Protocol Number: 0157

Official Title: A Phase 2B/3 Multi-Center, Randomized, Double-Blind, Multi-Dose, Placebo-Controlled, Parallel-Group Set of Studies to Evaluate the Efficacy and Safety of Induction and Maintenance Therapy with TD-1473 in Subjects with Moderately-to-Severely Active Ulcerative Colitis

NCT Number: NCT03758443

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CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2b/3 Multi-Center, Randomized, Double-Blind, Multi-Dose, Placebo-Controlled, Parallel-Group Set of Studies to Evaluate the Efficacy and Safety of Induction and Maintenance Therapy with TD-1473 in Subjects with Moderately-to-Severely Active Ulcerative Colitis
Study Short Title:	Rhea: Efficacy and Safety of TD-1473 in Ulcerative Colitis
Sponsor Study No.:	0157
Date:	14 May 2020 – [redacted]
Test Product:	TD-1473
US IND:	128299
EudraCT No.:	2018-002136-24
Sponsor:	Theravance Biopharma Ireland Limited Connaught House 1 Burlington Road Dublin 4 D04 C5Y6 Ireland
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This study will be conducted according to the principles of Good Clinical Practice.

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PROTOCOL SYNOPSIS

Study Number and Title: Protocol 0157: A Phase 2b/3 Multi-Center, Randomized, Double-Blind, Multi-Dose, Placebo-Controlled, Parallel-Group Set of Studies to Evaluate the Efficacy and Safety of Induction and Maintenance Therapy with TD-1473 in Subjects with Moderately-to-Severely Active Ulcerative Colitis

Study Short Title: Rhea: Efficacy and Safety of TD-1473 in Ulcerative Colitis

Estimated Number of Study Centers and Countries or Regions: [redacted]

Background and Rationale: [redacted]

Objectives:

This single protocol includes three randomized, double-blind, and placebo-controlled studies: a Phase 2b dose-finding Induction Study, a Phase 3 dose-confirming Induction Study, and a randomized-withdrawal Maintenance Study in subjects with moderately-to-severely active UC. Subjects from the Phase 2b or Phase 3 Induction Studies who achieve clinical response by adapted Mayo score (total Mayo score without physician global assessment [PGA]) may roll into the Maintenance Study.

Phase 2b Dose-Finding Induction Study

The objectives of the Study are as follows:

- Assess the effect of TD-1473 taken daily for 8 weeks at daily doses of 20 mg, 80 mg, and 200 mg on the change from baseline in the total Mayo score
- Assess the effect of TD-1473 on rates of clinical remission, endoscopic healing, clinical response, and mucosal (i.e., histologic and endoscopic) healing
- Upon completion, select dose(s) of TD-1473, based on safety, tolerability, and efficacy data for evaluation in the Phase 3 dose-confirming Induction Study and the Phase 3 Maintenance Study

Phase 3 Dose-Confirming Induction Study

Enrollment into the Phase 3 Induction Study begins after data analysis and interpretation of the Phase 2b Induction Study is complete and a dose of TD-1473 is selected for the Phase 3 Induction Study.

The primary objective(s) are to:

- Establish the clinical remission rate associated with TD-1473 compared to placebo treatment at Week 8
- Establish the safety and tolerability of TD-1473 taken for up to 16 weeks

The key secondary objective(s) of the Study are to assess the rates of the following associated with TD-1473 compared to placebo treatment:

- Endoscopic healing, symptomatic remission, clinical response, mucosal healing (endoscopic and histologic), and deep symptomatic remission at Week 8

Maintenance Study

Subjects who achieve clinical response to induction therapy with a total of 8 weeks of any dose of TD--1473 will be re-randomized into the Maintenance Study and contribute to the primary analysis of the study.

The primary objective(s) of the Study are as follows:

- Establish the clinical remission rate associated with TD-1473 compared to placebo treatment at Maintenance Week 44
- Establish the safety and tolerability of TD-1473 with up to 44 additional weeks of treatment

The key secondary objectives of the Study are to assess the rates of the following associated with TD-1473 compared to placebo treatment:

- Clinical response, endoscopic healing, symptomatic remission, mucosal (endoscopic & histologic) healing, and deep symptomatic remission at Maintenance Week 44
- Corticosteroid-free remission at Maintenance Week 44
- Maintenance of clinical remission at Maintenance Week 44 in those who were in remission at Maintenance Week 0

Study Design:

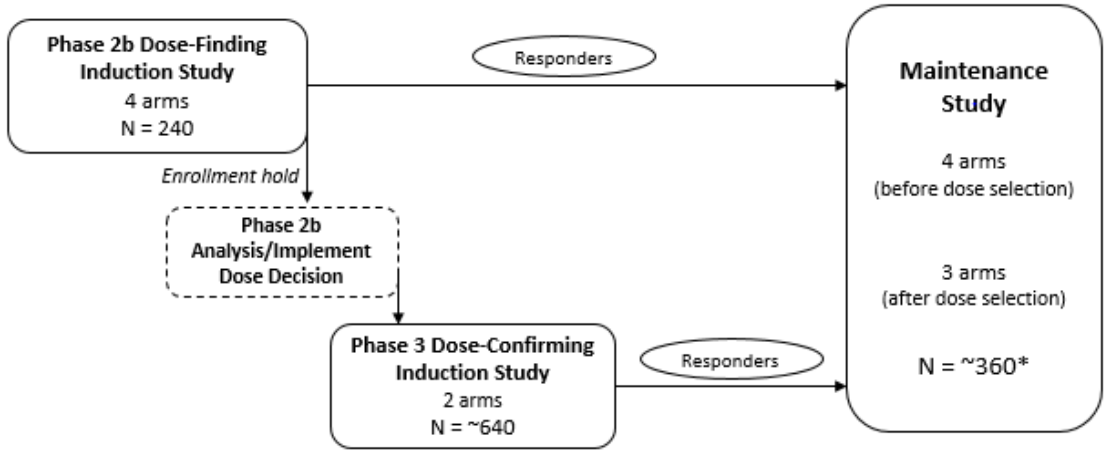
Summary: This protocol includes three studies: a Phase 2b dose-finding Induction Study (8-16 weeks), a Phase 3 dose-confirming Induction Study (8-16 weeks), and a Phase 3 randomized-withdrawal Maintenance Study (up to 44 weeks) [Figure 1] characterizing the general treatment paradigm in UC. Each of the studies will utilize multi-center, randomized, double blind, placebo-controlled, and parallel-group designs to evaluate 1 or more dose(s) of TD-1473 compared to placebo in subjects with moderately-to-severely active UC.

The duration of treatment in the Phase 2b and Phase 3 Induction Studies will be 8 weeks for those who achieve clinical response, as defined by an adapted Mayo score (total Mayo score without inclusion of the Physician Global Assessment [PGA] component, using a centrally read Mayo endoscopic subscore), at Week 8. For subjects who do not achieve clinical response at Week 8, dosing will continue for an extended induction period of 8 weeks (16 weeks in total; TD-1473 subjects will receive the same dose for a total of 16 weeks and placebo subjects will receive a dose of 80 mg for the extended duration period). Subjects who achieve clinical response at either at Week 8 or Week 16 of the Induction Study will enter the Maintenance Study. Subjects who do not achieve clinical response by Week 16 will complete the study at Week 16 plus the End of Study visit.

During the Maintenance Study, subjects will be treated with either placebo or one of several TD-1473 doses for 44 weeks. Subjects who A) demonstrate persistent loss of response (no improvement at approximately 8 weeks after meeting loss of response criteria) or B) experience repeated (two) Clinical Flares during the Maintenance Study after loss of response or C) complete the Maintenance Study will exit the Maintenance Study and may be eligible for the long-term safety (LTS) Study (separate protocol, Protocol 0164).

Subjects will be required to maintain an electronic symptom diary to be completed on a daily basis. See below for details of the Induction and Maintenance Studies.

Figure 1: Protocol Schema



* Estimated number of subjects for the re-randomized maintenance population

Phase 2b Dose-Finding Induction and Phase 3 Dose-Confirming Induction Studies

To determine initial eligibility, subjects will undergo assessments during the Screening Stage 1 period. Refer to Schedule of Study Procedures (Table 1) for a schedule of the screening requirements. Disease activity will be assessed by partial, adapted, and total Mayo scores. Subjects who meet inclusion criteria and no exclusion criteria, as described in Section 4, will undergo an endoscopic exam (i.e., sigmoidoscopy or colonoscopy) with biopsies to complete screening Stage 2.

If the subject meets eligibility criteria, including a Mayo endoscopic subscore ≥ 2 points from the Screening Stage 2 visit and an adapted Mayo score between 4 and 9 points, inclusive, on Day 1, the subject may be randomized. Randomization will be stratified by prior biologics failure status (yes or no) and corticosteroid use at enrollment (yes or no) into the Induction Study.

The Induction Studies consist of treatment for 8 weeks for those who demonstrate clinical response at Week 8 or 16 weeks for those who did not have a response. Subjects will return for safety, PK, biomarker, and disease assessments, as well as an endoscopy with biopsies according to the Schedule of Study Procedures provided in Table 1.

The Phase 2b Induction Study will enroll approximately 240 subjects, randomized 1:1:1:1 to placebo or 1 of the 3 TD-1473 doses (20 mg, 80 mg, or 200 mg). After all 240 subjects have

either completed Week 8 or been withdrawn from the Study prior to Week 8, an analysis of all efficacy and safety data up to Week 8 will be conducted (Refer to Section 8). Results from the Phase 2b dose-finding Induction Study analysis will be used to inform the dose selection for the Phase 3 dose-confirming Induction Study as well as the remainder of the Maintenance Study.

Following the 240th subject enrolled, recruitment will be placed on hold until the Phase 2b Induction study analysis is complete. A component of the analysis and interpretation is dose selection for further development. The Phase 3 Induction Study will commence after dose selection.

Extended Induction

Subjects who do not demonstrate clinical response at Week 8 will receive an additional 8 weeks of treatment with TD-1473 staying on the same dose as the first 8 weeks, except those who had received placebo during the first 8 weeks will now receive TD-1473 at 80 mg (Figure 3). All subjects who undergo extended induction treatment will receive active drug, and thus, this portion of the Induction Study will not be placebo-controlled but blinding as to the specific dose of TD-1473 will be maintained. During this time, at the discretion of the investigator, subjects are permitted but are not required to begin corticosteroid taper. Those who demonstrate clinical response at the end of Week 16 will enter the Maintenance Study; those who do not demonstrate clinical response at the end of Week 16 will have an EOS visit and exit the study.

Maintenance Study

Subjects who are eligible (i.e., achieving clinical response by adapted Mayo score) for the Maintenance Study at Week 8 of the Induction Study will continue directly from the Induction Studies to the Maintenance study. Previously TD-1473 dosed subjects will be re-randomized to receive placebo or one of the TD-1473 doses. Subjects who achieved clinical response on placebo at Week 8 during Induction will continue on placebo in a blinded manner and will not be included in the primary efficacy analysis population of the Maintenance Study.

Subjects who are eligible (i.e., achieving clinical response by adapted Mayo score) for the Maintenance Study at Week 16 of one of the Induction Studies will continue from the Induction Studies to the Maintenance Study. Subjects who received 16 weeks of TD-1473 treatment will continue on the same study drug treatment in a blinded manner and will not be included in the primary efficacy analysis. Subjects who received 8 weeks of placebo and 8 weeks of TD-1473 80 mg will be re-randomized to placebo or one of the TD-1473 doses and contribute to the primary efficacy analysis population of the Maintenance Study.

The Maintenance Study consists of treatment for 44 weeks. During the Maintenance Study, subjects must start (or continue if they started during extended induction) tapering their corticosteroid dose using the regimen outlined in Section 6.5.3 if they entered the study on corticosteroids.

Prior to the Phase 2b Induction Study Week 8 data analysis and subsequent dose selection, qualifying subjects from the Phase 2 Induction Study will be randomized 1:1:1:1 to placebo or 1 of the 3 TD-1473 doses (20 mg, 80 mg or 200 mg) into the Maintenance study.

After the Phase 2b Induction primary Week 8 data analysis and subsequent dose selection have been completed, subjects enrolling into the remaining of the Maintenance Study will be randomized to either placebo or one of up to two selected TD-1473 doses in a 1:1:1 ratio. Those who are still completing the Maintenance Study on a de-selected dose will remain on that dose unless there is a safety signal detected up to point of dose selection. The randomization will be stratified by clinical remission status (yes or no) (using adapted Mayo score component definition) at Maintenance Week 0 (mWeek 0) and corticosteroid use at enrollment (yes or no) into the Maintenance Study. Separate randomization schedules will be prepared for subjects who reach clinical response after receiving 8 weeks of TD-1473 and subjects who reach clinical response after receiving placebo during the first 8 weeks and then TD-1473 80 mg during extended induction.

During the Maintenance Study, subjects will return for safety, PK, biomarker, and disease assessments, as well as a final endoscopy with biopsies according to the Schedule of Study Procedures provided in Table 2. Subjects who experience a clinical flare (Refer to DEFINITION OF TERMS) of their symptoms during the Maintenance Study will undergo assessment for loss of response as per Table 3. Loss of response may lead to initiation of rescue medication (e.g., initiation or increase in corticosteroid dose [Refer to Section 6.5.4]), which may lead to meeting the definition of treatment failure during the Maintenance Study. Subjects who complete the Maintenance Study or experience persistent loss of response or Clinical Flare twice after loss of response may enter the LTS Study (separate protocol) if they meet the applicable eligibility criteria. Subjects who do not enter into the LTS study will need to complete an End of Study visit 4 weeks after the last dose of study drug.

Refer to Section 2 Study Design in the main body of the protocol for further information.

Duration of Study Participation: Maximum of 68 weeks (4 weeks screening, 52/60 weeks treatment [includes 8 weeks of Extended Induction], and 4 weeks follow-up)

Number of Subjects: Approximately 880 subjects including 240 subjects enrolled in the Phase 2b dose-finding Induction Study. The total sample size could vary depending on the outcome of the Phase 2b Induction data analysis.

Study Population:

Subjects with moderately-to-severely active UC as defined by a baseline adapted Mayo score between 4 and 9 points, inclusive, and a Mayo endoscopic subscore ≥ 2 points (where endoscopic subscore of 1 requires absence of friability), who are corticosteroid-dependent or demonstrate an inadequate response or a loss of response or a failure to tolerate conventional therapy (aminosalicylates, corticosteroids and immunomodulators [i.e., azathioprine or 6-mercaptopurine]) or biologic therapy [e.g., anti-TNF therapy or anti-integrin].

Inclusion Criteria for Induction Studies:

To be eligible subjects must meet all the following criteria:

1. Are male or female 18 years of age or older at Screening

2. Has ≥ 3 months history of UC prior to screening (with involvement beyond the rectum to at least 15 cm from the anal verge)
    a. Diagnosed by sigmoidoscopy or colonoscopy AND
    b. If possible, corroborated by histology report or documentation of histological results in a physician note. However, if there was no biopsy done previously or if no prior endoscopy or histology report is available for review, the subject must have a colonoscopy instead of a sigmoidoscopy at screening.
3. Must be willing to have a sigmoidoscopy or colonoscopy at screening. Colonoscopy will be performed instead of a sigmoidoscopy at screening in the following scenarios, (outlined in Section 6.4.1.20):
    a. If UC diagnosis precedes screening by ≥ 8 years for pan-colitis or ≥12 years for left-sided colitis and the subject does not have documentation of a surveillance colonoscopy within 12 months prior to screening to rule out dysplasia (report must be reviewed by the investigator and included in the source documents). During colonoscopy, if chromoendoscopy or surveillance biopsies are indicated as per locally adopted guidelines, these should be performed.
    b. If UC diagnosis precedes screening by < 12 years and the subject does not have documentation of a colonoscopy within 2 years prior to screening (report must be reviewed by investigator and included in the source documents).
    c. If there is no documented histology report from prior endoscopy showing chronic colitis or other signs of UC. In this case, consideration should be made to do biopsies during the screening endoscopy with histology sent locally to confirm diagnosis of UC, if there is doubt of diagnosis

    If chromoendoscopy has to be performed or ≥ 10 biopsies are to be collected for dysplasia surveillance, either should be done after completion of a full colonoscopy to avoid chromoendoscopy dye or biopsy-related bleeding artifact from interfering with endoscopic images for central reading.
4. Has moderately-to-severely active UC, defined as having:
    a. a centrally read Mayo endoscopic subscore of ≥ 2 points based on the results of the Screening Stage 2 endoscopy
    AND
    b. an adapted Mayo score between 4 and 9 points, inclusive, on Day 1.
5. Is corticosteroid-dependent or had intolerance or inadequate response to any of the following: aminosalicylates, corticosteroids, immunomodulators (azathioprine or 6-mercaptopurine), or biologics (anti-TNF, anti-integrin, or anti-IL-12/23) [Refer to Appendix 7]

    NOTE: For subjects in **Portugal**, subject must have had intolerance or inadequate response to biologics
6. If currently receiving an oral corticosteroid, subject is eligible if:
    a. the subject has been on corticosteroids for a minimum of 4 weeks prior to Day 1
    AND

b. the dose is equivalent to or less than:
   - prednisone 25 mg/day ***OR***
   - beclomethasone diproprionate (i.e., Clipper) at 5 mg/day ***OR***
   - budesonide 9 mg/day

   AND

c. the dose is stable for at least 2 weeks prior to Screening Stage 2 visit

7. If subject is currently receiving oral aminosalicylate (e.g., mesalamine products, balsalazide, or sulfasalazine): subject is eligible provided the subject has been on it at a stable dose for ≥ 4 weeks prior to Day 1.
8. During the Study and for 7 days after receiving the last dose of the Study drug, females of childbearing potential or men capable of fathering children must agree to use highly effective birth control measures (failure rate <1% when used consistently and correctly) or agree to abstain from sexual intercourse. Females of childbearing potential must test negative for pregnancy at screening and at Day 1 (Refer to Section 4.3).
9. All male subjects must agree to refrain from semen donation during the Study and for 7 days after the last dose of Study drug.
10. Must be able and willing to adhere to the Study visit schedule and comply with other protocol requirements.
11. Are capable of providing informed consent, which must be obtained prior to any Study-related procedures.

Inclusion Criteria for Extended Induction (additional 8 weeks):

12. Did not meet criteria for clinical response by adapted Mayo score using centrally read endoscopic subscore at Week 8a

Inclusion Criteria for Maintenance Study:

13. Must have met the criteria for a clinical response by adapted Mayo score using centrally read endoscopic subscore during Induction at Week 8a or during Extended Induction Study at Week 16

Exclusion Criteria for Induction Study:

Subjects meeting any of the following criteria may not be enrolled in the Study:

Gastrointestinal:

1. Has symptoms or signs suggestive of fulminant colitis, toxic megacolon, intestinal perforation
2. Has primary sclerosing cholangitis (PSC)
3. Is likely to require surgery for UC or any other type of major surgery (i.e., surgical procedure requiring general anesthesia) during the Study

4. Has had a clinically significant, as deemed by the investigator, prior intestinal resection for UC or for other gastrointestinal diseases (e.g., that may have resulted in chronic diarrhea)
5. Has carried or carries a diagnosis of Crohn's disease, microscopic colitis, ischemic colitis, radiation colitis, diverticular disease associated with colitis, or indeterminate colitis, or the subject has a current or past diagnosis of a fistula or abdominal abscess.
6. Has unresected colonic mucosal dysplasia or history of resected high-grade colonic dysplasia within 3 years prior to screening (Subjects with raised adenomas that have been completely resected or with pathology results of indefinite dysplasia with reactive atypia will not be excluded).

Concomitant or previous medications received:

7. Taken or taking any prohibited medications as listed in Appendix 6, including:
   a. Immunomodulators (azathioprine, 6-mercaptopurine [6-MP], methotrexate) within the 14 days prior to Day 1
   b. anti-TNFs (e.g., adalimumab, infliximab, golimumab, etanercept, certolizumab, or biosimilars) taken within the 60 days or 5 half-lives, whichever is longer, prior to Day 1
   c. intravenous corticosteroids within the 14 days prior to Day 1
   d. rectal mesalamine or corticosteroid (i.e., enemas or suppositories) taken within the 14 days prior to Day 1
   e. vedolizumab, ustekinumab, mycophenolic acid, tacrolimus, sirolimus, or cyclosporine taken within 60 days or 5 half-lives, whichever is longer, prior to Day 1
   f. Any prior exposure to an approved JAK inhibitor (e.g. tofacitinib) or potential exposure to an experimental JAK inhibitor that was stopped due to intolerance or lack of efficacy; This does not include subjects with prior exposure to another JAK inhibitor that was stopped for any other reason (e.g., loss/lack of insurance coverage)
   g. Any prior exposure to natalizumab, rituximab, efalizumab, fingolimod, daclizumab cyclophosphamide, or thalidomide
   h. NSAIDs taken on a regular (more than 3 times per week, on average) basis (regular use of aspirin ≤ 325 mg per day for cardiovascular protection is allowed).
   i. Anakinra, abatacept, or any other immune-modifying biologic agent taken within 90 days prior to Day 1
   j. A JAK inhibitor (e.g. tofacitinib) within 60 days prior to Day 1
   k. Any prior exposure to TD-1473

   Note: For biologics specified in items b and e above, there is no requirement for a washout period if there is a documented finding of undetectable drug level by a validated assay (e.g., through commercially available testing).
8. If subject has recently discontinued aminosalicylates or corticosteroids, these must have been stopped at minimum of 2 weeks before screening endoscopic procedure.

9. Has had inadequate response (i.e., either primary or secondary non-response) to ≥ 3 biologics of ≥ 3 different mechanisms of action (i.e., anti-TNF, anti-integrin, and anti-IL12/23, refer to Appendix 8).
   Note: Up to approximately 10% of the study population can have had inadequate response to all 3 biologics mechanisms approved for UC, regardless of total number of biologics.
10. Currently taking or has taken within 14 days prior to Day 1 any concomitant medication, herbal supplement or dietary substance (e.g., grapefruit) known to be a strong inhibitor or inducer of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), or CYP450 3A4 or is a substrate of P-gp or BCRP and has a narrow therapeutic index (refer to Appendix 6 for Prohibited medications).
11. Taking non-UC concomitant prescription medications that the investigator deems may confound the safety assessment of the study drug and that have started or have had a dose adjustment within 28 days prior to Day 1 (with the exception of corticosteroids, antibiotics for infections, sedating agents for sigmoidoscopy or colonoscopy, hormonal contraceptives, hormone replacement therapy, iron, vitamin D, insulin therapy, and replacement thyroid hormone - Refer to Appendix 6 for Prohibited medications). Anti-diarrheal medications and probiotics are allowed only if dose has been stable for minimum of 14 days prior to Day 1.
12. Taking over-the-counter medications or dietary supplements that the investigator deems may confound the safety assessment of the study drug and that have started or have had a dose adjustment within 14 days prior to Day 1 with the exception of up to 3 times per week use of non-steroid anti-inflammatory drugs or acetaminophen used on an as needed basis, aspirin ≤ 325 mg per day for cardiovascular prophylaxis, and over the counter doses of vitamin D, (Refer to Appendix 6 for Prohibited medications).

Infections or predisposition to infections

13. Subject is positive for:
    a. Hepatitis B virus (HBV) surface antigen
    b. Hepatitis B virus core antibody (unless subject has positive hepatitis B surface antibody and undetectable serum hepatitis B DNA).
    c. Hepatitis C virus (HCV) antibody unless: a) there is evidence of undetectable viral load measured twice six months apart after successful completion of treatment regimen and b) viral load during Screening is undetectable
    d. Hepatitis E immunoglobulin M (IgM) antibody
       Human immunodeficiency virus (HIV) antibody
14. Subject has had a live viral vaccine (e.g., MMR, varicella zoster, herpes zoster, oral polio virus, FluMist®, attenuated typhoid fever vaccine, attenuated rotavirus vaccine, yellow fever vaccine, or any investigational live vaccine) within 4 weeks prior to screening and/or is unwilling or unable to avoid live viral vaccines during the Study and for 8 weeks following completion of the Study. Subject must be willing to avoid contact with any household member who has been vaccinated with a live attenuated vaccine within 2 weeks after vaccination.

15. Has or may have untreated active or latent TB as evidenced by any of the following:
    a. Two indeterminate or one positive QuantiFERON®-TB Gold result within 90 days prior to Screening Stage 1 or during the Screening Period (Stage 1/Stage 2), without having completed an adequate treatment for latent or active TB before screening, **or**
    b. Chest X-ray or equivalent chest imaging within 90 days prior to screening in which active or latent pulmonary TB cannot be excluded.
    c. Subject who has a history of latent or active tuberculosis (TB) may be included if criteria outlined in Section 6.4.1.11 are met.

    Note: In case of a suspected false positive QuantiFERON®-TB Gold result (e.g., a negative result by the local laboratory and suspicion of sample processing error, both of which must be documented in the source document), a second sample may be sent to the central laboratory and the result of the second test will be used.

16. Has any of the following:
    a. An active, clinically significant, bacterial, parasitic, fungal, mycobacterial (including atypical infection), or viral infection, except for local skin or nail bed infection, within 2 weeks prior to Day 1.
    b. Any infection requiring intravenous antibiotics within 30 days prior to screening.
    c. Any infection requiring oral antimicrobial treatment within 2 weeks prior to Day 1.
    d. A history of more than two episodes of herpes zoster or one or more episodes of disseminated/complicated herpes zoster (complicated: multi-dermatomal, ophthalmic, or CNS involvement or post-herpetic neuralgia) or disseminated herpes simplex.
    e. Has had a chest radiograph or equivalent chest imaging within 90 days prior to Screening or at Screening that shows an abnormality suggestive of a malignancy of current active infection, including TB, chronic lung disease or a potentially active fungal, viral, or bacterial infection.
    f. Has C. difficile or other gastrointestinal infections (e.g., Salmonella, Shigella, Yersinia, Campylobacter, E. coli 0157, etc.) on stool testing or cytomegalovirus (CMV) colitis suspected on endoscopy within 30 days of Day 1.

