A Phase 2 Study of MORF-057, an Oral $\alpha4\beta7$ Integrin Inhibitor in Moderately to Severely Active Ulcerative Colitis

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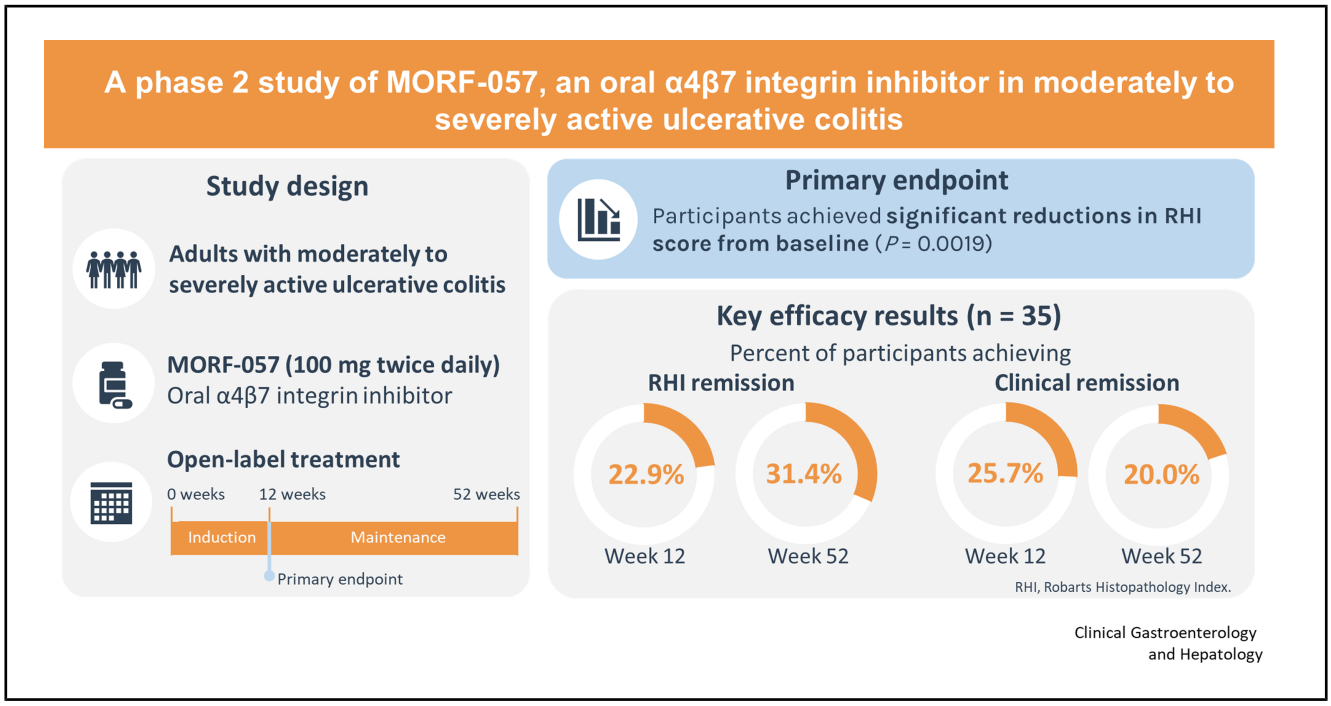

BACKGROUND & AIMS: **MORF-057 is an orally administered small-molecule drug that inhibits $\alpha4\beta7$ integrin-mediated recruitment of $\alpha4\beta7$-expressing lymphocytes to the gut, a process implicated in the pathology of ulcerative colitis (UC). This study evaluated the efficacy, pharmacokinetics, pharmacodynamics, safety, and tolerability of MORF-057 in participants with moderately to severely active UC.**

Abbreviations used in this paper: **AE, adverse event; AT, advanced therapy; CCR9, C-C chemokine receptor 9 gene; C_{max}, maximum observed plasma concentration; CV, coefficient of variation; IL, interleukin; JAK, Janus kinase; MAdCAM-1, mucosal vascular addressin cell adhesion molecule-1; MES, Mayo Endoscopic Score; mMCS, modified Mayo Clinic Score; NI, Nancy Index; PD, pharmacodynamics; PK, pharmacokinetics; RHI, Robarts Histopathology Index; RO, receptor occupancy; SAE, serious adverse event; SD, standard deviation; $t_{1/2}$, half-life; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event; t_{max}, time to reach the maximum observed plasma concentration; TNF, tumor necrosis factor; UC, ulcerative colitis.**

Most current article

1542-3565
https://doi.org/10.1016/j.cgh.2025.07.030

METHODS: **This open-label, phase 2a, single-arm, multicenter trial comprised a 6-week screening period, a 52-week active treatment period (including a 12-week induction period and 40-week maintenance period), and a 4-week safety follow-up period. Of the 35 participants enrolled in the main cohort, 18 participants received 100 mg of oral MORF-057 twice daily for the entire treatment period. The primary efficacy endpoint was a change in the Robarts Histopathology Index (RHI) score from baseline to week 12 and was assessed in all participants with evaluable data. Additional clinical, endoscopic, and histological variables were assessed at screening and at weeks 12 and 52.**

RESULTS: **MORF-057 was well tolerated, and no treatment-emergent serious adverse events were observed. At week 12, participants (n = 35) exhibited a mean change from baseline in RHI score of −6.4 (standard deviation, 11.2). Additionally, 22.9% of participants (8/35) achieved RHI remission (RHI score ≤3). In participants with evaluable data (n = 18), the effects of MORF-057 on pharmacokinetics, pharmacodynamics, and clinical efficacy were achieved at week 12 and remained consistent to week 52.**

CONCLUSIONS: **Overall, this study demonstrated that oral MORF-057 is well tolerated, with promising efficacy for individuals with moderately to severely active UC.**
ClinicalTrials.gov, Number: NCT05291689

Keywords: Clinical Trials; Endoscopy; Pathology; Ulcerative Colitis.

Ulcerative colitis (UC) is a chronic inflammatory bowel disease that commonly presents with blood in the stool and diarrhea.[1] Currently, UC is treated using a stepwise approach—anti-inflammatory drugs are introduced sequentially, with dose escalation guided by response to therapy and disease activity.[1,2] Initial therapy for patients with mild disease activity consists of 5-aminosalicylates or corticosteroids.[1] However, these agents fail to control disease activity in many patients.[3,4] In the past 2 decades, multiple advanced therapies became available for the management of UC, including tumor necrosis factor (TNF) antagonists, vedolizumab, interleukin (IL)-12 and IL-23 antagonists, sphingosine-1-phosphate receptor modulators, and Janus kinase (JAK) inhibitors.[2,5] However, the majority of these agents require parenteral administration, and although JAK inhibitors are effective oral drugs, they have some safety concerns.[2,5] Thus, an unmet need exists for oral advanced therapies that are safe and effective.

Recently, integrins emerged as an effective target for treating UC.[6] Integrin $\alpha4\beta7$ mediates the homing of T lymphocytes to gut-associated lymphoid tissues by binding to mucosal vascular addressin cell adhesion molecule-1 (MAdCAM-1).[7] Notably, MAdCAM-1 is upregulated in intestinal biopsy specimens from patients with UC.[8] Inhibiting $\alpha4\beta7$ integrin in primates resulted in an anti-inflammatory effect in the gut.[9] In phase 3 clinical trials, inhibition of $\alpha4\beta7$ integrin was achieved with vedolizumab, a monoclonal anti-integrin antibody used to treat UC.[10,11] Vedolizumab was approved as an advanced treatment for UC in 2014 in multiple jurisdictions, but it requires parenteral administration.[12,13]

MORF-057 is an orally administered small-molecule drug that selectively inhibits integrin $\alpha4\beta7$ to block recruitment of $\alpha4\beta7$-expressing lymphocytes to the gut.[14] In an ongoing phase 1 program, including 4 completed studies in healthy participants, MORF-057 was well tolerated, with no drug-related safety signals identified.[14] As an oral drug targeting a clinically validated mechanism of $\alpha4\beta7$ integrin inhibition, MORF-057 could be an important therapeutic option for UC, with an advantageous route of administration.[14] Here, we report the efficacy and safety of MORF-057, as well as pharmacokinetic (PK) and pharmacodynamic (PD) measures, from the 52-week treatment period of the EMERALD-1 study.

Materials and Methods

Study Design and Participants

The EMERALD-1 study (NCT05291689) is an open-label, single-arm, multicenter, phase 2a trial consisting of a 6-week screening period, a 52-week active treatment period (with a 12-week induction period and 40-week maintenance period), a 4-week safety follow-up period, and a 26-week extension (Supplementary Figure 1). Participants were 18 to 85 years of age with symptoms of moderately to severely active UC for at least 3 months prior to screening, and a confirmed diagnosis during the screening period (modified Mayo Clinic Score [mMCS] of 5 to 9 with a Mayo Endoscopic Score [MES] $\geq$2 confirmed by a central reader). Other key eligibility criteria, including a Robarts Histopathology Index (RHI) score $\geq$10, are presented in the Supplementary Material.

In the main cohort, participants were naïve to advanced therapy (AT) or experienced prior treatment failure. Participants on prior UC therapy had to meet the washout criteria for the respective therapy class relative to study day 1. Participants receiving any nonprohibited medications for UC, except for tapering oral corticosteroids after week 12, had to discontinue use at least 5 half-lives before study day 1 or agree to maintain stable doses of these concomitant medications for a predetermined time period relative to study dates. Washout periods for stable doses of each medication are listed in the Supplementary Material.

The study also included an exploratory group of participants with intolerance to or secondary nonresponse to vedolizumab, if dosed with vedolizumab within the last 5 years, with their last dose at least 6 weeks prior to study day 1 to allow sufficient washout. Additional details and criteria are in the Supplementary Material.

This study was approved by the Institutional Review Board of Advarra Central (registration number Pro00060075), the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products, and the Ethics Committee of the Silesian Medical Chamber in Katowice. All patients provided written informed consent at the start of the study. All authors had access to the study data and reviewed and approved the final manuscript.

What You Need to Know

Background

There is an unmet need for a safe, effective, and advanced oral therapy for ulcerative colitis. Inhibitors of $\alpha4\beta7$ integrins have emerged as an effective therapeutic target.

Findings

This study provides initial evidence of efficacy, pharmacokinetics, pharmacodynamics, safety, and tolerability of MORF-057, an orally administered small-molecule inhibitor of $\alpha4\beta7$ integrins, to treat moderately to severely active ulcerative colitis.

Implications for patient care

These initial results suggest that MORF-057 is a potentially safe and effective advanced oral therapy for ulcerative colitis, suitable for further development.

Treatment

As an open-label, single-arm study, randomization and blinding were not employed. Participants were dosed orally with 100 mg of MORF-057 (25 mg per immediate-release capsule) twice daily for up to 52 weeks, including the 12-week induction period. Participants underwent 2 screening visits at weeks −6 and −1 and multiple treatment visits at weeks 0, 2, 6, 12, 20, 28, 36, 44, and 52. Upon completion of this treatment period, participants had the option to continue their treatment in a 26-week, long-term extension of the same 100-mg twice-daily dosage. A safety follow-up visit occurred 4 weeks after the last dose of the study drug at the end of the long-term extension, at week 56 for participants who did not continue in the extension, or earlier for those who prematurely discontinued treatment. All dropouts were considered treatment failures in the analysis.

Assessments

Endoscopies were performed at screening and treatment visits at weeks 6 (optional), 12, and 52 or at the end of treatment. At the time of endoscopy, 12 colonic mucosa biopsy specimens were collected for histopathology and subsequent determination of the RHI score and Nancy Index (NI) score. The RHI evaluates chronic inflammatory infiltrate, lamina propria neutrophils, neutrophils in epithelium, and erosion or ulceration; higher scores indicate more severe inflammation.[15] To assess clinical improvement, the mMCS was used. The full MCS is a composite of the MES, MCS stool frequency subscore, MCS rectal bleeding subscore, and Physicians' Global Assessment, whereas the mMCS excluded the Physicians' Global Assessment. Rectal bleeding subscores and stool frequency subscores were calculated based on participant-reported measures from their diaries.

Blood samples were collected at each visit to determine plasma MORF-057 concentration for PK analysis, and for 2 pharmacologically relevant receptor occupancy (RO) assays that assessed drug inhibition of $\alpha4\beta7$ integrin binding to MAdCAM-1 and evaluated drug inhibition of the off-target integrin $\alpha4\beta1$ using a ligand, the Leu-Asp-Val peptide fragment of fibronectin. PK parameters included maximum observed plasma concentration (C_{max}), time to reach C_{max} (t_{max}), and half-life ($t_{1/2}$). Additional blood samples were collected in PAXgene RNA tubes to assess changes in C-C chemokine receptor 9 (*CCR9*) transcript levels, as *CCR9* expression is significantly increased during active intestinal inflammation.[16] More information detailing the complete schedule of activities for both cohorts is provided in the Supplementary Material.

To assess safety, participants received physical examinations (complete physical examination at screening and week 52 or end of treatment), had vital signs recorded, and were administered electrocardiograms and clinical safety laboratory tests (serum chemistry, hematology, coagulation, and urinalysis). Assessments of adverse events (AEs) and serious AEs (SAEs) occurred at each study visit. At screening, participants reported their medical history and underwent testing for pathogens, drugs, and alcohol. Exploratory participants were

screened for blood levels of vedolizumab and anti-vedolizumab antibodies.

Outcomes

The primary efficacy endpoint was the change from baseline to week 12 in RHI score. Additional efficacy endpoints included assessment of clinical improvement at week 12 via change from baseline to week 12 in mMCS and characterization of the PK and PD of MORF-057. Safety and tolerability were assessed via the frequency and proportion of treatment-emergent AEs (TEAEs), treatment-emergent SAEs (TESAEs), and TEAEs leading to study drug discontinuation. Identified AEs were graded according to the Common Terminology Criteria for Adverse Events Version 5 with attribution by the investigator. Exploratory endpoints are described in the Supplementary Material.

Statistical Analyses and Sample Size Estimation

The full analysis dataset was used for efficacy analyses and included all participants in the main cohort and exploratory participants who took $\geq$1 dose of study medication. The safety, PK, and PD populations are described in the Supplementary Material. The study sample was estimated based on the number of participants required to evaluate efficacy in the main cohort. Assuming a 1-sided alpha at 0.025 for the final analysis, a standard deviation (SD) of 12, and a 1-sample t-test, a mean treatment effect of a $\geq$7-point reduction in RHI score could be detected with $>$80% power using 28 participants. Up to 10 additional participants were to be enrolled in the exploratory group. Additional details regarding statistical analyses and sample size estimation are in the Supplementary Material.

