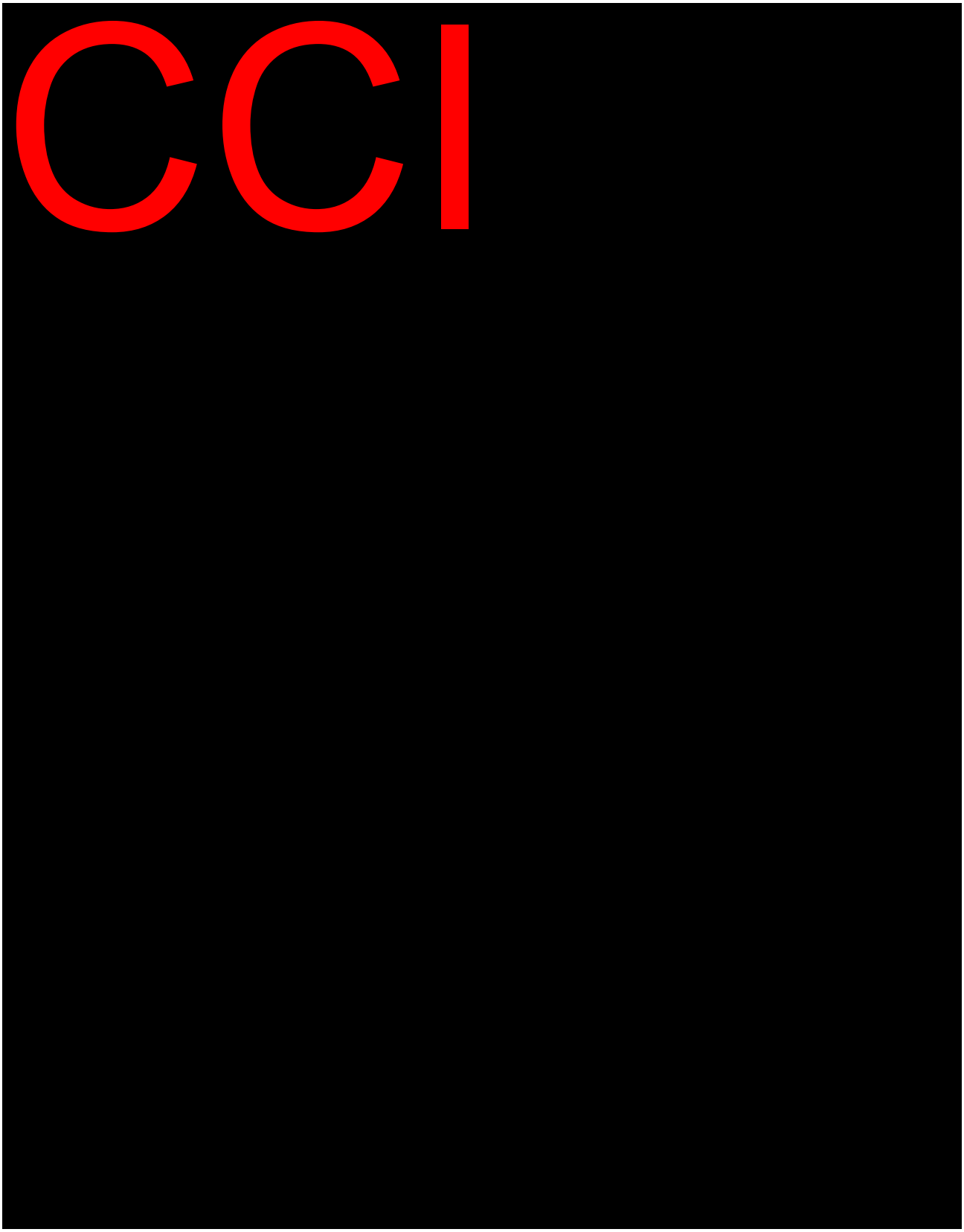
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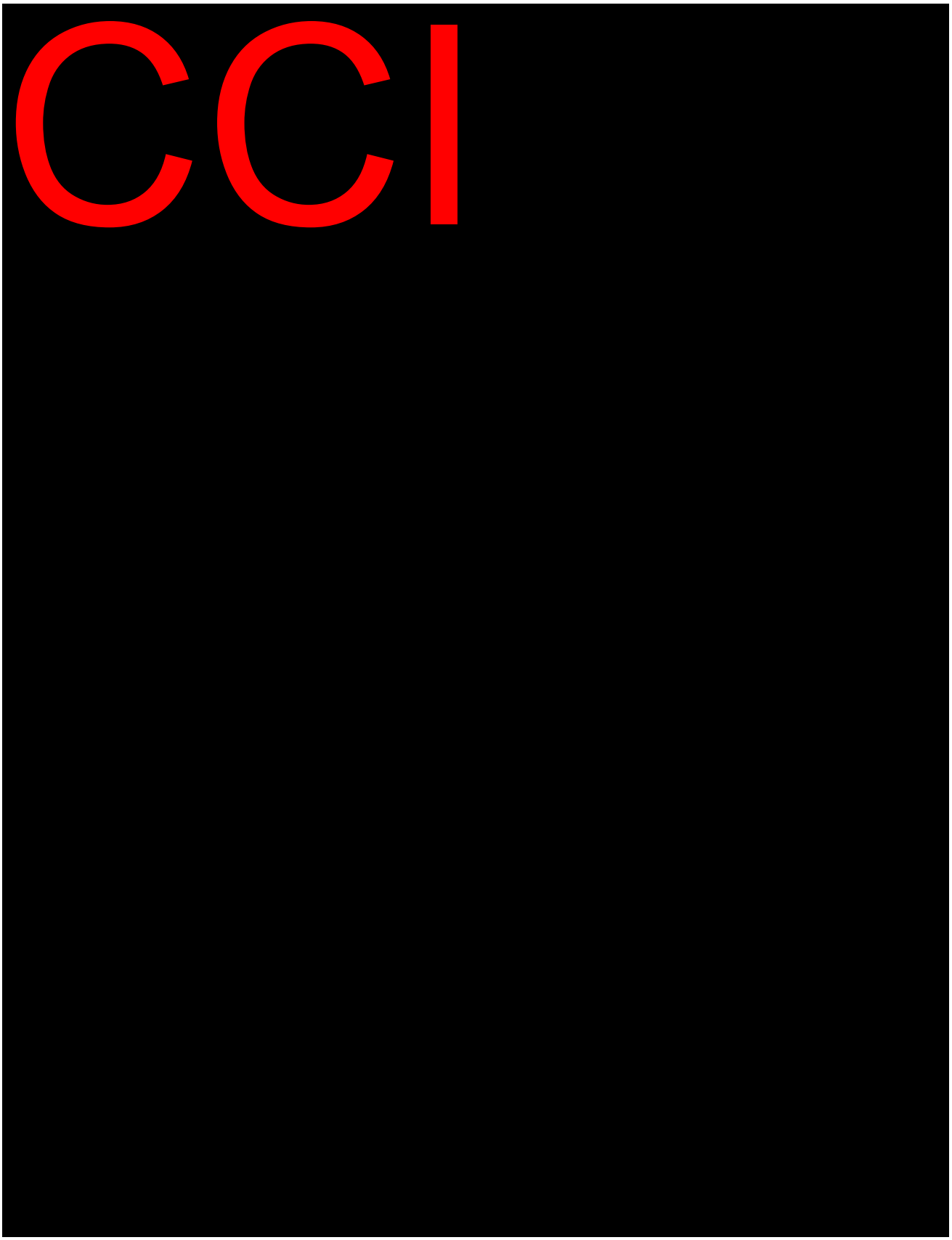

CCI

10.9. Appendix 9: Genetics

Use/analysis of DNA for optional future pharmacogenomics research (see Section 8.12 and SoA in Section 1.2)

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

10.10. Appendix 10: Investigator's Agreement

By signing below, I agree that:

I have read Protocol MORF-057-202 and agree to conduct the study as outlined. Furthermore, I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

10.11. Appendix 11: Changes to This Protocol in Previous Amendments

Version 2.0 dated 26 April 2023

Overall Rationale for the Amendment

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

- Add a 52-week Maintenance Extension following the 52-week Treatment Period, add corresponding endpoints, and update the study design/schema and statistical analyses
- Clarify the enrollment plan for prior advanced therapy-experienced participants
- Extend the Screening Period to ensure sufficient time for screening activities
- Revise the Inclusion/Exclusion criteria regarding inadequate response, washout criteria of prior UC therapy, tuberculosis screening, and testing of SARS-CoV-2
- Update the Schedule of Activities for clarity and add study activities for the Maintenance Extension Period
- Remove the Week 24 clinical improvement assessment timepoint
- Revise the sequence of events for Week 12, Week 52/EOT, and Week 104/LTE EOT wherein the endoscopy occurs during Stage 1, followed by the clinic visit at Stage 2
- Add a follow-up contact on the day after the Week 12 clinic visit to ensure participants begin using the study drugs for the Maintenance Period
- Update risks of MORF-057
- Clarify the re-screening process and the blinding process after Week 12
- Specify the process of reporting and capturing the overdose information
- Clarify the acceptable use of aspirin
- Clarify the discontinuation/withdrawal criteria regarding lack of efficacy, ineligible participants, and male participant whose partner becomes pregnant
- Specify the number of biopsies for histopathology and the optional future research
- Clarify the additional informed consents
- Update the exclusion criteria regarding participant allergies/hypersensitivities
- Add a justification for use of placebo
- Explain the adjustment for multiple testing
- Identify the calculation for determining sample size

This protocol amendment is considered Substantial by the Sponsor, according to the criteria specified in the European Union Clinical Trials Regulation 536/2014.

Summary of Changes Table

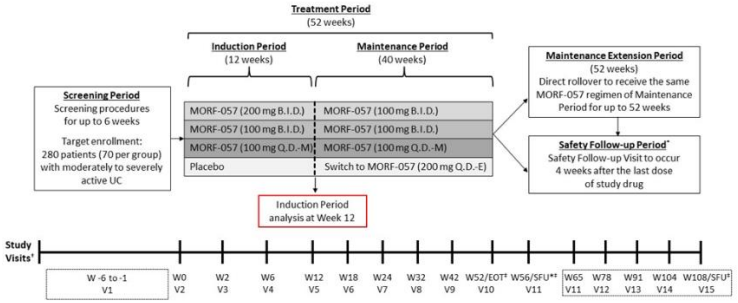
This protocol amendment is considered Substantial by the Sponsor, according to the criteria specified in the European Union Clinical Trials Regulation 536/2014. Changes to the protocol as implemented by this amendment are summarized in the Summary of Changes table below. New text is shown in *italics*, deleted text is shown in ~~strikeout~~, and **bold** text is informational. In addition to the changes provided in the Summary of Changes table, minor editorial changes have been made throughout the protocol.

Section No. and Name	Description of Change	Brief Rationale
Global change	**'Patients' was changed to 'participants' throughout the Protocol when referring to a study participant.**	Administrative change
Global change	~~TNF~~ *TNF-α*	To correct protein name
Abbreviations	~~5-ASA 5-aminosalicylates~~ ~~AST Aspartate transaminase~~ ~~AUC_{0-12} Area under the concentration-time curve from time 0 to 12 hours post-dose~~ ~~AUC_{tau} Area under the concentration-time curve across the dosing interval~~ ~~C_{12} Plasma concentration at 12 hours post-dose~~ *C. difficile* *Clostridiodes difficile* *CI* *Confidence interval* *CMH* *Cochran-Mantel-Haenszel* *CRA* *Clinical Research Associate* *CRO* *Contract Research Organization* EDC Electronic data capture~~ database~~ *EEA* *European Economic Area* ~~ESR Erythrocyte sedimentation rate~~ *FSH* *Follicle-stimulating hormone* *HRT* *Hormonal Replacement Therapy* *IBDQ* *Inflammatory Bowel Disease Questionnaire* IC_{90} 90% *of maximal* inhibitory concentration ICH International Council for Harmonisation ~~of Technical Requirements for Pharmaceuticals for Human Use~~ *IGRA* *Interferon gamma release assay* ~~MDRD Modification of Diet in Renal Disease~~ ~~M~~*m*MCS Modified Mayo Clinic Score *mRNA* *Messenger ribonucleic acid* ~~PI Principal Investigator~~ *PP* *Per Protocol* *PRO* *Patient-reported outcome* *Q.D. – E* *Once a day (evening)* *Q.D. – M* *Once a day (morning)*	To update the abbreviations used throughout the protocol

Section No. and Name	Description of Change		Brief Rationale
	~~RO Receptor occupancy~~ *SC Subcutaneous* TNF-*α* Tumor necrosis factor *alpha* *WOCBP Woman of Childbearing Potential* *WONCBP Woman of Non-childbearing Potential*		
1.1. Synopsis – Objectives and Endpoints 3. Objectives and Endpoints	To determine time to symptomatic response by Week 12	• Time to symptomatic response by Week 12 as determined using the *Partial* mMCS	To clarify the endpoint
1.1. Synopsis – Objectives and Endpoints 3. Objectives and Endpoints	*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*	To include endpoints corresponding to the Maintenance Extension
1.1. Synopsis – Efficacy Analysis Definitions 3. Objectives and Endpoints	Histologic remission by RHI: RHI ≤~~3~~*2* (with 0 for lamina propria neutrophils score and neutrophils in the epithelium score and without ulcers or erosions)		To clarify efficacy analysis definitions
1.1. Synopsis – Efficacy Analysis Definitions 3. Objectives and Endpoints	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~~*12* consecutive weeks prior to Week 52.		To clarify efficacy analysis definitions

Section No. and Name	Description of Change	Brief Rationale
1.1. Synopsis – Overall Design 4.1. Overall Design	**The overall design section was reorganized for clarity and updated to reflect study changes. Text revisions are summarized below.**	To reorganize paragraphs for clarity
1.1. Synopsis – Overall Design 4.1. Overall Design	~~For each treatment group, the~~*The* study will enroll ~~at least 30% of the participants from each of the~~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)~~ strata~~, *with at least 30%* but no more than 40% of ~~the~~ advanced therapy-experienced ~~patients~~*participants*.	To clarify the enrollment plan for prior advanced therapy-experienced participants
1.1. Synopsis – Overall Design 4.1. Overall Design	~~This~~*The main part of this* Phase 2b study will consist of ~~3 study periods:~~ a Screening Period (up to ~~4~~ *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 ~~-4~~*-6* to -1), multiple Treatment Visits (Visits 2-10 at Weeks 0, 2, 6, 12, 18, 24, ~~36~~*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 ~~Visit 11~~ at Week 56 if the full *Treatment Period*~~study~~ is completed or earlier if treatment is discontinued early).	To reflect the expanded Screening Period
1.1. Synopsis – Overall Design 4.1. Overall Design	*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.*	To reflect the addition of the 52-week Maintenance Extension Period
1.1. Synopsis – Overall Design 4.1. Overall Design	~~Any participant who has not shown clinical improvement (as determined by the Investigator) by Week 24 will be discontinued from the study following an End of Treatment (EOT) Visit and a SFU Visit.~~	To remove the Week 24 clinical improvement assessment timepoint
1.1. Synopsis 4.1. Overall Design 6.1. Study Treatment Description	**Descriptions of study treatment in the synopsis section were consolidated and updated to reflect study changes. Maintenance Extension Period (52 Weeks) was added to the dosing regimens for the 4 treatment groups and Table 4 in Section 6.1.** ~~After completion of the 12-week Induction Period, all participants randomized into the placebo group (Group 4) will be switched to receive an active MORF-057 regimen during the Maintenance Period.~~	To reflect the addition of the 52-week Maintenance Extension Period

<table>
<tr><th>Section No. and Name</th><th>Description of Change</th><th>Brief Rationale</th></tr>
<tr><td></td><td>~~The dosing regimens for the 4 treatment groups during the Induction and Maintenance Periods are shown below.~~
Study Treatment:
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~~treatment phase~~ 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. ~~Participants~~ All participants who ~~complete~~choose to continue in the ~~final SFU Period, including the Week 56 Visit (4 weeks after~~Maintenance Extension will continue receiving the ~~last dose of~~same MORF-057~~), will have a maximum time on study of 60~~ 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>
<tr><td></td><td>Induction Period (12 Weeks)</td><td>Maintenance Period (40 Weeks)/
Maintenance Extension Period (52 Weeks)</td></tr>
<tr><td>Group 1</td><td>MORF-057 (200 mg B.I.D.)</td><td>MORF-057 (100 mg B.I.D.)</td></tr>
<tr><td>Group 2</td><td>MORF-057 (100 mg B.I.D.)</td><td>MORF-057 (100 mg B.I.D.)</td></tr>
<tr><td>Group 3</td><td>MORF-057 (100 mg Q.D.-M)</td><td>MORF-057 (100 mg Q.D.-M)</td></tr>
<tr><td>Group 4</td><td>Placebo</td><td>MORF-057 (200 mg Q.D.-E)</td></tr>
</table>
~~The Sponsor may decide to allow participants to continue receiving MORF-057 by adding a Maintenance Extension Period via a subsequent regulatory submission. In this case, participants who complete the 52-week Treatment Period and associated assessments will continue receiving MORF-057 through the Maintenance Extension Period before completing the SFU Period.~~</td><td></td></tr>
<tr><td>1.1. Synopsis – Study Treatment</td><td>The study drug will be supplied as IR capsules for oral administration (MORF-057 100 mg capsule or placebo). 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.” Each participant ~~may~~will be instructed to take ~~up to~~ 4 capsules per day during the Induction Period and 3 capsules per day during the Maintenance Period/Maintenance Extension Period~~depending on the number of bottles dispensed to the participant~~.</td><td>To clarify treatment description and add the Maintenance Extension Period</td></tr>
</table>

Section No. and Name	Description of Change	Brief Rationale
1.1. Synopsis – Study Schema 4.1. Overall Design	**The study schema and corresponding footnotes were updated to include the 52-week Maintenance Extension Period. The new schema also shows the expanded Screening Period.** 	To reflect the addition of the 52-week Maintenance Extension Period and the expanded Screening Period
1.1. Synopsis – Study Schema 4.1. Overall Design	Study Schema: Abbreviations: ~~D, day;~~ ~~P.O., by mouth~~ *V, visit;* ~~§ Sponsor may decide to allow participants to continue receiving MORF-057 by adding a Maintenance Extension Period via a subsequent regulatory submission.~~	To reflect updated study schema
1.1. Synopsis – Main Inclusion Criteria 5.1. Inclusion Criteria	Type of Participant and Disease Characteristics 4. Demonstrated an inadequate response, loss of response, or intolerance to at least one of the following treatments (including oral aminosalicylates, corticosteroids, immunosuppressants, and/or advanced therapies for UC) in the opinion of the Investigator, as defined below: a. Oral aminosalicylates (e.g., mesalamine, sulfasalazine, olsalazine, or balsalazide) • Signs and symptoms of persistently active disease during a current or prior course of at least 4 weeks of treatment with ≥2.4*0* g/day mesalamine, 4 g/day sulfasalazine, 1 g/day olsalazine, or 6.75 g/day balsalazide Note: ~~Patient~~*Participant* cannot have had inadequate response, loss of response, or intolerance to more than 3 drugs in 2 classes of the following advanced therapies: c. JAK antagonists, including tofacitinib *or upadacitinib* e. Any investigational product with the same mechanism as one of those outlined above (a through d) *or a novel mechanism of action* Note: ~~Patient~~*Participant* who have a history of primary non-response to 2 *or more* of the advanced therapy classes above will not be eligible. ~~Patient~~*Participant* who have received treatment with these agents at sub-therapeutic doses or durations should be discussed with the Medical Monitor to assess eligibility.	To revise inclusion criteria