17. Has ever had a bone marrow transplant.

Coexisting medical conditions or past medical history:

18. Are pregnant, lactating, breastfeeding or planning to become pregnant during the Study or within 7 days after the last dose of Study Drug

19. Has known moderate or severe hepatic impairment (e.g., Child-Pugh Class B or C)

20. Has clinically significant abnormalities in the results of laboratory evaluations at screening visit as determined by the investigator, including:
    a. AST, ALT, or alkaline phosphatase ≥ 2x the upper limit of normal (ULN)
    b. Total bilirubin > 2x ULN (unless diagnosis of Gilbert's syndrome)
    c. Creatinine clearance as calculated by the Cockcroft-Gault formula < 30 mL/min (Refer to Appendix 2)
    d. Total white blood cell count (WBC) < 3 x 10^9/L

e. Absolute neutrophil count < 1.5 x 10^9/L
f. Absolute lymphocyte count < 0.8 x 10^9/L
g. Hemoglobin < 8 g/dL, or
h. Platelet count < 100 x 10^9/L.

21. Has a clinically significant abnormal electrocardiogram (ECG) at screening, including QTcF > 450 msec for males and > 470 msec for females.
22. Has unstable or uncontrolled and clinically significant allergic (except for untreated, asymptomatic, seasonal allergies), hematological, endocrine/metabolic, coagulation, immunologic, pulmonary, cardiovascular, hepatic (except hepatic steatohepatitis), GI (except UC), genitourinary, psychiatric, oncologic or neurological disease or other medical disorder that would compromise subject safety or confound Study safety assessment as determined by the investigator at screening and Day 1. In addition, subjects with a prior history of thrombotic events, including deep vein thromboses (DVT), and those with known inherited conditions that predispose to hypercoagulability should be excluded.
23. Has known hypersensitivity to excipients or contents of the Study drug.
24. Has participated in another clinical trial of an investigational drug (or medical device) within 30 days prior to Screening or 5x the half-life of the investigational drug, whichever is longer, or is currently participating in another trial of an investigational drug (or medical device).
25. Have or has a history of alcohol or drug abuse within 1 year of screening, per the judgment of the investigator.
26. Has a current, or history of, malignancy requiring radiation or pharmacologic treatment within 5 years prior to screening, except for completely resected basal cell carcinoma or squamous cell carcinoma of the skin without recurrence for ≥1 year, cervical carcinoma in situ that has been adequately treated and without recurrence for ≥ 5 years. Subjects with a history of cervical dysplasia within 3 years prior to screening or who currently have unresected cervical dysplasia should be excluded.
27. Is deemed by the investigator to be inappropriate for this Study; or has any condition which would confound or interfere with the evaluation of the safety, tolerability, or PK of the investigational drug; or is unable or unwilling to comply with the Study protocol.

Exclusion Criteria Maintenance Study

28. Subjects who required change of UC medications (such as initiated or increased oral corticosteroid dose or initiated rectal aminosalicylates or corticosteroids) or any prohibited medication to control UC symptoms during Induction Study, including during extended induction, if applicable.

Exclusion Criterion for Induction Study Related to SARS-CoV-2

29. Within 4 weeks of screening or during screening, has [1] confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (coronavirus disease 2019 [COVID-19]) (test positive), OR [2] suspected SARS-CoV-2 infection (clinical

features without documented test results) unless has a negative test for SARS-CoV-2 two weeks after resolution of symptoms and remains asymptomatic until Day 1, OR [3] close contact with a person with known or suspected SARS-CoV-2 infection unless has a negative test for SARS-CoV-2 two weeks after contact and remains asymptomatic until Day 1.

Test Product, Dose, and Route of Administration; Regimen; Duration of Treatment:

- TD-1473 20 mg once daily: Taken orally for up to 60 (including Extended Induction when applicable) weeks in the morning
- TD-1473 80 mg once daily: Taken orally for up to 60 (including Extended Induction when applicable) weeks in the morning
- TD-1473 200 mg once daily: Taken orally for up to 60 (including Extended Induction when applicable) weeks in the morning.

Reference Therapy, Dose, and Route of Administration; Regimen; Duration of Treatment:

- Placebo once daily: Taken orally for up to 52 weeks in the morning.

Study Evaluations

Efficacy Assessments:

- Mayo score components: Mayo endoscopic sub score, stool frequency sub score, rectal bleeding sub score, and Physician's Global Assessment sub score
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Safety Assessments:

Subject safety will be assessed throughout the Study using standard measures, including vital signs, 12--lead ECGs, blood and urine safety laboratory tests, physical examinations, concomitant medication usage, and adverse event (AE) monitoring. Additional details may be collected for adverse events of special interest, including perforation, opportunistic infections, malignancies, non-melanoma skin cancer, serious infections, cardiovascular events, thromboembolic disease, complicated herpes zoster, and clinical laboratory abnormalities of concern.

Pharmacokinetic Assessments:

A sparse plasma PK sampling strategy is being employed in this Study where random samples will be taken at select Study visits both immediately prior to treatment with Study drug and during treatment with Study drug; time of Study drug ingestion needs to be carefully documented the day before and the day of each Study visit where PK samples will be collected.

Statistical Methods

Efficacy endpoints will be evaluated using the following hypothesis testing schema: Each TD-1473 dose will be compared with placebo. The null hypothesis for the treatment comparison will be that there is no difference between a given dose of TD-1473 and placebo. The alternative hypothesis will be that there is a difference.

Sample Size:

Phase 2b Induction Sample Size Considerations

A sample size of 60 subjects per group is estimated to give approximately 90% power to detect a 2-point improvement relative to placebo in total Mayo score at all three doses, under the following assumptions:

- Hochberg step-up procedure adjustment for multiple comparisons (2-sided tests)
- Family-wise type 1 error rate to be controlled at 5%
- Residual change standard deviation (SD) of 3 points
- The estimated power to detect a 2-point improvement relative to placebo for at least one of the three doses is greater than 98%.

Assuming a slightly larger residual change SD of 3.5 points, then the estimated power to detect a 2-point active dose group vs. placebo improvement in total Mayo score at all three doses was approximately 73% and the estimated power to detect a 2-point improvement at one or more of the doses was approximately 94%.

Estimates were obtained using East software, with 10,000 simulations per case.

Phase 3 Induction Sample Size Considerations

Upon completion of the analyses based on the Phase 2b Induction data, the sample size may be refined. Currently, it is estimated that 320 subjects per dose group (640 subjects total) will provide at least 90% power to demonstrate the selected TD-1473 dose is effective compared to placebo for the primary endpoint of clinical remission at Week 8 under the following assumptions:

- Type 1 error rate of 5% (2-sided tests)
- Clinical remission rate of 9.5% for placebo at Week 8
- Clinical remission rate of 23.5% for TD-1473 at Week 8

If two TD-1473 doses are selected, then 320 subjects per group will have 90% disjunctive power to demonstrate at least one of the two TD-1473 doses is effective compared to placebo for clinical remission at Week 8 under the following assumptions:

- Hochberg step up procedure adjustment for multiple comparisons
- Family-wise type 1 error rate to be controlled at 5% (2-sided)
- Clinical remission rate of 9.5% for placebo at Week 8
- Clinical remission rate of 23.5% for the more effective TD-1473 dose and 16.5% for the less effective TD-1473 dose.

For the Phase 2 and Phase 3 Inductions studies, subjects will be stratified by prior biologics failure and baseline corticosteroids use at randomization. In addition, randomization caps will be placed on both prior biologics failure subgroups (no to biologics failure [60%] and yes to biologics failure [60%]) to ensure that neither subgroup is overrepresented.

Phase 3 Maintenance Sample Size Considerations

Upon completion of the analyses based on the Phase 2b Induction data, the sample size may be refined. Currently, it is estimated that 120 subjects per dose group (360 subjects total) will provide at least 90% disjunctive power to demonstrate at least one of the two TD-1473 doses is effective compared to placebo for the primary endpoint of clinical remission at Maintenance Week 44 under the following assumptions:

- Hochberg step-up procedure adjustment for multiple comparisons
- Family-wise type 1 error rate to be controlled at 5% (2-sided)
- Clinical remission rate of 15% for placebo at Week 44
- Clinical remission rate of 30% and 40% for the two active TD-1473 doses at Maintenance Week 44

A total of 360 subjects total will provide 80% conjunctive power to demonstrate both doses of TD-1473 are effective compared to placebo for clinical remission at Maintenance.

Study Endpoints:

Phase 2b Induction Primary and Secondary Efficacy Endpoints:

Primary:

- Change in total Mayo score from baseline at Week 8

Key Secondary (with multiplicity control):

- Clinical remission by adapted Mayo score at Week 8

Phase 3 Induction Primary and Key Secondary Efficacy Endpoints (with multiplicity control) in order of testing:

Primary:

- Clinical remission by adapted Mayo score at Week 8

Key Secondary:

- Endoscopic healing at Week 8
- Symptomatic remission at Week 8
- Clinical response by adapted Mayo score definition at Week 8
- Mucosal healing at Week 8
- Deep symptomatic remission at Week 8

Phase 3 Maintenance Primary and Key Secondary Efficacy Endpoints (with multiplicity control) in order of testing:

Primary:

- Clinical remission by adapted Mayo score at Maintenance (m)Week 44

Key Secondary:

- Maintenance of clinical response at mWeek 44
- Endoscopic healing at mWeek 44
- Symptomatic remission at mWeek 44
- Corticosteroid-free remission at mWeek 44
- Maintenance of clinical remission at mWeek 44 in those who were in remission at mWeek 0
- Mucosal healing at mWeek 44
- Deep symptomatic remission at mWeek 44

Refer to DEFINITION OF TERMS for detailed definition of primary and key secondary endpoints

Safety Endpoints:

Incidence and severity of treatment-emergent adverse events; changes in laboratory test results, ECG intervals and abnormalities, and vital sign measurements

Analysis:

In general, binary endpoints will be analyzed using Cochran-Mantel-Haenszel tests, stratifying by randomization stratum. Subjects with missing binary outcomes will be counted as not meeting the endpoint for analysis purpose. Logistic regression models may be fitted for selected endpoints to evaluate dose-response curves.

Continuous endpoints will be analyzed by fitting mixed effect or analysis of covariance models which include terms for treatment, stratification factors, and baseline score.

The primary analysis set for efficacy endpoints will be a modified intent-to-treat (mITT) set comprising all subjects who receive at least one dose of study drug, summarized by randomized treatment.

For each Study, the family-wise type 1 error rate for primary and key secondary endpoints included in the statistical testing hierarchy will be controlled at 5% by use of a gatekeeping procedure with a pre-specified testing sequence. All comparisons will be 2-sided.

Safety data will be summarized by actual treatment received using frequency of events or descriptive summary statistics, as appropriate.

Individual data listings will be prepared for all data collected.

Further details can be found in Section 8 of the main body of the protocol.

Table 1: Schedule of Study Procedures – Induction and Extended Induction Studies

Procedures	Screening Period		INDUCTION VISITS				EXTENDED INDUCTION VISITS[33]			Early Study Drug D/C[5]	End of Study (4 weeks post last study dose)
			Day 1	Week 2	Week 4	Week 8a [1]	Week 8b[2],[3]	Week 12 [2]	Week 16 [2][4]		
Study Day/Week	**Day -28 to – 1**										
	Stage 1	**Stage 2**									
Window				± 3 days	± 3 days	-3 to + 5 days	+ 1 to 7 days from week 8a visit[6]	-3 to + 5 days	-3 to + 7 days	+ 5 days	-3 to + 5 days
Informed Consent	X										
Review Inclusion/Exclusion Criteria	X	X	X				X				
Medication and Medical History	X										
Smoking Status			X								
Height	X										
Weight	X		X			X[29]		X	X	X	X
Vital Signs [7]	X		X[8]	X	X	X[29]		X	X	X	X
12-Lead ECG [9]	X		X [32]			X[29]			X	X	X
Physical Examination[10]	X		X	X	X	X[29]			X	X	X
Chest X-Ray or equivalent chest imaging	X [11]										
Tuberculosis Test (QuantiFERON) [12]	X										
Plasma PK Samples [13]			X		X		X	X	X		

Table 1: Schedule of Study Procedures – Induction and Extended Induction Studies

Procedures	Screening Period		INDUCTION VISITS				EXTENDED INDUCTION VISITS[33]			Early Study Drug D/C[5]	End of Study (4 weeks post last study dose)
			Day 1	Week 2	Week 4	Week 8a [1]	Week 8b[2],[3]	Week 12 [2]	Week 16 [2][4]		
Study Day/Week	**Day -28 to – 1**										
	Stage 1	**Stage 2**									
Window				± 3 days	± 3 days	-3 to + 5 days	+ 1 to 7 days from week 8a visit[6]	-3 to + 5 days	-3 to + 7 days	+ 5 days	-3 to + 5 days
Overnight Fasting Lipid Panel	X[19]		X		X	X[29]		X	X	X	X
[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
Fecal Sample for stool infectious analysis[14]	X										
[redacted]			[redacted]			[redacted]			[redacted]	[redacted]	
Serology Panel[16][19]	X										
Pregnancy Test (females of child-bearing potential only)[17]	X[19]		X	X	X		X	X	X	X	X
FSH[18] [19]	X										
Chemistry, Hematology	X[19]		X	X	X	X[29]		X	X	X	X
Urinalysis	X[19]		X			X[29]			X	X	X
Whole Blood and Serum Biomarker Samples	X		X		X	X[29]		X	X	X	X
Genetic Blood Sample *(optional – only collected for subjects who provide genetic testing consent)*			X								

Table 1: Schedule of Study Procedures – Induction and Extended Induction Studies

Procedures	Screening Period		INDUCTION VISITS				EXTENDED INDUCTION VISITS[33]			Early Study Drug D/C[5]	End of Study (4 weeks post last study dose)
			Day 1	Week 2	Week 4	Week 8a [1]	Week 8b[2],[3]	Week 12 [2]	Week 16 [2][4]		
Study Day/Week	**Day -28 to – 1**										
	Stage 1	**Stage 2**									
Window				± 3 days	± 3 days	-3 to + 5 days	+ 1 to 7 days from week 8a visit[6]	-3 to + 5 days	-3 to + 7 days	+ 5 days	-3 to + 5 days
Endoscopy and Biopsies		X [20]				X[21]			X[21]		
Concomitant Medication review [22]	X		X	X	X	X	X	X	X	X	X
Adverse Events Assessment [23]	X	X	X	X	X	X	X	X	X	X	X
[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
Partial Mayo score		X									
Adapted Mayo score			X[31]			X[31]			X[31]		
Dispense Subject Diary[25]	X										
Subject Diary Completion and Compliance Review [26]		X	X	X	X	X	X	X	X	X	X
[redacted]			[redacted]			[redacted]			[redacted]	[redacted]	
[redacted]			[redacted]			[redacted]			[redacted]	[redacted]	
[redacted]			[redacted]			[redacted]			[redacted]	[redacted]	
[redacted]			[redacted]			[redacted]			[redacted]	[redacted]	
Randomization			X[27]								

Table 1: Schedule of Study Procedures – Induction and Extended Induction Studies

Procedures	Screening Period		INDUCTION VISITS				EXTENDED INDUCTION VISITS[33]			Early Study Drug D/C[5]	End of Study (4 weeks post last study dose)
			Day 1	Week 2	Week 4	Week 8a [1]	Week 8b[2],[3]	Week 12 [2]	Week 16 [2][4]		
Study Day/Week	**Day -28 to – 1**										
	Stage 1	**Stage 2**									
Window				± 3 days	± 3 days	-3 to + 5 days	+ 1 to 7 days from week 8a visit[6]	-3 to + 5 days	-3 to + 7 days	+ 5 days	-3 to + 5 days
Study Drug Dispensing			X	X	X		X				
In Clinic Dosing - Study Drug Dosing[28]			X		X		X		X		
Non-Site Study Procedures (Calculations for Programming/Statisticians and applicable suppliers)											
partial Mayo score and PRO2 scores calculation		X	X	X	X	X		X	X	X	X
adapted and total Mayo score calculations			X			X			X		

Abbreviations: D/C, discontinue; ECG, electrocardiogram; EOS, End of Study; FSH, follicle stimulating hormone; [redacted]; PK, pharmacokinetic; PRO2, two-item patient reported outcome; [redacted]; EOS, End of Study

Induction Studies:

[1] Subjects will continue on study drug at the same Induction dose until they return to clinic for **post-central read endoscopy results visit.** Depending on the week 8a adapted Mayo score (using centrally read endoscopy), the subject will proceed with one of the following:

- **Week 8b** visit if subject **did not achieve clinical response**, or
- **Maintenance Week 0** (mWeek 0) if subject **achieved clinical response** (see Table 2 Maintenance Phase Schedule of Study Procedures)

Subject to be reminded not to take study drug on the morning of this next clinic visit, whether Week 8b or mWeek 0, to allow for re-randomization and initiation of study drug of either Extended Induction or Maintenance Study, whichever he or she qualifies for

[2] Week 8b, Week 12, and Week 16 visits pertain only to subjects who undergo extended induction (i.e., who do not demonstrate clinical response based on the adapted Mayo score from Week 8a visit)

[3] Subject should be instructed not to take study drug from their Induction study drug bottles at home to allow for re-randomization and to receive the first dose of extended induction in the clinic.

[4] Week 16 visit may be done over a period of 1 to 3 visits to complete: a) the Week 16 endoscopy, b) Week 16 clinical assessments (e.g., vital signs, weight, laboratory testing, and Quality-of-Life assessments), and c) an optional visit to bring subjects back (or could be done over the phone) to inform them that they should stop study drug and proceed to EOS visit if they did not achieve clinical response (those who achieve clinical response will proceed to mWeek 0 visit). [redacted]

[5] Early Study Drug Discontinuation visit is for subjects who prematurely discontinue the Study drug during the Induction Study. Visit to be conducted within 5 days of the last dose of Study drug, if possible. Subject will also return for the EOS visit for collection of safety data and assessment of disease activity four weeks after last study drug. An EOS visit will be required for all subjects 4 weeks following their last dose of study drug, regardless if they completed the full duration of study drug treatment.

[6] Seven-day window provided to allow time to receive results from the central reading of endoscopy performed at Week 8a.

[7] Blood pressure and heart rate will be measured after the subject has been resting for at least 5 minutes in the seated or supine position. Vital sign measurements should be obtained prior to scheduled blood draws.

[8] Obtain blood pressure and heart rate any time pre-dose at all visits and approximately 1-hour post-dose (any time ≥ 1 hour and < 2 hours) on Day 1 only.

[9] ECGs should be performed after the subject has been resting in a supine position for at least 10 minutes.

[10] Physical Exam will be performed as per local standard practice (Section 6.4.1.9).

[11] A chest X-ray will be performed at screening to assess for signs of latent or active TB or other active viral, fungal or bacterial infections unless one has been performed within 90 days of screening, documented to be negative, and reviewed by investigator. Posterior anterior (PA) and lateral views (lateral view may not be necessary if PA view is deemed adequate by the investigator) will be obtained. Subjects who have had a chest X-ray or equivalent chest imaging within 90 days prior to screening will not require a repeat X-ray unless subject is deemed to be at high risk of recent pulmonary infection. If a chest X-ray is indicated, it may be performed anytime between Screening Stage 1 and Screening Stage 2 visits.

[12] Subjects who have had a documented chest X-ray or equivalent chest imaging or TB testing within 90 days prior to Screening do not require a repeat X-ray or TB testing, respectively, unless subject is deemed by the investigator to be at high risk of recent pulmonary infection. Subjects with a history of latent TB should not have a TB test but must not live in a region with high prevalence of multidrug-resistant TB and have completed a well-accepted treatment regimen (e.g., a ≥ 9-month course of INH or equivalent therapy) within 5 years (3 years in countries where TB is endemic) prior to Screening, the documentation for which must be included in the source document. Subjects who had treated active TB must still have a TB test. Subjects who has a history of latent or active tuberculosis (TB) may be eligible for the Study if criteria outlined in Section 6.4.1.11 are met.

[13] PK sampling will be performed in subjects at the following time points:

- **Day 1** (n= 3 samples): one sample collected **pre-dose** (within 1 hour prior to study drug administration) and one sample collected **anytime between 0.25 to 0.5 hours post-dose**; and one sample collected **anytime between 1 to 6 hours post-dose;**
- **Week 4** (n= 2 samples): one **pre-dose** and one **post-dose** sample collected **anytime between 1 to 6 hours post-dose**
- **Week 8b** (n = 2 samples): one **pre-dose** and one **post-dose** sample collected **anytime between 1 to 6 hours post-dose**; samples may be obtained up to -7 days from the Week 8a endoscopy visit, but cannot be obtained within 24 hours of endoscopy prep
- **Week 12** (n= 1 sample): One sample to be collected **anytime between 0.5 to 6 hours post-doses**

- **Week 16** (n=2 samples): one **pre-dose** and one **post-dose** sample collected **anytime between 0.5 to 6 hours**. The Week 16 sample may be obtained -3 to + 7 days from the endoscopy visit
  NOTE: Post-dose sampling times are defined relative to the time of Study drug administration on the day of collection. All PK sampling times will be accurately recorded by collection date, hour, and minute. Study drug dosing time on the day before each PK collection will also be accurately recorded by dosing date, hour, and minute by the subject; Study drug dosing time on the day of each PK collection will be accurately recorded by dosing date, hour, and minute by the Study staff.

[14] For stool infectious analysis: Including C. difficile, other bacterial pathogens (including Shigella, Salmonella, Yersinia, E. coli O157, and Campylobacter), and ova and parasite. This can be done **any time after written consent and prior to Screening Stage 2 visit, and results reviewed before Screening Stage 2 visit**.

[15] [redacted]

[16] Serology testing: Subjects with positive hepatitis B core antibody will undergo testing for hepatitis B DNA and hepatitis B surface antibody during Screening. Subjects with known hepatitis C will also undergo testing for hepatitis C RNA viral load (Refer to Section 6.4.1.18 for details on Serology testing). Serologies do not need to be repeated during re-screening if results from the first screening were negative and within 90 days of re-screening.

[17] B-hCG testing (serum for Screening and urine for all other visits) will be performed for females of childbearing potential to confirm absence of pregnancy. If urine b-hCG test is positive, confirm with serum b-hCG test.

[18] Required for postmenopausal females.

[19] Screening Labs including urinalysis may be obtained anytime during the 28-day window for Screening, but results must be available before Screening Stage 2 endoscopy with the exception of [redacted] and fasting lipid panel. ***NOTE:** Subjects **must not** be requested to come in fasting for study specific assessments prior to signing the informed consent. Exception: The overnight fasting lipid panel may be obtained on Day -28 if subjects are fasting as per institutions standard of care procedure, which must be clearly documented in the source documents.

[20] Endoscopy with biopsies will be performed at the Screening Stage 2 visit after subject's eligibility from Screening Stage 1 is confirmed. This screening endoscopy must occur at **≥ 5 days before Day 1 to allow ≥ 3 days of symptom reporting for adapted Mayo score calculation on Day 1**. This Screening Stage 2 endoscopic subscore, determined by central reading, will be used to calculate any clinical score for Day 1 that requires the endoscopic subscore. The centrally read endoscopic subscore will be used for all endpoints and for eligibility criteria to enroll a subject into the Induction and Maintenance Studies. Local reading of the endoscopic subscore will also be collected. The aMS will be calculated by the electronic tablet at all applicable visits.

[21] Centrally read endoscopic subscore from Week 8a visit will used to calculate adapted Mayo score to determine whether subject should undergo extended induction or continue into Maintenance Study depending on whether the subject meets criteria for clinical response at Week 8a. Centrally read endoscopic subscore from Week 16 visit will used to calculate adapted Mayo score to determine whether subject should continue into Maintenance Study or discontinue study drug and proceed to EOS visit depending on whether the subject meets criteria for clinical response at Week 16. Local reading of the endoscopic subscore will also be collected.

[22] All concomitant UC and non-UC medications (i.e., Prescription and over-the-counter medications, herbals, vitamins, and supplements) that were used within 60 days of screening, including name of medication, date started and stopped, route of administration, indication, and dose will be recorded.

[23] AE assessments are to include collection and reporting of AEs, SAEs, and AEs of Special Interest (AESIs). Please refer to protocol Section 7 for further details.

[24] PGA from Screening Stage 1 visit will be used for the partial Mayo score calculation as a guide to assess if subject should proceed with endoscopy at Screening Stage 2 visit. It is suggested that subjects with a partial Mayo score ≥ 3 (reflecting disease that is **at least moderate in severity**) should proceed

with endoscopy screening. This partial Mayo Score can be assessed at any time between Screening Stage 1 visit and Screening Stage 2 visit as long as there are **≥ 3 days of symptom reporting.** The pMS is calculated by the electronic tablet at the Screening Stage 2 visit page and it is recommended that this is completed before the subject proceeds with the Screening Stage 2 visit endoscopy.

[25] Subjects will be provided with an electronic diary at the Screening (Stage 1) visit and instructed on diary completion, including symptom monitoring and Study drug dosing details. Diaries of symptoms will be collected daily from Screening through the EOS visit.

[26] Diary completion will be monitored for completeness at each Study visit. Subjects will be counseled on missed Study drug doses and missed diary entries. Subjects who discontinue study drug early due to AE are permitted to optionally complete their daily diary through to the EOS visit.

[27] Subject will be randomized on Day 1 after all pre-dose procedures have been completed and subject is confirmed to be eligible for the Study. The adapted Mayo score criteria for randomization on Day 1 may be calculated within 48 hours of Day 1.

[28] Study drug administration will be in-clinic on Day 1, Week 4, Week 8b and Week 16. All study procedures must be done prior to drug administration with the exception of the **post-dose PK sample** and [redacted] **samples.** Refer to **footnote** 13 for the post-dose instructions for PK collections and **footnote** 15 for the [redacted] collection window. All other days, subjects will take study drug at home for the rest of the Induction period.

[29] Procedures may be done -3 to +7 days after week 8a visit (i.e., at the next visit, either Week 8b or mWeek0).

[30] [redacted]

[31] The adapted Mayo Score at these visits will be calculated by the electronic tablet using the symptoms in the applicable days prior to Day 1, Week8a or Week 16 and the centrally read endoscopy score. This will be available once the centrally read endoscopy score has been received by the site and entered into the electronic tablet.

[32] ECG at Day 1 is only required during the Phase 2b Dose-finding Induction study.

[33] If the Week 8b visit occurs out of window, the dates of subsequent visits will be based on the Week 8b visit start date to ensure a full 8 weeks of treatment in Extended Induction.

Note: See Appendix 11 for general guidance on study conduct during the coronavirus disease 2019 (COVID-19) pandemic. Variations from planned assessments will still constitute protocol deviations.