Results

Participant Disposition

Thirty-nine participants were enrolled in the study: 35 in the main cohort and 4 in the exploratory group (Figure 1). Baseline demographics and clinical characteristics were similar between the main cohort and exploratory group (Table 1). Overall, 19 participants in the main cohort were male, the mean age was 39.2 years, and the mean years since UC diagnosis was 7.5; only one-quarter of participants used corticosteroids at baseline. Eighteen participants (51.4%) had moderate disease, and 17 (48.6%) had severe disease. In the main cohort, 34.3% of participants had proctosigmoiditis, 28.6% had left-sided colitis, and 28.6% had extensive colitis. The mean fecal calprotectin level was 2043.0 mg/kg (SD, 1827.50 mg/kg). The full 52-week treatment period was completed on November 12, 2023. Eighteen participants in the main cohort completed treatment, were included in the primary analysis, and continued in the long-term follow-up extension.

Efficacy

Main cohort. During the treatment induction period, 3 participants discontinued treatment due to lack of efficacy, and 1 discontinued treatment due to an AE. The 4 participants who discontinued treatment at the week 12 induction phase had RHI and endoscopy data available and were included in the primary endpoint analysis (Figure 1). At 12 weeks, participants achieved significant reductions from baseline in RHI scores (mean change, −6.4; SD, 11.2; $P = .0019$) (Table 2). Additionally, 22.9% of participants (8/35) achieved RHI remission, 34.3% (12/35) achieved an RHI score reduction of $\geq$50%, and 48.6% (17/35) achieved an RHI score reduction of $\geq$7 points (Table 2). Nine participants (25.7%) achieved clinical remission, per mMCS, with endoscopic improvement observed in the same number of participants (Supplementary Table 1). Three of the four participants who reached endoscopic remission achieved RHI remission.

During the treatment maintenance period from weeks 12 through 52, 13 participants in the main cohort discontinued treatment (4 withdrew consent, 2 discontinued due to AEs, and 7 discontinued due to lack of efficacy) (Figure 1). At 52 weeks, MORF-057 demonstrated a consistent effect on RHI and clinical remission. The mean change from baseline in RHI score was −13.5 (SD, 11.7 [n = 18]) (Table 2). Additionally, 31.4% of participants (11/35) achieved RHI remission, 40.0% (14/35) achieved an RHI score reduction of $\geq$50%, and 40.0% (14/35) achieved an RHI score reduction of $\geq$7 points (Table 2). Seven participants (20%) achieved clinical remission, per mMCS, with endoscopic improvement observed in 12 participants (34.3%) (Supplementary Table 1). At week 52, the mean change from baseline in NI score was −1.9 (SD, 1.49).

MORF-057 efficacy was further assessed in various subgroup populations, including AT-naïve vs AT-experienced participants, participants who completed 52 weeks of treatment, participants with a baseline MES of 2 vs 3, and induction responders (Supplementary Table 1; Figure 2; Supplementary Figure 2). Overall, a higher proportion of AT-naïve participants (38.1%) achieved symptomatic remission, comprising stool frequency and rectal bleeding subscores, compared with AT-experienced participants (28.6%), but symptomatic remission scores improved for AT-experienced participants from week 12 to week 52 with MORF-057 treatment (Figure 2). Two-thirds of participants (12/18) who completed 52 weeks of treatment achieved symptomatic remission.

Exploratory group. MORF-057 also demonstrated clinical benefit in the exploratory group, with a mean change from baseline in RHI score of −9.0 (SD, 7.9) at 12 weeks (n = 3) (Table 2). Three participants exhibited a

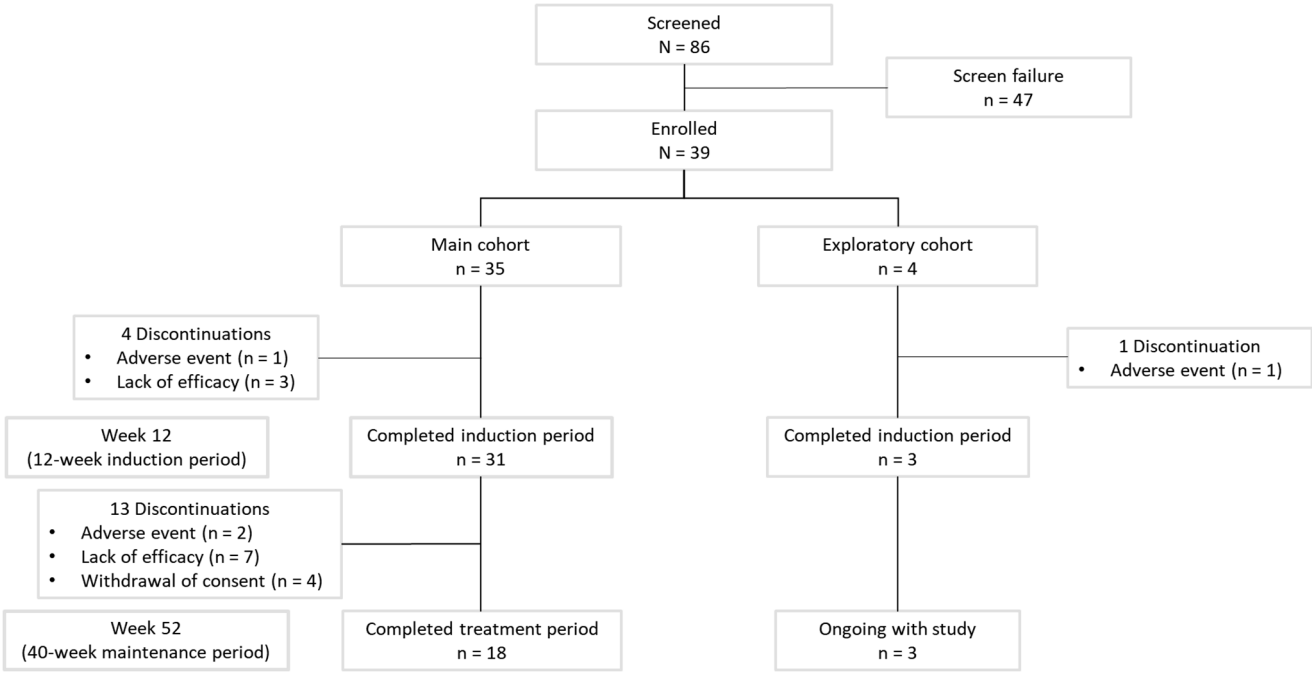

Figure 1. Participant disposition.

clinical response by mMCS, and 1 achieved endoscopic improvement, though none achieved clinical remission.

Pharmacokinetics and Pharmacodynamics

Main cohort. The geometric mean (coefficient of variation [CV]) MORF-057 C_{max} was 645 ng/mL (CV, 81%) and median t_{max} was 2.0 hours; median $t_{1/2}$ ranged from 2.0 to 2.3 hours through week 12 (Table 3). The mean $\alpha4\beta7$ RO was 100% for weeks 2 and 12. Similarly, mean $\alpha4\beta1$ RO percentages at weeks 2 and 12 were below the limit of quantitation of the testing method.

The relative expression of *CCR9* transcripts in blood was measured throughout the 52-week treatment period and reported as a ratio of fold change from baseline (week 0). The main cohort had mean *CCR9* transcript levels of 1.6 (SD, 0.6) at week 12 and 1.7 (SD, 0.8) at week 52 relative to predose levels. During the induction period, *CCR9* transcript levels were significantly higher in responders (n = 15) than in nonresponders (n = 17) (Supplementary Figure 3).

Exploratory group. For the exploratory group, the geometric mean MORF-057 C_{max} was 512 ng/mL (CV, 85%), median t_{max} was 2.0 hours, and median $t_{1/2}$ ranged from 2.7 to 3.8 hours during the induction period (Table 3). The mean $\alpha4\beta1$ RO was 32.2% at week 2 and 64.2% at week 12 (with 1 participant remaining in the study).

Safety

Main cohort. At 12 weeks, MORF-057 appeared to be well tolerated; 37.1% of participants experienced a TEAE, and 5.7% (n = 2) experienced grade ≥3 TEAEs. The 2 grade ≥3 TEAEs were worsening UC and UC relapse. At 52 weeks, the safety profile of MORF-057 continued to be favorable, with no new safety signals compared with the results in the 12-week period (Table 4). The rate of TEAEs was low (n = 18; 51.4%) at 52 weeks, with no TESAEs reported and grade ≥3 TEAEs remaining unchanged since week 12 (n = 2; 5.7%). However, treatment-related AEs occurred in 2 participants with 6 related nonserious events (headache, palpitations, tongue discomfort, tongue coated, upper respiratory infection, and viral upper respiratory infection); none led to discontinuation. This study had a 6-month extension period, and 17 of the 18 participants completed treatment with no TESAEs or grade ≥3 TEAEs reported.

Exploratory group. Before week 12, no TESAEs were reported in the exploratory participants (n = 4); 1 TEAE that led to discontinuation of the study drug occurred, which was an exacerbation of UC (Table 4).

Discussion

The preliminary efficacy data from EMERALD-1 are promising. At week 12, a clinically meaningful improvement from baseline was observed in participants, with a reduction in the RHI score of ≥6 points, meeting the prespecified criterion. Consistent with the primary results of the study, the safety of MORF-057 was favorable through week 52. The effects of MORF-057 on PK, PD, and clinical efficacy remained consistent from week 12 to week 52. Overall, MORF-057 was well tolerated, with safety results through week 52

Table 1. Baseline Participant Characteristics

Baseline characteristics	Main cohort (n = 35)	Exploratory participants (n = 4)	Total (N = 39)
Age, *years*	39.2 (14.10)	59.5 (14.36)	41.3 (15.27)
Sex			
Male	19 (54.3)	3 (75.0)	22 (56.4)
Female	16 (45.7)	1 (25.0)	17 (43.6)
Race			
White	35 (100)	4 (100)	39 (100)
Geography			
United States	7 (20.0)	1 (25.0)	8 (20.5)
Poland	28 (80.0)	3 (75.0)	31 (79.5)
RHI	22.7 (7.32)	16.3 (7.89)	22.0 (7.53)
mMCS	6.7 (1.07)	6.8 (0.96)	6.7 (1.05)
tMCS	8.9 (1.35)	8.8 (0.96)	8.9 (1.31)
Fecal calprotectin, *mg/kg*	2043.0 (1827.50)	855.5 (813.84)	–
Extent of disease, *cm*	49.1 (28.81)	51.3 (16.52)	49.4 (27.55)
Proctosigmoiditis	12 (34.3)	0	12 (30.8)
Left-sided colitis	10 (28.6)	2 (50.0)	12 (30.8)
Extensive colitis	10 (28.6)	2 (50.0)	12 (30.8)
MES			
2	18 (51.4)	0	18 (46.2)
3	17 (48.6)	4 (100)	21 (53.8)
Previous use of AT			
Naïve	21 (60.0)	0	21 (53.8)
Experienced	14 (40.0)	4 (100)	18 (46.2)
Corticosteroid use at baseline			
Yes	9 (25.7)	1 (25.0)	10 (25.6)
No	26 (74.3)	3 (75.0)	29 (74.4)

NOTE. Data are presented as number (%) or mean (standard deviation).
AT, advanced therapy; MES, Mayo Endoscopic Score; mMCS, modified Mayo Clinic Score; RHI, Robarts Histopathology Index; tMCS, total Mayo Clinic Score.

Table 2. RHI Over Time

	Main cohort (n = 35)	Exploratory participants (n = 4)
Week 12		
Change from baseline in RHI	−6.4 (11.18)	−9.0 (7.94)
RHI histological remission	8 (22.9)	0
RHI ≥50% reduction	12 (34.3)	1 (25.0)
RHI ≥7-point reduction	17 (48.6)	1 (25.0)
Week 52[a]		
Change from baseline in RHI	−13.5 (11.69)	–
RHI histological remission	11 (31.4)	–
RHI ≥50% reduction	14 (40.0)	–
RHI ≥7-point reduction	14 (40.0)	–

NOTE. Data are presented as number (%) or mean (standard deviation).
RHI, Robarts Histopathology Index.
[a]Based on the remaining 18 participants with evaluable data who completed week 52.

yielding no TESAEs. Only 2 participants reported treatment-related TEAEs; these were nonserious events that did not lead to study discontinuation. Additionally, 18 participants continued the study for an additional 6 months, and no SAEs were observed (MORF-057-101, data on file).

The histological efficacy of MORF-057 reported here is similar to that of vedolizumab at week 52 of the VARSITY trial, a phase 3 trial (n = 771), in which the mean change from baseline in RHI score was −10.9 (SD, 11.04), and 37.6% of participants achieved RHI remission.[10,17] Participants treated with adalimumab, an anti-TNF-α monoclonal antibody, had a change in RHI score of −8.1 (SD, 13.08), and 19.9% of participants achieved RHI remission at 52 weeks.[10,17] The histological efficacy of the participants who stayed in the EMERALD-1 trial (n = 18) was numerically similar to that of those in the VARSITY trial, although the comparison is limited by the

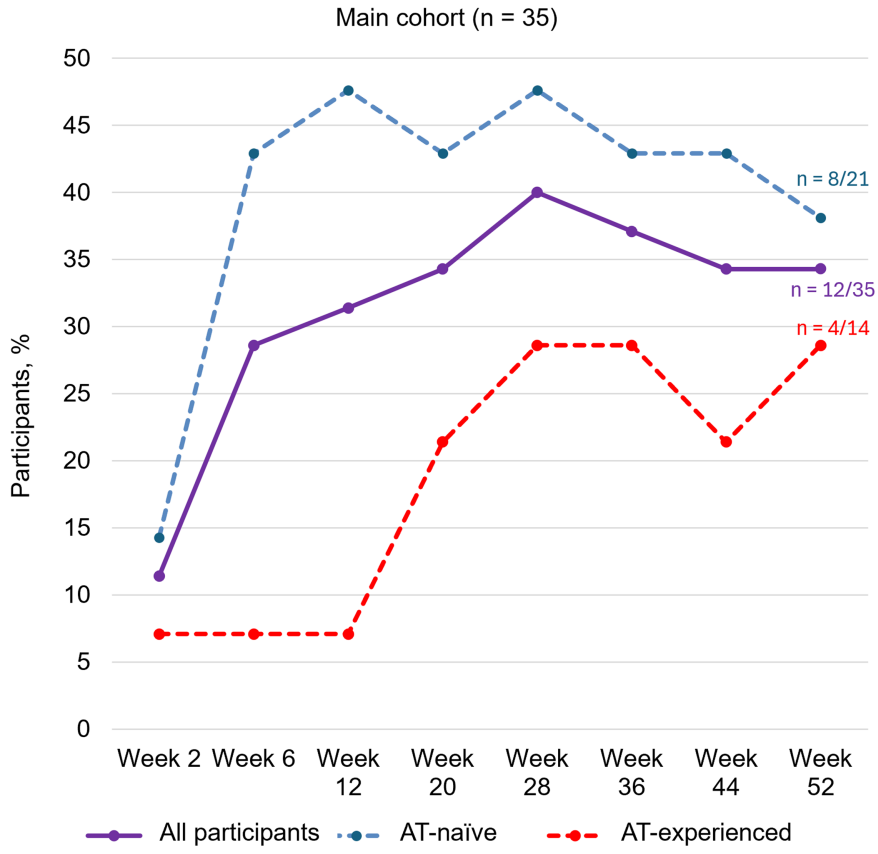

Figure 2. Symptomatic remission at week 52 by advanced therapy (AT) status in the main cohort. Symptomatic remission was defined as a stool frequency subscore of 0 (or 1 with a ≥1-point decrease from baseline) and a rectal bleeding subscore of 0.

small sample size and high dropout rate by week 52 in the overall EMERALD-1 population.

