CLINICAL STUDY PROTOCOL

Protocol Number:	VTX002-201
Protocol Title:	A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Clinical Efficacy and Safety of VTX002 in Subjects with Moderately to Severely Active Ulcerative Colitis
Short Title:	VTX002 versus Placebo for the Treatment of Moderately to Severely Active Ulcerative Colitis
Compound:	VTX002
Study Phase:	2
IND Number:	[redacted]
EudraCT Number:	2021-003050-23
Sponsor:	Oppilan Pharma Ltd, a wholly owned subsidiary of Ventyx Biosciences, Inc. 5 New Street Square London UK EC4A 3TW
Sponsor's Responsible Medical Officer:	[redacted]
Sponsor's Clinical Lead:	[redacted] 12790 El Camino Real, Suite 200 San Diego, CA 92130 USA [redacted]
SAE Reporting:	[redacted]
Date of Protocol:	Version 6.0, 21 July 2023

Protocol Amendment Summary of Changes

DOCUMENT HISTORY	
Document	**Date**
Protocol V1.0	24 June 2021
Protocol V2.0*	17 January 2022
Protocol V3.0	01 June 2022
Protocol V4.0	19 January 2023
Protocol V5.0	09 May 2023
Protocol V6.0	21 July 2023

*Protocol V2.0 was submitted only to the FDA.

Version 6.0 dated 21 July 2023

Overall Rationale for the Amendment

The overall rationale for the protocol amendment Version 6.0 is to make the following changes and administrative updates:

- Clarify the sample size calculation
- Update and clarify endpoint definitions
- Update the follow-up period for partner pregnancy outcomes
- Update address for Sponsor's Clinical Lead

This protocol amendment Version 6.0 is considered Substantial by the Sponsor, in accordance with international regulations.

Summary of Changes Table

The changes of the protocol amendment Version 6.0 in comparison to Version 5.0 are summarized in a tabular fashion below. New text is shown in *italics*, deleted text is shown in ~~strikeout~~, and **bold** text is informational. In addition to the changes provided in the Summary of Changes table, minor editorial changes have been made throughout the protocol.

Version 6.0 vs Version 5.0

Section No. and Name	Description of Change	Brief Rationale
Title Page	[redacted] *12790 El Camino Real, Suite 200* *San Diego, CA 92130 USA*~~*662 Encinitas Boulevard, Suite 250*~~ ~~*Encinitas, CA 92024 USA*~~	To update the address for Sponsor's Clinical Lead
Synopsis – Overall Design Section 4.1: Overall Design	Approximately ~~*180*~~ *189* eligible participants will be randomized in a 1:1:1 ratio to receive VTX002 30 mg, VTX002 60 mg, or matching placebo, once daily (approximately ~~*60*~~ *63* participants per treatment group).	To update the approximate number of participants in the study and each treatment group based on the clarified sample size calculation (Section 9.2)
Synopsis – Overall Design Section 4.2: Schema	**The value for N was changed from 180 to 189.**	To update the Study Schema to reflect the approximate number of participants in the study
Synopsis – Study Periods Section 4.1.2: Induction Treatment Period	On Day 1, eligible participants will be randomized in a 1:1:1 ratio to receive VTX002 30 mg, VTX002 60 mg, or matching placebo orally once a day (approximately ~~*60*~~ *63* participants per treatment group).	To update the approximate number of participants in each treatment group based on the clarified sample size definition (Section 9.2)
Section 3.3: Endpoint Definitions	Clinical remission: stool frequency (SF) subscore = 0 *or 1* ~~(or = 1 with a ≥ 1 point decrease from baseline)~~, RB subscore = 0, and endoscopic subscore (ES) ≤ 1 (excluding friability)	To update the definition for clinical remission based on FDA feedback
Section 3.3: Endpoint Definitions	Clinical remission using total MCS: Total MCS ≤ 2 points with no individual subscore > 1 point (SF subscore = 0 *or 1* ~~[or = 1 with a ≥ 1 point decrease from baseline]~~, RB subscore = 0, ES ≤ 1 [excluding friability], Physician Global Assessment [PGA] ≤ 1, and SF + RB + ES + PGA ≤ 2)	To update the definition for clinical remission using total MCS based on FDA feedback
Section 3.3: Endpoint Definitions	Symptomatic remission: SF subscore = 0 *or 1* ~~(or = 1 with a ≥ 1 point decrease from baseline)~~ and RB subscore = 0	To update the definition for symptomatic remission based on FDA feedback
Section 9.2: Determination of Sample Size	Under these assumptions and with a 1:1 randomization ratio*, two-group chi-squared test,* and two-sided significance level of 5%, a sample of ~~*54*~~ *57* participants	To clarify the sample size calculation

	per treatment group will be sufficient to achieve *at least* 80~~.1~~% power. Adding a 10% inflation for dropouts results in ~~60~~ *63* participants per treatment group and ~~180~~ *189* in total.	
Appendix 5 Collection of Pregnancy Information	*Pregnant partners should be followed until 12 months after their delivery date for outcomes of both the mother and child.* ~~Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date.~~	To update the follow-up period for partner pregnancy outcomes based on FDA feedback

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1.0 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Clinical Efficacy and Safety of VTX002 in Subjects with Moderately to Severely Active Ulcerative Colitis

Short Title: VTX002 versus Placebo for the Treatment of Moderately to Severely Active Ulcerative Colitis

Rationale

Ulcerative colitis (UC) is a chronic recurrent, remittent, or progressive inflammatory condition that affects the colonic mucosa and is associated with an increased risk for colon cancer. Existing standard of care agents for UC primarily work by treating the acute symptoms of UC, inducing remission in the majority of cases, with approximately 60% to 70% of patients achieving remission with first-line corticosteroid therapy. Of the patients who receive second-line therapy such as biologics, about 30% to 40% of patients do not respond to treatment despite optimal therapy, while another 23% to 46% of patients lose response over time or discontinue treatment, resulting in limited clinical benefits. There remains meaningful unmet medical need, including a significant underserved set of patients who will not respond or become unresponsive to current therapies. VTX002 (formerly known as OPL-002) is an oral small molecule compound being developed for the treatment of moderately to severely active UC. VTX002 is a selective sphingosine-1-phosphate receptor (S1PR) modulator. The sphingosine-1-phosphate (S1P) signal transduction through the S1PRs plays an important role in a series of responses, including inflammation and repair processes, which play an important role in several immune-mediated inflammatory diseases. The available nonclinical and clinical data support the initiation of a Phase 2 study of VTX002 in participants with moderate to severe UC. This Phase 2 study aims to evaluate the efficacy and safety of VTX002 tablets for daily oral administration in participants with moderately to severely active UC.

Overall Design

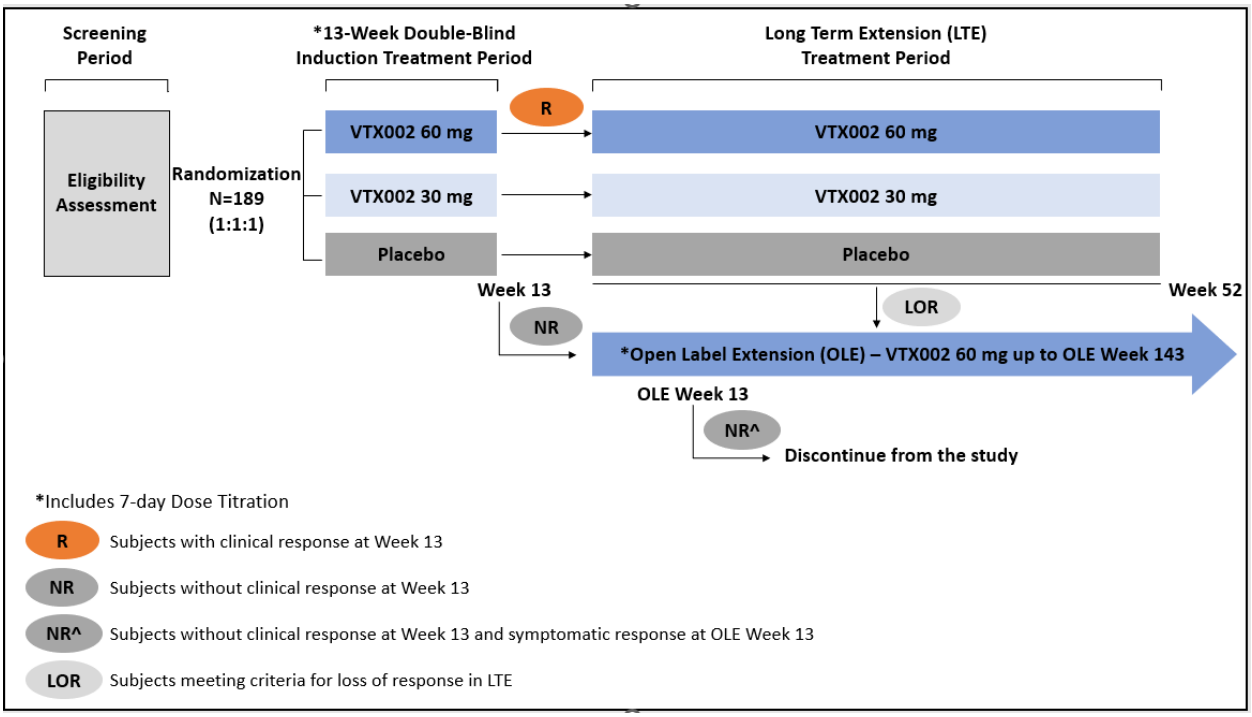
This is a multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of VTX002 30 mg and 60 mg in participants with moderately to severely active UC following daily oral administration of VTX002 as a tablet. Approximately 189 eligible participants will be randomized in a 1:1:1 ratio to receive VTX002 30 mg, VTX002 60 mg, or matching placebo, once daily (approximately 63 participants per treatment group).

The target patient population will include:

- Patients who have had an inadequate response, loss of response, or intolerance to conventional therapy and are naïve to biologic/Janus kinase (JAK) inhibitors (conventional failed).
- Patients who have had an inadequate response, loss of response, or intolerance to a biologic/JAK inhibitor (biologic/JAK inhibitor failed). Patients in this category may have received prior conventional therapy. It is expected that approximately 35% of participants in the study will have had an inadequate response to biologics.

The study consists of a 28-day Screening Period, a 13-week double-blind Induction Treatment Period (including 7 days of titration followed by 12 weeks of treatment at the assigned dose), a Long-Term Extension (LTE) Treatment Period of up to 39 weeks, an Open-Label Extension (OLE) Treatment Period of up to 143 weeks, and a 2-week Follow-Up Period. The maximal duration of treatment including the Induction Period, LTE and OLE will be 36 months.

A study schema is presented below.



The duration of study participation for each participant is planned to be approximately 162 weeks, and the total duration of the study is planned to be approximately 60 months. Approximately 120 study centers in 15 countries are expected to participate.

Objectives

Primary Objective

- Assess the efficacy of VTX002 when administered for 13 weeks on clinical remission

Secondary Objectives

- Assess the efficacy of VTX002 when administered for 13 weeks on endoscopic changes, symptomatic response and remission, histology, and mucosal healing
- Assess the safety and tolerability of VTX002
- Assess the pharmacokinetics (PK) of VTX002

Long-Term and Open-Label Extension Objectives

- Assess the efficacy of VTX002 through the LTE and OLE Treatment Periods on endoscopic changes, symptomatic response and remission, histology, and mucosal healing
- Assess the safety of VTX002 through the LTE and OLE Treatment Periods

Exploratory Objectives

- Assess the effect of VTX002 on health-related quality of life (HRQoL) outcomes and biomarkers

Endpoints

The primary and four key secondary endpoints will be tested for superiority of VTX002 60 mg vs placebo and VTX002 30 mg vs placebo. The remaining endpoints will be presented descriptively.

Primary Endpoint

- The proportion of participants with clinical remission at Week 13 using modified Mayo score (MMS)

Key Secondary Endpoints

- The proportion of participants with endoscopic improvement at Week 13
- The proportion of participants with symptomatic remission at Week 13
- The proportion of participants with histologic remission at Week 13
- The proportion of participants with endoscopic improvement-histologic remission at Week 13

Other Secondary Endpoints

- The proportion of participants with clinical response using MMS at Week 13
- The proportion of participants with endoscopic remission at Week 13
- The proportion of participants with endoscopic and histologic remission at Week 13
- The proportion of participants with endoscopic and clinical remission at Week 13
- The proportion of participants with endoscopic, histologic, and clinical remission at Week 13
- The proportion of participants with symptomatic remission at Weeks 4, 8, 10
- The proportion of participants with symptomatic response at Weeks 4, 8, 10, 13
- The proportion of participants with clinical remission using total Mayo Clinic score (MCS) at Week 13
- The proportion of participants with clinical response using total MCS at Week 13
- The proportion of participants with histologic improvement at Week 13
- Proportion of participants with any decrease from baseline in Geboes Index score at Week 13
- The proportion of participants with histologic-endoscopic mucosal improvement (HEMI) at Week 13
- The proportion of participants with UC-related hospitalizations

- The proportion of participants requiring UC-related surgeries, including colectomy
- Plasma concentrations of VTX002, assessed from samples collected predose at Weeks 0, 1, 4, 8, and 13 in the Induction Treatment Period, and Weeks 18, 26, 36, and 52 in the LTE Treatment Period; at the 1-Week and 2-Week Follow-Up visits; and at 2, 4, and 6 hours (± 15 minutes) postdose at Week 0

Safety Endpoints

- Incidence and severity of adverse events
- Incidence and severity of laboratory abnormalities, and change from baseline in laboratory values (eg, hematology and serum chemistry)
- Incidence of clinically significant vital sign abnormalities and changes from baseline

Exploratory Endpoints

The endpoints described here will be analyzed separately for the Induction Treatment Period, LTE Treatment Period, and OLE Treatment Period. OLE analyses will be described in detail in the Statistical Analysis Plan (SAP).

- Proportion of participants with clinical remission after 52 weeks of treatment
- Proportion of participants with clinical remission after 13 and 52 weeks of treatment
- Proportion of participants with symptomatic remission at Weeks 18, 26, 36, and 52
- Proportion of participants with endoscopic and histologic remission after 52 weeks of treatment
- Proportion of participants with endoscopic improvement-histologic remission after 52 weeks of treatment
- Proportion of participants with endoscopic and clinical remission after 52 weeks of treatment
- Proportion of participants with endoscopic, histologic, and clinical remission after 52 weeks of treatment
- Proportion of participants with HEMI after 52 weeks of treatment
- Proportion of participants with clinical response after 52 weeks of treatment
- Proportion of participants with symptomatic response at Weeks 18, 26, 36, and 52
- Proportion of participants with symptomatic response at OLE Week 13, and at each additional OLE visit
- Proportion of participants with any decrease from baseline in Geboes Index score at Week 52
- Change from baseline in fecal calprotectin (FCP) at Weeks 1, 4, 8, 13, 26, 36, 52, and at visits during the OLE
- Change from baseline in C-reactive protein (CRP) at Weeks 1, 4, 8, 13, 26, 36, 52, and at visits during the OLE
- Change from baseline in partial Mayo score (PMS) at Weeks 4, 8, 13, 18, 26, 36, 52, and at visits during the OLE
- Change from baseline in total MCS at Week 52
- Change from baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) score at Weeks 13 and 52

- Change and percentage change from baseline in lymphocyte counts at Weeks 1, 4, 8, 13, 26, 36, and 52

Inclusion Criteria

Participants must meet ALL of the following inclusion criteria to be eligible for enrollment into the study:

1. Men or women, 18 to 80 years of age, inclusive, at the time of consent
2. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the Informed Consent Form

Disease-Specific

3. Diagnosed with UC ≥ 3 months prior to Screening. The diagnosis of UC must be confirmed by endoscopic and histologic evidence. The endoscopy and histology report should be present in the source documents; however, if not available, the Screening endoscopy and histology may serve as such.
4. Active UC confirmed by endoscopy with ≥ 10 cm rectal involvement. Participants with proctitis only at baseline who meet the other eligibility criteria for inclusion, including the endoscopic and rectal bleeding criteria for moderate to severe disease, will be capped at 10% of the total participants enrolled.
5. Moderately to severely active UC, defined as an MMS of 5 to 9, including an endoscopic subscore (ES) ≥ 2 and a rectal bleeding (RB) subscore ≥ 1
6. Surveillance colonoscopy (performed according to local standard) within 12 months before baseline to rule out dysplasia in participants with pancolitis > 8 years duration or participants with left-sided colitis > 12 years duration. Participants without a surveillance colonoscopy within the prior 12 months will have a colonoscopy at Screening (ie, in place of Screening proctosigmoidoscopy). Any adenomatous polyps must be removed per local standard of care prior to the first dose of study drug.

Prior Treatment Failure

7. Demonstrated inadequate response to, loss of response to, or intolerance to at least 1 of the following therapies:
    a. Conventional therapy:
        i. Oral 5-aminosalicylic acid (5-ASA) compounds
        ii. Corticosteroids
        iii. Thiopurines (eg, azathioprine or 6-mercaptopurine)
    b. Biologic therapy or JAK inhibitor therapy:
        i. Anti-tumor necrosis factor alpha (TNFα) antibodies (eg, infliximab, adalimumab, or golimumab)
        ii. Anti-interleukin (anti-IL)12/23 (eg, ustekinumab)
        iii. Anti-integrin antibodies (eg, vedolizumab)

iv. JAK inhibitors (eg, tofacitinib, upadacitinib)

Note: The medication used to qualify the participant for entry into this category of biologic therapy or JAK inhibitor therapy must be approved for the treatment of UC in the country of use.

General Safety

8. Adequate hepatic function, defined as a total bilirubin level of ≤ 1.5 × upper limit of normal (ULN) and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels of ≤ 2.0 × ULN. Participants with Gilbert's syndrome who have an isolated total bilirubin and normal AST and ALT levels may participate.
9. Adequate renal function, defined as an estimated glomerular filtration rate ≥ 60 mL/min/1.73 m^2 by the Chronic Kidney Disease Epidemiology Collaboration equation at Screening

Concomitant Medications

10. Participants are permitted to receive the following concomitant medications:
    a. Oral 5-ASA compounds at a stable dose or discontinued for ≥ 2 weeks prior to Screening endoscopy
    b. Oral corticosteroid therapy at a stable dose or discontinued for ≥ 2 weeks prior to Screening endoscopy (prednisone at a stable dose ≤ 20 mg/day, budesonide at a stable dose ≤ 9 mg/day)
    c. Probiotics, provided the dose has been stable for ≥ 2 weeks prior to Screening endoscopy

Contraception

11. Women must meet either a or b of the following criteria and men must meet criterion c to qualify for the study:
    a. A woman who is not of childbearing potential must meet 1 of the following:
        i. Postmenopausal, defined as no menses for 12 months without an alternative medical cause
        ii. Permanent sterilization procedure, such as hysterectomy, bilateral salpingectomy, or bilateral oophorectomy
    b. A nonpregnant woman of childbearing potential must agree to use a highly effective contraception method that can achieve a failure rate of less than 1% per year when used consistently and correctly. The highly effective contraception must be used through the duration of the study and for 30 days after the last dose of study treatment. The following are considered highly effective birth control methods:
        i. Combined (estrogen- and progesterone-containing) hormonal contraception associated with inhibition of ovulation, which may be oral, intravaginal, or transdermal.
        ii. Progesterone-only hormonal contraception associated with inhibition of ovulation, which may be oral, injected, or implanted
        iii. Intrauterine device

iv. Intrauterine hormone-releasing system

v. Bilateral tubal occlusion

vi. Vasectomized partner, provided that the partner is the sole sexual partner of the woman of childbearing potential study participant and the vasectomized partner has received medical assessment of the surgical success

vii. Sexual abstinence (complete sexual abstinence, defined as refraining from heterosexual intercourse for the entire period of risk associated with study treatments). The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant. Periodic abstinence (calendar, symptothermal, postovulation methods) is not acceptable.

c. A man with a pregnant or nonpregnant partner who is a woman of childbearing potential must agree to use condoms through the duration of the study and for 30 days after the last dose of study treatment.

Exclusion Criteria

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

Inflammatory Bowel Disease and Gastrointestinal Conditions

1. Severe extensive colitis as evidenced by:
   a. Physician judgment that the participant is likely to require surgery (surgical intervention of any kind for UC [eg, colectomy]) within 12 weeks of baseline
   b. Current evidence of fulminant colitis or toxic megacolon, or recent history (within last 6 months) of toxic megacolon or bowel perforation
   c. Previous total colectomy
2. Diagnosis of Crohn's disease or indeterminate colitis or the presence or history of a fistula consistent with Crohn's disease
3. Diagnosis of microscopic colitis, ischemic colitis, or infectious colitis
4. Positive assay or stool culture for pathogens (ova and parasite examination, bacteria) or **positive test for *Clostridium difficile* at Screening**. Note: If *C. difficile* or pathogen test is positive, the participant may be treated and retested ≥ 4 weeks after completing treatment.

General Safety

5. Pregnancy, lactation, or a positive serum β-hCG measured during Screening
6. Clinically relevant hematologic, hepatic, neurological, pulmonary, ophthalmological, endocrine, metabolic (including, but not limited to, hypo- and hyperkalemia), psychiatric, or other major systemic disease that will make implementation of the protocol or interpretation of the study difficult or will put the participant at risk
7. Forced expiratory volume in 1 second (FEV1) or forced vital capacity (FVC) < 70% of predicted values and FEV1/FVC ratio < 0.70 at Screening

8. Have any of the following conditions or receiving treatments that may affect cardiovascular function:
    a. Myocardial infarction, unstable angina, stroke/transient ischemic attack, decompensated heart failure requiring hospitalization, or Class III/IV heart failure within ≤ 6 months prior to or during the Screening Period
    b. Screening or prerandomization vital signs (taken in the sitting position) with a heart rate (HR) < 50 bpm OR systolic blood pressure (BP) < 90 mmHg OR diastolic BP < 55 mmHg. Vital signs may be repeated up to 3 times during a visit to confirm abnormal readings.
    c. Screening or prerandomization electrocardiogram (ECG) with PR interval > 200 msec or Fridericia's corrected QT interval (QTcF) ≥ 450 msec in men or ≥ 470 msec in women
    d. History of any of the following unless treated with an implanted pacemaker or an implanted cardioverter-defibrillator with pacing:
        i. History or presence of recurrent symptomatic bradycardia
        ii. Second- or third-degree atrioventricular block
        iii. Periods of asystole > 3 seconds
        iv. History of sick sinus syndrome or recurrent cardiogenic syncope
    e. Start, stop, or change in dosage of any Class I-IV anti-arrhythmic drugs ≤ 1 week prior to dose titration starting at randomization and up to 1 week after titration to the assigned dose. This criterion also applies to the OLE Treatment Period titration: 1 week prior to and 1 week after the dose titration period.
9. Uncontrolled diabetes as determined by hemoglobin A1c (HbA1c) > 9%, or participants with diabetes with significant comorbid conditions, such as retinopathy
10. History or presence of macular edema or retinopathy
11. History of cancer within the last 5 years, including solid tumors and hematological malignancies (except basal cell and in situ squamous cell carcinomas of the skin that have been excised and resolved) or precancerous conditions such as colonic mucosal dysplasia, cervical dysplasia, and cervical intraepithelial neoplasia
12. History of lymphoproliferative disorder, lymphoma, leukemia, myeloproliferative disorder, or multiple myeloma
13. History of alcohol or drug abuse within 1 year prior to randomization
14. Any of the following laboratory abnormalities during the Screening Period:
    a. Absolute white blood cell (WBC) count < 3500/μL
    b. Neutrophils < 1500/μL
    c. Absolute lymphocyte count < 800/μL
    d. Platelet count < 100,000/μL
    e. Hemoglobin < 8 g/dL

Infection Risk

15. Active or latent tuberculosis (TB) infection at Screening. History of untreated or inadequately treated latent TB infection. The following are EXCEPTIONS to this exclusion criterion:
    a. Participants with latent TB, who have been ruled out for active TB, have completed an appropriate course of TB prophylaxis treatment per national/local medical guidelines or WHO guidelines, have a chest radiograph without changes suggestive of active TB infection, and have not had recent close contact with a person with active TB are eligible to enroll in the study. It is the responsibility of the Investigator to verify the adequacy of previous TB treatment and provide appropriate documentation of treatment compliance.
    b. Participants diagnosed with latent TB at Screening, ruled out for active TB and have received at least 4 weeks of an appropriate TB prophylaxis regimen may be rescreened for enrollment. Participant will complete their prophylactic regimen during the trial.
16. Known active bacterial, viral, fungal, mycobacterial, or other infection (including TB or atypical mycobacterial disease) or any major episode of infection that required hospitalization or treatment with intravenous (IV) antibiotics within 30 days of Screening or oral antibiotics within 14 days prior to Screening. Fungal infection of nail beds is allowed.
17. Human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) or positive test for HIV antibodies at Screening
18. Acute or chronic hepatitis B infection or test positive for hepatitis B virus (HBV) at Screening (positive for hepatitis B surface antigen [HBsAg], or negative for HBsAg and positive for anti-hepatitis B core antibody in conjunction with detectable HBV deoxyribonucleic acid [DNA])
19. Current hepatitis C infection or test positive for hepatitis C virus (HCV) at Screening, as defined by positive hepatitis C antibody and detectable HCV ribonucleic acid
20. History of an opportunistic infection (eg, *Pneumocystis jirovecii*, cryptococcal meningitis), progressive multifocal leukoencephalopathy (PML), or history of disseminated herpes zoster or disseminated herpes simplex
21. History of currently active primary or secondary immunodeficiency

Previous or Concomitant Treatment

22. Hypersensitivity to VTX002 or any of the excipients or placebo compounds
23. Treatment with an investigational therapy ≤ 3 months prior to randomization
24. Treatment with cyclosporine, tacrolimus, sirolimus, methotrexate, or mycophenolate mofetil ≤ 8 weeks prior to Screening
25. Prior treatment with S1P receptor modulators including but not limited to fingolimod, siponimod, ozanimod, ponesimod, and etrasimod
26. Treatment with a biologic agent (ie, anti-TNFs, anti-integrins, and anti-IL-12/23) meeting the following criteria:
    a. Treatment with infliximab, adalimumab, golimumab, or vedolizumab ≤ 60 days prior to randomization

b. Treatment with ustekinumab ≤ 90 days prior to randomization

c. Treatment with any other approved biologic agent ≤ 5 half-lives prior to randomization

Note: A trough drug level can be obtained during Screening to confirm absence of biologic drug levels in lieu of the washout periods

27. Treatment with JAK inhibitors ≤ 4 weeks prior to randomization
28. Use of IV corticosteroids and/or topical steroids ≤ 2 weeks prior to Screening endoscopy. Alternative forms of steroids require consultation with the Medical Monitor.
29. Use of immunosuppressant drugs including thiopurines ≤ 2 weeks prior to Screening endoscopy
30. Prior treatment failure with ≥ 3 biologic agents with different mechanisms of action or ≥ 2 biologics with different mechanisms of action plus a JAK inhibitor approved for the treatment of UC
31. Treatment with topical rectal 5-ASA or short-chain fatty acid enemas ≤ 2 weeks prior to Screening endoscopy
32. Receipt of a live vaccine ≤ 4 weeks prior to randomization and until 2 weeks post last dose. Approved nonlive vaccines, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), can be administered according to local vaccination standards.
33. Previous treatment with natalizumab
34. Previous treatment with lymphocyte-depleting therapies (eg, anti-CD4, cladribine, rituximab, ocrelizumab, cyclophosphamide, mitoxantrone, total body irradiation, bone marrow transplantation, alemtuzumab, daclizumab)
35. Previous treatment with D-penicillamine, thalidomide, dimethyl fumarate, or pyrimidine synthesis inhibitors
36. Treatment with IV immune globulin or plasmapheresis ≤ 3 months prior to randomization

Study Periods

Participant eligibility will be determined during a 4-week (28-day) Screening Period. Entry criteria will be based on confirmation of moderately to severely active UC, defined by an MMS of 5 to 9 with an ES ≥ 2 and RB ≥ 1.