Table 2: Schedule of Study Procedures – Maintenance Study

Procedures	mWeek 0 [1]	mWeek 4	mWeek 12	mWeek 20	mWeek 28	mWeek 36	mWeek 44	Early Study Drug Discontinuation[2]	End of Study[3]
Window	+1 to +7 days after Week 8a or 16 visit	-3 to +5 days					- 3 to +2 days	+5 days	- 3 to + 5 days
Review Inclusion/Exclusion Criteria	X[4]								
Weight	X[15]						X	X	X
Vital Signs [5]	X	X	X	X	X	X	X	X	X
12-Lead ECG [6]	X[15]						X	X	X
Physical Examination [7]	X[15]	X		X			X	X	X
Plasma PK Samples [8]	X		X		X		X		
Concomitant Medication Review	X	X	X	X	X	X	X	X	X
Adverse Events Assessment [9]	X	X	X	X	X	X	X	X	X
Pregnancy Test (females of child-bearing potential only) [10]	X	X	X	X	X	X	X	X	X
Chemistry, Hematology	X[15]	X	X	X	X	X	X	X	X
Urinalysis	X[15]						X	X	
Overnight Fasting Lipid Panel	X[15]		X	X	X		X	X	X
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Endoscopy and Biopsies							X[17]		
[redacted]	[redacted]			[redacted]			[redacted]	[redacted]	
Whole Blood and Serum Biomarker Samples	X[15]	X			X		X	X	X
Physician Global Assessment (PGA)	X	X	X	X	X	X	X	X	X
Partial Mayo score	X	X	X	X	X	X	X	X	X
Adapted Mayo score							X		
Clinical Flare Assessment[12]		X	X	X	X	X			
Subject Diary Completion and Compliance Review [13]	X	X	X	X	X	X	X	X	X
[redacted]	[redacted]			[redacted]			[redacted]	[redacted]	

Table 2: Schedule of Study Procedures – Maintenance Study

Procedures	mWeek 0 (1)	mWeek 4	mWeek 12	mWeek 20	mWeek 28	mWeek 36	mWeek 44	Early Study Drug Discontinuation(2)	End of Study(3)
[redacted]	[redacted]			[redacted]			[redacted]	[redacted]	
[redacted]	[redacted]			[redacted]			[redacted]	[redacted]	
[redacted]	[redacted]			[redacted]			[redacted]	[redacted]	
Re-Randomization	X								
Study Drug Dispensing	X	X	X	X	X	X			
In Clinic Dosing - Study Drug Dosing	X(1)						X(14)		
Non-Site Study Procedures (Calculations for Programming/Statisticians and applicable suppliers)									
Partial Mayo score and PRO2 score calculation	X	X	X	X	X	X	X	X	X
Adapted Mayo score calculation	X						X		

Abbreviations: ECG, electrocardiogram; EOS, End of Study; [redacted]; PK, pharmacokinetic; PRO2, two-item patient reported outcome; [redacted]; LTS, Long Term Safety Study, (Protocol 0164); EOS, End of Study

Maintenance Studies:

1. Subject should be instructed to not take their allocated Induction Study drug at home on mWeek 0 to allow for in-clinic administration of the Maintenance study drug at this visit.
2. This visit is for subjects who prematurely discontinue the Study drug during the Maintenance phase and are not eligible for the 0164 LTS study. This visit will be conducted within 5 days of the last dose of Study drug. Subject will also return for the EOS visit for collection of safety data and assessment of disease activity four weeks after last study drug.
3. The EOS visit is only applicable to subjects who do not proceed to the 0164 LTS study.
4. Subject will be reassessed for inclusion specific to Maintenance Study.
5. Blood pressure and heart rate will be measured after the subject has been resting for at least 5 minutes in the seated or supine position. Vital sign measurements should be obtained prior to scheduled blood draws.
6. ECGs must be performed after the subject has been resting in a supine position for at least 10 minutes. ECG at mWeek0 needs to be performed only if none performed within the prior 14 days.
7. Physical Exam will be performed in accordance with local standard practice. (Section 6.4.1.19).
8. PK sampling will be performed in subjects at the following time points:

a. **mWeek 0** (n =2 samples): **One <u>predose</u>** and **one <u>postdose</u>** sample collected any time between 0.5 and 6 hours
b. **mWeek 12** and **mWeek 28 (n = 1 sample)**: One sample to be collected **anytime** during the clinic visit
c. **mWeek 44 (n = 3 samples): one <u>predose</u>**, and **two <u>postdose</u> samples** collected any time between 0.5 and 6 hours postdose and separated by at least 1 hour. **NOTE**: this PK sample should be obtained either **prior** to subject receiving bowel prep for endoscopy or **>24** hours post bowel prep

Predose samples will be taken within 1 hour prior to Study drug administration. Postdose sampling times are defined relative to the time of Study drug administration on the day of collection. All PK sampling times will be accurately recorded by collection date, hour, and minute. Study drug dosing time on the day **before each** PK collection will also be accurately recorded by dosing date, hour, and minute by the subject; Study drug dosing time on the day of each PK collection will be accurately recorded by dosing date, hour, and minute by the Study staff if drug is administered in the clinic or by the subject if drug is administered outside of the clinic.

9. AE assessments are to include collection and reporting of AEs, SAEs, and AEs of Special Interest (AESIs). Please refer to protocol Section 7 for further details.
10. Urine b-hCG testing will be performed before dosing when dosing in-clinic and anytime during all other visits for females of childbearing potential to confirm absence of pregnancy. If urine b-hCG test is positive, confirm with serum b-hCG test.
11. Fecal samples may be collected within 3 full days (approximately 72 hours) of the respective visits up to the end of the day following the visit (but before bowel preparation) and has to be delivered to the study site within 24 hours. It is preferable that these stool samples be collected during the first bowel movement in the morning.
12. Refer to Section 6.3.12 for further details on Clinical Flare Assessment Visits
13. Diaries of symptoms will be collected daily. Diary completion will be monitored for completeness at each Study visit. Subjects will be counseled on missed Study drug doses and missed diary entries. Subjects who discontinue study drug early due to AE are permitted to optionally complete their daily diary through to the EOS visit.
14. Study drug administration will be in-clinic on mWeek 44 visit after all pre-dose assessments [mWeek 44: All blood tests need to be collected and procedures have been completed prior to dose (except for post-dose PK blood collection and [redacted], which may be done post--visit)]. Subject will take the Study drug at home for the rest of the Study (including Clinical Flare Assessment Visits). On days of endoscopy (mWeek and Clinical Flare Assessment Visit 2, if applicable), study drug can be administered before or after endoscopy; if done before endoscopy, study drug will be taken with whatever the volume of water is allowed by the endoscopy team before endoscopic sedation.
15. Applicable assessments should be done only if not done within the prior 14 days.
16. [redacted].
17. The centrally read endoscopic subscore will be used for all endpoints and for eligibility criteria to enroll a subject into the Long-Term Safety Study. Local reading of the endoscopic subscore will also be collected.

Note: See Appendix 11 for general guidance on study conduct during the coronavirus disease 2019 (COVID-19) pandemic. Variations from planned assessments will still constitute protocol deviations.

Table 3: Schedule for Clinical Flare Assessment Visits

Procedures	**CFA Visit 1[1]**	**CFA Visit 2[1]**	**CFA Visit 3[1] [2]**
Window	**0 to 14 days of initial reporting**	**0 to 14 days after CFA Visit 1**	**8 weeks after CFA Visit 1** (window -3 to +5 days)
Vital Signs	X[5]		X
Physical Examination	X[5]		X
Concomitant Medications	X	X	X
Adverse Events Assessment	X	X	X
Chemistry, Hematology	X[5]		X[3]
[redacted]	[redacted]		[redacted]
[redacted]	X		
ECG			X[3]
Endoscopy		X	
PGA to calculate partial Mayo score	X		X
Adapted and total Mayo scores		X	
Subject Diary Completion and Compliance Review	X	X	X
[redacted]			[redacted]
[redacted]			[redacted]
[redacted]			[redacted]
[redacted]			[redacted]

Abbreviations: CFA; Clinical Flare Assessment

1. Refer to Section 6.3.12 for further details
2. Allowed window - 3 to + 5 days approximately 8 weeks after CFA Visit 1, i.e., within 10 weeks after initial reporting of symptom worsening.
3. These only need to be completed during the CFA visit 3 if subjects meet criteria to discontinue from study drug administration.
4. Stool can be collected up to 72 hours before to the end of the day following this visit. If investigator deems stool should be sent for infectious evaluation, that can be done, but it is not required.
5. Applicable assessments should be done only if not done within the prior 7 days.
6. [redacted]

Note: See Appendix 11 for general guidance on study conduct during the coronavirus disease 2019 (COVID-19) pandemic. Variations from planned assessments will still constitute protocol deviations.

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LIST OF ABBREVIATIONS

Abbreviation	Description
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANCOVA	analyzed by fitting analysis of covariance
AST	aspartate aminotransferase
BCG	Bacille Calmette Guerin
BCRP	breast cancer resistance protein
BMI	body mass index
BP	blood pressure
CFA	Clinical Flare Assessment
CFR	(United States) Code of Federal Regulations
CI	confidence interval
CMV	cytomegalovirus
COVID-19	coronavirus disease 2019
CRF	case report form
[redacted]	[redacted]
CYP	cytochrome P450
CSR	Clinical Study Report
DDI	drug-drug interaction
DNA	deoxyribonucleic acid
DVT	deep vein thrombosis
[redacted]	[redacted]
IDMC	independent data monitoring committee
ECG	electrocardiogram
eCOA	Electronic Clinical Outcome Assessments
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
EOS	End-of-Study
[redacted]	[redacted]
FDA	(United States) Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice

Abbreviation	Description
GI	gastrointestinal
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HDPE	high-density polyethylene
HPMC	hydroxypropyl methylcellulose
HR	heart rate
IDAP	Induction data analysis plan
IB	Investigator's Brochure
IBD	Inflammatory Bowel Disease
IC_{50}	quantity of a particular drug/substance needed to inhibit a given biological process by half
ICF	informed consent form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
INH	Isoniazid
INR	international normalized ratio
IRB	Institutional Review Board
IRSG	Independent Reporting Statistical Group
ITT	intent to treat
IUD	intrauterine device
JAK	Janus kinase
LTS	Long Term Safety Study
MAD	multiple ascending dose
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities (MedDRA®)
mITT	Modified intent-to-treat
MMRM	mixed model repeated measures
mRNA	messenger ribonucleic acid
mWeek	Maintenance Week
NK	natural killer
NOAEL	no-observed-adverse-effect level
OTC	Over-the-Counter
PA	posterior anterior

Abbreviation	Description
PD	Pharmacodynamics(s)
PI	principal investigator
P-gp	p-glycoprotein
PIC	powder in capsule
PK	pharmacokinetic(s)
pMS	partial Mayo score
PP	Per-Protocol
PPI	protein pump inhibitor
[redacted]	[redacted]
PT	Preferred Term
QD	Once daily
QTc	corrected QT interval
QTcF	Fridericia-corrected QT interval
REB	Research Ethics Board
RNA	ribonucleic acid
RR	Re-Randomized
RT-PCR	reverse transcriptase polymerase chain reaction
RTSM	randomization and trial supply management
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAS	Statistical Analysis System
SD	Standard Deviation
SF	Stool Frequency
SOC	System Organ Class
SOP	standard operating procedure
STAT	signal transducer and activator of transcription
TEAE	Treatment Emergent Adverse Event
TESAE	Treatment Emergent Serious Adverse Event
TB	Tuberculosis
TBPH	Theravance Biopharma
tMS	total Mayo score
TNF	tumor necrosis factor

Abbreviation	Description
UC	ulcerative colitis
ULN	upper limit of normal
WOCBP	Women of Childbearing Potential
[redacted]	[redacted]

DEFINITION OF TERMS

[redacted]

[redacted]

[redacted]

1. INTRODUCTION

1.1. Background and Rationale

[redacted]

1.2. Nonclinical Profile

A review of the nonclinical profile of TD-1473 can be found in the current version of the TD-1473 Investigator's Brochure (IB). The following is a brief summary of the pertinent findings.

1.3. Pharmacology

[redacted]

1.3.1. Toxicology

[redacted]

[redacted]

1.3.2. Pharmacokinetics

[redacted]

[redacted]

1.4. Clinical Experience

[redacted]

[redacted]

1.5. Risks and Benefits

TD-1473 is being evaluated for the treatment of inflammatory intestinal disorders. Tofacitinib, a systemic pan-JAK inhibitor, has demonstrated statistically significantly higher rates of remission compared to placebo[8]. However, given limited data from the Phase 1b Study in a small number of subjects with moderately-to-severely active UC treated with TD-1473 for 4 weeks, efficacy with TD-1473 in UC has not been established.

Some patients receiving repeated doses of tofacitinib, a systemic JAK inhibitor, have exhibited alterations in cholesterol (LDL, HDL, and total cholesterol), liver function tests, serum creatinine, decreased red blood cell and white blood cell (particularly neutrophils and lymphocytes) counts, infection (particularly herpes zoster and tuberculosis), cancer (including lymphoma), intestinal perforation, and thromboembolic events. In addition to these, diarrhea and rash have also been reported. However, given the anticipated relatively low systemic exposure of TD-1473, these risks are anticipated to be minimal in the current study.

In the Phase 1 Study in healthy volunteers, all treatment-emergent adverse events (TEAEs) in subjects dosed with TD-1473 (most commonly noted were headaches at 100 mg and 300 mg with similar or lower prevalence as placebo) were mild in severity and short in duration. In the Phase 1b Study in UC subjects, TD-1473 was generally well tolerated with only two adverse events (urticaria at 80 mg and papular rash at 20 mg) deemed by the Principal Investigator (PI) to be possibly related to Study drug; the adverse events were considered mild in severity in both cases and resolved within a few days after the last dose of study drug. No adverse event led to drug interruption or discontinuation. Similar to the healthy volunteer study, there were no adverse alterations in vital signs, electrocardiogram parameters, or laboratory evaluations relative to placebo. There have been additional Phase 1 studies in healthy volunteers that, together, have not yielded a repeated pattern of TEAEs frequently observed in every study.

The potential risks described in this section will be carefully assessed during the Study. Assessments include scheduled physical exams, and frequent monitoring of complete blood cell counts with differential, kidney and liver function, and fasting cholesterol panel. The clinical and laboratory observations planned for this clinical trial are sufficient to monitor for the key observations noted in the nonclinical evaluation of TD-1473 at doses relevant to this Study as well as many of the effects noted with use of tofacitinib.

The current protocol requires pregnancy prevention measures for a duration of the study from Screening Stage 1 visit to 7 days after the last dose of Study medication for both male and female subjects. The 7 day-duration for pregnancy prevention measures after the last dose is to ensure that TD-1473 is eliminated from the systemic circulation (i.e., ~ 5 half-lives) before conception to avoid potential exposure to a developing embryo/fetus. This is based upon the following 4 considerations: 1) TD-1473 is not genotoxic, 2) in the definitive embryo-fetal developmental toxicity studies there was no evidence of direct embryo-fetal toxicity or teratogenicity up to 1000 mg/kg/day and 60 mg/kg/day in rats and rabbits, respectively, 3) systemic exposures in Study subjects 7 days after the last dose are estimated to be >150-fold below the exposures in rats or rabbits at doses without significant findings (1000 mg/kg/day and 60 mg/kg/day in rats and rabbits, respectively), and 4) TD-1473 was not measurable in fetal blood in animals treated with TD-1473.

Pregnancy prevention measures in men are typically recommended when there are concerns about genotoxicity. If a compound is genotoxic, there is a need to require effective contraceptive use for male subjects during exposure and for five terminal half-lives- plus 74 days (one human spermatogenesis cycle).[9] For small molecules with genotoxic potential, taking into account a spermatogenesis cycle is essential given the potential for DNA damage or impairment of chromosome replication which may be passed on to progeny at conception when damage occurs to genetic material of germ cells. However, TD-1473 has been shown to be non-genotoxic in a standard battery of genotoxicity assays; thus, ensuring a spermatogenesis cycle has elapsed is not required. Therefore, since accounting for a spermatogenesis cycle is not necessary and for simplicity matching the timeframe required for females, the Sponsor has incorporated a requirement for pregnancy prevention procedures and avoidance of semen donation to be followed by all males for 7 days after the last dose of study drug.

2. OBJECTIVES

This single protocol includes three randomized, double-blind, and placebo-controlled studies: a Phase 2b dose-finding Induction Study, a Phase 3 dose-confirming Induction Study, and a Phase 3 randomized-withdrawal Maintenance Study in subjects with moderately-to-severely active UC. Subjects from both the Phase 2b and Phase 3 induction studies who achieve clinical response at Week 8 based on adapted Mayo score are eligible to enroll into the Maintenance Study.

Phase 2b Dose-Finding Induction Study

The objectives of the Study are as follows:

- Assess the effect of TD-1473 taken daily for 8 weeks at daily doses of 20 mg, 80 mg, and 200 mg on the change in total Mayo score
- Assess the effect of TD-1473 on rates of clinical remission, endoscopic healing, clinical response, and mucosal (i.e., histologic and endoscopic) healing
- Upon completion, select dose(s) of TD-1473, based on safety, tolerability, and efficacy data, including exposure-response data, for continued evaluation in the Phase 3 dose-confirming Induction Study and the Phase 3 Maintenance Study

Phase 3 Dose-Confirming Induction Study

Following completion of Phase 2b Induction Study enrollment, recruitment will be placed on hold until the Phase 2b Induction study analysis is complete and dose selection is made. The Phase 3 Induction Study will commence after dose selection. Assuming one TD-1473 dose is selected, it is estimated that approximately 640 subjects (final number to be determined after the Phase 2b Induction Study data analysis is completed) will be randomized in a 1:1 ratio to placebo into the Phase 3 Induction Study.

The primary objectives are:

- Assess the clinical remission rates associated with TD-1473 compared to placebo treatment at Week 8
- Assess the safety and tolerability of TD-1473 taken for up to 16 weeks

The key secondary objective(s) of the Study are to assess the rates of the following associated with TD-1473 compared to placebo treatment:

- Endoscopic healing, symptomatic remission, clinical response, mucosal healing (endoscopic and histologic), and deep symptomatic remission at Week 8

Additional objectives:

- [redacted]

Phase 3 Maintenance Study

The primary objectives of the Study are as follows:

- Assess the clinical remission rates associated with TD-1473 compared to placebo treatment at mWeek 44
- Assess the safety and tolerability of TD-1473 with up to 44 additional weeks of treatment

The key secondary objectives of the Study are to assess the rates of the following associated with TD-1473 compared to placebo treatment:

- Clinical response, endoscopic healing, symptomatic remission, mucosal healing, and deep symptomatic remission at mWeek 44
- Corticosteroid-free remission at mWeek 44
- Maintenance of clinical remission at mWeek 44 in those who were in clinical remission at mWeek 0

3. STUDY DESIGN

3.1. Overview

This single protocol includes three studies: a Phase 2b dose-finding Induction Study, a Phase 3 dose-confirming Induction Study, and a Phase 3 randomized-withdrawal Maintenance Study (Figure 1). Each of the three studies will utilize a multi-center, randomized, double-blind, placebo-controlled, parallel-group design to evaluate various dose(s) of TD-1473 compared to placebo in subjects with moderately-to-severely active UC. The Induction Studies will target subjects with moderately-to-severely active UC who demonstrate an inadequate response or failure to tolerate conventional or biologic therapy. The Maintenance Study will be a randomized withdrawal study targeting subjects with moderately-to severely-active UC who demonstrate a clinical response to induction treatment with TD-1473.

Induction Studies:

To determine initial eligibility, subjects will undergo assessments during the Screening Stage 1 period. Refer to Schedule of Study Procedures (Table 1) for a schedule of the Screening requirements. Disease activity will be assessed by the total, adapted, and partial Mayo scores and PRO2 score. Subjects who meet inclusion and no exclusion criteria, as described in Section 4, will undergo an endoscopic exam (i.e., sigmoidoscopy or colonoscopy) with biopsies to complete screening Stage 2.

If the subject meets all eligibility criteria, including a centrally read Mayo endoscopic subscore ≥ 2 during Screening Stage 2 and an adapted Mayo score between 4 and 9, inclusive, on Day 1, the subject may be randomized. The randomization will be stratified by prior biologic failure status and corticosteroid use at enrollment into the Induction Study. Biologic failure is defined as having demonstrated primary or secondary non-response or intolerance to one or more biologics (i.e., anti-TNF and anti-integrin), as described in more detail in Appendix 7.

The Induction Studies consist of treatment for: a) 8 weeks for those who demonstrate clinical response at Week 8 and b) 16 weeks for those who do not, during which, subjects will return for safety, PK, biomarker, and disease assessments, as well as a endoscopy with biopsies according to the Schedule of Study Procedures provided in Table 1.

Subjects who do not demonstrate clinical response at Week 8 will receive an additional 8 weeks of treatment during an extended induction period. Those that had been randomized to TD-1473 during the first 8 weeks will remain on the same dose; those who received placebo during the first 8 weeks will receive TD-1473 80 mg from Week 8 to 16. This portion of the Induction Study will not be placebo-controlled but blinding as to the specific dose of TD-1473 will be maintained. Those who demonstrate clinical response at Week 16 will enter the Maintenance Study; those who do not exit the study.

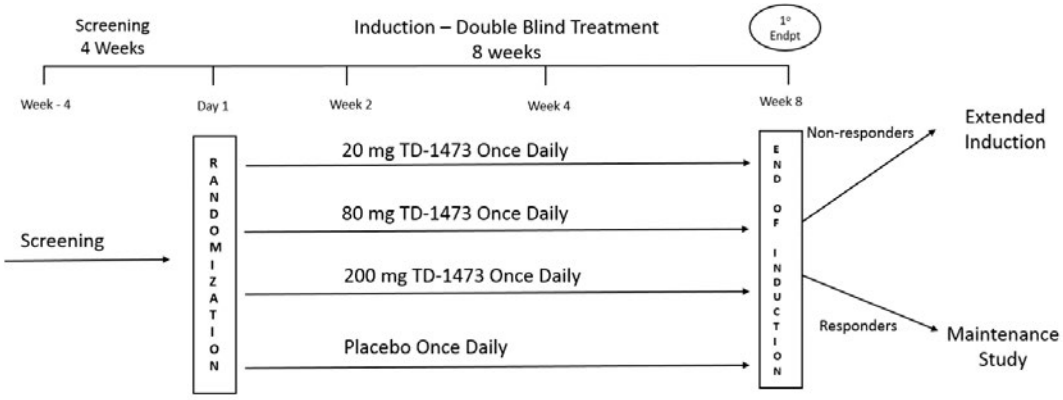
Randomization ratios and dosing regimens are described below:

a) Phase 2b Dose-Finding Induction Study

The Phase 2b-Dose Finding Induction Study (Figure 2) will enroll approximately 240 subjects, randomized 1:1:1:1 to placebo or 1 of the 3 active TD-1473 doses (20 mg,

80 mg or 200 mg). After all 240 subjects have either completed the Week 8 visit or terminated participation prior to Week 8, an analysis of all efficacy and safety data up to Week 8 will be performed (Refer to Section 8). Results from this analysis will be used to inform the dose selection for the Phase 3 dose-confirming Induction Study and the remainder of the Phase 3 Maintenance Study, which would be ongoing at that time.

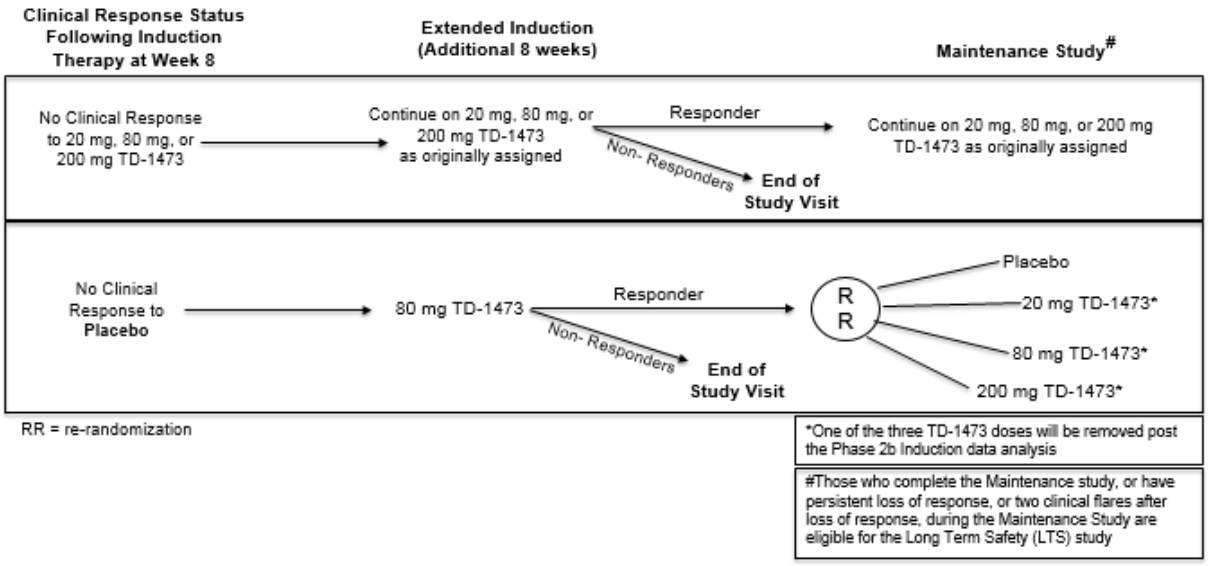
Figure 2: Phase 2b Dose-Finding Induction Study



b) EXTENDED INDUCTION

Subjects who do not demonstrate clinical response at Week 8 will receive an additional 8 weeks of treatment with active drug staying on the same dose of TD-1473 as the first 8 weeks, and those who had received placebo during the first 8 weeks will now receive TD-1473 at 80 mg (Figure 3). All subjects who undergo extended induction treatment will receive active drug, and thus, this portion of the Induction Study will not be placebo-controlled but blinding as to the specific dose of TD-1473 will be maintained. During this time, at the discretion of the investigator, subjects are permitted but are not required to begin corticosteroid taper. Those who demonstrate clinical response at Week 16 will enter the Maintenance Study; those who do not demonstrate clinical response at Week 16 will have an EOS visit and exit the study.