RHI was chosen as the primary efficacy assessment because it is an objective measure that can be assessed in a blinded fashion, which was critical given the open-label study design. RHI also allows for a deeper, more quantitative probe than endoscopy, with the sensitivity to detect statistically significant differences within a

Table 3. PK Profiles in the Main Cohort and Exploratory Participants

Time	Week 0		Week 2		Week 12	
Cohort	Main (n = 35)	Exploratory (n = 4)	Main (n = 35)	Exploratory (n = 4)	Main (n = 35)	Exploratory (n = 4)
AUC_{tau}, *h·ng/mL*, geometric mean (n; CV%)	1420 (33; 72)	1700 (4; 51)	2420 (28; 57)	3650 (3; 10)	2720 (27; 59)	3350 (3; 38)
C_{max}, *ng/mL*, geometric mean (n; CV%)	437 (33; 74)	446 (4; 65)	529 (32; 73)	922 (3; 27)	645 (28; 81)	512 (3; 85)
C_{12} or C_{trough}, *ng/mL*, geometric mean (n; CV%)	13.1 (13; 242)	30.5 (3; 40)	37.9 (28; 118)	70.9 (3; 138)	28.1 (27; 130)	119 (3; 70)
t_{max}, *hours*, median (n; min–max)	2.1 (33; 0.9–5.9)	2.5 (4; 1.0–5.9)	2.0 (32; 0.9–6.0)	2.0 (3; 1.0–3.0)	2.0 (28; 0–5.3)	2.0 (3; 2.0–2.8)
$t_{1/2}$, *hours*, median (n; min–max)	2.0 (13; 1.3–4.6)	2.9 (3; 2.1–4.6)	2.1 (15; 1.7–3.1)	2.7 (2; 2.0–3.4)	2.3 (19; 1.2–5.3)	3.8 (2; 3.0–4.6)

AUC_{tau}, area under the concentration-time curve across the dosing interval; C_{12}, plasma concentration at 12 hours postdose; C_{max}, maximum observed plasma concentration; C_{trough}, trough plasma concentration; CV, coefficient of variation; max, maximum; min, minimum; PK, pharmacokinetic; $t_{1/2}$, half-life; t_{max}, time to reach C_{max}.

Table 4. Overall Summary of TEAEs[a]

	Main cohort (n = 35)	Exploratory participants (n = 4)	Total (N = 39)
Participants with at least 1 TEAE	18 (51.4)	2 (50.0)	20 (51.3)
Serious TEAE	0	0	0
Grade ≥3 TEAE	2 (5.7)	0	2 (5.1)
Treatment-related TEAE	2 (5.7)	0	2 (5.1)
TEAE leading to permanent treatment discontinuation	3 (8.6)	1 (25.0)	4 (10.3)
TEAE leading to death	0	0	0

NOTE. Data are presented as number (%).
TEAE, treatment-emergent adverse event.
[a]Safety assessed at 52 weeks for the main cohort and 12 weeks (induction period) for exploratory participants.

small number of participants. Although there is substantial correlation between endoscopy and histology, a wide range of inflammatory activity can be detected by histology in patients with an MES of 1.[18] Furthermore, histological features may be more reliable because they are associated with better long-term disease outcomes, including lower relapse rates and a lower risk of cancer.[19] RHI is also a validated histology endpoint that provides standardized scoring and a robust framework for assessing changes over time.[15] Therefore, this is an important endpoint in smaller trials such as ours, as therapies for UC are being developed that have changing definitions of treatment response that endoscopic assessment alone is incapable of quantifying.[15]

In addition to the primary results, secondary endpoints of this study support the clinical efficacy of MORF-057. The notion that MORF-057 may be an effective drug based on endoscopic evaluations is consistent with a previous analysis demonstrating that the absence of histological activity was a predictor of clinical remission.[20] Thus, the estimated effect size compares favorably with the other induction agents available. Furthermore, analysis of continuous outcomes, including change in mean MCS, support the clinical efficacy of MORF-057. These results are promising, but their interpretation requires a cautious approach due to the limited sample size and participant discontinuations during the study.

The PK and PD results of this study are comparable to those of Study MORF-057-101, in which healthy volunteer participants receiving 100 mg of MORF-057 twice daily for 14 days exhibited a C_{max} of 519.5 ng/mL, with a 2-hour t_{max} and a $t_{1/2}$ of 2.7 hours (data on file). Participants also exhibited $\alpha4\beta7$ RO of >99% throughout the 14-day treatment. All $\alpha4\beta1$ measurements were below the lower limit of quantitation. Importantly, participants in the exploratory cohort had a mean $\alpha4\beta1$ RO of 64.2% at week 12. As vedolizumab does not bind to $\alpha4\beta1$ integrins, the previous inhibition of $\alpha4\beta7$ receptors may lead to compensatory mechanisms (ie, increased $\alpha4\beta1$ RO) in participants with prior vedolizumab use.[21] This suggests that participants with a loss of response to vedolizumab may benefit from UC treatment with MORF-057. Further investigation may be warranted due to the small number of participants with prior vedolizumab use in the study.

CCR9 transcript levels increased with treatment. A significant difference in *CCR9* transcript levels between responders and nonresponders was seen as early as 2 weeks after the initial dose, suggesting that *CCR9* transcripts may have the potential to discriminate between responders and nonresponders during the induction phase of treatment. These results are consistent with earlier MORF-057 studies and other studies on $\alpha4\beta7$/MAdCAM binding inhibition.[22] It should be noted that, although *CCR9* is increased during active inflammation, *CCR9*-mediated homing of T cells to the gut is also activated during the recovery phase, which may lead to tissue regeneration and reduced inflammation.[23] Further investigation is needed to completely understand the role of *CCR9* in proinflammatory and anti-inflammatory responses in UC.

This study had several limitations. First, sample size was small, and there was a high dropout rate due to AEs or lack of efficacy (13 of 35 participants). Despite the small number of participants analyzed, the study assessed safety over 52 weeks, which helped confirm that MORF-057 was well tolerated with no SAEs. Having a high dropout rate in clinical trials is not unusual, as larger UC studies, such as the ELEVATE-52 trial, had an even higher dropout rate at week 52 (128 of 289 participants in the etrasimod group).[24] Nonetheless, interpretation of these results is limited due to the small sample size and high dropout rate. Second, a placebo or comparator arm was not included, which can make interpretation of the efficacy data challenging. Finally, based on the reliable estimates for clinical remission rates available for UC induction studies and the relatively unbiased histopathology and endoscopic data generated, a phase 2b, placebo-controlled, dose-finding study is underway.

Conclusion

In this small and open-label phase 2a proof-of-concept study, we successfully ascertained the initial efficacy, safety, and tolerability of MORF-057. These data suggest a potential for MORF-057 to be a safe and effective advanced oral therapy for patients with UC.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org and at https://doi.org/10.1016/j.cgh.2025.07.030.

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Acknowledgments
The authors thank the participants and all the study site personnel who participated in this study. The authors would also like to thank Simon Cooper for his contribution to the manuscript. Medical writing support was provided by Amy Holbrook, MS, of Morphic Therapeutic, a wholly owned subsidiary of Eli Lilly and Company, and Samantha Tener, PhD, of Red Nucleus and was funded by Morphic Therapeutic, a wholly owned subsidiary of Eli Lilly and Company.

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Conflicts of interest

These authors disclose the following: Bruce E. Sands declares grants or contracts from Bristol Myers Squibb and Janssen; consulting fees from AbbVie, Abivax, Adiso Therapeutics, Agomab Therapeutics, Alimentiv, Amgen, AnaptysBio, AstraZeneca, Biolojic Design, Biora Therapeutics, Boehringer Ingelheim, Bristol Myers Squibb, Celltrion, Eli Lilly, Ensho Therapeutics, Enthera Pharmaceuticals, Enveda Biosciences, Equillium, Evommune, Ferring Pharmaceuticals, Fzata, Galapagos, Genentech, Gilead Sciences, GSK, Gossamer Bio, Imhotex, Immunyx Therapeutics, Index Pharmaceuticals, Innovation Pharmaceuticals, Janssen, Johnson & Johnson, Kaleido Biosciences, Kallyope, Merck, Microba, Microbiotica, Mitsubishi Tanabe Pharma, Mobius Care, Morphic Therapeutic, MRM Health, Nexus Therapeutics, Nimbus Discovery, Odyssey Therapeutics, Palisade Bio, Pfizer, Progenity, Prometheus Biosciences, Prometheus Laboratories, Protagonist Therapeutics, Q32 Bio, Rasayana Therapeutics, Recludix Pharma, Reistone Biopharma, Sorriso Pharmaceuticals, Spyre Therapeutics, Surrozen, Takeda, Target RWE, Teva Pharmaceuticals, Theravance Biopharma, TLL Pharmaceutical, Tr1X, UNION Therapeutics, and Ventyx Biosciences; honoraria from AbbVie, Abivax, Bristol Myers Squibb, Celltrion, Eli Lilly, Janssen, Mitsubishi Tanabe Pharma, Pfizer, and Takeda; travel support from Eli Lilly, Janssen, and Takeda; participation on a data safety monitoring board or advisory board for Agomab Therapeutics and Amgen; stock or stock options for Ventyx Biosciences; and receipt of equipment, materials, drugs, medical writing, gifts, or other services from AbbVie, Abivax, Bristol Myers Squibb, Celltrion, Eli Lilly, Janssen, Merck, Morphic Therapeutic, Pfizer, Takeda, and Ventyx Biosciences. Silvio Danese reports consulting fees from AbbVie, Alimentiv, Allergan, Amgen, AstraZeneca, Athos Therapeutics, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene Corporation, Celltrion, CSL Vifor, Dr Falk Pharma, Eli Lilly, Enthera Pharmaceuticals, Ferring Pharmaceuticals, Gilead Sciences, Hospira, Inotrem, Janssen, Johnson & Johnson, Merck Sharp & Dohme, Morphic Therapeutic, Mundipharma, Mylan, Pfizer, Roche, Sandoz, Sublimity Therapeutics, Takeda, Teladoc Health, TiGenix, UCB, and Vial, and honoraria from AbbVie, Amgen, Ferring Pharmaceuticals, Gilead Sciences, Janssen, Mylan, Pfizer, and Takeda. Jarosław Kierkus reports grants or contracts from Nestlé, and honoraria from Danon, Janssen, Lilly, and Nestlé. Brihad Abhyankar, Michael Y. Choi, Carolyn Soo, Yujun Wu, Fangui Sun, Dooyoung Lee, Dan Cui, Maloy Mangada, Prabhat Singhal, Ali Hussain, and Bruce N. Rogers are employees of Morphic Therapeutic. Laurent Peyrin-Biroulet reports consulting fees from AbbVie, Abivax, Adacyte, Alimentiv, Amgen, Applied Molecular Transport, Arena Pharmaceuticals, Banook, Biogen, Bristol Myers Squibb, Celltrion, Connect Biopharma, Cytoki Pharma, Enthera Pharmaceuticals, Ferring Pharmaceuticals, Fresenius Kabi, Galapagos, Genentech, Gilead Sciences, Gossamer Bio, GSK, IAC Image Analysis, Index Pharmaceuticals, Inotrem, Janssen, Lilly, Medac, Mopac Biologics, Merck Sharp & Dohme, Morphic Therapeutic, Nordic Pharma, Novartis, Oncodesign Precision Medicine, Ono Pharmaceutical, OSE Immunotherapeutics, Pandion Therapeutics, Par'-Immune, Pfizer, Prometheus Biosciences, Protagonist Therapeutics, Roche, Samsung, Sandoz, Sanofi, Satisfay, Takeda, Telavant, Theravance Biopharma, Thermo Fisher Scientific, TiGenix, Viatris, VectivBio, Ventyx Biosciences, and Ysopia. Brian G. Feagan reports consulting fees from AbbVie, Agomab Therapeutics, AllianThera Biopharma, Amgen, AnaptysBio, Applied Molecular Transport, Arena Pharmaceuticals, Azora Therapeutics, BioJAMP, Biora Therapeutics, Boehringer Ingelheim, Boston Pharma, Boxer Capital, Celgene Corporation/Bristol Myers Squibb, Connect Biopharma, Cytoki Pharma, Disc Medicine, Duality Biologics, EcoR1, Equillium, Ermium Therapeutics, Everest Clinical Research, Ferring Pharmaceuticals, First Wave BioPharma, Galapagos, GalenAtlantica, Genentech/Roche, Gilead Sciences, Glenmark Pharmaceuticals, Gossamer Bio, GSK, HotSpot Therapeutics, Index Pharmaceuticals, Imhotex, ImmuNext, Immunic Therapeutics, Intact Therapeutics, JAKAcademy, Janssen, Japan Tobacco, Kaleido Biosciences, Landos Biopharma, Leadiant Biosciences, LifeSci Capital, Lilly, Lument AB, Merck, Millennium Pharmaceuticals, MiroBio, Morphic Therapeutic, Mylan, OM Pharma, Origo Biopharma, Orphagen Pharmaceuticals, Otsuka, Pandion Therapeutics, Pfizer, Play to Know AG, Progenity, Prometheus Therapeutics and Diagnostics, Protagonist Therapeutics, PTM Therapeutics, Q32 Bio, Rebiotix, RedHill Biopharma, Redx, Roche, Sandoz, Sanofi, Seres Therapeutics, Silverback Therapeutics, Surrozen, Takeda, Teva Pharmaceuticals, Thelium Therapeutics, Theravance Biopharma, TiGenix, Tillotts Pharma, UCB, VHsquared, Viatris, and Zealand Pharma; honoraria from AbbVie, Eli Lilly, Janssen, Pfizer, and Takeda; travel support from AbbVie, Bristol Myers Squibb, Eli Lilly, Janssen, Pfizer, Takeda, and Sanofi; and stock or stock options from Connect Biopharma and enGene. The remaining authors disclose no conflicts.

Funding

This work was supported by Morphic Therapeutic, a wholly owned subsidiary of Eli Lilly and Company.

Data Availability

Eli Lilly and Company provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the United States and the European Union and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents—including the study protocol, statistical analysis plan, clinical study report, and blank or annotated case report forms—will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.