On Day 1, eligible participants will be randomized in a 1:1:1 ratio to receive VTX002 30 mg, VTX002 60 mg, or matching placebo orally once a day (approximately 63 participants per treatment group). During the first week of the Induction Treatment Period, participants will undergo a 7-day dose titration up to the full assigned double-blind treatment dose. At the end of the 13-week Induction Treatment Period, all participants will be evaluated for efficacy and safety.

Participants who complete the Induction Week 13 visit, and meet criteria for clinical response at Induction Week 13, will continue into the blinded LTE Period at their previously assigned treatment for up to an additional 39 weeks. Participants who complete the Week 52 visit of the LTE may continue into the OLE. If at any time after Week 13, a participant experiences loss of response, the participant will have the option to enroll into the OLE.

Participants who enter the OLE from the LTE will undergo a 7-day titration period and remain in the OLE for a possible total of 36 months of treatment (including the 13-week Induction Period, plus the duration in the LTE and the duration in the OLE).

Participants who complete the Induction Week 13 visit, and do not meet the criteria for clinical response at Induction Week 13, will have the option to enroll into the OLE for up to an additional 143 weeks of treatment (which includes a 7-day titration period followed by treatment with VTX002 60 mg for up to 142 weeks).

Regardless of previous blinded treatment during the Induction Period, if a participant's condition worsens or does not improve after 13 weeks in the OLE with VTX002 60 mg, the participant will be discontinued from the study.

The Sponsor may consider potential expansion of open-label access beyond the 36-month period, when the primary analysis results are available.

For all participants, Follow-Up visits will be performed at 1 and 2 weeks after the last dose of study treatment, as indicated in the Schedule of Activities (SoA). All participants who discontinue the study prematurely will be asked to return to the clinic for the Early Termination (ET) visit. If an ET visit is ≥ 1 week after the last dose of study treatment, the 1-Week Follow-Up visit is not required; however, the 2-Week Follow-Up visit should be scheduled and completed.

If the absolute peripheral lymphocyte count is not within normal limits at the 2-Week Follow-Up visit, participants should return for a complete blood count (CBC) with differential according to local standard of care (captured as a subsequent Follow-Up visit or unscheduled visit).

Statistical Methods

The primary efficacy analysis will be completed based on the Full Analysis Set (FAS) for the study drug. The primary endpoint is the proportion of participants with clinical remission at 13 weeks.

The testing will be done using a Cochran-Mantel-Haenszel test (CMH) test with biologic/JAK inhibitor prior use status (Yes or No), baseline corticosteroid use (Yes or No), and baseline disease activity (MMS 4-6 or 7-9) as the stratification factors. The CMH chi-square p-value and stratified risk differences with 95% confidence interval (CI) using the Newcombe method will be provided for pairwise comparisons between each dose group and placebo. Only the two treatment groups – VTX002 60 mg and placebo – will be included in the primary analysis of the primary endpoint.

Key secondary endpoints will be analyzed similarly to the primary endpoint, using the CMH test with similar stratification factors. Comparisons between VTX002 60 mg and placebo for all key secondary endpoints will be considered key secondary analyses. Comparisons between VTX002 30 mg and placebo for the primary endpoint and the key secondary endpoints will be considered key secondary analyses. The family-wise Type I error rate across the primary analysis of the primary efficacy endpoint and all key secondary analyses will be maintained at $\alpha = 0.05$ using a sequentially rejective method. Details will be provided in the SAP.

Categorical exploratory endpoints will be analyzed similarly to the primary endpoint.

Continuous exploratory endpoints will be analyzed using a general linear model (analysis of covariance [ANCOVA]) with fixed effects for treatment, biologic/JAK inhibitor prior use status (Yes or No), baseline corticosteroid use (Yes or No), and baseline disease activity (MMS 4-6 or 7-9).

Symptomatic response and symptomatic remission at Weeks 4, 8, 10, 13, 18, 26, 36, and 52 will be analyzed using an appropriate categorical repeated measurements methodology. Change from baseline in FCP and CRP at Weeks 1, 4, 8, 13, 26, 36, and 52; and also for change from baseline in PMS at Weeks 4, 8, 13, 18, 26, 36, and 52 will be analyzed using an appropriate continuous repeated measurements methodology. Details will be provided in the SAP, and will include a specification of how the results will be reported.

All the exploratory endpoints collected during the LTE Treatment Period and the OLE Treatment Period will be summarized with appropriate summary statistics over time, using the same definitions given above.

All safety data (eg, Holter ECG monitoring, 12-lead ECG, optical coherence tomography [OCT], pulmonary function test [PFT], and physical examination) will be listed and summarized using descriptive statistics.

1.2 Schedule of Activities

The SoA for the Induction Treatment Period is provided in Table 1. The SoA for the LTE Treatment Period, ET, and Follow-Up Period is provided in Table 2. The SoA for the OLE Treatment Period, ET, and Follow-Up Period is provided in Table 3, Table 4, Table 5, and Table 6.

Table 1 Schedule of Activities for the Double-Blind Induction Treatment Period

Study Procedures	Screening (4 weeks)	Induction Treatment Period (13 weeks)						Early Termination/ Follow-Up Period	
		7-day Dose Titration							
Study Visit[a]	Visit 1	Visit 2[a]	Visit 3	Visit 4	Visit 5	Visit 6[a]	Visit 7	ET Visit[b]	1-Week & 2-Week Follow-Up Visits[b]
Study Day	Day -28 to 0	Day 1	Day 8	Day 29	Day 57	Day 71	Day 92		
Window (days)			+ 2	± 3	± 3	± 3	± 3		
Study Week		Week 0	Week 1	Week 4	Week 8	Week 10	Week 13		
Informed consent	X								
Inclusion/exclusion criteria	X	X							
Demographics	X								
Medical history	X	X							
Urine drug screen[c]	X								
TB screening[d]	X								
Chest X-ray[e]	X								
Viral serology[f]	X								
Stool culture[g]	X								
Hemoglobin A1c	X								
Randomization		X							
Dispense/redispense study drug		X	X	X	X				
Administer study drug at clinic[h]		X	X	X	X		X		
Return study drug			X	X	X		X	X	
Review drug compliance			X	X	X		X	X	
Prior and concomitant medications[i]	X	X	X	X	X	X	X	X	X

Study Procedures	Screening (4 weeks)	Induction Treatment Period (13 weeks)						Early Termination/ Follow-Up Period	
		7-day Dose Titration							
Study Visit[a]	**Visit 1**	**Visit 2[a]**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6[a]**	**Visit 7**	**ET Visit[b]**	**1-Week & 2-Week Follow-Up Visits[b]**
Study Day	**Day -28 to 0**	**Day 1**	**Day 8**	**Day 29**	**Day 57**	**Day 71**	**Day 92**		
Window (days)			**+ 2**	**± 3**	**± 3**	**± 3**	**± 3**		
Study Week		**Week 0**	**Week 1**	**Week 4**	**Week 8**	**Week 10**	**Week 13**		
SAFETY									
Adverse events	X	X	X	X	X	X	X	X	X
12-lead ECG[j]	X	X	X				X	X	
Holter ECG monitoring[k]		X							
Vital signs[l]	X	X	X	X	X		X	X	
Clinical laboratory tests									
Hematology[m]	X	X	X	X	X		X	X	X[m]
[redacted]		X			X		X	X	
Blood chemistry[o]	X	X	X	X	X		X	X	
Pregnancy test[p]	X	X	X	X	X		X	X	X
Coagulation panel[q]	X						X	X	
Urinalysis	X						X	X	
Physical examination[r]	X	X	X	X	X		X	X	
Pulmonary function test[s]	X						X	X	
Ophthalmoscopy with OCT[t]	X						X	X	
PHARMACOKINETICS/EFFICACY BIOMARKER									
Stool collection for fecal calprotectin[u]		X	X	X	X		X	X	
Blood collection for C-reactive protein		X	X	X	X		X	X	
[redacted]		X							
[redacted]		X			X		X	X	
PK blood sampling[x]		X	X	X	X		X	X	X
[redacted]		X					X	X	

Study Procedures	Screening (4 weeks)	Induction Treatment Period (13 weeks)						Early Termination/ Follow-Up Period	
		7-day Dose Titration							
Study Visit[a]	Visit 1	Visit 2[a]	Visit 3	Visit 4	Visit 5	Visit 6[a]	Visit 7	ET Visit[b]	1-Week & 2-Week Follow-Up Visits[b]
Study Day	Day -28 to 0	Day 1	Day 8	Day 29	Day 57	Day 71	Day 92		
Window (days)			+ 2	± 3	± 3	± 3	± 3		
Study Week		Week 0	Week 1	Week 4	Week 8	Week 10	Week 13		
EFFICACY									
Endoscopy[y]	X						X	X	
eDiary[z]	X	X	X	X	X	X	X	X	
Mayo Clinic score[aa]		X					X	X	
Physician's Global Assessment		X		X	X		X	X	
Colonic biopsy[bb]	X						X	X	
IBDQ[cc]		X					X	X	

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; β-hCG = beta-human chorionic gonadotropin; BP = blood pressure; DLCO = diffusing capacity of the lungs for carbon monoxide; ECG = electrocardiogram; EDC = electronic data capture database; eDiary = electronic diary; ET = Early Termination; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HR = heart rate; IBDQ = Inflammatory Bowel Disease Questionnaire; MMS = modified Mayo score; OCT = optical coherence tomography; PK = pharmacokinetics; RB = rectal bleeding; SF = stool frequency; TB = tuberculosis; [redacted] ULN = upper limit of normal

a. All assessments scheduled for Visit 2 will be performed prior to study drug administration, unless otherwise indicated. All visits beyond Visit 2 may be virtual/hybrid visits (see Section 8.2). Visit 6 is planned as a phone call visit. Assessments scheduled for Visit 7 may be performed within 7 days prior to the date of visit.
b. All participants who discontinue the study prematurely will be asked to return to the clinic for the ET visit, and the 1-Week Follow-Up and 2-Week Follow-Up visits after the last dose of study treatment. If the ET visit is ≥ 1 week after the last dose of study treatment, the 1-Week Follow-Up visit is not required; however, the 2-Week Follow-Up visit should be scheduled and completed. In the unlikely event that the ET visit is ≥ 2 weeks after the last dose of study treatment, the 2-Week Follow-Up visit is not required.
c. A standard urine drug screen will be performed (Appendix 3). Participants who test positive will be assessed for eligibility for study participation by the Investigator after discussion with the Medical Monitor.
d. TB screening includes any of the following: 1) history of untreated or inadequately treated latent TB (see Exclusion Criterion 15 for exceptions); 2) a positive diagnostic TB test within 1 month of enrollment (defined as a positive QuantiFERON test or 2 successive indeterminate QuantiFERON tests; or a tuberculin skin test reaction ≥ 10 mm [≥ 5 mm in participants receiving the equivalent of > 15 mg/day prednisone], if a QuantiFERON test is unavailable).
e. Chest X-ray to be performed if not done in previous 6 months.
f. Includes HIV, HBV, and HCV testing.
g. Stool culture for bacterial pathogens, ova, and parasites, and for *Clostridium difficile* test.

h. Study drug should be administered after completion of all initial assessments on the day of visit. On Day 1, the participant will remain in clinic for 6 hours of cardiac monitoring after dosing.
i. Concomitant medications include over-the-counter or prescription medicines, blood products, vaccines, vitamins, holistic products, and radiotherapy.
j. ECGs to be obtained after an at least 5-minute supine resting period. At Visit 2, 12-lead ECGs will be collected predose and at 1, 2, 4, and 6 hours (± 10 minutes) postdose. The predose ECG at Visit 2 should be performed and assessed prior to randomization. When study drug is to be administered at the clinic, ECG will be obtained predose.
k. At Visit 2, continuous Holter ECG monitoring will be performed for at least 1 hour predose and at least 24 hours postdose.
l. Vital signs (including HR and BP) will be collected in the sitting position prior to the ECG assessment and before any simultaneously scheduled blood collections. At Visit 2, vital signs will be collected predose and at 1, 2, 4, and 6 (± 10 minutes) hours postdose.
m. At the 2-Week Follow-Up visit, if the absolute peripheral lymphocyte count is not within normal limits, participants should return for CBC with differential according to local standard of care (captured as subsequent Follow-Up visit or unscheduled visit).
n. Blood samples will be collected as detailed in the Laboratory Manual. [redacted]
o. An increase in AST or ALT > 3 × ULN should be followed by repeat testing within 72 hours of receiving results to confirm the abnormality and determine whether AST or ALT is increasing or decreasing.
p. For women of childbearing potential, the first pregnancy test at Screening is a serum β-hCG test that is evaluated by a central laboratory. All subsequent pregnancy testing will be performed using a urine dipstick pregnancy test. Home urine pregnancy test kits may be provided to the participant for any virtual/hybrid visit or to perform a monthly pregnancy test at home during non-visit months, if permitted by local regulations. Participants will confirm the performance of a monthly pregnancy test in the eDiary, if performed at home, and provide the results to the study site. Any positive urine pregnancy test will be confirmed with a serum β-hCG test by a central laboratory.
q. Coagulation panel to be performed at an unscheduled visit in case of elevated ALT/AST.
r. Complete physical examination at Screening, brief physical examinations during the study, and complete physical examination at Visit 12/ET (see Table 2). A complete physical examination will include evaluation of heart, lung, head and neck, abdomen, neurological function, skin, and extremities. An interim (or brief) physical examination will include areas with previously noted abnormalities and/or that are associated with any new complaints from the participant.
s. Pulmonary function includes assessment of FEV1 and FVC. If the pulmonary function test results are not within normal range, the results should be verified by a pulmonologist, and potential confounding factors identified. If the participant has a decline in pulmonary function test values, the participant should be evaluated by a pulmonologist. If values (FEV1 and/or FVC) decline below 50% of the predicted values, treatment should be discontinued with follow-up evaluation initiated as appropriate. At sites where available, DLCO measurements will also be performed.
t. A general ophthalmologist can perform the examination, although a retinal specialist would be preferred wherever possible. A complete ophthalmoscopy and OCT assessment should be performed according to the SoA. Site should retain a copy of the OCT result and the ophthalmologist report. For participants with a suspicion of new onset of macular edema and/or retinopathy, along with evaluation using ophthalmoscopy and OCT, additional testing should be considered at the discretion of the ophthalmologist (eg, general retinal examinations, including eye history, visual acuity, dilated ophthalmoscopy).
u. Participants will receive a stool sampling kit at a previous visit and be asked to collect a stool sample within 24 hours before the next visit. Participants are to bring stool samples to the clinic.

[redacted]

x. PK samples will be collected (measuring trough concentrations) after completion of vital sign assessments and ECGs. When study drug is administered at the clinic, PK sample will be collected predose. On Day 1 only, PK samples will also be collected at 2, 4, and 6 hours (± 10 minutes) postdose (see Table 10).
y. Sigmoidoscopy is sufficient at both Screening and Visit 7. Colonoscopy can be performed if a surveillance colonoscopy is needed or based on the clinical judgment of the Investigator.
z. Participants will begin eDiary entries beginning on the first day of Screening after diary training is completed. The eDiary should be completed daily to capture data, including daily SF and RB (the 2 patient-reported outcome measures of the MMS), and study drug administration. Study center personnel should review the diary data at every visit at the timepoints in the table and in between visits via EDC to confirm compliance with eDiary completion. In addition, the RB score should be assessed during the Screening Period to ensure the RB score will meet eligibility criteria prior to performing the endoscopy.
aa. The MMS will be calculated electronically during Screening for eligibility and at Visit 7 for determination of clinical response. The subscores for RB and SF are derived from the participant eDiary entries using the scores from the 3 most recent consecutive days within the 7 days prior to the day of bowel preparation, averaged and rounded to the nearest integer.
bb. When endoscopy is performed (see footnote y) and colonic biopsy is collected, samples are sent to the central laboratory. If there is no histologic report present at the time of Screening corroborating the diagnosis, additional colonic samples should be taken and sent to a local laboratory for confirmation of the diagnosis. Colonic biopsy may be used for histology [redacted] Biopsy samples will be processed by a central laboratory, and histopathologic scoring using the Geboes, Robarts, and Nancy histopathology indices will be performed by a blinded central reader (Appendix 7).
cc. If and when available in the appropriate local language.

Table 2 Schedule of Activities in the Long-Term Extension Treatment Period

Study Procedures	Long-Term Extension Treatment Period (39 weeks)					Early Termination/ Follow-Up Period	
Study Visit[a]	**Visit 8[a]**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**ET Visit[b]**	**1-Week & 2-Week Follow-Up Visits[b]**
Study Day	**Day 92**	**Day 127**	**Day 183**	**Day 253**	**Day 365**		
Window (days)	± 3	± 7	± 7	± 7	± 7		
Study Week	**Week 13**	**Week 18**	**Week 26**	**Week 36**	**Week 52**		
Dispense/redispense study drug	X	X	X	X			
Administer study drug at clinic		X	X	X	X		
Return study drug		X	X	X	X	X	
Review drug compliance		X	X	X	X	X	
Prior and concomitant medications		X	X	X	X	X	X
SAFETY							
Adverse events		X	X	X	X	X	X
12-lead ECG[c]			X		X	X	
Vital signs[d]		X	X	X	X	X	
Clinical laboratory tests							
Hematology[e]		X	X	X	X	X	X[e]
[redacted]					X	X	
Blood chemistry[g]		X	X	X	X	X	
Pregnancy test[h]		X	X	X	X	X	X
Coagulation panel[i]					X	X	
Urinalysis			X	X	X	X	
Physical examination[j]		X	X	X	X	X	
Pulmonary function test[k]			X		X	X	
Ophthalmoscopy with OCT[l]					X	X	
PHARMACOKINETICS/EFFICACY BIOMARKER							
Stool collection for fecal calprotectin[m]			X	X	X	X	
Blood collection for C-reactive protein			X	X	X	X	
[redacted]					X	X	
PK blood sampling[o]		X	X	X	X	X	X
[redacted]					X	X	

Study Procedures	Long-Term Extension Treatment Period (39 weeks)					Early Termination/ Follow-Up Period	
Study Visit[a]	Visit 8[a]	Visit 9	Visit 10	Visit 11	Visit 12	ET Visit[b]	1-Week & 2-Week Follow-Up Visits[b]
Study Day	Day 92	Day 127	Day 183	Day 253	Day 365		
Window (days)	± 3	± 7	± 7	± 7	± 7		
Study Week	Week 13	Week 18	Week 26	Week 36	Week 52		
EFFICACY							
Endoscopy[p]					X	X	
eDiary[q]		X	X	X	X	X	
Mayo Clinic Score[r]					X	X	
Physician's Global Assessment[s]		X	X	X	X	X	
Colonic biopsy[t]					X	X	
IBDQ[u]					X	X	

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; β-hCG = beta-human chorionic gonadotropin; CBC = complete blood count; DLCO = diffusing capacity of the lungs for carbon monoxide; ECG = electrocardiogram; EDC = electronic data capture database; eDiary = electronic diary; ET = Early Termination; FEV1 = forced expiratory volume at 1 second; FVC = forced vital capacity; IBDQ = Inflammatory Bowel Disease Questionnaire; MMS = modified Mayo score; OCT = optical coherence tomography; OLE = Open-Label Extension; PGA = Physician's Global Assessment; PK = pharmacokinetics; RB = rectal bleeding; SF = stool frequency; [redacted] ULN = upper limit of normal

a. For participants entering the LTE, Visit 8 will be on the same day as Visit 7 (see Table 1). Assessments scheduled for Visit 7 may be performed within 7 days prior to the date of visit. All visits beyond Visit 8 may be virtual/hybrid visits (see Section 8.2). For Visit 12 only, if a wider window is needed, contact the Medical Monitor for the study.
b. All participants who discontinue the study prematurely will be asked to return to the clinic for the ET visit, and the 1-Week Follow-Up and 2-Week Follow-Up visits after the last dose of study treatment. If the ET visit is ≥ 1 week after the last dose of study treatment, the 1-Week Follow-Up visit is not required; however, the 2-Week Follow-Up visit should be scheduled and completed. In the unlikely event that the ET visit is ≥ 2 weeks after the last dose of study treatment, the 2-Week Follow-Up visit is not required.
c. ECGs to be obtained after an at least 5-minute supine resting period. When study drug is to be administered at the clinic, ECG will be obtained predose.
d. Vital signs will be collected in the sitting position prior to the ECG assessment and before any simultaneously scheduled blood collections.
e. At the 2-Week Follow-Up visit, if the absolute peripheral lymphocyte count is not within normal limits, participants should return for CBC with differential according to local standard of care (captured as subsequent Follow-Up visit or unscheduled visit).
f. [redacted]
g. An increase in AST or ALT > 3 × ULN should be followed by repeat testing within 72 hours of receiving results to confirm the abnormality and determine whether AST or ALT is increasing or decreasing.

h. For women of childbearing potential, all pregnancy testing will be performed using a urine dipstick pregnancy test. Home urine pregnancy test kits may be provided to the participant for any virtual/hybrid visit or to perform a pregnancy test at home during non-visit months, if permitted by local regulations. Participants will confirm the performance of a monthly pregnancy test in the eDiary, if performed at home, and provide the results to the study site. Any positive urine pregnancy test result will be confirmed with a serum β-hCG test by a central laboratory.
i. Coagulation panel to be performed at an unscheduled visit in case of elevated ALT/AST.
j. Complete physical examination at Visit 12/ET visit and brief physical examinations during the study. A complete physical examination will include evaluation of heart, lung, head and neck, abdomen, neurological function, skin, and extremities. An interim (or brief) physical examination will include areas with previously noted abnormalities and/or that are associated with any new complaints from the participant.
k. Pulmonary function includes assessment of FEV1 and FVC. If the pulmonary function test results are not within normal range, the results should be verified by a pulmonologist, and potential confounding factors identified. If the participant has a decline in pulmonary function test values, the participant should be evaluated by a pulmonologist. If values (FEV1 and/or FVC) decline below 50% of the predicted values, treatment should be discontinued with follow-up evaluation initiated as appropriate. At sites where available, DLCO measurements will also be performed. The ET visit assessment is required only if results from the Visit 12 or last on-treatment visit are abnormal. Visit 10 (Week 26) assessment will be performed if clinically indicated.
l. A general ophthalmologist can perform the examination, although a retinal specialist would be preferred wherever possible. A complete ophthalmoscopy and OCT assessment should be performed according to the SoA. Site should retain a copy of the OCT result and the ophthalmologist report. For participants with a suspicion of new onset of macular edema and/or retinopathy, along with evaluation using ophthalmoscopy and OCT, additional testing should be considered at the discretion of the ophthalmologist (eg, general retinal examinations, including eye history, visual acuity, dilated ophthalmoscopy).
m. Participants will receive a stool sampling kit at a previous visit and be asked to collect a stool sample within 24 hours of the visit. Participants are to bring stool samples to the clinic.
[redacted]
o. PK samples will be collected (measuring trough concentrations) after completion of vital sign assessments and ECGs. When study drug is administered at the clinic, PK sample will be collected predose (see Table 10).
p. Endoscopy at ET visit is required only for participants who discontinue the study at or after Week 26.
q. The eDiary should be completed daily to capture data, including daily SF and RB, and study drug administration. Study center personnel should review the diary data at every visit at the timepoints in the table and in between visits via EDC to confirm compliance with eDiary completion.
r. The MMS will be calculated electronically at the Week 52/ET visit. The subscores for RB and SF are derived from the participant eDiary entries using the scores from the 3 most recent consecutive days within the 7 days prior to the day of bowel preparation, averaged and rounded to the nearest integer.
s. Partial Mayo Score will include SF, RB and PGA assessments, and will be used to determine loss of response as described in Section 8.3.1.5.
t. When endoscopy is performed (see footnote p) and colonic biopsy is collected, samples are sent to the central laboratory. Colonic biopsy may be used for histology [redacted] Biopsy samples will be processed by a central laboratory, and histopathologic scoring using the Geboes, Robarts, and Nancy histopathology indices will be performed by a blinded central reader (Appendix 7).
u. If and when available in the appropriate local language.