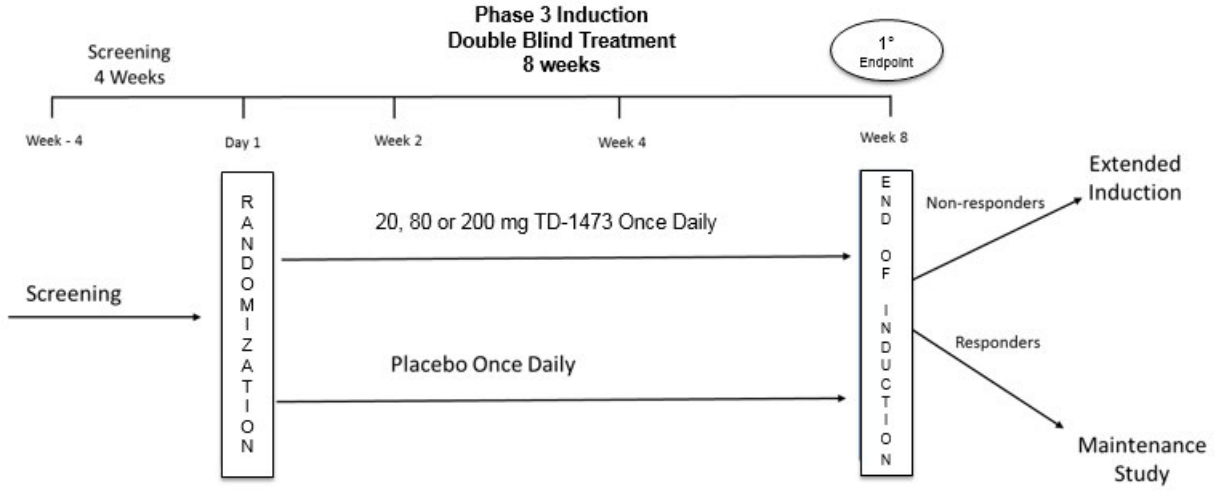
Figure 3: Extended Induction Treatment Regimen



Phase 3 Dose-Confirming Induction Study

The Sponsor plans to identify 1 dose for the Phase 3 dose-confirming Induction Study, guided by the results of the Phase 2b Induction Study. The Phase 3 Induction Study will not begin until an induction dose has been selected. In that study, a to-be-determined number of subjects (currently estimated as 640, but the final number will be determined after the Phase 2b Induction Study data analysis is completed) will be randomized in a 1:1 ratio to placebo or TD-1473. The Phase 3 Induction Study has the same study design as the Phase 2b Induction Study, with the exception of the number of treatment arms.

Figure 4: Phase 3 Dose-Confirming Induction Study Schema



PHASE 3 MAINTENANCE STUDY

Subjects who are considered to have achieved clinical response by adapted Mayo score (Refer to DEFINITION OF TERMS) using centrally read endoscopic subscore at either Week 8 or Week 16 during the Induction studies will continue in the Maintenance Study:

- Subjects who achieved clinical response on TD-1473 during induction at Week 8 will be re-randomized into the Maintenance Study to placebo or one of the TD-1473 doses and contribute to the primary efficacy analysis population of the Maintenance Study.
- Subjects who achieved clinical response on placebo during Induction at Week 8 will continue to receive placebo in the Maintenance Study in a blinded manner to maintain blind. However, these subjects will not be included in the primary efficacy analysis population of the Maintenance Study.
- Subjects who did not achieve clinical response by adapted Mayo score using centrally read endoscopic subscores to the first 8 weeks of induction treatment but responded at Week 16 will continue into the Maintenance Study:
  - Subjects who received 8 weeks of placebo and 8 weeks of TD-1473 80 mg will be re-randomized into the Maintenance Study to placebo or one of the TD-1473 doses and contribute to the primary efficacy analysis population of the Maintenance Study.
  - Subjects who received 16 weeks of TD-1473 during Induction will continue to receive same dose of TD-1473 in the Maintenance Study in a blinded manner to maintain blind. However, these subjects will not be included in the primary efficacy analysis population of the Maintenance Study.

In summary, subjects who demonstrate clinical response to a total of 8 weeks of TD-1473 induction therapy, either at Week 8 or Week 16, will be re-randomized. Those who demonstrate response to placebo at Week 8 or those who demonstrate response to a total of 16 weeks of TD-1473 treatment at Week 16 will enter the Maintenance Study on the same study drug treatment as during Induction for the purpose of maintaining blinding. The Maintenance Study consists of treatment for 44 weeks. During the Maintenance Study, subjects must taper their corticosteroid dose using the regimen outlined in Section 6.5.3 if they entered the study on corticosteroids.

Before the Phase 2b Induction Week 8 primary data analysis and subsequent dose selection, responders to a total of 8 weeks of TD-1473 from the 240 subjects in Phase 2b Induction Study will be re-randomized 1:1:1:1 to placebo or 1 of the 3 active TD-1473 doses (20 mg, 80 mg or 200 mg) when they roll over into the Maintenance Study.

After the Phase 2b Induction Week 8 primary data analysis and subsequent dose selection have been completed, subjects enrolling into the Phase 3 Maintenance Study will be randomized to either placebo or 1 of the 2 selected doses of TD-1473 doses in a 1:1:1 ratio. Those who are still completing the Maintenance Study on a de-selected dose will remain on that dose unless there is a concerning safety signal detected up to point of dose selection, in which case, they will be transitioned to the closest of the doses that have been selected. The Sponsor plans to identify

2 doses for the Phase 3 dose-confirming Maintenance Study, guided by the results of the Phase 2b Induction Study.

The randomization will be stratified by clinical remission status at mWeek 0 using adapted Mayo score component definition, and corticosteroid use at enrollment into the Phase 3 Maintenance Study. In addition, randomization will also be stratified by subjects who reach clinical response after receiving 8 weeks of TD-1473 versus subjects who reach clinical response after receiving placebo during the first 8 weeks and then TD-1473 80 mg during extended induction.

In order to maintain blind, subjects who achieved clinical response on placebo during Induction at Week 8, or subjects who achieved clinical response on TD-1473 after 16 weeks of treatment will continue to receive the same treatment as assigned in the Induction study in the Maintenance study in a blinded manner. These subjects will not be re-randomized, nor would they be included in the primary efficacy analysis population of the Maintenance Study.

It is currently estimated that 880 subjects enrolled in the Induction Studies (240 subjects from Phase 2b and 640 subjects from Phase 3) will result in approximately 360 subjects eligible to be re-randomized into the Phase 3 Maintenance Study. This number will be re-evaluated after the results from the Phase 2b Induction data are available.

Figure 5: Phase 3 Maintenance Study Treatment Regimen

During the Maintenance Study, subjects will return for safety, PK, biomarker, and disease assessments, as well as a final endoscopy with biopsies according to the Schedule of Study Procedures provided in Table 2. Subjects who experience an increase (Refer to DEFINITION OF TERMS) of their symptoms during the Maintenance Study will undergo assessment for Clinical Flare and loss of response as per Table 3. Loss of response may lead to initiation of rescue medication (e.g., initiation or increase in corticosteroid dose [Refer to Section 6.5.3]). Subjects who have completed the Maintenance Study or experience persistent loss of response despite permitted rescue medication, or repeated Clinical Flare twice after loss of response, may enter the Long Term Safety (LTS) Study (Protocol 0164) if they meet the applicable eligibility criteria. Subjects who do not enter into the 0164 LTS Study will need to complete an End of Study visit 4 weeks after the last dose of study drug.

Long Term Safety (LTS) Study (Protocol 0164)

The following subjects may be eligible to enter the 0164 LTS Study if they meet the applicable eligibility criteria, (refer to Protocol 0164 for complete list of inclusion and exclusion criteria):

- Those who have completed the Maintenance Study
- Those who demonstrated persistent loss of response (no improvement approximately 6-8 weeks after meeting loss of response criteria) or two Clinical Flares after an episode of loss of response during the Maintenance Study.

3.2. Rationale for Study Design

[redacted]

[redacted]

3.3. Selection of Dose Ranges and Duration of Treatment

[redacted]

[redacted]

3.4. Study Endpoints

3.4.1. Phase 2b Induction Efficacy Endpoints

Refer to DEFINITION OF TERMS

Primary:

- Change in total Mayo score from baseline at Week 8

Key Secondary (with multiplicity control):

- Clinical remission by adapted Mayo score components at Week 8

Additional:

[redacted]

[redacted]

3.4.2. Phase 3 Induction Efficacy Endpoints

Primary:

- Clinical remission by adapted Mayo score components at Week 8

Key Secondary (with multiplicity control):

- Endoscopic healing at Week 8
- Symptomatic remission at Week 8
- Clinical response by adapted Mayo score definition at Week 8
- Mucosal healing at Week 8
- Deep symptomatic remission at Week 8

Additional:

[redacted]

[redacted]

3.4.3. Phase 3 Maintenance Efficacy Endpoints

Primary:

- Clinical remission by adapted Mayo score components at mWeek 44

Key Secondary (with multiplicity control):

- Maintenance of clinical response by adapted Mayo score at mWeek 44
- Endoscopic healing at mWeek 44
- Symptomatic remission at mWeek 44
- Corticosteroid-free remission at mWeek 44
- Maintenance of clinical remission at mWeek 44 in those who were in clinical remission at mWeek 0
- Mucosal healing at mWeek 44
- Deep symptomatic remission at mWeek 44

Additional:

[redacted]

[redacted]

3.4.4. Safety Endpoints

Incidence and severity of treatment-emergent adverse events (defined in Section 8.8.2); changes in laboratory safety test results, ECG intervals and abnormalities, and vital sign measurements.

3.5. Minimization of Bias

Bias will be minimized through the use of randomization, blinding, and inclusion of a placebo group.

3.5.1. Blinding

When the data for the Phase 2b Induction Study are unblinded for dose selection, data from subjects in the Maintenance Study will remain blinded. In order to maintain blind of treatment assignments in the Induction Study, treatment assignments in the Maintenance Study will be assigned by RTSM for those who are eligible for re-randomization to receive placebo or one of the TD-1473 doses, and those who continue to receive the same treatment as assigned in the Induction Study without re-randomization.

Subjects who achieved clinical response on placebo during Induction at Week 8, or subjects who achieved clinical response on TD-1473 after 16 weeks of treatment will continue to receive the same treatment as assigned in the Induction study in the Maintenance study in a blinded manner. The RTSM system will be designed to ensure that the user interface is identical for subjects who are re-randomized into the Maintenance Study and subjects who enter the Maintenance Study without being re-randomized, and hence cannot reveal whether re-randomization has occurred. For instance, sites will be required to report steroid use status at enrollment into the Maintenance Study for all subjects, rather than only those subjects whose Maintenance Study randomization stratum must be determined.

TD-1473 and placebo tablets will be of the same shape, size, and color to ensure that the blind is maintained. Also, subjects who are randomized to receive placebo will receive the equivalent number of tablets as those randomized to receive TD-1473.

A subject's treatment assignment will only be unblinded when knowledge of the treatment is essential for the further clinical management of the subject on this study or may potentially impact the safety of subjects currently enrolled or subjects in subsequent enrollment. Unblinding at the Study site for any other reason will be considered a protocol deviation. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a subject's treatment assignment is warranted, and unblinding could be done through the RTSM system. Subject safety must always be the first consideration in making such a determination. Any investigator unblinding will be documented within the appropriate CRF and will be captured in the RTSM system.

Sponsor Drug Safety personnel may independently unblind cases for expedited reporting of suspected unexpected serious adverse reactions (SUSARs). Sponsor personnel involved in the conduct of the Study, data cleaning, or data analysis will remain blinded to subject treatment assignments until each database has been locked for final analysis. Currently, it is estimated that there will be 3 final analyses conducted: 1) after 240 subjects either completed the Week 8 assessment or prematurely withdrew from the Phase 2b Induction Study, 2) at the conclusion of the Phase 3 Induction Study, and 3) at the conclusion of the Phase 3 Maintenance Study.

To facilitate PK analysis, PK data may be provided in a blinded fashion (i.e., PK data cannot be linked to an individual subject) to the Sponsor for analysis or analyzed by an independent exposure-response analyst in an unblinded fashion and provided to the Sponsor for interpretation. If PK data are to be analyzed by an independent exposure-response analyst, a guidance document detailing the procedures to maintain the Sponsor's blind will be written. For clarity, this independent exposure-response analyst may be either an external company or an individual or group within the Sponsor who are separate from the clinical Study team.

3.5.2. Treatment Assignment

Once the subject has been determined to be eligible to receive Study treatment, the PI or their delegate will use the RTSM system to randomize the subject and dispense Study drug. Four sets of randomization schedules will be prepared to support study conduct before and after dose selection:

- Initial Induction schedules
- Induction schedules modified to include only the active dose(s) selected for continued evaluation for Induction
- Initial Maintenance schedules
- Maintenance schedules modified to include only the active dose(s) selected for continued evaluation for Maintenance

Subjects who achieved clinical response on placebo during Induction at Week 8, or subjects who achieved clinical response on TD-1473 after 16 weeks of treatment are not eligible to be re-randomized into the Maintenance study. They will continue to receive the same treatment as assigned in the Induction study in the Maintenance study in a blinded manner.

The Phase 2b and Phase 3 Induction Study randomizations will be stratified by prior biologics failure status and corticosteroid use at enrollment into the Induction Studies (4 strata). Biologic failure is defined as having had primary or secondary non-response or intolerance to biologics therapy.

Randomization of the Maintenance Study will be stratified by 3 stratification factors (8 strata): 1) clinical remission status using adapted Mayo score component definition, 2) corticosteroid use at enrollment into the Maintenance Study (4 strata), and 3) subjects who achieved clinical response on TD-1473 during Induction at Week 8 versus subjects who reach clinical response after receiving placebo during the first 8 weeks and then TD-1473 80 mg during extended induction.

All individual-stratum randomization schedules will be reproducible (through use of a prespecified random number seed) sequences of randomly permuted treatment assignment blocks, generated or reviewed by a Sponsor statistician not involved in the conduct of the Study.

Randomization schedule requirements such as block sizes and the method of generating pseudorandom numbers will be specified in a randomization specifications document. Except for cases of emergency unblinding as described above, investigational site staff will remain blinded to treatment assignments until all Study (Induction and Maintenance) databases have been finalized AND locked.

For the Phase 2b and Phase 3 Induction studies, the RTSM system will implement enrollment caps designed to ensure that at least 40% of subjects will have a history of prior biologics failure and at least 40% of subjects will not have a history of prior biologics failure [Section 4.1]. These enrollment caps will be “soft caps,” i.e., the system will be designed to send notifications that an enrollment cap is being approached and enrollment will be closed to subjects in the overrepresented category only after confirmation is received from the Sponsor.

Further details regarding the randomization procedure will be provided in the RTSM system manual.

3.6. End of Trial Definition

The end of the study is defined as the date of the global, **last subject study visit** (including the 4 week follow up visit) in the Phase 3 Maintenance study.

4. STUDY POPULATION

The study population consists of subjects with moderately-to-severely active UC as defined by an adapted Mayo score between 4 and 9 with a Mayo endoscopic subscore ≥ 2 who are corticosteroid-dependent or had intolerance or demonstrate an inadequate response or loss of response to conventional therapy (aminosalicylates, corticosteroids or immunomodulators) [i.e., as azathioprine or 6-mercaptopurine] or biologics [i.e., anti-TNF-therapy or anti-integrin].

4.1. Induction Studies and Maintenance Study Inclusion Criteria

To be eligible subjects must meet all the following criteria:

1. Are male or female 18 years of age or older at Screening
2. Has ≥ 3 months history of UC prior to screening (with involvement beyond the rectum to at least 15 cm from the anal verge)
    a. Diagnosed by sigmoidoscopy or colonoscopy AND
    b. If possible, corroborated by histology report or documentation of histological results in a physician note. However, if there was no biopsy done previously or if no prior endoscopy or histology report is available for review, the subject must have a colonoscopy instead of a sigmoidoscopy at screening.
3. Must be willing to have a sigmoidoscopy or colonoscopy at screening. Colonoscopy will be performed instead of a sigmoidoscopy at screening in the following scenarios, (outlined in Section 6.4.1.20):
    a. If UC diagnosis precedes screening by ≥ 8 years for pan-colitis or ≥12 years for left-sided colitis and the subject does not have documentation of a surveillance colonoscopy within 12 months prior to screening to rule out dysplasia (report must be reviewed by the investigator and included in the source documents). During colonoscopy, if chromoendoscopy or surveillance biopsies are indicated as per locally adopted guidelines, these should be performed.
    b. If UC diagnosis precedes screening by < 12 years and the subject does not have documentation of a colonoscopy within 2 years prior to screening (report must be reviewed by investigator and included in the source documents).
    c. If there is no documented pathology report from prior endoscopy showing chronic colitis or other signs of UC. In this case, consideration should be made to do biopsies during the screening endoscopy with histology sent locally to confirm diagnosis of UC, if there is doubt of diagnosis

    If chromoendoscopy has to be performed or ≥ 10 biopsies are to be collected for dysplasia surveillance, either should be done after completion of a full colonoscopy to avoid chromoendoscopy dye or biopsy-related bleeding artifact from interfering with endoscopic images for central reading.
4. Has moderately-to-severely active UC, defined as having
    a. a centrally read Mayo endoscopic sub score of ≥ 2 points based on the results of the Screening Stage 2 endoscopy

    AND

b. an adapted Mayo score between 4 and 9 points, inclusive, on Day 1.

5. Is corticosteroid-dependent or had intolerance or inadequate response to any of the following: aminosalicylates, corticosteroids, immunomodulators (azathioprine or 6-mercaptopurine), or biologics (anti-TNF, anti-integrin, or anti-IL-12/23) [Refer to Appendix 7].

   NOTE: For subjects in **Portugal**, subject must have had intolerance or inadequate response to biologics.

6. If currently receiving an oral corticosteroid, subject is eligible if:

   a. the subject has been on corticosteroids for a minimum of 4 weeks prior to Day 1 ***AND***
   b. the dose is equivalent to or less than:
      - prednisone 25 mg/day ***OR***
      - beclomethasone diproprionate (i.e., Clipper) at 5 mg/day ***OR***
      - budesonide 9 mg/day

      AND
   c. the dose is stable for at least 2 weeks prior to Screening Stage 2 visit

7. If subject is currently receiving oral aminosalicylate (e.g., mesalamine products, balsalazide, or sulfasalazine): subject is eligible provided the subject has been on it at a stable dose for ≥ 4 weeks prior to Day 1.

8. During the Study and for 7 days after receiving the last dose of the Study drug, females of childbearing potential or men capable of fathering children must agree to use highly effective birth control measures (failure rate <1% when used consistently and correctly) or agree to abstain from sexual intercourse. Females of childbearing potential must test negative for pregnancy at screening and at Day 1 (Refer to Section 4.3).

9. All male subjects must agree to refrain from semen donation during the Study and for 7 days after the last dose of Study drug.

10. Must be able and willing to adhere to the Study visit schedule and comply with other protocol requirements.

11. Are capable of providing informed consent, which must be obtained prior to any Study-related procedures.

Inclusion Criteria for Extended Induction (additional 8 weeks):

12. Did not meet criteria for clinical response by adapted Mayo score using centrally read endoscopic subscore at Week 8a

Inclusion Criteria for Maintenance Study:

13. Must have met the criteria for a clinical response by adapted Mayo score using centrally read endoscopic subscore during Induction at Week 8a or during Extended Induction at Week 16

4.2. Induction Studies and Maintenance Study Exclusion Criteria

Subjects meeting any of the following criteria may not be enrolled in the Study:

Gastrointestinal:

1. Has symptoms or signs suggestive of fulminant colitis, toxic megacolon, intestinal perforation
2. Has primary sclerosing cholangitis (PSC)
3. Is likely to require surgery for UC or any other type of major surgery (i.e., surgical procedure requiring general anesthesia) during the Study
4. Has had a clinically significant, as deemed by the investigator, prior intestinal resection for UC or for other gastrointestinal diseases (e.g., that may have resulted in chronic diarrhea)
5. Has carried or carries a diagnosis of Crohn's disease, microscopic colitis, ischemic colitis, radiation colitis, diverticular disease associated with colitis, or indeterminate colitis, or the subject has a current or past diagnosis of a fistula or abdominal abscess.
6. Has unresected colonic mucosal dysplasia or history of resected high-grade colonic dysplasia within 3 years prior to screening (Subjects with raised adenomas that have been completely resected or with pathology results of indefinite dysplasia with reactive atypia will not be excluded).

Concomitant or previous medications received:

7. Taken or taking any prohibited medications as listed in Appendix 6, including:
   a. Immunomodulators (azathioprine, 6-mercaptopurine [6-MP], methotrexate) within the 14 days prior to Day 1
   b. anti-TNFs (e.g., adalimumab, infliximab, golimumab, etanercept, certolizumab, or biosimilars) taken within the 60 days or 5 half-lives, whichever is longer, prior to Day 1
   c. intravenous corticosteroids within the 14 days prior to Day 1
   d. rectal mesalamine or corticosteroid (i.e., enemas or suppositories) taken within the 14 days prior to Day 1
   e. vedolizumab, ustekinumab, mycophenolic acid, tacrolimus, sirolimus, or cyclosporine taken within 60 days or 5 half-lives, whichever is longer, prior to Day 1
   f. Any prior exposure to an approved JAK inhibitor (e.g. tofacitinib) or potential exposure to an experimental JAK inhibitor that was stopped due to intolerance or lack of efficacy; This does not include subjects with prior exposure to another JAK inhibitor that was stopped for any other reason (e.g., loss/lack of insurance coverage)
   g. Any prior exposure to natalizumab, rituximab, efalizumab, fingolimod, daclizumab cyclophosphamide, or thalidomide

h. NSAIDs taken on a regular (more than 3 times per week, on average) basis (regular use of aspirin ≤ 325 mg per day for cardiovascular protection is allowed).

i. Anakinra, abatacept, or any other immune-modifying biologic agent taken within 90 days prior to Day 1

j. A JAK inhibitor (e.g., Tofacitinib) within 60 days prior to Day 1

k. Any prior exposure to TD-1473

Note: For biologics specified in items b and e above, there is no requirement for a washout period if there is a documented finding of undetectable drug level by a validated assay (e.g., through commercially available testing).

8. If subject has recently discontinued aminosalicylates or corticosteroids, these must have been stopped at minimum of 2 weeks before screening endoscopic procedure.

9. Has had inadequate response (i.e., either primary or secondary non-response) to ≥ 3 biologics of ≥ 3 different mechanisms of action (i.e., anti-TNF, anti-integrin, and anti-IL12/23, refer to Appendix 8).

   Note: Up to approximately 10% of the study population can have had inadequate response to all 3 biologics mechanisms approved for UC, regardless of total number of biologics.

10. Currently taking or has taken within 14 days prior to Day 1 any concomitant medication, herbal supplement or dietary substance (e.g., grapefruit) known to be a strong inhibitor or inducer of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), or CYP450 3A4 or is a substrate of P-gp or BCRP and has a narrow therapeutic index (refer to Appendix 6 for Prohibited medications).

11. Taking non-UC concomitant prescription medications that the investigator deems may confound the safety assessment of the study drug and that have started or have had a dose adjustment within 28 days prior to Day 1 (with the exception of corticosteroids, antibiotics for infections, sedating agents for sigmoidoscopy or colonoscopy, hormonal contraceptives, hormone replacement therapy, iron, vitamin D, insulin therapy, and replacement thyroid hormone - Refer to Appendix 6 for Prohibited medications). Anti-diarrheal medications and probiotics are allowed only if dose has been stable for minimum of 14 days prior to Day 1.

12. Taking over-the-counter medications or dietary supplements that the investigator deems may confound the safety assessment of the study drug and that have started or have had a dose adjustment within 14 days prior to Day 1 with the exception of up to 3 times per week use of non-steroid anti-inflammatory drugs or acetaminophen used on an as needed basis, aspirin ≤ 325 mg per day for cardiovascular prophylaxis, and over the counter doses of vitamin D, (Refer to Appendix 6 for Prohibited medications).

Infections or predisposition to infections

13. Subject is positive for:

    a. Hepatitis B virus (HBV) surface antigen

b. Hepatitis B virus core antibody (unless subject has positive hepatitis B surface antibody and undetectable serum hepatitis B DNA).
c. Hepatitis C virus (HCV) antibody unless: a) there is evidence of undetectable viral load measured twice six months apart after successful completion of treatment regimen (reviewed by Study Medical Monitor) and b) viral load during Screening is undetectable
d. Hepatitis E Immunoglobulin M (IgM) antibody
e. Human immunodeficiency virus (HIV) antibody

14. Subject has had a live viral vaccine (e.g., MMR, varicella zoster, herpes zoster, oral polio virus, FluMist®, attenuated typhoid fever vaccine, attenuated rotavirus vaccine, yellow fever vaccine, or any investigational live vaccine) within 4 weeks prior to screening and/or is unwilling or unable to avoid live viral vaccines during the Study and for 8 weeks following completion of the Study. Subject must be willing to avoid contact with any household member who has been vaccinated with a live attenuated vaccine within 2 weeks after vaccination.

15. Has or may have untreated active or latent TB as evidenced by any of the following:

a. Two indeterminate or one positive QuantiFERON®-TB Gold result within 90 days prior to Screening Stage 1 or during the Screening Period (Stage 1/Stage 2), without having completed an adequate treatment for latent or active TB before screening, **or**

b. Chest X-ray or equivalent chest imaging within 90 days prior to screening in which active or latent pulmonary TB cannot be excluded.

c. Subject who has a history of latent or active tuberculosis (TB) may be included if criteria outlined in Section 6.4.1.11 are met.

Note: In case of a suspected false positive QuantiFERON®-TB Gold result (e.g., a negative result by the local laboratory and suspicion of sample processing error, both of which must be documented in the source document), a second sample may be sent to the central laboratory and the result of the second test will be used.

16. Has any of the following:

a. An active, clinically significant, bacterial, parasitic, fungal, mycobacterial (including atypical infection), or viral infection, except for local skin or nail bed infection, within 2 weeks prior to Day 1.
b. Any infection requiring intravenous antibiotics within 30 days prior to screening.
c. Any infection requiring oral antimicrobial treatment within 2 weeks prior to Day 1.
d. A history of more than two episodes of herpes zoster or one or more episodes of disseminated/complicated herpes zoster (complicated: multi-dermatomal, ophthalmic, or CNS involvement or post-herpetic neuralgia) or disseminated herpes simplex.
e. Has had a chest radiograph or equivalent chest imaging within 90 days prior to Screening or at Screening that shows an abnormality suggestive of a malignancy of current active infection, including TB, chronic lung disease or a potentially active fungal, viral, or bacterial infection.

f. Has C. difficile or other gastrointestinal infections (e.g., Salmonella, Shigella, Yersinia, Campylobacter, E. coli 0157, etc.) on stool testing or cytomegalovirus (CMV) colitis suspected on endoscopy within 30 days of Day 1.