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Supplemental information

A Phase 2 Study of MORF-057, an Oral $\alpha4\beta7$ Integrin Inhibitor in Moderately to Severely Active Ulcerative Colitis

Bruce E. Sands, Stefan Schreiber, Silvio Danese, Jarosław Kierkus, Brihad Abhyankar, Michael Y. Choi, Carolyn Soo, Yujun Wu, Fangui Sun, Dooyoung Lee, Dan Cui, Maloy Mangada, Prabhat Singhal, Ali Hussain, Bruce N. Rogers, Laurent Peyrin-Biroulet, and Brian G. Feagan

Supplemental material

Inclusion and exclusion criteria

Main cohort inclusion criteria

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

Age

1. Aged 18 to 85 years, inclusive, at the time of signing the informed consent form (ICF)

Type of participant and disease characteristics

2. Signs/symptoms of moderately to severely active ulcerative colitis (UC) for at least 3 months prior to screening, and the diagnosis was confirmed during the screening period with the following criteria: a modified Mayo Clinic Score (mMCS) of 5 to 9 (inclusive) with a Mayo Endoscopic Score (MES) ≥2 (confirmed by central reader)
3. Robarts Histopathology Index (RHI) score ≥10
4. Evidence of UC extending at least 15 cm from the anal verge
5. Advanced therapy (AT) naïve or had an inadequate response, loss of response or intolerance to no more than three drugs in two classes of the following:
    a. Tumor necrosis factor alpha (TNF-α) antagonists, including infliximab, adalimumab or golimumab
    b. Interleukin (IL)-12 and IL-23 antagonists, including ustekinumab
    c. Janus kinase (JAK) antagonists, including tofacitinib and upadacitinib
    d. Sphingosine-1-phosphate (S1P) receptor agonists, including ozanimod
    e. Any investigational product with the same mechanism as one of those outlined above (5a through 5d)

f. Integrin inhibitors, including vedolizumab (participants in the exploratory group only)

Note: Participants who have a history of primary nonresponse to two of the classes above will not be eligible. Participants who have received treatment with these agents at subtherapeutic doses, or durations, should be discussed with the medical monitor to assess eligibility

6. Meets the following washout criteria of prior UC therapy relative to study day 1:
    a. TNF-α antagonists: at least 8 weeks
    b. IL-12/IL-23 antagonists, including ustekinumab: at least 8 weeks
    c. JAK antagonists, including tofacitinib and upadacitinib: at least 2 weeks
    d. S1P receptor agonists, including ozanimod: at least 4 weeks
7. If the participant has been receiving any of the nonprohibited medications for UC listed below, he/she must discontinue use at least five half-lives before study day 1 or must agree to maintain stable doses of these concomitant medications starting from the time specified below until the end of the safety follow-up period, with the exception of tapering oral corticosteroid dose after 12 weeks of being in the trial

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

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

Weight

9. Body mass index (BMI) within the range of 18.0 and 40.0 kg/m^2 (inclusive) at screening

Sex and contraceptive/barrier requirements

10. Agrees to abide by the guidelines set forth in the study 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, when having sexual intercourse with a woman of childbearing potential who is not currently pregnant
- Agrees to use a male condom when engaging in any activity that allows for passage of ejaculate to another person

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

- Is a woman of non-childbearing potential

OR

- Is a woman of childbearing potential and agrees to use a contraceptive method that is highly effective with a failure rate of <1% per year during

the study treatment period and for at least 28 days after receiving the last dose of MORF-057

Note: Women who use any oral hormonal contraception must use an additional physical barrier method

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

Informed consent

12. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the ICF and in the study protocol

Exploratory group inclusion criteria

In addition to meeting inclusion criteria 1 through 12, the following criteria must be met for participants to be included in the exploratory group:

13. Intolerant to (eg, infusion-related skin reaction, allergy or side effects unrelated to α4β7 inhibition) or secondary nonresponder to vedolizumab who has been dosed within the past 5 years with the drug. Up to five participants of the 10 exploratory group may be included based on clinical criteria only. The remaining participants must also meet at least one of the following criteria:

a. Documented vedolizumab levels in blood of ≤10 µg/mL 6 to 8 weeks after the most recent dose or at what is considered a clinical trough. If the participant has had vedolizumab levels in blood tested and documented in their medical chart prior to screening, the test does not need to be repeated

b. Non-saturating receptor occupancy of vedolizumab in blood 6 to 8 weeks after the most recent dose

c. Documented presence of antidrug antibodies against vedolizumab. If the participant has had a positive antidrug antibody test documented prior to screening, the test does not need to be repeated

> **Note:** Secondary nonresponse is defined as having initially responded to induction therapy and then had recurrence of symptoms after receiving at least two of the maintenance doses, 300 mg every 8 weeks (discontinuation despite clinical benefit does not qualify)

14. Received the last dose of vedolizumab at least 6 weeks prior to study day 1 to allow sufficient washout

Exclusion criteria

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

Medical conditions

1. Diagnosed with indeterminate colitis, microscopic colitis, ischemic colitis, UC of the rectum (proctitis), radiation colitis, or Crohn's disease or has clinical findings suggestive of Crohn's disease
2. Has current evidence of unresected colonic dysplasia, unresected adenomatous colonic polyps, toxic megacolon, abdominal abscess, symptomatic colonic stricture, fistula, stoma, ileostomy or colostomy at screening
3. Currently requires or is anticipated to require surgical intervention for UC during the study or is planning to undergo major surgery during the study period
4. Surgical procedure requiring general anesthesia within 30 days prior to screening

5. 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. Positive findings on a subjective neurological screening questionnaire or progressive multifocal leukoencephalopathy subjective symptom checklist during screening or prior to the administration of the first dose of study drug on study day 1
7. Active bacterial, viral or parasitic pathogenic enteric infection, including *Clostridium difficile*; cytomegalovirus, hepatitis B or C virus or human immunodeficiency virus (HIV); an infection requiring hospitalization or intravenous antimicrobial therapy, or an opportunistic infection within 3 months prior to screening; any infection requiring oral antimicrobial therapy within 2 weeks prior to screening; or a history of more than one episode of herpes zoster or any episode of disseminated herpes zoster infection
8. Positive diagnostic tuberculosis (TB) test at screening (defined as a positive QuantiFERON test). If the participant has had a confirmed negative QuantiFERON or other interferon gamma release assay test within 90 days prior to screening, the test does not need to be repeated. In cases where the QuantiFERON test result is indeterminate, the participant may have the test repeated once, and if the second test is negative, the participant will be eligible. In the event the second test also has an indeterminate result or QuantiFERON is unavailable, the investigator has the option to perform a purified protein derivative (PPD) skin test. If the PPD reaction is <5 mm, then the participant is eligible. If the reaction is ≥5 mm or PPD testing is not done, the participant is not eligible. An exception can be made for participants with a history of latent TB who are currently receiving treatment for latent TB per local standard care, who will initiate treatment for latent TB before the first dose of study drug or who have

documentation of completing appropriate treatment for latent TB within 2 years prior to study day 1

9. Tests positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) during the screening period. Participants who test positive for SARS-CoV-2 can undergo retesting throughout the screening period. Testing to be performed according to site-specific testing procedures and country-specific requirements
10. 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 (eg, SARS-CoV-2 two-shot vaccination series)
11. Concurrent, clinically significant, serious, unstable comorbidity (such as uncontrolled cardiovascular, pulmonary, hepatic, renal, gastrointestinal, genitourinary, hematologic, coagulation, immunological, endocrine/metabolic or other medical disorder) that, in the judgment of the investigator, would compromise compliance with the protocol, interfere with interpretation of the study results or predispose participants to safety risks
12. Known primary or secondary immunodeficiency
13. 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. History of left ventricular ejection fraction <50%

15. Clinically significant abnormal electrocardiogram at screening, including a QT interval corrected through use of Fridericia's formula (QTcF) ≥450 ms for males and ≥470 ms for females
16. Abnormal hematology (hemoglobin level, white blood cell [WBC] count or platelet count) or coagulation results at screening, as evidenced by the ranges provided below:*

a. Hemoglobin level <8.0 g/dL
b. Absolute WBC count $<3.0 \times 10^9$/L
c. Absolute lymphocyte count $<0.5 \times 10^9$/L
d. Absolute lymphocyte count $>5.0 \times 10^9$/L
e. Absolute neutrophil count $<1.2 \times 10^9$/L
f. Platelet count $<100 \times 10^9$/L or $>1000 \times 10^9$/L
g. International normalized ratio >1.5

17. Clinically significant abnormal urinalysis results, as deemed by the investigator or designee
18. Abnormal organ function at screening, as evidenced by the following:*
    a. Alanine aminotransferase or aspartate aminotransferase >2.5 × upper limit of normal (ULN)
    b. Chronic kidney disease stages 4 and 5, defined as having a glomerular filtration rate <30 mL/min/1.73 m^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 five half-lives (whichever is shorter) prior to study day 1
21. Any previous treatment with vedolizumab or other integrin inhibitors (except participants for the exploratory group)
22. Experiencing toxicities from prior therapy with grade >1 within 1 week prior to first dose of study drug
23. Fecal microbiota transplantation within 3 months prior to screening
24. If treatment with a moderate-to-strong CYP3A4 inducer or inhibitor was received, a washout period of at least 30 days or five half-lives (whichever is shorter) is required prior to study day 1
25. If treatment with a moderate-to-strong organic anion transporter polypeptide-1B inhibitor was received, a washout period of at least 14 days or five half-lives (whichever is shorter) is required prior to study day 1

Prior/concurrent clinical study experience

26. Concurrent participation in any other interventional study

27. Received any investigational therapy within 30 days or five half-lives (whichever is longer) prior to study day 1
28. Previous exposure to MORF-057 and/or a known hypersensitivity to drugs with a similar mechanism to MORF-057

Other exclusions

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

Study Design

Prior treatment failure was defined as inadequate response, loss of response or intolerance to up to three drugs or investigational products in any two of the following drug classes: TNF-α antagonists, IL-12/IL-23 antagonists, JAK antagonists, sphingosine-1-phosphate (S1P) receptor agonists, or integrin inhibitors (including vedolizumab for only the exploratory group).

Nonprohibited medications for UC were 5-ASA, ≤4.8 g/day; oral corticosteroids: prednisone, ≤30 mg/day or budesonide, ≤9 mg/day; 6-mercaptopurine, any stable dose; azathioprine, any stable dose; methotrexate, any stable dose.

Exploratory Endpoints

Exploratory endpoints included the evaluation of the effects of MORF-057 on histological improvement (change from baseline to week 52 in RHI score) and clinical improvement (change from baseline to weeks 6 and 52 in mMCS, and change from baseline to weeks 6, 12, and 52 in full MCS). RHI remission or histologic remission was also assessed and defined as an RHI score of ≤3 (with 0 for lamina propria neutrophils score and neutrophils in the epithelium score and without ulcers or erosions). Clinical remission was determined using mMCS and was defined as a rectal bleeding subscore of 0, a stool frequency subscore of ≤1 and an MES of ≤1 without friability. Symptomatic remission was defined as a stool frequency subscore of 0 (or of 1 with ≥1-point decrease from baseline) and a rectal bleeding subscore of 0, and endoscopic response or improvement was defined as an MES of ≤1. Additional exploratory endpoints included characterizing the PD of MORF-057 in peripheral blood over time via α4β7 and α4β1 ROs and determining blood *CCR9* transcript levels.

Statistical Analyses and Sample Size Estimation

The safety analysis population included all participants in the full analysis set. The PK population included all participants with adequate measurable concentrations to define the maximum observed plasma concentration or the area under the curve. The PD population included all participants in the full analysis set who had at least one measurable postdose PD measurement and its corresponding predose PD measurement for, at minimum, one of the PD biomarkers.

Descriptive statistics are used for all primary, secondary, and exploratory data. Categorial parameters are reported using frequencies and proportions. Continuous parameters are reported using mean, SD, median, minimum, and maximum. A two-sided

one-sample t-test was used to calculate the *P*-value for testing the primary efficacy endpoint for the main cohort. The main cohort and the exploratory group were analyzed separately, unless specified otherwise.

Efficacy Results in Main Cohort Subpopulations

At week 52, AT-naïve participants had a mean (SD) change from baseline in RHI score of –15.8 (8.1). Six participants (28.6%) achieved clinical remission by mMCS, and eight (38.1%) showed endoscopic improvement. Comparatively, AT-experienced participants had a mean (SD) change from baseline in RHI score of –10.6 (15.2); one participant (7.1%) achieved clinical remission, and four (28.6%) showed endoscopic improvement (**table S1**). At week 52, participants with a baseline MES of 2 had a mean (SD) change from baseline in RHI score of –15.3 (6.5); five of these participants (27.8%) achieved clinical remission by mMCS, and eight (44.4%) showed endoscopic improvement. However, participants with a baseline MES of 3 had a mean (SD) change from baseline in RHI score of –10.7 (7.4); two of these participants achieved clinical remission (11.8%), and four showed endoscopic improvement (23.5%; **table S1**). Overall, a greater proportion of participants with a baseline MES of 2 showed clinical improvement compared with participants with a baseline MES of 3 (**table S1**; **figure S2**). Generally, induction responders (n = 13) continued to respond in the maintenance phase, showing a mean (SD) change from baseline in RHI score of –14.6 (11.5) at 52 weeks. Additionally, the 13 induction responders (81.2%) maintained clinical response by mMCS, 7 (43.7%) achieved clinical remission by mMCS and 10 (62.5%) achieved endoscopic improvement.

Table S1. Schedule of activities for the treatment period

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

Dispense stool collection kit[p]	X	X	X	X	X	X	X	X	X	X[p]		
Discuss participation and informed consent in the long-term extension[q]									X	X		
Safety assessments												
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X			X	X					X		
Physical exam[f]	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[s]	X	X	X	X	X	X	X	X	X	X	X	X
PML checklist[t]	X	X	X	X	X	X	X	X	X	X	X	
Haematology and coagulation[u]	X	X	X	X	X	X	X	X	X	X	X	X[b]
Serum chemistry[u]	X	X	X	X	X	X	X	X	X	X	X	X[b]
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X[b]
AE/SAE assessment[v]	X	X	X	X	X	X	X	X	X	X	X	X
PK assessment												
Plasma sample for PK analysis		X[w]	X[w]	X[x]	X[w]	X[x]	X[x]	X[x]	X[x]	X[y]		
PD biomarkers												
Faecal sample for microbiome analyses		X	X	X	X	X	X	X	X	X		
Blood sample for microbiome derived metabolite analysis[z]		X	X	X	X	X	X	X	X	X		
Whole blood sample for RO[aa]		X	X		X							
Whole blood sample for immunophenotyping[bb]		X	X	X	X	X	X	X	X	X		
Blood sample for PIMS[cc]		X	X		X							
PAXgene RNA blood sample for gene expression[dd]		X	X	X	X	X	X	X	X	X		
Blood sample for protein biomarkers[ee]		X	X	X	X	X	X	X	X	X		
Future biomarker research												
Blood PD sample collection for future analysis[ff]		X	X	X	X	X	X	X	X	X		
Blood pharmacogenomics sample collection for future analysis[ff]		X										
Efficacy assessments												
Sigmoidoscopy with biopsy[gg]	X			X[hh]	X					X[ii]		

MCS Physician's Global Assessment	X	X	X	X	X	X	X	X	X	X		
MCS rectal bleeding subscore	X	X	X	X	X	X	X	X	X	X		
MCS stool frequency subscore	X	X	X	X	X	X	X	X	X	X		
Locally and centrally read MES	X			X	X					X		
Centrally read RHI score, continuous Geboes score and NI	X			X	X					X		
Serum for hs-CRP test[jj]	X	X	X	X	X	X	X	X		X		
Faecal sample for faecal calprotectin test	X		X	X	X	X	X	X		X		
Study drug												
Study drug accountability			X	X	X	X	X	X	X	X		
Dispense study drug		X	X	X	X	X	X	X	X	X[kk]		
Study drug administration on site[ll]		X	X	X	X	X	X	X	X	X[mm]		

AE, adverse event; *CCR9*, C-C chemokine receptor 9 gene; *C. diff*, *Clostridium difficile*; ECG, electrocardiogram; EOT, end of treatment; HIV, human immunodeficiency virus; hs-CRP, high-sensitivity C-reactive protein; ICF, informed consent form; MCS, Mayo Clinic Score; MES, Mayo Endoscopic Score; NI, Nancy Index; PD, pharmacodynamics; PIMS, physiological intermolecular modulation spectroscopy; PK, pharmacokinetics; PML, progressive multifocal leukoencephalopathy; RHI, Robarts Histopathology Index; 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 listed procedures may be performed at any time during the SCR period.