Section No. and Name	Description of Change	Brief Rationale
	5. Meets the following washout criteria of prior UC therapy relative to study Day 1: c. JAK antagonists, including tofacitinib *or upadacitinib*: at least ~~3 days~~*1 week* d. S1P receptor agonists, including ozanimod: at least ~~8~~ *4* weeks *Note: Participants who do not meet the full washout period but have the results of a local drug concentration level performed during the Screening window deemed by the Medical Monitor to be sub-therapeutic may be eligible for the study earlier than the full washout period.* 6. If the ~~patient~~*participant* has been receiving any of the non-prohibited medications for UC listed below, he/she must discontinue use at least 5 half-lives before study Day 1 or must agree to maintain stable doses of these concomitant medications starting from the time specified below until the end of the SFU Period, with the exception of tapering oral corticosteroid dose after 12 weeks of being in the trial. a. *Oral* 5-Aminosalicylates (not exceeding 4.8 g per day): at least 2 weeks prior to study Day 1	
1.1. Synopsis – Exclusion Criteria 5.2. Exclusion Criteria	Medical Conditions 7. Has ~~an~~*a potentially* active bacterial*, viral,* or parasitic pathogenic enteric infection, including ~~Clostridium~~*Clostridiodes* difficile *(C. difficile)*; has hepatitis B or C virus, or human immunodeficiency virus (HIV); had an infection requiring hospitalization or intravenous antimicrobial therapy, or an opportunistic infection within 3 months prior to Screening; had any infection requiring oral antimicrobial therapy within 2 weeks prior to Screening; or has a history of more than 1 episode of herpes zoster or any episode of disseminated herpes zoster infection 8. Has ~~an~~ active ~~or latent~~ tuberculosis (TB), as evidenced by any of the following: a. A diagnostic test for TB performed within 30 days ~~of~~*prior to* Screening or during the Screening Period that is positive, *as* defined ~~as~~ *below*: • *A positive interferon gamma release assay (IGRA) test (e.g.,* ~~Positive~~ [redacted] *TB* test*)* or 2 consecutive indeterminate [redacted] *IGRA* tests OR • A purified protein derivative (PPD) skin test ≥5 mm b. ~~Chest~~*A chest* X-ray *or imaging per local guidelines* within 3 months ~~of~~*prior to* Screening where active or latent pulmonary TB cannot be excluded *Note: Participants who have tested negative for TB at a certified local lab using an IGRA test within 3 months prior to Screening are not required to repeat this test during the Screening Period if that participant has no clinical signs or symptoms of TB and no known exposures/increased risk factors since the last negative TB test (according to the Investigator's clinical judgement), and the test result is available in the participant's medical record* Note: ~~Patients~~*Participants* with a history of latent TB may be enrolled if ~~it is being treated per local~~*they complete an assessment for evidence of active TB versus latent TB. Documentation will include a chest X-ray or imaging* per local *guidelines during the Screening Window and no signs, symptoms, or evidence of ongoing active TB. Participants have had treatment per the local* standard *of* care *for a minimum of 2 weeks* before *the* first dose of study drug ~~with no evidence of ongoing active TB or who have~~*OR* documentation of completing appropriate treatment for latent TB within 2 years before Day 1	To revise exclusion criteria

Section No. and Name	Description of Change	Brief Rationale
	~~Participants with inadequate documentation of treatment should be cleared by a TB specialist before enrollment~~*of the study. See Section 8.2.2.1 for more details.* 9. ~~Tests positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) during the Screening Period. Testing to be performed according to site-specific testing procedures and country-specific requirements.~~*Has a positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) test result during the Screening Period. Testing for SARS-CoV-2 is required only per local regulations. Participants who have a positive test result can be randomized after a subsequent negative test result during the Screening Period.* 16. g. International normalized ratio >1.5. *Participants with an international normalized ratio >1.5 due to anticoagulant therapy (e.g., Coumadin) may only be enrolled after a consultation with the Medical Monitor.*	
1.1. Synopsis – Exclusion Criteria 5.2. Exclusion Criteria	Prior/Concurrent Clinical Study Experience 28. ~~Previous~~*Known allergies/hypersensitivity to any component of the study drug and/or previous* exposure to MORF-057 and/or a known hypersensitivity to drugs with a similar mechanism to MORF-057	To update exclusion criteria regarding participant allergies/hypersensitivities
1.1. Synopsis – Study Treatment	~~Study Treatment:~~ ~~MORF-057 is a small molecule therapy that selectively inhibits the α4β7 integrin. The study drug will be supplied as immediate-release capsules for oral administration (MORF-057 100 mg capsule or placebo). The dose regimens for the 4 treatment groups are provided below:~~	To update for clarity
1.1. Synopsis – Statistical Methods: Sample Size Determination 9.5. Sample Size Determination	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%.	To identify the calculation for determining sample size
1.1. Synopsis – Statistical Methods: Primary Efficacy Endpoint 9.2.3.1. Primary Efficacy Endpoint	The primary analysis will be repeated on the PP Population as a sensitivity analysis. Other sensitivity analyses for the primary efficacy endpoints may also be performed as appropriate. The primary efficacy endpoint will be analyzed for the subgroups defined based on ~~some~~*selected* categorized demographic and baseline variables, e.g., age, gender, race, exposure to an advanced therapy treatment for UC (advanced therapy-naïve and advanced therapy-experienced). The details will be described in the *Statistical Analysis Plan (*SAP*)*.	To clarify the primary efficacy endpoint
1.1. Synopsis – Statistical Methods: Exploratory Efficacy Endpoints 9.2.3.3. Exploratory Efficacy Endpoints	All the continuous exploratory efficacy endpoints expressed as change from baseline at Week 12 as defined in Section 3 (e.g., non-endoscopic biomarkers *of inflammation*, PROs) will be 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.	To identify the type of biomarkers

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1.1. Synopsis – Statistical Methods: Safety Analyses 9.2.4. Safety Analyses	The safety analyses will be performed for the 12-week Induction Period ~~and~~*,* the~~ overall~~ 52-week Treatment Period*, and the 52-week Maintenance Extension Period plus the Safety Follow-up Period*. In the safety analyses for the 12-week Induction Period, the participants initially randomized into the placebo group and switched to an active MORF-057 regimen after the Week 12 assessments will be analyzed as the placebo group. In the safety analyses for the ~~overall~~ 52-week Treatment *Period and 52-week Maintenance Extension* Period, the placebo recipients switched to an active MORF-057 regimen will be analyzed according to the active MORF-057 regimen they received after Week 12, and their data will be presented separately based on only the safety data collected after the *start of the MORF-057 dose.* ~~Week 12 assessments, i.e., during the 40-week Maintenance Period and Safety Follow-up Period~~.	To add safety analyses of the Maintenance Extension
1.1. Synopsis – Statistical Methods: Pharmacodynamics Analyses 9.2.6. Pharmacodynamics Analyses	The exploratory PD endpoints (changes over time in $\alpha_4\beta_7$ and $\alpha_4\beta_1$ receptor ~~occupancy,~~*occupancies and* blood CCR9 mRNA level~~, and blood lymphocyte subsets~~) will be summarized descriptively. Additional analysis of PD endpoints may be described in a biomarker analysis plan separate from the study SAP and reported separately. The PD Population will be used for the summarization and analysis of PD exploratory endpoints. **Section 9.2.6.** The exploratory PD endpoints (changes over time in α4β7 ~~receptor occupancy, changes over time in~~ *and* α4β1 receptor ~~occupancy,~~*occupancies and* blood CCR9 mRNA level~~, and blood lymphocyte subsets~~) will be summarized descriptively.	To clarify how the exploratory PD endpoints will be reported
1.1. Synopsis – Statistical Methods: Analyses for Induction Period, 52-week Treatment Period, and Maintenance Extension Period 9.3. Analyses for Induction Period, 52-week Treatment Period, and Maintenance Extension Period	<u>Analyses for Induction Period ~~and Total~~*, 52-week* Treatment Period*, and Maintenance Extension Period*</u> The *Treatment Period in the main part of the* study includes ~~2 treatment periods:~~ the 12-week Induction Period and the 40-week Maintenance Period. For the purpose of statistical analyses, the Induction Period and the Maintenance Period will be treated as 2 independent parts. There will be 2 analyses planned: one for the 12-week Induction Period (i.e., the period for the primary efficacy endpoint) and one for the 52-week ~~Total~~ Treatment Period (i.e., the 12-week Induction Period plus the 40-week Maintenance Period and Safety Follow-up *Period*). *The details of the analyses will be described in the SAP. The results for the main part of the study will be reported in the Clinical Study Report. Additional analysis of the optional 52-week Maintenance Extension Period for the participants enrolled into the Maintenance Extension will also be performed as appropriate. The results for the Maintenance Extension will be reported in a Clinical Study Report Addendum.* <u>Induction Period Analysis</u> The analysis of the 12-week Induction Period will be performed after all the participants have completed the ~~Induction Period (i.e., completed the~~ Week 12 ~~visit~~*assessments* or discontinued the study before the Week 12 assessment*s*~~)~~. The analysis will formally evaluate the ~~efficacy (including the~~ primary and secondary efficacy endpoints, ~~and~~ all the exploratory *efficacy* endpoints defined by Week 12~~)~~*,* and safety of MORF-057 vs. placebo during the 12-week Induction Period. The PK and PD data *during the 12-week Induction Period* will also be summarized.	To add statistical analyses of the Maintenance Extension and clarify each analysis period

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	~~Total~~ *52-week* ~~-~~Treatment Period Analysis The analysis of the 52-week ~~Total~~ Treatment Period 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 ~~Total~~ Treatment Period *(*and the Safety Follow-up Period *for participants not rolling over into the Maintenance Extension Period)*. The cumulative data, including those from the Induction Period, will be used in this analysis. *Maintenance Extension Analysis* *The analysis of the Maintenance Extension will be performed after all the participants enrolled into the Maintenance Extension have completed the 52-week Maintenance Extension Period and the Safety Follow-up Period or discontinued the study before the Week 104 assessment. The analysis will evaluate the safety of MORF-057 and selected efficacy endpoints as appropriate during the Maintenance Extension plus the Safety Follow-up Period.*	
1.2. Schedule of Activities (SoA)	**Section 1.2. was updated to reflect the changes in study procedures. Table 1 Schedule of Activities for the Treatment Period was added. A new SoA table (Table 2) identifies the timepoints and assessments of the Maintenance Extension Period. Addition of these 2 tables required renumbering tables.** *The SoA for the Treatment Period is provided in Table 1. The SoA for the Maintenance Extension Period is provided in Table 2.* Abbreviations: ~~Clostridium~~*Clostridiodes* *ICF, Informed Consent Form;* *IGRA, interferon gamma release assay;*	To reflect changes to the Induction Period and include activities during the Maintenance Extension Period
1.2. Schedule of Activities (SoA)	**The SoA Table 1 was updated to clarify the Induction and Maintenance Periods, reflect the expanded Screening Period, add Stage 1 and 2 at Visits 5 and 10 with testing updated per respective stage, collect information on participant's change in substance use at Stage 2 of Visits 5 and 10/EOT, remove Visit 11 from the SFU label, add /EOT to the corresponding mentions of Visit 10, clarify SARS-CoV-2 and TB testing, clarify back-up stool collection at Screening Stage 1 and optional stool collection for future research, clarify PK time windows, clarify endoscopy biopsies, include informed consent for the Maintenance Extension, remove the Week 24 clinical improvement review, and add confirm initiation of study drug for the Maintenance Period at Visit 5 Stage 2.**	To update study activities during the 52-week Treatment Period
1.2. Schedule of Activities (SoA)	**Dispense study drug was added to Visit 10.**	To update study activities
1.2. Schedule of Activities (SoA)	**Table 1, Footnote "b":** No specific tests *or procedures* are required for unscheduled visits. Results of any study procedures performed at an unscheduled visit will be recorded and collected for the study. ~~b.~~ Clinically relevant	To clarify study procedures for unscheduled visits

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	laboratory testing or re-testing (e.g., hematology, coagulation, serum chemistry, or urinalysis) may be performed at unscheduled visits.	
1.2. Schedule of Activities (SoA)	**Addition of definition of Visit 5 Stage 1 and Stage 2 to Table 1, footnote "c" required reorganization of footnotes.**	To include definitions of Visit 5 Stage 1 and Stage 2
1.2. Schedule of Activities (SoA)	**Table 1, Footnote "c":** ~~If participant discontinues early from the study Treatment Period, perform the Visit 10/EOT procedures and schedule Visit 11/SFU for 28 days (+7 days) after the participant takes the last dose of study drug (unless consent is withdrawn).~~ *Visit 5 is split into Stage 1 and Stage 2 to clarify the timing of the endoscopy procedure. The endoscopy procedure at Visit 5 Stage 1 should be performed before the Visit 5 Stage 2 in-clinic assessments have been completed.*	To include timing of the endoscopy procedure
1.2. Schedule of Activities (SoA)	**Addition of definition of Visit 10 Stage 1 and Stage 2 to Table 1, footnote "d" required reorganization of footnotes.**	To include definitions of Visit 10 Stage 1 and Stage 2
1.2. Schedule of Activities (SoA)	**Table 1, Footnote "d":** ~~Participants not participating in Maintenance Extension Period will complete the SFU Visit, which should be performed 28 days (+7 days) after the participant takes the last dose of study drug. Eligible participants who choose to participate in the Maintenance Extension Period after Visit 10/EOT will not attend the SFU Visit.~~ *Visit 10 is split into Stage 1 and Stage 2 to clarify the timing of the endoscopy procedure. The endoscopy procedure at Visit 10 Stage 1 should be performed before the Visit 10 Stage 2 in clinic assessments have been completed.*	To include timing of the endoscopy procedure
1.2. Schedule of Activities (SoA)	**Table 1, Footnote "~~c~~*e*":** If *the* participant discontinues early from the study Treatment Period, perform the ~~Visit 10/~~EOT procedures and schedule ~~Visit 11/~~SFU for 28 days (+7 days) after the participant takes the last dose of study drug (unless consent is withdrawn).	To clarify the visits after early discontinuation
1.2. Schedule of Activities (SoA)	**Table 1, Footnote "~~d~~*f*":** Participants not participating in *the* Maintenance Extension Period will complete the SFU Visit, which should be performed 28 days (+7 days) after the participant takes the last dose of study drug. Eligible participants who choose to participate in the Maintenance Extension Period after Visit 10~~/EOT~~ will ~~not attend the SFU Visit~~ *complete a separate SFU Visit at Week 108 (Table 2).*	To clarify study procedures
1.2. Schedule of Activities (SoA)	**Table 1, Footnote "~~e~~*g*":** If the participant discontinues early from the study Treatment Period, perform the ~~Visit 11/~~SFU procedures 28 days (+7 days) after the participant takes the last dose of study drug (unless consent is withdrawn).	To reflect the removal of Visit 11

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1.2. Schedule of Activities (SoA)	**Table 1, Footnote "~~f~~/*h*":** The SFU Visit is to occur 28 days (+7 *days*) after the last dose of study drug is received. If the EOT Visit occurs before Day 365, the day for the SFU Visit can be adjusted according to the date of last study drug dose.	To clarify the timing of the study procedure
1.2. Schedule of Activities (SoA)	**Table 1, Footnote "~~h~~*j*":** Enrollment may occur at any point within a ~~28~~*42*-day window of when all screening procedures have been completed and all results required to assess eligibility are available. *Enrolled participants will be randomized to a treatment group.* Enrollment will usually occur the same day as first dosing, but if dosing the same day is not feasible, then enrollment will be considered Day -1 and first dose will be considered Day 1.	To reflect the expanded Screening Period and clarify study procedures
1.2. Schedule of Activities (SoA) 8.2.2.2. SARS-CoV-2	**Table 1, Footnote "~~i~~*k*":** ~~SARS-CoV-2 test will be performed during the Screening Period according to site-specific procedures and country-specific requirements.~~*Testing for SARS-CoV-2 is required only per local regulations. Participants who have a positive test result will be excluded from randomization until a subsequent test result is negative.* **Section 8.2.2.2.:** ~~All participants will complete SARS-CoV-2 screening to determine eligibility.~~*Testing for SARS-CoV-2 is required only per local regulations. Participants who have a positive test result will be excluded from randomization until a subsequent test result is negative.*	To allow re-testing of participants who tested positive for SARS-CoV-2 during the Screening Period
1.2. Schedule of Activities (SoA)	**Table 1, Footnote "~~j~~*l*":** [redacted] ~~TB test.~~ *Participants who have tested* negative *for TB at a certified local lab using an interferon gamma release assay (IGRA) test (e.g.,* [redacted] *TB test) within 3 months prior to Screening are not required to repeat this test* during the Screening Period *if that participant has no clinical signs or symptoms of TB and no known exposures/increased risk factors since* the *last negative TB test (*according to ~~site-specific procedures and country-specific requirements~~ *the Investigator's clinical judgement).* In cases where the [redacted] *IGRA* test is indeterminate, the participant may have the test repeated once, and if their second test is negative, they will be eligible. ~~In the event [redacted] is unavailable, the Investigator has the option to perform a~~*The* purified protein derivative skin test *should be performed when the IGRA test is not possible or if both tests are required by local guidelines.*	To clarify TB screening requirements
1.2. Schedule of Activities (SoA)	**Addition of review of change in substance use to Table 1, footnote "m" required reorganization of footnotes.**	To include review of change in substance use
1.2. Schedule of Activities (SoA) 5.3. Lifestyle Considerations	**Table 1, Footnote "m":** *Collect information on the participant's change in substance use (e.g., alcohol, tobacco, and drugs).* **Section 5.3.:** No new non-pharmacological therapies should be started during the study period. *Information should be collected on the participant's change in substance use (e.g., alcohol, tobacco, and drugs) per the SoA in Section 1.2.*	To include review of change in substance use