17. Has ever had a bone marrow transplant.

Coexisting medical conditions or past medical history:

18. Are pregnant, lactating, breastfeeding or planning to become pregnant during the Study or within 7 days after the last dose of Study Drug
19. Has known moderate or severe hepatic impairment (e.g., Child-Pugh Class B or C)
20. Has clinically significant abnormalities in the results of laboratory evaluations at screening visit as determined by the investigator, including:
    a. AST, ALT, or alkaline phosphatase ≥ 2x the upper limit of normal (ULN)
    b. Total bilirubin > 2x ULN (unless diagnosis of Gilbert's syndrome)
    c. Creatinine clearance as calculated by the Cockcroft-Gault formula < 30 mL/min (Refer to Appendix 2)
    d. Total white blood cell count (WBC) < 3 x 10^9/L
    e. Absolute neutrophil count < 1.5 x 10^9/L
    f. Absolute lymphocyte count < 0.8 x 10^9/L
    g. Hemoglobin < 8 g/dL, or
    h. Platelet count < 100 x 10^9/L.
21. Has a clinically significant abnormal electrocardiogram (ECG) at screening, including QTcF > 450 msec for males and > 470 msec for females.
22. Has unstable or uncontrolled and clinically significant allergic (except for untreated, asymptomatic, seasonal allergies), hematological, endocrine/metabolic, coagulation, immunologic, pulmonary, cardiovascular, hepatic (except hepatic steatohepatitis), GI (except UC), genitourinary, psychiatric, oncologic or neurological disease or other medical disorder that would compromise subject safety or confound Study safety assessment as determined by the investigator at screening and Day 1. In addition, subjects with a prior history of thrombotic events, including deep vein thromboses (DVT), and those with known inherited conditions that predispose to hypercoagulability should be excluded.
23. Has known hypersensitivity to excipients or contents of the Study drug
24. Has participated in another clinical trial of an investigational drug (or medical device) within 30 days prior to Screening or 5x the half-life of the investigational drug, whichever is longer, or is currently participating in another trial of an investigational drug (or medical device).
25. Have or has a history of alcohol or drug abuse within 1 year of screening, per the judgment of the investigator.
26. Has a current, or history of, malignancy requiring radiation or pharmacologic treatment within 5 years prior to screening, except for completely resected basal cell

carcinoma or squamous cell carcinoma of the skin without recurrence for ≥1 year, cervical carcinoma in situ that has been adequately treated and without recurrence for ≥ 5 years. Subjects with a history of cervical dysplasia within 3 years prior to screening or who currently have unresected cervical dysplasia should be excluded.

27. Is deemed by the investigator to be inappropriate for this Study; or has any condition which would confound or interfere with the evaluation of the safety, tolerability, or PK of the investigational drug; or is unable or unwilling to comply with the Study protocol.

Exclusion Criteria for Phase 3 Maintenance Study

28. Subjects who required change of UC medications (such as initiated or increased oral corticosteroid dose or initiated rectal aminosalicylates or corticosteroids) or any prohibited medication to control UC symptoms during Induction Study

Exclusion Criterion for Induction Study Related to SARS-CoV-2

29. Within 4 weeks of screening or during screening, has [1] confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (coronavirus disease 2019 [COVID-19]) (test positive), OR [2] suspected SARS-CoV-2 infection (clinical features without documented test results) unless has a negative test for SARS-CoV-2 two weeks after resolution of symptoms and remains asymptomatic until Day 1, OR [3] close contact with a person with known or suspected SARS-CoV-2 infection unless has a negative test for SARS-CoV-2 two weeks after contact and remains asymptomatic until Day 1.

4.3. Women of Childbearing Potential (WOCBP) and Acceptable Birth Controls

Women of childbearing potential must have documentation of a negative pregnancy test at screening and prior to dosing. All female subjects of childbearing potential must agree to abstain from sexual intercourse or to use a highly effective method of birth control during the Study and for at least 7 days after completion of Study drug dosing.

Females are considered not of childbearing potential if they have had a total hysterectomy and/or bilateral tubal ligation or hysteroscopic sterilization (documentation for surgeries must be provided before randomization) or are in a postmenopausal state (i.e., females who have had cessation of prior occurring menses for ≥24 months without alternative causes or females with premature ovarian failure).

Follicle-stimulating hormone (FSH) will be tested at screening in post-menopausal females only to confirm post-menopausal state.

Highly effective birth control methods are defined as methods that can achieve a failure rate of less than 1% per year when used consistently and correctly. Such methods include: combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral/intravaginal/transdermal); progestogen-only hormonal contraception associated with inhibition of ovulation (oral/injectable/implantable); intrauterine device; intrauterine

hormone-releasing system (IUS); bilateral tubal occlusion; vasectomised partner; sexual abstinence (if this is in line with the preferred and usual lifestyle). Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success. Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. More restrictive methods of birth control may be required as per local country requirements, and this will be defined in the IRB/IEC approved subject informed consent form.

5. STUDY DRUGS

All Study drug supplied by the Sponsor must be stored in a secure location accessible only to designated Study personnel.

5.1. Description of Study Drugs

5.1.1. TD-1473

[redacted]

5.1.2. Placebo

[redacted]

5.2. Dosage and Administration

5.2.1. TD-1473

5.2.1.1. Induction Study

Subjects will take TD-1473 tablets once daily for approximately 8 weeks. Study drug will be self-administered orally in the morning. With the exception of clinic visit days noted in the Table 1 Schedule of Procedures, subjects will be instructed to take two tablets once daily at approximately the same time each morning.

TD-1473 may be taken with or without food. Results from a clinical pharmacology study in healthy subjects showed that there was minimal decrease in plasma exposure of TD-1473 (30% on average) when administered with a high fat meal, relative to fasted conditions. The impact of food on the exposure of TD-1473 is not considered to be clinically meaningful.

Subjects will be instructed to continue dosing beyond Week 8 before they return for either a Week 8b visit or maintenance Week 0 visit depending on whether clinical response was achieved according to the adapted Mayo score post Week 8. Subjects will continue to complete a daily diary to record UC symptoms and Study drug administration.

Extended Induction

Subjects who do not demonstrate clinical response at Week 8 will receive an additional 8 weeks of treatment with active drug staying on the same dose as the first 8 weeks, except those who had received placebo during the first 8 weeks will now receive TD-1473 at 80 mg. This portion of the Induction Study will not be placebo-controlled but blinding as to the specific dose of TD-1473 will be maintained. Those who demonstrate clinical response at the end of Week 16 will enter the Maintenance Study; those who do not demonstrate clinical response at Week 16 will have an EOS visit and exit the study.

Subjects will be instructed not to take their Study drug in the morning of the Week 8b visit since Study drug administration of the extended induction regimen will be in-clinic at Week 8b and Week 16. Subjects will continue to complete a daily diary to record UC symptoms and Study drug administration. Subjects will be instructed to continue dosing beyond Week 16 until they return for the mWeek 0 visit if they are deemed to have achieved clinical response from the Week 16 adapted Mayo score or until they are deemed not achieved clinical response, in which case, Study drug administration should stop.

5.2.1.2. Maintenance Study

The subject will be continued on their Induction Study drug assignment in a blinded manner or re-randomized to receive placebo or one of the TD-1473 doses at mWeek 0. During the Maintenance Study, subjects will take TD-1473 dose once daily for up to 44 weeks.

Study drug administration will be in-clinic as per Table 2 Schedule of Procedures. On all other Study days, subjects will self-administer their Study drug at home. Subjects will continue to complete a daily diary to record UC symptoms and Study drug administration.

5.2.2. Placebo

5.2.2.1. Induction Studies

Subjects will take placebo once daily for up to 8 weeks. Study drug will be self-administered orally in the morning. Subjects will be instructed to take two tablets once daily at approximately the same time each morning.

With the exception of clinic visit days noted in the Table 1 Schedule of Procedures, subjects will be instructed to take two tablets once daily at approximately the same time each morning

Subjects will be instructed to continue dosing beyond Week 8 before they return for either a Week 8b visit or maintenance Week 0 visit depending on whether clinical response was achieved according to the Week 8 adapted Mayo score. Subjects will continue to complete a daily diary to record UC symptoms and Study drug administration.

5.2.2.2. Maintenance Study

Subjects will be randomized or re-randomized to receive placebo or one of the TD-1473 doses at mWeek 0. If the subject is deemed to have experienced a clinical response by the same criteria at the end of Induction but had received placebo during Induction, the subject will continue on placebo during the Maintenance phase.

Study drug administration will be in-clinic as per Table 2 Schedule of Procedure for the purpose of collecting pre-dose and post-dose PK samples. On all other Study days, subjects will self-administer their Study drug at home. Subjects will continue to complete a daily diary to record UC symptoms and Study drug administration.

Instructions will be provided to the subject to take two tablets once daily at approximately the same time each morning.

5.3. Treatment Compliance

Compliance will be assessed in subjects when accountability is performed at visits where study drug is dispensed to or returned by subjects. Treatment compliance will be assessed by reconciliation of used and unused tablets.

The subjects' diary entries will also be reviewed at applicable study visits to assess compliance with study drug administration per documentation of the daily dosing times.

Subjects with poor dosing compliance (i.e., < 80% or ≥ 120%), as assessed by tablet counts, should receive counseling or assistance, and re-training as appropriate.

5.4. Missed Dose(s)

Study drug will be taken orally and must be swallowed whole with liquid and not chewed, divided, dissolved, or crushed. If the subject dose is missed in the morning, it can still be taken up to 12 hours after the subject's normal dosing time. If the subject does not take the Study drug within 12 hours after the usual time each day, the dose of Study drug should be skipped for that day and the subject should be instructed to take the Study drug on the following day at the usual time.

5.5. Drug Accountability and Reconciliation

The investigator or designee is responsible for maintaining accountability records for all Study drug(s) received from the Sponsor, in accordance with applicable government regulations and Study procedures. The accountability record for Study medication (TD-1473 and placebo) will be maintained in a secure location, accessible only to authorized staff members. The accountability record will include entries for receipt, distribution or dispensing, and destruction of the material(s).

Subjects will be instructed to return all used and unused Study medication at each applicable study visit as detailed in the Schedule of Study Procedures.

Unused and expired Study drug will be disposed of in accordance with written instructions from the Sponsor. Drug accountability is maintained in the Randomization and Trial supply management system (RTSM), managed by RTSM supplier.

6. STUDY PROCEDURES

6.1. Schedule of Study Procedures

Study procedures will be performed only after written informed consent is obtained. A subject is considered to be enrolled once the informed consent has been signed.

The Screening Induction visits (i.e., Stage 1 and Stage 2) will be performed within 28 days before dosing. One repeat Screening Stage 1 visit is allowed for each subject per the investigator's discretion. If the subject does not begin the Day 1 Induction treatment following this 28-day window, all Screening evaluation procedures (i.e., Stage 1 and Stage 2) must be repeated. Subjects may be considered for re-screening of both Screening Stage 1 and Screening Stage 2 procedures with approval from the Sponsor.

The schedule of Study procedures is summarized in Table 1, Table 2, and Table 3.

Additional safety tests (beyond those required per protocol), such as vital signs (BP, heart rate, respiratory rate, and body temperature), physical exams, ECGs, and laboratory safety tests, may be obtained during the course of the Study as clinically indicated to ensure appropriate safety monitoring.

6.2. Total Blood Volume

The total estimated volume of blood to be drawn from each subject for safety laboratory assessments, serology panel, lipid panel, FSH (if applicable), [redacted], QuantiFERON®-TB Gold test, PK, biomarker assessments, and genetic testing (if applicable) is approximately: **148 mL** in the Induction Study (8 weeks); an additional **114 mL** if subject participates in the Extended Induction (additional 8 weeks); and **210 mL** if subject participates in the Maintenance Study (48 weeks with EOS visit). Additional samples may be drawn for safety laboratory testing as considered necessary by the investigator.

6.3. Procedures by Visit

6.3.1. Induction Study – Screening Stage 1

Screening Stage 1 visit assessments will be performed between 28 and -1 days prior to Day 1. Initial eligibility assessments will be reviewed and confirmed by the investigator prior to each subject continuing on to the endoscopy with biopsy assessments at Screening Stage 2.

The schedule of Study procedures is summarized in Table 1.

6.3.2. Induction Study – Screening Stage 2

Subjects meeting initial eligibility criteria following completion of the Screening Stage 1 evaluations will return to the clinic for Screening Stage 2 assessments. The Screening Stage 2 endoscopy should be performed at least 5 calendar days prior to Day 1 randomization to enable results from the central reader to be obtained and reviewed and for at least 3 days of symptoms starting 2 days after the Screening Stage 2 endoscopy to be recorded for Day 1 Mayo score calculations.

Subjects should be instructed to fast from food and non-clear fluids on the evening prior to the Screening Stage 2 visit to ensure a minimum 8-hour fast prior to the fasted blood sample collection.

The schedule of Study procedures is summarized in Table 1.

6.3.3. Induction Study – Day 1

Subjects should be instructed to fast from food and non-clear fluids on the evening prior to the Day 1 visit to ensure a minimum 8-hour fast prior to the fasted blood sample collection.

Subjects meeting all eligibility criteria following completion of the Screening Stage 1 and Screening Stage 2 evaluations will return to the clinic for enrollment assessments on Day 1.

The schedule of Study procedures is summarized in Table 1.

6.3.4. Induction Study – Week 2

Subjects will return to the clinic at Induction Week 2 for completion of assessments.

The schedule of Study procedures is summarized in Table 1.

6.3.5. Induction Study – Week 4

Subjects should be instructed to fast from food and non-clear fluids on the evening prior to the Week 4 visit to ensure a minimum 8-hour fast prior to the fasted blood sample collection.

The schedule of Study procedures is summarized in Table 1.

6.3.6. Induction Study – Week 8a

Subjects should be instructed to fast from food and non-clear fluids on the evening prior to the Week 8a visit to ensure a minimum 8-hour fast prior to the fasted blood sample collection.

The schedule of Study procedures is summarized in Table 1 and Table 2.

If a subject is deemed to have experienced a clinical response (Refer to DEFINITION OF TERMS) at Induction Week 8a and was on active drug (TD-1473), the subject will be re-randomized to receive placebo or one of the TD-1473 doses during Maintenance. If the subject is deemed to have experienced a clinical response at Induction Week 8a but had received placebo during Induction, the subject will continue on placebo during the Maintenance phase. If the subject does not demonstrate clinical response at Week 8a, the subject will continue in the Extended Induction Phase for another 8 weeks, during which time, the subject will be administered TD-1473. Study treatment will remain blinded (Refer to Section 3.5.1).

6.3.7. Extended Induction – Week 12 and Week 16 (only for subjects who do not demonstrate clinical response to Induction at Week 8)

The schedule of Study procedures is summarized in Table 1.

6.3.8. Maintenance Study – mWeek 0

Subjects should be instructed to fast from food and non-clear fluids on the evening prior to the mWeek 0 visit to ensure a minimum 8-hour fast prior to the fasted blood sample collection.

The schedule of Study procedures is summarized in Table 2. Regardless of Study drug treatment assignment during Maintenance, subjects must start tapering corticosteroids using the regimen recommended in the protocol at mWeek 0 (Refer to Section 6.5.3).

6.3.9. Maintenance Study – mWeek 4 and mWeek 36

The schedule of Study procedures is summarized in Table 2.

6.3.10. Maintenance Study – mWeek 12 to mWeek 28

Subjects should be instructed to fast from food and non-clear fluids on the evening prior to the visit to ensure a minimum 8-hour fast prior to the fasted blood sample collection.

The schedule of Study procedures is summarized in Table 2.

6.3.11. Maintenance Study – mWeek 44

Subjects should be instructed to fast from food and non-clear fluids on the evening prior to the visit to ensure a minimum 8-hour fast prior to the fasted blood sample collection.

The schedule of Study procedures is summarized in Table 2.

6.3.12. Clinical Flare Assessment

During the Maintenance Study, ongoing assessments for Clinical Flare using the partial Mayo score will be conducted at each scheduled visit. Subjects will also be encouraged to contact the study site in between scheduled visits if the subject notes an increase in stool frequency or rectal bleeding.

Subjects who meet the following criteria during the Maintenance Study will be considered to have a Clinical Flare:

- an increase from Maintenance baseline in the partial Mayo score of ≥ 3 points with an absolute partial Mayo score ≥ 4; **OR**
- an absolute partial Mayo score ≥ 7 points.

If increased symptoms are reported outside of a scheduled visit (Table 2), a Clinical Flare Assessment (CFA) Visit 1 will be conducted within 14 days of the subject's reporting of increased stool frequency and/or rectal bleeding (Table 3). If increased symptoms are reported or found during a scheduled visit, Clinical Flare assessment will be conducted as part of the scheduled visit and any assessment that must be done at CFA Visit 1 (Table 3) and not performed yet for the scheduled Maintenance Study visit, should be performed (Table 3).

The schedule for Clinical Flare Assessment visits is summarized in Table 3.

Note: since each full CFA cycle takes 8 weeks to complete, subjects with increased symptoms after mWeek36 (i.e., those who have <8 weeks of the Maintenance Study left) do not undergo evaluation through the CFA algorithm. In these cases, it will be up to the investigator to determine whether the increased symptoms are due to a UC exacerbation and to decide whether to use rescue medication. If such a subject completes the Maintenance Study, then the subject may be eligible to enter the LTS Study.

Clinical Flare Assessment Visit 1:

This could be at a scheduled visit or conducted within 14 days after the subject contacts the site reporting increasing symptoms. The schedule for Clinical Flare Assessment visits is summarized in Table 3. Partial Mayo scores should be calculated with the PGA from this visit. At this visit, the Investigator should also assess whether there may be other etiologies for increased symptoms (infection, change in diet, etc.). The subject will continue on study drug during this time unless they meet criteria defined in Section 6.6.1.

These are the subjects who should undergo an endoscopy (CFA Visit 2) after CFA Visit 1 to assess the Mayo endoscopy subscore:

a) meet the criteria for Clinical Flare at CFA Visit 1

b) have no other obvious etiology for increased symptoms

c) are in Clinical Flare for the first time or have flared previously but had an adapted Mayo Score at CFA visit 2 that did not meet the criteria for loss of response [Refer to DEFINITION OF TERMS].

Note, those who decline endoscopy (CFA Visit 2) during the first flare are not eligible for the LTS Study (unless they complete the mWeek 44 visit of the Maintenance Study [i.e., have endoscopic assessment of disease activity at the end of the study]) and should not undergo endoscopy on any subsequent episode of clinical flares. These subjects would be considered to have had presumed (and not documented) loss of response, and are able to start rescue medication if the investigator deems this to be appropriate.

Rescue medications should not be withheld if, in the opinion of the investigator, failure to prescribe them would compromise subject safety while waiting for their endoscopy subscore.

Permitted rescue medication (Refer to Section 6.5.2 Permitted Medication) includes corticosteroids and aminosalicylates; although initiation in a subject who did not enter the Induction Study on corticosteroids or increase above baseline dose may trigger treatment failure definition (Refer to Section 8.9). Other immune-modulating agents are prohibited medications.

- If the subject initiates a permitted rescue medication, the subject will continue to attend clinic as specified in the Schedule of Study procedures summarized in Table 2.

- If the subject initiates a prohibited medication (Appendix 6), the subject will discontinue treatment with study medication.

Clinical Flare Assessment Visit 2 (Endoscopy Visit):

CFA Visit 2 will be conducted on or within 14 days after CFA Visit 1. A subject who declines to undergo an endoscopy or who is not required to undergo an endoscopy will skip the CFA Visit 2 but still proceed to have CFA Visit 3 to be assessed for improvement by partial Mayo score 8 weeks after the initial flare (CFA Visit 1). Subjects who are supposed to undergo endoscopy during the first clinical flare visit but decline the procedure will be presumed, but not documented, to be in loss of response and will not be eligible for the LTS study (unless they complete the mWeek 44 visit of the Maintenance Study [i.e., have endoscopic assessment of

disease activity at the end of the study]). Subjects who have met Clinical Flare criteria previously but declined an endoscopy (and therefore had presumed but not documented loss of response) should not undergo endoscopy with subsequent flares. **Note:** if documented loss of response is **not** confirmed following the endoscopy at CFA Visit 2, the endoscopy will need to be completed at subsequent CFA Visit 2, until loss of response is confirmed.

After endoscopy, the adapted Mayo score at CFA Visit 2 should be calculated as the sum of the rectal bleeding and stool frequency subscores obtained at the assessment for Clinical Flare (CFA Visit 1 or a scheduled visit) and the Mayo endoscopy subscore at CFA Visit 2. This adapted Mayo Score will then be compared with the Induction Study baseline adapted Mayo Score (at Day 1) to determine whether the subject is still in clinical response, and if not, then the subject has met criteria for loss of response.

Subjects should continue on study drug after meeting Clinical Flare criteria and while waiting for their endoscopy subscore. However, rescue medications (Refer to Section 6.5.2 Permitted Medication) should not be withheld if, in the opinion of the investigator, failure to prescribe them would compromise subject safety while waiting for their endoscopy subscore. Otherwise, subjects with a Clinical Flare are eligible for rescue medication only if they meet the criteria for loss of response. Unless the subject initiates a prohibited medication, the subject stays on study drug and return for CFA Visit 3.

The addition of a corticosteroid or oral aminosalicylate or an increase in corticosteroid or oral aminosalicylate dose at or above the dose received at Maintenance Study baseline for subjects who lose clinical response will be considered a permitted rescue medication (refer to Section 6.5). Use of a prohibited medication (e.g., initiation of an immunomodulator, another JAK inhibitor or biologics, refer to Appendix 6) requires the subject to discontinue study drug and be withdrawn from the Phase 3 Maintenance Study after an EOS visit.

Clinical Flare Assessment Visit 3:

At CFA Visit 3, which is to occur approximately 8 weeks after the CFA Visit 1 if the subject has presumed or documented loss of response, subject will be assessed for improvement to stay in the study. During this 8-week interval between CFA Visits 1 and 3, Clinical Flare criteria will not be assessed again, including during regularly scheduled visits. Subjects who have not demonstrated improvement (i.e., subjects who have not achieved a decrease from partial Mayo score at CFA Visit 1 by ≥2) at CFA Visit 3 will be discontinued from study drug administration. If they do not enroll into the LTS study, they should return for an End of Study Visit 4 weeks after their last study drug dose. Subjects who are assessed as having shown improvement (i.e., have decreased the partial Mayo score by ≥ 2 since CFA Visit 1) will continue in the study on study drug.

After the CFA Visit 3, subjects who remain in the study will continue with the regularly scheduled visits and continue to be assessed for recurrence of Clinical Flare during the rest of the Maintenance Study using the criteria based on the partial Mayo score.

Repeated Clinical Flares:

Once subjects meet criteria for loss of response, they will not undergo another endoscopy (i.e., CFA Visit 2) if they subsequently meet the criteria for Clinical Flare. Thus, subjects should

undergo endoscopy only once during all series of CFA visits if that endoscopic subscore leads to an adapted Mayo Score meeting criteria for loss of response. However, if the endoscopic subscore results in an adapted Mayo Score not meeting criteria for loss of response, the subject should undergo another endoscopy at a subsequent flare to assess for loss of response. If subjects decline an endoscopy at the initial clinical flare, then the subject has presumed loss of response and should not undergo endoscopy at any subsequent clinical flares and will not be eligible for the LTS study (unless they complete the mWeek 44 visit of the Maintenance Study [i.e., have endoscopic assessment of disease activity at the end of the study]).

Subjects who meet criteria for documented loss of response or have presumed loss of response (due to lack of endoscopy) previously will be eligible to receive permitted rescue medication as noted above at the time of any subsequent Clinical Flares and be assessed for partial Mayo score improvement approximately 8 weeks after the visit at which Clinical Flare was assessed and managed. A subject who meets the criteria of Clinical Flare on a second occasion after meeting loss of response during the Maintenance Study will be discontinued from study drug administration and may be eligible for the LTS study. If they do not enroll into the separate LTS study, they will be required to complete an EOS Visit.

The schedule for Clinical Flare Assessment visits is summarized in Table 3.

6.3.13. Early Study Drug Discontinuation

Subjects who prematurely discontinue the Study drug due to AEs, lack of response or any other reason besides withdrawal of consent during the Phase Induction Studies or Maintenance Study will be asked to return for an Early Study Drug Discontinuation visit. This visit will be conducted within 5 days after the last dose of Study drug. Subjects will also return for the End of Study visit for collection of safety data and assessment of disease activity.

The Schedule of Study Procedures is summarized in Table 1 and Table 2.

6.3.14. End of Study (EOS)

An EOS visit will be required for all subjects 4 weeks following their last dose of Study drug unless the subject is rolling over into the LTS Study. Subjects who complete an Early Study Drug Discontinuation visit during the Phase 2b/ Phase 3 Induction Studies or Phase 3 Maintenance Study will also be required to return for an EOS visit. Subjects should be instructed to fast from food and non-clear fluids on the evening prior to the EOS visit to ensure a minimum 8-hour fast prior to the fasted blood sample collection.

The schedule of Study procedures is summarized in Table 1 and Table 2.

6.4. Description of Study Assessments

6.4.1. Demographic and Baseline Assessments

6.4.1.1. Informed Consent, Demographics, and Inclusion/Exclusion Criteria

Written informed consent must be obtained, signed, and dated after the nature of the Study has been explained to the subject and before any Study procedure is performed.

Demographic information to be collected will include: year of birth, gender, race, and ethnicity, as allowed per local regulations.

Inclusion and exclusion criteria will be assessed at screening and on Day 1 prior to randomization. Subjects will only be eligible for enrollment into the Study if they meet all of the inclusion and none of the exclusion criteria.

6.4.1.2. Medication History

All non-UC and UC medications (i.e., prescription and over-the-counter medications, herbals, vitamins, and supplements) used within 60 days of the screening visit will be recorded. Subjects should be asked at screening as to whether, since diagnosis, they ever had been or are currently on aminosalicylates, immunomodulators, corticosteroids, anti-TNF therapy (how many TNF inhibitors and reason for stopping), vedolizumab, ustekinumab, or alternative therapies, the names, duration of use of such therapies, and the reasons for discontinuation (lack of efficacy, loss of efficacy, intolerance, or other, where applicable) and should be recorded. Subject's medication history including the name of medication, date started (at minimum, the year) and stopped (at minimum, the year), route of administration, indication, dose and reason for stopping (if applicable) should be recorded. Please refer to inclusion/exclusion criteria Section 4 and Appendix 6 for Prohibited medications.