Table 3 Schedule of Activities in the Open-Label Extension Treatment Period from OLE Week 0 to OLE Week 13

Study Procedures	Open-Label Extension Treatment Period (OLE Week 0 to OLE Week 13)					Early Termination/ Follow-Up Period	
	7-day Dose Titration						
OLE Visit[a]	OLE Visit 1[a]	OLE Visit 2	OLE Visit 3	OLE Visit 4	OLE Visit 5	ET Visit[b]	1-Week & 2-Week Follow-Up Visits[b]
OLE Day	OLE Day 1	OLE Day 8	OLE Day 29	OLE Day 57	OLE Day 92		
Window (days)		+ 2	± 3	± 3	± 3		
OLE Week	OLE Week 0	OLE Week 1	OLE Week 4	OLE Week 8	OLE Week 13		
Dispense/redispense study drug	X	X	X	X	X		
Administer study drug at clinic[c]	X	X	X	X	X		
Return study drug	X	X	X	X	X	X	
Review drug compliance	X	X	X	X	X	X	
Prior and concomitant medications	X	X	X	X	X	X	X
SAFETY							
Adverse events	X	X	X	X	X	X	X
12-lead ECG[d]	X	X			X	X	
Holter ECG monitoring[e]	X						
Vital signs[f]	X	X	X	X	X	X	
Clinical laboratory tests							
Hematology[g]	X	X	X	X	X	X	X[g]
[redacted]	X			X	X	X	
Blood chemistry[i]	X	X	X	X	X	X	
Pregnancy test[j]	X	X	X	X	X	X	X
Coagulation panel[k]	X					X	
Urinalysis	X					X	
Physical examination[l]	X	X	X	X	X	X	
Pulmonary function test[m]					X	X	
Ophthalmoscopy with OCT[n]					X	X	
PHARMACOKINETICS/EFFICACY BIOMARKER							
Stool collection for fecal calprotectin[o]	X	X	X	X	X	X	
Blood collection for C-reactive protein	X	X	X	X	X	X	
[redacted]	X			X	X	X	
PK blood sampling[q]	X	X	X	X	X	X	X

Study Procedures	Open-Label Extension Treatment Period (OLE Week 0 to OLE Week 13)					Early Termination/ Follow-Up Period	
	7-day Dose Titration						
OLE Visit[a]	OLE Visit 1[a]	OLE Visit 2	OLE Visit 3	OLE Visit 4	OLE Visit 5	ET Visit[b]	1-Week & 2-Week Follow-Up Visits[b]
OLE Day	OLE Day 1	OLE Day 8	OLE Day 29	OLE Day 57	OLE Day 92		
Window (days)		+ 2	± 3	± 3	± 3		
OLE Week	OLE Week 0	OLE Week 1	OLE Week 4	OLE Week 8	OLE Week 13		
[redacted]	X				X	X	
EFFICACY							
eDiary[r]	X	X	X	X	X	X	
Physician's Global Assessment[s]	X		X	X	X	X	

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; β-hCG = beta-human chorionic gonadotropin; BP = blood pressure; CBC = complete blood count; DLCO = diffusing capacity of the lungs for carbon monoxide; ECG = electrocardiogram; EDC = electronic data capture database; eDiary = electronic diary; ET = Early Termination; FEV1 = forced expiratory volume at 1 second; FVC = forced vital capacity; HR = heart rate; LTE = Long-Term Extension; OCT = optical coherence tomography; OLE = Open-Label Extension; PGA = Physician's Global Assessment; PK = pharmacokinetics; RB = rectal bleeding; SF = stool frequency; [redacted]; ULN = upper limit of normal

a. If OLE Visit 1 is on the same day as Week 13 visit (Table 1) or the LTE visit when criteria for loss of response is met (after Week 13, Table 2), then assessments at OLE Visit 1 do not need to be repeated. If the visit cannot be on the same day, OLE Visit 1 should occur within 3 days after Week 13 visit and assessments to be repeated must be confirmed with the Medical Monitor. All participants rolling into the OLE will start at OLE Visit 1 and remain on the OLE visit schedule. All assessments scheduled for OLE Visit 1 will be performed prior to study drug administration, unless otherwise indicated. All visits beyond OLE Visit 2 may be hybrid visits (see Section 8.2). OLE Visit 2 should occur 1 week after OLE Visit 1.
b. All participants who discontinue the study prematurely will be asked to return to the clinic for the ET visit, and the 1-Week Follow-Up and 2-Week Follow-Up visits after the last dose of study treatment. If the ET visit is ≥ 1 week after the last dose of study treatment, the 1-Week Follow-Up visit is not required; however, the 2-Week Follow-Up visit should be scheduled and completed. In the unlikely event that the ET visit is ≥ 2 weeks after the last dose of study treatment, the 2-Week Follow-Up visit is not required.
c. Study drug should be administered after completion of all initial assessments on the day of visit. On OLE Day 1, the participant will remain in clinic for 6 hours of cardiac monitoring after dosing.
d. ECGs to be obtained after an at least 5-minute supine resting period. At OLE Visit 1, 12-lead ECGs will be collected predose and at 1, 2, 4 and 6 hours (± 10 minutes) postdose. When study drug is to be administered at the clinic, ECG will be obtained predose.
e. At OLE Visit 1, continuous Holter ECG monitoring will be performed for at least 1 hour predose and at least 24 hours postdose.
f. Vital signs (including HR and BP) will be collected in the sitting position prior to the ECG assessment and before any simultaneously scheduled blood collections. At OLE Visit 1, vital signs will be collected predose and at 1, 2, 4, and 6 (± 10 minutes) hours postdose.
g. At the 2-Week Follow-Up visit, if the absolute peripheral lymphocyte count is not within normal limits, participants should return for CBC with differential according to local standard of care (captured as subsequent Follow-Up visit or unscheduled visit).

[redacted]

i. An increase in AST or ALT > 3 × ULN should be followed by repeat testing within 72 hours of receiving results to confirm the abnormality and determine whether AST or ALT is increasing or decreasing.
j. For women of childbearing potential, all pregnancy testing will be performed using a urine dipstick pregnancy test. Home urine pregnancy test kits may be provided to the participant for any virtual/hybrid visit or to perform a monthly pregnancy test at home during non-visit months, if permitted by local regulations. Participants will confirm the performance of a monthly pregnancy test in the eDiary, if performed at home, and provide the results to the study site. Any positive urine pregnancy test result will be confirmed with a serum β-hCG test by a central laboratory.
k. Coagulation panel to be performed at an unscheduled visit in case of elevated ALT/AST.
l. Complete physical examination at OLE Visit 17/ET visit (see Table 6) and brief physical examinations during the study. A complete physical examination will include evaluation of heart, lung, head and neck, abdomen, neurological function, skin, and extremities. An interim (or brief) physical examination will include areas with previously noted abnormalities and/or that are associated with any new complaints from the participant.
m. Pulmonary function includes assessment of FEV1 and FVC. If the pulmonary function test results are not within normal range, the results should be verified by a pulmonologist, and potential confounding factors identified. If the participant has a decline in pulmonary function test values, the participant should be evaluated by a pulmonologist. If values (FEV1 and/or FVC) decline below 50% of the predicted values, treatment should be discontinued with follow-up evaluation initiated as appropriate. At sites where available, DLCO measurements will also be performed.
n. A general ophthalmologist can perform the examination, although a retinal specialist would be preferred wherever possible. A complete ophthalmoscopy and OCT assessment should be performed according to the SoA. Site should retain a copy of the OCT result and the ophthalmologist report. For participants with a suspicion of new onset of macular edema and/or retinopathy, along with evaluation using ophthalmoscopy and OCT, additional testing should be considered at the discretion of the ophthalmologist (eg, general retinal examinations, including eye history, visual acuity, dilated ophthalmoscopy).
o. Participant will receive a stool sampling kit at a previous visit and be asked to collect a stool sample within 24 hours before the next visit. Participants are to bring stool samples to the clinic.
[redacted]
q. PK samples will be collected (measuring trough concentrations) after completion of vital sign assessments and ECGs. When study drug is administered at the clinic, PK sample will be collected predose. At OLE Visit 1 (OLE Day 1), PK samples will be collected predose and also at 2, 4, 6, and 24 hours (± 10 minutes) postdose (24 hours postdose is an optional timepoint and applies only to participants who consent to return to the clinic on OLE Day 2). At OLE Visit 2 and OLE Visit 3, PK samples will be collected predose and at 2, 4, 6, and 24 hours (± 10 minutes) postdose (postdose timepoints are optional, but all 4 timepoints are required for participants who consent) (see Table 10).
r. The eDiary should be completed daily to capture data, including daily SF and RB, and study drug administration. Study center personnel should review the diary data at every visit at the timepoints in the table and in between visits via EDC to confirm compliance with eDiary completion. Symptomatic response, using RB and SF scores, will be assessed by the Investigator at OLE Week 13 only for participants who failed to achieve clinical response at the end of the Induction Period (Table 1, Week 13).
s. Partial Mayo Score will include SF, RB and PGA assessments, and will be used to determine loss of response as described in Section 8.3.1.5.

Table 4 Schedule of Activities in the Open-Label Extension Treatment Period from OLE Week 18 to OLE Week 39

Study Procedures	Open-Label Extension Treatment Period (OLE Week 18 to OLE Week 39)				Early Termination/ Follow-Up Period	
OLE Visit[a]	OLE Visit 6	OLE Visit 7	OLE Visit 8	OLE Visit 9	ET Visit[b]	1-Week & 2-Week Follow-Up Visits[b]
OLE Day	OLE Day 127	OLE Day 183	OLE Day 253	OLE Day 274		
Window (days)	± 7	± 7	± 7	± 7		
OLE Week	OLE Week 18	OLE Week 26	OLE Week 36	OLE Week 39		
Dispense/redispense study drug	X	X	X	X		
Administer study drug at clinic[c]	X	X	X	X		
Return study drug	X	X	X	X	X	
Review drug compliance	X	X	X	X	X	
Prior and concomitant medications	X	X	X	X	X	X
SAFETY						
Adverse events	X	X	X	X	X	X
12-lead ECG[d]		X		X	X	
Vital signs[e]	X	X	X	X	X	
Clinical laboratory tests						
Hematology[f]	X	X	X	X	X	X[f]
[redacted]				X	X	
Blood chemistry[h]	X	X	X	X	X	
Pregnancy test[i]	X	X	X	X	X	X
Coagulation panel[j]				X	X	
Urinalysis		X	X	X	X	
Physical examination[k]	X	X	X	X	X	
Pulmonary function test[l]				X	X	
Ophthalmoscopy with OCT[m]				X	X	
PHARMACOKINETICS/EFFICACY BIOMARKER						
Stool collection for fecal calprotectin[n]		X	X	X	X	
Blood collection for C-reactive protein		X	X	X	X	
[redacted]				X	X	
PK blood sampling[p]	X	X	X	X	X	X
[redacted]				X	X	

Study Procedures	Open-Label Extension Treatment Period (OLE Week 18 to OLE Week 39)				Early Termination/ Follow-Up Period	
OLE Visit[a]	OLE Visit 6	OLE Visit 7	OLE Visit 8	OLE Visit 9	ET Visit[b]	1-Week & 2-Week Follow-Up Visits[b]
OLE Day	OLE Day 127	OLE Day 183	OLE Day 253	OLE Day 274		
Window (days)	± 7	± 7	± 7	± 7		
OLE Week	OLE Week 18	OLE Week 26	OLE Week 36	OLE Week 39		
EFFICACY						
Endoscopy[q]				X	X	
eDiary[r]		X	X	X	X	
Mayo Clinic Score[s]				X	X	
Physician's Global Assessment[t]		X	X	X	X	
Colonic biopsy[u]				X	X	
IBDQ[v]				X	X	

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; β-hCG = beta-human chorionic gonadotropin; CBC = complete blood count; DLCO = diffusing capacity of the lungs for carbon monoxide; ECG = electrocardiogram; EDC = electronic data capture database; eDiary = electronic diary; EOT = end of treatment; ET = Early Termination; FEV1 = forced expiratory volume at 1 second; FVC = forced vital capacity; IBDQ = Inflammatory Bowel Disease Questionnaire; LTE = Long-Term Extension; MMS = modified Mayo score; OCT = optical coherence tomography; OLE = Open-Label Extension; PGA = Physician's Global Assessment; PK = pharmacokinetics; RB = rectal bleeding; SF = stool frequency; [redacted] ULN = upper limit of normal

a. All visits beyond OLE Visit 2 (Table 3) may be virtual/hybrid visits (see Section 8.2). Participants who enter the OLE from the LTE will remain in the OLE for a possible total of 36 months of treatment (including the 13-week Induction Period, plus the duration in the LTE and the duration in the OLE). Regardless of when a participant rolls over to the OLE, when a participant completes 36 months of treatment, they need to complete all assessments for OLE Visit 17/EOT visit (Table 6).
b. All participants who discontinue the study prematurely will be asked to return to the clinic for the ET visit, and the 1-Week Follow-Up and 2-Week Follow-Up visits after the last dose of study treatment. If the ET visit is ≥ 1 week after the last dose of study treatment, the 1-Week Follow-Up visit is not required; however, the 2-Week Follow-Up visit should be scheduled and completed. In the unlikely event that the ET visit is ≥ 2 weeks after the last dose of study treatment, the 2-Week Follow-Up visit is not required.
c. Study drug should be administered after completion of all initial assessments on the day of visit.
d. ECGs to be obtained after an at least 5-minute supine resting period. When study drug is to be administered at the clinic, ECG will be obtained predose.
e. Vital signs will be collected in the sitting position prior to the ECG assessment and before any simultaneously scheduled blood collections.
f. At the 2-Week Follow-Up visit, if the absolute peripheral lymphocyte count is not within normal limits, participants should return for CBC with differential according to local standard of care (captured as subsequent Follow-Up visit or unscheduled visit).

[redacted]

h. An increase in AST or ALT > 3 × ULN should be followed by repeat testing within 72 hours of receiving results to confirm the abnormality and determine whether AST or ALT is increasing or decreasing.
i. For women of childbearing potential, all pregnancy testing will be performed using a urine dipstick pregnancy test. Home urine pregnancy test kits may be provided to the participant for any virtual/hybrid visit or to perform a monthly pregnancy test at home during non-visit months, if permitted by local regulations. Participants will confirm the performance of a monthly pregnancy test in the eDiary, if performed at home, and provide the results to the study site. Any positive urine pregnancy test result will be confirmed with a serum β-hCG test by a central laboratory.
j. Coagulation panel to be performed at an unscheduled visit in case of elevated ALT/AST.
k. Complete physical examination at OLE Visit 17/ET visit (see Table 6) and brief physical examinations during the study. A complete physical examination will include evaluation of heart, lung, head and neck, abdomen, neurological function, skin, and extremities. An interim (or brief) physical examination will include areas with previously noted abnormalities and/or that are associated with any new complaints from the participant.
l. Pulmonary function includes assessment of FEV1 and FVC. If the pulmonary function test results are not within normal range, the results should be verified by a pulmonologist, and potential confounding factors identified. If the participant has a decline in pulmonary function test values, the participant should be evaluated by a pulmonologist. If values (FEV1 and/or FVC) decline below 50% of the predicted values, treatment should be discontinued with follow-up evaluation initiated as appropriate. At sites where available, DLCO measurements will also be performed. The ET visit assessment is required only if results from the last on-treatment visit are abnormal.
m. A general ophthalmologist can perform the examination, although a retinal specialist would be preferred wherever possible. A complete ophthalmoscopy and OCT assessment should be performed according to the SoA. Site should retain a copy of the OCT result and the ophthalmologist report. For participants with a suspicion of new onset of macular edema and/or retinopathy, along with evaluation using ophthalmoscopy and OCT, additional testing should be considered at the discretion of the ophthalmologist (eg, general retinal examinations, including eye history, visual acuity, dilated ophthalmoscopy).
n. Participants will receive a stool sampling kit at a previous visit and be asked to collect a stool sample within 24 hours of the visit. Participants are to bring stool samples to the clinic.
[redacted]
p. PK samples will be collected (measuring trough concentrations) after completion of vital sign assessments and ECGs. When study drug is administered at the clinic, PK sample will be collected predose (see Table 10).
q. Endoscopy is not required if ET visit is before OLE Week 13 (Table 3).
r. The eDiary should be completed daily to capture data, including daily SF and RB, and study drug administration. Study center personnel should review the diary data at every visit at the timepoints in the table and in between visits via EDC to confirm compliance with eDiary completion.
s. The MMS will be calculated electronically at OLE Week 39/ET visit. The subscores for RB and SF are derived from the participant eDiary entries using the scores from the 3 most recent consecutive days within the 7 days prior to the day of bowel preparation, averaged and rounded to the nearest integer.
t. Partial Mayo Score will include SF, RB and PGA assessments, and will be used to determine loss of response as described in Section 8.3.1.5.
u. When endoscopy is performed (see footnote q) and colonic biopsy is collected, samples are sent to the central laboratory. Colonic biopsy may be used for histology [redacted] Biopsy samples will be processed by a central laboratory, and histopathologic scoring using the Geboes, Robarts, and Nancy histopathology indices will be performed by a blinded central reader (Appendix 7).
v. If and when available in the appropriate local language.

Table 5 Schedule of Activities for the Open-Label Extension Treatment Period Year 2

Study Procedures	Open-Label Extension Treatment Period (OLE Year 2)				Early Termination/ Follow-Up Period	
OLE Visit[a]	OLE Visit 10	OLE Visit 11	OLE Visit 12	OLE Visit 13	ET Visit[b]	1-Week & 2-Week Follow-Up Visits[b]
OLE Day	OLE Day 358	OLE Day 442	OLE Day 526	OLE Day 638		
Window (days)	± 14	± 14	± 14	± 14		
OLE Week	OLE Week 51	OLE Week 63	OLE Week 75	OLE Week 91		
Dispense/redispense study drug	X	X	X	X		
Administer study drug at clinic[c]	X	X	X	X		
Return study drug	X	X	X	X	X	
Review drug compliance	X	X	X	X	X	
Prior and concomitant medications	X	X	X	X	X	X
SAFETY						
Adverse events	X	X	X	X	X	X
12-lead ECG[d]		X		X	X	
Vital signs[e]	X	X	X	X	X	
Clinical laboratory tests						
Hematology[f]	X	X	X	X	X	X[f]
Blood chemistry[g]	X	X	X	X	X	
Pregnancy test[h]	X	X	X	X	X	X
Coagulation panel[i]				X	X	
Urinalysis		X		X	X	
Physical examination[j]	X	X	X	X	X	
Pulmonary function test[k]		X		X	X	
Ophthalmoscopy with OCT[l]		X		X	X	
PHARMACOKINETICS/EFFICACY BIOMARKER						
Stool collection for fecal calprotectin[m]		X		X	X	
Blood collection for C-reactive protein		X		X	X	
PK blood sampling[n]				X	X	X
EFFICACY						
Endoscopy[o]				X	X	
eDiary[p]	X	X	X	X	X	
Mayo Clinic Score[q]				X	X	

Study Procedures	Open-Label Extension Treatment Period (OLE Year 2)				Early Termination/ Follow-Up Period	
OLE Visit[a]	**OLE Visit 10**	**OLE Visit 11**	**OLE Visit 12**	**OLE Visit 13**	**ET Visit[b]**	**1-Week & 2-Week Follow-Up Visits[b]**
OLE Day	**OLE Day 358**	**OLE Day 442**	**OLE Day 526**	**OLE Day 638**		
Window (days)	**± 14**	**± 14**	**± 14**	**± 14**		
OLE Week	**OLE Week 51**	**OLE Week 63**	**OLE Week 75**	**OLE Week 91**		
Physician's Global Assessment[r]				X	X	
Colonic biopsy[s]				X	X	

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; β-hCG = beta-human chorionic gonadotropin; CBC = complete blood count; DLCO = diffusing capacity of the lungs for carbon monoxide; ECG = electrocardiogram; eDiary = electronic diary; EOT = end of treatment; ET = Early Termination; FEV1 = forced expiratory volume at 1 second; FVC = forced vital capacity; LTE = Long-Term Extension; MMS = modified Mayo score; OCT = optical coherence tomography; OLE = Open-Label Extension; PGA = Physician's Global Assessment; PK = pharmacokinetics; RB = rectal bleeding; SF = stool frequency; ULN = upper limit of normal

a. All visits beyond OLE Visit 2 (Table 3) may be virtual/hybrid visits (see Section 8.2). Participants who enter the OLE from the LTE will remain in the OLE for a possible total of 36 months of treatment (including the 13-week Induction Period, plus the duration in the LTE and the duration in the OLE). Regardless of when a participant rolls over to the OLE, when a participant completes 36 months of treatment, they need to complete all assessments for OLE Visit 17/EOT visit (Table 6).
b. All participants who discontinue the study prematurely will be asked to return to the clinic for the ET visit, and the 1-Week Follow-Up and 2-Week Follow-Up visits after the last dose of study treatment. If the ET visit is ≥ 1 week after the last dose of study treatment, the 1-Week Follow-Up visit is not required; however, the 2-Week Follow-Up visit should be scheduled and completed. In the unlikely event that the ET visit is ≥ 2 weeks after the last dose of study treatment, the 2-Week Follow-Up visit is not required.
c. Study drug should be administered after completion of all initial assessments on the day of visit.
d. ECGs to be obtained after an at least 5-minute supine resting period. When study drug is to be administered at the clinic, ECG will be obtained predose.
e. Vital signs will be collected in the sitting position prior to the ECG assessment and before any simultaneously scheduled blood collections.
f. At the 2-Week Follow-Up visit, if the absolute peripheral lymphocyte count is not within normal limits, participants should return for CBC with differential according to local standard of care (captured as subsequent Follow-Up visit or unscheduled visit).
g. An increase in AST or ALT > 3 × ULN should be followed by repeat testing within 72 hours of receiving results to confirm the abnormality and determine whether AST or ALT is increasing or decreasing.
h. For women of childbearing potential, all pregnancy testing will be performed using a urine dipstick pregnancy test. Home urine pregnancy test kits may be provided to the participant for any virtual/hybrid visit or to perform a monthly pregnancy test at home during non-visit months, if permitted by local regulations. Participants will confirm the performance of a monthly pregnancy test in the eDiary, if performed at home, and provide the results to the study site. Any positive urine pregnancy test result will be confirmed with a serum β-hCG test by a central laboratory.
i. Coagulation panel to be performed at an unscheduled visit in case of elevated ALT/AST.

j. Complete physical examination at OLE Visit 17/ET visit (Table 6) and brief physical examinations during the study. A complete physical examination will include evaluation of heart, lung, head and neck, abdomen, neurological function, skin, and extremities. An interim (or brief) physical examination will include areas with previously noted abnormalities and/or that are associated with any new complaints from the participant.
k. Pulmonary function includes assessment of FEV1 and FVC. If the pulmonary function test results are not within normal range, the results should be verified by a pulmonologist, and potential confounding factors identified. If the participant has a decline in pulmonary function test values, the participant should be evaluated by a pulmonologist. If values (FEV1 and/or FVC) decline below 50% of the predicted values, treatment should be discontinued with follow-up evaluation initiated as appropriate. At sites where available, DLCO measurements will also be performed. The ET visit assessment is required only if results from the last on-treatment visit are abnormal.
l. A general ophthalmologist can perform the examination, although a retinal specialist would be preferred wherever possible. A complete ophthalmoscopy and OCT assessment should be performed according to the SoA. Site should retain a copy of the OCT result and the ophthalmologist report. For participants with a suspicion of new onset of macular edema and/or retinopathy, along with evaluation using ophthalmoscopy and OCT, additional testing should be considered at the discretion of the ophthalmologist (eg, general retinal examinations, including eye history, visual acuity, dilated ophthalmoscopy).
m. Participants will receive a stool sampling kit at a previous visit and be asked to collect a stool sample within 24 hours of the visit. Participants are to bring stool samples to the clinic.
n. PK samples will be collected (measuring trough concentrations) after completion of vital sign assessments and ECGs. When study drug is administered at the clinic, PK sample will be collected predose (see Table 10).
o. Endoscopy is an optional assessment in OLE Years 2-3.
p. In OLE Years 2-3, the eDiary will be completed daily for a minimum of 2 weeks prior to each scheduled visit to capture daily SF and RB, and study drug administration. Study center personnel should review the diary data during schedule visits.
q. If endoscopy is performed, the MMS will be calculated electronically at OLE Week 91/ET visit. The subscores for RB and SF are derived from the participant eDiary entries using the scores from the 3 most recent consecutive days within the 7 days prior to the day of bowel preparation, averaged and rounded to the nearest integer.
r. Partial Mayo Score will include SF, RB and PGA assessments, and will be used to determine loss of response as described in Section 8.3.1.5.
s. If endoscopy is performed (see footnote p) and colonic biopsy is collected, samples are sent to the central laboratory. Colonic biopsy may be used for histology [redacted] Biopsy samples will be processed by a central laboratory, and histopathologic scoring using the Geboes, Robarts, and Nancy histopathology indices will be performed by a blinded central reader (Appendix 7).

Table 6 Schedule of Activities for the Open-Label Extension Treatment Period Year 3

Study Procedures	Open-Label Extension Treatment Period (OLE Year 3)				Early Termination/ Follow-Up Period	
OLE Visit[a]	OLE Visit 14	OLE Visit 15	OLE Visit 16	OLE Visit 17/EOT	ET Visit[b]	1-Week & 2-Week Follow-Up Visits[b]
OLE Day	OLE Day 722	OLE Day 806	OLE Day 890	OLE Day 1002		
Window (days)	± 14	± 14	± 14	± 14		
OLE Week	OLE Week 103	OLE Week 115	OLE Week 127	OLE Week 143		
Dispense/redispense study drug	X	X	X			
Administer study drug at clinic[c]	X	X	X	X		
Return study drug	X	X	X	X	X	
Review drug compliance	X	X	X	X	X	
Prior and concomitant medications	X	X	X	X	X	X
SAFETY						
Adverse events	X	X	X	X	X	X
12-lead ECG[d]		X		X	X	
Vital signs[e]	X	X	X	X	X	
Clinical laboratory tests						
Hematology[f]	X	X	X	X	X	X[f]
Blood chemistry[g]	X	X	X	X	X	
Pregnancy test[h]	X	X	X	X	X	X
Coagulation panel[i]				X	X	
Urinalysis		X		X	X	
Physical examination[j]	X	X	X	X	X	
Pulmonary function test[k]		X		X	X	
Ophthalmoscopy with OCT[l]		X		X	X	
PHARMACOKINETICS/EFFICACY BIOMARKER						
Stool collection for fecal calprotectin[m]		X		X	X	
Blood collection for C-reactive protein		X		X	X	
PK blood sampling[n]				X	X	X
EFFICACY						
Endoscopy[o]				X	X	
eDiary[p]	X	X	X	X	X	
Mayo Clinic Score[q]				X	X	

Study Procedures	Open-Label Extension Treatment Period (OLE Year 3)				Early Termination/ Follow-Up Period	
OLE Visit[a]	**OLE Visit 14**	**OLE Visit 15**	**OLE Visit 16**	**OLE Visit 17/EOT**	**ET Visit[b]**	**1-Week & 2-Week Follow-Up Visits[b]**
OLE Day	**OLE Day 722**	**OLE Day 806**	**OLE Day 890**	**OLE Day 1002**		
Window (days)	**± 14**	**± 14**	**± 14**	**± 14**		
OLE Week	**OLE Week 103**	**OLE Week 115**	**OLE Week 127**	**OLE Week 143**		
Physician's Global Assessment[r]				X	X	
Colonic biopsy[s]				X	X	

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; β-hCG = beta-human chorionic gonadotropin; CBC = complete blood count; DLCO = diffusing capacity of the lungs for carbon monoxide; ECG = electrocardiogram; eDiary = electronic diary; EOT = end of treatment; ET = Early Termination; FEV1 = forced expiratory volume at 1 second; FVC = forced vital capacity; LTE = Long-Term Extension; MMS = modified Mayo score; OCT = optical coherence tomography; OLE = Open-Label Extension; PGA = Physician's Global Assessment; PK = pharmacokinetics; RB = rectal bleeding; SF = stool frequency; ULN = upper limit of normal

a. All visits beyond OLE Visit 2 (Table 3) may be virtual/hybrid visits (see Section 8.2). Participants who enter the OLE from the LTE will remain in the OLE for a possible total of 36 months of treatment (including the 13-week Induction Period, plus the duration in the LTE and the duration in the OLE). Regardless of when a participant rolls over to the OLE, when a participant completes 36 months of treatment, they need to complete all assessments for OLE Visit 17/EOT visit.

b. All participants who discontinue the study prematurely will be asked to return to the clinic for the ET visit, and the 1-Week Follow-Up and 2-Week Follow-Up visits after the last dose of study treatment. If the ET visit is ≥ 1 week after the last dose of study treatment, the 1-Week Follow-Up visit is not required; however, the 2-Week Follow-Up visit should be scheduled and completed. In the unlikely event that the ET visit is ≥ 2 weeks after the last dose of study treatment, the 2-Week Follow-Up visit is not required.

c. Study drug should be administered after completion of all initial assessments on the day of visit.

d. ECGs to be obtained after an at least 5-minute supine resting period. When study drug is to be administered at the clinic, ECG will be obtained predose.

e. Vital signs will be collected in the sitting position prior to the ECG assessment and before any simultaneously scheduled blood collections.

f. At the 2-Week Follow-Up visit, if the absolute peripheral lymphocyte count is not within normal limits, participants should return for CBC with differential according to local standard of care (captured as subsequent Follow-Up visit or unscheduled visit).

g. An increase in AST or ALT > 3 × ULN should be followed by repeat testing within 72 hours of receiving results to confirm the abnormality and determine whether AST or ALT is increasing or decreasing.

h. For women of childbearing potential, all pregnancy testing will be performed using a urine dipstick pregnancy test. Home urine pregnancy test kits may be provided to the participant for any virtual/hybrid visit or to perform a monthly pregnancy test at home during non-visit months, if permitted by local regulations. Participants will confirm the performance of a monthly pregnancy test in the eDiary, if performed at home, and provide the results to the study site. Any positive urine pregnancy test result will be confirmed with a serum β-hCG test by a central laboratory.

i. Coagulation panel to be performed at an unscheduled visit in case of elevated ALT/AST.
j. Complete physical examination at OLE Visit 17/ET visit and brief physical examinations during the study. A complete physical examination will include evaluation of heart, lung, head and neck, abdomen, neurological function, skin, and extremities. An interim (or brief) physical examination will include areas with previously noted abnormalities and/or that are associated with any new complaints from the participant.
k. Pulmonary function includes assessment of FEV1 and FVC. If the pulmonary function test results are not within normal range, the results should be verified by a pulmonologist, and potential confounding factors identified. If the participant has a decline in pulmonary function test values, the participant should be evaluated by a pulmonologist. If values (FEV1 and/or FVC) decline below 50% of the predicted values, treatment should be discontinued with follow-up evaluation initiated as appropriate. At sites where available, DLCO measurements will also be performed. The ET visit assessment is required only if results from the last on-treatment visit are abnormal.
l. A general ophthalmologist can perform the examination, although a retinal specialist would be preferred wherever possible. A complete ophthalmoscopy and OCT assessment should be performed according to the SoA. Site should retain a copy of the OCT result and the ophthalmologist report. For participants with a suspicion of new onset of macular edema and/or retinopathy, along with evaluation using ophthalmoscopy and OCT, additional testing should be considered at the discretion of the ophthalmologist (eg, general retinal examinations, including eye history, visual acuity, dilated ophthalmoscopy).
m. Participants will receive a stool sampling kit at a previous visit and be asked to collect a stool sample within 24 hours of the visit. Participants are to bring stool samples to the clinic.
n. PK samples will be collected (measuring trough concentrations) after completion of vital sign assessments and ECGs (see Table 10).
o. Endoscopy is an optional assessment in OLE Years 2-3.
p. In OLE Years 2-3, the eDiary will be completed daily for a minimum of 2 weeks prior to each scheduled visit to capture daily SF and RB, and study drug administration. Study center personnel should review the diary data during schedule visits.
q. If endoscopy is performed, the MMS will be calculated electronically at OLE Week 143/ET visit. The subscores for RB and SF are derived from the participant eDiary entries using the scores from the 3 most recent consecutive days within the 7 days prior to the day of bowel preparation, averaged and rounded to the nearest integer.
r. Partial Mayo Score will include SF, RB and PGA assessments, and will be used to determine loss of response as described in Section 8.3.1.5.
s. If endoscopy is performed (see footnote p) and colonic biopsy is collected, samples are sent to the central laboratory. Colonic biopsy may be used for histology [redacted] Biopsy samples will be processed by a central laboratory, and histopathologic scoring using the Geboes, Robarts, and Nancy histopathology indices will be performed by a blinded central reader (Appendix 7).