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1.2. Schedule of Activities (SoA) 8.8.6. Pregnancy/Menopause Testing	**Table 1, Footnote "~~m~~*p*":** Serum test for follicle-stimulating hormone level to be performed only for female participants of non-childbearing potential~~ who are not surgically sterile~~. **Section 8.8.6.:** A serum test for follicle-stimulating hormone (FSH) level will be performed at Screening only for female participants of non-childbearing potential~~ who are not surgically sterile~~.	To align with central lab processes and Appendix 3
1.2. Schedule of Activities (SoA) 8.6. Stool Collection	**Table 1, Footnote "~~n~~*q*":** Stool collection kits are to be dispensed to participants at the visits indicated. The participant should use this kit to collect one sample at home within 24 hours before the next site visit. The sample should be stored as described in the sample collection instructions and brought to the clinic on the day of the site visit. *If the participant is unable to produce a stool sample at the Stage 1 Screening Visit, they can collect a sample at home and return it to the site.* Note: Sample is to be collected prior to bowel preparation for Visits 5 and 10/EOT. **Section 8.6.:** In addition, stool collection kits are to be dispensed to participants at the visits indicated in the SoA. The participant should use this kit to collect one sample at home within 24 hours before the next site visit. The sample should be stored as described in the sample collection instructions and brought to the clinic on the day of the site visit. *If the participant is unable to produce a stool sample at the Stage 1 Screening Visit, they can collect a sample at home and return it to the site.*	To clarify back-up stool sample collection at Screening Stage 1 Visit
1.2. Schedule of Activities (SoA)	**Table 1, Footnote "~~o~~*r*":** *Participants will be provided the option to participate in the Maintenance Extension Period. Participants who want to continue in the Maintenance Extension will be required to provide informed consent.* ~~If the Sponsor decides to add a Maintenance Extension Period, willing participants should sign the relevant revised ICF, as required.~~	To identify when the separate ICF for the Maintenance Extension Period must be signed
1.2. Schedule of Activities (SoA)	**Table 1, Footnote "~~p~~*s*":** ECGs to be performed before the AM dose and 2 hours *(±30 minutes)* after the AM dose during the Induction and Maintenance Periods. *ECGs will be obtained after the participant has rested for at least 10 minutes in the supine position.*	To clarify the ECG procedure
1.2. Schedule of Activities (SoA) 8.8.1. Physical Examinations	**Table 1, Footnote "~~q~~*t*":** A complete physical exam is to be performed at Screening and Visit 10/EOT, and a targeted exam may be performed at all other required visits (see Section 8.8.1 for descriptions). For unscheduled visits, the type of exam *(if necessary to be performed at all)* will be at the Investigator's discretion and determined based on the reason for the visit. The Screening exam will include collection of height and weight. **Section 8.8.1.:** A complete physical exam is required at Screening ~~and~~, Visit 10/EOT, and *Visit 14/EOT; and* a targeted exam may be performed at all other required visits. For unscheduled visits, the choice of whether to perform a complete or targeted physical exam *(if necessary to be performed at all)* is at the discretion of the Investigator and will depend on the reason for the unscheduled visit.	To clarify type of physical exam at which timepoints

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1.2. Schedule of Activities (SoA) 8.8.2. Vital Signs	**Table 1, Footnote "~~r~~*u*":** Vital signs to be recorded at ~~all~~*most* visits. *At unscheduled visits, vital signs are not required and are at the discretion of the Investigator.* These will include blood pressure, heart rate, respiratory rate, and temperature. *Vital signs are to be taken before blood collection for laboratory tests. Blood pressure and pulse measurements should be preceded by at least 10 minutes of rest for the participant.* **Section 8.8.2.:** Vital signs to be recorded at ~~all~~*most* visits *as summarized in the SoA (Section 1.2). At unscheduled visits, vital signs are not required and are at the discretion of the Investigator.* These will include blood pressure, heart rate, respiratory rate, and temperature.	To clarify the vital signs recording times
1.2. Schedule of Activities (SoA)	**Table 1, Footnote "~~x~~*y*":** PK testing at Visits 2, 3, 5, 7, and 10/EOT: Blood samples will be collected before the AM dose and at 1~~,~~ *(±10 min)*, 2~~,~~ *(±15 min)*, and 4 *(±30 min)* hours after the AM dose. ~~Time windows for PK sampling can be found in Section 8.10.1.~~ *For all pre-AM dose sampling, the samples should be obtained before the AM dose is administered. If consent is provided by the participant, these samples may also be used for future PK research studies.* **Table 1, Footnote "~~w~~*z*":** PK testing at Visits 4, 6, 8, and 9: Blood sample will be collected before the AM dose and 1 hour *(±10 min)* after the AM dose. *For all pre-AM dose sampling, the samples should be obtained before the AM dose is administered. If consent is provided by the participant, these samples may also be used for future PK research studies*.	To clarify the PK samples from participants who consent may also be used for future PK research studies
1.2. Schedule of Activities (SoA)	**Addition of optional stool sample to Table 1, footnote "gg" required reorganization of footnotes.**	To clarify optional stool sample for future research
1.2. Schedule of Activities (SoA)	**Table 1, Footnote "*gg*":** *Participation in future research sample collection is optional. Fecal samples for microbiome analysis will be collected before the AM dose on Visits 2, 5, and 10/EOT. Fecal samples may be collected at any time on the day prior to the scheduled visit day.*	To clarify optional stool sample for future research
1.2. Schedule of Activities (SoA)	**Removal of footnote "hh" Table 1 required reorganization of footnotes.** ~~Any patient who has not shown clinical improvement (as determined by the Investigator) by Week 24 will be discontinued from the study following an EOT Visit and a SFU Visit.~~	To remove the Week 24 clinical improvement assessment timepoint
1.2. Schedule of Activities (SoA)	**Table 1, Footnote "~~dd~~*hh*":** Full colonoscopy is optional at any timepoint if the Investigator deems it necessary. However, if the ~~patient~~*participant* has had UC for over 7 years, he/she must undergo a full colonoscopy (rather than sigmoidoscopy) at Screening if a full colonoscopy has not been performed in the last 2 years. ~~Colonic mucosa biopsies will be collected for histopathology and optional future research studies.~~	To identify the number of biopsies for histopathology and the optional future research (for participants who consent) and clarify the procedures
1.2. Schedule of Activities (SoA)	**Addition of a separate footnote on the specifics of the Screening endoscopy biopsies to Table 1, footnote "ii" required reorganization of footnotes.**	To clarify the Screening endoscopy biopsies

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1.2. Schedule of Activities (SoA)	**Table 1, Footnote "*ii*":** *During the Screening endoscopy, up to 6 colonic mucosa biopsies will be collected. Two biopsies for the required histopathology must be collected from the worst inflamed area, 15-25 cm from the anus. Record the extent of disease in centimeters from the anal verge. If consent is provided by the participant, 4 additional mucosa biopsies may be collected for the optional future research studies (2 biopsies from the worst inflamed area and 2 from a non-inflamed/least inflamed area). If consent is provided by the participant, any remaining tissue from the required histopathology biopsies may be used for future research studies. See Section 8.7.1 for details on biopsy requirements.*	To clarify the Screening endoscopy biopsies
1.2. Schedule of Activities (SoA)	**Table 1, Footnote "~~ee~~*jj*":** The Visit 5 *Stage 1* endoscopy procedure should be performed ~~after~~*before* the in-clinic assessments *at Visit 5 Stage 2* have been completed.	To clarify the timing of the Visit 5 endoscopy
1.2. Schedule of Activities (SoA)	**Table 1, Footnote "~~ff~~*kk*":** For the Visit 10/EOT endoscopy procedure, there is a window of ~~±~~+7 days from the actual visit date. For participants who discontinue treatment before Week 6, a repeat sigmoidoscopy will be performed any time after MORF-057 dosing Day 14. For participants who discontinue treatment after Week 6, a repeat sigmoidoscopy will be performed any time. *Participants who complete the EOT Visit within 2 months after the Week 12 endoscopy are not required to repeat the procedure.*	To clarify the endoscopy requirements
1.2. Schedule of Activities (SoA)	**Addition of a separate footnote on the endoscopy biopsy specifics of the Visit 5 Stage 1 and Visit 10/EOT Stage 1 to Table 1, footnote "ll" required reorganization of footnotes.**	To clarify the Visits 5 and 10/EOT endoscopy biopsies
1.2. Schedule of Activities (SoA)	**Table 1, Footnote "*ll*":** *Collect up to 6 biopsy samples total (2 for required histopathology and 4 for optional future research studies [if consent is provided by the participant]). If consent is provided by the participant, any remaining tissue from the required histopathology biopsies may be used for future research studies. All biopsies should be collected from the same distance from the anus as collected at the Screening Visit, regardless of the tissue state at the time of the sampling. Record the extent of disease in centimeters from the anal verge. Record the number of centimeters from the anus in which biopsies are collected at all follow-up visits into the Requisition Form.*	To clarify the Visits 5 and 10/EOT endoscopy biopsies
1.2. Schedule of Activities (SoA)	**Addition of a footnote on clarifying study treatment handling for participants not participating in the Maintenance Extension Period to Table 1, footnote "nn" required reorganization of footnotes.**	To clarify study treatment handling for participants not participating in the Maintenance Extension Period
1.2. Schedule of Activities (SoA)	**Table 1, Footnote "*nn*":** *Participants not participating in the Maintenance Extension Period should return all study drug to the site. No additional dosing should occur after the completion of the EOT Visit.*	To clarify study treatment handling for participants not participating in the

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		Maintenance Extension Period
1.2. Schedule of Activities (SoA)	**Table 1, Footnote "~~ii~~*oo*":** At Visit 5, the *Induction Period* study drug~~s~~ *kits* supplied at the previous visit should be used for the AM ~~and PM~~ dose. Please note, a new supply of *Maintenance Period* study drug~~s~~ *kits* will be provided at *the conclusion of* Visit 5~~, but the new supply should be started the day AFTER the required sigmoidoscopy is performed. This is to ensure that participants moving onto the Maintenance Period are on the appropriate MORF-057 treatment and dose~~. *Participants should use the Maintenance Period study drug kits for all future doses after the completion of Visit 5.*	To clarify study drug dispensing at Visit 5
1.2. Schedule of Activities (SoA)	**Addition of a footnote on clarifying study drug dispensing at Visit 10/EOT to Table 1, footnote "pp" required reorganization of footnotes.**	To clarify study drug dispensing at Visit 10/EOT
1.2. Schedule of Activities (SoA)	**Table 1, Footnote "*pp*":** *For participants continuing treatment in the Maintenance Extension, additional study drug will be dispensed at Visit 10.*	To clarify study drug dispensing at Visit 10/EOT
1.2. Schedule of Activities (SoA)	**Table 1, Footnote "~~jj~~*qq*":** AM dosing required on-site for all visits except *the* SFU *Visit*.	To align with document
1.2. Schedule of Activities (SoA)	**Table 1, Footnote "~~kk~~*rr*":** At Visit 10/EOT, participants *not participating in the Maintenance Extension Period* will only receive an AM dose for the day. No PM dose will be provided.	To clarify dosing instructions for participants not participating in the Maintenance Extension Period
1.2. Schedule of Activities (SoA)	**Addition of a footnote to add a follow-up contact to Table 1, footnote "ss"**	To add a follow-up contact to ensure participants begin using the study drugs for the Maintenance Period
1.2. Schedule of Activities (SoA) 6.4. Study Treatment Compliance	**Table 1, Footnote "*ss*":** *Site staff will contact the participants, by phone or other forms, on the next business day after the Visit 5 clinic visit is complete to confirm the participants are using the new supply of study drugs for the Maintenance Period. Record the date and time of the participant's first Maintenance Period dose.* **Section 6.4.:** *The site staff will contact participants, by phone or other forms, on the next business day after the Visit 5 clinic visit to confirm the participants have switched from the Induction Period study drug to the new Maintenance Period study drug bottles.*	To add a follow-up contact to ensure participants begin using the study drugs for the Maintenance Period
2.1. Study Rationale	~~Another~~*Other* therapeutic option*s* recently approved for the treatment of UC ~~is~~*are* Janus kinase (JAK) inhibitors, such as the small molecule tofacitinib ([redacted]) *or upadacitinib* ([redacted]).	Upadacitinib was added to reflect currently

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		approved JAK inhibitors
2.3.2.1. Risks of MORF-057	• *Progressive multifocal leukoencephalopathy (*PML*)* is a fatal opportunistic infection of the central nervous system and has been associated with systemic immunosuppressants, including integrin receptor antagonists (e.g., natalizumab and vedolizumab). Natalizumab, a monoclonal antibody that inhibits both $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrins, has been associated with PML, a serious brain infection. One case of PML ~~was reported in a patient treated with vedolizumab ($\alpha_4\beta_7$ integrin antagonist) during post-marketing setting~~ *in an* [redacted] *(vedolizumab)-treated patient with multiple contributory factors has been reported in the post-marketing setting (e.g., human immunodeficiency virus [HIV] infection).* Data from human whole blood ex vivo assay suggests that MORF-057 has significant selectivity (~700 fold at IC_{90}) for binding integrin $\alpha_4\beta_7$ over integrin $\alpha_4\beta_1$. However, out of an abundance of caution, all participants enrolled in this study will be monitored for PML through the use of a PML Risk Assessment and Minimization ~~p~~*P*rogram (RAMP).	To update risks of MORF-057
4.2. Scientific Rationale for Study Design	*The 52-week treatment will be followed by an optional 52-week Maintenance Extension Period. This extension will provide the participants further access to the study drug and collect additional safety and efficacy data up to 104 weeks of exposure.*	To add rationale for adding the Maintenance Extension
4.3. Justification for Dose	*The ICH E4 guidelines as well as the Guideline on the development of new medicinal products for the treatment of UC (CHMP/EWP/18463/2006 Rev.1) accept placebo as an acceptable comparator (monotherapy or add-on to established therapy) in clinical trials.* *The placebo group serves as a control to evaluate the safety as well as efficacy of MORF-057 in a contemporaneous population.* *All participants will be allowed to continue stable background therapy to which either MORF-057 or placebo will be added for 12 weeks.*	To add a justification for use of placebo
4.4. End of Study Definition	A participant is considered to have completed the study if he/she has completed ~~all periods~~*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 ~~s~~*S*chedule of ~~a~~*A*ctivities *(SoA)* for the last participant in the *main part of the* study globally.	To define participant study completion
5.1. Inclusion Criteria	Weight 9. Has a body mass index (BMI) ≥~~17~~*18*.0 at Screening	To align with synopsis
5.4. Screen Failures	Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened based on discussion and agreement between the Investigator and the Sponsor Medical Monitor. ~~For example, participants who test positive for SARS-CoV-2 during screening can be re-screened once they have a negative PCR test and are symptom free.~~ Re-screened participants should be assigned a new participant number for every ~~s~~*S*creening/re-screening event.	To allow re-testing of participants who test positive for SARS-CoV-2 during Screening
5.4. Screen Failures	*Note: Participants who are unable to complete all required procedures or assessments within the Screening Window due to technicalities may be eligible to extend their Screening Period up to 2 weeks based on an agreement between the Investigator and the Sponsor Medical Monitor. Screening activities*	To clarify the re-screening process

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	that require repeating will be determined by the Sponsor Medical Monitor and the process outlined in the Monitoring Plan.					
6.1. Study Treatment Description – Table 3.	**Table 3. Study Treatment was renumbered from Table 1 due to addition of tables.**					To update table numbering
6.1. Study Treatment Description – Table 3.	Packaging and ~~L~~*l*abeling	*30* Capsules are packaged in a high-density polyethylene bottle containing an oxygen absorber canister and coil and closed with a child-resistant cap equipped with a heat-sealed foil liner. Each bottle will be labeled as per country requirements.	*30* Capsules are packaged in a high-density polyethylene bottle containing an oxygen absorber canister and coil and closed with a child-resistant cap equipped with a heat-sealed foil liner. Each bottle will be labeled as per country requirements.			To clarify the number of capsules per bottle
6.1. Study Treatment Description – Table 3.	Abbreviations: ~~B.I.D., twice a day;~~ *IR, immediate-release*.					To update abbreviations for the table
6.1. Study Treatment Description – Table 4.	**Table 4. Treatment Groups was renumbered from Table 2 due to addition of tables.**					To update table numbering
6.1. Study Treatment Description – Table 4.	Group title	Group 1	Group 2	Group 3	Group 4	To include the Experimental Maintenance Period
	Type	• Induction: Experimental • Maintenance */Maintenance Extension*: Experimental	• Induction: Experimental • Maintenance */Maintenance Extension*: Experimental	• Induction: Experimental • Maintenance */Maintenance Extension*: Experimental	• Induction: Experimental • Maintenance */Maintenance Extension*: Experimental	
	Maintenance Period dosing regimen (40 Weeks)*/ Maintenance Extension Period dosing regimen (52 Weeks)*					
6.3.2. Blinding	This is a double-blind study in which the Sponsor, participants, site staff, *site pharmacy,* Investigators, and outcome~~s~~ assessors will be blinded to the study treatment through Week 12. …. Each participant will receive the same number of "morning bottles" and "evening bottles" according to the respective study period (Induction or Maintenance~~).~~*/Maintenance Extension*). …. ~~The~~*After the database lock for the Induction Period analyses, the* analysis results will be unblinded at the population level. However,					To clarify the blinding process

Section No. and Name	Description of Change	Brief Rationale
	the access to treatment assignment for individual participants will be limited ~~within a very small subgroup, including~~*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. If the report requires expedited reporting to one or more regulatory ~~agencies~~*agency*, a copy of the report, identifying the participant's treatment assignment, ~~may~~*will* be sent to the ~~R~~*r*egulatory ~~A~~*a*gency in accordance with local regulations and/or Sponsor policy.	
6.6. Overdose	• Overdose with or without clinical symptoms or abnormal laboratory results should be recorded on the overdose *electronic Case Report Form (e*CRF*) within 24 hours of becoming aware.* • AEs and SAEs associated with overdose will be recorded on the AE ~~CRF~~*eCRF*, and SAEs associated with overdose will be reported via the SAE reporting procedure outlined in Section 8.9.	To specify the process of capturing overdose information
6.7.2. Allowed Medications for the Treatment of Ulcerative Colitis – Table 5.	**Table 5. Corticosteroid Equivalent Doses† was renumbered from Table 3 due to addition of tables.**	To update table numbering
6.7.2.2. Rescue Therapies	*Anti-diarrheals for control of chronic diarrhea and antibiotics for control of infection are not considered rescue medication.*	To align with Section 7.1.1.
6.7.3. Prohibited Medications	• Nonsteroidal anti-inflammatory drugs ~~(NSAIDs)~~ including but not limited to ibuprofen, naproxen, indomethacin, and celecoxib. *(*However, participants may take aspirin for cardio-protection at a dose *as per local guidelines but* not exceeding ~~81~~*325* mg per day.*)*	To clarify the acceptable use of aspirin
6.7.3. Prohibited Medications – Table 6.	**Table 6. Examples of Drugs Potentially Altering Exposures to MORF-057# was renumbered from Table 4 due to addition of tables.**	To update table numbering
7.1.1. Permanent Discontinuation	• Lack of efficacy, defined as: o Administration of a rescue medication (a new medication or increase in dose of a baseline medication to treat new or unresolved UC symptoms *with the exception of returning the background corticosteroid therapy dose to baseline level*). Anti-diarrheals for control of chronic diarrhea *and antibiotics for control of infection* are not considered rescue medication. • Pregnancy or planned pregnancy *of the female participant or female partner of a male participant as the participant will be unblinded* (see Section 8.9.5) • Non-compliance with study treatment (see Section 6.4) *or study procedures* If a participant who does not meet the enrollment criteria is inadvertently enrolled, that participant must be discontinued from the study drug, and the Sponsor or Sponsor designee must be contacted. *In rare circumstances, consideration may be given to the participant when there is a compelling reason to allow the participant to continue. In these rare cases, the Investigator must obtain documented approval from the Sponsor or Sponsor's designee to allow the participant to continue in the study.*	To clarify permanent discontinuation criteria
7.2. Participant Discontinuation/Withdrawal from the Study	The participant should be encouraged to complete the EOT Visit ~~(Visit 10)~~ at the time of study drug discontinuation and the SFU Visit ~~(Visit 11)~~ at 28 days (+7 *days*) after the last dose of study drug.	To clarify discontinuation procedures