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

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

[d]Participants who will not enroll into the long-term extension will complete the SFU visit, which should be performed 28 days (+7 days) after the participant takes the last dose of study drug. Participants who choose to enroll into the long-term extension after visit 10/EOT will complete an SFU visit at week 82.

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

[f]The 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.

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

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

[i]SARS-CoV-2 testing will be performed during the SCR period according to site-specific procedures and country-specific requirements. Participants who test positive for SARS-CoV-2 can undergo retesting throughout the SCR period.
[j]If QuantiFERON or other interferon gamma release assay testing occurred within 90 days prior to SCR, the test does not need to be repeated. In cases where the QuantiFERON test is indeterminate, the participant may have the test repeated once, and if their second test is negative, they will be eligible. In the event a second test is also indeterminate or QuantiFERON is unavailable, the investigator has the option to perform a purified protein derivative skin test.
[k]Cytomegalovirus will be tested with the biopsy sample collected at SCR.
[l]Participants being considered for the exploratory group will require testing for vedolizumab blood levels, RO of vedolizumab and antidrug antibodies against vedolizumab. If the participant has had vedolizumab levels in blood or presence of antidrug antibodies against vedolizumab tested and documented in their medical chart prior to SCR, the test does not need to be repeated.
[m]Participant diaries are to be completed at the end of each day by the participant at home and brought to each study visit for review by study personnel. See Section 8.5 of the study protocol for the required contents of the participant diaries.
[n]Only required for women of childbearing potential. A serum test should be used at SCR, and a urine test should be used throughout rest of the study. On day 1, a urine test must be completed, and results must be reviewed prior to start of the study drug.
[o]Serum test for follicle-stimulating hormone level to be performed only for female participants of non-childbearing potential who are not surgically sterile.
[p]Stool collection kits are to be dispensed to participants at the visits indicated. The participant should use this kit to collect one sample at home within 24 hours before the next site visit. The sample should be frozen immediately and brought to the clinic on the day of the site visit. Note: Sample is to be collected prior to bowel preparation for visits 4, 5 and 10/EOT. Stool collection kits will be dispensed at visit 10 only for participants continuing in the long-term extension.
[q]Participants will be provided the option to participate in the long-term extension. Participants who want to continue in the long-term extension will sign a separate ICF.
[r]A complete physical exam is to be performed at SCR and visit 10/EOT, and a targeted exam may be performed at all other required visits (see Section 8.8.1 of the study protocol for descriptions). For unscheduled visits that involve the investigator or clinical assessment and not the visits that would be for dispensing study drug or for laboratory draws only, the type of exam will be at the investigator's discretion and determined based on the reason for the visit.
[s]Vital signs to be recorded at all visits that involve the investigator or clinical assessment visits and not the visits that would be for dispensing study drug or for laboratory draws only. These will include blood pressure, heart rate, respiratory rate and temperature.
[t]If the results of the questionnaire are suggestive of PML, a full neurological exam and, if indicated, additional testing are to be performed.
[u]Blood samples for hematology, coagulation and serum chemistry assessments will be collected before the AM dose on visits 2–10.
[v]Record AEs from the time the ICF is signed. Participants are to be contacted by phone as needed to monitor the status of the event.
[w]PK testing at visits 2, 3 and 5: Blood sampling will be required before the AM dose and at 1, 2, 3, 4 and 6 hours after the AM dose. Blood sampling will be optional at 8, 10 and 12 hours after the AM dose. The 12-hour post-AM dose sample will be collected prior to the second daily dose. Time windows for PK sampling can be found in Section 8.10.1 of the study protocol. Each pre-AM dose sample should be obtained within approximately 30 minutes before the AM dose is administered.
[x]PK testing at visits 4, 6, 7, 8 and 9: Blood sampling will be required before the AM dose and at 1 and 3 hours after the AM dose. Time windows for PK sampling can be found in Section 8.10.1 of the study protocol. Each pre-AM sample should be obtained within approximately 30 minutes before the AM dose is administered and at 12 hours (±1 hour) after the previous evening's PM dose.
[y]PK testing at visit 10/EOT: Blood sampling will be required before the AM dose. The sample should be obtained within approximately 30 minutes before the AM dose is administered and at 12 hours (±1 hour) after the previous evening's PM dose.

[z]Blood samples for microbiome-derived metabolite analysis will be collected before the AM dose on visits 2–10. Microbiome sampling to occur at the corresponding PK sampling time.
[aa]RO testing at visits 2, 3 and 5: The blood samples for RO testing collected before the AM dose are required. The 12-hour post-AM dose samples for RO testing are optional. The 12-hour post-AM dose sample will be collected prior to the second daily dose. RO sampling to occur at the corresponding PK sampling time.
[bb]Blood samples for immunophenotyping (lymphocyte subset analysis) will be collected before the AM dose on visits 2–10. Collection time at visits 3–10 must be consistent with baseline (visit 2) collection ±2 hours. Immunophenotype sampling to occur at the corresponding PK sampling time.
[cc]Blood samples for PIMS analysis will be collected before the AM dose on visits 2 and 5. PIMS sampling to occur at the corresponding PK sampling time.
[dd]PAXgene RNA blood samples (for *CCR9* analysis) will be collected before the AM dose on visits 2–10. Collection time at visits 3–10 must be consistent with baseline (visit 2) collection ±2 hours. PAXgene sampling to occur at the corresponding PK sampling time.
[ee]Blood samples for protein biomarkers will be collected before the AM dose on visits 2–10. Protein biomarker sampling to occur at the corresponding PK sampling time.
[ff]Participation in future biomarker research sample collection is optional. Blood PD samples will be collected before the AM dose on visits 2–10. Blood pharmacogenomics samples will be collected before the AM dose on visit 2. PD and pharmacogenomics sampling to occur at the corresponding PK sampling time.
[gg]Full colonoscopy is optional at any time if the investigator deems it necessary. The SCR endoscopy procedure should be scheduled at least 16 days prior to the planned start of the study drug (day 1) to allow for central reading. Colonic mucosa biopsies will be collected for cytomegalovirus testing (SCR only), histopathology, microbiome, spatial transcriptomics/proteomics and gene expression analyses.
[hh]The visit 4 endoscopy is optional.
[ii]For the visit 10/EOT endoscopy procedure, there is a window of ±7 days from the actual visit date. For participants who discontinue treatment before week 6, a repeat sigmoidoscopy will be performed any time after MORF-057 dosing on day 14. For participants who discontinue treatment after week 6, a repeat sigmoidoscopy will be performed any time if the optional week 6 sigmoidoscopy was not performed. If the week 6 optional sigmoidoscopy was performed, a repeat sigmoidoscopy will be performed after the 28th day after the week 6 sigmoidoscopy. Participants who complete a sigmoidoscopy/colonoscopy within 12 weeks of the EOT visit are not required to repeat the procedure. If the procedure was performed further than 12 weeks, please consult the sponsor medical monitor.
[jj]Blood samples for hs-CRP analysis will be collected before the AM dose on visits 2–8 and visit 10.
[kk]At visit 10/EOT, the study drug will be dispensed only for participants continuing treatment in the long-term extension.
[ll]AM dosing required on site for all visits. For visits 2, 3 and 5, if optional PK/RO sampling will be performed at 8–12 hours after the AM dose, the PM dose must not be taken until PK/RO sampling is complete for that day.
[mm]At visit 10/EOT, participants will only receive an AM dose for the day. No PM dose will be provided.

Table S1. Main Cohort Efficacy Results by Subgroup Analysis.

Week 12	Main cohort (N = 35)	AT naïve (n = 21)	AT experienced (n = 14)	MES = 2 (n = 18)	MES = 3 (n = 17)
Change from baseline in RHI, mean (SD)	–6.4 (11.2)	–7.4 (11.9)	–4.8 (10.3)	–6.9 (12.1)	–5.8 (10.4)
RHI remission,[a] n (%)	8 (22.9)	6 (28.6)	2 (14.3)	6 (33.3)	2 (11.8)
RHI ≥50% reduction, n (%)	12 (34.3)	9 (42.9)	3 (21.4)	9 (50.0)	3 (17.6)
RHI ≥7-point reduction, n (%)	17 (48.6)	12 (57.1)	5 (35.7)	10 (55.6)	7 (41.2)
Change in mMCS, mean (SD)	–2.3 (2.1)	–2.9 (2.4)	–1.6 (1.5)	–2.7 (2.4)	–1.9 (1.9)
Clinical response (mMCS),[b] n (%)	16 (45.7)	11 (52.4)	5 (35.7)	9 (50.0)	7 (41.2)
Clinical remission (mMCS),[c] n (%)	9 (25.7)	9 (42.9)	0	6 (33.3)	3 (17.6)
Symptomatic remission,[d] n (%)	11 (31.4)	10 (47.6)	1 (7.1)	7 (38.9)	4 (23.5)
Endoscopic response/improvement,[e] n (%)	9 (25.7)	9 (42.9)	0	6 (33.3)	3 (17.6)
Change in SFS, mean (SD)	–0.8 (1.1)	–1.0 (1.2)	–0.5 (0.7)	–0.9 (1.3)	–0.7(0.8)
Change in RBS, mean (SD)	–1.1 (0.8)	–1.1 (0.9)	–0.9 (0.8)	–1.4 (0.9)	–0.7 (0.7)
Week 52[f]	**Main cohort (N = 18)**	**AT naïve (n = 10)**	**AT experienced (n = 8)**	**MES = 2 (n = 11)**	**MES = 3 (n = 7)**
Change from baseline in RHI,[f] mean (SD)	–13.5 (11.7)	–15.8 (8.1)	–10.6 (15.2)	–15.3 (6.5)	–10.7 (17.4)
RHI remission,[a] n (%)	11 (31.4)	7 (33.3)	4 (28.6)	7 (38.9)	4 (23.5)
RHI ≥50% reduction, n (%)	14 (40.0)	9 (42.9)	5 (35.7)	10 (55.6)	4 (23.5)
RHI ≥7-point reduction, n (%)	14 (40.0)	9 (42.9)	5 (35.7)	10 (55.6)	4 (23.5)
Change in mMCS,[f] mean (SD)	–4.4 (1.8)	–4.3 (2.0)	–4.5 (1.7)	–4.4 (1.9)	–4.4 (1.8)
Clinical response (mMCS),[b] n (%)	16 (45.7)	10 (47.6)	6 (42.9)	11 (61.1)	5 (29.4)
Clinical remission (mMCS),[c] n (%)	7 (20.0)	6 (28.6)	1 (7.1)	5 (27.8)	2 (11.8)
Symptomatic remission,[d] n (%)	12 (34.3)	8 (38.1)	4 (28.6)	8 (44.4)	4 (23.5)
Endoscopic response/improvement,[e] n (%)	12 (34.3)	8 (38.1)	4 (28.6)	8 (44.4)	4 (23.5)
Change in SFS,[g] mean (SD)	–1.5 (1.1)	–1.6 (1.3)	–1.4 (0.9)	–1.5 (1.2)	–1.4 (1.0)
Change in RBS,[g] mean (SD)	–1.6 (0.7)	–1.5 (0.5)	–1.6 (0.9)	–1.7 (0.6)	–1.3 (0.8)

AT, advanced therapy; MES, Mayo Endoscopic Score; mMCS, modified Mayo Clinic Score; RBS, rectal bleeding subscore; RHI, Robarts Histopathology Index; SD, standard deviation; SFS, stool frequency subscore.

[a]RHI remission is an RHI score of ≤3 (with 0 for lamina propria neutrophils score and neutrophils in the epithelium score and without ulcers or erosions).

[b]Clinical response (mMCS) is defined as a decrease from baseline in mMCS of ≥2 points and ≥30% from baseline, plus a decrease in RBS of ≥1 or an absolute RBS of ≤1.

[c]Clinical remission (mMCS) is defined as an RBS of 0, an SFS of ≤1 and an MES of ≤1 without friability.

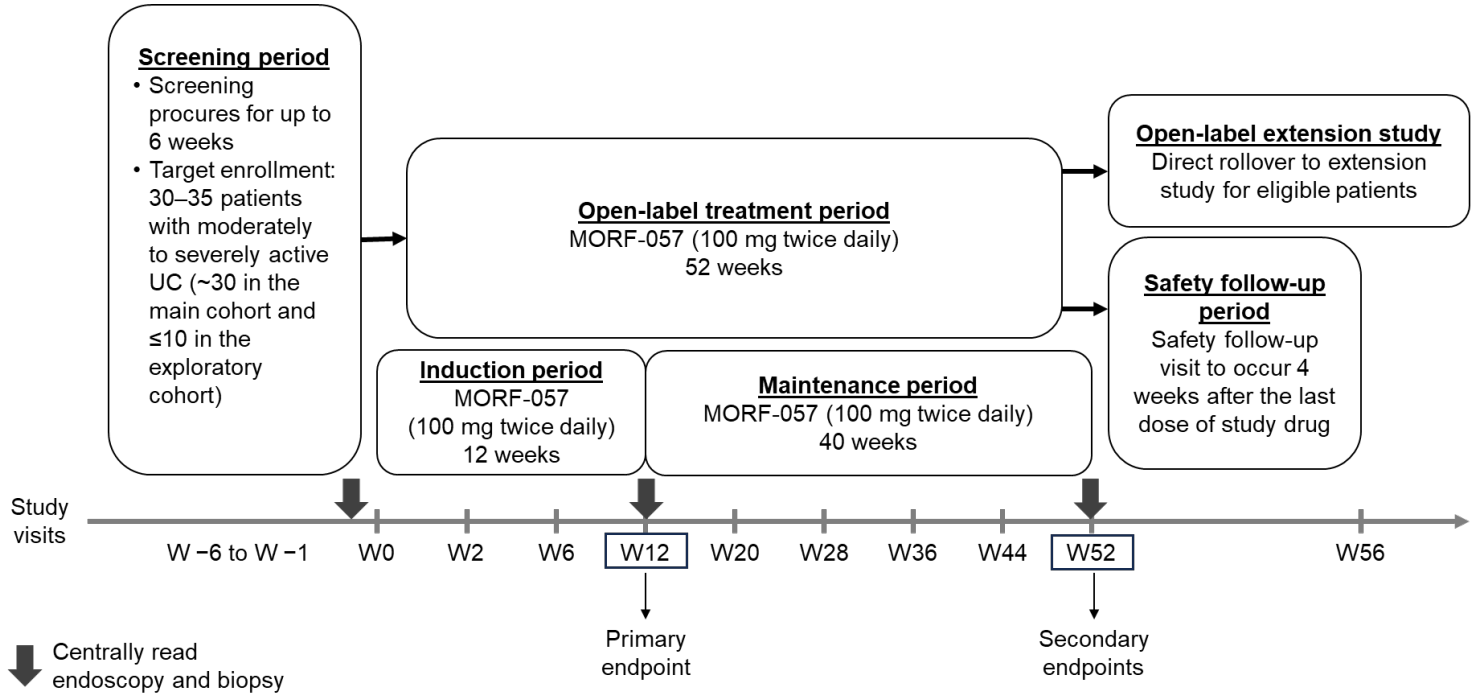
[d]Symptomatic remission is defined as an SFS of 0 (or of 1 with a ≥1-point decrease from baseline) and an RBS of 0.