2.0 INTRODUCTION

2.1 Study Rationale

Ulcerative colitis (UC) is a chronic recurrent, remittent, or progressive inflammatory condition that affects the colonic mucosa and is associated with an increased risk for colon cancer.[1] Existing standard of care agents for UC primarily work by treating the acute symptoms of UC, inducing remission in the majority of cases, with approximately 60% to 70% of patients achieving remission with first-line corticosteroid therapy.[2] Of the patients who receive second-line therapy such as biologics, about 30% to 40% of patients do not respond to treatment despite optimal therapy, while another 23% to 46% of patients lose response over time or discontinue treatment, resulting in limited clinical benefits.[3] There remains meaningful unmet medical need, including a significant underserved set of patients who will not respond or become unresponsive to current therapies. VTX002 (formerly known as OPL-002) is an oral small molecule compound being developed for the treatment of moderately to severely active UC. VTX002 is a selective sphingosine-1-phosphate receptor (S1PR) modulator. The sphingosine-1-phosphate (S1P) signal transduction through the S1PRs plays an important role in a series of responses, including inflammation and repair processes, which play an important role in several immune-mediated inflammatory diseases. The available nonclinical and clinical data support the initiation of a Phase 2 study of VTX002 in participants with moderate to severe UC. This Phase 2 study aims to evaluate the efficacy and safety of VTX002 tablets for daily oral administration in participants with moderately to severely active UC.

2.2 Background

Ulcerative colitis is a chronic disease of unknown etiology that is characterized by inflammation of the rectum and colon. Symptoms include diarrhea, rectal bleeding (RB), urgency, and tenesmus. Ulcerative colitis has a relapsing-remitting course, which means that many patients have intermittent disease flares that are interspersed with periods of remission.

The treatment goals for UC include acute treatment of symptoms (ie, induction of clinical remission) and prevention of flare-ups (maintenance of remission). Medications currently available in the market for UC include 5-aminosalicylic acid (5-ASA)-containing medications, corticosteroids, immunomodulators such as azathioprine (AZA) and 6-mercaptopurine (6-MP) (off-label use), biologic medications (eg, anti-tumor necrosis factor [TNF] and anti-integrins), and Janus kinase (JAK) inhibitor therapy. As many patients do not fully respond to available treatment, there continues to be an unmet medical need for the development of easily administered, oral targeted therapies for the acute symptomatic and maintenance treatment of UC, particularly as most patients treated with biologics experience inadequate response. Moreover, many patients who receive biologics lose responsiveness over time, even though their initial response may have been positive.[4]

VTX002 is an oral small molecule compound being developed for the treatment of moderately to severely active UC. VTX002 is a selective S1PR modulator. The S1P signal transduction through the S1PRs plays an important role in a series of responses, including inflammation and repair processes, which play an important role in several immune-mediated inflammatory diseases.

2.2.1 Nonclinical Findings

A series of studies in mouse, rat, dog, and monkey show potent activity of VTX002 as a S1P1 receptor modulator with modest activity against S1P5 and selectivity over S1P2, S1P3, and S1P4 receptor subtypes. These primary and secondary pharmacology studies have demonstrated that oral dosing of VTX002 leads to a robust and persistent reduction in circulating lymphocyte levels that correlates with the plasma concentration of VTX002. In addition, rapid recovery of normal lymphocyte trafficking is observed when VTX002 dosing is terminated. In the rat, doses of 3 mg/kg and above showed significant suppression of circulating lymphocytes. In mouse, dog, and primate, approximately 80% suppression of circulating lymphocytes was attained with doses of 10 mg/kg. In a trinitrobenzene sulfonic acid-induced acute UC model in the rat, efficacy was evident at doses ranging from 1 to 10 mg/kg. These data suggest a therapeutic effect can be obtained at a human equivalent dose of 0.48 to 1.67 mg/kg. These studies have also demonstrated that VTX002 has low central nervous system penetration and brain levels upon oral administration.

VTX002 was found to have no significant secondary pharmacological effects when screened at a concentration of 10 μM against a panel of receptors, ion channels, enzymes, and neurotransmitter transporters. VTX002 had no effect on human sodium channel ($Na_v1.5$) at concentrations up to 10 μM and caused a small reduction (14%) in human calcium channel ($Ca_v1.5$) currents at 10 μM. This interaction is not considered to be physiologically significant as plasma concentrations required to elicit a Cav1.5 response are not expected to be attained following therapeutic doses. Core battery safety pharmacology studies conducted with VTX002 showed a modest effect on the hERG current with an IC_{50} of 3.5 μM. The no effect level was 0.1 μM.

In a cardiovascular function study in telemetered dogs, there was no increase in QT interval (QT or QTc) at doses up to 30 mg/kg/day and corresponding peak plasma concentrations of 4600 ng/mL (8.4 μM). There was also no effect on blood pressure (BP), electrocardiogram (ECG) intervals, and body temperature, and no effects on respiratory function. Detailed analysis of heart rate (HR) showed no physiologically relevant changes and no transient decreases in HR in the dog, which has been reported with other S1P receptor modulators.[5] VTX002 also had no effect on central and peripheral nervous system function in the rat.

In summary, primary and secondary pharmacology studies show potent activity of VTX002 as a S1P1 receptor modulator with modest activity against S1P5 and selectivity over S1P2, S1P3, and S1P4 receptor subtypes and no other significant off target interactions. S1P1 receptor modulation resulted in reduced circulating lymphocytes in vivo, and efficacy was demonstrated in a model of

colitis in the rat. Safety pharmacology studies demonstrate no effects of oral dosing of VTX002 on cardiovascular, respiratory, and central and peripheral nervous systems.

2.2.2 Clinical Findings

2.2.2.1 Phase 1 Study

Safety findings from the Phase 1 study showed that VTX002 was safe and generally well tolerated when administered orally as an oral suspension (VTX002 SDD) at single (up to 40 mg) and multiple (up to 45 mg) ascending oral doses to healthy adult male participants for 21 to 28 days.[6]

2.2.2.2 Pharmacokinetics

Exposure to VTX002 following single doses of the reconstituted powder ranging from 2.5 to 40 mg increased with dose. The exposure values increased in a somewhat more than dose-proportional manner with respect to the increase in VTX002 doses administered.

However, when the multiple-dose study dose proportionality of plasma VTX002 was performed on the pharmacokinetic (PK) parameters maximum concentration (C_{max}) and AUC from time zero to 24 hours [$AUC_{(0-24)}$] following administrations of 10 mg VTX002 on Day 8, 20 mg VTX002 on Day 9, 35 mg VTX002 on Day 8, and 45 mg VTX002 on Day 8, each after a 7-day dose titration, the results indicated that exposure to VTX002 increased statistically proportional with increased VTX002 doses. Similarly, the dose proportionality analysis results following 13, 14, or 21 days of once daily (QD) dosing indicated that exposure to VTX002 increased in proportion to increases in the VTX002 dose. Steady-state analyses of plasma VTX002 concentrations following the administration of 10 mg VTX002 QD on Days 8 through 21 and 20 mg VTX002 QD on Days 9 through 21 indicated that steady state was attained on Day 11 and Day 12, respectively. Moreover, steady-state analysis of plasma VTX002 concentrations following the administration of 35 mg VTX002 QD and 45 mg VTX002 QD on Days 8 through 28 showed that steady state had been achieved by Day 14. The results from the multiple-dose administration showed that the PK of VTX002 is linear (ie, it is invariant with respect to time). The accumulation test results showed that exposure to VTX002 increased more than the 2-fold following 21 days of multiple VTX002 dosing.

Food effect was also assessed in this Phase 1 study and did not affect the exposure to VTX002, as the geometric mean ratio values of C_{max} and AUC were similar (differences were < 2.4%). There was an apparent 2-hour delay in the time to reach C_{max} (T_{max}) under fed conditions. However, this difference did not reach statistical significance (p-value > 0.05).

2.2.2.3 Pharmacodynamics

There was a dose-related mean reduction in absolute lymphocyte counts (ALC), as measured by percent change from baseline, following all single and multiple oral doses of VTX002 compared with placebo. Maximum mean percent change from baseline across all treatments occurred at

approximately 3 to 8 hours after dosing. Based on maximum mean percent change from baseline following a single oral dose of VTX002, the greatest reduction in ALC (65.4%) was associated with the largest plasma VTX002 C_{max} value attained following the 40 mg VTX002 dose. Similarly, the largest reductions in ALC were associated with the highest plasma VTX002 trough concentration values following multiple oral VTX002 QD doses. At steady state, the mean percent reductions in ALC were similar for the 35 and 45 mg QD VTX002 doses (62% and 65%, respectively), as were the mean maximum observed reductions in ALC for the 35 and 45 mg QD VTX002 doses (75% and 74%, respectively).

2.2.2.4 Cardiodynamics

Assessment of QT intervals through linear regression of corrected QT using Fridericia's formula (QTcF) versus RR indicated adequacy of QTcF. QTcF versus time profiles were similar across all VTX002 doses, with slightly greater mean values noted following 25 mg VTX002 (single ascending dose [SAD]) and 10 mg VTX002 (multiple ascending dose [MAD]). All participants in the SAD and MAD cohorts exhibited QTcF intervals ≤ 450 msec, and there were no participants with change from baseline values > 30 msec.

2.2.2.5 Heart Rate Analysis

In the SAD cohorts, there was a dose-related decrease in HR after dosing with VTX002 compared with placebo, with the maximum HR decrease from baseline (defined as the interval time between -1 hour to dose) occurring during Hour 1 (defined as the interval time between 1 and 2 hours postdose) with rapid increase after the nadir, returning to baseline by Hour 3 (defined as the interval time between 3 and 4 hours postdose). The maximum decrease from baseline of -21.2 beats per minute (bpm) (-30.80%) occurred during Day 1, Hour 1 (defined as the interval time between 1 and 2 hours postdose) among participants in the 40 mg VTX002 cohort.

In the MAD cohorts, after a 7-day titration, there was no clinically significant decrease in HR after the administration of the target VTX002 dose. On the first day of the target dose administration, the maximum HR changes from predose occurred during Hour 1 (defined as the interval time between 1 and 2 hours postdose) and were -3.5 bpm in the 35 mg VTX002 QD cohort and -3.3 bpm in the 45 mg VTX002 QD cohort.

2.2.2.6 Safety

<u>Single Ascending Dose Cohorts</u>

There were no deaths, serious adverse events (SAEs), or participant discontinuations due to adverse events (AEs) in the SAD part of this study. Overall, 18 (30%) participants dosed reported 28 treatment-emergent adverse events (TEAEs) under fasted conditions (active drug or placebo) and an additional 5 TEAEs occurred in the food effect cohort under fed conditions. Adverse events incidence did not increase with rising VTX002 level. The most common TEAE was headache, experienced by 3 (5%) participants in the fasted cohorts and 1 (13%) participant in the food effect

cohort of the study. One participant in the 40 mg cohort reported an AE of Mobitz Type 1 second-degree AV block. Overall, 32 TEAEs (27 in the fasted cohorts and 5 in the fed cohort) were mild (Grade 1) in severity and 1 (headache, pooled placebo, fasted) was moderate (Grade 2) in severity. No treatment- or dose-related trends were observed regarding vital sign, ECG, physical examination (PE), ophthalmic examination, or pulmonary function test (PFT) results with respect to participant safety in the SAD cohorts.

Multiple Ascending Dose Cohorts

There were no deaths or SAEs in the MAD cohorts in this study. Three participants were discontinued from the study due to AEs (including 1 event of urticaria, 1 event of first-degree AV block, and 1 event of Mobitz Type I second-degree atrioventricular [AV] block) that were considered drug related. The event of second-degree AV block led to temporary 1-day dosing holiday during the dose titration phase of the study for the 20 mg VTX002 MAD cohort. Overall, 35 (88%) participants reported a total of 82 TEAEs, with similar numbers of participants reporting AEs across all cohorts. The most frequently reported TEAE was mild (Grade 1) contact dermatitis secondary to placement of Holter ECG electrode leads, experienced by 31 (78%) participants. Eighty-one TEAEs were mild (Grade 1) in severity and 1 (Mobitz Type 1 second-degree AV block, 20 mg VTX002 once daily [QD]) was moderate (Grade 2) in severity. No treatment- or dose-related trends were observed regarding vital sign, ECG, PE, ophthalmic examination, or PFT results with respect to participant safety in the MAD cohorts.

2.2.2.7 Relative Bioavailability Study

Recently, a tablet formulation was developed for VTX002, and a relative bioavailability study was performed comparing the relative bioavailability of the 20 mg tablet to 20 mg of the free base suspension used in the Phase 1 study. The ratio of the AUC_{0-t} for the tablet compared with the suspension was [redacted]. For the low dose in this study of 30 mg daily, that is equivalent to [redacted] of the free base suspension used in the Phase 1 study, and the high dose of 60 mg daily is equivalent to [redacted] of the free base suspension. Based on the similarity in PK characteristics (C_{max} and AUC) of the suspension and tablet formulation and a half-life of approximately 20 hours, it is presumed that as with the suspension formulation, there would be minimal effect of food on exposure to the VTX002 tablet formulation.

2.3 Benefit/Risk Assessment

VTX002 may benefit patients with moderately to severely active UC whose disease has progressed or is unresponsive to currently approved standard of care agents. Nonclinical results suggest that VTX002 administration would result in reduced circulating lymphocytes in vivo, and efficacy was demonstrated in a model of colitis in the rat. Results from the Phase 1 study demonstrated a strong relationship between dose, exposure, and lowering of circulating lymphocyte levels.

Potential risks for study participation have been associated with VTX002 include the following:

Decreased Heart Rate and/or Atrioventricular Conduction

- Guidance for cardiac monitoring is provided, including first dose and extended cardiac monitoring postdose as needed. On Day 1 and OLE Day 1 (OLE Week 0/OLE Visit 1), following the first dose of study drug, participants will remain in the clinic for 6 hours to monitor vital signs and cardiac conduction. Upon release from the clinic, participants will be monitored closely throughout study participation (see Section 6.5).
- A dose titration schedule will be implemented to minimize the risk for cardiovascular events related to administration of the first dose of study treatment (Section 6.2).
- Availability of emergency equipment should be within close proximity to study site. Personnel experienced in the use of advanced life support must be readily accessible during the first-dose monitoring and reinitiation of treatment, as well as in case of an emergency (see Section 6.5).
- Criteria for study treatment discontinuation are outlined in Section 7.0.

Infections

- Given the mechanism of action of decreased peripheral lymphocytes, VTX002 may increase the risk of infections, including opportunistic infections. Participants should be monitored for signs and symptoms of infection during the study and throughout the Follow-Up Period. Participants with active acute or chronic infection should not be enrolled. Participants who develop an active infection during the study should be monitored and may need to have study treatment temporarily discontinued (Section 7.0).

Macular Edema

- Although not observed in any of the VTX002 preclinical safety or clinical Phase 1 studies, treatment with agents in the same class have been associated with cases of macular edema, with or without visual symptoms. As described in Section 8.4.6 of the protocol, participants should be monitored for visual symptoms during the study, and, if symptoms develop, an ophthalmologic evaluation and optical coherence tomography (OCT) should be performed.

Decrease in Pulmonary Function

- Although not observed in any of the VTX002 preclinical safety studies or clinical Phase 1 studies, treatment with agents in the same class have been associated with a decrease in pulmonary function. As described in Section 8.4.5 of the protocol, participants should be monitored for dyspnea and other pulmonary symptoms, and, if pulmonary symptoms develop, a PFT, including diffusing capacity of lung for carbon monoxide, should be performed.

Drug-Drug Interactions

In vitro studies suggested that VTX002 may be an inhibitor of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) transporters. As described in Section 6.10.2, therapies that are substrates or inhibitors of P-gp and BCRP are prohibited.

In addition, risk for reproductive and developmental toxicity cannot be excluded; thus, inclusion/exclusion criteria regarding pregnancy are noted to mitigate this risk (see Section 5.0). The risk for reproductive and developmental toxicity has also been observed for all other approved S1P receptor modulators.

Results from preclinical safety studies showed that VTX002 has a low risk of phototoxicity. Participants may be evaluated for any signs of phototoxicity as part of the PE.

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

Other risks for study participation may include treatment with placebo and a potentially ineffective treatment, and delay of treatment with other approved medicinal products. For vulnerable populations as geriatric patients, risks for study participation should be considered, given the potential higher number of comorbidities and concomitant medications that may be present in this population. Ultimately, the Investigator should consider if the benefits outweigh the risks for patients to participate in this study.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of VTX002 may be found in the Investigator's Brochure.[7]

3.0 OBJECTIVES AND ENDPOINTS

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the clinical efficacy and safety of VTX002 in participants with moderately to severely active UC.

3.1 Objectives

Primary Objective

- Assess the efficacy of VTX002 when administered for 13 weeks on clinical remission

Secondary Objectives

- Assess the efficacy of VTX002 when administered for 13 weeks on endoscopic changes, symptomatic response and remission, histology, and mucosal healing
- Assess the safety and tolerability of VTX002
- Assess the PK of VTX002

Long-Term and Open-Label Extension Objectives

- Assess the efficacy of VTX002 through the Long-Term Extension (LTE) and Open-Label Extension (OLE) Treatment Periods on endoscopic changes, symptomatic response and remission, histology, and mucosal healing
- Assess the safety of VTX002 through the LTE and OLE Treatment Periods

Exploratory Objectives

- Assess the effect of VTX002 on health-related quality of life (HRQoL) outcomes and biomarkers

3.2 Endpoints

The endpoints for the study are listed below, and definitions are provided in Section 3.3. The primary and four key secondary endpoints will be tested for superiority of VTX002 60 mg vs placebo and VTX002 30 mg vs placebo. The remaining endpoints will be presented descriptively. Details of the statistical plan are presented in Section 9.0.

Primary Endpoint

- The proportion of participants with clinical remission at Week 13 using modified Mayo score (MMS)

Key Secondary Endpoints

- The proportion of participants with endoscopic improvement at Week 13
- The proportion of participants with symptomatic remission at Week 13

- The proportion of participants with histologic remission at Week 13
- The proportion of participants with endoscopic improvement-histologic remission at Week 13

Other Secondary Endpoints

- The proportion of participants with clinical response using MMS at Week 13
- The proportion of participants with endoscopic remission at Week 13
- The proportion of participants with endoscopic and histologic remission at Week 13
- The proportion of participants with endoscopic and clinical remission at Week 13
- The proportion of participants with endoscopic, histologic, and clinical remission at Week 13
- The proportion of participants with symptomatic remission at Weeks 4, 8, 10
- The proportion of participants with symptomatic response at Weeks 4, 8, 10, 13
- The proportion of participants with clinical remission using total Mayo Clinic score (MCS) at Week 13
- The proportion of participants with clinical response using total MCS at Week 13
- The proportion of participants with histologic improvement at Week 13
- Proportion of participants with any decrease from baseline in Geboes Index score at Week 13
- The proportion of participants with histologic-endoscopic mucosal improvement (HEMI) at Week 13
- The proportion of participants with UC-related hospitalizations
- The proportion of participants requiring UC-related surgeries, including colectomy
- Plasma concentrations of VTX002, assessed from samples collected predose at Weeks 0, 1, 4, 8, and 13 in the Induction Treatment Period, and Weeks 18, 26, 36, and 52 in the LTE Treatment Period; at the 1-Week and 2-Week Follow-Up visits; and at 2, 4, and 6 hours (± 15 minutes) postdose at Week 0

Safety Endpoints

- Incidence and severity of AEs
- Incidence and severity of laboratory abnormalities, and change from baseline in laboratory values (eg, hematology and serum chemistry)
- Incidence of clinically significant vital sign abnormalities and changes from baseline

Exploratory Endpoints

The endpoints described here will be analyzed separately for the Induction Treatment Period, LTE Treatment Period, and OLE Treatment Period. OLE analyses will be described in detail in the Statistical Analysis Plan (SAP).

- Proportion of participants with clinical remission after 52 weeks of treatment
- Proportion of participants with clinical remission after 13 and 52 weeks of treatment
- Proportion of participants with symptomatic remission at Weeks 18, 26, 36, and 52
- Proportion of participants with endoscopic and histologic remission after 52 weeks of treatment

- Proportion of participants with endoscopic improvement-histologic remission after 52 weeks of treatment
- Proportion of participants with endoscopic and clinical remission after 52 weeks of treatment
- Proportion of participants with endoscopic, histologic, and clinical remission after 52 weeks of treatment
- Proportion of participants with HEMI after 52 weeks of treatment
- Proportion of participants with clinical response after 52 weeks of treatment
- Proportion of participants with symptomatic response at Weeks 18, 26, 36, and 52
- Proportion of participants with symptomatic response at OLE Week 13, and at each additional OLE visit
- Proportion of participants with any decrease from baseline in Geboes Index score at Week 52
- Change from baseline in fecal calprotectin (FCP) at Weeks 1, 4, 8, 13, 26, 36, 52, and at visits during the OLE
- Change from baseline in C-reactive protein (CRP) at Weeks 1, 4, 8, 13, 26, 36, 52, and at visits during the OLE
- Change from baseline in partial Mayo score (PMS) at Weeks 4, 8, 13, 18, 26, 36, 52, and at visits during the OLE
- Change from baseline in total MCS at Week 52
- Change from baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) score at Weeks 13 and 52
- Change and percentage change from baseline in lymphocyte counts at Weeks 1, 4, 8, 13, 26, 36, and 52

3.3 Endpoint Definitions

Clinical remission: stool frequency (SF) subscore = 0 or 1, RB subscore = 0, and endoscopic subscore (ES) ≤ 1 (excluding friability)

Clinical response using MMS: A ≥ 2-point and ≥ 30% decrease from baseline in MMS, and a ≥ 1-point decrease from baseline in RB subscore or an absolute RB subscore ≤ 1

Clinical remission using total MCS: Total MCS ≤ 2 points with no individual subscore > 1 point (SF subscore = 0 or 1, RB subscore = 0, ES ≤ 1 [excluding friability], Physician Global Assessment [PGA] ≤ 1, and SF + RB + ES + PGA ≤ 2)

Clinical response using total MCS: A ≥ 3-point and ≥ 30% decrease from baseline in total MCS, and a ≥ 1-point decrease from baseline in RB subscore or an absolute RB ≤ 1.

Endoscopic improvement: ES ≤ 1 (excluding friability)

Endoscopic remission: ES = 0

Histologic improvement: Geboes Index score < 3.1. Histology will also be assessed by the Robarts Histopathology Index and Nancy Index.

Histologic remission: Geboes Index score < 2.0. Histology will also be assessed by the Robarts Histopathology Index and Nancy Index.

Endoscopic improvement-histologic remission: ES ≤ 1 (excluding friability) and histologic remission measured by a Geboes Index score < 2.0

Endoscopic and histologic remission: ES = 0 and histologic remission measured by a Geboes Index score < 2.0

Histologic-endoscopic mucosal improvement (HEMI): ES ≤ 1 (excluding friability) and histologic remission measured by a Geboes Index score < 3.1

Symptomatic remission: SF subscore = 0 or 1 and RB subscore = 0

Symptomatic response: Decrease from baseline ≥ 30% of the combined RB and SF subscores

Endoscopic and clinical remission: SF subscore ≤ 1, RB subscore = 0, and ES = 0

Endoscopic, histologic, and clinical remission: SF subscore ≤ 1, RB subscore = 0, ES = 0, and histologic remission measured by a Geboes Index score < 2.0

4.0 STUDY DESIGN

4.1 Overall Design

This is a multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of VTX002 30 mg and 60 mg in participants with moderately to severely active UC following daily oral administration of VTX002 as a tablet. Approximately 189 eligible participants will be randomized in a 1:1:1 ratio to receive VTX002 30 mg, VTX002 60 mg, or matching placebo, once daily (approximately 63 participants per treatment group).

The target patient population will include the following categories:

- Patients who have had an inadequate response, loss of response, or intolerance to conventional therapy and are naïve to biologic/JAK inhibitors (conventional failed)
- Patients who have had an inadequate response, loss of response, or intolerance to a biologic/JAK inhibitor (biologic/JAK inhibitor failed). Patients in this category may have received prior conventional therapy. It is expected that approximately 35% of participants in the study will have had an inadequate response to biologics.