<table>
<tr><th>Section No. and Name</th><th>Description of Change</th><th>Brief Rationale</th></tr>
<tr><td>8.1. Medical History</td><td>The participant's demographics and complete medical and surgical history, including initial UC diagnosis date~~, UC onset date,~~ and history of UC medication use, will be collected during Screening and recorded in the participant's eCRF.</td><td>To clarify medical history details</td></tr>
<tr><td>8.2.2.1. Tuberculosis</td><td>All participants will complete TB screening to determine eligibility. Participants with a negative TB test and chest X-ray (or imaging per local guidelines) not suggestive of active ~~or~~ TB may be enrolled. Participants with a history of active TB may be enrolled if it has been adequately treated with no evidence of current active TB. Participants with a positive TB test must be assessed for evidence of active TB versus latent TB ~~will be excluded, including~~. Please refer to Table 7 for TB Screening and eligibility details. Exclusion criteria includes those participants with a positive TB diagnostic test performed within 30 days ~~of~~prior to Screening or during the Screening Period (e.g., a positive IGRA test such as a [redacted] [redacted] TB test, 2 consecutive indeterminate IGRA tests, or a PPD skin test ≥5 mm), and those who had a chest X-ray within 3 months ~~of~~prior to Screening where active or latent pulmonary TB could not be ~~ruled out~~excluded.
The [redacted] GRA test should be performed at Screening on all participants~~.~~, except for those who have had a confirmed negative IGRA test within 3 months prior to Screening. The PPD skin test should be performed when the [redacted] IGRA test is not possible or if both tests are required by local guidelines. Test results should be interpreted as shown below:
• For regions that require both [redacted] IGRA and PPD tests, if either test is positive, the TB test is considered positive.
If the [redacted] IGRA test is indeterminate, then the Investigator should perform a second [redacted] IGRA test to rule out a positive test result. If testing remains indeterminate or is positive, then the participant is considered TB positive.
The PPD skin test should be ~~performed when [redacted] test is not possible. PPD should be~~ read by a licensed healthcare professional between 48 and 72 hours after administration. A reaction of induration ≥5 mm is considered a positive reaction.
Participants who have tested negative for TB at a certified local lab using an IGRA test within 3 months prior to Screening are not required to repeat this test during the Screening Period if that participant has no clinical signs or symptoms of TB, no known exposures/increased risk factors since the last negative TB test (according to the Investigator's clinical judgement), and the test result is available and adequately documented in the participant's medical record.</td><td>To update the TB test methods</td></tr>
<tr><td>8.2.2.1. Tuberculosis – Table 7.</td><td>Table 7. Summary of Tuberculosis Screening and Eligibility was added. The table depicts inclusion/exclusion criteria based on IGRA, [redacted] [redacted] TB test results. Addition of the table required renumbering tables.</td><td>To clarify TB testing inclusion/exclusion criteria</td></tr>
<tr><td>8.2.2.1. Tuberculosis – Table 7.</td><td>
<table>
<tr><th>Test Performed Within 30 Days Prior to Screening or During the Screening Period</th><th>Inclusion</th><th>Exclusion</th></tr>
<tr><td>A positive interferon gamma release assay (IGRA) test (e.g., [redacted] or T-SPOT® TB test)</td><td></td><td>X</td></tr>
<tr><td>2 consecutive indeterminate IGRA tests</td><td></td><td>X</td></tr>
</table>
</td><td>To clarify TB testing inclusion/exclusion criteria</td></tr>
</table>

<table>
<tr><th>Section No. and Name</th><th>Description of Change</th><th>Brief Rationale</th></tr>
<tr><td></td><td>
<table>
<tr><td>A purified protein derivative (PPD) skin test ≥5 mm</td><td></td><td>X</td></tr>
<tr><td>Test Performed Within 3 Months Prior to Screening</td><td>Inclusion</td><td>Exclusion</td></tr>
<tr><td>A chest X-ray within 3 months prior to Screening where active or latent pulmonary TB cannot be excluded</td><td></td><td>X</td></tr>
<tr><td>A negative test for TB at a certified local lab using an IGRA test (e.g., [redacted] TB test) within 3 months prior to Screening AND
Has no clinical signs or symptoms of TB
No known exposures/increased risk factors since the last negative TB test (according to the Investigator's clinical judgement)
The test result is available and adequately documented in the participant's medical record
Note: Re-testing is not required at Screening if all the above criteria are met</td><td>X</td><td></td></tr>
<tr><td>History of Latent TB</td><td>Inclusion</td><td>Exclusion</td></tr>
<tr><td>Study participants with a positive TB test must be assessed for evidence of active TB versus latent TB. Documentation will include:
Chest X-ray or imaging per local guidelines during the Screening Window
No signs and symptoms (no evidence of ongoing active TB
Study participant is being treated per local standard of care for a minimum of 2 weeks before the first dose of study drug OR
Study participant has documentation of completing appropriate treatment for latent TB within 2 years before Day 1 of the study</td><td>X</td><td></td></tr>
</table>
Abbreviations: IGRA, interferon gamma release assay; PPD, purified protein derivative; TB, tuberculosis.</td><td></td></tr>
<tr><td>8.3.1. Dosing Instructions</td><td>The first dose of the study drug will be administered in the clinic on study Day 1 under the supervision of study personnel. All subsequent doses will be self-administered at home, with the exception of the morning doses for Visits 2-10, which will be administered during the study visits after pre-dose blood samples have been drawn (see details in the SoA, Section 1.2). Participants will be instructed to record all details about the doses administered at home in the Participant Diary.</td><td>To clarify dosing instructions</td></tr>
</table>

Section No. and Name	Description of Change	Brief Rationale
	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*). *For the Induction Period, each 30-day study drug supply will consist of 2 cartons (1 for morning and 1 for evening). Inside each carton, there will be 2 corresponding bottles of study drug. Thus, an Induction Period 30-day study drug supply will consist of the following bottles: morning bottle #1, morning bottle #2, evening bottle #1, and evening bottle #2. For the Maintenance Period/Maintenance Extension Period, each 30-day study drug supply will consist of 1 carton. Inside the single carton, there will be 3 bottles of study drug: morning bottle, evening bottle #1, and evening bottle #2.* In the morning, participants should take 1 capsule from EACH "morning bottle." In the evening, participants should take 1 capsule from EACH "evening bottle." Each participant ~~may~~*will be instructed to* take ~~up to~~ 4 capsules per day ~~depending on the number of bottles dispensed to the participant~~*during the Induction Period and 3 capsules per day during the Maintenance Period/Maintenance Extension Period.*	
8.5. Participant Diary	*Participants who remain chronically non-compliant with diary entries despite intervention and follow-up by the Investigator and site team may be subject to discontinuation as per Section 7.1.* Detailed descriptions regarding Participant Diary recordings can be found in the corresponding ~~Study Manual~~*Patient Guide*.	To align with Section 7.1. and update the source for Participant Diary instructions
8.7.1. Endoscopy with Biopsy	Endoscopy will be performed at ~~Stage 2 of~~ Screening (Visit 1) and *during Stage 1 of* Visits 5 ~~and~~, 10/EOT*, and 14/EOT*. Flexible sigmoidoscopy with colonoscopy scope is the suggested procedure, but full colonoscopy is optional at any timepoint if the Investigator deems it necessary. During these procedures, colonic mucosa biopsies will be collected for histopathology and *optional* future research studies. Up to 6 biopsies will be collected during each endoscopy procedure *(2 biopsies for the required histopathology and 4 biopsies for the optional future research). The biopsies for future studies will only be collected from the participants who consent to the optional future research. The remaining tissue from the histopathology biopsies may also be used for future research from participants who consent to the optional future research.* ~~Detailed instructions for endoscopic biopsies (e.g., anatomic site, normal or inflamed mucosa) can be found in the Laboratory Manual. A brief description is provided below:~~ ~~• At Screening (Visit 1), collect 6 biopsy samples total: 4 from the most inflamed/affected area and 2 from a non-inflamed area.~~ ~~o Record the number of centimeters from the anus the biopsy is collected for from inflamed and the non-inflamed area into the Requisition Form Label.~~ ~~o Inflamed biopsies should be collected from the worst affected area, 15-25 cm from the anus.~~ ~~o Non-inflamed biopsies can be collected from anywhere in the colon and are not limited to 15-25 cm from the anus. If there are no non-inflamed areas, biopsies are to be collected from the least inflamed areas.~~	To identify the number of biopsies for histopathology and the optional future research and clarify the procedures

<table>
<tr><th>Section No. and Name</th><th>Description of Change</th><th>Brief Rationale</th></tr>
<tr><td></td><td>~~• For follow-up at Visits 5 (Week 12) and Visit 10/EOT biopsies from both the inflamed and non-inflamed areas should be collected from the same distance (cm) from the anus as collected at the Screening Visit. Record the number of centimeters from the anus in which biopsies are collected at all follow-up visits into the Requisition Form.~~
Biopsy specimen transfer, processing, slide preparation, and digitization of slides for histopathologic scoring procedures will be detailed ~~in a~~ *within the applicable Laboratory Manual or* Histopathology ~~Manual~~ *Reference Guide*. Histopathology results will not be made available to study sites *but will be located within the histopathology laboratory database and added to the electronic Trial Master File after the completion of the trial*.
The MES will be scored by a central reader. However, treatment decisions *post-randomization* will be made by the treating Investigator.

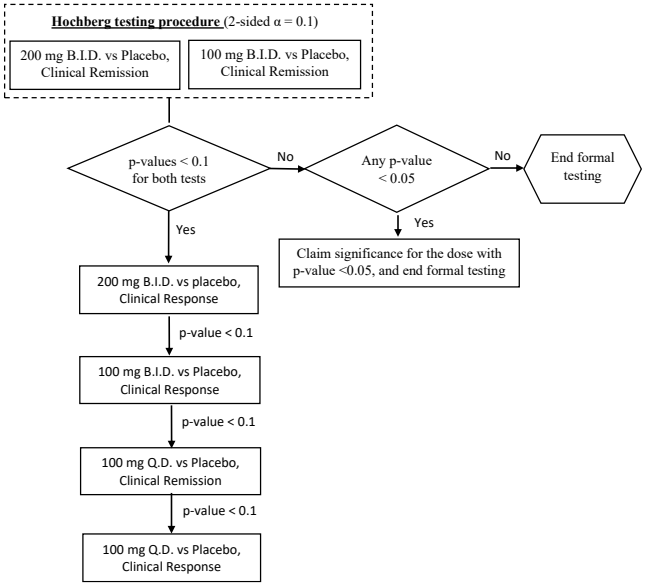
For all biopsies in Table 8:
• *Record the extent of disease in centimeters from the anal verge*
• *Record the distance in centimeters from the anus where biopsies are taken into the Requisition Form*
• *Always review the Laboratory Manual for full instructions related to biopsy sample collection containers, labeling, and storage*
• *Biopsies for histopathology are the required part of the study*
• *Optional biopsies are only to be taken in participants who have consented for future research*</td><td></td></tr>
<tr><td>8.7.1. Endoscopy with Biopsy – Table 8.</td><td colspan="2">Table 8. Instructions for Endoscopic Biopsies was added to clarify biopsy procedures. Addition of the table required renumbering tables.</td><td>To clarify biopsy procedures</td></tr>
<tr><td>8.7.1. Endoscopy with Biopsy – Table 8.</td><td colspan="2"><table>
<tr><td>Visit 1
(Screening)</td><td><u>Worst inflamed area</u>
Take biopsies of the worst inflamed area within 15-25 cm from the anus.
• 2 required biopsies for histopathology
• 2 optional biopsies for future research

<u>Non-inflamed/least inflamed area</u>
Take biopsies from a non-inflamed or least inflamed area of the colon.
• 2 optional biopsies for future research</td></tr>
<tr><td>Visit 5
(Week 12)

Visit 10
(Week 52 or EOT)</td><td><u>Take all biopsies at the same distance (cm) from the anus as collected at Visit 1, regardless of tissue state at the time of the sampling.</u>
• 2 required biopsies for histopathology
• 4 optional biopsies for future research</td></tr>
</table></td><td>To clarify biopsy procedures</td></tr>
</table>

Section No. and Name	Description of Change	Brief Rationale
	Visit 14 (Week 104 or EOT) |	
	Abbreviations: EOT, End of Treatment.	
8.7.3. Mayo Clinic Score	The Investigator will record the PGA in the site ~~tablet or other relevant device or system~~*source documents and eCRF* at the specified study visits.	To clarify the PGA recording procedure
8.8.4. Clinical Safety Laboratory Tests	If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (e.g., SAE or AE), then the results must be recorded in the EDC *database*.	To align with the protocol
8.9.4. Regulatory Reporting Requirements for SAEs, SUSARs, and Periodic Reports	The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the *Member States Concerned, the applicable* regulatory authority, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and Investigators.	To clarify regulatory reporting requirements
8.9.5. Pregnancy	Male participant with a partner who becomes pregnant The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. *Pregnancy in a male participant's partner will require unblinding. The male study participant will be withdrawn from the study and the participant should complete the EOT and SFU Visits.* After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours. The female partner will then undergo pregnancy follow-up to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the mother and the neonate, and the information will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure. ~~The male study participant may continue taking the study drug.~~	To clarify the criteria and procedures for discontinuing a male study participant with a partner who becomes pregnant during the study
8.10.1. Collection of Blood Samples for MORF-057 Concentration Determination in Plasma – Table 9.	**Table 9. Pharmacokinetics Sampling Windows was renumbered from Table 5 due to addition of tables.**	To update table numbering
8.10.1. Collection of Blood Samples for MORF-057 Concentration Determination in Plasma – Table 9.	**Section 8.10.1.:** ~~These~~*If consent is provided by the participant, these* samples may also be used for future PK research studies. Table 9. Pharmacokinetics Sampling Windows Visit | Collection *T*~~t~~imepoints and *A*~~a~~ssociated *W*~~w~~indows	To clarify the PK samples from participants who consent may also be used for future PK research studies

Section No. and Name	Description of Change	Brief Rationale
	2, 3, 5, 7, and 10/EOT: Before AM dose ~~(60 min)~~ and at 1hr (±10 min), 2hr (±15 min), and 4hr (±30 min) after AM dose 4, 6, 8, and 9: Before AM dose ~~(60 min)~~ and 1 hr (±10 min) after the AM dose *Abbreviations: EOT, End of Treatment; hr, hour; min, minute.* For all pre-AM dose sampling, the samples should be obtained ~~within approximately 60 minutes~~ before the AM dose is administered. ~~Furthermore, the samples should be obtained at 12 hours (60 min) after the previous evening's PM dose.~~	
8.12. Future Research	~~Blood~~, *If consent is provided by the participant, blood,* stool, and *colonic* tissue samples will be collected and *may be* used for further PD, pharmacogenomics, ~~and~~ microbiome-related research, *and future research*~~by Morphic Therapeutics~~. *If consent is provided by the participant, the remaining blood and colonic tissue samples from the study-required procedures may also be used for future research, including future PK research. The purpose of future research is* to contribute to the understanding of UC or related diseases, to the development of related or new treatments, or to the development of new research methods. Participation in ~~this~~*the* collection of samples for future research is optional *(see Section 10.1.4 for additional consents)*.	To clarify sampling and analyses for future research
9. Statistical Considerations	Any ~~deviation~~*change* from the planned statistical analyses specified in the protocol will be fully described in the SAP and Clinical Study Report.	To clarify terminology
9.2.3.4. 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 purpose*s* only. The details will be specified in the SAP.	To explain the adjustment for multiple testing

Section No. and Name	Description of Change	Brief Rationale
9.2.3.4. Multiplicity Adjustments	*Figure 2. Hierarchical Testing Procedure* 	To illustrate the adjustment for multiple testing
9.4. Interim Analysis	*The analysis of the 12-week Induction Period (Induction Period Analysis) 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 9.3.* *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.*	To clarify there is no interim analysis planned for this study
10.1.1. Regulatory and Ethical Considerations	• Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European *Union* Clinical ~~Trials Directive 2001/20/EC or European regulation~~*Trials Regulation* 536/2014 for clinical studies ~~*(as applicable),*~~ and all other applicable local regulations	To clarify the Investigator responsibilities
10.1.1. Regulatory and Ethical Considerations	*If the Investigator identifies a potential instance of a serious breach, the Sponsor and Contract Research Organization (CRO) should be notified immediately at* CCI [redacted] *Include any available information at the time of the incident and copies of all documentation, if any, supporting the suspicion.*	To identify a contact email for serious breaches
10.1.4. Informed Consent Process	**"if applicable" was added after legally authorized representative.** Additional Consents The *main* ICF will contain separate sections for the following additional consents:	To clarify additional informed consent forms

Section No. and Name	Description of Change	Brief Rationale
	~~• Optional sampling for additional receptor occupancy testing (see Section 8.11.1 and the SoA in Section 1.2).~~ • Optional ~~sampling~~ *collection of blood, colonic tissue, and stool samples* for future PD, ~~and~~ microbiome-related analyses *and future research, and use of the remaining blood and colonic tissue samples from the study-required procedures for future research, including future PK research* (see Section*s 8.7.1, 8.10,* 8.12*,* and the SoA in Section 1.2). • Optional *blood* sampling for future pharmacogenomics analysis, which will involve genetic testing (see Section 8.12, Section 10.9, and the SoA in Section 1.2). *Additional ICFs will be provided to participants or their partners for review and signature, as needed:* *• Optional Maintenance Extension (see Section 4.1 and the SoA in Section 1.2)* • Consent to courier deliveries/pick-ups (see Section 8.13) *• Pregnant Partner (see Section 8.9.5)*	
10.1.5. Data Protection	• Organizational and technical arrangements that will be implemented to avoid unauthorized access, disclosure, dissemination, alteration, or loss of personal data ~~processed~~ must be described.	To clarify data protection
10.1.9. Data Quality Assurance	All participant data relating to the study will be recorded on paper-based *Case Report Forms (*CRFs*)* or eCRFs unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for *having quality system processes and procedures in place* verifying that *CRF* data entries *against source data* are accurate and correct ~~by~~. *The Investigator is responsible for ensuring source records are maintained in real-time, eCRFs are completed per eCRF Completion Guidelines,* and physically or electronically signing the CRF. Guidance on completion of CRFs *and eCRFs* will be provided in the corresponding guidelines. The Sponsor or designee is responsible for the data management of this study, including ~~quality checking of the data~~*scheduled data audits and verification against original source data/documentation.* Essential *source* documents for this study should be retained by the Investigator/institution until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. *Please reference ICH E6 (R2) Section 8 for the minimum list of essential documents required for the conduct of a clinical trial. Additional documentation may be required by the Sponsor or CRO before, during, and after completion of the trial.*	To clarify the responsibilities of the Investigator and data quality assurance
10.1.10. Source Documents	Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site *and digitized copies are maintained in the site section of the electronic Trial Master File.* Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained~~.~~ *by the Investigator and documented in the CRF*. The Investigator may need to request previous ~~medical records or transfer records, depending on the study. Also,~~*and* current medical records ~~must be available~~*or transfer records as source documents for participants involvement (or enrollment) in this study.*	To clarify the management of documents