[e]Endoscopic response/improvement is defined as an MES of ≤1.

[f]Percentages were calculated using the total number of patients enrolled as the denominator.

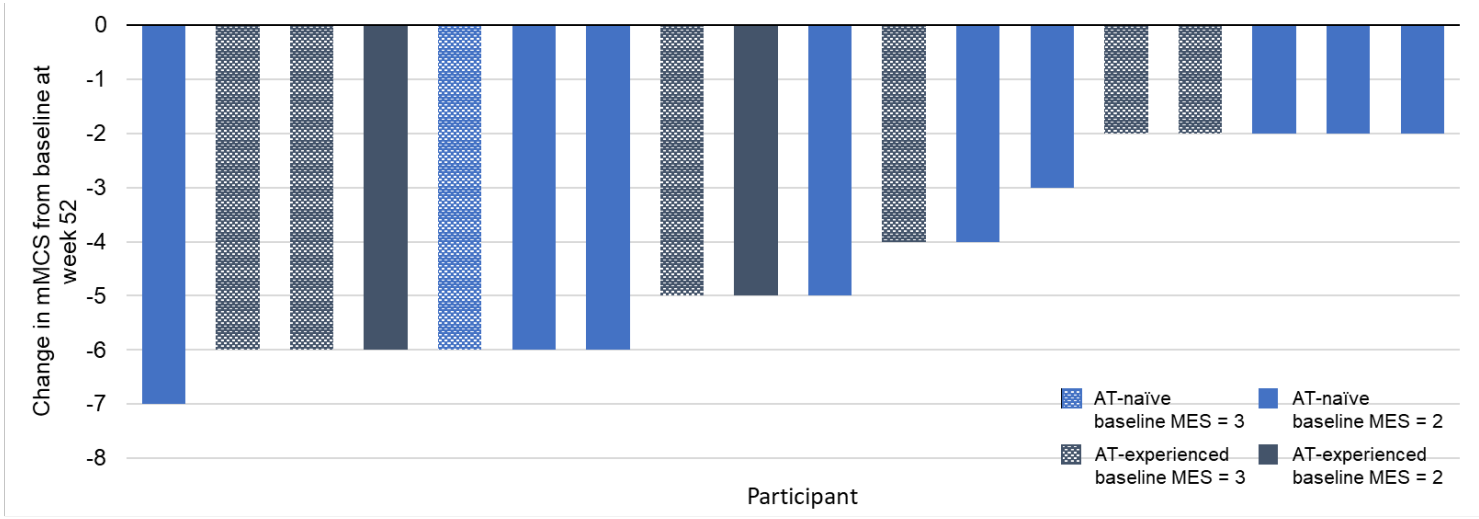
[g]Based on the number of participants who completed the week 52 visit.

Figure S1. Study Design



UC, ulcerative colitis; W, week.

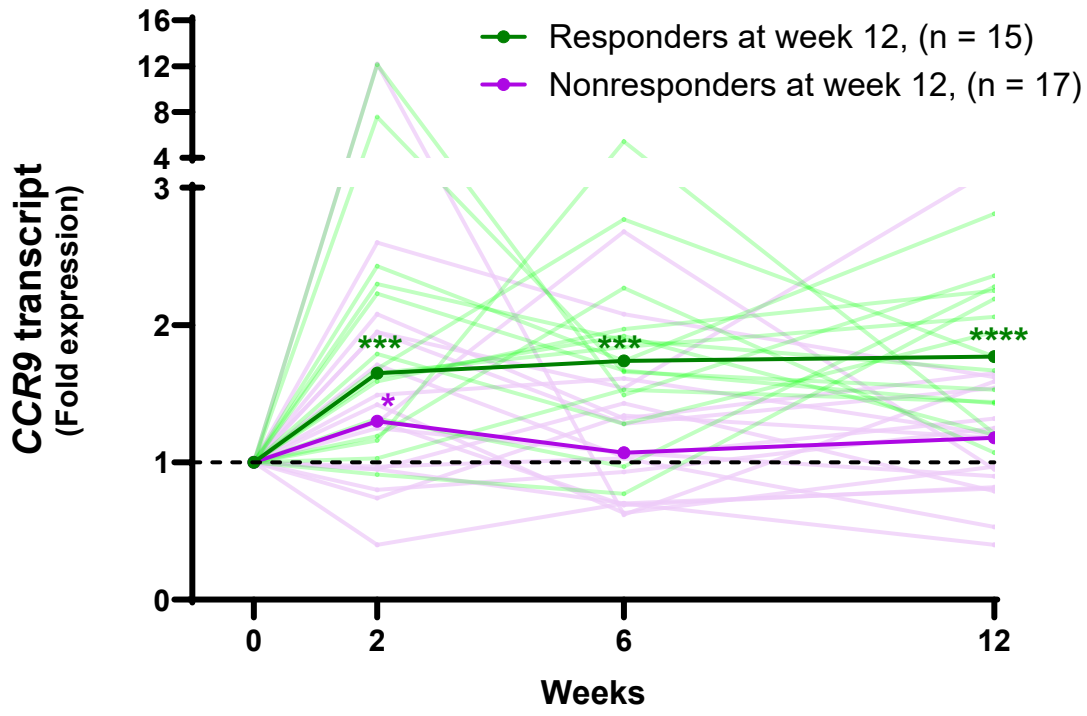
Figure S2. Clinical Improvement Across Key Subpopulations



mMCS response	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			✓	✓	✓
mMCS remission	✓	✓			✓	✓	✓			✓		✓						
RHI decrease from baseline ≥7	✓	✓	✓	✓	✓	✓	✓		✓	✓		✓	✓	✓		✓	✓	
Endoscopic response	✓	✓	✓	✓	✓	✓	✓			✓		✓	✓	✓			✓	

AT, advanced therapy; MES, Mayo Endoscopic Score; mMCS, modified Mayo Clinic Score; RHI, Robarts Histopathology Index.

Figure S3. *CCR9* expression: responders vs nonresponders (main cohort)



Median analysis showing individual sample distribution.
Fold change from baseline/week 0.
One-sample Wilcoxon test: *(*P*-value <0.05); ***(*P*-value <0.001); ****(*P*-value <0.0001).
CCR9, C-C chemokine receptor 9 gene.

Supplemental material

Inclusion and exclusion criteria

Main cohort inclusion criteria

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

Age

1. Aged 18 to 85 years, inclusive, at the time of signing the informed consent form (ICF)

Type of participant and disease characteristics

2. Signs/symptoms of moderately to severely active ulcerative colitis (UC) for at least 3 months prior to screening, and the diagnosis was confirmed during the screening period with the following criteria: a modified Mayo Clinic Score (mMCS) of 5 to 9 (inclusive) with a Mayo Endoscopic Score (MES) ≥2 (confirmed by central reader)
3. Robarts Histopathology Index (RHI) score ≥10
4. Evidence of UC extending at least 15 cm from the anal verge
5. Advanced therapy (AT) naïve or had an inadequate response, loss of response or intolerance to no more than three drugs in two classes of the following:
    a. Tumor necrosis factor alpha (TNF-α) antagonists, including infliximab, adalimumab or golimumab
    b. Interleukin (IL)-12 and IL-23 antagonists, including ustekinumab
    c. Janus kinase (JAK) antagonists, including tofacitinib and upadacitinib
    d. Sphingosine-1-phosphate (S1P) receptor agonists, including ozanimod
    e. Any investigational product with the same mechanism as one of those outlined above (5a through 5d)

f. Integrin inhibitors, including vedolizumab (participants in the exploratory group only)

Note: Participants who have a history of primary nonresponse to two of the classes above will not be eligible. Participants who have received treatment with these agents at subtherapeutic doses, or durations, should be discussed with the medical monitor to assess eligibility

6. Meets the following washout criteria of prior UC therapy relative to study day 1:
    a. TNF-α antagonists: at least 8 weeks
    b. IL-12/IL-23 antagonists, including ustekinumab: at least 8 weeks
    c. JAK antagonists, including tofacitinib and upadacitinib: at least 2 weeks
    d. S1P receptor agonists, including ozanimod: at least 4 weeks
7. If the participant has been receiving any of the nonprohibited medications for UC listed below, he/she must discontinue use at least five half-lives before study day 1 or must agree to maintain stable doses of these concomitant medications starting from the time specified below until the end of the safety follow-up period, with the exception of tapering oral corticosteroid dose after 12 weeks of being in the trial

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

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

Weight

9. Body mass index (BMI) within the range of 18.0 and 40.0 kg/m^2 (inclusive) at screening

Sex and contraceptive/barrier requirements

10. Agrees to abide by the guidelines set forth in the study 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, when having sexual intercourse with a woman of childbearing potential who is not currently pregnant
- Agrees to use a male condom when engaging in any activity that allows for passage of ejaculate to another person

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

- Is a woman of non-childbearing potential

OR

- Is a woman of childbearing potential and agrees to use a contraceptive method that is highly effective with a failure rate of <1% per year during

the study treatment period and for at least 28 days after receiving the last dose of MORF-057

Note: Women who use any oral hormonal contraception must use an additional physical barrier method

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

Informed consent

12. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the ICF and in the study protocol

Exploratory group inclusion criteria

In addition to meeting inclusion criteria 1 through 12, the following criteria must be met for participants to be included in the exploratory group:

13. Intolerant to (eg, infusion-related skin reaction, allergy or side effects unrelated to α4β7 inhibition) or secondary nonresponder to vedolizumab who has been dosed within the past 5 years with the drug. Up to five participants of the 10 exploratory group may be included based on clinical criteria only. The remaining participants must also meet at least one of the following criteria:

a. Documented vedolizumab levels in blood of ≤10 µg/mL 6 to 8 weeks after the most recent dose or at what is considered a clinical trough. If the participant has had vedolizumab levels in blood tested and documented in their medical chart prior to screening, the test does not need to be repeated

b. Non-saturating receptor occupancy of vedolizumab in blood 6 to 8 weeks after the most recent dose

c. Documented presence of antidrug antibodies against vedolizumab. If the participant has had a positive antidrug antibody test documented prior to screening, the test does not need to be repeated

> **Note:** Secondary nonresponse is defined as having initially responded to induction therapy and then had recurrence of symptoms after receiving at least two of the maintenance doses, 300 mg every 8 weeks (discontinuation despite clinical benefit does not qualify)

14. Received the last dose of vedolizumab at least 6 weeks prior to study day 1 to allow sufficient washout

Exclusion criteria

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

Medical conditions

1. Diagnosed with indeterminate colitis, microscopic colitis, ischemic colitis, UC of the rectum (proctitis), radiation colitis, or Crohn's disease or has clinical findings suggestive of Crohn's disease
2. Has current evidence of unresected colonic dysplasia, unresected adenomatous colonic polyps, toxic megacolon, abdominal abscess, symptomatic colonic stricture, fistula, stoma, ileostomy or colostomy at screening
3. Currently requires or is anticipated to require surgical intervention for UC during the study or is planning to undergo major surgery during the study period
4. Surgical procedure requiring general anesthesia within 30 days prior to screening

5. 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. Positive findings on a subjective neurological screening questionnaire or progressive multifocal leukoencephalopathy subjective symptom checklist during screening or prior to the administration of the first dose of study drug on study day 1
7. Active bacterial, viral or parasitic pathogenic enteric infection, including *Clostridium difficile*; cytomegalovirus, hepatitis B or C virus or human immunodeficiency virus (HIV); an infection requiring hospitalization or intravenous antimicrobial therapy, or an opportunistic infection within 3 months prior to screening; any infection requiring oral antimicrobial therapy within 2 weeks prior to screening; or a history of more than one episode of herpes zoster or any episode of disseminated herpes zoster infection
8. Positive diagnostic tuberculosis (TB) test at screening (defined as a positive QuantiFERON test). If the participant has had a confirmed negative QuantiFERON or other interferon gamma release assay test within 90 days prior to screening, the test does not need to be repeated. In cases where the QuantiFERON test result is indeterminate, the participant may have the test repeated once, and if the second test is negative, the participant will be eligible. In the event the second test also has an indeterminate result or QuantiFERON is unavailable, the investigator has the option to perform a purified protein derivative (PPD) skin test. If the PPD reaction is <5 mm, then the participant is eligible. If the reaction is ≥5 mm or PPD testing is not done, the participant is not eligible. An exception can be made for participants with a history of latent TB who are currently receiving treatment for latent TB per local standard care, who will initiate treatment for latent TB before the first dose of study drug or who have

documentation of completing appropriate treatment for latent TB within 2 years prior to study day 1

9. Tests positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) during the screening period. Participants who test positive for SARS-CoV-2 can undergo retesting throughout the screening period. Testing to be performed according to site-specific testing procedures and country-specific requirements
10. 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 (eg, SARS-CoV-2 two-shot vaccination series)
11. Concurrent, clinically significant, serious, unstable comorbidity (such as uncontrolled cardiovascular, pulmonary, hepatic, renal, gastrointestinal, genitourinary, hematologic, coagulation, immunological, endocrine/metabolic or other medical disorder) that, in the judgment of the investigator, would compromise compliance with the protocol, interfere with interpretation of the study results or predispose participants to safety risks
12. Known primary or secondary immunodeficiency
13. 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. History of left ventricular ejection fraction <50%

15. Clinically significant abnormal electrocardiogram at screening, including a QT interval corrected through use of Fridericia's formula (QTcF) ≥450 ms for males and ≥470 ms for females
16. Abnormal hematology (hemoglobin level, white blood cell [WBC] count or platelet count) or coagulation results at screening, as evidenced by the ranges provided below:*

a. Hemoglobin level <8.0 g/dL
b. Absolute WBC count $<3.0 \times 10^9$/L
c. Absolute lymphocyte count $<0.5 \times 10^9$/L
d. Absolute lymphocyte count $>5.0 \times 10^9$/L
e. Absolute neutrophil count $<1.2 \times 10^9$/L
f. Platelet count $<100 \times 10^9$/L or $>1000 \times 10^9$/L
g. International normalized ratio >1.5

17. Clinically significant abnormal urinalysis results, as deemed by the investigator or designee
18. Abnormal organ function at screening, as evidenced by the following:*
    a. Alanine aminotransferase or aspartate aminotransferase >2.5 × upper limit of normal (ULN)
    b. Chronic kidney disease stages 4 and 5, defined as having a glomerular filtration rate <30 mL/min/1.73 m^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 five half-lives (whichever is shorter) prior to study day 1
21. Any previous treatment with vedolizumab or other integrin inhibitors (except participants for the exploratory group)
22. Experiencing toxicities from prior therapy with grade >1 within 1 week prior to first dose of study drug
23. Fecal microbiota transplantation within 3 months prior to screening
24. If treatment with a moderate-to-strong CYP3A4 inducer or inhibitor was received, a washout period of at least 30 days or five half-lives (whichever is shorter) is required prior to study day 1
25. If treatment with a moderate-to-strong organic anion transporter polypeptide-1B inhibitor was received, a washout period of at least 14 days or five half-lives (whichever is shorter) is required prior to study day 1

Prior/concurrent clinical study experience

26. Concurrent participation in any other interventional study

27. Received any investigational therapy within 30 days or five half-lives (whichever is longer) prior to study day 1
28. Previous exposure to MORF-057 and/or a known hypersensitivity to drugs with a similar mechanism to MORF-057

Other exclusions

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

Study Design

Prior treatment failure was defined as inadequate response, loss of response or intolerance to up to three drugs or investigational products in any two of the following drug classes: TNF-α antagonists, IL-12/IL-23 antagonists, JAK antagonists, sphingosine-1-phosphate (S1P) receptor agonists, or integrin inhibitors (including vedolizumab for only the exploratory group).