Participant randomization will be stratified based on (*a*) biologic/JAK inhibitor prior use status (Yes or No) and (*b*) baseline corticosteroid use (Yes or No), and *(c)* baseline disease activity (MMS 5-6 or 7-9).

As shown in Figure 1, the study consists of a 28-day Screening Period, a 13-week double-blind Induction Treatment Period (including 7 days of titration followed by 12 weeks of treatment at the assigned dose), an LTE Treatment Period of up to 39 weeks, an OLE Treatment Period of up to 143 weeks, and a 2-week Follow-Up Period. The maximal duration of treatment including the Induction Period, LTE and OLE will be 36 months.

The duration of study participation for each participant is planned to be approximately 162 weeks, and the total duration of the study is planned to be approximately 60 months. Approximately 120 study centers in 15 countries are expected to participate in this study.

The Schedule of Activities (SoA) for the study is provided in Section 1.2.

4.1.1 Screening Period

Participant eligibility will be determined during a 4-week (28-day) Screening Period. Entry criteria will be based on confirmation of moderately to severely active UC, defined by an MMS of 5 to 9 with an ES $\geq$ 2 and RB $\geq$ 1.

4.1.2 Induction Treatment Period

On Day 1, eligible participants will be randomized in a 1:1:1 ratio to receive VTX002 30 mg, VTX002 60 mg, or matching placebo orally once a day (approximately 63 participants per

treatment group). During the first week of the Induction Treatment Period, participants will undergo a 7-day dose titration up to the full assigned double-blind treatment dose (see Section 6.2 for more information).

At the end of the 13-week Induction Treatment Period, all participants will be evaluated for efficacy and safety.

4.1.3 Long-Term Extension Treatment Period

Participants who complete the Induction Week 13 visit, and meet criteria for clinical response at Induction Week 13, will continue into the blinded LTE Period at their previously assigned treatment for up to an additional 39 weeks.

Participants in the LTE who lose response after Week 13 will have the option to enroll into the OLE. Loss of response in LTE will be assessed by the Investigator according to the criteria below:

- Increase in UC disease activity as defined by an increase in PMS ≥ 2 points compared to PMS at Week 13 with an absolute PMS ≥ 4, based on 3 most recent consecutive days of diary entries within 7 consecutive days, **AND**
- Exclusion of other causes of an increase in disease activity unrelated to underlying UC (eg, *C. difficile* infection, change in medication)

Participants who complete the Week 52 visit of the LTE may continue into the OLE.

4.1.4 Open-Label Extension Treatment Period

Participants who complete the Induction Week 13 visit, and do not meet the criteria for clinical response at Induction Week 13, will have the option to enroll into the OLE for up to an additional 143 weeks of treatment (which includes a 7-day titration period followed by treatment with VTX002 60 mg for up to 142 weeks).

Participants who enter the OLE from the LTE will undergo a 7-day titration period (see Section 6.3.1)and remain in the OLE for a possible total of 36 months of treatment (including the 13-week Induction Period, plus the duration in the LTE and the duration in OLE).

Participants who were nonresponders at the end of the Induction Period (Week 13) will be assessed again for response at OLE Week 13. At OLE Week 13, participants who fail to achieve symptomatic response (defined as decrease from baseline ≥ 30% of the combined RB and SF scores) will be discontinued from the study drug. However, participants who respond to treatment by OLE Week 13 will continue treatment with VTX002 60 mg in the OLE Treatment Period for up to an additional 130 weeks (until a total treatment duration of 36 months).

Regardless of previous blinded treatment during the Induction Period, if a participant's condition worsens or does not improve after 13 weeks in the OLE with VTX002 60 mg, the participant will be discontinued from the study.

The Sponsor will consider potential expansion of open-label access beyond the 36-month period, when the primary analysis results are available.

4.1.5 Follow-Up Period

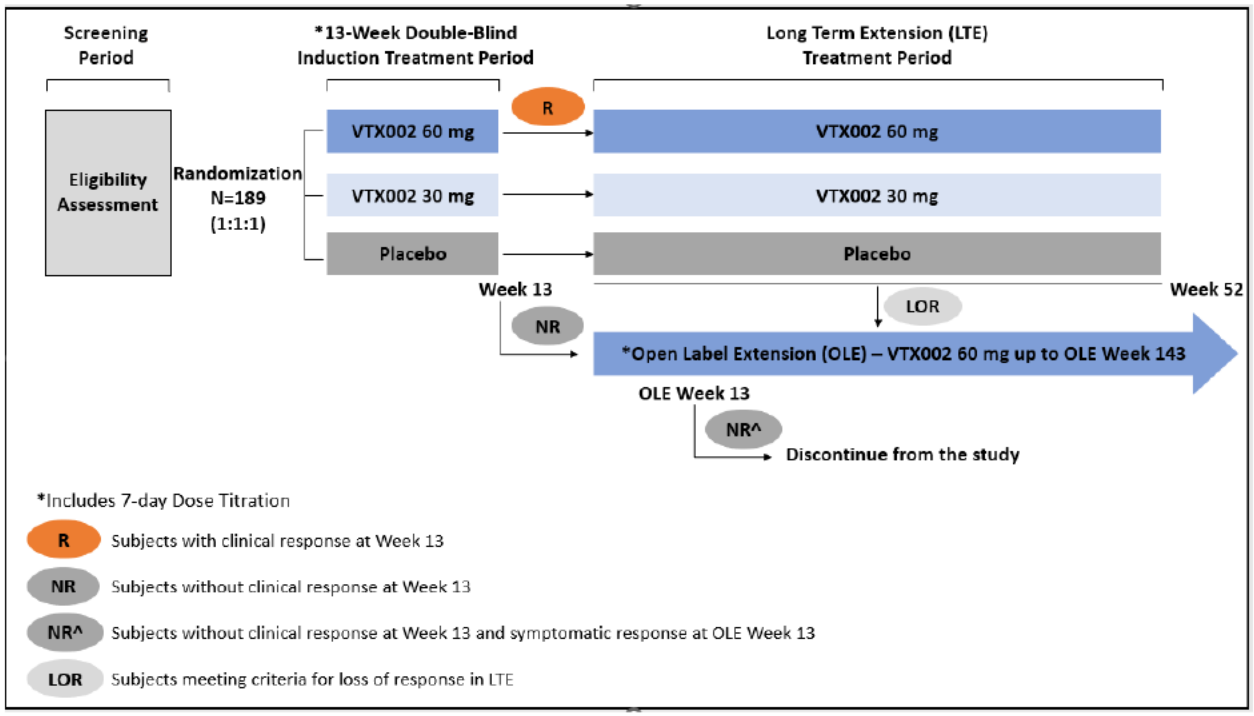
For all participants, Follow-Up visits will be performed at 1 and 2 weeks after the last dose of study treatment, as indicated in the SoA (Section 1.2). All participants who discontinue the study prematurely will be asked to return to the clinic for the Early Termination (ET) visit. If an ET visit is ≥ 1 week after the last dose of study treatment, the 1-Week Follow-Up visit is not required; however, the 2-Week Follow-Up visit should be scheduled and completed.

If the absolute peripheral lymphocyte count is not within normal limits at the 2-Week Follow-Up visit, participants should return for a complete blood count (CBC) with differential according to local standard of care (captured as a subsequent Follow-Up visit or unscheduled visit).

Participants will be evaluated for safety and efficacy in accordance with the SoA (Section 1.2). For PK, blood samples will be collected as shown in the SoA (Section 1.2).

4.2 Schema

Figure 1 Study Schema



4.3 Scientific Rationale for Study Design

This is a multicenter, randomized, double-blind, placebo-controlled study consisting of a 28-day Screening Period, a 13-week double-blind Induction Treatment Period (including 7 days of titration and 12 weeks of treatment at the assigned dose), an LTE Treatment Period of up to 39 weeks, an OLE Treatment Period of up to 143 weeks, and a 2-week Follow-Up Period. The maximal duration of treatment including the Induction Period, LTE and OLE will be 36 months.

Randomization and blinding during the Induction Treatment Period and LTE are designed to reduce bias and to increase the confidence in the efficacy and safety results that will be obtained from this study. Moreover, this Phase 2 study design simulates assessment of treatment goals for UC in clinical practice, wherein participants are evaluated for induction of remission, followed by assessment of maintenance of remission over a longer period of time (usually assessed over 52 weeks of continuous treatment in clinical studies).

4.4 Justification for Dose

In the Phase 1 study, there was a dose-related mean reduction in ALC, as measured by percent change from baseline, following all single and multiple oral doses of VTX002 compared with placebo. The largest reductions in ALC were associated with the highest dose of 45 mg/day following multiple oral VTX002 QD doses. A tablet dose equivalent to ~20 mg/day of the suspension used in Phase 1 was selected to evaluate the efficacy of a dose that would be expected to be on the lower end of the dose/efficacy curve based on the Phase 1 MAD dose/lymphocyte lowering relationship. A tablet dose equivalent to ~45 mg/day of the suspension was selected as the highest, well-tolerated dose with maximal lymphocyte lowering in the MAD study.

In the relative bioavailability study, the mean ratio and mean geometric ratio of the tablet formulation of VTX002 compared with the free base suspension of VTX002 were the following: those of AUC_{0-t} were [redacted], respectively, those of $AUC_{0-\infty}$ were [redacted], respectively, and those of C_{max} were [redacted], respectively. The relative bioavailability value of the tablet formulation of VTX002 is [redacted]. The coefficient of variation (CV) of these PK parameters were as follows: [redacted].

Two dose levels using tablets have been selected for use in this Phase 2 study based upon the data from the Phase 1 MAD study, which used a suspension of VTX002, and the data from the relative bioavailability study comparing the bioavailability of the tablet to the Phase 1 suspension. The lower dose level, 30 mg QD, is equivalent to [redacted] of the free base suspension, and the higher dose level, 60 mg tablet QD, is equivalent to [redacted] of the free base suspension. The lower tablet dose is projected to result in [redacted], and the higher tablet dose is projected to result in [redacted].

4.5 End of Study Definition

A participant will be considered to have completed the study after completing all pertinent phases of the study including the Follow-Up visits. Further details will be provided in the SAP.

A participant is considered to end the study when he/she completes the study or withdraws from the study for any reason prior to completion.

The end of the whole study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA (Section 1.2) for the last participant in the study globally.

5.0 STUDY POPULATION

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

5.1 Inclusion Criteria

Participants must meet ALL of the following inclusion criteria to be eligible for enrollment into the study:

1. Men or women, 18 to 80 years of age, inclusive, at the time of consent
2. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the Informed Consent Form (ICF)

Disease-Specific

3. Diagnosed with UC ≥ 3 months prior to Screening. The diagnosis of UC must be confirmed by endoscopic and histologic evidence. The endoscopy and histology report should be present in the source documents; however, if not available, the Screening endoscopy and histology may serve as such.
4. Active UC confirmed by endoscopy with ≥ 10 cm rectal involvement. Participants with proctitis only at baseline who meet the other eligibility criteria for inclusion, including the endoscopic and RB criteria for moderate to severe disease, will be capped at 10% of the total participants enrolled.
5. Moderately to severely active UC, defined as an MMS of 5 to 9, including an ES ≥ 2 and an RB subscore ≥ 1
6. Surveillance colonoscopy (performed according to local standard) within 12 months before baseline to rule out dysplasia in participants with pancolitis > 8 years duration or participants with left-sided colitis > 12 years duration. Participants without a surveillance colonoscopy within the prior 12 months will have a colonoscopy at Screening (ie, in place of Screening proctosigmoidoscopy). Any adenomatous polyps must be removed per local standard of care prior to the first dose of study drug.

Prior Treatment Failure

7. Demonstrated inadequate response to, loss of response to, or intolerance to at least 1 of the following therapies:
    a. Conventional therapy:
        i. Oral 5-ASA compounds
        ii. Corticosteroids
        iii. Thiopurines (eg, AZA or 6-MP)
    b. Biologic therapy or JAK inhibitor therapy:
        i. Anti-tumor necrosis factor alpha (TNFα) antibodies (eg, infliximab, adalimumab, or golimumab)
        ii. Anti-interleukin (anti-IL)12/23 (eg, ustekinumab)

iii. Anti-integrin antibodies (eg, vedolizumab)

iv. JAK inhibitors (eg, tofacitinib, upadacitinib)

Note: The medication used to qualify the participant for entry into this category of biologic therapy or JAK inhibitor therapy must be approved for the treatment of UC in the country of use.

General Safety

8. Adequate hepatic function, defined as a total bilirubin level of ≤ 1.5 × upper limit of normal (ULN) and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels of ≤ 2.0 × ULN. Participants with Gilbert's syndrome who have an isolated total bilirubin and normal AST and ALT levels may participate.
9. Adequate renal function, defined as an estimated glomerular filtration rate ≥ 60 mL/min/1.73 m^2 by the Chronic Kidney Disease Epidemiology Collaboration equation at Screening

Concomitant Medications

10. Participants are permitted to receive the following concomitant medications:
    a. Oral 5-ASA compounds at a stable dose or discontinued for ≥ 2 weeks prior to Screening endoscopy
    b. Oral corticosteroid therapy at a stable dose or discontinued for ≥ 2 weeks prior to Screening endoscopy (prednisone at a stable dose ≤ 20 mg/day, budesonide at a stable dose ≤ 9 mg/day)
    c. Probiotics, provided the dose has been stable for ≥ 2 weeks prior to Screening endoscopy

Contraception

11. Women must meet either a or b of the following criteria and men must meet criterion c to qualify for the study:
    a. A woman who is not of childbearing potential must meet 1 of the following:
        i. Postmenopausal, defined as no menses for 12 months without an alternative medical cause
        ii. Permanent sterilization procedure, such as hysterectomy, bilateral salpingectomy, or bilateral oophorectomy
    b. A nonpregnant woman of childbearing potential must agree to use a highly effective contraception method that can achieve a failure rate of less than 1% per year when used consistently and correctly. The highly effective contraception must be used through the duration of the study and for 30 days after the last dose of study treatment. The following are considered highly effective birth control methods:
        i. Combined (estrogen- and progesterone-containing) hormonal contraception associated with inhibition of ovulation, which may be oral, intravaginal, or transdermal.
        ii. Progesterone-only hormonal contraception associated with inhibition of ovulation, which may be oral, injected, or implanted

iii. Intrauterine device

iv. Intrauterine hormone-releasing system

v. Bilateral tubal occlusion

vi. Vasectomized partner, provided that the partner is the sole sexual partner of the woman of childbearing potential study participant and the vasectomized partner has received medical assessment of the surgical success

vii. Sexual abstinence (complete sexual abstinence, defined as refraining from heterosexual intercourse for the entire period of risk associated with study treatments). The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant. Periodic abstinence (calendar, symptothermal, postovulation methods) is not acceptable.

c. A man with a pregnant or nonpregnant partner who is a woman of childbearing potential must agree to use condoms through the duration of the study and for 30 days after the last dose of study treatment.

5.2 Exclusion Criteria

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

Inflammatory Bowel Disease and Gastrointestinal Conditions

1. Severe extensive colitis as evidenced by:
   a. Physician judgment that the participant is likely to require surgery (surgical intervention of any kind for UC [eg, colectomy]) within 12 weeks of baseline
   b. Current evidence of fulminant colitis or toxic megacolon, or recent history (within last 6 months) of toxic megacolon or bowel perforation
   c. Previous total colectomy
2. Diagnosis of Crohn's disease or indeterminate colitis or the presence or history of a fistula consistent with Crohn's disease
3. Diagnosis of microscopic colitis, ischemic colitis, or infectious colitis
4. Positive assay or stool culture for pathogens (ova and parasite examination, bacteria) or **positive test for *Clostridium difficile* at Screening**. Note: If *C. difficile* or pathogen test is positive, the participant may be treated and retested ≥ 4 weeks after completing treatment.

General Safety

5. Pregnancy, lactation, or a positive serum β-hCG measured during Screening
6. Clinically relevant hematologic, hepatic, neurological, pulmonary, ophthalmological, endocrine, metabolic (including, but not limited to, hypo- and hyperkalemia), psychiatric, or other major systemic disease that will make implementation of the protocol or interpretation of the study difficult or will put the participant at risk
7. Forced expiratory volume in 1 second (FEV1) or forced vital capacity (FVC) < 70% of predicted values and FEV1/FVC ratio < 0.70 at Screening

8. Have any of the following conditions or receiving treatments that may affect cardiovascular function:
    a. Myocardial infarction, unstable angina, stroke/transient ischemic attack, decompensated heart failure requiring hospitalization, or Class III/IV heart failure within ≤ 6 months prior to or during the Screening Period
    b. Screening or prerandomization vital signs (taken in the sitting position) with a HR < 50 bpm OR systolic BP < 90 mmHg OR diastolic BP < 55 mmHg. Vital signs may be repeated up to 3 times during a visit to confirm abnormal readings.
    c. Screening or prerandomization ECG with PR interval > 200 msec or Fridericia's corrected QT interval (QTcF) ≥ 450 msec in men or ≥ 470 msec in women
    d. History of any of the following unless treated with an implanted pacemaker or an implanted cardioverter-defibrillator with pacing:
        i. History or presence of recurrent symptomatic bradycardia
        ii. Second- or third-degree AV block
        iii. Periods of asystole > 3 seconds
        iv. History of sick sinus syndrome or recurrent cardiogenic syncope
    e. Start, stop, or change in dosage of any Class I-IV anti-arrhythmic drugs ≤ 1 week prior to dose titration starting at randomization and up to 1 week after titration to the assigned dose. This criterion also applies to the OLE Treatment Period titration: 1 week prior to and 1 week after the dose titration period.
9. Uncontrolled diabetes as determined by hemoglobin A1c (HbA1c) > 9%, or participants with diabetes with significant comorbid conditions, such as retinopathy
10. History or presence of macular edema or retinopathy
11. History of cancer within the last 5 years, including solid tumors and hematological malignancies (except basal cell and in situ squamous cell carcinomas of the skin that have been excised and resolved) or precancerous conditions such as colonic mucosal dysplasia, cervical dysplasia, and cervical intraepithelial neoplasia
12. History of lymphoproliferative disorder, lymphoma, leukemia, myeloproliferative disorder, or multiple myeloma
13. History of alcohol or drug abuse within 1 year prior to randomization
14. Any of the following laboratory abnormalities during the Screening Period:
    a. Absolute white blood cell (WBC) count < 3500/µL
    b. Neutrophils < 1500/µL
    c. Absolute lymphocyte count < 800/µL
    d. Platelet count < 100,000/µL
    e. Hemoglobin < 8 g/dL

Infection Risk

15. Active or latent TB infection at Screening. History of untreated or inadequately treated latent TB infection. The following are EXCEPTIONS to this exclusion criterion:
    a. Participants with latent TB, who have been ruled out for active TB, have completed an appropriate course of TB prophylaxis treatment per national/local medical guidelines or WHO guidelines, have a chest radiograph without changes suggestive of active TB infection, and have not had recent close contact with a person with active TB are eligible to enroll in the study. It is the responsibility of the Investigator to verify the adequacy of previous TB treatment and provide appropriate documentation of treatment compliance.
    b. Participants diagnosed with latent TB at Screening, ruled out for active TB and have received at least 4 weeks of an appropriate TB prophylaxis regimen may be rescreened for enrollment. Participant will complete their prophylactic regimen during the trial.
16. Known active bacterial, viral, fungal, mycobacterial, or other infection (including TB or atypical mycobacterial disease) or any major episode of infection that required hospitalization or treatment with intravenous (IV) antibiotics within 30 days of Screening or oral antibiotics within 14 days prior to Screening. Fungal infection of nail beds is allowed.
17. Human immunodeficiency virus (HIV) / acquired immune deficiency syndrome (AIDS) or positive test for HIV antibodies at Screening
18. Acute or chronic hepatitis B infection or test positive for hepatitis B virus (HBV) at Screening (positive for hepatitis B surface antigen [HBsAg], or negative for HBsAg and positive for anti-hepatitis B core antibody in conjunction with detectable HBV deoxyribonucleic acid [DNA])
19. Current hepatitis C infection or test positive for hepatitis C virus (HCV) at Screening, as defined by positive hepatitis C antibody and detectable HCV ribonucleic acid
20. History of an opportunistic infection (eg, *Pneumocystis jirovecii*, cryptococcal meningitis), progressive multifocal leukoencephalopathy (PML), or history of disseminated herpes zoster or disseminated herpes simplex
21. History of currently active primary or secondary immunodeficiency

Previous or Concomitant Treatment

22. Hypersensitivity to VTX002 or any of the excipients or placebo compounds
23. Treatment with an investigational therapy ≤ 3 months prior to randomization
24. Treatment with cyclosporine, tacrolimus, sirolimus, methotrexate, or mycophenolate mofetil ≤ 8 weeks prior to Screening
25. Prior treatment with S1P receptor modulators including but not limited to fingolimod, siponimod, ozanimod, ponesimod, and etrasimod
26. Treatment with a biologic agent (ie, anti-TNFs, anti-integrins, and anti-IL-12/23) meeting the following criteria:
    a. Treatment with infliximab, adalimumab, golimumab, or vedolizumab ≤ 60 days prior to randomization

b. Treatment with ustekinumab ≤ 90 days prior to randomization

c. Treatment with any other approved biologic agent ≤ 5 half-lives prior to randomization

Note: A trough drug level can be obtained during Screening to confirm absence of biologic drug levels in lieu of the washout periods

27. Treatment with JAK inhibitors ≤ 4 weeks prior to randomization
28. Use of IV corticosteroids and/or topical steroids ≤ 2 weeks prior to Screening endoscopy. Alternative forms of steroids require consultation with the Medical Monitor.
29. Use of immunosuppressant drugs including thiopurines ≤ 2 weeks prior to Screening endoscopy
30. Prior treatment failure with ≥ 3 biologic agents with different mechanisms of action or ≥ 2 biologics with different mechanisms of action plus a JAK inhibitor approved for the treatment of UC
31. Treatment with topical rectal 5-ASA or short-chain fatty acid enemas ≤ 2 weeks prior to Screening endoscopy
32. Receipt of a live vaccine ≤ 4 weeks prior to randomization and until 2 weeks post last dose. Approved nonlive vaccines, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), can be administered according to local vaccination standards.
33. Previous treatment with natalizumab
34. Previous treatment with lymphocyte-depleting therapies (eg, anti-CD4, cladribine, rituximab, ocrelizumab, cyclophosphamide, mitoxantrone, total body irradiation, bone marrow transplantation, alemtuzumab, daclizumab)
35. Previous treatment with D-penicillamine, thalidomide, dimethyl fumarate, or pyrimidine synthesis inhibitors
36. Treatment with IV immune globulin or plasmapheresis ≤ 3 months prior to randomization

5.3 Lifestyle Considerations

There are no restrictions regarding lifestyle.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study treatment/entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

Individuals who do not meet the criteria for participation in this study (screen failures) may be rescreened. If a participant is being considered to be rescreened more than once, please contact the

Medical Monitor. Rescreened participants should not be assigned the same participant number as for the initial screening.

If a participant is considered for rescreening, the need for repeat testing should be discussed with the Medical Monitor. Upon approval by the Medical Monitor, if a participant is rescreened within 6 months a repeat chest X-ray is not required. If a participant is rescreened within 3 months, OCT does not need to be repeated if the participant does not have any visual symptoms, and PFTs do not need to be repeated if the participant does not have any respiratory symptoms.

6.0 STUDY TREATMENT

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a participant according to the study protocol.

6.1 Study Treatment Description

The physical descriptions of study drug treatments are provided in Table 7.

VTX002 tablets will be manufactured, quality control tested, and released in accordance with Good Manufacturing Practice.

Table 7 Study Treatment Description

Study Drug	**VTX002**	**Placebo**
Dosage Formulation	3 mg, 7 mg, 10 mg, and 20 mg Tablets	Matching placebo for 3 mg, 7 mg, 10 mg, and 20 mg Tablets
Dosage Level(s)	30 mg, 60 mg	Not applicable
Route of Administration	Oral	Oral
Dosing Instructions	Study drug should be taken by participants with approximately 240 mL (one cup) of water. The study drug can be taken with or without food. All doses on clinical days should be administered in the clinic.	Study drug should be taken by participants with approximately 240 mL (one cup) of water. The study drug can be taken with or without food. All doses on clinical days should be administered in the clinic.
Packaging and Labeling	Study treatment will be provided as orange tablets in weekly blister cards for Induction and LTE Periods (Weeks 0-52) of blinded treatment. Blister packs for dose titration for Weeks 0 and OLE Week 0 will have each day of the regimen labeled. Blister packs for assigned dose for Induction and LTE Periods (Weeks 1-52) will contain 7 rows of 4 tablets. Open-label bottles of 30 × 20 mg tablets or 100 × 20 mg tablets will be provided after conclusion of OLE Week 0 dose titration. Each blister/bottle will be labeled as required per country requirement.	Study treatment will be provided as orange tablets in weekly blister cards for Induction and LTE Periods (Weeks 0-52) of blinded treatment. Blister packs for assigned dose for Induction and LTE Periods (Weeks 1-52) will contain 7 rows of 4 tablets. Each blister will be labeled as required per country requirement.
Storage	15°C to 25°C 59°F to 77°F	15°C to 25°C 59°F to 77°F

6.2 Induction Treatment

6.2.1 Induction Treatment Week 0

Participants randomized to study drug will undergo a 7-day dose titration to receive their respective double-blinded drug doses (Days 1 to 7) in accordance to Table 8 below. Although dose titration is not applicable for placebo and VTX002 30 mg after Day 6, the same number of tablets will be given to all participants to simulate dose titration and maintain blinding.

Table 8 Dose Titration in the Induction Treatment Period

Study treatment	Day 1 (Visit 2)	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8 and Onwards (Visit 3)
VTX002 30 mg	3 mg	7 mg	10 mg	14 mg	20 mg	30 mg	30 mg	30 mg
VTX002 60 mg	3 mg	7 mg	10 mg	14 mg	20 mg	30 mg	50 mg	60 mg
Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo

Blister cards for Week 0 will contain 9 rows and up to 4 columns. Participants will take one tablet from each blister in the row for that day.

6.2.2 Induction and Long-Term Extension Treatment Weeks 1 to 52

Dosing configuration for Weeks 1-52 will contain 4 rows with 7 columns. Participants will take all tablets from each blister in the column for that day.

In the case where a participant attends a virtual visit (see Section 8.2) and requires additional study treatment to continue on the study, study treatment may be dispensed and delivered by an approved courier where permitted by local law and regulation. Alternatively, a future supply of study treatment may be dispensed to the participant at an onsite visit or an unscheduled dispensation visit to cover study treatment to be dispensed at the next planned virtual visit. Advanced planning and communication will be needed to dispense future supply of study treatment at an earlier onsite visit. Shipping guidelines and instruction will be provided separately.

6.3 Open-Label Extension Treatment

6.3.1 Open-Label Extension Dose Titration

Participants entering the OLE Treatment Period will undergo a 7-day dose titration (OLE Days 1 to 8) to receive VTX002 60 mg following the same titration schedule for the VTX002 60 mg as shown in Table 8. Although dose titration would not be needed for participants who received VTX002 60 mg during the Induction Period/LTE Period, all participants entering the OLE Treatment Period will go through a full dose titration regimen to maintain the blind of the Induction Period/LTE treatment assignments.