Section No. and Name	Description of Change	Brief Rationale
	The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF *and eCRF*. *Sponsor-designated* study monitors will perform ongoing source data verification to confirm that data entered into the CRF*/eCRF* by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.	
10.1.11.2. Study/Site Termination	A study site is considered closed when all required documents and study supplies have been collected*, all quality compliance activities have been completed,* and a study site closure visit has been performed. •Total number of participants ~~included~~*enrolled* earlier than expected	To clarify study/site termination
10.3. Appendix 3: Clinical Laboratory Tests- Table 10.	**Table 10. Protocol-required Laboratory Tests. Addition of other tables required renumbering the table from Table 6 to Table 10.**	Renumber of tables due to addition of tables
10.3. Appendix 3: Clinical Laboratory Tests – Table 10.	Table 10. Protocol-required Laboratory Tests Coagulation • *a*PTT	To update coagulation parameters
10.3. Appendix 3: Clinical Laboratory Tests – Table 10.	Table 10. Protocol-required Laboratory Tests Pregnancy testing • Urine hCG test (at ~~Visits 2–11~~*all subsequent visits* for women of childbearing potential only) [a]	To align with Section 8.8.6.
10.3. Appendix 3: Clinical Laboratory Tests – Table 10.	Table 10. Protocol-required Laboratory Tests • SARS-CoV-2 test (test to be determined by *the* site) • Tuberculosis test (CCI test~~, with~~ *to be determined by the site*)	To align with other sections of the protocol
10.3. Appendix 3: Clinical Laboratory Tests – Table 10.	Table 10. Protocol-required Laboratory Tests Abbreviations: *aPTT, activated partial thromboplastin time* ~~ESR, erythrocyte sedimentation rate~~ ~~PTT, partial thromboplastin time~~	To update abbreviations
10.3. Appendix 3: Clinical Laboratory Tests – Table 11.	**Table 11. Abnormal Liver Function Results: Re-testing and Follow-up Procedures. Addition of other tables required renumbering the table from Table 7 to Table 11.**	Renumber of tables due to addition of tables
10.3. Appendix 3: Clinical Laboratory Tests – Table 11.	Table 11. Abnormal Liver Function Results: Re-testing and Follow-up Procedures *Re-test Review*	To clarify, a cell was added
10.4.4. Reporting of SAEs	**"Event" was replaced by "The SAE".**	To align with the section
10.5.2. Contraception Guidance	• Bilateral tubal occlusion*/ligation*	To clarify contraception

Section No. and Name	Description of Change	Brief Rationale
10.7. Appendix 7: Mayo Clinic Scoring System for Assessment of Ulcerative Colitis Activity	Endoscopy: The endoscopy subscore will be determined ~~both locally and~~ centrally by qualified personnel.	To align with Section 8.7.1.
11. References	[redacted]. Package insert. Takeda Pharmaceuticals America, Inc., ~~2020~~*2022*.	To update protocol references

Version 2.1 dated 26 April 2023

Overall Rationale for the Amendment

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

- Add a 52-week Maintenance Extension following the 52-week Treatment Period, add corresponding endpoints, and update the study design/schema and statistical analyses
- Clarify the enrollment plan for prior advanced therapy-experienced participants
- Extend the Screening Period to ensure sufficient time for screening activities
- Revise the Inclusion/Exclusion criteria regarding inadequate response, washout criteria of prior UC therapy, tuberculosis screening, and testing of SARS-CoV-2
- Update the Schedule of Activities for clarity and add study activities for the Maintenance Extension Period
- Remove the Week 24 clinical improvement assessment timepoint
- Revise the sequence of events for Week 12, Week 52/EOT, and Week 104/LTE EOT wherein the endoscopy occurs during Stage 1, followed by the clinic visit at Stage 2
- Add a follow-up contact on the day after the Week 12 clinic visit to ensure participants begin using the study drugs for the Maintenance Period
- Update risks of MORF-057
- Clarify the re-screening process and the blinding process after Week 12
- Specify the process of reporting and capturing the overdose information
- Clarify the acceptable use of aspirin
- Clarify the discontinuation/withdrawal criteria regarding lack of efficacy, ineligible participants, and male participant whose partner becomes pregnant
- Specify the number of biopsies for histopathology and the optional future research
- Clarify the additional informed consents

This protocol amendment is considered Substantial by the Sponsor, according to the criteria specified in the European Union Clinical Trials Regulation 536/2014.

Protocol Summary of Changes Table

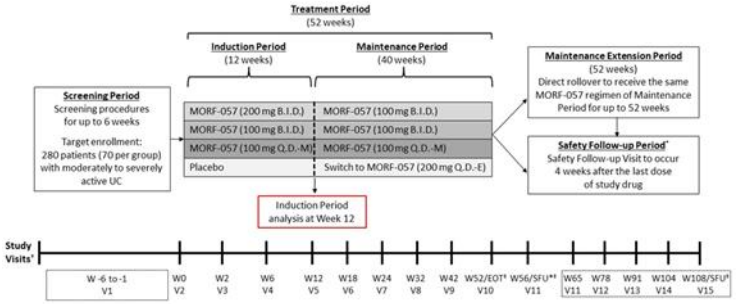
This protocol amendment is considered Substantial by the Sponsor, according to the criteria specified in the European Union Clinical Trials Regulation 536/2014. Changes to the protocol as implemented by this amendment are summarized in the Summary of Changes table below. New text is shown in *italics*, deleted text is shown in ~~strikeout~~, and **bold** text is informational. In addition to the changes provided in the Summary of Changes table, minor editorial changes have been made throughout the protocol.

Section No. and Name	Description of Change	Brief Rationale
Global change	**'Patients' was changed to 'participants' throughout the Protocol when referring to a study participant.**	Administrative change
Global change	~~TNF~~ *TNF-α*	To correct protein name
Abbreviations	~~5-ASA 5-aminosalicylates~~ ~~AST Aspartate transaminase~~ ~~AUC_{0-12} Area under the concentration-time curve from time 0 to 12 hours post-dose~~ ~~AUC_{tau} Area under the concentration-time curve across the dosing interval~~ ~~C_{12} Plasma concentration at 12 hours post-dose~~ *C. difficile* *Clostridiodes difficile* *CI* *Confidence interval* *CMH* *Cochran-Mantel-Haenszel* *CRA* *Clinical Research Associate* *CRO* *Contract Research Organization* EDC Electronic data capture~~ database~~ *EEA* *European Economic Area* ~~ESR Erythrocyte sedimentation rate~~ *FSH* *Follicle-stimulating hormone* *HRT* *Hormonal Replacement Therapy* *IBDQ* *Inflammatory Bowel Disease Questionnaire* IC_{90} 90% *of maximal* inhibitory concentration ICH International Council for Harmonisation ~~of Technical Requirements for Pharmaceuticals for Human Use~~ *IGRA* *Interferon gamma release assay* ~~MDRD Modification of Diet in Renal Disease~~ ~~M~~*m*MCS Modified Mayo Clinic Score *mRNA* *Messenger ribonucleic acid* ~~PI Principal Investigator~~ *PP* *Per Protocol* *PRO* *Patient-reported outcome* *Q.D. – E* *Once a day (evening)* *Q.D. – M* *Once a day (morning)*	To update the abbreviations used throughout the protocol

Section No. and Name	Description of Change		Brief Rationale
	~~RO Receptor occupancy~~ *SC* *Subcutaneous* TNF-*α* Tumor necrosis factor *alpha* *WOCBP* *Woman of Childbearing Potential* *WONCBP* *Woman of Non-childbearing Potential*		
1.1. Synopsis – Objectives and Endpoints 3. Objectives and Endpoints	To determine time to symptomatic response by Week 12	• Time to symptomatic response by Week 12 as determined using the *Partial* mMCS	To clarify the endpoint
1.1. Synopsis – Objectives and Endpoints 3. Objectives and Endpoints	*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*	To include endpoints corresponding to the Maintenance Extension
1.2. Synopsis – Efficacy Analysis Definitions 3. Objectives and Endpoints	Histologic remission by RHI: RHI ≤~~3~~*2* (with 0 for lamina propria neutrophils score and neutrophils in the epithelium score and without ulcers or erosions)		To clarify efficacy analysis definitions
1.2. Synopsis – Efficacy Analysis Definitions 3. Objectives and Endpoints	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~~*12* consecutive weeks prior to Week 52.		To clarify efficacy analysis definitions

Section No. and Name	Description of Change	Brief Rationale
1.1. Synopsis – Overall Design 4.1. Overall Design	**The overall design section was reorganized for clarity and updated to reflect study changes. Text revisions are summarized below.**	To reorganize paragraphs for clarity
1.1. Synopsis – Overall Design 4.1. Overall Design	~~For each treatment group, the~~*The* study will enroll ~~at least 30% of the participants from each of the~~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)~~ strata~~, *with at least 30%* but no more than 40% of ~~the~~ advanced therapy-experienced ~~patients~~*participants*.	To clarify the enrollment plan for prior advanced therapy-experienced participants
1.1. Synopsis – Overall Design 4.1. Overall Design	~~This~~*The main part of this* Phase 2b study will consist of ~~3 study periods:~~ a Screening Period (up to ~~4~~ *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 ~~-4~~*-6* to -1), multiple Treatment Visits (Visits 2-10 at Weeks 0, 2, 6, 12, 18, 24, ~~36~~*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 ~~Visit 11~~ at Week 56 if the full *Treatment Period*~~study~~ is completed or earlier if treatment is discontinued early).	To reflect the expanded Screening Period
1.1. Synopsis – Overall Design 4.1. Overall Design	*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.*	To reflect the addition of the 52-week Maintenance Extension Period
1.1. Synopsis – Overall Design 4.1. Overall Design	~~Any participant who has not shown clinical improvement (as determined by the Investigator) by Week 24 will be discontinued from the study following an End of Treatment (EOT) Visit and a SFU Visit.~~	To remove the Week 24 clinical improvement assessment timepoint
1.1. Synopsis 4.1. Overall Design 6.1. Study Treatment Description	**Descriptions of study treatment in the synopsis section were consolidated and updated to reflect study changes. Maintenance Extension Period (52 Weeks) was added to the dosing regimens for the 4 treatment groups and Table 4 in Section 6.1.** ~~After completion of the 12-week Induction Period, all participants randomized into the placebo group (Group 4) will be switched to receive an active MORF-057 regimen during the Maintenance Period. The dosing regimens for the 4 treatment groups during the Induction and Maintenance Periods are shown below.~~	To reflect the addition of the 52-week Maintenance Extension Period

<table>
<tr><th>Section No. and Name</th><th>Description of Change</th><th>Brief Rationale</th></tr>
<tr><td></td><td>Study Treatment:
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<s>treatment phase</s> 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.-EJ) 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. <s>Participants</s> All participants who <s>complete</s>choose to continue in the <s>final SFU Period, including the Week 56 Visit (4 weeks after</s>Maintenance Extension will continue receiving the <s>last dose of</s>same MORF-057<s>), will have a maximum time on study of 60</s> 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>
<tr><td></td><td>Induction Period (12 Weeks)</td><td>Maintenance Period (40 Weeks)/
Maintenance Extension Period
(52 Weeks)</td></tr>
<tr><td>Group 1</td><td>MORF-057 (200 mg B.I.D.)</td><td>MORF-057 (100 mg B.I.D.)</td></tr>
<tr><td>Group 2</td><td>MORF-057 (100 mg B.I.D.)</td><td>MORF-057 (100 mg B.I.D.)</td></tr>
<tr><td>Group 3</td><td>MORF-057 (100 mg Q.D.-M)</td><td>MORF-057 (100 mg Q.D.-M)</td></tr>
<tr><td>Group 4</td><td>Placebo</td><td>MORF-057 (200 mg Q.D.-E)</td></tr>
</table>
<s>The Sponsor may decide to allow participants to continue receiving MORF-057 by adding a Maintenance Extension Period via a subsequent regulatory submission. In this case, participants who complete the 52-week Treatment Period and associated assessments will continue receiving MORF-057 through the Maintenance Extension Period before completing the SFU Period.</s></td><td></td></tr>
<tr><td>1.1. Synopsis – Study Treatment</td><td>The study drug will be supplied as IR capsules for oral administration (MORF-057 100 mg capsule or placebo). 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.” Each participant <s>may</s>will be instructed to take <s>up to</s> 4 capsules per day during the Induction Period and 3 capsules per day during the Maintenance Period/Maintenance Extension Period<s>depending on the number of bottles dispensed to the participant</s>.</td><td>To clarify treatment description and add the Maintenance Extension Period</td></tr>
</table>

Section No. and Name	Description of Change	Brief Rationale
1.1. Synopsis – Study Schema 4.1. Overall Design	**The study schema and corresponding footnotes were updated to include the 52-week Maintenance Extension Period. The new schema also shows the expanded Screening Period.** 	To reflect the addition of the 52-week Maintenance Extension Period and the expanded Screening Period
1.1. Synopsis – Study Schema 4.1. Overall Design	Study Schema: Abbreviations: ~~D, day;~~ ~~P.O., by mouth~~ *V, visit;* ~~§ Sponsor may decide to allow participants to continue receiving MORF-057 by adding a Maintenance Extension Period via a subsequent regulatory submission.~~	To reflect updated study schema
1.1. Synopsis – Main Inclusion Criteria 5.1. Inclusion Criteria	Type of Participant and Disease Characteristics Note: ~~Patient~~*Participant* cannot have had inadequate response, loss of response, or intolerance to more than 3 drugs in 2 classes of the following advanced therapies: c. JAK antagonists, including tofacitinib *or upadacitinib* e. Any investigational product with the same mechanism as one of those outlined above (a through d) *or a novel mechanism of action* Note: ~~Patient~~*Participant* who have a history of primary non-response to 2 *or more* of the advanced therapy classes above will not be eligible. ~~Patient~~*Participant* who have received treatment with these agents at sub-therapeutic doses or durations should be discussed with the Medical Monitor to assess eligibility. 5. Meets the following washout criteria of prior UC therapy relative to study Day 1: c. JAK antagonists, including tofacitinib *or upadacitinib*: at least ~~3 days~~*1 week* d. S1P receptor agonists, including ozanimod: at least ~~8~~ *4* weeks *Note: Participants who do not meet the full washout period but have the results of a local drug concentration level performed during the Screening window deemed by the Medical Monitor to be sub-therapeutic may be eligible for the study earlier than the full washout period.* 6. If the ~~patient~~*participant* has been receiving any of the non-prohibited medications for UC listed below, he/she must discontinue use at least 5 half-lives before study Day 1 or must agree to maintain stable doses	To revise inclusion criteria

Section No. and Name	Description of Change	Brief Rationale
	of these concomitant medications starting from the time specified below until the end of the SFU Period, with the exception of tapering oral corticosteroid dose after 12 weeks of being in the trial. a. *Oral* 5-Aminosalicylates (not exceeding 4.8 g per day): at least 2 weeks prior to study Day 1	
1.1. Synopsis – Exclusion Criteria 5.2. Exclusion Criteria	Medical Conditions 7. Has ~~an~~*a potentially* active bacterial*, viral,* or parasitic pathogenic enteric infection, including ~~Clostridium~~*Clostridiodes* difficile *(C. difficile)*; has hepatitis B or C virus, or human immunodeficiency virus (HIV); had an infection requiring hospitalization or intravenous antimicrobial therapy, or an opportunistic infection within 3 months prior to Screening; had any infection requiring oral antimicrobial therapy within 2 weeks prior to Screening; or has a history of more than 1 episode of herpes zoster or any episode of disseminated herpes zoster infection 8. Has ~~an~~ active ~~or latent~~ tuberculosis (TB), as evidenced by any of the following: a. A diagnostic test for TB performed within 30 days ~~of~~*prior to* Screening or during the Screening Period that is positive, *as* defined ~~as~~ *below*: • *A positive interferon gamma release assay (IGRA) test (e.g.,* ~~Positive~~ [redacted] *TB* test*)* or 2 consecutive indeterminate [redacted] *IGRA* tests OR • A purified protein derivative (PPD) skin test ≥5 mm b. ~~Chest~~*A chest* X-ray *or imaging per local guidelines* within 3 months ~~of~~*prior to* Screening where active or latent pulmonary TB cannot be excluded *Note: Participants who have tested negative for TB at a certified local lab using an IGRA test within 3 months prior to Screening are not required to repeat this test during the Screening Period if that participant has no clinical signs or symptoms of TB and no known exposures/increased risk factors since the last negative TB test (according to the Investigator's clinical judgement), and the test result is available in the participant's medical record* Note: ~~Patients~~*Participants* with a history of latent TB may be enrolled if ~~it is being treated per local~~*they complete an assessment for evidence of active TB versus latent TB. Documentation will include a chest X-ray or imaging* per local *guidelines during the Screening Window and no signs, symptoms, or evidence of ongoing active TB. Participants have had treatment per the local* standard *of* care *for a minimum of 2 weeks* before *the* first dose of study drug ~~with no evidence of ongoing active TB or who have~~*OR* documentation of completing appropriate treatment for latent TB within 2 years before Day 1 ~~Participants with inadequate documentation of treatment should be cleared by a TB specialist before enrollment~~*of the study. See Section 8.2.2.1 for more details.* 9. ~~Tests positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) during the Screening Period. Testing to be performed according to site-specific testing procedures and country-specific requirements.~~*Has a positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) test result during the Screening Period. Testing for SARS-CoV-2 is required only per local regulations. Participants who have a positive test result can be randomized after a subsequent negative test result during the Screening Period.*	To revise exclusion criteria