Nonprohibited medications for UC were 5-ASA, ≤4.8 g/day; oral corticosteroids: prednisone, ≤30 mg/day or budesonide, ≤9 mg/day; 6-mercaptopurine, any stable dose; azathioprine, any stable dose; methotrexate, any stable dose.

Exploratory Endpoints

Exploratory endpoints included the evaluation of the effects of MORF-057 on histological improvement (change from baseline to week 52 in RHI score) and clinical improvement (change from baseline to weeks 6 and 52 in mMCS, and change from baseline to weeks 6, 12, and 52 in full MCS). RHI remission or histologic remission was also assessed and defined as an RHI score of ≤3 (with 0 for lamina propria neutrophils score and neutrophils in the epithelium score and without ulcers or erosions). Clinical remission was determined using mMCS and was defined as a rectal bleeding subscore of 0, a stool frequency subscore of ≤1 and an MES of ≤1 without friability. Symptomatic remission was defined as a stool frequency subscore of 0 (or of 1 with ≥1-point decrease from baseline) and a rectal bleeding subscore of 0, and endoscopic response or improvement was defined as an MES of ≤1. Additional exploratory endpoints included characterizing the PD of MORF-057 in peripheral blood over time via α4β7 and α4β1 ROs and determining blood *CCR9* transcript levels.

Statistical Analyses and Sample Size Estimation

The safety analysis population included all participants in the full analysis set. The PK population included all participants with adequate measurable concentrations to define the maximum observed plasma concentration or the area under the curve. The PD population included all participants in the full analysis set who had at least one measurable postdose PD measurement and its corresponding predose PD measurement for, at minimum, one of the PD biomarkers.

Descriptive statistics are used for all primary, secondary, and exploratory data. Categorial parameters are reported using frequencies and proportions. Continuous parameters are reported using mean, SD, median, minimum, and maximum. A two-sided

one-sample t-test was used to calculate the *P*-value for testing the primary efficacy endpoint for the main cohort. The main cohort and the exploratory group were analyzed separately, unless specified otherwise.

Efficacy Results in Main Cohort Subpopulations

At week 52, AT-naïve participants had a mean (SD) change from baseline in RHI score of –15.8 (8.1). Six participants (28.6%) achieved clinical remission by mMCS, and eight (38.1%) showed endoscopic improvement. Comparatively, AT-experienced participants had a mean (SD) change from baseline in RHI score of –10.6 (15.2); one participant (7.1%) achieved clinical remission, and four (28.6%) showed endoscopic improvement (**table S1**). At week 52, participants with a baseline MES of 2 had a mean (SD) change from baseline in RHI score of –15.3 (6.5); five of these participants (27.8%) achieved clinical remission by mMCS, and eight (44.4%) showed endoscopic improvement. However, participants with a baseline MES of 3 had a mean (SD) change from baseline in RHI score of –10.7 (7.4); two of these participants achieved clinical remission (11.8%), and four showed endoscopic improvement (23.5%; **table S1**). Overall, a greater proportion of participants with a baseline MES of 2 showed clinical improvement compared with participants with a baseline MES of 3 (**table S1**; **figure S2**). Generally, induction responders (n = 13) continued to respond in the maintenance phase, showing a mean (SD) change from baseline in RHI score of –14.6 (11.5) at 52 weeks. Additionally, the 13 induction responders (81.2%) maintained clinical response by mMCS, 7 (43.7%) achieved clinical remission by mMCS and 10 (62.5%) achieved endoscopic improvement.

Table S1. Schedule of activities for the treatment period

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

Dispense stool collection kit[p]	X	X	X	X	X	X	X	X	X	X[p]		
Discuss participation and informed consent in the long-term extension[q]									X	X		
Safety assessments												
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X			X	X					X		
Physical exam[f]	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[s]	X	X	X	X	X	X	X	X	X	X	X	X
PML checklist[t]	X	X	X	X	X	X	X	X	X	X	X	
Haematology and coagulation[u]	X	X	X	X	X	X	X	X	X	X	X	X[b]
Serum chemistry[u]	X	X	X	X	X	X	X	X	X	X	X	X[b]
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X[b]
AE/SAE assessment[v]	X	X	X	X	X	X	X	X	X	X	X	X
PK assessment												
Plasma sample for PK analysis		X[w]	X[w]	X[x]	X[w]	X[x]	X[x]	X[x]	X[x]	X[y]		
PD biomarkers												
Faecal sample for microbiome analyses		X	X	X	X	X	X	X	X	X		
Blood sample for microbiome derived metabolite analysis[z]		X	X	X	X	X	X	X	X	X		
Whole blood sample for RO[aa]		X	X		X							
Whole blood sample for immunophenotyping[bb]		X	X	X	X	X	X	X	X	X		
Blood sample for PIMS[cc]		X	X		X							
PAXgene RNA blood sample for gene expression[dd]		X	X	X	X	X	X	X	X	X		
Blood sample for protein biomarkers[ee]		X	X	X	X	X	X	X	X	X		
Future biomarker research												
Blood PD sample collection for future analysis[ff]		X	X	X	X	X	X	X	X	X		
Blood pharmacogenomics sample collection for future analysis[ff]		X										
Efficacy assessments												
Sigmoidoscopy with biopsy[gg]	X			X[hh]	X					X[ii]		

MCS Physician's Global Assessment	X	X	X	X	X	X	X	X	X	X		
MCS rectal bleeding subscore	X	X	X	X	X	X	X	X	X	X		
MCS stool frequency subscore	X	X	X	X	X	X	X	X	X	X		
Locally and centrally read MES	X			X	X					X		
Centrally read RHI score, continuous Geboes score and NI	X			X	X					X		
Serum for hs-CRP test[jj]	X	X	X	X	X	X	X	X		X		
Faecal sample for faecal calprotectin test	X		X	X	X	X	X	X		X		
Study drug												
Study drug accountability			X	X	X	X	X	X	X	X		
Dispense study drug		X	X	X	X	X	X	X	X	X[kk]		
Study drug administration on site[ll]		X	X	X	X	X	X	X	X	X[mm]		

AE, adverse event; *CCR9*, C-C chemokine receptor 9 gene; *C. diff*, *Clostridium difficile*; ECG, electrocardiogram; EOT, end of treatment; HIV, human immunodeficiency virus; hs-CRP, high-sensitivity C-reactive protein; ICF, informed consent form; MCS, Mayo Clinic Score; MES, Mayo Endoscopic Score; NI, Nancy Index; PD, pharmacodynamics; PIMS, physiological intermolecular modulation spectroscopy; PK, pharmacokinetics; PML, progressive multifocal leukoencephalopathy; RHI, Robarts Histopathology Index; 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 listed procedures may be performed at any time during the SCR period.

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

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

[d]Participants who will not enroll into the long-term extension will complete the SFU visit, which should be performed 28 days (+7 days) after the participant takes the last dose of study drug. Participants who choose to enroll into the long-term extension after visit 10/EOT will complete an SFU visit at week 82.

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

[f]The 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.

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

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

[i]SARS-CoV-2 testing will be performed during the SCR period according to site-specific procedures and country-specific requirements. Participants who test positive for SARS-CoV-2 can undergo retesting throughout the SCR period.
[j]If QuantiFERON or other interferon gamma release assay testing occurred within 90 days prior to SCR, the test does not need to be repeated. In cases where the QuantiFERON test is indeterminate, the participant may have the test repeated once, and if their second test is negative, they will be eligible. In the event a second test is also indeterminate or QuantiFERON is unavailable, the investigator has the option to perform a purified protein derivative skin test.
[k]Cytomegalovirus will be tested with the biopsy sample collected at SCR.
[l]Participants being considered for the exploratory group will require testing for vedolizumab blood levels, RO of vedolizumab and antidrug antibodies against vedolizumab. If the participant has had vedolizumab levels in blood or presence of antidrug antibodies against vedolizumab tested and documented in their medical chart prior to SCR, the test does not need to be repeated.
[m]Participant diaries are to be completed at the end of each day by the participant at home and brought to each study visit for review by study personnel. See Section 8.5 of the study protocol for the required contents of the participant diaries.
[n]Only required for women of childbearing potential. A serum test should be used at SCR, and a urine test should be used throughout rest of the study. On day 1, a urine test must be completed, and results must be reviewed prior to start of the study drug.
[o]Serum test for follicle-stimulating hormone level to be performed only for female participants of non-childbearing potential who are not surgically sterile.
[p]Stool collection kits are to be dispensed to participants at the visits indicated. The participant should use this kit to collect one sample at home within 24 hours before the next site visit. The sample should be frozen immediately and brought to the clinic on the day of the site visit. Note: Sample is to be collected prior to bowel preparation for visits 4, 5 and 10/EOT. Stool collection kits will be dispensed at visit 10 only for participants continuing in the long-term extension.
[q]Participants will be provided the option to participate in the long-term extension. Participants who want to continue in the long-term extension will sign a separate ICF.
[r]A complete physical exam is to be performed at SCR and visit 10/EOT, and a targeted exam may be performed at all other required visits (see Section 8.8.1 of the study protocol for descriptions). For unscheduled visits that involve the investigator or clinical assessment and not the visits that would be for dispensing study drug or for laboratory draws only, the type of exam will be at the investigator's discretion and determined based on the reason for the visit.
[s]Vital signs to be recorded at all visits that involve the investigator or clinical assessment visits and not the visits that would be for dispensing study drug or for laboratory draws only. These will include blood pressure, heart rate, respiratory rate and temperature.
[t]If the results of the questionnaire are suggestive of PML, a full neurological exam and, if indicated, additional testing are to be performed.
[u]Blood samples for hematology, coagulation and serum chemistry assessments will be collected before the AM dose on visits 2–10.
[v]Record AEs from the time the ICF is signed. Participants are to be contacted by phone as needed to monitor the status of the event.
[w]PK testing at visits 2, 3 and 5: Blood sampling will be required before the AM dose and at 1, 2, 3, 4 and 6 hours after the AM dose. Blood sampling will be optional at 8, 10 and 12 hours after the AM dose. The 12-hour post-AM dose sample will be collected prior to the second daily dose. Time windows for PK sampling can be found in Section 8.10.1 of the study protocol. Each pre-AM dose sample should be obtained within approximately 30 minutes before the AM dose is administered.
[x]PK testing at visits 4, 6, 7, 8 and 9: Blood sampling will be required before the AM dose and at 1 and 3 hours after the AM dose. Time windows for PK sampling can be found in Section 8.10.1 of the study protocol. Each pre-AM sample should be obtained within approximately 30 minutes before the AM dose is administered and at 12 hours (±1 hour) after the previous evening's PM dose.
[y]PK testing at visit 10/EOT: Blood sampling will be required before the AM dose. The sample should be obtained within approximately 30 minutes before the AM dose is administered and at 12 hours (±1 hour) after the previous evening's PM dose.

[z]Blood samples for microbiome-derived metabolite analysis will be collected before the AM dose on visits 2–10. Microbiome sampling to occur at the corresponding PK sampling time.
[aa]RO testing at visits 2, 3 and 5: The blood samples for RO testing collected before the AM dose are required. The 12-hour post-AM dose samples for RO testing are optional. The 12-hour post-AM dose sample will be collected prior to the second daily dose. RO sampling to occur at the corresponding PK sampling time.
[bb]Blood samples for immunophenotyping (lymphocyte subset analysis) will be collected before the AM dose on visits 2–10. Collection time at visits 3–10 must be consistent with baseline (visit 2) collection ±2 hours. Immunophenotype sampling to occur at the corresponding PK sampling time.
[cc]Blood samples for PIMS analysis will be collected before the AM dose on visits 2 and 5. PIMS sampling to occur at the corresponding PK sampling time.
[dd]PAXgene RNA blood samples (for *CCR9* analysis) will be collected before the AM dose on visits 2–10. Collection time at visits 3–10 must be consistent with baseline (visit 2) collection ±2 hours. PAXgene sampling to occur at the corresponding PK sampling time.
[ee]Blood samples for protein biomarkers will be collected before the AM dose on visits 2–10. Protein biomarker sampling to occur at the corresponding PK sampling time.
[ff]Participation in future biomarker research sample collection is optional. Blood PD samples will be collected before the AM dose on visits 2–10. Blood pharmacogenomics samples will be collected before the AM dose on visit 2. PD and pharmacogenomics sampling to occur at the corresponding PK sampling time.
[gg]Full colonoscopy is optional at any time if the investigator deems it necessary. The SCR endoscopy procedure should be scheduled at least 16 days prior to the planned start of the study drug (day 1) to allow for central reading. Colonic mucosa biopsies will be collected for cytomegalovirus testing (SCR only), histopathology, microbiome, spatial transcriptomics/proteomics and gene expression analyses.
[hh]The visit 4 endoscopy is optional.
[ii]For the visit 10/EOT endoscopy procedure, there is a window of ±7 days from the actual visit date. For participants who discontinue treatment before week 6, a repeat sigmoidoscopy will be performed any time after MORF-057 dosing on day 14. For participants who discontinue treatment after week 6, a repeat sigmoidoscopy will be performed any time if the optional week 6 sigmoidoscopy was not performed. If the week 6 optional sigmoidoscopy was performed, a repeat sigmoidoscopy will be performed after the 28th day after the week 6 sigmoidoscopy. Participants who complete a sigmoidoscopy/colonoscopy within 12 weeks of the EOT visit are not required to repeat the procedure. If the procedure was performed further than 12 weeks, please consult the sponsor medical monitor.
[jj]Blood samples for hs-CRP analysis will be collected before the AM dose on visits 2–8 and visit 10.
[kk]At visit 10/EOT, the study drug will be dispensed only for participants continuing treatment in the long-term extension.
[ll]AM dosing required on site for all visits. For visits 2, 3 and 5, if optional PK/RO sampling will be performed at 8–12 hours after the AM dose, the PM dose must not be taken until PK/RO sampling is complete for that day.
[mm]At visit 10/EOT, participants will only receive an AM dose for the day. No PM dose will be provided.