6.4.1.3. Medical History

A medical history will be taken during screening and will include evaluation for past and present cardiovascular, respiratory, GI, renal, hepatic, neurological, endocrine, lymphatic, hematologic, immunologic, dermatologic, psychiatric, genitourinary diseases, surgical history, or any other diseases or disorders. An updated medical history will be obtained on Day 1 prior to dosing. Medical events or conditions that arise or worsen in severity or frequency following informed consent will be recorded as an AE; those after initiation of Study drug will be recorded as a treatment-emergent AE.

Regarding the subject's history of UC, the years since diagnosis and extent of disease (categorized as proctosigmoiditis, left sided, extensive or pancolitis) should be documented. The number of stools per day (rounded to the nearest whole digit) when the subject was feeling normal (without a flare or before the diagnosis of UC) should be recorded. This will be used to calculate the stool frequency subscore.

6.4.1.4. Smoking Status

Subject's current use of tobacco, number of years used, and annual pack years used will be obtained according to the Schedule of Study Procedures (Table 1).

6.4.1.5. Height Measurements

Height measurement (in cm and without shoes) will be obtained at screening.

6.4.1.6. Body Weight

Weight measurement (in kg and without shoes) will be obtained according to the Schedule of Study Procedures (Table 1 and Table 2).

6.4.1.7. Vital Signs

Heart rate (HR), systolic and diastolic blood pressure (BP), respiratory rate, and body temperature will be recorded according to the Schedule of Study Procedures (Table 1, Table 2, and Table 3).

Blood pressure and heart rate will be measured after the subject has been resting for at least 5 minutes in the seated or supine position. Subject position, measurement device, and arm (left vs. right) should be kept consistent throughout the Study. Blood pressure will be measured using a manual or automatic blood pressure device. Heart rate will be recorded by palpation of the radial pulse over at least a 30-second period or by the automated blood pressure device.

Body temperature will be measured and reported in degrees Celsius. The method used to collect temperature needs to be consistent throughout the subject's participation.

Any vital sign outside the normal range may be repeated at the discretion of the investigator. The vital sign measurements (BP and HR) should be performed after the subject has rested sufficiently as determined by the appropriate site staff. Collection of additional vital sign measurements for routine safety monitoring at additional time points or Study days may be performed at the discretion of the investigator, or upon request by the Sponsor.

6.4.1.8. 12-Lead Electrocardiograms

Interpretable ECG recordings (e.g., without artifacts) will be obtained according to the Schedule of Study Procedures (Table 1 and Table 2). Twelve-lead safety ECGs will be collected in singlet at each scheduled time point.

ECGs must be performed after the subject has been resting in a supine position for at least 10 minutes.

For monitoring purposes, the investigator must review, provide interpretation for ECG recordings other than sinus rhythm on the ECG tracing, sign, and date all safety ECG tracings. Paper copies of ECG tracings will be kept as part of the subject's Study file at the site.

If at a particular post dose time point, the QTcF is > 500 msec and/or 60 msec longer than the value at screening or Day 1 or the mean QRS interval is > 130 msec, the investigator should consider study drug discontinuation if the investigator deems this finding to be clinically significant and poses a safety risk for the subject. The investigator should also consider evaluating the subject for potential concurrent risk factors (e.g., electrolyte abnormalities, concomitant medications known to prolong the QT interval, severe bradycardia).

Results from a plasma TD-1473 exposure-QTc analysis of data obtained from the SAD and MAD Study in healthy subjects and preclinical data were used in considering the frequency and replicate ECGs required for this Study

6.4.1.9. Physical Examination

The physical examination will be performed by a physician, nurse practitioner, physician's assistant, or equivalent, according to local practice standards, at each scheduled time point as specified in the Schedule of Study Procedures (Table 1, Table 2, and Table 3).

Completion of additional physical examinations for routine safety monitoring at additional time points or Study days may be performed at the discretion of the investigator, or upon request by the Sponsor. A physical exam of the organ system associated with any reported AE, even if resolved, should be performed at subsequent Study visits.

6.4.1.10. Chest X-ray or equivalent imaging

A chest X-ray will be performed at screening to assess for signs of latent or active TB or other active viral, fungal or bacterial infections unless one has been performed within 90 days prior to screening, documented to be negative and reviewed by the investigator. Posterior anterior (PA) and lateral views (lateral view may not be necessary if PA view is deemed adequate by the investigator) will be obtained. Subjects who have had a chest X-ray or equivalent chest imaging within 90 days prior to screening will not require a repeat X-ray unless subject is deemed to be at high risk of recent pulmonary infection.

6.4.1.11. Tuberculosis (TB) Test

History of latent or signs of latent TB:

Subjects with a history of latent TB or signs of latent TB on chest X-ray or equivalent chest imaging or with positive result on QuantiFERON®-TB Gold test may be eligible for the Study if the subject:

1. Has completed an adequate course of treatment (e.g., 9-month course of INH or equivalent therapy for latent TB) within 5 years (3 years for countries where TB is endemic) prior to Screening, the documentation for which must be included in the source document and reviewed by the PI, or currently undergoing an appropriate course of treatment (e.g., 9-month course of INH or equivalent therapy for latent TB) and has completed at least 3 months of this treatment before Screening with adequate compliance (as determined by the investigator), and
2. Has not lived in a region with high prevalence of multidrug-resistant TB.

Subjects with a history of latent TB should not undergo TB testing during Screening but must undergo X-ray if none has been performed within 90 days prior to screening.

History of active TB:

Subjects with a history of active TB may be eligible for the Study if:

a. He or she has completed an adequate course of treatment within 5 years (3 years for countries where TB is endemic) prior to Screening (the documentation for which must be included in the source document and reviewed by the PI)
b. The QuantiFERON®-TB Gold within 90 days of screening is negative, and
c. The subject has not lived in a region with high prevalence of multidrug-resistant TB
d. Has a benign chest X-ray within 90 days of screening

All subjects no matter status of TB:

A QuantiFERON®-TB Gold test will be conducted at Screening to assess for signs of latent TB unless:

a. An exam has been done with negative findings within 90 days of Screening, or
b. Subject has a history of latent TB that has been adequately treated (e.g., with ≥ 9 months of INH or equivalent therapy or currently being treated with an appropriate course of treatment.
c. In either case a) or b), there must be documentation in the source document, which must be reviewed by the investigator.

If the QuantiFERON®-TB Gold result is indeterminate, then repeat QuantiFERON®-TB Gold. If results from both tests are indeterminate, then the subject should be excluded and considered a Screen Failure.

In case of a suspected false-positive QuantiFERON®-TB Gold result (e.g., a negative result by the local laboratory and suspicion of sample processing error, both of which must be documented in the source document), a second sample may be sent to the central laboratory and the result of the second test will be used.

Detailed instructions and collection kits for QuantiFERON®-TB Gold test, handling, and shipping will be provided by the central laboratory.

6.4.1.12. Concomitant Medications

All concomitant non-UC and UC medications (i.e., prescription and over-the-counter medications, herbals, vitamins, and supplements) that were used within 60 days of screening, including name of medication, date started and stopped, route of administration, indication, and dose will be recorded. Doses of non-UC prescription and over-the-counter medications may be altered or new medications may be added during the Study only if medically indicated and do not confound safety assessment, as deemed by the investigator or Medical Monitor; however, such changes should be minimized. Administration of a prohibited medication may result in the subject being discontinued from the Study.

Refer to Section 6.5 for further details.

6.4.1.13. Adverse Events (AEs)

Adverse events, including serious adverse events (SAEs) and adverse events of special interest (AESI) will be reviewed and recorded following the time the subject signed the Informed Consent Form through the follow-up visit. AEs may be observed by the site Study personnel or spontaneously reported by the subject or reported in response to standard questions from site Study personnel. Subjects will be reminded to call the site to report AEs that occur between visits. Refer to Section 7.1.4 for definition, assessment, and reporting of AEs.

6.4.1.14. Pregnancy Test (females of child-bearing potential only)

Urine b-hCG testing will be performed during specified visits, as listed in the Schedule of Study Procedures (Table 1 and Table 2), before study drug dosing, on females of childbearing potential to confirm the absence of pregnancy. Serum b-hCG testing must be done at Screening. If the

urine b-hCG test is positive, a serum b-hCG test must be performed. The pregnancy test must be confirmed negative for a subject to be eligible for this Study unless the PI deems the test is falsely positive.

Detailed instructions and collection kits for sample collection, handling, and shipping will be provided by the central laboratory.

6.4.1.15. Follicle-Stimulating Hormone (FSH)

Follicle-stimulating hormone (FSH) will be tested at screening in post-menopausal females only to confirm post-menopausal state. FSH will be performed as specified in Schedule of Study Procedures (Table 1)

6.4.1.16. Chemistry, Hematology, and Urinalysis

Laboratory assessments will be performed as specified in Schedule of Study Procedures (Table 1, Table 2, and Table 3).

Additional and repeat laboratory safety testing for the evaluation of abnormal results and/or adverse events during the study may be performed at the discretion of the investigator or upon request of the Sponsor. One repeat laboratory testing of abnormal potentially clinically significant or clinically significant results for screening evaluation of the subject may be repeated at the discretion of the investigator.

Chemistry samples will be analyzed for the following: sodium, potassium, calcium, magnesium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, total bilirubin, direct and indirect bilirubin, total protein, albumin, alkaline phosphatase, lactate dehydrogenase, ALT, AST, gamma-glutamyl transferase, and creatine phosphokinase.

Hematology samples will be analyzed for the following: hematocrit and hemoglobin; red blood cell count; mean corpuscular volume; mean corpuscular hemoglobin; mean corpuscular hemoglobin concentration; reticulocyte count; white blood cell count, including differential count (percent and absolute) of neutrophils, eosinophils, basophils, monocytes, lymphocytes; and platelet count.

Urinalysis includes determination of specific gravity; presence of blood, glucose, protein, nitrite, and leukocytes; and microscopic examination of sediment, if clinically indicated.

Detailed instructions and collection kits for sample collection, handling, and shipping will be provided by the central laboratory.

6.4.1.17. Overnight Fasting Lipid Panel

Fasting low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride, and total cholesterol will be measured at the time points designated in Schedule of Study Procedures (Table 1 and Table 2). Subject must fast from food and non-clear fluids for a minimum of 8 hours overnight prior to blood collection.

Detailed instructions and collection kits for sample collection, handling, and shipping will be provided by the central laboratory.

6.4.1.18. Serology Panel

Testing will be performed at screening for the following: Hepatitis B virus (HBV) surface antigen and core antibody (total, which includes IgG and IgM), HCV antibody, hepatitis E (IgG and IgM), and Human Immunodeficiency (HIV) antibody. If HBV core antibody is positive and the HBV surface antigen is negative, the subject may still be eligible if the HBV DNA is undetectable and the HBV surface antibody is present. If HCV antibody is positive, the subject may still be eligible for the Study if there is documentation of completion of HCV treatment followed by two subsequent undetectable viral load test results ≥ 6 months apart before screening and an HCV RNA viral load during Screening is negative. These additional tests may be done at screening Stage 1 or subsequent to it during screening. HIV, hep B, hep C, and Hep E serologies do not need to be repeated for re-screening if the results were negative during the first screening and within 90 days of re-screening.

Detailed instructions and collection kits for sample collection, handling, and shipping will be provided by the central laboratory.

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6.4.1.20. Endoscopy and Biopsies

Endoscopy and biopsies will be performed as specified in Schedule of Study Procedures (Table 1, Table 2, and Table 3)

Endoscopy and biopsies will be performed at Screening Stage 2 visit after subject's eligibility is confirmed. It is strongly recommended to proceed with screening only if the partial Mayo score is ≥ 3 upon review at any time between Screening Stage 1 visit and immediately prior to the procedure using the PGA from Screening Stage 1 visit. Endoscopy could be either a colonoscopy or sigmoidoscopy at Screening Stage 2 visit (see paragraph below), and is to be performed within 5-14 days prior to Day 1 to allow ≥ 3 days for symptom reporting to calculate Mayo score at Day 1. Sigmoidoscopy will be preferred over colonoscopy for all other defined time points after Screening (Table 1, Table 2, and Table 3) to avoid use of oral preparation and to minimize procedure time. Subjects who meet locally adapted guidelines for colon cancer surveillance should undergo the locally adapted method of surveillance.

Subjects must undergo colonoscopy (including visualization of the cecum or at least an attempt to reach the cecum or whatever is the most proximal portion of the colon present) in place of sigmoidoscopy at Screening Stage 2 visit if:

- Subject's UC diagnosis precedes screening by ≥ 8 years for pan-colitis or ≥12 years for left-sided colitis and the subject has not had a colonoscopy within 12 months prior to screening. During colonoscopy, if chromoendoscopy or surveillance biopsies are indicated as per local guidelines, these should also be performed, OR

- Subject has had UC for <12 years and does not have the documentation of a colonoscopy within 2 years prior to screening, OR
- If there is no documented pathology report from prior endoscopy showing chronic colitis or other signs of UC or no report of prior endoscopies is available for review.

During this Screening Stage 2 endoscopy, if chromoendoscopy or multiple (>10) surveillance biopsies are necessary, they need to be performed after a full recorded colonoscopy (including full withdrawal) has been completed to avoid confounding factors from bleeding from biopsies and dye artifact from chromoendoscopy for images submitted for central reading.

The preparation for any endoscopic procedure is up to the discretion of the investigator. The endoscopic score from the screening procedure performed at screening Stage 2, assessed by a central reader, will be used for eligibility criteria. If possible, it is preferable that all endoscopic procedures for each subject are performed by the same endoscopist and using the same bowel preparation for all procedures after screening.

All procedures can be performed by the investigator or qualified designee using the institution's standard procedure with or without sedation (conscious sedation or general anesthesia) for endoscopic assessment of disease activity and for biopsies. All procedures will be recorded and the images will be uploaded to the central reader imagining platform. An endoscopic video instruction manual will be provided separately. The centrally read endoscopic subscore will be used for all endpoints and for eligibility criteria to enroll a subject into the Induction and Maintenance Studies. Local reading of the endoscopic subscore will also be collected. Of note, an endoscopic central reading charter has been developed to outline the central reading process.

Subjects may undergo approximately five endoscopic procedures, (Table 1, Table 2, and Table 3) during their participation in the studies (Screening, Week 8, Week 16 if applicable, CFA Visit 2 if applicable, mWeek 44). However, this may be more if multiple CFA Visit 2 assessments are completed. Up to six biopsies will be taken at each of the defined time points. These biopsies may be used for histology and evaluation of exploratory inflammatory biomarker levels (and potentially tissue PK for Phase 2b Induction Study). Biopsies should be performed at the location of the worst inflammation in the rectum and/or sigmoid during the Screening endoscopy. During subsequent procedures after Screening, every effort should be made to take biopsies in the same area as done during the Screening endoscopy regardless of the area of worst inflammation in the current endoscopy. The location of biopsy site must be recorded.

A biopsy manual will be provided with detailed instructions for biopsy site identification, sample collection, handling, and shipping. Biopsy sample collection kits will be provided.

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6.4.1.22. Whole Blood and Serum Biomarker Sampling

Whole blood and serum samples will be collected as stated in the Schedule of Study Procedures (Table 1 and Table 2). Approximately 16 mL blood will be collected from each subject at each time point.

Actual time of collection must be recorded for each sample. Samples may be immediately analyzed for, but not limited to, disease or pathway relevant proteins, mRNA transcript levels, and levels of various miRNAs. It is understood that as our understanding of the gastrointestinal diseases evolves additional analyses may be warranted. Therefore, portions of these samples may be stored for up to 20 years after the end of the Study for potential future analysis of, but not limited to, relevant mRNA, protein or other non-DNA markers.

Detailed instructions and collection kits for sample collection, handling and shipping will be provided by the central laboratory.

6.4.1.23. Optional Genetic Testing

For subjects who provide consent, an additional blood sample will be obtained for possible genetic discovery research to identify or validate genetic markers (e.g., pharmacogenomics) that may be predictive of the safety, tolerability, efficacy, and/or pharmacokinetics of TD-1473 and/or to provide further knowledge of inflammatory bowel disease. This sample should be collected at Day 1 visit if consent for a genetic sample is provided.

Subjects are not required to consent for optional future genetic research in order to participate in this Study. If a subject wishes to withdraw consent to the testing of his or her genetic specimen, the investigator must inform the Sponsor.

The optional pharmacogenomics specimen will be stored for up to 20 years after the end of the Study for possible future analyses.

6.4.1.24. Pharmacokinetic Sampling

Blood samples for assessment of plasma TD-1473 concentrations are to be taken as described in the Schedule of Study Procedures (Table 1 and Table 2). Approximately 6 mL blood will be collected from each subject at each time point.

The post-dose samples with a prescribed sampling time (e.g., 1-hour postdose) will be collected ±10 minutes from the nominal time. Actual PK sample collection times will be recorded.

Unscheduled PK samples may be collected and analyzed. For all unscheduled PK samples, the collection date and time as well as the date and time that the Study drug was last taken should be recorded.

A portion of each plasma sample may be stored up to 20 years after the end of the Study for future analyses related to this Study (e.g., metabolite profiling, expanded exposure-response analyses) or to further our knowledge of inflammatory bowel disease.

Detailed instructions and collection kits for sample collection, handling and shipping will be provided by the central laboratory.

6.4.2. Efficacy Assessments

6.4.2.1. Mayo score

The total, adapted, and partial Mayo scores and the Patient-Reported Outcome 2 (PRO2) score will be assessed as specified in Schedule of Study Procedures (Table 1, Table 2, and Table 3).These scores are comprised of:

- The total Mayo score (0-12 points with 12 reflecting the highest severity) is comprised of four subscores: rectal bleeding (0 - 3), stool frequency (0 - 3), physician's global assessment (0 -3), and Mayo endoscopic subscore (0 – 3).
- The Partial Mayo score (0-9) is comprised of the first three Mayo subscores without the endoscopic subscore.
- The Adapted Mayo score (0-9) is comprised of the rectal bleeding, stool frequency, and endoscopic subscore (i.e., total Mayo score but without the PGA).
- The PRO-2 score (0-6 points with 6 reflecting the highest severity) is comprised of two subscores: rectal bleeding (0 - 3), stool frequency (0 - 3) subscores.

The stool frequency subscore of each day is the number of bowel movements exceeding the normal frequency (before onset of symptoms from UC or when subject is not in a flare, whichever is lower) and will be the averaged over the last 3 days (which may or may not be consecutive) for which symptom data are available during the week prior to each Study visit; the rectal bleeding subscore reflects the worst bleeding of each day and will also be averaged over the last 3 days (which may or may not be consecutive) for which symptom data are available during the week prior to each Study visit. Note that symptoms on the day of an oral bowel preparation, the day of an endoscopy, and the day following an endoscopy should be excluded in any symptom score calculation to avoid diarrhea and/or rectal bleeding from the bowel preparation or the endoscopy or the biopsy. Refer to Appendix 3 for further details. It is ideal, if possible, that the physician global assessment of each visit is completed by the same investigator of each subject. Of note, endoscopic subscore of 1 requires absence of friability.

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6.4.2.6.5. Subject Diary

Subjects are required to enter diary data continuously throughout each Study (from Screening Stage 1 to last visit on study). Subjects will be provided an electronic diary at the Screening Stage 1 visit and will be required to bring the Study diary to each of their Study visits. Diary data will be reviewed and collected at the site at each Study visit until the last visit of each Study.

Subjects will report on a daily basis items including the following:

- Total stool frequency over the preceding 24-hour period
- Presence and description of blood in the stools (if any): none, streak of blood <50% of stools, obvious blood with ≥ 50% of stools, or blood alone without stool
- Time (hour and minute) of Study drug administration (should be in the morning)

The information extracted will be used for calculation of the clinical scores. Symptoms on the day of and the day after any endoscopic procedure will not be used to calculate the clinical scores in order to avoid confounding effects from bowel preparation-related altered bowel frequency and/or rectal bleeding from the biopsies. On days where subject takes an oral bowel preparation for an endoscopic procedure, the symptoms on the day of the bowel preparation are also not counted to avoid confounding effects from the prep.

6.4.3. Pharmacokinetic and Pharmacodynamics Assessments

A sparse PK sampling strategy is being employed in this Study where random samples will be taken at select Study visits both immediately prior to treatment with Study drug and during treatment with Study drug; time of Study drug ingestion needs to be carefully documented the day before and the day of each Study visit where PK samples will be collected.

Disease-related surrogate markers (e.g., [redacted]) will be assessed. Other disease-related biomarkers may be assessed.

Whole blood, serum, and plasma samples will be collected and stored for potential future additional biomarker profiling.

6.4.4. Safety Assessments

Subject safety will be assessed throughout the Study using standard measures, including vital signs, 12-lead ECGs, blood and urine safety laboratory tests, physical examinations, concomitant medication usage, and adverse event (AE) monitoring. These will be collected from all subjects at visits as indicated in Table 1, Table 2, and Table 3.

6.4.4.1. Adverse Events

Refer to Section 6.4.1.13

6.4.4.2. Medical History

Refer to Section 6.4.1.3

6.4.4.3. Physical Examination

Refer to Section 6.4.1.9

6.4.4.4. Vital Signs

Refer to Section 6.4.1.7

6.4.4.5. Laboratory Tests

Refer to Section 6.4.1

6.5. Concomitant Medications

Refer to Section 6.4.1.12

6.5.1. Prohibited Medications

Immunomodifying agents (Refer to Appendix 6) are prohibited until the End of Study visit. The use of any prohibited UC Medication would result in subject discontinuation as defined in Section 6.6.1, except for the use of rectal aminosalicylates or rectal corticosteroids for clinical management during clinical flare assessment (during the Maintenance Study) if there is a contraindication for oral corticosteroids (see Section 6.5.2).

The use of the following medications, which may confound the safety evaluation of the Study, are prohibited:

- Any prescription drugs started or which had a dose adjustment within the 28 days prior to Day 1 until the day of the last dose (with the exception of hormonal contraceptives, hormone replacement therapy, vitamin D, insulin therapy, iron, corticosteroid [see below], and replacement thyroid hormone) unless deemed by the investigator to be medically necessary and unlikely to confound the efficacy assessment of Study drug. New medications that may confound the efficacy assessment may be considered with Sponsor approval on an individual basis.
- Any initiation or dose adjustment of over-the-counter medications including herbals, vitamins, or supplements within 14 days prior to Day 1 until the day of the last Study dose, unless deemed unlikely to confound safety assessment of Study drug by the investigator. New medications that may confound the efficacy assessment may be considered with Sponsor approval on an individual basis.
- Strong P-gp, BCRP and/or CYP3A4 inhibitors and inducers. This exclusion applies to concomitant medications, herbal supplements and ordinary dietary intake. The package insert, FDA website, and clinical judgment may be used to assess the potential of concomitant medications to interact with Study Drug. Refer to Appendix 6 Prohibited Medications. For clarity:
    - Any amount of grapefruit in the diet is prohibited;
    - Curcumin is prohibited as a concentrated supplement, but dietary intake is allowed;
    - Corticosteroids at doses not excluded elsewhere in the protocol are not considered strong CYP3A4/P-gp/BCRP inducers.
- Subject must avoid live viral vaccines (e.g., MMR, varicella zoster, herpes zoster, oral polio virus, FluMist®, attenuated typhoid fever vaccine, attenuated rotavirus vaccine, yellow fever vaccine, or any investigational live vaccine) during the Study and for 8 weeks following completion of the Study. Subject must be willing to avoid close contact with any household member who has been vaccinated with a live attenuated vaccine within 2 weeks after vaccination.

6.5.2. Permitted Medications

Permitted medications include, but are not limited to:

- Oral corticosteroids for UC are allowed during either the Phase 2b or the Phase 3 Induction Study but need to stay at a stable dose until Week 8. Note that steroid tapering during Induction is discouraged unless medically necessary. During extended induction, the subjects may, but are not required to, taper corticosteroids according to the regimen suggested below in Section 6.5.3. Reductions or increases in doses during the Maintenance Study are permitted as defined in Section 6.5.3. Corticosteroids are permitted rescue medications.

- Oral corticosteroids for non-UC indications are allowed, if medically necessary, after discussion with the Sponsor. The dose should, but does not need to, be tapered as outlined in Section 6.5.3.
- Doses of oral aminosalicylate, probiotics, or antibiotics prescribed for UC should be stable during the Phase 2b Induction/Phase 3 Induction Studies and Phase 3 Maintenance Study. However, they can be discontinued or undergo dose adjustment if the investigator deems their use has resulted in adverse effects. Oral aminosalicylates are also permitted rescue medications.
- Rectal aminosalicylates or rectal corticosteroids for clinical management during clinical flare assessment (during the Maintenance Study) if there is a contraindication for oral corticosteroids. If these are to be used, the best effort should be made to taper or stop these as soon as possible and before mWeek 40, if possible.
- Anti-diarrheal agents, which can be tapered or stopped if symptoms are improved during the Study; however, it is encouraged to continue at the same dose of anti-diarrheal medications throughout all studies. The addition of anti-diarrheal agents, although allowed, should be discouraged during the study if subject was not on an anti-diarrheal agent upon enrollment into the Induction Study.
- Sedating medications for endoscopy are permitted
- Antibiotics for infections
- Addition of, cessation of, or dose adjustments for the following are allowed during Screening or any other time during the study:
    a. Hormonal therapy for post-menopausal females
    b. Oral contraception for women of child-bearing potential
    c. NSAIDs taken on a regular (≤ 3 times per week, on average) basis
    d. Aspirin for cardioprotection is permitted at a maximum dose of 325 mg/day
    e. Vitamin D
    f. Insulin therapy
    g. Replacement thyroid hormone,
    h. Iron, if investigator deems this is medically indicated

6.5.3. Corticosteroid Tapering

- Oral corticosteroids are permitted at a stable dose ≤ 25 mg/day of prednisone or beclomethasone diproprionate (ie, Clipper) at ≤ 5 mg/day or equivalent or ≤ 9 mg/day budesonide during Induction Studies (Weeks 1-8).
- During Extended Induction, the Investigator may taper corticosteroids if he or she feels it is indicated, using the tapering regimen for the Maintenance Study described below.
- Upon entering the Phase 3 Maintenance Study (mWeek 0), subjects must start tapering their corticosteroid dose **OR** where corticosteroids have been used as rescue

medications, tapering must begin 2 weeks after an increase in corticosteroid therapy, using the regimen outlined below:

- Prednisone (or equivalent) dose should be tapered by 5 mg/day every week until 10 mg/day (or prednisone equivalent) and then by 2.5 mg/day every week (or prednisone equivalent) until completely off.
- If subject is on budesonide or beclomethasone, then the dose should be tapered according to local clinical practice.
- If subject is on corticosteroids as a rescue medication during the Maintenance Study, the dose may be tapered as outlined above or more quickly than recommended above. It is recommended, but not required, to start tapering the corticosteroid dose within 2 weeks after initiation or dose increase.