Section No. and Name	Description of Change	Brief Rationale
	16. g. International normalized ratio >1.5. *Participants with an international normalized ratio >1.5 due to anticoagulant therapy (e.g., Coumadin) may only be enrolled after a consultation with the Medical Monitor.*	
1.1. Synopsis – Study Treatment	~~Study Treatment:~~ ~~MORF-057 is a small molecule therapy that selectively inhibits the α4β7 integrin. The study drug will be supplied as immediate-release capsules for oral administration (MORF-057 100 mg capsule or placebo). The dose regimens for the 4 treatment groups are provided below:~~	To update for clarity
1.1. Synopsis – Statistical Methods: Primary Efficacy Endpoint 9.2.3.1. Primary Efficacy Endpoint	The primary analysis will be repeated on the PP Population as a sensitivity analysis. Other sensitivity analyses for the primary efficacy endpoints may also be performed as appropriate. The primary efficacy endpoint will be analyzed for the subgroups defined based on ~~some~~*selected* categorized demographic and baseline variables, e.g., age, gender, race, exposure to an advanced therapy treatment for UC (advanced therapy-naïve and advanced therapy-experienced). The details will be described in the *Statistical Analysis Plan (*SAP*)*.	To clarify the primary efficacy endpoint
1.1. Synopsis – Statistical Methods: Exploratory Efficacy Endpoints 9.2.3.3. Exploratory Efficacy Endpoints	All the continuous exploratory efficacy endpoints expressed as change from baseline at Week 12 as defined in Section 3 (e.g., non-endoscopic biomarkers *of inflammation*, PROs) will be 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.	To identify the type of biomarkers
1.1. Synopsis – Statistical Methods: Safety Analyses 9.2.4. Safety Analyses	The safety analyses will be performed for the 12-week Induction Period ~~and~~*,* the~~ overall~~ 52-week Treatment Period*, and the 52-week Maintenance Extension Period plus the Safety Follow-up Period*. In the safety analyses for the 12-week Induction Period, the participants initially randomized into the placebo group and switched to an active MORF-057 regimen after the Week 12 assessments will be analyzed as the placebo group. In the safety analyses for the ~~overall~~ 52-week Treatment *Period and 52-week Maintenance Extension* Period, the placebo recipients switched to an active MORF-057 regimen will be analyzed according to the active MORF-057 regimen they received after Week 12, and their data will be presented separately based on only the safety data collected after the *start of the MORF-057 dose.* ~~Week 12 assessments, i.e., during the 40-week Maintenance Period and Safety Follow-up Period~~.	To add safety analyses of the Maintenance Extension
1.1. Synopsis – Statistical Methods: Pharmacodynamics Analyses 9.2.6. Pharmacodynamics Analyses	The exploratory PD endpoints (changes over time in $\alpha_4\beta_7$ and $\alpha_4\beta_1$ receptor ~~occupancy,~~*occupancies and* blood CCR9 mRNA level~~, and blood lymphocyte subsets~~) will be summarized descriptively. Additional analysis of PD endpoints may be described in a biomarker analysis plan separate from the study SAP and reported separately. The PD Population will be used for the summarization and analysis of PD exploratory endpoints. **Section 9.2.6.** The exploratory PD endpoints (changes over time in α4β7 ~~receptor occupancy, changes over time in~~ *and* α4β1 receptor ~~occupancy,~~*occupancies and* blood CCR9 mRNA level~~, and blood lymphocyte subsets~~) will be summarized descriptively.	To clarify how the exploratory PD endpoints will be reported
1.1. Synopsis – Statistical Methods:	Analyses for Induction Period ~~and Total~~*, 52-week* Treatment Period*, and Maintenance Extension Period*	To add statistical analyses of the

Section No. and Name	Description of Change	Brief Rationale
Analyses for Induction Period, 52-week Treatment Period, and Maintenance Extension Period 9.3. Analyses for Induction Period, 52-week Treatment Period, and Maintenance Extension Period	The *Treatment Period in the main part of the* study includes ~~2 treatment periods:~~ the 12-week Induction Period and the 40-week Maintenance Period. For the purpose of statistical analyses, the Induction Period and the Maintenance Period will be treated as 2 independent parts. There will be 2 analyses planned: one for the 12-week Induction Period (i.e., the period for the primary efficacy endpoint) and one for the 52-week ~~Total~~ Treatment Period (i.e., the 12-week Induction Period plus the 40-week Maintenance Period and Safety Follow-up *Period*). *The details of the analyses will be described in the SAP. The results for the main part of the study will be reported in the Clinical Study Report.* *Additional analysis of the optional 52-week Maintenance Extension Period for the participants enrolled into the Maintenance Extension will also be performed as appropriate. The results for the Maintenance Extension will be reported in a Clinical Study Report Addendum.* <u>Induction Period Analysis</u> The analysis of the 12-week Induction Period will be performed after all the participants have completed the ~~Induction Period (i.e., completed the~~ Week 12 ~~visit~~*assessments* or discontinued the study before the Week 12 assessment*s*~~)~~. The analysis will formally evaluate the ~~efficacy (including the~~ primary and secondary efficacy endpoints, ~~and~~ all the exploratory *efficacy* endpoints defined by Week 12~~)~~*,* and safety of MORF-057 vs. placebo during the 12-week Induction Period. The PK and PD data *during the 12-week Induction Period* will also be summarized. ~~Total~~ *52-week* ~~Total~~ Treatment Period Analysis The analysis of the 52-week ~~Total~~ Treatment Period 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 ~~Total~~ Treatment Period *(*and the Safety Follow-up Period *for participants not rolling over into the Maintenance Extension Period)*. The cumulative data, including those from the Induction Period, will be used in this analysis. *<u>Maintenance Extension Analysis</u>* *The analysis of the Maintenance Extension will be performed after all the participants enrolled into the Maintenance Extension have completed the 52-week Maintenance Extension Period and the Safety Follow-up Period or discontinued the study before the Week 104 assessment. The analysis will evaluate the safety of MORF-057 and selected efficacy endpoints as appropriate during the Maintenance Extension plus the Safety Follow-up Period.*	Maintenance Extension and clarify each analysis period
1.2. Schedule of Activities (SoA)	**Section 1.2. was updated to reflect the changes in study procedures. Table 1 Schedule of Activities for the Treatment Period was added. A new SoA table (Table 2) identifies the timepoints and assessments of the Maintenance Extension Period. Addition of these 2 tables required renumbering tables.** *The SoA for the Treatment Period is provided in Table 1. The SoA for the Maintenance Extension Period is provided in Table 2.* Abbreviations: ~~Clostridium~~*Clostridiodes*	To reflect changes to the Induction Period and include activities during the Maintenance Extension Period

Section No. and Name	Description of Change	Brief Rationale
	ICF, Informed Consent Form; *IGRA, interferon gamma release assay;*	
1.2. Schedule of Activities (SoA)	**The SoA Table 1 was updated to clarify the Induction and Maintenance Periods, reflect the expanded Screening Period, add Stage 1 and 2 at Visits 5 and 10 with testing updated per respective stage, collect information on participant's change in substance use at Stage 2 of Visits 5 and 10/EOT, remove Visit 11 from the SFU label, add /EOT to the corresponding mentions of Visit 10, clarify SARS-CoV-2 and TB testing, clarify back-up stool collection at Screening Stage 1 and optional stool collection for future research, clarify PK time windows, clarify endoscopy biopsies, include informed consent for the Maintenance Extension, remove the Week 24 clinical improvement review, and add confirm initiation of study drug for the Maintenance Period at Visit 5 Stage 2.**	To update study activities during the 52-week Treatment Period
1.2. Schedule of Activities (SoA)	**Dispense study drug was added to Visit 10.**	To update study activities
1.2. Schedule of Activities (SoA)	**Table 1, Footnote "b":** No specific tests *or procedures* are required for unscheduled visits. Results of any study procedures performed at an unscheduled visit will be recorded and collected for the study. ~~b.~~ Clinically relevant laboratory testing or re-testing (e.g., hematology, coagulation, serum chemistry, or urinalysis) may be performed at unscheduled visits.	To clarify study procedures for unscheduled visits
1.2. Schedule of Activities (SoA)	**Addition of definition of Visit 5 Stage 1 and Stage 2 to Table 1, footnote "c" required reorganization of footnotes.**	To include definitions of Visit 5 Stage 1 and Stage 2
1.2. Schedule of Activities (SoA)	**Table 1, Footnote "c":** ~~If participant discontinues early from the study Treatment Period, perform the Visit 10/EOT procedures and schedule Visit 11/SFU for 28 days (+7 days) after the participant takes the last dose of study drug (unless consent is withdrawn).~~ *Visit 5 is split into Stage 1 and Stage 2 to clarify the timing of the endoscopy procedure. The endoscopy procedure at Visit 5 Stage 1 should be performed before the Visit 5 Stage 2 in-clinic assessments have been completed.*	To include timing of the endoscopy procedure
1.2. Schedule of Activities (SoA)	**Addition of definition of Visit 10 Stage 1 and Stage 2 to Table 1, footnote "d" required reorganization of footnotes.**	To include definitions of Visit 10 Stage 1 and Stage 2
1.2. Schedule of Activities (SoA)	**Table 1, Footnote "d":** ~~Participants not participating in Maintenance Extension Period will complete the SFU Visit, which should be performed 28 days (+7 days) after the participant takes the last dose of study drug. Eligible participants who choose to participate in the Maintenance Extension Period after Visit 10/EOT will not attend the SFU Visit.~~ *Visit 10 is split into Stage 1 and Stage 2 to clarify the timing of the endoscopy procedure. The endoscopy procedure at Visit 10 Stage 1 should be performed before the Visit 10 Stage 2 in clinic assessments have been completed.*	To include timing of the endoscopy procedure

Section No. and Name	Description of Change	Brief Rationale
1.2. Schedule of Activities (SoA)	**Table 1, Footnote "~~e~~*e*":** If *the* participant discontinues early from the study Treatment Period, perform the ~~Visit 10/~~EOT procedures and schedule ~~Visit 11/~~SFU for 28 days (+7 days) after the participant takes the last dose of study drug (unless consent is withdrawn).	To clarify the visits after early discontinuation
1.2. Schedule of Activities (SoA)	**Table 1, Footnote "~~d~~*f*":** Participants not participating in *the* Maintenance Extension Period will complete the SFU Visit, which should be performed 28 days (+7 days) after the participant takes the last dose of study drug. Eligible participants who choose to participate in the Maintenance Extension Period after Visit 10~~/EOT~~ will ~~not attend the SFU Visit~~ *complete a separate SFU Visit at Week 108 (Table 2).*	To clarify study procedures
1.2. Schedule of Activities (SoA)	**Table 1, Footnote "~~e~~*g*":** If the participant discontinues early from the study Treatment Period, perform the ~~Visit 11/~~SFU procedures 28 days (+7 days) after the participant takes the last dose of study drug (unless consent is withdrawn).	To reflect the removal of Visit 11
1.2. Schedule of Activities (SoA)	**Table 1, Footnote "~~f~~*h*":** The SFU Visit is to occur 28 days (+7 *days*) after the last dose of study drug is received. If the EOT Visit occurs before Day 365, the day for the SFU Visit can be adjusted according to the date of last study drug dose.	To clarify the timing of the study procedure
1.2. Schedule of Activities (SoA)	**Table 1, Footnote "~~h~~*j*":** Enrollment may occur at any point within a ~~28~~*42*-day window of when all screening procedures have been completed and all results required to assess eligibility are available. *Enrolled participants will be randomized to a treatment group.* Enrollment will usually occur the same day as first dosing, but if dosing the same day is not feasible, then enrollment will be considered Day -1 and first dose will be considered Day 1.	To reflect the expanded Screening Period and clarify study procedures
1.2. Schedule of Activities (SoA) 8.2.2.2. SARS-CoV-2	**Table 1, Footnote "~~i~~*k*":** ~~SARS-CoV-2 test will be performed during the Screening Period according to site-specific procedures and country-specific requirements.~~*Testing for SARS-CoV-2 is required only per local regulations. Participants who have a positive test result will be excluded from randomization until a subsequent test result is negative.* **Section 8.2.2.2.:** ~~All participants will complete SARS-CoV-2 screening to determine eligibility.~~*Testing for SARS-CoV-2 is required only per local regulations. Participants who have a positive test result will be excluded from randomization until a subsequent test result is negative.*	To allow re-testing of participants who tested positive for SARS-CoV-2 during the Screening Period
1.2. Schedule of Activities (SoA)	**Table 1, Footnote "~~j~~*l*":** [redacted] *Participants who have tested* negative *for TB at a certified local lab using an interferon gamma release assay (IGRA) test (e.g.,* [redacted] *TB test) within 3 months prior to Screening are not required to repeat this test* during the Screening Period *if that participant has no clinical signs or symptoms of TB and no known exposures/increased risk factors since* the *last negative TB test (*according to ~~site-specific procedures and country-specific requirements~~ *the Investigator's clinical judgement).* In cases where the [redacted] *IGRA* test is indeterminate, the participant may have the	To clarify TB screening requirements

Section No. and Name	Description of Change	Brief Rationale
	test repeated once, and if their second test is negative, they will be eligible. ~~In the event [redacted] is unavailable, the Investigator has the option to perform a~~*The* purified protein derivative skin test *should be performed when the IGRA test is not possible or if both tests are required by local guidelines.*	
1.2. Schedule of Activities (SoA)	**Addition of review of change in substance use to Table 1, footnote "m" required reorganization of footnotes.**	To include review of change in substance use
1.2. Schedule of Activities (SoA) 5.3. Lifestyle Considerations	**Table 1, Footnote "m":** *Collect information on the participant's change in substance use (e.g., alcohol, tobacco, and drugs).* **Section 5.3.:** No new non-pharmacological therapies should be started during the study period. *Information should be collected on the participant's change in substance use (e.g., alcohol, tobacco, and drugs) per the SoA in Section 1.2.*	To include review of change in substance use
1.2. Schedule of Activities (SoA) 8.8.6. Pregnancy/Menopause Testing	**Table 1, Footnote "~~m~~*p*":** Serum test for follicle-stimulating hormone level to be performed only for female participants of non-childbearing potential ~~who are not surgically sterile~~. **Section 8.8.6.:** A serum test for follicle-stimulating hormone (FSH) level will be performed at Screening only for female participants of non-childbearing potential ~~who are not surgically sterile~~.	To align with central lab processes and Appendix 3
1.2. Schedule of Activities (SoA) 8.6. Stool Collection	**Table 1, Footnote "~~n~~*q*":** Stool collection kits are to be dispensed to participants at the visits indicated. The participant should use this kit to collect one sample at home within 24 hours before the next site visit. The sample should be stored as described in the sample collection instructions and brought to the clinic on the day of the site visit. *If the participant is unable to produce a stool sample at the Stage 1 Screening Visit, they can collect a sample at home and return it to the site.* Note: Sample is to be collected prior to bowel preparation for Visits 5 and 10/EOT. **Section 8.6.:** In addition, stool collection kits are to be dispensed to participants at the visits indicated in the SoA. The participant should use this kit to collect one sample at home within 24 hours before the next site visit. The sample should be stored as described in the sample collection instructions and brought to the clinic on the day of the site visit. *If the participant is unable to produce a stool sample at the Stage 1 Screening Visit, they can collect a sample at home and return it to the site.*	To clarify back-up stool sample collection at Screening Stage 1 Visit
1.2. Schedule of Activities (SoA)	**Table 1, Footnote "~~o~~*r*":** *Participants will be provided the option to participate in the Maintenance Extension Period. Participants who want to continue in the Maintenance Extension will be required to provide informed consent.* ~~If the Sponsor decides to add a Maintenance Extension Period, willing participants should sign the relevant revised ICF, as required.~~	To identify when the separate ICF for the Maintenance Extension Period must be signed

Section No. and Name	Description of Change	Brief Rationale
1.2. Schedule of Activities (SoA)	**Table 1, Footnote "~~p~~*s*":** ECGs to be performed before the AM dose and 2 hours *(±30 minutes)* after the AM dose during the Induction and Maintenance Periods. *ECGs will be obtained after the participant has rested for at least 10 minutes in the supine position.*	To clarify the ECG procedure
1.2. Schedule of Activities (SoA) 8.8.1. Physical Examinations	**Table 1, Footnote "~~q~~*t*":** A complete physical exam is to be performed at Screening and Visit 10/EOT, and a targeted exam may be performed at all other required visits (see Section 8.8.1 for descriptions). For unscheduled visits, the type of exam *(if necessary to be performed at all)* will be at the Investigator's discretion and determined based on the reason for the visit. The Screening exam will include collection of height and weight. **Section 8.8.1.:** A complete physical exam is required at Screening ~~and~~, Visit 10/EOT, and *Visit 14/EOT; and* a targeted exam may be performed at all other required visits. For unscheduled visits, the choice of whether to perform a complete or targeted physical exam *(if necessary to be performed at all)* is at the discretion of the Investigator and will depend on the reason for the unscheduled visit.	To clarify type of physical exam at which timepoints
1.2. Schedule of Activities (SoA) 8.8.2. Vital Signs	**Table 1, Footnote "~~r~~*u*":** Vital signs to be recorded at ~~all~~*most* visits. *At unscheduled visits, vital signs are not required and are at the discretion of the Investigator.* These will include blood pressure, heart rate, respiratory rate, and temperature. *Vital signs are to be taken before blood collection for laboratory tests. Blood pressure and pulse measurements should be preceded by at least 10 minutes of rest for the participant.* **Section 8.8.2.:** Vital signs to be recorded at ~~all~~*most* visits *as summarized in the SoA (Section 1.2). At unscheduled visits, vital signs are not required and are at the discretion of the Investigator.* These will include blood pressure, heart rate, respiratory rate, and temperature.	To clarify the vital signs recording times
1.2. Schedule of Activities (SoA)	**Table 1, Footnote "~~v~~*y*":** PK testing at Visits 2, 3, 5, 7, and 10/EOT: Blood samples will be collected before the AM dose and at 1~~,~~ *(±10 min)*, 2~~,~~ *(±15 min)*, and 4 *(±30 min)* hours after the AM dose. ~~Time windows for PK sampling can be found in Section 8.10.1.~~ *For all pre-AM dose sampling, the samples should be obtained before the AM dose is administered. If consent is provided by the participant, these samples may also be used for future PK research studies.* **Table 1, Footnote "~~w~~*z*":** PK testing at Visits 4, 6, 8, and 9: Blood sample will be collected before the AM dose and 1 hour *(±10 min)* after the AM dose. *For all pre-AM dose sampling, the samples should be obtained before the AM dose is administered. If consent is provided by the participant, these samples may also be used for future PK research studies*.	To clarify the PK samples from participants who consent may also be used for future PK research studies
1.2. Schedule of Activities (SoA)	**Addition of optional stool sample to Table 1, footnote "gg" required reorganization of footnotes.**	To clarify optional stool sample for future research