Table S1. Main Cohort Efficacy Results by Subgroup Analysis.

Week 12	Main cohort (N = 35)	AT naïve (n = 21)	AT experienced (n = 14)	MES = 2 (n = 18)	MES = 3 (n = 17)
Change from baseline in RHI, mean (SD)	–6.4 (11.2)	–7.4 (11.9)	–4.8 (10.3)	–6.9 (12.1)	–5.8 (10.4)
RHI remission,[a] n (%)	8 (22.9)	6 (28.6)	2 (14.3)	6 (33.3)	2 (11.8)
RHI ≥50% reduction, n (%)	12 (34.3)	9 (42.9)	3 (21.4)	9 (50.0)	3 (17.6)
RHI ≥7-point reduction, n (%)	17 (48.6)	12 (57.1)	5 (35.7)	10 (55.6)	7 (41.2)
Change in mMCS, mean (SD)	–2.3 (2.1)	–2.9 (2.4)	–1.6 (1.5)	–2.7 (2.4)	–1.9 (1.9)
Clinical response (mMCS),[b] n (%)	16 (45.7)	11 (52.4)	5 (35.7)	9 (50.0)	7 (41.2)
Clinical remission (mMCS),[c] n (%)	9 (25.7)	9 (42.9)	0	6 (33.3)	3 (17.6)
Symptomatic remission,[d] n (%)	11 (31.4)	10 (47.6)	1 (7.1)	7 (38.9)	4 (23.5)
Endoscopic response/improvement,[e] n (%)	9 (25.7)	9 (42.9)	0	6 (33.3)	3 (17.6)
Change in SFS, mean (SD)	–0.8 (1.1)	–1.0 (1.2)	–0.5 (0.7)	–0.9 (1.3)	–0.7(0.8)
Change in RBS, mean (SD)	–1.1 (0.8)	–1.1 (0.9)	–0.9 (0.8)	–1.4 (0.9)	–0.7 (0.7)
Week 52[f]	**Main cohort (N = 18)**	**AT naïve (n = 10)**	**AT experienced (n = 8)**	**MES = 2 (n = 11)**	**MES = 3 (n = 7)**
Change from baseline in RHI,[f] mean (SD)	–13.5 (11.7)	–15.8 (8.1)	–10.6 (15.2)	–15.3 (6.5)	–10.7 (17.4)
RHI remission,[a] n (%)	11 (31.4)	7 (33.3)	4 (28.6)	7 (38.9)	4 (23.5)
RHI ≥50% reduction, n (%)	14 (40.0)	9 (42.9)	5 (35.7)	10 (55.6)	4 (23.5)
RHI ≥7-point reduction, n (%)	14 (40.0)	9 (42.9)	5 (35.7)	10 (55.6)	4 (23.5)
Change in mMCS,[f] mean (SD)	–4.4 (1.8)	–4.3 (2.0)	–4.5 (1.7)	–4.4 (1.9)	–4.4 (1.8)
Clinical response (mMCS),[b] n (%)	16 (45.7)	10 (47.6)	6 (42.9)	11 (61.1)	5 (29.4)
Clinical remission (mMCS),[c] n (%)	7 (20.0)	6 (28.6)	1 (7.1)	5 (27.8)	2 (11.8)
Symptomatic remission,[d] n (%)	12 (34.3)	8 (38.1)	4 (28.6)	8 (44.4)	4 (23.5)
Endoscopic response/improvement,[e] n (%)	12 (34.3)	8 (38.1)	4 (28.6)	8 (44.4)	4 (23.5)
Change in SFS,[g] mean (SD)	–1.5 (1.1)	–1.6 (1.3)	–1.4 (0.9)	–1.5 (1.2)	–1.4 (1.0)
Change in RBS,[g] mean (SD)	–1.6 (0.7)	–1.5 (0.5)	–1.6 (0.9)	–1.7 (0.6)	–1.3 (0.8)

AT, advanced therapy; MES, Mayo Endoscopic Score; mMCS, modified Mayo Clinic Score; RBS, rectal bleeding subscore; RHI, Robarts Histopathology Index; SD, standard deviation; SFS, stool frequency subscore.

[a]RHI remission is an RHI score of ≤3 (with 0 for lamina propria neutrophils score and neutrophils in the epithelium score and without ulcers or erosions).

[b]Clinical response (mMCS) is defined as a decrease from baseline in mMCS of ≥2 points and ≥30% from baseline, plus a decrease in RBS of ≥1 or an absolute RBS of ≤1.

[c]Clinical remission (mMCS) is defined as an RBS of 0, an SFS of ≤1 and an MES of ≤1 without friability.

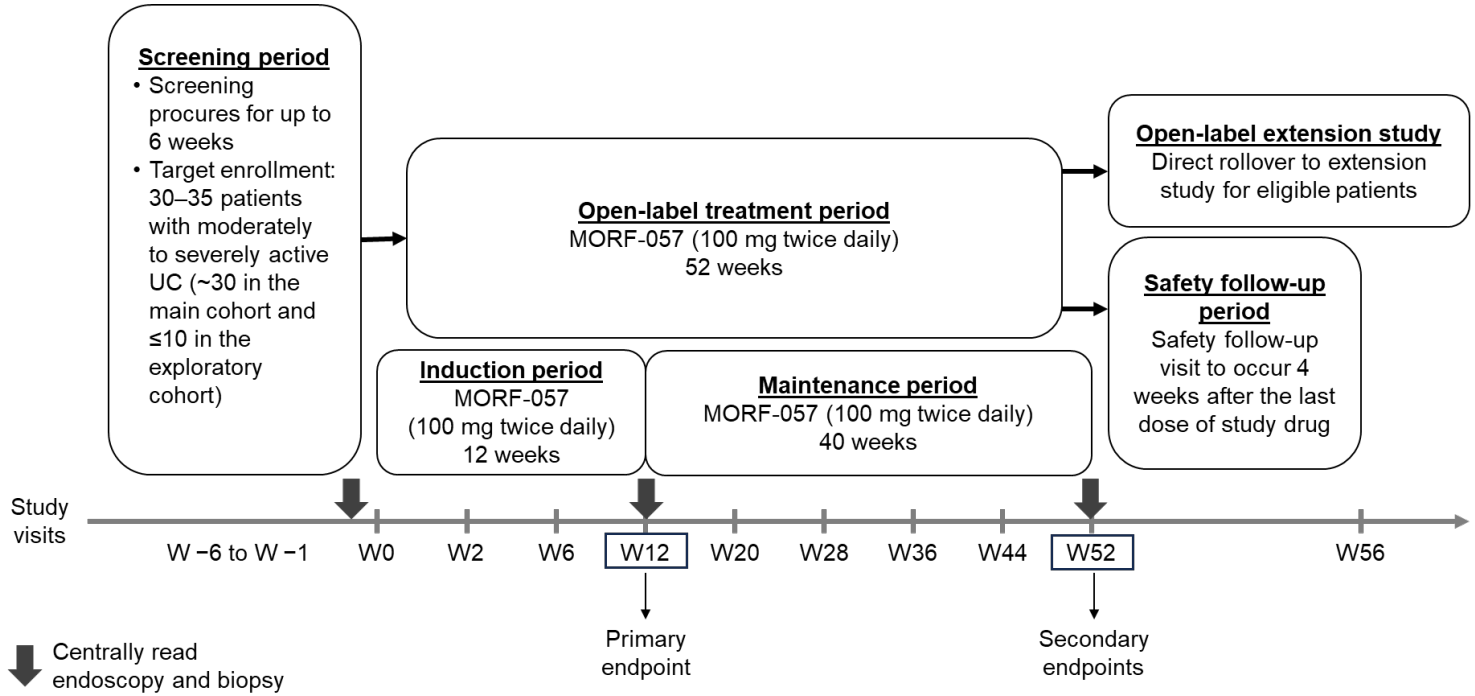
[d]Symptomatic remission is defined as an SFS of 0 (or of 1 with a ≥1-point decrease from baseline) and an RBS of 0.

[e]Endoscopic response/improvement is defined as an MES of ≤1.

[f]Percentages were calculated using the total number of patients enrolled as the denominator.

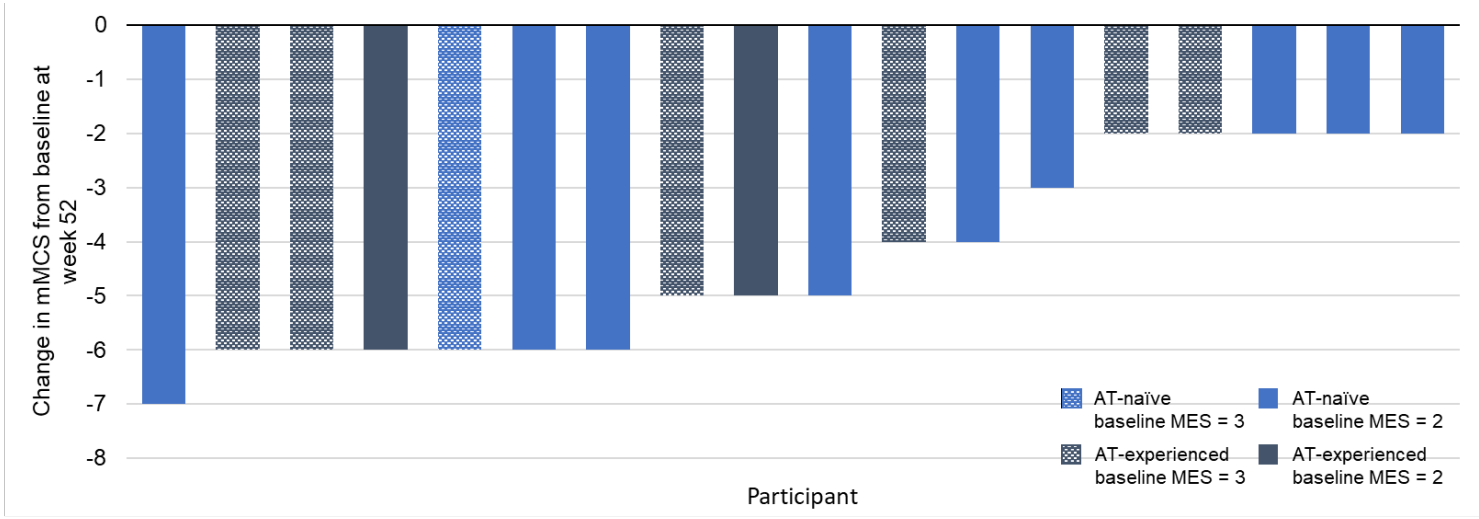
[g]Based on the number of participants who completed the week 52 visit.

Figure S1. Study Design



UC, ulcerative colitis; W, week.

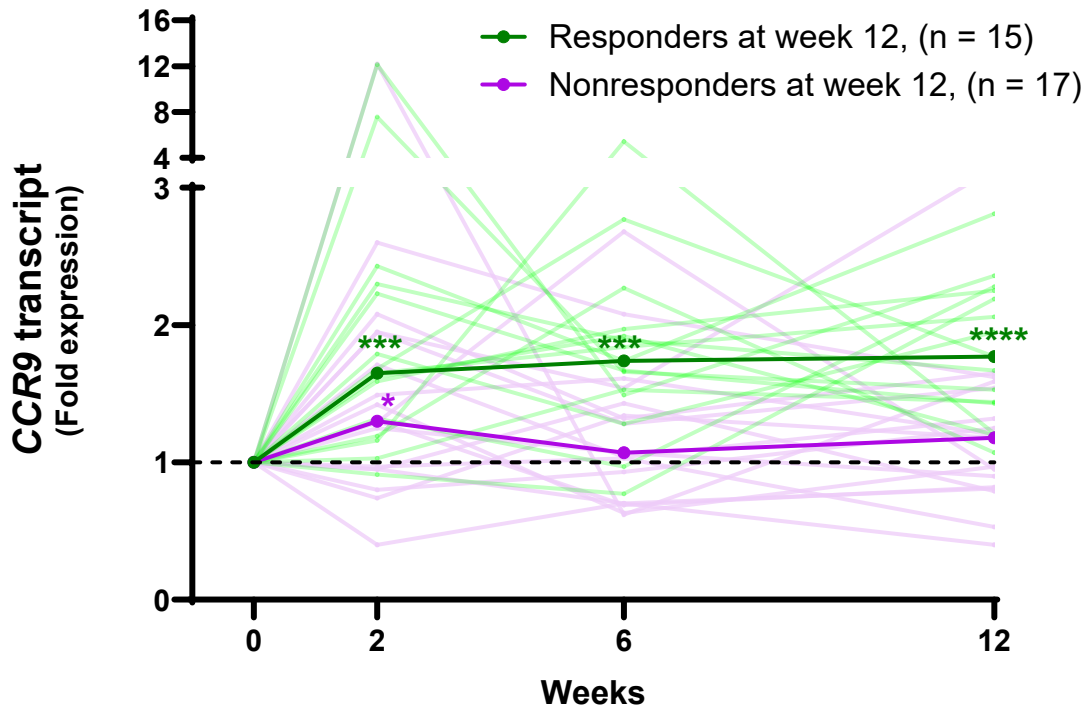
Figure S2. Clinical Improvement Across Key Subpopulations



mMCS response	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			✓	✓	✓
mMCS remission	✓	✓			✓	✓	✓			✓		✓						
RHI decrease from baseline ≥7	✓	✓	✓	✓	✓	✓	✓		✓	✓		✓	✓	✓		✓	✓	
Endoscopic response	✓	✓	✓	✓	✓	✓	✓			✓		✓	✓	✓			✓	

AT, advanced therapy; MES, Mayo Endoscopic Score; mMCS, modified Mayo Clinic Score; RHI, Robarts Histopathology Index.

Figure S3. *CCR9* expression: responders vs nonresponders (main cohort)



Median analysis showing individual sample distribution.
Fold change from baseline/week 0.
One-sample Wilcoxon test: *(*P*-value <0.05); ***(*P*-value <0.001); ****(*P*-value <0.0001).
CCR9, C-C chemokine receptor 9 gene.