6.5.4. Rescue Medications During Maintenance Study

Subjects meeting loss of response definition during the Maintenance Study may initiate permitted rescue medications, which consist of corticosteroids and aminosalicylates.

- An increase up to the Induction Study Day 1 corticosteroid or aminosalicylate dose is allowed as often as clinically indicated and subject can still stay on study drug.
- Certain increases above the Maintenance Study Week 0 (which should be the same as Induction Study Day 1, in most cases) corticosteroid dose or initiation of corticosteroid without subject having been on corticosteroid upon Induction Study enrollment is allowed, and the subject should remain on study drug, but may lead to the subject meeting criteria for treatment failure (further defined in the statistical analysis plan).
- Increases above baseline (the Maintenance Study Week 0, which should be the same as Induction Study Day 1) or new initiation of aminosalicylates are permitted but may lead to the subject meeting criteria for treatment failure (further defined in the statistical analysis plan).

6.5.5. Restrictions on Alcohol Consumption and Illicit Drug Use

Alcohol abuse or illicit drug abuse, per the judgment of the investigator, within 1 year of Screening until the EOS visit is not allowed.

6.6. Discontinuation

6.6.1. Subject Discontinuation

Any subject may withdraw their consent to participate in the Study at any time without prejudice. The investigator must withdraw from the Study any subject who requests to be withdrawn.
A subject's participation in the Study may be discontinued at any time at the discretion of the investigator and in accordance with his or her clinical judgment. Subjects must also be discontinued on study drug for any AESI (except non-melanoma skin cancer, mono-dermatomal

herpes zoster, and certain laboratory abnormalities that are deemed by the investigator to not place subjects at immediate safety risk) or if the subject becomes pregnant. When possible, the tests and evaluations listed for the termination visit should be carried out. If a subject withdraws before completing the Study, the reason for withdrawal is to be documented on the CRF.

The Sponsor will be notified of all subject withdrawals.

Reasons for which the investigator or the Sponsor may withdraw a subject from the Phase 2b/Phase 3 Induction Studies or Phase 3 Maintenance Study or a subject may choose to terminate participation before completion include the following:

- Adverse event
- Subject choice/Withdrawal of consent
- Major violation of the protocol
- Termination of the Study by the Sponsor
- Initiation of a prohibited medication (Appendix 6) for UC (except for rectal aminosalicylates and rectal corticosteroids during the clinical flare assessment)
- Lost to follow-up
- Pregnancy
- Colectomy

Subjects with laboratory abnormalities as outlined in Section 7.2 (i.e., two sequential occurrences of renal, leukocyte, leukocyte subset, or hepatic panel abnormalities or hepatic panel abnormalities with clinical sign or symptom of acute liver failure) should discontinue the study drug. Any non-laboratory-related AE considered an AESI defined in Section 7.1.4, except for non-melanoma skin cancer and mono-dermatomal herpes zoster, should also lead to study drug discontinuation. Subjects who discontinue Study drug early because of an adverse reaction should be encouraged to continue their participation in the follow-up safety assessments. If a subject fails to return for scheduled visits, a documented effort must be made to determine the reason.

Subject study completion is defined as completing the last study visit whether or not the subject discontinued study drug prematurely.

6.6.2. Subject Replacement

At the Sponsor's discretion, subjects who withdraw or are withdrawn before taking study drug may be replaced. Should greater than 10% of treated patients withdraw before the primary endpoint visit or miss the primary endpoint visit due to events that could not be foreseen during study design planning (e.g., COVID-19 pandemic) then treated subjects may be replaced. Safety data will be presented for all subjects in the Clinical Study Report (CSR) regardless of whether the subject was a replacement.

6.6.3. Study Discontinuation

The Sponsor reserves the right to discontinue these studies at any time for any reason.

Periodic reviews of accumulating data by the IDMC may lead to the committee's recommendation of pausing dosing or terminating the Studies. In the event of premature Study termination, best efforts to guarantee appropriate safety follow-up of subjects who have already been enrolled will be made and IRB/IEC/REBs and the Regulatory Authorities will be informed.

6.7. Pregnancy

If a female subject or the partner of a male subject becomes pregnant during the Study or within 7 days of the subject's last dose of Study drug, the Sponsor clinical Study director (or designee) must be notified immediately. If the female subject is still on Study drug treatment, the Study drug must be discontinued immediately. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

All pregnancies whether by the subject participating in the Study or the female partner of the male subject in the Study should be reported within 24 hours of awareness using the Pregnancy Notification Form.

7. ADVERSE EVENTS

7.1. Definitions

The definitions below are based on International Conference on Harmonization (ICH) guideline E2A, "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting".

7.1.1. Adverse Events (AE)

An AE is any untoward medical occurrence in a patient or clinical trial subject administered a pharmaceutical product that does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

- AEs may be new events
- Preexisting events that increase in frequency, severity or change in nature or seriousness during or as a consequence of participation in clinical studies.
- Pre- or post-treatment complications that occur as a result of a protocol-mandated procedure (such as a biopsy).
- AEs may be clinically significant changes from baseline in physical examination, laboratory tests, or other diagnostic investigation (e.g., laboratory results, x-ray findings).
- AEs may result from an overdose of the Study medication.

Whenever possible, the diagnosis (rather than a series of terms related to a diagnosis) should be recorded as the AE term.

An AE does not include the following:

- Medical or surgical procedures (such as surgery, endoscopy, tooth extraction, or transfusion); the condition that leads to the procedure is an adverse event
- Preexisting diseases or conditions present or detected before signing an informed consent form that do not worsen
- Situations where an untoward medical occurrence has not occurred (such as hospitalization for elective surgery or social and/or convenience admissions)
- Overdose of either Study drug or concomitant medication without any signs or symptoms, unless the subject is hospitalized for observation

Any medical condition or clinically significant laboratory abnormality with an onset date prior to the time the subject signed the informed consent form is considered to be preexisting and should be documented in the medical history CRF.

Pregnancy is not an AE; however, if a female subject becomes pregnant during the conduct of the Study, the sponsor, will be notified according to the procedures for SAE reporting as outlined

in Section 6.4.3. Follow-up information regarding the outcome of the pregnancy and any fetal or neonatal sequelae will be obtained and documented.

7.1.2. Serious Adverse Event (SAE)

A serious adverse event (SAE) is defined as any untoward medical occurrence occurring at any dose that results in any of the following outcomes:

- Death
- Life-threatening situation. "Life-threatening" refers to a situation in which the patient was at risk of death at the time of the event; it does not refer to an event which might have caused death if it were more severe.
- Inpatient hospitalization or prolongation of existing hospitalization
    - Note: "Inpatient hospitalization" means the subject has been formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. It does not include presentation and care within an emergency department. A scheduled hospitalization for a pre-existing condition that has not worsened during participation in the study does not meet this criterion. Pre-planned hospitalizations for an elective medical/surgical procedure, scheduled treatments, or routine check-ups do not meet this criterion. Complications that occur during hospitalizations are AEs. If a complication prolongs hospitalization, it is an SAE.
- Disability. A persistent or significant incapacity or substantial disruption to the ability to conduct normal life functions.
- Congenital anomaly/birth defect in the offspring of a subject who received Study drug
- Important medical events that may not result in death, be immediately life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are as follows:
    - Intensive treatment in an emergency room or at home for allergic bronchospasm
    - Blood dyscrasias or convulsions that do not result in hospitalization
    - Development of drug dependency or drug abuse

7.1.3. Additional Considerations for Serious Adverse Events

- Death is an outcome of an adverse event and not an adverse event in itself. Deaths of unknown cause for which the investigator cannot identify a cause of death will be captured as death of unknown cause or death not otherwise specified.
- All deaths, regardless of cause, must be reported for subjects if the death occurs while the subject is participating in the Study.

- "Occurring at any dose" does not imply that the subject is receiving Study drug at the time of the event; dosing may have been given as treatment cycles or interrupted temporarily before the onset of the SAE but may have contributed to the event.

7.1.4. Adverse Events of Special Interest (AESI)

At each Study visit, the Investigator (or designee) will specifically query for any adverse events of special interest (AESI). The following events are considered AESIs for this Study:

- Suspected or confirmed intestinal perforation
- Complicated herpes zoster (multi-dermatomal, disseminated, or with ophthalmic or CNS involvement)
- Malignancy excluding non-melanoma skin cancer
- Non-melanoma skin cancer
- Serious infection (e.g., that requires hospitalization or intravenous antibiotics)
- Opportunistic infections
- Thromboembolic disease (e.g., DVT, pulmonary embolism)
- Clinical laboratory abnormalities of concern (Refer to Section 7.2)
- Major cardiovascular event (e.g., myocardial infarction or cerebrovascular accident)

All AESIs, except for non-melanoma skin cancers and mono-dermatomal herpes zoster, must be reported to TBPH Clinical Safety and Pharmacovigilance within 24 hours of the time the Investigator or his/her designee becomes aware of an AESI (Refer to Section 7.4.3). Except for non-melanoma skin cancer that has been fully resected, mono-dermatomal herpes zoster, and certain laboratory abnormalities that are deemed by the investigator to not place subjects at immediate safety risk, all of these AESI's should lead to discontinuation of the study drug. For each of these AESI, an additional targeted questionnaire needs to be completed to assess for risk factors. For thromboembolic events in particular, the subject should undergo evaluation for hypercoagulable state (e.g., with clinically relevant investigations, such as referral to a specialist and/or blood testing for a predisposition to a hypercoagulable state) and repeat imaging to assess resolution of the finding.

Besides these AESI, for other AEs, study drug may be interrupted and resumed as deemed medically appropriate by the investigator (e.g. during an infection that requires oral antimicrobial treatment).

7.2. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Abnormal laboratory findings (such as clinical chemistry, hematology, or urinalysis) or other abnormal assessments (such as electrocardiograms [ECGs], X-rays, or vital signs) that are associated with signs and/or symptoms or are considered clinically significant in the judgment of the investigator must be recorded as AEs or SAEs if they meet the definition of an adverse event

(or serious adverse event), as described in Section 7.1.1 (Adverse Event) and Section 7.1.2 (Serious Adverse Event).

Clinical laboratory abnormalities of concern may include, but are not limited to, the following where the investigator must recheck within 2-7 days, except for AST or ALT > 3x ULN where these need to be rechecked within 48-72 hours, as deemed appropriate by the investigator:

- clinically significant reduction in neutrophils or leukocytes or lymphocytes that may place subjects at higher risk for infection such as:
    - moderate or severe neutropenia (e.g., absolute neutrophil count of $< 1.0 \times 10^9$/L)
    - moderate or severe leukopenia (e.g., white blood cell count of $< 2.0 \times 10^9$/L)
    - moderate or severe lymphocytopenia (e.g., absolute lymphocyte count of $< 0.5 \times 10^9$/L)
- abnormal hepatic panel (AST or ALT > 3x ULN)
- an excessive decrease in creatinine clearance (e.g., a reduction by ≥ 50% from baseline (baseline for this purpose is defined as creatinine clearance calculated for Day 1, predose activities)

Depending on the subject's baseline and individual scenario, the investigator should report as an AESI and stop study drug treatment if any of the below is seen:

- moderate or severe neutropenia (e.g., absolute neutrophil count of $< 1.0 \times 10^9$/L) on two sequential laboratory reports
- moderate or severe leukopenia (e.g., white blood cell count of $< 2.0 \times 10^9$/L) on two sequential laboratory reports
- moderate or severe lymphocytopenia (e.g., absolute lymphocyte count of $< 0.5 \times 10^9$/L) on two sequential laboratory reports
- a reduction by ≥ 50% from baseline in creatinine clearance on two sequential laboratory reports
- Abnormal AST or ALT > 3x ULN on two sequential laboratory reports with bilirubin > 2x ULN on at least one of the two laboratory reports or international normalized ratio (INR) > 1.5 on at least one of the two reports (INR will be checked locally)
- AST or ALT > 5x ULN on two sequential laboratory reports at least 2 weeks apart
- AST or ALT > 3x ULN associated with signs or symptoms suggestive of acute liver injury (e.g., the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia [> 5%])
- AST or ALT > 8x ULN on one laboratory report

Note: See Appendix 10 for an algorithm of evaluating and managing subjects with ALT or AST > 3x ULN.

Merely repeating an abnormal test does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

If there are any AE questions, the investigator is encouraged to contact the Sponsor to discuss.

7.3. Assessment of Adverse Events

All AEs will be assessed by the investigator and recorded in the case report form, including the dates of onset and resolution, severity, relationship to Study drug, outcome, and action taken with Study medication.

7.3.1. Severity

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe nausea). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. The severity of AEs will be assessed according to the following definitions:

- **Mild**: the AE is noticeable to the patient and/or the Investigator but does not interfere with routine activity.
- **Moderate**: the AE interferes with routine activity but responds to symptomatic therapy or rest.
- **Severe**: the AE significantly limits the patient's ability to perform routine activities despite symptomatic therapy.

7.3.2. Causal Relationship to Study Medication

The Investigator's assessment of causality is based on clinical judgment regarding the reasonable possibility that the Study medication caused the event and may include consideration of some or all of the following factors:

- Possible alternative causes of the AE, including the disease under treatment, co-morbid conditions, other drugs, and environmental factors.
- The temporal association between drug exposure and onset of the AE.
- Whether the clinical or laboratory manifestations of the AE are consistent with known actions or toxicity of the Study medication.
- Whether the AE resolved or improved with decreasing the dose or stopping the Study medication ("dechallenge") or recurred or worsened upon re-exposure to the Study medication ("rechallenge").

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

- **Not Related:** Evidence exists that the adverse event has an etiology other than the Study drug (such as a preexisting condition, underlying disease, intercurrent illness, or concomitant medication).
- **Related:** A temporal relationship exists between the event onset and administration of the Study drug. It cannot be readily explained by the subject's clinical state or concomitant

therapies and appears with some degree of certainty to be related based on the known therapeutic and pharmacologic actions of the drug. In case of cessation or reduction of the dose, the event abates or resolves and reappears upon rechallenge. It should be emphasized that ineffective treatment should not be considered as causally related in the context of adverse event reporting.

7.3.3. Clinical Events Committee (CEC)

A clinical events committee (CEC) has been established with external experts and will adjudicate thromboembolic and major cardiovascular events. If deemed necessary, the same or a different CEC may also be requested to adjudicate other AEs of interest (e.g., for opportunistic infections, herpes zoster, malignancy). To allow for unbiased assessment, the CEC will remain blinded to treatment assignment. A CEC charter will be drafted with descriptions of membership, the scope of the CEC members' responsibilities, adjudication processes, and definitions used to review and assess specific AEs.

7.4. AE Reporting and Recording

7.4.1. AE Reporting

Timely, accurate, and complete reporting and analysis of safety information from clinical trials is crucial for the protection of subjects and is mandated by regulatory agencies. Sponsor has established standard operating procedures in compliance with regulatory requirements worldwide to ensure appropriate reporting of safety information. All clinical trials sponsored by TBPH will be conducted in accordance with these procedures.

7.4.2. AE, SAE and AESI Recording

All AEs, regardless of seriousness, severity, or causal relationship to Study medication, will be recorded from signing informed consent through the last Study visit (or last subject contact in the case of a follow-up telephone call). AEs will be recorded on the AE page of the CRF. SAEs, regardless of relationship to Study medication will be recorded from signing informed consent through the last Study visit (or last subject contact in the case of a follow-up telephone call). Additionally, investigators may report SAEs assessed as related to Study medication through 30 days following the last Study visit (or last subject contact in the case of a follow-up telephone call). All SAEs will be recorded on both the SAE Report Form and the AE page of the CRF and should include the following:

Description of event:

- Signs and symptoms due to a common etiology should be reported as a single diagnosis; for example, cough, runny nose, sneezing, sore throat, and head congestion would be reported as "upper respiratory infection".
- A diagnosis or description must be as specific and as complete as possible (e.g., "lower extremity edema" instead of "edema").
- Hospitalization or surgical procedures should not be used as adverse event terms (e.g., if a subject was hospitalized for cholecystectomy due to cholecystitis, the

adverse event term should be recorded as cholecystitis, and not as the procedure, cholecystectomy).

- "Death" should not be used as an adverse event term unless the cause of death is unknown. For events with a fatal outcome, the cause of death should be the adverse event term (e.g., if a subject died of an acute myocardial infarction, the adverse event term should be recorded as "Myocardial Infarction" and the event outcome as fatal).

- Relationship to Study medication: The Investigator will make an assessment of the causal relationship of the Study medication to the AE using the guidelines in Section 7.3.2.
- Severity: The severity of the AE will be assessed using the guidelines in Section 7.3.1.
- Outcome: The outcome of AEs will be recorded.
- Therapeutic measures: Measures taken for the treatment or management of the AEs will be recorded.

7.4.3. SAE and AESI Reporting Timeline

SAEs and AESIs will be reported to Clinical Safety and Pharmacovigilance within 24 hours of the time the Investigator or his/her designee becomes aware that a SAE or AESI has occurred, whether or not the event is considered to be related to Study medication. If the initial SAE is reported by telephone, a written report signed by the Investigator must be submitted within 24 hours.

The SAE/AESI Report Form must be completed in accordance with the SAE/AESI Report Form Completion Guidelines. If all information on the SAE/AESI Report Form is not available at the time of the initial report, follow-up SAE/AESI reports will be completed and submitted.

To report an SAE or AESI, complete and fax or email the SAE/AESI Report Form to the following:

Theravance Biopharma Clinical Safety and Pharmacovigilance

[redacted]

For medical questions regarding an SAE, contact the Sponsor medical monitor by telephone as follows:

Sponsor Medical Monitor Contact Information:

Telephone: [redacted]

For fatal or life-threatening events, also fax copies of hospital case reports, autopsy reports, and other documents when requested. Additional information may be requested from the investigator to ensure the timely completion of accurate safety reports.

An SAE may qualify for reporting to regulatory authorities if the SAE is possibly attributable to the Study drug and is unexpected/unlisted based on the current TD-1473 Investigator's Brochure. In this case, all investigators will receive notification of the event. The investigator is responsible for notifying the Institutional Review Board or Ethics Committee and documenting the notification, as required by local regulatory authorities and in accordance with the local institutional policy.

7.5. Adverse Event Follow-up

A subject experiencing an AE or SAE or AESI will be followed by the investigator or his/her trained delegate(s) through the follow-up visit or until the investigator and/or the Sponsor has determined that the AE or SAE or AESI has resolved or a stable clinical endpoint is reached, whichever is longer. The Sponsor may request follow-up of certain adverse events until resolution and documentation of assessments made during this period.

The investigator must take all therapeutic measures necessary for resolution of an SAE or an AESI. Any medications necessary for treatment of the SAE or AESI must be recorded in the concomitant medication section of the case report form.

8. STATISTICAL CONSIDERATIONS

8.1. General Considerations

This section outlines the data summaries and analyses that will be specified in the applicable analysis plan and included in a CSR. A CSR statistical analysis plan (SAP) and separate PK SAP will be prepared and finalized by the Sponsor prior to each database lock. In addition, Biomarker SAPs will be prepared as required. Also, specifications will be prepared by the Independent Reporting Statistical Group and independent exposure-response analyst for the dose selection analyses and data reviews described in Section 8.10, Independent Data Monitoring Committee.

The following formal analyses are planned:

- Analyses of Phase 2b Induction data after all subjects have either completed the Week 8 assessments or prematurely withdrawn from the study
- Analyses of Phase 3 Induction data
- Analyses of Phase 3 Maintenance data, with primary efficacy summaries restricted to placebo and the maintenance doses selected for continued evaluation based on the Induction Phase 2b dose selection analyses

Prior to each analysis, the database for the relevant study will be cleaned and locked.

Study Day 1 is defined as the day of the first study drug dose. The preceding day is Study Day -1. For the Phase 3 Maintenance Study, Study Day 1 is defined as the day of the first Maintenance study drug dose.

All data for each subject will be listed as collected. All statistical summaries and analyses will be performed using [redacted].

Quantitative data and scores (e.g., adapted Mayo score) will be summarized using an 8-point summary (n, mean, standard deviation [SD], median, interquartile range [25th percentile Q1, 75th percentile Q3], minimum, and maximum) unless otherwise specified in the SAP or table shell. Categorical data will be summarized using counts and percentages.

In general, baseline is the last value (scheduled or unscheduled) obtained before the start of study drug dosing. For efficacy endpoints, baseline for those having more than one component (e.g., adapted Mayo score) is calculated from the individual component baselines, whether or not they were assessed during the same visit, and baseline at Maintenance study entry is the value at the last Induction study visit (Week 8 or Week 16).

Values that are derived from symptom diary data will be derived from the last 3 consecutive days for which evaluable data are available during the 7 days preceding the visit; this applies to both baseline and postbaseline values. If not found, values will be derived from the 3 most recent days for which evaluable data are available.

Any changes to the data summaries and analyses outlined in this section will be described in the applicable SAP. Any major changes to primary and key secondary endpoints will be described in a protocol amendment.

8.2. Sample Size and Power

It is currently estimated that approximately 880 subjects (240 for Phase 2b Induction and 640 for Phase 3 Induction) will be enrolled.

The number of enrolled subjects is expected to provide at least 90% power for the primary endpoints of the Induction Studies and also allow a sufficient number of subjects eligible for re-randomization into the Phase 3 Maintenance Study because:

1. A subset of subjects from the initial Phase 3 Maintenance study before final dose selection is determined will be excluded from the analysis of primary and secondary efficacy endpoints: i.e., the subjects assigned to doses that were not selected.
2. Only subjects who received TD-1473 and are considered responders after 8 weeks of Induction therapy, including subjects who are randomized to placebo during the first 8 weeks of Induction Therapy who demonstrate clinical response at Week 16 after receiving TD-1473 80 mg from Weeks 9 to 16, are eligible to be re-randomized in the Phase 3 Maintenance study.
3. The average responder rate for the active treatment groups is estimated to be 60%.
4. It is also estimated that approximately 10% of subjects who are eligible to be re-randomized into the Phase 3 Maintenance study will elect not to participate.

8.2.1. Induction Phase 2b Sample Size Considerations

A sample size of 60 subjects per group was estimated to give approximately 90% (89%) power to detect a 2-point active dose group vs. placebo improvement in total Mayo score at all three doses, given the following:

- Hochberg step-up procedure adjustment for multiple comparisons, with family-wise type 1 error rate to be controlled at 5% (2-sided tests)
- Residual change SD of 3 points

The estimated power to detect a 2-point improvement relative to placebo for at least one of the three doses was greater than 98%.

Assuming a slightly higher residual change SD of 3.5 points, the estimated power to detect a 2-point active dose group vs. placebo improvement in total Mayo score at all three doses was approximately 73% and the estimated power to detect a 2-point improvement at one or more of the doses was approximately 94%. Estimates were obtained using East software, with 10,000 simulations per case.

Subjects will be stratified by prior biologics failure and baseline corticosteroids use at randomization. In addition, randomization caps will be placed on both prior biologics failure subgroups [no to biologics failure (60%) and yes to biologics failure (60%)] to ensure that neither subgroup is overrepresented.

8.2.2. Induction Phase 3 Sample Size Considerations

Upon completion of the analyses based on the Phase 2b Induction data, the sample size may be refined. Currently, it is estimated that 320 subjects per dose group (640 subjects total) will

provide at least 90% power to demonstrate TD-1473 is effective compared to placebo for the primary endpoint of clinical remission at Week 8 under the following assumptions:

- Type 1 error rate of 5% (2-sided)
- Clinical remission rate of 9.5% for placebo at Week 8
- Clinical remission rate of 23.5% for TD-1473 at Week 8:

It is also estimated that 320 subjects per group will provide at least 90% power to demonstrate TD-1473 is effective compared to placebo for the key secondary endpoints of symptomatic remission and endoscopic healing.

In the case where two TD-1473 doses are selected, then 320 subjects per group will have at least 90% disjunctive power to demonstrate at least one of the two TD-1473 doses is effective compared to placebo for clinical remission at Week 8 under the following assumptions:

- Hochberg step up procedure adjustment for multiple comparisons
- Family-wise type 1 error rate to be controlled at 5% (2-sided)
- Clinical remission rate of 9.5% for placebo at Week 8
- Clinical remission rate of 23.5% for more effective TD-1473 dose and 16.5% for the less effective TD-1473 dose

Subjects will be stratified by prior biologics failure and baseline corticosteroids use at randomization. In addition, randomization caps will be placed on both prior biologics failure subgroups (no to biologics failure (60%) and yes to biologics failure (60%)) to ensure that neither subgroup is overrepresented.

8.2.3. Phase 3 Maintenance Sample Size Considerations

Upon completion of the analyses based on the Phase 2b Induction data, the sample size may be refined. Currently, it is estimated that 120 subjects per dose group (360 subjects total) will provide at least 90% disjunctive power to demonstrate at least one of the two TD-1473 doses is effective compared to placebo for the primary endpoint of clinical remission at Maintenance Week 44 under the following assumptions:

- Hochberg step-up procedure adjustment for multiple comparisons
- Family-wise type 1 error rate to be controlled at 5% (2-sided)
- Clinical remission rate of 15% for placebo at Week 44
- Clinical remission rates of 30% and 40% for the two active TD-1473 doses at Maintenance Week 44

A total of 360 subjects total will provide 80% conjunctive power to demonstrate both doses of TD-1473 are effective compared to placebo for clinical remission at Maintenance. In addition, 360 subjects total will also provide adequate power (at least 80%) to demonstrate that at least one of the two TD-1473 doses is effective compared to placebo for the key secondary endpoints of symptomatic remission and endoscopic healing at Maintenance Week 44.

It is estimated that with 880 subjects enrolled in the Induction studies, approximately 400 subjects will be eligible for re-randomization into the Maintenance study. However, about 30 of these 400 subjects will be assigned to the dose that is de-selected based on the analyses of the Phase 2b Induction Study data and therefore not included in the primary efficacy analysis population of the Phase 3 Maintenance Study. In addition, approximately 170 subjects will also enter Maintenance and continue to receive the same treatment as assigned in the Induction study in order to maintain blind. These subjects will also not be included in the primary efficacy analysis population of the Phase 3 Maintenance Study.