Section No. and Name	Description of Change	Brief Rationale
1.2. Schedule of Activities (SoA)	**Table 1, Footnote "*gg*":** *Participation in future research sample collection is optional. Fecal samples for microbiome analysis will be collected before the AM dose on Visits 2, 5, and 10/EOT. Fecal samples may be collected at any time on the day prior to the scheduled visit day.*	To clarify optional stool sample for future research
1.2. Schedule of Activities (SoA)	**Removal of footnote "hh" Table 1 required reorganization of footnotes.** ~~Any patient who has not shown clinical improvement (as determined by the Investigator) by Week 24 will be discontinued from the study following an EOT Visit and a SFU Visit.~~	To remove the Week 24 clinical improvement assessment timepoint
1.2. Schedule of Activities (SoA)	**Table 1, Footnote "~~dd~~*hh*":** Full colonoscopy is optional at any timepoint if the Investigator deems it necessary. However, if the ~~patient~~*participant* has had UC for over 7 years, he/she must undergo a full colonoscopy (rather than sigmoidoscopy) at Screening if a full colonoscopy has not been performed in the last 2 years. ~~Colonic mucosa biopsies will be collected for histopathology and optional future research studies.~~	To identify the number of biopsies for histopathology and the optional future research (for participants who consent) and clarify the procedures
1.2. Schedule of Activities (SoA)	**Addition of a separate footnote on the specifics of the Screening endoscopy biopsies to Table 1, footnote "ii" required reorganization of footnotes.**	To clarify the Screening endoscopy biopsies
1.2. Schedule of Activities (SoA)	**Table 1, Footnote "*ii*":** *During the Screening endoscopy, up to 6 colonic mucosa biopsies will be collected. Two biopsies for the required histopathology must be collected from the worst inflamed area, 15-25 cm from the anus. Record the extent of disease in centimeters from the anal verge. If consent is provided by the participant, 4 additional mucosa biopsies may be collected for the optional future research studies (2 biopsies from the worst inflamed area and 2 from a non-inflamed/least inflamed area). If consent is provided by the participant, any remaining tissue from the required histopathology biopsies may be used for future research studies. See Section 8.7.1 for details on biopsy requirements.*	To clarify the Screening endoscopy biopsies
1.2. Schedule of Activities (SoA)	**Table 1, Footnote "~~ee~~*jj*":** The Visit 5 *Stage 1* endoscopy procedure should be performed ~~after~~*before* the in-clinic assessments *at Visit 5 Stage 2* have been completed.	To clarify the timing of the Visit 5 endoscopy
1.2. Schedule of Activities (SoA)	**Table 1, Footnote "~~ff~~*kk*":** For the Visit 10/EOT endoscopy procedure, there is a window of ~~±~~+7 days from the actual visit date. For participants who discontinue treatment before Week 6, a repeat sigmoidoscopy will be performed any time after MORF-057 dosing Day 14. For participants who discontinue treatment after Week 6, a repeat sigmoidoscopy will be performed any time. *Participants who complete the EOT Visit within 2 months after the Week 12 endoscopy are not required to repeat the procedure.*	To clarify the endoscopy requirements
1.2. Schedule of Activities (SoA)	**Addition of a separate footnote on the endoscopy biopsy specifics of the Visit 5 Stage 1 and Visit 10/EOT Stage 1 to Table 1, footnote "ll" required reorganization of footnotes.**	To clarify the Visits 5 and 10/EOT endoscopy biopsies

Section No. and Name	Description of Change	Brief Rationale
1.2. Schedule of Activities (SoA)	**Table 1, Footnote "*ll*":** *Collect up to 6 biopsy samples total (2 for required histopathology and 4 for optional future research studies [if consent is provided by the participant]). If consent is provided by the participant, any remaining tissue from the required histopathology biopsies may be used for future research studies. All biopsies should be collected from the same distance from the anus as collected at the Screening Visit, regardless of the tissue state at the time of the sampling. Record the extent of disease in centimeters from the anal verge. Record the number of centimeters from the anus in which biopsies are collected at all follow-up visits into the Requisition Form.*	To clarify the Visits 5 and 10/EOT endoscopy biopsies
1.2. Schedule of Activities (SoA)	**Addition of a footnote on clarifying study treatment handling for participants not participating in the Maintenance Extension Period to Table 1, footnote "nn" required reorganization of footnotes.**	To clarify study treatment handling for participants not participating in the Maintenance Extension Period
1.2. Schedule of Activities (SoA)	**Table 1, Footnote "*nn*":** *Participants not participating in the Maintenance Extension Period should return all study drug to the site. No additional dosing should occur after the completion of the EOT Visit.*	To clarify study treatment handling for participants not participating in the Maintenance Extension Period
1.2. Schedule of Activities (SoA)	**Table 1, Footnote "~~ii~~*oo*":** At Visit 5, the *Induction Period* study drug~~s~~ *kits* supplied at the previous visit should be used for the AM ~~and PM~~ dose. Please note, a new supply of *Maintenance Period* study drug~~s~~ *kits* will be provided at *the conclusion of* Visit 5~~, but the new supply should be started the day AFTER the required sigmoidoscopy is performed. This is to ensure that participants moving onto the Maintenance Period are on the appropriate MORF-057 treatment and dose~~. *Participants should use the Maintenance Period study drug kits for all future doses after the completion of Visit 5.*	To clarify study drug dispensing at Visit 5
1.2. Schedule of Activities (SoA)	**Addition of a footnote on clarifying study drug dispensing at Visit 10/EOT to Table 1, footnote "pp" required reorganization of footnotes.**	To clarify study drug dispensing at Visit 10/EOT
1.2. Schedule of Activities (SoA)	**Table 1, Footnote "*pp*":** *For participants continuing treatment in the Maintenance Extension, additional study drug will be dispensed at Visit 10.*	To clarify study drug dispensing at Visit 10/EOT
1.2. Schedule of Activities (SoA)	**Table 1, Footnote "~~jj~~*qq*":** AM dosing required on-site for all visits except *the* SFU *Visit*.	To align with document
1.2. Schedule of Activities (SoA)	**Table 1, Footnote "~~kk~~*rr*":** At Visit 10/EOT, participants *not participating in the Maintenance Extension Period* will only receive an AM dose for the day. No PM dose will be provided.	To clarify dosing instructions for participants not

Section No. and Name	Description of Change	Brief Rationale
		participating in the Maintenance Extension Period
1.2. Schedule of Activities (SoA)	**Addition of a footnote to add a follow-up contact to Table 1, footnote "ss"**	To add a follow-up contact to ensure participants begin using the study drugs for the Maintenance Period
1.2. Schedule of Activities (SoA) 6.4. Study Treatment Compliance	**Table 1, Footnote "*ss*":** *Site staff will contact the participants, by phone or other forms, on the next business day after the Visit 5 clinic visit is complete to confirm the participants are using the new supply of study drugs for the Maintenance Period. Record the date and time of the participant's first Maintenance Period dose.* **Section 6.4.:** *The site staff will contact participants, by phone or other forms, on the next business day after the Visit 5 clinic visit to confirm the participants have switched from the Induction Period study drug to the new Maintenance Period study drug bottles.*	To add a follow-up contact to ensure participants begin using the study drugs for the Maintenance Period
2.1. Study Rationale	~~Another~~*Other* therapeutic option*s* recently approved for the treatment of UC ~~is~~*are* Janus kinase (JAK) inhibitors, such as the small molecule tofacitinib ([redacted]) *or upadacitinib* ([redacted]).	Upadacitinib was added to reflect currently approved JAK inhibitors
2.3.2.1. Risks of MORF-057	• *Progressive multifocal leukoencephalopathy (*PML*)* is a fatal opportunistic infection of the central nervous system and has been associated with systemic immunosuppressants, including integrin receptor antagonists (e.g., natalizumab and vedolizumab). Natalizumab, a monoclonal antibody that inhibits both $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrins, has been associated with PML, a serious brain infection. One case of PML ~~was reported in a patient treated with vedolizumab ($\alpha_4\beta_7$ integrin antagonist) during post-marketing setting~~ *in an* [redacted] *(vedolizumab)-treated patient with multiple contributory factors has been reported in the post-marketing setting (e.g., human immunodeficiency virus [HIV] infection).* Data from human whole blood ex vivo assay suggests that MORF-057 has significant selectivity (~700 fold at IC_{90}) for binding integrin $\alpha_4\beta_7$ over integrin $\alpha_4\beta_1$. However, out of an abundance of caution, all participants enrolled in this study will be monitored for PML through the use of a PML Risk Assessment and Minimization ~~p~~*P*rogram (RAMP).	To update risks of MORF-057
4.2. Scientific Rationale for Study Design	*The 52-week treatment will be followed by an optional 52-week Maintenance Extension Period. This extension will provide the participants further access to the study drug and collect additional safety and efficacy data up to 104 weeks of exposure.*	To add rationale for adding the Maintenance Extension
4.4. End of Study Definition	A participant is considered to have completed the study if he/she has completed ~~all periods~~*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*.	To define participant study completion

Section No. and Name	Description of Change					Brief Rationale
	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 ~~s~~*S*chedule of ~~a~~*A*ctivities *(SoA)* for the last participant in the *main part of the* study globally.					
5.1. Inclusion Criteria	Weight 9. Has a body mass index (BMI) ≥~~17~~*18*.0 at Screening					To align with synopsis
5.4. Screen Failures	Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened based on discussion and agreement between the Investigator and the Sponsor Medical Monitor. ~~For example, participants who test positive for SARS-CoV-2 during screening can be re-screened once they have a negative PCR test and are symptom free.~~ Re-screened participants should be assigned a new participant number for every ~~s~~*S*creening/re-screening event.					To allow re-testing of participants who test positive for SARS-CoV-2 during Screening
5.4. Screen Failures	*Note: Participants who are unable to complete all required procedures or assessments within the Screening Window due to technicalities may be eligible to extend their Screening Period up to 2 weeks based on an agreement between the Investigator and the Sponsor Medical Monitor. Screening activities that require repeating will be determined by the Sponsor Medical Monitor and the process outlined in the Monitoring Plan.*					To clarify the re-screening process
6.1. Study Treatment Description – Table 3.	**Table 3. Study Treatment was renumbered from Table 1 due to addition of tables.**					To update table numbering
6.1. Study Treatment Description – Table 3.	Packaging and ~~L~~*l*abeling	*30* Capsules are packaged in a high-density polyethylene bottle containing an oxygen absorber canister and coil and closed with a child-resistant cap equipped with a heat-sealed foil liner. Each bottle will be labeled as per country requirements.	*30* Capsules are packaged in a high-density polyethylene bottle containing an oxygen absorber canister and coil and closed with a child-resistant cap equipped with a heat-sealed foil liner. Each bottle will be labeled as per country requirements.			To clarify the number of capsules per bottle
6.1. Study Treatment Description – Table 3.	Abbreviations: ~~B.I.D., twice a day;~~ *IR, immediate-release*.					To update abbreviations for the table
6.1. Study Treatment Description – Table 4.	**Table 4. Treatment Groups was renumbered from Table 2 due to addition of tables.**					To update table numbering
6.1. Study Treatment Description – Table 4.	Group title	Group 1	Group 2	Group 3	Group 4	To include the Experimental Maintenance Period
	Type	• Induction: Experimental • Maintenance */Maintenance Extension*: Experimental	• Induction: Experimental • Maintenance */Maintenance Extension*: Experimental	• Induction: Experimental • Maintenance */Maintenance Extension*: Experimental	• Induction: Experimental • Maintenance */Maintenance Extension*: Experimental	

Section No. and Name	Description of Change					Brief Rationale
	Maintenance Period dosing regimen (40 Weeks)*/ Maintenance Extension Period dosing regimen (52 Weeks)*					
6.3.2. Blinding	This is a double-blind study in which the Sponsor, participants, site staff, *site pharmacy,* Investigators, and outcome~~s~~ assessors will be blinded to the study treatment through Week 12. …. Each participant will receive the same number of "morning bottles" and "evening bottles" according to the respective study period (Induction or Maintenance~~).~~*/Maintenance Extension*). …. ~~The~~*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 ~~within a very small subgroup, including~~*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. If the report requires expedited reporting to one or more regulatory ~~agencies~~*agency*, a copy of the report, identifying the participant's treatment assignment, ~~may~~*will* be sent to the ~~R~~*r*egulatory ~~A~~*a*gency in accordance with local regulations and/or Sponsor policy.					To clarify the blinding process
6.6. Overdose	• Overdose with or without clinical symptoms or abnormal laboratory results should be recorded on the overdose *electronic Case Report Form (e*CRF*) within 24 hours of becoming aware.* • AEs and SAEs associated with overdose will be recorded on the AE ~~CRF~~*eCRF*, and SAEs associated with overdose will be reported via the SAE reporting procedure outlined in Section 8.9.					To specify the process of capturing overdose information
6.7.2. Allowed Medications for the Treatment of Ulcerative Colitis – Table 5.	**Table 5. Corticosteroid Equivalent Doses† was renumbered from Table 3 due to addition of tables.**					To update table numbering
6.7.2.2. Rescue Therapies	*Anti-diarrheals for control of chronic diarrhea and antibiotics for control of infection are not considered rescue medication.*					To align with Section 7.1.1.
6.7.3. Prohibited Medications	• Nonsteroidal anti-inflammatory drugs ~~(NSAIDs)~~ including but not limited to ibuprofen, naproxen, indomethacin, and celecoxib. *(*However, participants may take aspirin for cardio-protection at a dose *as per local guidelines but* not exceeding ~~81~~*325* mg per day*.)*					To clarify the acceptable use of aspirin
6.7.3. Prohibited Medications – Table 6.	**Table 6. Examples of Drugs Potentially Altering Exposures to MORF-057# was renumbered from Table 4 due to addition of tables.**					To update table numbering

Section No. and Name	Description of Change	Brief Rationale
7.1.1. Permanent Discontinuation	• Lack of efficacy, defined as: o Administration of a rescue medication (a new medication or increase in dose of a baseline medication to treat new or unresolved UC symptoms *with the exception of returning the background corticosteroid therapy dose to baseline level*). Anti-diarrheals for control of chronic diarrhea *and antibiotics for control of infection* are not considered rescue medication. • Pregnancy or planned pregnancy *of the female participant or female partner of a male participant as the participant will be unblinded* (see Section 8.9.5) • Non-compliance with study treatment (see Section 6.4) *or study procedures* If a participant who does not meet the enrollment criteria is inadvertently enrolled, that participant must be discontinued from the study drug, and the Sponsor or Sponsor designee must be contacted. *In rare circumstances, consideration may be given to the participant when there is a compelling reason to allow the participant to continue. In these rare cases, the Investigator must obtain documented approval from the Sponsor or Sponsor's designee to allow the participant to continue in the study.*	To clarify permanent discontinuation criteria
7.2. Participant Discontinuation/Withdrawal from the Study	The participant should be encouraged to complete the EOT Visit ~~(Visit 10)~~ at the time of study drug discontinuation and the SFU Visit ~~(Visit 11)~~ at 28 days (+7 *days*) after the last dose of study drug.	To clarify discontinuation procedures
8.1. Medical History	The participant's demographics and complete medical and surgical history, including initial UC diagnosis date~~, UC onset date,~~ and history of UC medication use, will be collected during Screening and recorded in the participant's eCRF.	To clarify medical history details
8.2.2.1. Tuberculosis	All participants will complete TB screening to determine eligibility. Participants with *a negative TB test and chest X-ray (or imaging per local guidelines) not suggestive of* active ~~or~~ *TB may be enrolled. Participants with a history of active TB may be enrolled if it has been adequately treated with no evidence of current active TB. Participants with a positive TB test must be assessed for evidence of active TB versus* latent TB ~~will be excluded, including~~. *Please refer to Table 7 for TB Screening and eligibility details. Exclusion criteria includes* those *participants* with a positive TB diagnostic test *performed* within 30 days ~~of~~*prior to* Screening or during the Screening Period *(e.g., a positive IGRA test such as a* [redacted] *TB test, 2 consecutive indeterminate IGRA tests, or a PPD skin test ≥5 mm)*, and those who had a chest X-ray within 3 months ~~of~~*prior to* Screening where active or latent pulmonary TB could not be ~~ruled out~~*excluded.* The [redacted] *IGRA* test should be performed at Screening on all participants~~.~~, *except for those who have had a confirmed negative IGRA test within 3 months prior to Screening*. The PPD skin test should be	To update the TB test methods

<table>
<tr><th>Section No. and Name</th><th>Description of Change</th><th>Brief Rationale</th></tr>
<tr><td></td><td>performed when the [redacted] IGRA test is not possible or if both tests are required by local guidelines. Test results should be interpreted as shown below:
• For regions that require both [redacted] IGRA and PPD tests, if either test is positive, the TB test is considered positive.
If the [redacted] IGRA test is indeterminate, then the Investigator should perform a second [redacted] IGRA test to rule out a positive test result. If testing remains indeterminate or is positive, then the participant is considered TB positive.
The PPD skin test should be ~~performed when [redacted] test is not possible. PPD should be~~ read by a licensed healthcare professional between 48 and 72 hours after administration. A reaction of induration ≥5 mm is considered a positive reaction.
Participants who have tested negative for TB at a certified local lab using an IGRA test within 3 months prior to Screening are not required to repeat this test during the Screening Period if that participant has no clinical signs or symptoms of TB, no known exposures/increased risk factors since the last negative TB test (according to the Investigator's clinical judgement), and the test result is available and adequately documented in the participant's medical record.</td><td></td></tr>
<tr><td>8.2.2.1. Tuberculosis – Table 7.</td><td>Table 7. Summary of Tuberculosis Screening and Eligibility was added. The table depicts inclusion/exclusion criteria based on IGRA, [redacted] [redacted] TB test results. Addition of the table required renumbering tables.</td><td>To clarify TB testing inclusion/exclusion criteria</td></tr>
<tr><td>8.2.2.1. Tuberculosis – Table 7.</td><td>
<table>
<tr><td>Test Performed Within 30 Days Prior to Screening or During the Screening Period</td><td>Inclusion</td><td>Exclusion</td></tr>
<tr><td>A positive interferon gamma release assay (IGRA) test (e.g., [redacted] [redacted] TB test)</td><td></td><td>X</td></tr>
<tr><td>2 consecutive indeterminate IGRA tests</td><td></td><td>X</td></tr>
<tr><td>A purified protein derivative (PPD) skin test ≥5 mm</td><td></td><td>X</td></tr>
<tr><td>Test Performed Within 3 Months Prior to Screening</td><td>Inclusion</td><td>Exclusion</td></tr>
<tr><td>A chest X-ray within 3 months prior to Screening where active or latent pulmonary TB cannot be excluded</td><td></td><td>X</td></tr>
<tr><td>A negative test for TB at a certified local lab using an IGRA test (e.g., [redacted] [redacted] TB test) within 3 months prior to Screening AND
• Has no clinical signs or symptoms of TB
• No known exposures/increased risk factors since the last negative TB test (according to the Investigator's clinical judgement)
• The test result is available and adequately documented in the participant's medical record
Note: Re-testing is not required at Screening if all the above criteria are met</td><td>X</td><td></td></tr>
</table>
</td><td>To clarify TB testing inclusion/exclusion criteria</td></tr>
</table>