6.3.2 Open-Label Extension Study Drug Supplies

Following titration to 60 mg, participants will be dispensed a sufficient number of bottles containing 30 or 100 tablets of VTX002 20 mg to provide drug until the next study visit. Participants will be instructed to take 3 tablets (60 mg) at the same time each day.

6.4 Additional Dosing Instructions

Study treatment should be taken at approximately the same time each day, preferably in the morning. Tablets should be taken with approximately 240 mL of water and can be taken with or without food. On study visit days, participants should wait and take their dose at the study site after all predose assessments and procedures have been completed, including blood draws for predose PK. The time of PK sample collection and last dosing prior to the PK sample should be documented. At Week 13 (Visit 8), study treatment administration should be performed in the clinic as part of the initial LTE visit.

6.4.1 Missed Dose Instructions

Participants should be instructed that if they forget to take a dose, they can take the dose within 8 hours of the normal dosing time; otherwise, they should take their next dose at the regular time on the following day. Participants who vomit a tablet should be instructed not to take another dose on the same day, but to take the next dose at the regular time on the following day. Participants will record their daily dose in a provided electronic diary (eDiary). Missed doses that occur at any time during a week prior to PK sampling should be recorded in the electronic Case Report Form (eCRF). Participants should be instructed to contact the Investigator if they miss more than 2 consecutive doses.

6.4.2 Dose Interruption

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

If the Investigator deems it necessary to withhold study treatment, temporary withholding is permitted for up to 4 days without obtaining prior approval from the Medical Monitor. If study treatment interruption for ≥ 5 days is required due to a medical reason, the Investigator must contact the Medical Monitor.

The first-dose cardiac monitoring, as outlined in Section 6.5.1, and dose titration as outlined in Section 6.2.1, should be performed when study treatment dosing is interrupted as follows:

- Missed treatment ≥ 2 consecutive days within the first week of treatment or
- Missed treatment ≥ 5 consecutive days after the first week of treatment

6.5 Guidance for Cardiac Monitoring Following Treatment Initiation or Reinitiation

Prerandomization (ie, predose on Day 1) ECG should be performed and assessed prior to randomization.

Following treatment initiation or reinitiation, participants will remain in the clinic for at least 6 hours after study drug administration for safety assessments.

Prerandomization (ie, predose on Day 1) vital signs (ie, pulse, systolic and diastolic BP, temperature, and respiratory rate) will be used as baseline measurements. Pulse and BP will be measured using calibrated equipment (as appropriate) after the participant has been sitting for at least 5 minutes.

Atropine and epinephrine should be readily available at all study sites. Availability of emergency equipment should be within close proximity to study site. Personnel experienced in the use of advanced life support must be readily accessible during the first-dose monitoring (Week 0 [Day 1/Visit 2] and OLE Week 0 [OLE Day 1/OLE Visit 1]) and reinitiation of treatment, as well as in case of an emergency. A member of the Investigator team should be available to monitor the participant for the 6-hour monitoring period and report any abnormalities to the Investigator.

6.5.1 First-Dose Cardiac Monitoring

Participants will undergo in-clinic monitoring for at least 6 hours on Day 1 and OLE Day 1, with measurements taken prior to dose and at 1, 2, 4, and 6 hours (± 10 minutes) following study drug administration. Cardiac assessments should be performed as shown in Table 9.

Participants experiencing a cardiovascular treatment-related symptomatic event (eg, chest pain, dizziness, palpitations, lightheadedness, shortness of breath, or syncope) associated with a clinically significant reduction of HR or associated with clinically relevant ECG changes at any time during the 6-hour monitoring period should be discontinued from treatment.

Participants will be released from the clinical site after dosing on Day 1 (Week 0/Visit 2) and OLE Day 1 (OLE Week 1/OLE Visit 1) when they fulfill the discharge criteria outlined in Section 6.5.1.1, but no sooner than 6 hours postdose.

Table 9 Cardiac Assessments to Be Performed

Procedure	Clinic		Ambulatory
	Predose	1, 2, 4, and 6 hours postdose[b]	From 6 to 24 hours postdose
Vital signs[a]	X	X	
12-lead ECG	X	X	
Holter ECG monitoring[c]	X	X	X
Adverse events	X	X	
Assess discharge criteria		X[d]	

Abbreviations: BP = blood pressure; ECG = electrocardiogram

Note: The order of assessments should be rest for 5 minutes (sitting), vital signs (sitting), 12-lead ECG (supine), and then blood draws as applicable.

a. Participants must be at rest for at least 5 minutes in sitting position. After the participant has been sitting for at least 5 minutes, pulse and BP will be measured.
b. Measurements may be taken within ± 10 minutes of the scheduled time.
c. Holter ECG monitoring will begin 1 hour predose and continue through 24 hours postdose. Participants who meet the discharge criteria (Section 6.5.1.1) at 6 hours postdose will be sent home for continued Holter ECG monitoring from 6 to 24 hours postdose.
d. Discharge criteria assessed only at 6 hours postdose.

6.5.1.1 Discharge Criteria After Cardiac Monitoring

After 6 hours of cardiac monitoring postdose, participants who meet the following discharge criteria will be released:

- No presence of bradycardia, defined as HR < 50 bpm or no more than 10 bpm lower than the predose (baseline) value

  Note**:** If the HR at 6 hours postdose is at the lowest value postdose, participants should undergo extended cardiac monitoring.

- No evidence of second-degree AV block or higher
- No cardiac symptoms (eg, chest pain, dizziness, palpitations, lightheadedness, shortness of breath, or syncope)

First-dose cardiac monitoring should be repeated on Day 8/OLE Day 8 if cardiac safety issues were observed on Day 1/OLE Day 1.

Note: Participants should have written instructions on when to return to the clinic and a 24-hour contact phone number to call in the event of any new (eg, chest pain, dizziness, palpitations, syncope, nausea, vomiting) or worsened cardiovascular symptoms.

6.5.1.2 Extended Cardiac Monitoring

Participants who do not meet the discharge criteria at 6 hours postdose will require extended cardiac monitoring, as described below:

- Vital signs will be assessed hourly and 12-lead ECG may be performed, as clinically indicated, until the participant meets the discharge criteria (Section 6.5.1.1).
- Should a participant require pharmacologic intervention for symptomatic bradycardia, continuous overnight ECG monitoring in a medical facility should be instituted, and the first dose monitoring strategy should be repeated after the second dose of VTX002.
- Should postdose bradycardia (eg, HR < 50 bpm) or potentially related symptoms (eg, dizziness) occur, then initiate appropriate medical management, assess vital signs, begin continuous ECG monitoring, and continue observation until the symptoms have resolved.
- The Medical Monitor should be contacted if the participant does not meet the discharge criteria after ≥ 6 hours of extended cardiac monitoring.
- Any participant who requires extended monitoring on Day 1 (Week 0/Visit 2) or OLE Day 1 (OLE Week 0/OLE Visit 1) must return on the following day for the second dose and will be remonitored as on Day 1 (Week 0/Visit 2) or OLE Day 1 (OLE Week 0/OLE Visit 1), respectively. These participants will be discontinued from study treatment if they do not meet the discharge criteria at 6 hours after the second dose. Extended cardiac monitoring should be continued until the participant meets the discharge criteria (Section 6.5.1.1).
- Participants experiencing a symptomatic event (eg, chest pain, dizziness, palpitations, lightheadedness, shortness of breath, or syncope) during the 6-hour monitoring period that is not associated with either a reduction in HR or clinically relevant change in 12-lead ECG, and who continue to experience symptoms during the extended cardiac monitoring period, may be discharged provided the symptoms are not associated with a reduction in HR or clinically relevant changes in ECG during the extended cardiac monitoring period, and the Investigator deems it appropriate; however, these participants must return on Day 2/OLE Day 2 for the second dose and will be remonitored as on Day 1 (Week 0/Visit 2) or OLE Day 1 (OLE Week 0/OLE Visit 1). These participants should be discontinued from treatment if they do not meet the discharge criteria at 6 hours after the second dose on Day 2/OLE Day 2 or if they experienced the symptoms (eg, chest pain, dizziness, palpitations, lightheadedness, shortness of breath, or syncope) on Day 2/OLE Day 2, and extended cardiac monitoring should be continued until the participant meets the discharge criteria (Section 6.5.1.1).

6.5.2 Study Treatment Discontinuation Related to Postdose Cardiac Monitoring

A complete list of reasons for study treatment discontinuation is provided in Section 7.1. All treatment discontinuations should be discussed with the Medical Monitor.

Reasons for study treatment discontinuation specific to postdose cardiac monitoring include the following:

- Participants who have a cardiovascular treatment-related symptomatic event (eg, chest pain, dizziness, palpitations, lightheadedness, shortness of breath, or syncope) associated with a clinically significant reduction of HR or associated with clinically relevant 12-lead ECG changes at any time during the 6-hour monitoring period on Day 1/OLE Day 1 or Day 2/OLE Day 2 (as applicable).
- Participants who have not met the discharge criteria on Day 1 (Week 0/Visit 2) or OLE Day 1 (OLE Week 0/OLE Visit 1) after ≥ 6 hours of extended monitoring and on Day 2/OLE Day 2 by 6 hours postdose (see Section 6.5.1.2).

6.5.3 Cardiac Monitoring Upon Treatment Reinitiation Following Dose Interruption

Participants should undergo the same first-dose cardiac monitoring, as outlined in Section 6.5.1, and dose titration, as outlined in Section 6.2.1, procedures as the original treatment initiation when study treatment dosing is interrupted as follows:

- Missed treatment ≥ 2 consecutive days within the first week of treatment or
- Missed treatment ≥ 5 consecutive days after the first week of treatment

6.6 Guidance for Hepatic Monitoring

An increase in AST or ALT > 3 × ULN should be followed by repeat testing within 72 hours of receiving results to confirm the abnormality and determine whether AST or ALT is increasing or decreasing.

Discontinuation of study treatment for abnormal liver function should be considered by the Investigator when a participant meets one of the conditions outlined below or if the Investigator believes that it is in best interest of the participant. See also Section 7.1 for more information.

- ALT or AST > 8 × ULN
- ALT or AST > 5 × ULN for > 2 weeks
- ALT or AST > 3 × ULN and total bilirubin > 2 × ULN or international normalized ratio (INR) > 1.5
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)

All events of ALT or AST > 3 × ULN and total bilirubin > 2 × ULN (> 35% direct bilirubin), or ALT or AST > 3 × ULN and INR > 1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE. See Section 8.5 for follow-up and reporting of SAEs.

Because transient fluctuations of ALT or AST are common, and progression to severe drug-induced liver injury or acute liver failure is uncommon, automatic discontinuation of study treatment upon finding a greater than 3 × ULN elevation of ALT or AST may be unnecessary.

6.7 Preparation/Handling/Storage/Accountability

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

Only participants enrolled in the study may receive study treatment. The study treatment should be dispensed by the Investigator or by a qualified individual under the Investigator's supervision, according to the procedures described in this study protocol. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized study center staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). The Study Monitor will ensure that all unused study treatment and all medication containers are returned or destroyed on site. Study treatment can be destroyed on site as long as proper documentation is available and permitted by local law.

Further guidance and information for the final disposition of unused study treatment and all the medication containers can be found in the Study Manual.

The Investigator, a designated member of the study center staff, or a hospital pharmacist must maintain an adequate record of the receipt and distribution of all study treatment using the Drug Accountability Form. These forms must be available for inspection at any time.

6.8 Measures to Minimize Bias: Randomization and Blinding

The study will employ a double-blind design for the Induction Treatment Period. Participants, Investigators, study center staff, persons performing the assessments, and the Sponsor are to remain blinded to the identity of the Induction Period treatment from the time of randomization until the interim database lock for the study.

All participants will be centrally assigned to randomized study treatment using an Interactive Web Response System (IWRS). Before the study is initiated, the log in information and directions for the IWRS will be provided to each study center. Participants will be randomized to a study treatment via stratified block randomization. The following will be used for stratification: (*a*) biologic/JAK inhibitor prior use status (Yes or No), (*b*) baseline corticosteroid use (Yes or No), and (*c*) baseline disease activity (MMS 5-6 or 7-9).

The study treatment and placebo tablets will be identical in physical appearance. There will be limited access to the randomization codes for the Induction Treatment Period. The treatment each participant will receive will not be disclosed to the Investigator, study center staff, participant, Sponsor, or study vendors (eg, central readers). The treatment codes will be held by the Clinical Supplies Department of the contract research organization (CRO). The IWRS will be programmed with blind-breaking instructions.

Investigators, study center staff, participants, and study vendors not engaged in data analysis associated with the interim database lock for the Induction Treatment Period will remain blinded to the identity of the LTE Period treatment. The Sponsor will be unblinded to study treatment for the LTE Period after the interim database lock and unblinding for the Induction Treatment Period.

Lymphocyte, neutrophils, [redacted] CRP, and FCP are considered markers for the mechanism of action for VTX002 or efficacy. For Investigators, study center staff, participants, and study vendors, total WBC, differentials, lymphocyte, neutrophils, [redacted] CRP, and FCP results will be blinded during the double-blind Induction Treatment Period, LTE Treatment Period, and the first 4 weeks of the OLE Treatment Period (see Section 8.3.4). These results will also be blinded to the Sponsor in the same manner until the interim database lock and unblinding for the Induction Treatment Period is completed. Then, the Sponsor will be unblinded to total WBC, differentials, lymphocyte, neutrophil, [redacted] CRP and FCP.

6.8.1 Emergency Unblinding Procedure

The participant's treatment group assignment blind will not be broken until the end of the study unless medical treatment of that participant depends upon knowing whether the participant is receiving active study treatment. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Medical Monitor or their designee prior to unblinding a participant's treatment assignment unless this can delay emergency treatment of the participant. If a participant's treatment assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and eCRF, as applicable.

6.9 Study Treatment Compliance

The prescribed dosage, timing, and mode of administration may not be changed, except as defined in Section 6.4.2. Any departures from the assigned regimen must be recorded in the eCRFs.

Study treatment compliance will be measured by tablet count. At each visit, prior to dispensing the study treatment, the Investigator will retrieve the previously dispensed study treatment and assess compliance.

Overall, study noncompliance is defined as taking less than 80% or more than 120% of study treatment during the Induction Treatment Period and LTE Treatment Period. Participants will record tablet intake in the eDiary, which will be reviewed periodically by site staff and the Study Team. At each visit, the Investigator will collect the previously dispensed study treatment tablets and assess compliance. If there is a discrepancy between the compliance recorded in the eDiary and the tablet count, it should be discussed with the participant and noted in the source documents.

Participants exhibiting poor compliance should be counseled on the importance of good compliance to the study dosing regimen. Participants who are persistently noncompliant (< 80% or > 120%) should be discussed with the Medical Monitor to determine whether they should be withdrawn from the study.

Details of VTX002 study treatment administration will be documented in the eDiary. The participant will be provided with an eDiary to allow, at minimum, documentation of the date and time of the dose, date(s) of missed doses or partial dose administered while not in the clinic. This information will be transcribed into the participants' eCRF, as appropriate. Participants will be instructed to not take study drug prior to their clinic visits (except for the visits when study drug is not to be administered at the clinic), as predose samples will need to be collected prior to dose administration. While in the clinic, the date/time of doses administered in the clinic will be documented in the eCRF and eDiary. The time and date of study drug administration and the participant's most recent ingestion of food will also be recorded.

6.10 Prior and Concomitant Therapy

All concomitant medications, including over-the-counter or prescription medicines, blood products, vaccines, vitamins, holistic products, and radiotherapy, will be collected from Screening through the 2-Week Follow-Up visit and recorded in the eCRF. Any medication given for a study-related AE should be recorded from the time of informed consent.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy. Medication history should be collected for at least 4 weeks prior to Screening.

6.10.1 Allowed Medications for the Treatment of Ulcerative Colitis

Oral 5-ASA, oral corticosteroids, or medicinal probiotics are allowed at the time of Screening; however, these products should not be started during Screening or during the treatment period in participants who are not already receiving them.

Immunosuppressive agents such as oral AZA or 6-MP must be discontinued > 2 weeks prior to Screening endoscopy.

Participants receiving 5-ASA or medicinal probiotics should maintain a stable dose throughout the Screening Period and study and can only be discontinued or reduced in dose if Investigator judgment requires it because of toxicity or medical necessity.

6.10.1.1 Corticosteroid Therapy

Oral corticosteroid therapy (prednisone at a stable dose of ≤ 20 mg/day, budesonide at a stable dose of ≤ 9 mg/day, or equivalent steroid) is allowed to be continued during the 13-week Induction Treatment Period provided the dose has been stable for the 2 weeks immediately prior to the Screening endoscopy assessment.

Participants entering the LTE Treatment Period will be tapered from corticosteroids. Participants entering the OLE Treatment Period may be tapered after 13 weeks of treatment in the OLE. The recommended tapering schedule for oral corticosteroids (other than budesonide extended release tablets [budesonide MMX]) is as follows:

- Dose > 10 mg/day prednisone or equivalent: taper daily dose by 5 mg/week until receiving 10 mg/day, and then continue tapering by 2.5 mg/week until 0 mg/day
- Dose ≤ 10 mg/day prednisone or equivalent: taper daily dose by 2.5 mg/week until 0 mg/day

The recommended tapering schedule for participants receiving oral budesonide MMX 9 mg/day is to reduce tablets to 9 mg two days out of three for 2 weeks, followed by 9 mg one day out of three for 2 weeks, and then discontinue.

For participants who cannot tolerate the corticosteroid taper without recurrence of clinical symptoms of either UC or steroid withdrawal, the corticosteroid dose may be increased (up to the dose at study entry if required), but tapering should be attempted again within 2 weeks.

6.10.2 Prohibited Medications

In vitro studies suggested that VTX002 may be an inhibitor of P-gp and breast cancer resistance BCRP transporters (Section 2.3). Any necessary concomitant use of any of the following must be discussed with Medical Monitor.

- P-gp transporter substrates or inhibitors: amiodarone, carvedilol, clarithromycin, cyclosporine, dabigatran etexilate, digoxin, dronedarone, fexofenadine, itraconazole, ketoconazole, lapatinib, loperamide, lopinavir, propafenone, quinidine, ranolazine, reserpine, ritonavir, saquinavir, tacrolimus, talinolol, telaprevir, tipranavir, verapamil, vinblastine
- BCRP transporter substrates or inhibitors: coumestrol, curcumin, cyclosporine A, daidzein, dantrolene, eltrombopag, estrone-3-sulfate, genistein, novobiocin, prazosin, rosuvastatin, sulfasalazine

The following concomitant medications/therapy are prohibited for the entire duration of the study:

- Treatments for UC other than those listed in the eligibility criteria (see Section 5.1 and 5.2)
- Chronic nonsteroidal anti-inflammatory drug (NSAID) use (Note: Occasional use of NSAIDs and aspirin up to 325 mg/day is permitted)
- Marketed biologic therapies

- Immunosuppressive agents (eg, AZA, 6-MP, tofacitinib)
- Any per rectum therapy including enemas (eg, 5-ASA, corticosteroid), other than that required for endoscopy preparation
- Treatment with cyclosporine, tacrolimus, sirolimus, methotrexate, or mycophenolate mofetil
- Cholestyramine or other drug interfering with enterohepatic circulation unless the dose has been stable for > 6 months prior to Screening
- S1P receptor modulators including but not limited to fingolimod, siponimod, ozanimod, ponesimod, and etrasimod
- Receipt of a live vaccine from 4 weeks prior to randomization and/or until 2 weeks post last dose. Nonlive vaccines, including SARS-CoV-2, can be administered according to local vaccination standards.
- Treatment with lymphocyte-trafficking inhibitors
- Treatment with lymphocyte-depleting therapies (eg, alemtuzumab, anti-CD4, cladribine, rituximab, ocrelizumab, cyclophosphamide, mitoxantrone, total body irradiation, bone marrow transplantation, daclizumab)
- Treatment with D-penicillamine, or thalidomide, dimethyl fumarate, or pyrimidine synthesis inhibitors
- Start, stop or change in dosage of any Class I-IV anti-arrhythmic drugs ≤ 1 week prior to dose titration starting at randomization and up to 1 week after titration to the assigned dose. This criterion also applies to the OLE Treatment Period titration: 1 week prior to and up to 1 week after the dose titration period.

The following concomitant procedures are prohibited during the study:

- Major elective surgery
- Immunoadsorption columns
- Intravenous immunoglobulin or plasmapheresis
- Blood donations during the study and for 14 days after the last dose of study treatment
- Sperm or oocyte donations during the study and for 30 days after the last dose of study treatment.

6.11 Treatment After the End of the Study

The Sponsor will not provide any additional care to participants after they leave the study because such care should not differ from what is normally expected for patients with the medical condition.

7.0 DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Treatment

A participant's study treatment may be discontinued for any of the following reasons:

- Worsening of disease, defined as:
  - Induction Treatment Period:
    - Based on Investigator's decision, administration of prohibited medication for treatment of UC during the Induction Period
  - LTE Treatment Period:
    - Based on Investigator's decision, administration of prohibited medication for treatment of UC during the LTE Treatment Period
  - OLE Treatment Period:
    - Participant fails to achieve symptomatic response by OLE Week 13 (among participants who had no clinical response at the end of the Induction Period)
    - Participant experiences loss of response
- AE, see Appendix 4:
  - A participant may be discontinued from the study drug if, in the judgment of the Investigator, the participant develops an AE such as an intercurrent illness or complication that is not consistent with the protocol requirements or that, in any way, justifies withdrawal from the study.
- Discontinuation of study treatment for abnormal liver function should be considered by the Investigator when a participant meets one of the conditions outlined below or if the Investigator believes that it is in best interest of the participant.
  - ALT or AST > 8 × ULN
  - ALT or AST > 5 × ULN for > 2 weeks
  - ALT or AST > 3 × ULN and total bilirubin > 2 × ULN or INR > 1.5
  - ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).
- Other, non-AE

A participant's study treatment must be discontinued temporarily (treatment interruption) for any of the following reasons:

- New onset QTcF interval prolongation
  - If an ECG shows a new onset QTcF interval > 450 msec in men and > 470 msec in women during the treatment period, a repeated ECG is required. If this abnormal finding is

confirmed, study treatment must be temporarily discontinued. Reinitiation of study treatment can be considered per criteria described in Section 8.4.3.

- Lymphopenia (ie, severe decrease in ALC)
  - If the ALC is confirmed to be below the 200 cells/µL limit, study treatment should be interrupted and should not be reinitiated if the ALC remains below this threshold. In this situation, the unblinded Medical Monitor will notify the Investigator and provide instructions on additional actions that the Investigator may need to take. When there is at least one measurement of ALC < 200 cells/µL, blinded values may be released to treating physicians and Investigators as deemed medically necessary to monitor infection and/or aid in diagnostic work-up as clinically indicated, and/or as a tool to assess the effectiveness of therapeutic interventions for an infection. Investigators will repeat CBC with differentials weekly until ALC > 500 cells/µL.
  - Reinitiation of study treatment can be considered only when ALC > 500 cells/µL.

A participant's study treatment must be discontinued permanently for any of the following reasons:

- Study participant is pregnant (see Section 8.5.5)
- Decline in PFT values (FEV1 and/or FVC) below 50% of the predicted values
- Confirmed diagnosis of clinically significant macular edema, see Section 8.4.6
- Confirmed diagnosis of PML: Cases of PML have occurred in patients who have received S1P1 modulators. At the first sign or symptom suggestive of PML, withhold VTX002 and perform an appropriate diagnostic evaluation. The magnetic resonance imaging findings may be apparent before clinical signs or symptoms. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes. The Investigator must notify the Medical Monitor of such symptoms.
- Cardiovascular events:
  - A participant experiencing a cardiovascular treatment-related symptomatic event (eg, chest pain, dizziness, palpitations, lightheadedness, shortness of breath, or syncope) associated with a clinically significant reduction of the HR or associated with clinically relevant 12-lead ECG changes at any time during the 6-hour monitoring period on Day 1 or Day 2 (as applicable) (Section 8.4.3). See also Section 6.5 for cardiac monitoring during treatment initiation or reinitiation.
  - Participants who have not met the discharge criteria on Week 0 (Day 1/Visit 2) or OLE Week 0 (OLE Day 1/OLE Visit 1) after ≥ 6 hours of extended monitoring and on Day 2/OLE Day 2 by 6 hours postdose (see Section 6.5.1.2).
- Noncompliance with study treatment (see Section 6.9)
- Investigator decision

- Withdrawal by participant
- Study termination by Sponsor or regulatory bodies/agency

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

See Section 6.4.2 for dose interruption of study treatment.

7.2 Follow-Up Period

For all participants, a Follow-Up visit will be performed at 1 and 2 weeks after the last dose of study treatment as indicated in the SoA.

All participants who discontinue the study prematurely will be asked to return to the clinic for the ET visit. If the ET visit is ≥ 1 week after the last dose of study treatment, the 1-Week Follow-Up visit is not required; however, the 2-Week Follow-Up visit should be scheduled and completed. If the ET visit is ≥ 2 weeks after the last dose of study treatment, the 2-Week Follow-Up visit is not required.

If the ALC is not within normal limits at the 2-Week Follow-Up visit, participants should return for CBC testing with differential according to local standard of care (captured as a subsequent Follow-Up visit or unscheduled visit).

All AEs should be recorded for 30 days after the last administration of study treatment (see Section 8.5.1).

7.3 Lost to Follow-Up

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

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

- The study center must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

7.4 Participant Discontinuation/Withdrawal

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

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

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

Participants who withdraw from the study will not be replaced. See the SoA (Section 1.2) for data to be collected at the time of withdrawal (ie, ET visit) and follow-up, and for any further evaluations that need to be completed.

Discontinuation of specific study centers or of the study as a whole are handled as described in Appendix 2.

8.0 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Section 1.2).

Protocol waivers or exemptions are not allowed.

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

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

8.1 Screening and Eligibility

Screening procedures must be completed within 28 days prior to receiving the first dose of study treatment. The Screening Period may be extended for participants who require additional diagnostic testing/consults to determine status of either latent TB or *C. difficile* infection. If the participant is planned to be randomized > 28 days from the signing of the ICF, the Medical Monitor should be consulted to see if repeated testing is needed. The 28-day Screening Period may also be extended on a case-by-case basis to accommodate reasonable delays in specific screening assessments (eg, PFTs, OCT) due to testing availability. The Medical Monitor must be consulted prior to extension in each case.

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

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for Screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

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

A social history including the amount and duration of tobacco, alcohol, and caffeine usage will be collected.

A standard urine drug screen will be performed. Participants who test positive will be assessed for eligibility for study participation by the Investigator after discussion with the Medical Monitor.

Consumption of poppy seeds within 48 hours prior to drug screening may cause a positive drug screen. Participants should be instructed not to consume food items that contain poppy seeds for 48 hours prior to the Screening visit. Participants who report that they have consumed poppy seeds

within 48 hours of the Screening visit should not be screened. They may return 48 hours after the last poppy seed consumption for screening.

8.2 Virtual/Hybrid Visits

Study visits after Day 1 may be conducted via onsite (in person at the study site or specialty lab), offsite (home health visit by study staff or designee), virtual (eg, telephone, video conference), or hybrid (a combination of aforementioned visit types), depending on the nature of the study assessment, technological capability, and acceptability with institutional practices and in alignment with local law and regulatory requirements. These may take place on different days within the study visit window.