<table>
<tr><th>Section No. and Name</th><th>Description of Change</th><th>Brief Rationale</th></tr>
<tr><td></td><td>
<table>
<tr><td>History of Latent TB</td><td>Inclusion</td><td>Exclusion</td></tr>
<tr><td>Study participants with a positive TB test must be assessed for evidence of active TB versus latent TB. Documentation will include:
Chest X-ray or imaging per local guidelines during the Screening Window
No signs and symptoms (no evidence of ongoing active TB
Study participant is being treated per local standard of care for a minimum of 2 weeks before the first dose of study drug OR
Study participant has documentation of completing appropriate treatment for latent TB within 2 years before Day 1 of the study</td><td>X</td><td></td></tr>
</table>
Abbreviations: IGRA, interferon gamma release assay; PPD, purified protein derivative; TB, tuberculosis.</td><td></td></tr>
<tr><td>8.3.1. Dosing Instructions</td><td>The first dose of the study drug will be administered in the clinic on study Day 1 under the supervision of study personnel. All subsequent doses will be self-administered at home, with the exception of the morning doses for Visits 2-10, which will be administered during the study visits after pre-dose blood samples have been drawn (see details in the SoA, Section 1.2). Participants will be instructed to record all details about the doses administered at home in the Participant Diary.
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).
For the Induction Period, each 30-day study drug supply will consist of 2 cartons (1 for morning and 1 for evening). Inside each carton, there will be 2 corresponding bottles of study drug. Thus, an Induction Period 30-day study drug supply will consist of the following bottles: morning bottle #1, morning bottle #2, evening bottle #1, and evening bottle #2. For the Maintenance Period/Maintenance Extension Period, each 30-day study drug supply will consist of 1 carton. Inside the single carton, there will be 3 bottles of study drug: morning bottle, evening bottle #1, and evening bottle #2.
In the morning, participants should take 1 capsule from EACH “morning bottle.” In the evening, participants should take 1 capsule from EACH “evening bottle.” Each participant ~~may~~will be instructed to take ~~up to~~ 4 capsules per day ~~depending on the number of bottles dispensed to the participant~~during the Induction Period and 3 capsules per day during the Maintenance Period/Maintenance Extension Period.</td><td>To clarify dosing instructions</td></tr>
<tr><td>8.5. Participant Diary</td><td>Participants who remain chronically non-compliant with diary entries despite intervention and follow-up by the Investigator and site team may be subject to discontinuation as per Section 7.1.
Detailed descriptions regarding Participant Diary recordings can be found in the corresponding ~~Study Manual~~Patient Guide.</td><td>To align with Section 7.1. and update the source for</td></tr>
</table>

Section No. and Name	Description of Change	Brief Rationale
		Participant Diary instructions
8.7.1. Endoscopy with Biopsy	Endoscopy will be performed at ~~Stage 2 of~~ Screening (Visit 1) and *during Stage 1 of* Visits 5 ~~and~~, 10/EOT*, and 14/EOT*. Flexible sigmoidoscopy with colonoscopy scope is the suggested procedure, but full colonoscopy is optional at any timepoint if the Investigator deems it necessary. During these procedures, colonic mucosa biopsies will be collected for histopathology and *optional* future research studies. Up to 6 biopsies will be collected during each endoscopy procedure *(2 biopsies for the required histopathology and 4 biopsies for the optional future research). The biopsies for future studies will only be collected from the participants who consent to the optional future research. The remaining tissue from the histopathology biopsies may also be used for future research from participants who consent to the optional future research.* ~~Detailed instructions for endoscopic biopsies (e.g., anatomic site, normal or inflamed mucosa) can be found in the Laboratory Manual. A brief description is provided below:~~ ~~• At Screening (Visit 1), collect 6 biopsy samples total: 4 from the most inflamed/affected area and 2 from a non-inflamed area.~~ ~~o Record the number of centimeters from the anus the biopsy is collected for from inflamed and the non-inflamed area into the Requisition Form Label.~~ ~~o Inflamed biopsies should be collected from the worst affected area, 15-25 cm from the anus.~~ ~~o Non-inflamed biopsies can be collected from anywhere in the colon and are not limited to 15-25 cm from the anus. If there are no non-inflamed areas, biopsies are to be collected from the least inflamed areas.~~ ~~• For follow-up at Visits 5 (Week 12) and Visit 10/EOT biopsies from both the inflamed and non-inflamed areas should be collected from the same distance (cm) from the anus as collected at the Screening Visit. Record the number of centimeters from the anus in which biopsies are collected at all follow-up visits into the Requisition Form.~~ Biopsy specimen transfer, processing, slide preparation, and digitization of slides for histopathologic scoring procedures will be detailed ~~in a~~ *within the applicable Laboratory Manual or* Histopathology ~~Manual~~ *Reference Guide*. Histopathology results will not be made available to study sites *but will be located within the histopathology laboratory database and added to the electronic Trial Master File after the completion of the trial*. The MES will be scored by a central reader. However, treatment decisions *post-randomization* will be made by the treating Investigator. *For all biopsies in Table 8:* • *Record the extent of disease in centimeters from the anal verge* • *Record the distance in centimeters from the anus where biopsies are taken into the Requisition Form* • *Always review the Laboratory Manual for full instructions related to biopsy sample collection containers, labeling, and storage*	To identify the number of biopsies for histopathology and the optional future research and clarify the procedures

<table>
<tr><th>Section No. and Name</th><th>Description of Change</th><th>Brief Rationale</th></tr>
<tr><td></td><td>• Biopsies for histopathology are the required part of the study
• Optional biopsies are only to be taken in participants who have consented for future research</td><td></td></tr>
<tr><td>8.7.1. Endoscopy with Biopsy – Table 8.</td><td>Table 8. Instructions for Endoscopic Biopsies was added to clarify biopsy procedures. Addition of the table required renumbering tables.</td><td>To clarify biopsy procedures</td></tr>
<tr><td>8.7.1. Endoscopy with Biopsy – Table 8.</td><td>
<table>
<tr><td>Visit 1
(Screening)</td><td><u>Worst inflamed area</u>
Take biopsies of the worst inflamed area within 15-25 cm from the anus.
• 2 required biopsies for histopathology
• 2 optional biopsies for future research

<u>Non-inflamed/least inflamed area</u>
Take biopsies from a non-inflamed or least inflamed area of the colon.
• 2 optional biopsies for future research</td></tr>
<tr><td>Visit 5
(Week 12)

Visit 10
(Week 52 or EOT)

Visit 14
(Week 104 or EOT)</td><td><u>Take all biopsies at the same distance (cm) from the anus as collected at Visit 1, regardless of tissue state at the time of the sampling.</u>
• 2 required biopsies for histopathology
• 4 optional biopsies for future research</td></tr>
</table>
Abbreviations: EOT, End of Treatment.</td><td>To clarify biopsy procedures</td></tr>
<tr><td>8.7.3. Mayo Clinic Score</td><td>The Investigator will record the PGA in the site ~~tablet or other relevant device or system~~source documents and eCRF at the specified study visits.</td><td>To clarify the PGA recording procedure</td></tr>
<tr><td>8.8.4. Clinical Safety Laboratory Tests</td><td>If laboratory values from non-protocol-specified laboratory tests performed at the institution’s local laboratory require a change in participant management or are considered clinically significant by the Investigator (e.g., SAE or AE), then the results must be recorded in the EDC database.</td><td>To align with the protocol</td></tr>
<tr><td>8.9.4. Regulatory Reporting Requirements for SAEs, SUSARs, and Periodic Reports</td><td>The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the Member States Concerned, the applicable regulatory authority, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and Investigators.
An Investigator who receives an Investigator Safety Report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator’s Brochure~~ and will notify the IRB/IEC, if appropriate, according to local requirements~~.
Morphic Therapeutic will make the determination whether the event is unexpected. ~~It is the Principal Investigator’s responsibility to notify the IRB/IEC according to the relevant regulatory timelines of all SUSARs of which the Investigator is notified by Morphic Therapeutic that occur at his or her site.~~</td><td>To clarify regulatory reporting requirements for Europe</td></tr>
</table>

<table>
<tr><th>Section No. and Name</th><th>Description of Change</th><th>Brief Rationale</th></tr>
<tr><td>8.9.5. Pregnancy</td><td>Male participant with a partner who becomes pregnant
The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. Pregnancy in a male participant's partner will require unblinding. The male study participant will be withdrawn from the study and the participant should complete the EOT and SFU Visits.
After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours. The female partner will then undergo pregnancy follow-up to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the mother and the neonate, and the information will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure. ~~The male study participant may continue taking the study drug.~~</td><td>To clarify the criteria and procedures for discontinuing a male study participant with a partner who becomes pregnant during the study</td></tr>
<tr><td>8.10.1. Collection of Blood Samples for MORF-057 Concentration Determination in Plasma – Table 9.</td><td>Table 9. Pharmacokinetics Sampling Windows was renumbered from Table 5 due to addition of tables.</td><td>To update table numbering</td></tr>
<tr><td>8.10.1. Collection of Blood Samples for MORF-057 Concentration Determination in Plasma – Table 9.</td><td>Section 8.10.1.:
~~These~~If consent is provided by the participant, these samples may also be used for future PK research studies.
Table 9. Pharmacokinetics Sampling Windows
<table>
<tr><td>Visit</td><td>Collection T~~t~~imepoints and A~~a~~ssociated W~~w~~indows</td></tr>
<tr><td>2, 3, 5, 7, and 10/EOT</td><td>Before AM dose ~~(-60 min)~~ and at 1hr (±10 min), 2hr (±15 min), and 4hr (±30 min) after AM dose</td></tr>
<tr><td>4, 6, 8, and 9</td><td>Before AM dose ~~(-60 min)~~ and 1 hr (±10 min) after the AM dose</td></tr>
</table>
Abbreviations: EOT, End of Treatment; hr, hour; min, minute.
For all pre-AM dose sampling, the samples should be obtained ~~within approximately 60 minutes~~ before the AM dose is administered. ~~Furthermore, the samples should be obtained at 12 hours (60 min) after the previous evening's PM dose.~~</td><td>To clarify the PK samples from participants who consent may also be used for future PK research studies</td></tr>
<tr><td>8.12. Future Research</td><td>~~Blood~~, If consent is provided by the participant, blood, stool, and colonic tissue samples will be collected and may be used for further PD, pharmacogenomics, ~~and~~ microbiome-related research, and future research~~by Morphic Therapeutics~~. If consent is provided by the participant, the remaining blood and colonic tissue samples from the study-required procedures may also be used for future research, including</td><td>To clarify sampling and analyses for future research</td></tr>
</table>

Section No. and Name	Description of Change	Brief Rationale
	future PK research. The purpose of future research is to contribute to the understanding of UC or related diseases, to the development of related or new treatments, or to the development of new research methods. Participation in ~~this~~*the* collection of samples for future research is optional *(see Section 10.1.4 for additional consents)*.	
9. Statistical Considerations	Any ~~deviation~~*change* from the planned statistical analyses specified in the protocol will be fully described in the SAP and Clinical Study Report.	To clarify terminology
9.4. Interim Analysis	*The analysis of the 12-week Induction Period (Induction Period Analysis) 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 9.3.* *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.*	To clarify there is no interim analysis planned for this study
10.1.1. Regulatory and Ethical Considerations	The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to ~~an IRB/IEC by the Investigator and~~, reviewed, and approved by the ~~IRB/IEC~~*Member States Concerned* before the study is initiated. Any amendments to the protocol will require ~~IRB/IEC~~*Member States Concerned* approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants. Protocols and any substantial amendments to the protocol will require ~~health authority~~*Member States Concerned* approval prior to initiation, in line with country-specific requirements. The Investigator will be responsible for the following: ~~• Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC~~ ~~• Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures~~ • Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the ~~IRB/IEC~~*Member States Concerned*, European *Union* Clinical ~~Trials Directive 2001/20/EC or European regulation~~*Trials Regulation* 536/2014 for clinical studies ~~*(as applicable),*~~ and all other applicable local regulations	To clarify regulatory responsibilities for Europe
10.1.1. Regulatory and Ethical Considerations	*If the Investigator identifies a potential instance of a serious breach, the Sponsor and Contract Research Organization (CRO) should be notified immediately at* CCI *Include any available information at the time of the incident and copies of all documentation, if any, supporting the suspicion.*	To identify a contact email for serious breaches
10.1.4. Informed Consent Process	**"if applicable" was added after legally authorized representative.** Each participant or his/her legally authorized representative*, if applicable,* will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, *Member States Concerned,* and the IRB/IEC or study center. Additional Consents The *main* ICF will contain separate sections for the following additional consents:	To clarify additional informed consent forms

Section No. and Name	Description of Change	Brief Rationale
	~~• Optional sampling for additional receptor occupancy testing (see Section 8.11.1 and the SoA in Section 1.2).~~ • Optional ~~sampling~~ *collection of blood, colonic tissue, and stool samples* for future PD*,* ~~and~~ microbiome-related analyses *and future research, and use of the remaining blood and colonic tissue samples from the study-required procedures for future research, including future PK research* (see Section*s 8.7.1, 8.10,* 8.12*,* and the SoA in Section 1.2). • Optional *blood* sampling for future pharmacogenomics analysis, which will involve genetic testing (see Section 8.12, Section 10.9, and the SoA in Section 1.2). *Additional ICFs will be provided to participants or their partners for review and signature, as needed:* *• Optional Maintenance Extension (see Section 4.1 and the SoA in Section 1.2)* • Consent to courier deliveries/pick-ups (see Section 8.13) *• Pregnant Partner (see Section 8.9.5)*	
10.1.5. Data Protection	• …. In particular, the participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate ~~IRB/IEC~~*Member States Concerned* members, and by inspectors from regulatory authorities. • Organizational and technical arrangements that will be implemented to avoid unauthorized access, disclosure, dissemination, alteration, or loss of personal data ~~processed~~ must be described.	To clarify data protection for Europe
10.1.9. Data Quality Assurance	All participant data relating to the study will be recorded on paper-based *Case Report Forms (*CRFs*)* or eCRFs unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for *having quality system processes and procedures in place* verifying that *CRF* data entries *against source data* are accurate and correct ~~by~~. *The Investigator is responsible for ensuring source records are maintained in real-time, eCRFs are completed per eCRF Completion Guidelines,* and physically or electronically signing the CRF. Guidance on completion of CRFs *and eCRFs* will be provided in the corresponding guidelines. The Investigator must permit study-related monitoring, audits~~, IRB/IEC review~~, and regulatory agency inspections and provide direct access to source data documents. The Sponsor or designee is responsible for the data management of this study, including ~~quality checking of the data~~*scheduled data audits and verification against original source data/documentation.* ~~Essential documents for this study should be retained by the Investigator/institution until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor.~~*The contents of the electronic Trial Master File pertaining to the conduct of this study must be retained by the Sponsor and the Investigator for at least 25 years after study completion unless local regulations, institutional policies, or by an agreement with the Sponsor require a longer retention period. However, the medical files of participants shall be archived in accordance with national law.* It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.	To clarify the responsibilities of the Investigator and data quality assurance for Europe

Section No. and Name	Description of Change	Brief Rationale
	Please reference ICH E6 (R2) Section 8 for the minimum list of essential documents required for the conduct of a clinical trial. Additional documentation may be required by the Sponsor or CRO before, during, and after completion of the trial.	
10.1.10. Source Documents	Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site *and digitized copies are maintained in the site section of the electronic Trial Master File.* Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained~~.~~ *by the Investigator and documented in the CRF*. The Investigator may need to request previous ~~medical records or transfer records, depending on the study. Also,~~*and* current medical records ~~must be available~~*or transfer records as source documents for participants involvement (or enrollment) in this study.* The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF *and eCRF*. *Sponsor-designated* study monitors will perform ongoing source data verification to confirm that data entered into the CRF*/eCRF* by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.	To clarify the management of documents
10.1.11.2. Study/Site Termination	A study site is considered closed when all required documents and study supplies have been collected*, all quality compliance activities have been completed,* and a study site closure visit has been performed. • Failure of the Investigator to comply with the protocol, the requirements of the *Member States Concerned,* IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines •Total number of participants ~~included~~*enrolled* earlier than expected If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the *Member States Concerned, the* IRBs/IECs, the regulatory authorities, and any ~~contract research organization(s)~~*CROs* used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements.	To clarify study/site termination for Europe
10.3. Appendix 3: Clinical Laboratory Tests- Table 10.	**Table 10. Protocol-required Laboratory Tests. Addition of other tables required renumbering the table from Table 6 to Table 10.**	Renumber of tables due to addition of tables
10.3. Appendix 3: Clinical Laboratory Tests – Table 10.	Table 10. Protocol-required Laboratory Tests Coagulation • *a*PTT	To update coagulation parameters
10.3. Appendix 3: Clinical Laboratory Tests – Table 10.	Table 10. Protocol-required Laboratory Tests Pregnancy testing • Urine hCG test (at ~~Visits 2-11~~*all subsequent visits* for women of childbearing potential only) [a]	To align with Section 8.8.6.
10.3. Appendix 3: Clinical Laboratory Tests – Table 10.	Table 10. Protocol-required Laboratory Tests • SARS-CoV-2 test (test to be determined by *the* site)	To align with other sections of the protocol

Section No. and Name	Description of Change	Brief Rationale
	• Tuberculosis test (CCI [redacted] test~~, with~~ *to be determined by the site*)	
10.3. Appendix 3: Clinical Laboratory Tests – Table 10.	Table 10. Protocol-required Laboratory Tests Abbreviations: *aPTT, activated partial thromboplastin time* ~~ESR, erythrocyte sedimentation rate~~ ~~PTT, partial thromboplastin time~~ a Local urine testing will be standard for the protocol unless serum testing is required by local regulation or ~~IRB/IEC~~*Member States Concerned*.	To update abbreviations and footnote for Europe
10.3. Appendix 3: Clinical Laboratory Tests – Table 11.	**Table 11. Abnormal Liver Function Results: Re-testing and Follow-up Procedures. Addition of other tables required renumbering the table from Table 7 to Table 11.**	Renumber of tables due to addition of tables
10.3. Appendix 3: Clinical Laboratory Tests – Table 11.	Table 11. Abnormal Liver Function Results: Re-testing and Follow-up Procedures *Re-test Review*	To clarify, a cell was added
10.4.4. Reporting of SAEs	**"Event" was replaced by "The SAE".**	To align with the section
10.5.2. Contraception Guidance	• Bilateral tubal occlusion*/ligation*	To clarify contraception
10.7. Appendix 7: Mayo Clinic Scoring System for Assessment of Ulcerative Colitis Activity	Endoscopy: The endoscopy subscore will be determined ~~both locally and~~ centrally by qualified personnel.	To align with Section 8.7.1.
10.9. Appendix 9: Genetics	• …. Therefore, where local regulations and ~~IRB/IEC~~*Member States Concerned* allow, blood samples will be collected for DNA analysis from consenting participants.	To clarify genetic regulations for Europe
11. References	[redacted]. Package insert. Takeda Pharmaceuticals America, Inc., ~~2020~~*2022*.	To update protocol references

11. References

[redacted]. Package insert. Takeda Pharmaceuticals America, Inc., 2022.

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