Certain assessments and/or procedures will not be performed in the home setting (eg, endoscopies, OCT, PFT, cardiac monitoring following treatment initiation or reinitiation, and 12-lead ECG).

Pregnancy testing and central laboratory assessments (eg, blood, stool, and urine samples) can be performed by either onsite visit or offsite visit.

Assessments or procedures that may be conducted virtually, if allowed by local law and regulation, include, for example: informed consent process including obtaining written informed consent, medical and medication history to assess eligibility criteria, review of demographic information, social history, AE query, review of concomitant medications, eDiary training, and compliance review/monitoring including study drug administration and questionnaires.

During a virtual assessment, a participant may report an AE that requires a follow-up symptom-focused physical exam or diagnostic test, as determined by the Investigator. In this scenario, the Investigator may have the participant return to the study site for an unscheduled study visit to perform the assessment.

For study drug accountability, the study treatment blister cards/bottles and remaining tablets may be visually inspected and counted on video conferencing. Participants must return the dispensed blister cards/bottles with the remaining tablets along with any empty blister cards/bottles to the study site at the next onsite visit. See Section 6.7 for study treatment management.

Some study visits may be virtual/hybrid, if so designated in the SoA (see Section 1.2). Regardless of how a study visit and its associated procedures are conducted, all study procedures should be performed by qualified study site staff or qualified individuals as delegated by the Investigator.

The safety of study participants and site staff is paramount, so it is at the Investigator's discretion whether PFT can be safely administered to study participants during the treatment period. The Investigator should evaluate on a case-by-case basis how best to proceed based on the participant's medical history, the Investigator's clinical judgment, and in consultation with the Medical Monitor. All reasonable efforts should be made to ensure safety and adherence to the protocol. When available, spirometry may be conducted at the clinical site instead of at the pulmonary

laboratory. If the decision is made that it is not appropriate to conduct PFTs due to safety concerns (eg, SARS-CoV-2 transmission), then this decision and rationale should be appropriately captured in the participant's source documentation. When available and safe (due to lifting of local restrictions, reopening of local PFT labs, or improved safety conditions), the tests should be conducted as soon as possible and as close to the timepoints as outlined in the protocol.

8.3 Efficacy Assessments

8.3.1 Mayo Clinic Scores

This study uses components of the MCS, which includes ES, RB, SF, and PGA, as well as MMS, which includes ES, RB, and SF (Appendix 6), to assess UC disease activity in support of the primary, secondary, and exploratory endpoints.

The total score range of the MCS is from 0 to 12, with each component ranging from 0 to 3. The total score range of the MMS is from 0 to 9, with each component ranging from 0 to 3. The PMS will also be assessed, which includes RB, SF, and PGA, for a total score range from 0 to 9.

Each component is described in more detail in the following paragraphs. The efficacy endpoint definitions using MMS and MCS components are outlined in Section 3.3.

Endoscopic subscore: Endoscopy will be used to visualize the mucosa to enable calculation of the ES. The ES reports the worst appearance of the mucosa on flexible sigmoidoscopy or colonoscopy, on a 4-point scale (Appendix 6). Consistent with regulatory advice, this study excludes friability from the definition of an ES of 1. The ES will be determined by a blinded central reader.

Rectal bleeding: The RB subscore is a patient-reported measure. This item reports the most severe amount of blood passed per rectum for a given day, on a 4-point scale (Appendix 6). The participant will record this in their eDiary daily.

Stool frequency: The SF subscore is a patient-reported measure. This item reports the number of patient-reported stools in a 24-hour period, relative to the normal number of stools for that participant in the same period (eg, remission), on a 4-point scale (Appendix 6). A stool is defined as a trip to the toilet when the participant has either a bowel movement, passage of blood alone, passage of blood and mucus, or passage of mucus only. The total number of stools passed in a 24-hour period will be recorded by the participant in their eDiary daily. The reference "normal" SF for that participant will be recorded electronically on the first day of the Screening visit and is the number of stools in a 24-hour period when the participant is in remission. If the participant has never achieved remission, the reported SF before initial onset of signs and symptoms of UC will be used as the reference SF.

Physician's Global Assessment: The PGA is a physician-reported measure that is a component of the MCS and is used in the calculation of the total MCS and PMS. The PGA summarizes the

Investigator's assessment of the participant's UC disease activity on a 4-point scale (Appendix 6). The Investigator will record the PGA in the electronic data capture database (EDC) at the specified study visits (Section 1.2). Consistent with regulatory guidance, the PGA will not be used for primary efficacy assessment in this study.

8.3.1.1 Electronic Diary

Participants will begin eDiary entries beginning on the first day of Screening after diary training is completed. Participant recording will be made each day for the previous 24-hour period. The eDiary should be completed daily to capture data, including daily SF and RB (the 2 patient-reported outcome measures of the MMS) and study drug administration. The participant's eDiary will be reviewed by study site staff to ensure the participant is compliant with diary entries through EDC and during each study visit at the times noted in the SoA (Section 1.2). The RB score should be monitored to ensure the participant meets eligibility criteria of RB $\geq$ 1, prior to performing the Screening endoscopy.

The MCS and MMS require daily patient-reported RB and SF subscores; therefore, the importance of daily recording of the RB and SF subscores by participants in their eDiary should be stressed by the Investigators.

Detailed description regarding eDiary recordings can be found in the Study Manual.

8.3.1.2 Endoscopy

A flexible proctosigmoidoscopy or full colonoscopy, performed with a video endoscope following cleansing preparation (oral or rectal cathartic), will be performed as outlined in the SoA (Section 1.2).

Proctosigmoidoscopy/colonoscopy must be performed prior to randomization to treatment to allow central reader review (may take approximately 5 to 12 days) and confirmation of eligibility. Preferably, proctosigmoidoscopy/colonoscopy should be performed after other criteria for inclusion (eg, laboratory criteria) have been met.

To ensure quality data and standardization, the same endoscopist should be used throughout the study wherever possible. Endoscopy images/video will be obtained during each endoscopy and will be sent for central reading and determination of the Mayo ES. A detailed image review charter from the central reading laboratory will outline the endoscopic procedures, video recordings, and equipment.

For each participant, a video recording of the entire endoscopic procedure will be performed using an acceptable storage medium. Investigators are encouraged to send endoscopic recording by the following day after endoscopy. The endoscopic recordings will be read centrally in a blinded manner for mucosal lesions and endoscopic severity by a qualified gastroenterologist according to the image review charter. The ES will be evaluated by the Investigator and the central reader. The

central read will be used for determination of efficacy endpoints; however, treatment decisions will be made by the treating Investigator.

Repeat flexible proctosigmoidoscopy may be permitted by the Sponsor when the central reader indicates that the video endoscope data were acquired incorrectly or did not meet the minimal required quality standards.

The detailed instructions for endoscopy can be found in the Study Manual.

8.3.1.3 Determination of MMS Score to Qualify for Randomization

The MMS will be evaluated on Day 1. The subscores for RB and SF are derived from the participant eDiary entries using the scores from the 3 most recent consecutive days within the 7 days prior to the day of bowel preparation (excluding the day of bowel preparation), averaged and rounded to the nearest integer. The scoring will be calculated electronically. Participants who do not have 3 consecutive days of eDiary data within that 7-day period and who do not have a minimum of 7 days of eDiary data prior to bowel preparation are not eligible for randomization. The MMS must be 5 to 9, including an ES ≥ 2 and RB ≥ 1, for the participant to be eligible for randomization.

8.3.1.4 Determination of Clinical Response

At Visit 7 (Week 13), clinical response will be calculated electronically to determine if the participant will continue in the LTE or have the option to enroll in the OLE. The subscores for RB and SF are derived from the participant eDiary entries using the scores from the 3 most recent consecutive days of diary entries within the 7 days prior to the day of bowel preparation, averaged and rounded to the nearest integer. In the rare case that 3 consecutive days of data are not available, the most recent 2 days may be used after discussion with the Medical Monitor.

8.3.1.5 Determination of Loss of Response in LTE

During the LTE, participants exhibiting loss of response will have the option to enroll in the OLE. The Investigator will assess loss of response according to the following criteria:

- Increase in UC disease activity as defined by an increase in PMS ≥ 2 points compared to PMS at Week 13 with an absolute PMS ≥ 4, based on 3 most recent consecutive days of diary entries within 7 consecutive days (averaged and rounded to the nearest integer), AND
- Exclusion of other causes of an increase in disease activity unrelated to underlying UC (eg, *C. difficile* infection, change in medication).

8.3.1.6 Determination of Symptomatic Response in OLE

Participants who failed to achieve clinical response at the end of the Induction Period (Week 13) and entered the OLE will be assessed again by the Investigator at OLE Week 13 for symptomatic response according to the following criteria: decrease from baseline $\geq 30\%$ of the combined RB

and SF scores, based on the 3 most recent consecutive days of diary entries within the 7 days prior to the visit, averaged and rounded to the nearest integer.

8.3.2 Endoscopic Biopsies

Per the inclusion criteria (Section 5.1), a histopathology report supporting the diagnosis of UC must be available in the source documents prior to randomization. If a histopathology report is not available, the Screening endoscopy may serve as such with histology evaluated at the local histology laboratory.

Biopsies will be obtained at each endoscopy to support assessment of the histopathology endpoints [redacted] Up to 4 biopsy pairs (ie, total of 8) will be collected from the most affected area 15 to 25 cm from the anal verge. For participants with proctitis only at baseline, biopsies should be taken 8 to 10 cm from the anal verge.

The original location (colonic segment) of biopsy specimens acquired at Screening must be clearly indicated. Detailed instructions for endoscopic biopsies (eg, number of biopsies, anatomic site, normal or inflamed mucosa) can be found in the Laboratory Manual.

Biopsy samples will be processed by a central laboratory, and histopathologic scoring using the Geboes, Robarts, and Nancy histopathology indices will be performed by a blinded central reader (Appendix 7).

Biopsy specimen transfer, processing, slide preparation, and digitization of slides for histopathologic scoring procedures will be detailed in a Histopathology Manual. [redacted] This will be further delineated in the Laboratory Manual. Histopathology results will not be made available to study sites.

8.3.3 Efficacy-Related Biomarkers

All efficacy-related and exploratory efficacy-related biomarkers will be analyzed by a central laboratory.

Samples for biomarker assessments will be collected according to the SoA (Section 1.2). Blood, tissue, and stool samples will be analyzed by the central or specialty laboratory. Details for collection, processing, and storage will be provided in the Laboratory Manual. Residual samples will be stored and may be used for additional analyses, if the participant has granted consent and where allowed by the regulatory authorities and local ethics committees.

C-reactive protein: Blood will be collected for measurement of CRP. C-reactive protein is an acute phase protein expressed by hepatocytes in response to inflammatory cytokines and will be assessed using a CRP assay. Investigators will be blinded to the CRP results during the 13-week

Induction Treatment Period, the LTE Treatment Period, and first 4 weeks of the OLE Treatment Period.

Fecal calprotectin: Stool samples will be collected for measurement of FCP. Fecal calprotectin is a complex consisting of calcium-binding proteins. It is expressed by activated neutrophils (and to a lesser extent by macrophages and monocytes), and fecal levels correlate with the number of neutrophils in the gut. It is used as a biomarker of intestinal inflammation. Investigators will be blinded to the FCP results during the 13-week Induction Treatment Period, the LTE Treatment Period, and first 4 weeks of the OLE Treatment Period.

Lymphocyte count: Blood will be collected for measurement of lymphocyte count. VTX002, through modulation of S1P receptors, is postulated to modulate lymphocyte trafficking, resulting in a reduction in peripheral lymphocyte count and lymphocyte availability for recruitment to sites of inflammation. During the 13-week Induction Treatment Period, the LTE Treatment Period, and first 4 weeks of the OLE Treatment Period, Investigators will be blinded to the WBC and differential counts results. The Investigator must take care to avoid ordering or viewing any local CBC during this time. During this time, the WBC differential results will be assessed by an unblinded Medical Monitor (not providing direct medical oversight of study conduct). If either one of the following events occurs, the unblinded Medical Monitor will notify the Investigator with additional instructions:

- ANC (absolute neutrophil count) < 1000/µL
- ALC < 200 cells/µL

If the ANC is confirmed to be below the 1000/µL limit, the Investigator will be requested to closely monitor for risk of serious infection and institute appropriate follow-up at his or her discretion.

If the ALC is confirmed to be below the 200 cells/µL limit, study treatment should be interrupted and should not be reinitiated if the ALC remains below this threshold. In this situation, the unblinded Medical Monitor will notify the Investigator and provide instructions on additional actions that the Investigator may need to take. When there is at least one measurement of ALC < 200 cells/µL, blinded values may be released to treating physicians and Investigators as deemed medically necessary to monitor infection and/or aid in diagnostic work-up as clinically indicated, and/or as a tool to assess the effectiveness of therapeutic interventions for an infection.

Investigators will repeat CBC with differentials weekly until ALC > 500 cells/µL. Reinitiation of study treatment can be considered only when ALC > 500 cells/µL.

8.3.4 Exploratory Efficacy-Related Biomarkers

Samples for exploratory biomarker assessments will be collected according to the SoA (Section 1.2). [redacted] will be analyzed by a central or specialty laboratory. Details for collection, processing, and storage will be provided in the Laboratory Manual. Residual

samples will be stored and may be used for additional analyses to further understand response to treatment and mechanism of action of VTX002 if the participant has granted consent. These additional analyses (as appropriate) will be conducted only where allowed by the regulatory authorities and local ethics committees.

Samples may be stored for a maximum of 15 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the Sponsor to enable further analysis of biomarker responses to VTX002, such as proteomics and transcriptomics, if needed.

8.3.5 Quality of Life

Patient-reported quality of life assessment will be completed electronically and checked for completeness at the study site as indicated in the SoA (Section 1.2) and will be used in support of the efficacy outcomes.

Inflammatory Bowel Disease Questionnaire: The IBDQ is a validated 32-item questionnaire used to assess HRQoL in participants with inflammatory bowel disease, including UC and Crohn's disease. Response to each of the questions is graded from 1 to 7 with overall score ranging from

32 (very poor HRQoL) to 224 (perfect HRQoL). The IBDQ will be collected if and when available in the appropriate local language.

8.4 Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Section 1.2).

8.4.1 Physical Examinations

A complete PE will include evaluation of heart, lung, head and neck, abdomen, neurological system, skin, and extremities. An interim (or brief) PE will include areas with previously noted abnormalities and/or that are associated with any new complaints from the participant. Please see SoA (Section 1.2) for more information.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.4.2 Vital Signs

Temperature, pulse, BP, and respiratory rate will be assessed. Vital signs will be measured prior to any blood draws that occur at the same study visit.

Blood pressure and pulse will be assessed in the sitting position with a calibrated automated device. Manual techniques will be used only if an automated device is not available. Proper technique should be utilized during the measurement of BP to include the following:

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

When obtaining the pulse and BP, the participant should rest in the sitting position for at least 5 minutes before measurement to establish an accurate baseline measurement. After the participant has been sitting for at least 5 minutes, pulse and BP will be measured using an automated validated device (if available). Blood pressure and pulse are to be collected prior to completion of the ECG assessment and before any simultaneously scheduled blood collections. See Section 6.5 for guidance for cardiac monitoring.

8.4.3 Electrocardiograms

A12-lead ECG will be obtained as outlined in the SoA (see Section 1.2) using an ECG machine that automatically calculates the HR and measures PR, QRS, QT, and QTc intervals.

Electrocardiograms should be preceded by at least 5 minutes of rest in the supine position without distractions (eg, television, cell phones) at each timepoint at which an ECG is required.

All ECGs will be recorded from a 12-lead ECG machine with the participant in the supine position. Every attempt should be made to ensure the participant's 12-lead ECG readings are obtained using the same machine throughout the study.

Intervals to be provided on the confirmed read for each safety 12-lead ECG are: RR, PR, QRS, QT and QTcF. If an ECG shows a new onset QTcF interval > 450 msec in men and > 470 msec in women during the treatment period, a repeated ECG is required. If this abnormal finding is confirmed, study treatment must be interrupted. Effective diagnostic and therapeutic strategies should be employed.

Reversible causes of prolonged QTc interval (eg, electrolyte abnormalities or hypomagnesemia) should be corrected as clinically indicated. When evaluating a participant with new onset QTc interval above 500 msec, referral to a cardiologist experienced in treating cardiac conduction disorders should be considered. Reinitiation of study treatment can be considered only after all of the following have occurred:

- The QTcF interval is < 450 msec (men) or < 470 msec (women)
- The QTc prolongation is considered by the Investigator and confirmed by the cardiologist as not related to study treatment and likely caused by other factors
- Individual risk-benefit is favorable (as determined by the Investigator, in agreement with the cardiologist), AND
- After discussion with the Medical Monitor

The Investigator will be responsible for review and interpretation of 12-lead ECGs on site and determining if the 12-lead ECG is normal, abnormal clinically insignificant, or abnormal clinically significant. Findings will be documented in the eCRF. All 12-lead ECG recordings will be transferred to a central reader for analysis. See Section 6.5 for guidance for cardiac monitoring.

8.4.4 Holter ECG Monitoring

Detailed instructions describing the process for recording and transmission of the digital ECGs and Holter can be found in the Study Manual and provided to the site before the start of the study.

Participants should be in the supine position prior to Holter application.

On Day 1 and OLE Day 1 (OLE Week 0/OLE Visit 1), continuous Holter ECG monitoring will be performed for at least 1 hour predose and at least 24 hours postdose using the same device and procedure, as outlined in the SoA (see Section 1.2). Participants who meet the discharge criteria (Section 6.5.1.1) will be sent home for continued Holter monitoring at least 24 hours postdose. Participants will be instructed regarding removal and return of the Holter monitor. All Holter recordings will be transferred to a central reader for analysis.

See Section 6.5 for guidance for cardiac monitoring.

8.4.5 Pulmonary Function Tests

Pulmonary function tests will be performed according to the SoA (Section 1.2) and include FEV1 and FVC measurements. At sites where available, diffusing capacity of the lungs for carbon monoxide (DLCO) measurements will also be performed. These tests will be performed at a qualified pulmonary function laboratory or respiratory department.

If the PFTs are not within normal range, the results should be verified by a pulmonologist, and potential confounding factors identified. If the participant has a decline in PFT values, the participant should be evaluated by a pulmonologist. If values (FEV1 and/or FVC) decline below 50% of the predicted values, treatment should be discontinued with follow-up evaluation initiated as appropriate. An inability to perform a test for DLCO should be discussed with the Sponsor.

The safety of study participants and site staff is paramount, so it is at the Investigator's discretion whether PFT can be safely administered to study participants during the treatment period. The Investigator should evaluate on a case-by-case basis how best to proceed based on the participant's medical history, the Investigator's clinical judgment, and in consultation with the Medical Monitor. All reasonable efforts should be made to ensure safety and adherence to the protocol. When available, spirometry may be conducted at the clinical site instead of at the pulmonary laboratory. If the decision is made that it is not appropriate to conduct PFTs due to the safety concerns (eg, SARS-CoV-2 transmission), then this decision and rationale should be appropriately captured in the participant's source documentation. When available and safe (due to lifting of local restrictions, reopening of local PFT labs, or improved safety conditions), the tests should be conducted as soon as possible and as close to the timepoints as outlined in the protocol.

8.4.6 Ophthalmoscopy and Optical Coherence Tomography

Ophthalmoscopy and OCT will be performed according to the SoA (Section 1.2). A general ophthalmologist can do the OCT examination, although a retinal specialist would be preferred to do the examinations, wherever possible.

For participants with abnormal OCT findings, with visual signs or symptoms of new onset macular edema, or a suspicion of new onset macular edema or worsening macular edema following initiation of treatment, general retinal examinations, including eye history, visual acuity, and dilated ophthalmoscopy should be obtained along with OCT. Additional testing should be considered at the discretion of the ophthalmologist.

8.4.7 Tuberculosis Screening and Chest X-Ray

All participants will complete TB screening to determine eligibility (see Exclusion Criterion 15).

A positive diagnostic TB test is defined as:

- A positive QuantiFERON test or 2 successive indeterminate QuantiFERON tests **OR**

- A tuberculin skin test reaction ≥ 10 mm (≥ 5 mm in participants receiving the equivalent of > 15 mg/day prednisone), if a QuantiFERON test is not available

Chest X-ray is to be performed at the time of Screening if not done in the previous 6 months.

Participants with active or latent TB infection at Screening, and history of untreated or inadequately treated latent TB infection will be excluded from the study. The following are EXCEPTIONS to this exclusion criterion:

a. Participants with latent TB, who have been ruled out for active TB, have completed an appropriate course of TB prophylaxis treatment per national/local medical guidelines or WHO guidelines, have a chest radiograph without changes suggestive of active TB infection, and have not had recent close contact with a person with active TB are eligible to enroll in the study. It is the responsibility of the Investigator to verify the adequacy of previous TB treatment and provide appropriate documentation of treatment compliance.
b. Participants diagnosed with latent TB at Screening, ruled out for active TB and have received at least 4 weeks of an appropriate TB prophylaxis regimen may be rescreened for enrollment. Participants will complete their prophylactic regimen during the trial.

8.4.8 Clinical Safety Laboratory Assessments

See Appendix 3 for the list of clinical laboratory tests to be performed and the SoA (Section 1.2) for the timing and frequency.

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 14 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor or their designee notified. All protocol-required laboratory assessments, as defined in Appendix 3, must be conducted in accordance with the Laboratory Manual and the SoA (Section 1.2). If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE), then the results must be recorded in the eCRF.

8.5 Adverse Events

The definitions of an AE and SAE can be found in Appendix 4.

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

The Investigator and their designees or site staff are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or study procedures, or that caused the participant to discontinue the study treatment (see Section 7.0).

8.5.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the signing of the ICF to 30 days after last study treatment administration. Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the eCRF, not the AE section.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours of learning of a participant's SAE, as indicated in Appendix 4. The Investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of becoming aware.

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

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

8.5.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.5.3 Follow-Up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow up on each AE at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 4.

In addition to appropriate reporting of these events as an AE or SAE, supplementary detailed information may be collected from the Investigator.

8.5.4 Regulatory Reporting Requirements for SAEs

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

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

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy, and forwarded to Investigators as necessary. The term SUSAR refers to an AE that occurs in a participant and which is assessed by the Sponsor and/or Investigator as being unexpected (ie, not listed in the Investigator's Brochure or not listed at the specificity or severity that has been observed), serious, and as having a reasonable possibility of a causal relationship with the study drug (ie, related to the study drug per causality assessment in Appendix 4). Reports of these reactions are participant to expedited submission to regulatory authorities.

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

8.5.5 Pregnancy

Reports of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study treatment and until 30 days after the participant's last dose of study drug.

The first pregnancy test at Screening is a serum β-hCG test that is evaluated by a central laboratory. All subsequent pregnancy testing will be performed using a urine dipstick pregnancy test that may be performed at the site or at home, if a virtual visit is performed as indicated in the SoA (Section 1.2). During non-visit months, participants will be provided with a home urine pregnancy test kit (as permitted by local regulations). Participants will confirm the performance of a monthly pregnancy test in the eDiary, if performed at home, and provide the results to the study site. If not permitted by local regulations, a pregnancy test will be performed at an unscheduled visit at the site during non-visit months. Any positive urine pregnancy test result will be confirmed with a serum β-hCG test.

If a pregnancy is reported in a female study participant, study treatment should be discontinued at once and the Investigator should inform the Sponsor or designee within 24 hours of learning of the

pregnancy, following the procedures outlined in Appendix 5. If a pregnancy is reported in the female partner of a male study participant, the pregnancy will be reported and followed the same way, but the study participant may continue with study treatment.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.5.6 Adverse Events of Special Interest

Based on the mechanism of action of VTX002 and prior experience with other agents acting via a similar mechanism, potential AESIs may be identified.

See reasons for study treatment discontinuation in Section 7.1 for more information.

8.6 Treatment of Overdose

An overdose is any dose of study treatment given to a participant or taken by a participant that exceeds the dose described in the protocol. There is no information yet regarding overdose with VTX002.

Any overdose, with or without associated AEs, must be promptly reported to the Sponsor or designee. Overdoses do not need to be recorded as AEs in the eCRF; only overdoses associated with an AE should be reported on relevant AE/SAE sections in the eCRF.

8.7 Pharmacokinetics

8.7.1 Collection of Blood Samples for VTX002 Concentration Determination in Plasma

Blood samples will be collected for measurement of plasma concentrations of VTX002 as specified in the SoA (Section 1.2) and as shown in Table 10 below. Blood samples may be taken either by direct venipuncture or an indwelling cannula inserted in a forearm vein.

Table 10 Blood Samples for Pharmacokinetics

	Pre-dose[a]	2, 4, and 6 hours postdose (± 10 minutes)	24 hours postdose (± 10 minutes)	Trough PK
Induction Visit 2 (Day 1)	X	X		
Induction Visits 3-5 and 7	X			
LTE Visits 9-12	X			
OLE Visit 1 (OLE Day 1)	X	X	X (Optional)[b]	
OLE Visits 2 and 3	X	X (Optional)[c]	X (Optional)[c]	
OLE Visits 4-9, 13, and 17/EOT	X			
ET and FU				X

Abbreviations: EOT = end of treatment; ET = Early Termination; FU = Follow-Up

a. When study drug is administered at the clinic, PK sample will be collected predose and after completion of vital sign assessments and ECGs.

b. Applies only to participants who consent to return to the clinic on OLE Day 2

c. Postdose timepoints are optional, but all 4 timepoints (2, 4, 6, and 24 hours postdose) are required for participants who consent

Blood samples for measurement of plasma concentrations of VTX002 will be collected predose at all study visits, and also at a few timepoints postdose in some visits. When timepoints are specified as optional, samples will be collected only from participants who consent for such samples.

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

8.7.2 Determination of Drug Concentration

Samples for the determination of VTX002 in plasma will be analyzed using an appropriate validated bioanalytical method. Full details of the bioanalytical methods and batch performance will be described in a separate Bioanalytical Report that will be included in the final Clinical Study Report.

Samples will be analyzed in accordance with the bioanalytical laboratory's standard operating procedures and the validated method. As bioanalytical concentrations have the potential to unblind a study, the concentration results will only be transferred from the bioanalytical laboratory in accordance with the Data Transfer Specifications.

Remaining plasma samples may be subjected to further analysis by the Sponsor or designee for the purpose of the development of additional bioanalytical assays and/or for VTX002 metabolite identification in human plasma, if warranted based on emerging data and if the participant gives consent for this purpose. Samples collected for analyses of VTX002 concentrations may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

8.8 Biomarkers

Biomarkers for efficacy or exploratory efficacy analyses are provided in Sections 8.3.3 and 8.3.4. Instructions for the collection and handling of biological samples will be provided in the Laboratory Manual. The actual date and time (24-hour clock time) of each sample will be recorded.

8.8.1 Determination of Biomarkers

All efficacy-related and exploratory efficacy-related biomarkers will be analyzed by a central laboratory. Additional details can be found in the Laboratory Manual.

[redacted]

9.0 STATISTICAL CONSIDERATIONS

9.1 General Considerations

All data listings, summaries, and analyses will be performed under the guidance and approval of the Sponsor.

Descriptive statistics will be used for all variables, as appropriate. Continuous variables will be summarized by the number of observations, mean, standard deviation (SD), median, first quartile, third quartile, minimum, and maximum. In addition to the aforementioned summary statistics, geometric mean and geometric CV will be calculated for certain PK parameters. Categorical variables will be summarized by frequency counts and percentages for each category. Unless otherwise stated, percentages will be calculated out of the total population for each treatment group and hypothesis tests will use a two-sided alpha = 0.05.

For change from baseline efficacy analyses (including the primary efficacy analysis), only participants with a baseline and at least one nonmissing postbaseline measurement will be included.

For primary analysis purposes, all efficacy endpoints will be analyzed using the Full Analysis Set (FAS). For sensitivity analysis purposes, the primary and key secondary endpoints will also be analyzed using the modified Full Analysis Set (mFAS) and Per Protocol Set, using the same statistical methodology as described in Section 9.4.1 and Section 9.4.3.

Additional details about the statistical methods will be provided in the SAP, which will be prepared as a separate document.

9.2 Determination of Sample Size

The study is powered to show superiority of VTX002 60 mg to placebo with respect to clinical remission. Based on literature data review, the expected proportion of clinical remission at Week 13 is 28% for VTX002 60 mg and 8% for placebo.[8,9] Under these assumptions and with a 1:1 randomization ratio, two-group chi-squared test, and two-sided significance level of 5%, a sample of 57 participants per treatment group will be sufficient to achieve at least 80% power. Adding a 10% inflation for dropouts results in 63 participants per treatment group and 189 in total.

All sample size calculations were conducted in SAS® (v9.4, SAS Institute Inc., Cary, NC).

9.3 Analysis Sets

The following analysis sets for the Induction Treatment Period are defined as follows:

Full Analysis Set (FAS): The FAS consists of all randomized participants who received at least one dose of study treatment. Participants will be analyzed according to the treatment to which they were randomized.

Modified Full Analysis Set (mFAS): For a given analysis, mFAS consists of all randomized participants who received at least 1 dose of study treatment, and have at least one non-missing post-baseline assessment(s) relevant to the analysis. Participants will be analyzed according to the treatment to which they were randomized.

Per Protocol Set: The Per Protocol Set consists of all participants in the mFAS who do not have a significant protocol deviation having a major effect on the primary efficacy evaluation.

Safety Set: The Safety Set consists of all randomized participants who received at least 1 dose of study treatment (VTX002 or placebo). For this population, participants are analyzed according to the treatment received, regardless of randomization. The Safety Set will be used for all safety analyses.

Pharmacokinetics Set: The Pharmacokinetics Set consists of all participants who receive VTX002, have at least 1 measured concentration at a scheduled PK timepoint after start of dosing for VTX002.

Biomarker Set: The Biomarker Set consists of all participants in the Safety Set who have at least 1 measured biomarker value at a scheduled timepoint after start of dosing for study treatment. The Biomarker Set will be used for all biomarker analyses.

The following analysis sets for the OLE Treatment Period are subsets of the analysis sets of the Induction Treatment Period, as defined below:

FAS-Extension Treatment (FAS-ET) Set: The FAS-ET Set consists of all randomized participants who received at least 1 dose of study treatment in the LTE or the OLE Treatment Periods. Under this approach, the original treatment groups as assigned at randomization will be used.

Safety-Extension Treatment (Safety-ET) Set: The Safety-ET Set includes all participants who received at least 1 dose of study treatment in the LTE or the OLE Treatment Periods. The Safety-ET Set will be used for all safety analyses. Participants will be analyzed according to treatments received in the LTE or the OLE Treatment Periods.

9.4 Statistical Analyses

The SAP will be developed and finalized before the interim database lock (see Section 9.4.7) for the purpose of primary analysis and will describe the participant analysis sets to be included in the analyses and the procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

All analyses, summaries, and listings will be performed using SAS (version 9.4 or higher).

The following descriptive statistics will be used as applicable to summarize the study data unless otherwise specified:

- Continuous variables: number of observations (n), mean, SD, median, first quartile, third quartile, minimum (min), and maximum (max)
- Categorical variables: frequencies and percentages
- Pharmacokinetic data will be presented in terms of number of participants (N), number of observations (n), arithmetic mean, SD, CV, median, first quartile, third quartile, minimum, and maximum value. In addition, geometric mean and geometric CV may also be presented.

Individual participant data will be presented in listings.

9.4.1 Efficacy Analyses

The study is designed to have a capability to show superiority of VTX002 60 mg to placebo for the primary endpoint. Apart from the primary analysis, four key secondary endpoints are defined for this study. Further on, comparing two different dose levels of VTX002 vs placebo brings a total number of inferential analyses in the study up to 10. The family-wise Type I error rate across the primary analysis of the primary efficacy endpoint and all key secondary analyses will be maintained at $\alpha = 0.05$ using a sequentially rejective method. Details will be provided in the SAP.

Additional details about secondary and exploratory efficacy analyses will be included in the SAP, which will be finalized before the interim database lock.

9.4.1.1 Primary Efficacy Analysis

The primary analysis of the primary efficacy endpoint will be completed based on the FAS, and will be a comparison between VTX002 60 mg and placebo. The primary efficacy endpoint is the proportion of participants with clinical remission at Week 13. The following null hypothesis:

$$\mathbf{H_0: p_{VTX002} - p_{placebo} = 0}$$

will be tested against a two-sided alternative:

$$\mathbf{H_A: p_{VTX002} - p_{placebo} \neq 0.}$$

The hypothesis will be tested at a 5% level of significance. Testing will be done using a Cochran-Mantel-Haenszel test (CMH) test with biologic/JAK inhibitor prior use status (Yes or No), baseline corticosteroid use (Yes or No), and baseline disease activity (MMS 4-6 or 7-9) as the stratification factors. The CMH chi-square p-value and stratified risk differences with 95% CI using the Newcombe method will be provided for pairwise comparisons between each dose group and placebo. Only the two treatment groups – VTX002 60 mg and placebo – will be included in the primary analysis of the primary endpoint.

9.4.1.2 Key Secondary Analyses

Key secondary endpoints will be analyzed similarly to the primary endpoint, using the CMH test with similar stratification factors. Comparisons between VTX002 60 mg and placebo for all key secondary endpoints will be considered key secondary analyses. Comparisons between VTX002 30 mg and placebo for the primary endpoint and the key secondary endpoints will be considered key secondary analyses.

9.4.1.3 Exploratory Analyses

Categorical exploratory endpoints will be analyzed similarly to the primary endpoint.

Continuous exploratory endpoints will be analyzed using a general linear model (analysis of covariance [ANCOVA]) with fixed effects for treatment, biologic/JAK inhibitor prior use status (Yes or No), baseline corticosteroid use (Yes or No), and baseline disease activity (MMS 4-6 or 7-9).

Repeated measures Induction/LTE data on clinical remission, endoscopic response, endoscopic remission, histologic improvement (Geboes), and histologic remission (Geboes) at Weeks 4, 8, 10, 13, 18, 26, 36, and 52 will be analyzed. This will be done using repeated measurements logistic regression specifying the distribution as binomial, the link function as logit and randomization stratification factors added as covariates in addition to randomized treatment.

Change from baseline in FCP and CRP at Weeks 1, 4, 8, 13, 26, 36, and 52; and also for change from baseline in PMS at Weeks 4, 8, 13, 18, 26, 36, and 52 will be analyzed using an appropriate continuous repeated measurements methodology. Details will be provided in the SAP, and will include a specification of how the results will be reported.

For clinical remission, endoscopic response, endoscopic remission, histologic improvement (Geboes), and histologic remission (Geboes) at Week 13, separate logistic regression models with stepwise selection will be built to assess the impact of the following covariates measured at baseline:

- ALC derived from blinded hematology laboratory results
- FCP
- CRP

The alpha level for both entering and removing a covariate will be 0.10. Point estimates and the corresponding 95% confidence intervals for the odds ratios will be calculated.

9.4.2 Analysis of LTE Treatment Period and OLE Treatment Period

All the exploratory endpoints collected during the LTE Treatment Period and the OLE Treatment Period will be summarized with appropriate summary statistics over time, using the same definitions given above.

9.4.3 Safety Analyses

All safety data (eg, Holter ECG monitoring, 12-lead ECG, OCT, PFT, and PE) will be listed and summarized using descriptive statistics. Separate summaries of safety data will be provided for the Induction, the LTE, and the OLE Treatment Periods. Additional details regarding analyses of the safety data (eg, Holter ECG monitoring, 12-lead ECG, OCT, PFT, and PE) will be provided in the SAP.

Treatment-emergent AEs are defined as AEs that first occurred or worsened in severity after the first administration of study treatment and prior to 30 days after the last administration of study treatment.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities. For each study treatment, numbers of TEAEs and incidence rates will be tabulated by Preferred Term and System Organ Class.

Treatment-emergent AEs by maximum severity, TEAEs by relationship to study treatment, SAEs, TEAEs leading to death, and TEAEs leading to discontinuation of study treatment will be tabulated for each treatment group. Commonly occurring TEAEs in either treatment group will be summarized using descriptive statistics.

All central laboratory test results, vital signs measurements, ECG results, and weight measurements will be summarized for each treatment group using descriptive statistics at each visit for raw numbers and change from baseline. The incidence of treatment-emergent abnormal laboratory, vital sign, and ECG values will also be summarized using descriptive statistics.

Incidence of AEs including pulmonary dysfunction and macular edema, as well as abnormalities in clinical laboratory assessments, vital signs, Holter ECG monitoring, 12-lead ECG, and PE will also be summarized.

9.4.4 Other Analyses

9.4.4.1 Pharmacokinetics Analyses

Full details of PK analysis will be provided in a PK Analysis Plan.

9.4.4.2 Biomarker Analyses

Biomarker analyses refer to assessment of efficacy-related (Section 8.3.3) and exploratory efficacy-related biomarkers (Section 9.4.1.3) as it relates to treatment with VTX002. Observed biomarker results and change from baseline results will be summarized by treatment and scheduled time, where appropriate, for the biomarker analysis set(s). Graphic presentations of biomarker results (and/or change from baseline results) by treatment and scheduled time may be prepared for select biomarkers of interest. Treatment differences in biomarker response may also be explored

using inferential analyses, if warranted by the data. Further details on any planned biomarker analyses and graphic presentations will be provided in the Biomarker Analysis Plan.

9.4.4.3 Subgroup Analyses

Subgroup analyses using biologic/JAK inhibitor prior status (Yes or No), baseline corticosteroid use (Yes or No), and baseline disease activity (MMS 4-6 or 7-9) will be performed.

All other subgroup analyses will be further described in the SAP.

9.4.5 Missing Data

Participants who discontinue treatment will be followed up as participants who do not discontinue treatment, unless consent is withdrawn. A detailed discussion of estimands, intercurrent events, and handling of missing data will be presented in the SAP.

9.4.6 Sensitivity Analyses

Sensitivity and supportive analyses based on estimands, intercurrent events, and missing data imputation methods are discussed in the SAP.

9.4.7 Timing of Analyses

After all randomized participants either complete the Induction Treatment Period or discontinue study drug, an interim database lock, treatment unblinding, and subsequent interim statistical analysis will be triggered. All data for the 13-week double-blind Induction Treatment Period will be analyzed following an interim database lock (Induction Period Analysis). As the primary efficacy endpoint and all the key secondary efficacy endpoints are measured at Week 13, the Induction Period Analysis will be the final analysis of the primary efficacy and key secondary efficacy endpoints.

After the last participant completes the study, data accumulated over the entire study will be presented in summaries and listings.

Detailed descriptions of the primary, supportive, and sensitivity analyses for each unique database lock will be given in the SAP.

9.5 Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will be utilized to monitor the safety of participants and to enhance the integrity and credibility of the study. The roles and responsibilities of the DMC are described in detail in the DMC Charter.

The DMC will abide by the principles set forth in the FDA Guidance for Industry, Clinical Trial Sponsors, Establishment and Operation of Clinical Trial Data Monitoring Committees (FDA 2006). As part of its role, the DMC will conduct reviews of accumulating safety and efficacy

data at specified intervals during the conduct of the trial, according to the guidelines detailed in the DMC Charter. DMC recommendations to the Study Team will be communicated in a blinded fashion (ie, treatment assignment for individual participants will not be shared). To ensure the scientific integrity of the study, members of the DMC will not be directly involved in the ongoing management of the study.

In addition to members of the DMC, an independent statistician responsible for interacting with the DMC will have access to unblinded study data. This statistician will not be directly involved in the conduct of the study.

10.0 REFERENCES

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11.0 APPENDICES

Appendix 1 Abbreviations

Abbreviation	Definition
β-hCG	beta-human chorionic gonadotropin
5-ASA	5-aminosalicylic acid
6-MP	6 mercaptopurine
AE	adverse event
AESI	adverse event of special interest
AIDS	acquired immune deficiency syndrome
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the curve
$AUC_{(0–24)}$	area under the concentration-time curve of the analyte in the sampled matrix from zero (predose) to 24 hours
$AUC_{(0-t)}$	area under the concentration-time curve of the analyte in the sampled matrix from zero (predose) to time 't'
$AUC_{(0–\infty)}$	area under the concentration-time curve of the analyte in the sampled matrix from zero (predose) to infinity
AV	atrioventricular
AZA	azathioprine
BCRP	breast cancer resistance protein
BP	blood pressure
bpm	beats per minute
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	observed maximum analyte concentration in the sampled matrix
CMH	Cochran-Mantel-Haenszel
CRO	contract research organization
CRP	C-reactive protein
CV	coefficient of variation
DLCO	diffusing capacity of the lungs for carbon monoxide

Abbreviation	Definition
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture database
eDiary	electronic diary
eGFR	estimated glomerular filtration rate
EOT	end of treatment
ES	endoscopic subscore
ET	early termination
FAS	Full Analysis Set
FAS-ET	Full Analysis Set-Extension Treatment
FCP	fecal calprotectin
FEV1	forced expiratory volume in 1 second
FVC	forced vital capacity
GCP	Good Clinical Practice
HbA1c	hemoglobin A1c
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HEMI	histologic-endoscopic mucosal improvement
HIV	human immunodeficiency virus
HR	heart rate
HRQoL	health-related quality of life
IBDQ	Inflammatory Bowel Disease Questionnaire
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobulin
IL	interleukin
INR	international normalized ratio
IRB	Institutional Review Board
IV	intravenous

Abbreviation	Definition
IWRS	interactive web response system
JAK	Janus kinase
LTE	Long-Term Extension
MAD	multiple ascending dose
MCS	Mayo Clinic score
mFAS	modified Full Analysis Set
MMS	modified Mayo score
MMX	extended release tablets
NSAID	nonsteroidal anti-inflammatory drug
OCT	optical coherence tomography
OLE	Open-Label Extension
[redacted]	[redacted]
PE	physical examination
PFT	pulmonary function test
PGA	Physician's Global Assessment
P-gp	P-glycoprotein
PK	pharmacokinetic
PML	progressive multifocal leukoencephalopathy
PMS	partial Mayo score
QD	once daily
QTcF	Fridericia's corrected QT interval
RB	rectal bleeding
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
S1P	sphingosine-1-phosphate
S1PR	sphingosine-1-phosphate receptor
SAD	single ascending dose
SAE	serious adverse event
Safety-ET	Safety-Extension Treatment
SAP	Statistical Analysis Plan
SD	standard deviation
SF	stool frequency
SoA	Schedule of Activities
SUSAR	suspected unexpected serious adverse reaction

Abbreviation	Definition
TB	tuberculosis
[redacted]	[redacted]
TEAE	treatment-emergent adverse event
T_{max}	time of maximum analyte concentration (C_{max})
TNF	tumor necrosis factor
UC	ulcerative colitis
ULN	upper limit of normal
WBC	white blood cell

Appendix 2 Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

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

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

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

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

The Investigator will be responsible for the following:

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

After reading the protocol, each Investigator will sign the protocol signature page (Appendix 9). The study will not start at any study center at which the Investigator has not signed the protocol.

Financial Disclosure

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

Insurance

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

Informed Consent Process

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

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.

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

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

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

Participants who are rescreened are required to sign a new ICF.

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

Data Protection

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

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

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

Dissemination of Clinical Study Data

The results of the study should be reported within 1 year from the end of the clinical study. Irrespective of the outcome, the Sponsor will submit to the European Union database a summary of the results of the clinical study within 1 year from the end of the clinical study. It shall be accompanied by a summary written in a manner that is understandable to laypersons.

Data Quality Assurance

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

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

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

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

The Sponsor or its representative may conduct audits at the investigative sites including, but not limited to, drug supply, presence of required documents, the informed consent process, and comparison of eCRFs with source documents. All medical records (progress notes) must be available for audit. The Investigator agrees to participate with audits conducted at a convenient time in a reasonable manner.

Government regulatory authorities may also inspect the Investigator during or after the study. The Investigator or designee should contact the Sponsor/CRO immediately if this occurs. He/she must cooperate fully with regulatory authorities or other audits conducted at a convenient time in a reasonable manner. The purpose of an audit is to assess whether ethics, regulatory, and quality requirements are fulfilled.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized study center personnel are accurate, complete, and verifiable from source

documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Source Documents

The Investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the study center's participants. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail).

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

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

Definition of what constitutes source data can be found in the Study Manual.

Study and Study Center Closure

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

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

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

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the Investigator.
- Discontinuation of further study treatment development.

Publication Policy

The data generated by this study are confidential information of the Sponsor. The Sponsor will make the results of the study publicly available. The publication policy with respect to the Investigator and study center will be set forth in the Clinical Trial Agreement.

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

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

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

Appendix 3 Clinical Laboratory Tests

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

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

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.0 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations. All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 14 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.

Investigators must document their review of each laboratory safety report.

Laboratory/analyte results that can unblind the study will not be reported to study centers or other blinded personnel until the study has been unblinded.

Table 11 Clinical Laboratory Tests

SCREENING Only **Virology** HIV, HBsAg, HCV (RIBA), QuantiFERON **Stool Sample** Bacterial culture, ova and parasites, *C. difficile* **Drug of Abuse** Amphetamine, barbiturates, benzodiazepines, cocaine, methadone, methamphetamine, methylenedioxymethamphetamine, opiate, oxycodone, phencyclidine, if and where available **Others** Hemoglobin A1c
PREGNANCY TESTING **Pregnancy Testing** Serum pregnancy test for β-hCG – Screening, and if any urine pregnancy test is positive Urine β-hCG (only for woman of childbearing potential), including home pregnancy testing, as applicable

CLINICAL CHEMISTRY, HEMATOLOGY, AND COAGULATION		
Hematology	**Serum Chemistry[b]**	**Coagulation**
Hematocrit Hemoglobin Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration Mean corpuscular volume Platelet count Red blood cell count WBC count with differential[a]	Albumin Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Bicarbonate Blood urea nitrogen Calcium Chloride Creatinine[c] Creatine kinase Potassium Sodium Total bilirubin Total cholesterol Total protein Triglycerides Uric acid Direct bilirubin Glucose Gamma-glutamyl transferase Lactate dehydrogenase Phosphorus	Prothrombin time Activated partial thromboplastin time INR
[redacted]		
URINALYSIS		
Appearance Bilirubin Color Glucose Ketones Microscopic examination of sediment	Nitrite Occult blood pH Protein Specific gravity Urobilinogen	
BIOMARKERS Lymphocytes[a] CRP[a] Fecal calprotectin[a] [redacted]		
PHARMACOKINETICS Blood samples for plasma concentrations of VTX002		

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; β-hCG = beta-human chorionic gonadotropin; CRP = C-reactive protein; eGFR = estimated glomerular filtration rate; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; INR = international normalized ratio; RIBA = recombinant immunoblot assay; SAE = serious adverse event; [redacted] ULN = upper limit of normal; WBC = white blood cell.

a) Total WBC, differentials, lymphocyte, neutrophil, [redacted], fecal calprotectin, and CRP will be blinded as defined in Section 6.8. Total WBC, neutrophil, lymphocyte, CD4 T-cell counts, fecal calprotectin, and CRP will be reviewed by an unblinded Medical Monitor who will provide instructions to the site Investigator in the event of significant lymphopenia (Section 8.3.3). Participants, Investigators, study staff, and study vendors are to remain blinded to the identity of the treatment during the double-blind Induction Treatment Period, LTE Treatment Period, and the first 4 weeks of the OLE Treatment Period. The Sponsor are blinded to the blinded results until the interim database lock and unblinding for the Induction Treatment Period is completed.

b) Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 6.6. An increase in AST or ALT > 3 × ULN should be followed by repeat testing within 72 hours of receiving results to confirm the abnormality and determine whether AST or ALT is increasing or decreasing. All events of ALT or AST > 3 × ULN and total bilirubin > 2 × ULN (> 35% direct bilirubin), or ALT or AST > 3 × ULN and INR > 1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE.

c) eGFR will be calculated each time the serum creatinine is tested.

[redacted]

Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

See Section 8.5 for additional information regarding AEs and SAEs.

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.
Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, coagulation, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsened from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease) • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition • New conditions detected or diagnosed after study drug administration even though it may have been present before the start of the study • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.
Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the eCRF, not the AE section. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital) • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen

Definition of SAE

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

An SAE is defined as any untoward medical occurrence that, at any dose:
a) Results in death
b) Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.
c) Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
d) Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e) Is a congenital anomaly/birth defect
f) Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the eCRF. Each event must be recorded separately.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Severity

The Investigator will make an assessment of severity for each AE and SAE reported during the study according to the Common Terminology Criteria for Adverse Events, version 5.0 (CTCAE v5.0):

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care ADL (eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money).
- Grade 4: Life-threatening consequences, urgent intervention indicated.
- Grade 5: Death related to AE.

An event is defined as "serious" when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The relationship of each AE to the investigational products will be assessed by the Investigator or Sub-Investigator on the basis of his/her clinical judgment and the following definitions:
    - Related:
        - The AE follows a reasonable temporal sequence from investigational product administration and cannot be reasonably explained by the participant's clinical state or other factors (eg, disease under study, concurrent diseases, or concomitant medications).
        - The AE follows a reasonable temporal sequence from investigational product administration and represents a known reaction to the investigational product or other drugs in its class or is predicted by the known pharmacological properties of the drug.
        - The AE resolves with discontinuation of the investigational product and/or recurs with re-challenge, if applicable.
    - Not Related:
        - The AE does not follow a reasonable temporal sequence from investigational product administration or can be reasonably explained by the participant's clinical state or

other factors (eg, disease under study, concurrent diseases, and concomitant medications).

- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study drug administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-Up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized Follow-Up Period, the Investigator will provide the Sponsor or designee with a copy of any postmortem findings, including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of receipt of the information.

Reporting of SAEs

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

- The primary mechanism for reporting an SAE to the Sponsor or designee will be the electronic data collection tool. If the electronic system is unavailable for more than 24 hours, then the study center will use the paper SAE data collection tool.
- The study center will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given study center, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a study center receives a report of a new SAE from a participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the study center can report this information on a paper SAE form or to the Sponsor or designee by telephone.
- After the whole study is completed or terminated, an SAE should be reported directly to the Sponsor.
- Contacts for SAE reporting can be found in the Study Manual.

Appendix 5 Collection of Pregnancy Information

Male participants with partners who become pregnant

The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study.

After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Pregnant partners should be followed until 12 months after their delivery date for outcomes of both the mother and child. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor or designee within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy and for 1 year after delivery for evaluation of outcomes of both the mother and child. The Investigator will collect follow-up information (may be conducted by telephone) on the mother and child and the information will be forwarded to the Sponsor. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such.

Any poststudy pregnancy-related SAE considered reasonably related to the study treatment by the Investigator will be reported to the Sponsor as described in Section 8.5.5. While the Investigator is not obligated to actively seek this information in former participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue study treatment or be withdrawn from the study.

Appendix 6 Mayo Scoring System for Assessment of Ulcerative Colitis Activity – Sample

The Mayo score ranges from 0 to 12, with higher scores indicating more severe disease.

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

0 = Normal number of stools for this participant

1 = 1 to 2 stools more than normal

2 = 3 to 4 stools more than normal

3 = 5 or more stools more than normal

Subscore: 0 to 3

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

0 = No blood seen

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

2 = Obvious blood with stool most of the time

3 = Blood alone passes

Subscore: 0 to 3

Findings on endoscopy: The endoscopy subscore will be determined by qualified personnel at a central laboratory.

0 = Normal or inactive disease

1 = Mild disease (erythema, decreased vascular pattern)

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

3 = Severe disease (spontaneous bleeding, ulceration)

Subscore: 0 to 3

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

0 = Normal

1 = Mild disease

2 = Moderate disease

3 = Severe disease

Subscore: 0 to 3

Appendix 7 Histological Scoring Indices

Geboes Grading System

The Geboes Grading System is a stepwise grading system used for the evaluation of microscopic inflammation and histopathologic disease activity in UC. The microscopic appearance of the mucosa is categorized into 6 grades. A decrease of the Geboes Score grading system to Grade zero (0) or one (1) indicates mucosal healing.[10]

Nancy Histological Index

The Nancy Histological Index is a validated index for assessing histological disease activity in UC. It is composed of 3 histological items defining 5 grades of disease activity: absence of significant histological disease (Grade 0), chronic inflammatory infiltrate with no acute inflammatory infiltrate (Grade 1), mildly active disease (Grade 2), moderately active disease (Grade 3), and severely active disease (Grade 4). The presence of ulceration on the biopsy specimen corresponds to severely active disease (Grade 4). If there is no ulceration, acute inflammatory cells infiltrate (presence of neutrophils) is assessed. Moderate or severe acute inflammatory cells infiltrate corresponds to moderately active disease (Grade 3), while mild acute inflammatory cells infiltrate correspond to mildly active disease (Grade 2). If there is no acute inflammatory cells infiltrate, assessment of chronic inflammatory infiltrate (lymphocytes and plasmacytes) is made. A biopsy specimen showing moderate or marked chronic inflammatory infiltrate corresponds to moderate or marked chronic acute inflammatory infiltrate (Grade 1). A biopsy specimen showing mild or no chronic inflammatory infiltrate corresponds to absence of significant histological disease (Grade 0).[11]

Robarts Histopathology Index

The Robarts Histopathology Index (RHI) is an evaluative index, derived from the Geboes score, that is designed to be reproducible and responsive to clinically meaningful change in disease activity over time. The total RHI score ranges from 0 (no disease activity) to 33 (severe disease activity) and is calculated as follows: RHI = 1 × Chronic inflammatory infiltrate + 2 × Lamina propria neutrophils + 3 × Neutrophils in epithelium + 5 × Erosion or ulceration.[12]

Appendix 8 Signature of Sponsor

I have read this Protocol Version 6.0 in its entirety and agree to conduct the study accordingly.

[redacted]

[redacted]

Date

[redacted]

Oppilan Pharma Ltd.

Appendix 9 Signature of Investigator

PROTOCOL TITLE: A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Clinical Efficacy and Safety of VTX002 in Subjects with Moderately to Severely Active Ulcerative Colitis

PROTOCOL NO: VTX002-201

VERSION: Protocol Version 6.0

This protocol is a confidential communication of Oppilan Pharma, Ltd. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from Ventyx Biosciences, Inc.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Investigator signature	Date

Printed name, title, and study center