8.3. Analysis Sets

8.3.1. Analysis Sets

For the Phase 2b Induction study and Phase 3 Induction study, the modified Intent-to-Treat (mITT) analysis set will include all randomized subjects who receive at least one dose of study drug. For the Phase 3 Maintenance study, the mITT analysis set comprises all randomized subjects who receive at least one dose of study drug and are assigned to receive either placebo or a TD-1473 dose selected based on the Phase 2b dose selection analyses, and the Full Analysis Set (FAS) comprises all randomized subjects who receive at least one dose of study drug. For each study, the mITT set is considered the primary analysis set for efficacy analyses.

The Per-Protocol (PP) analysis set comprises all subjects in the mITT analysis set with no major analysis protocol deviations (Section 8.3.3). Both the mITT and the PP analysis set will be used for selected efficacy summaries and analyses to be specified in the applicable SAP. In addition, for selected Induction Phase 2b dose-response analyses, a PP completers analysis set will be used. The PP completers analysis set comprises all subjects enrolled in the Induction Phase 2b Study with no major analysis protocol deviations and non-missing total Mayo score at Week 8.

The Safety analysis set comprises all subjects who receive at least one dose of study drug. The Safety analysis set will be the analysis set for general (baseline, exposure, and compliance) and safety analyses.

The PK analysis set will include all subjects in the Safety analysis set with at least one evaluable postbaseline TD-1473 PK measurement who are adherent to the protocol. Subjects may be excluded from the PK analysis set if they deviate significantly from the protocol or if the data are unavailable or incomplete, which may influence the PK analysis. The PK analysis set will be further defined in the PK SAP.

Except for the PK analysis set, which is restricted to subjects who received TD-1473, membership in each analysis set will be determined prior to database lock. Analyses using the mITT analysis set will be by randomized treatment. Analyses using the PP analysis set or the safety analysis set will be by actual treatment.

8.3.2. Examination of Subgroups

Predefined subgroups for the Phase 2b and Phase 3 Induction studies will include those defined by the randomization stratification variables:

- History of biologics failure at screening for the Induction study (Yes, No)

- Steroid use status at enrollment into the Induction study (Yes, No)

Additional subgroups may be defined in the applicable SAP.

Predefined subgroups for the Phase 3 Maintenance study likewise will include those defined by the randomization stratification variables:

- Clinical remission status (using adapted Mayo score component definition) at enrollment into the Maintenance study (Yes, No)
- Steroid use status at enrollment into the Maintenance study (Yes, No)

Additional subgroups may be defined in the applicable SAP, e.g., history of biologics failure group, randomization stratum, placebo non-responder who responded after 8 weeks on TD-1473, responder after 8 weeks.

For analysis purposes, values of randomization stratification variables will be determined from the information collected in the clinical database, rather than the information in the RTSM database.

8.3.3. Major Analysis Protocol Deviations

The following protocol deviations are considered as major and as having an impact on analyses of efficacy data:

[redacted]

Additional categories may be specified in the applicable SAP. Numbers of subjects with deviations in each category will be provided by both randomized and actual treatment.

8.4. General Analyses

8.4.1. Demographics and Other Baseline Characteristics

Demographics and baseline characteristics including age, sex, race, ethnicity, creatinine clearance, weight, BMI, UC characteristics, previous and current UC medications by category, and other medical history will be summarized. For subjects enrolled in the Maintenance Study, baseline characteristics at both the time of entry into the Induction Study and the time of entry into the Maintenance Study will be summarized.

8.5. Analysis of Efficacy

8.5.1. Phase 2b Induction Efficacy Endpoints

Refer to DEFINITION OF TERMS

Primary:

Change in total Mayo score from baseline at Week 8

Key Secondary (with multiplicity control):

- Clinical remission by adapted Mayo score components at Week 8

Additional:

[redacted]

8.5.2. Phase 3 Induction Efficacy Endpoints

Primary:

- Clinical remission by adapted Mayo score components at Week 8

Key Secondary (with multiplicity control):

- Endoscopic healing at Week 8
- Symptomatic remission at Week 8
- Clinical response by adapted Mayo score definition at Week 8
- Mucosal healing at Week 8
- Deep symptomatic remission at Week 8

Additional:

[redacted]

8.5.3. Phase 3 Maintenance Efficacy Endpoints

Primary:

- Clinical remission by adapted Mayo score components at mWeek 44

Key Secondary (with multiplicity control):

- Maintenance of clinical response by adapted Mayo score at mWeek 44
- Endoscopic healing at mWeek 44
- Symptomatic remission at mWeek 44
- Corticosteroid-free remission at mWeek 44
- Maintenance of clinical remission at mWeek 44 in those who were in clinical remission at mWeek 0
- Mucosal healing at mWeek 44
- Deep symptomatic remission at mWeek 44

Additional:

[redacted]

[redacted]

8.5.4. Primary Efficacy Evaluation

For efficacy evaluations, the null hypothesis for treatment comparisons will be that there is no difference between a given dose level of TD-1473 and placebo; the alternative hypothesis will be that there is a difference.

For primary endpoints of each study, missing data and sensitivity analyses will be performed. Further details will be given in each applicable SAP.

Phase 2b Induction:

The primary endpoint is reduction in total Mayo score at Week 8. An analysis of covariance (ANCOVA) model will be used with terms for the stratification factors, baseline score, and treatments, and each TD-1473 dose will be compared to placebo. Missing Week 8 scores will not be imputed.

Phase 3 Induction:

The primary endpoint is clinical remission at Week 8. Each active dose selected will be compared to placebo using a stratified Cochran-Mantel-Haenszel (CMH) test, stratifying by randomization stratum. Subjects with missing data or who meet a treatment failure criterion will be counted as not meeting the endpoint of clinical remission (Refer to Section 8.9).

Phase 3 Maintenance:

The primary endpoint is clinical remission at Maintenance Week 44. Each active dose selected for continued evaluation in the Maintenance Study will be compared to placebo using a stratified CMH test, stratifying by randomization stratum. Subjects with missing data or who meet a treatment failure criterion will be counted as not meeting the endpoint of clinical remission (Refer to Section 8.9).

8.5.5. Secondary and Additional Efficacy Evaluations

Unless otherwise specified, binary endpoints will be analyzed using stratified CMH tests, stratifying by randomization stratum, similar to the primary efficacy endpoint. As appropriate, subjects with missing data or who meet a treatment failure criterion will be counted as not meeting the endpoint. Criterion of treatment failure for each endpoint will be described in the SAP. Selected binary endpoints will also be analyzed by fitting logistic regression models and choosing a dose-response model by a method specified in the applicable SAP. Confidence intervals (95%) for treatment differences will be provided.

Quantitative and score efficacy endpoints collected at a single scheduled time point postbaseline will be analyzed by fitting ANCOVA models including terms for treatment effects and stratification factors. The baseline value of each endpoint (or transformed endpoint if a

transformation is specified) will be included as a covariate. For score endpoints, adequacy of the fitted ANCOVA/MMRM models will be assessed and models for ordinal categorical data may be fitted as sensitivity analyses.

Quantitative efficacy endpoints with multiple scheduled postbaseline assessments ([redacted]) will be analyzed by fitting mixed effects repeated measures models (MMRM). SAS procedure MIXED will be used to fit models with random subject effects, an unstructured covariance matrix, and including terms for stratification factors, visit, and baseline score by visit and treatment by visit interactions. [redacted]

For the Phase 2b and Phase 3 Induction studies, the primary assessment for all primary and secondary endpoints will be at Week 8; results from subjects who do not demonstrate clinical response at Week 8 and receive additional study treatment during the Extended Induction period will be summarized descriptively.

8.5.6. Multiplicity Adjustment

Within each study, hypothesis testing will be conducted with a gatekeeping approach to control the overall family-wise type 1 error rate at 5% (2-sided). How this will be achieved including the organization of hypothesis families will be described in the Statistical Analysis Plan (SAP). In general, if there are multiple hypotheses within a family, at least 1 hypothesis must be rejected in order for testing to proceed to later families. Logic gates will also be applied in that if a dose group does not pass an endpoint, this dose group will not be tested in subsequent families.

In addition, nominal p-values will be reported for all efficacy endpoints, including the additional efficacy endpoints.

8.6. Analysis of Pharmacokinetics

For all PK data analyses, the PK analysis set will be used. PK analyses will follow the PK SAP; additional analyses may also be conducted as appropriate.

Appropriate PK parameters and/or mathematical modeling results for TD-1473 will be listed and summarized using descriptive statistics by dose group, as appropriate.

Estimates of PK parameters will be calculated using a population PK approach; data may be pooled across studies to better inform the model. Population PK results will be presented in a separate report. Pertinent subject information such as actual dosing times and PK sampling times and concomitant medications will be recorded to enable PK parameter estimation in a population PK analysis. Plasma samples from selected subjects may be used for additional profiling studies with data summarized in a report separate from the CSR.

8.7. Analysis of Pharmacodynamics

Whole blood and serum samples will be collected as described in the Schedule of Study Procedures tables (Table 1 and Table 2). PD analyses (including PK exposure vs. response analyses for efficacy, safety and/or biomarkers) will be detailed as appropriate in a report separate from the CSR. Samples from selected subjects may be used for potential future exploratory biomarker profiling and reported elsewhere.

8.8. Safety Analyses

Safety summaries for the Phase 2b Induction, Phase 3 Induction, and Phase 3 Maintenance studies will include all subjects who received at least one dose of study drug. This will include subjects who are randomized to TD-1473 doses not selected for continued evaluation in the Phase 3 studies.

Summaries will be provided by scheduled visit and time point or for the entire treatment period, as appropriate. Quantitative data collected at unscheduled times will be listed but will not be included in summaries. Categorical data collected at unscheduled times (e.g., ECG finding categories) will not be included in summaries by time point but will be included in summaries of findings during the entire treatment period.

Safety variables to be summarized include vital signs, adverse events, clinical laboratory results (hematology, chemistry, and urinalysis), and corrected QT interval (QTcF).

For the Phase 2b and Phase 3 Induction studies, the primary assessment period for all safety endpoints will be the first 8 weeks.

8.8.1. Extent of Exposure

Extent of exposure will be calculated from data collected in the study drug administration page of the CRF and summarized. Reasons for study drug discontinuation will be summarized. For each subject, treatment compliance over the interval from first to last dose will be calculated from data collected in the study drug administration and drug accountability pages of the eCRF. Treatment compliance will be summarized by actual treatment received.

8.8.2. Adverse Event Data

AEs will be coded to the preferred terms of the Medical Dictionary for Regulatory Activities (MedDRA®). Summaries will present by system organ class (SOC), preferred term (PT), and severity (mild, moderate, severe), the number and percentage of subjects reporting each AE.

A Treatment Emergent Adverse Event (TEAE) will be defined as any AE that begins on or after the date of the first dose of study drug.

The number and percentage of subjects who reported TEAEs will be summarized as follows:

- All TEAEs, by SOC and PT and also by PT (by descending overall frequency)
- All TEAEs of Special Interest (Section 7.1.4) by SOC and PT.
- All TEAEs, by SOC, PT, and severity
- All study drug-related TEAEs, by SOC and PT
- All study drug-related TEAEs, by SOC, PT, and severity
- All TEAEs leading to premature discontinuation of study drug, by SOC and PT
- All TEAEs leading to temporary interruption of study drug, by SOC and PT
- All TESAEs, by SOC and PT
- All study drug-related TESAEs, by SOC and PT

A listing will be provided for all subjects who experience an SAE. Listings will also be provided for subjects who discontinued study treatment prematurely because of AEs and subjects who temporarily interrupted study treatment because of AEs. AESIs (Section 7.1.4) will also be listed.

8.8.3. Concomitant Medications

Medication names will be mapped according to the World Health Organization Drug Dictionary. The following summaries will be provided, by drug class and preferred name:

- Prior UC medications
- Prior medications with indications other than UC
- Concomitant medications, including those with indication for UC

The prior medications summaries will be restricted to medications stopped before the date of the first study drug dose. The summary of concomitant medications will comprise all medications taken during the treatment period, including medications ongoing at entry.

8.8.4. Laboratory Data

Laboratory values, changes from baseline, values relative to normal ranges, and values and changes meeting specified criteria of special interest (including those given in Section 6.2) will be summarized.

Reference ranges provided by the laboratory for each test will be used to evaluate the clinical significance of laboratory test results. Values falling outside the relevant reference range will be flagged, as appropriate, in the data listings. A separate listing or listings will be provided for abnormalities in clinical laboratory test results.

8.8.5. Vital Signs Data

HR, systolic and diastolic BP, respiratory rate, and body temperature values at each visit and time point and changes from baseline at each visit and time point after the first dose will be summarized, and counts and percentages will be shown for the categories in Table 4 by visit and time point.

Table 4: Thresholds for Vital Signs

Heart Rate (bpm)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)
< 40 > 110	< 85 > 160	< 45 > 100

8.8.6. ECG Data

HR, QT, QTcF, PR, and QRS values at each time point and changes from baseline at each time point after the first dose will be summarized and counts and percentages will be shown for SAP-specified value and change from baseline categories of special interest.

Table 5: Thresholds for ECG

Heart Rate (bpm)	Heart Rate Change from Baseline (bpm)	PR Interval (msec)	PR Percentage Change from Baseline (%)	QRS Interval (msec)	QTcF (msec)	QTcF Change from Baseline (msec)
> 120	≥ 20	≥ 200	≥ 15	≥ 120	Males:	≤ 30
> 130	≥ 30	≥ 220	≥ 25		< 430	> 30, ≤ 60
		Optional:			≥ 430	> 60
		≥ 240			≥ 450	
		≥ 260			≥ 470	
		≥ 280			≥ 480	
		≥ 300			≥ 500	
					Females:	
					< 450	
					≥ 450	
					≥ 470	
					≥ 480	
					≥ 500	

A listing of subjects with extreme values or changes, as specified in the SAP (e.g., values of QTcF > 500 msec, QTcF increases from baseline > 60 msec) will be provided.

8.9. Data Handling Rules

For primary analyses of all applicable efficacy endpoints, including secondary and additional endpoints, the following rules will be applied. For sensitivity analyses of primary and key secondary endpoints, different rules may be specified in the applicable SAP.

- Binary endpoints: Subjects who had non-missing data for a binary efficacy endpoint meeting the criterion for success but met definition of treatment failure prior to visit will be considered as not meeting endpoint. Full rules for the derivation of treatment failure will be outlined in the SAP.
- Missing = endpoint not met

Quantitative or score endpoints:

- The treatment failure criteria above are applied to exclude any assessments obtained following treatment failure
- MMRM analysis with data assumed to be “Missing at Random” for quantitative or score endpoints assessed more than once postbaseline
- The analysis of the Phase 2b primary endpoint will be a completers analysis. For other quantitative or score endpoints assessed only once post-baseline, imputation for missing data will be described in the SAP.

[redacted]

8.10. Independent Data Monitoring Committee (IDMC)

[redacted]

8.11. End of Induction Phase 2b Dose Selection

Following database lock of the Induction Phase 2b study after all subjects have either completed the Week 8 assessments or have prematurely withdrawn from the study prior to Week 8, data will be provided to the Independent Statistical Reporting Group (IRSG) to prepare the unblinded data summaries that will be used to select TD-1473 doses for continued evaluation in the Phase 3 Induction Study and the Phase 3 Maintenance Study.

The Sponsor will make the final selection of dose(s) to be further investigated in Phase 3 using a Dose Selection Committee. This committee will consist of subject matter experts from the Sponsor's Research and Development organization, who are otherwise not involved in the routine oversight and conduct of the study. The Dose Selection Committee will have access to the unblinded efficacy and safety summary tables and figures, but it will not have access to individual subject treatment assignment with the exception of data listings that are considered pertinent to safety evaluation such as unblinded listing of SAEs, AEs leading to discontinuation of study agent, and markedly abnormal laboratory values for the purpose of safety evaluation.

To assist with the dose selection process, general guidelines will be provided in the Phase 2b SAP and the committee will follow these guidelines to direct the choice of dose(s) for further evaluation in the Phase 3 dose-confirmatory Induction and Maintenance studies. The dose selection guidelines and the required data presentations and analyses will be prospectively described in detail in the Phase 2b SAP and a general framework is provided as follows:

1. Ruling out doses unlikely to have sufficient efficacy to warrant further evaluation (i.e., futility analysis)
2. Selecting an induction dose (or possibly doses) for which a clinically meaningful placebo-adjusted treatment effect is indicated for the primary endpoint of change from baseline in total Mayo score and the key secondary endpoint of clinical remission at Week 8
3. Evaluating the safety and tolerability of dose(s) identified in Step 2
4. If necessary, using Exposure-Response analyses to differentiate doses identified in Steps 2 and 3. In this setting, responses will focus on safety endpoints.

To optimize the therapeutic index for long-term therapy in this chronic disease, the Sponsor plans to study 2 doses in the Phase 3 Maintenance study, including the dose being proposed for Phase 3 Induction and likely a lower dose to assess long-term efficacy and safety.

No interim analysis is planned for the Phase 3 Induction and Phase 3 Maintenance studies.

9. STUDY ADMINISTRATION

This Study will be conducted in compliance with all applicable regulations.

9.1. Principal Investigator Responsibilities

Before beginning the Study, the principal investigator (PI) at each site must provide to the Sponsor or its designee a fully executed and signed Form FDA 1572 and, if applicable, a financial disclosure form. For applicable studies, financial disclosure forms must also be completed for all sub-investigators who will be directly involved in the treatment or evaluation of research subjects in this Study. (A subinvestigator is defined in ICH E6 as any individual member of the clinical Study team designated and supervised by the investigator at a Study site to perform critical Study-related procedures and/or to make important Study-related decisions [e.g., associates, residents, research fellows]).

The PI will ensure the following:

- He or she will conduct the Study in accordance with the relevant, current protocol and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.
- He or she will personally conduct or supervise the Study.
- He or she will inform any potential subjects, or any persons used as controls, that the drugs are being used for investigational purposes and he or she will ensure that the requirements relating to obtaining informed consent and institutional review board (IRB) review and approval are met in accordance with 21 CFR, ICH guidelines, and all other applicable local regulations.
- He or she will report to the sponsor adverse experiences that occur in the course of the investigation in accordance with 21 CFR, ICH guidelines, and all other applicable local regulations He or she has read and understands the information in the TD-1473 Investigator's Brochure, including potential risks and side effects of the drug.
- His or her staff and all persons who assist in the conduct of the Study are informed about their obligations in meeting the above commitments.
- He or she will ensure that adequate and accurate records are maintained and to make those records available for inspection in accordance with in 21 CFR, ICH guidelines, and all other applicable local regulations.
- He or she will ensure that the IRB/IEC complies with the requirements of 21 CFR Part 56, ICH guidelines and other applicable regulations, and conducts initial and ongoing reviews and approvals of the Study. He or she will also ensure that any change in research activity and all problems involving risks to human subjects or others are reported to the IRB/IEC. Additionally, he or she will not make any changes in the research without IRB/IEC approval, except where necessary to eliminate apparent immediate hazards to human subjects.

- He or she agrees to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR, ICH guidelines, and all other applicable local regulations.

9.2. Institutional Review Board/Independent Ethics Committee

Before beginning Study-specific research, the investigator will obtain written confirmation that the IRB, IEC, or Research Ethics Board (REB) is properly constituted and compliant with ICH and GCP requirements, applicable laws, and local regulations. A copy of the confirmation from the IRB/IEC/REB will be provided to the Sponsor or its designee. The protocol, informed consent form (ICF), IB, and any other appropriate written information provided to the subjects that the IRB/IEC/REB may require to fulfill its responsibilities will be submitted to the IRB/IEC/REB in advance of the Study. The Sponsor or its designee must approve the ICF and all subject recruitment materials before they are submitted to the IRB/IEC/REB. The Study will not proceed until appropriate documents from the IRB/IEC/REB confirming unconditional approval of the protocol and the ICF are obtained by the investigator and copies are received by the Sponsor or its designee. If possible, the approval document should refer to the Study by Study protocol title and the Sponsor Study number, identify the documents reviewed, and include the date of the review and approval. The written approval of the IRB/IEC/REB will be retained as part of the Study file. The Study may proceed before approval of consent forms and other Study documents translated to a language other than the native language of the clinical site, provided that written IRB/IEC/REB approval of the translated documents is obtained before they are used. Any amendments to the protocol should be reviewed promptly.

The investigator must provide the appropriate periodic reports on the progress of the Study to the IRB/IEC/REB and the Sponsor in accordance with local IRB/IEC/REB requirements and applicable governmental regulations, whichever is strictest.

9.3. Informed Consent

A properly written and executed ICF, in compliance with-ICH E6 (GCP Guideline, Section 4.8), 21 CFR §50, and other applicable local regulations, will be obtained for each subject before enrollment of the subject into the Study. The investigator will prepare the ICF or revise the template ICF and provide the documents to the Sponsor (or designee) for approval before submission to the IRB/IEC/REB. The Sponsor and the IRB/IEC/REB must approve the documents before they are implemented.

The investigator will provide copies of the signed ICF to each subject and will maintain the original in the subject's record file.

9.4. Data Recording and Quality Assurance

As used in this protocol, the term case report form (CRF) should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used.

Electronic data capture (EDC) technology will be used for this Study. All clinical information requested in this protocol will be recorded on the electronic case report forms approved by the Sponsor, or via other data collection methods, e.g., electronic laboratory data transfer. Study site personnel will enter (in English) Study data into the CRFs for each screened subject. Training on

the systems used by site personnel (e.g., EDC) or subjects (e.g., eDiary) will be completed and documented before access to the system is given.

In the event of a CRF data change (e.g., correction of an error or addition of new information), corrections will be made to the CRF. Corrections to the CRFs, including the reason for change, will be automatically documented through the EDC system's audit trail.

The investigator is responsible for reviewing all CRFs, verifying them for accuracy, and approving them via an electronic signature. The investigator is designated as the signatory coordinating investigator.

An electronic copy of the CRF casebooks, in-clinic assessments, and eDiary data will be sent to the site for retention with other Study documents after full completion of the Study, i.e., after database lock.

The investigator is responsible for maintaining accurate, authentic, complete, and up-to-date records for each subject. The investigator is also responsible for ensuring the availability of any original source documentation related to the Study (including any films, tracings, computer discs, tapes, and worksheets). In most cases the source is the subject's medical record. Data collected on the CRFs must match the source documents.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator's site and clearly identify those data that will be recorded in the CRF and for which the CRF will stand as the source document.

9.5. Document Retention

Until otherwise notified by the Sponsor, an investigative site must retain in a controlled manner all Study documents required by the Sponsor and by the applicable regulations. The investigative site must take measures to prevent accidental or premature destruction of essential documents, that is, documents that individually and collectively permit evaluation of the conduct of a Study and the quality of the data produced, including paper copies of Study records (e.g., subject charts) and any original source documents that are electronic, as required by applicable regulations.

The investigator must consult the Sponsor representative before disposal of any Study records and must notify the Sponsor of any change in the location or disposition of the Study files. If an investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the Study documents, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian and must approve this transfer of responsibility.

9.6. Confidentiality

The investigator or designee must explain to each subject, before enrollment into the Study, that, for evaluation of Study results, the subject's confidential medical information obtained during the Study may be shared with the Study sponsor, the Study sponsor's affiliated companies, the Study sponsor's designated service providers, regulatory agencies, and the institutional review board (IRB) or independent ethics committee (IEC). The investigator (or designee) is responsible for obtaining written permission to use confidential medical information in accordance with

country-specific regulations (such as the Health Insurance Portability and Accountability Act in the United States) from each subject. If permission to use confidential medical information is withdrawn, the investigator is responsible for documenting that no further data from the subject will be collected.

Subject medical information obtained during this Study is confidential, and disclosure to unauthorized third parties is prohibited. The pertinent sections of data protection laws will be complied with in full. Study records containing subject information will only be identified by the subject identification number, subject initials, date of birth, and Study number, and not by the subject's full name, except the subject consent form, which is archived at the Study center only. The subject's name will not be used in any public report of the Study.

During the course of the Study, a confidential subject identification list will be maintained by the investigator and archived at the investigative site.

Before and during the conduct of the Study, no Study-related details may be disclosed, i.e., placed on the internet, published, or otherwise publicized, or provided to a third party without prior written permission from the Sponsor. The policy for publication of data after completion of the Study is described in Section 9.9 (Publication).

9.7. Access to Data and Documents

Upon receipt of the subject's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare.

Study data recorded on the CRFs must be verifiable to the source data. All original recordings, laboratory reports, and subject records generated by this Study must be available to the Sponsor, representatives of the Sponsor, the IRB/IEC/REB, and applicable regulatory authorities, and they may be used for submission to regulatory authorities. In addition, all source data should be attributable (signed and dated), consistent with local medical practice. The investigator must therefore agree to allow direct access to all source data. Subjects must also allow access to their medical records, and subjects will be informed of this and will confirm their agreement when giving informed consent.

9.8. Quality Control: Study Monitoring and Auditing

Qualified individuals designated by the Sponsor will monitor all aspects of the Study according to GCP and standard operating procedures (SOPs) for compliance with applicable government regulations. The investigator agrees to allow these monitors direct access to the clinical data and supplies, dispensing, and storage areas and, if requested, agrees to assist the monitors. The investigator and staff are responsible for being present or available for consultation during routinely scheduled site visits conducted by the Sponsor or its designees.

Members of the Sponsor's GCP Quality Assurance Department or designees may conduct an audit of a clinical site at any time during or after completion of the Study. The investigator will be informed if an audit is to take place and advised as to the scope of the audit. Inspections and audits are typically carried out during the clinical and reporting phases of this Study to ensure that the Study is conducted and data are generated, documented, and reported in compliance with the protocol, GCP, written SOPs and applicable laws, rules, and regulations.

Representatives of the FDA or other Regulatory Agencies, including IRB/IEC representatives may also conduct an audit of the Study. If informed of such an inspection, the investigator should notify the Sponsor immediately. The investigator will ensure that the auditors have access to the clinical supplies, Study site facilities, laboratory and all data (including original source documentation) and all Study files are available, if requested.

Non-compliance with the protocol, ICH, GCP, or local regulatory requirements by an investigator, institution, institution staff, or representatives of the Sponsor will lead to prompt action by the Sponsor to secure compliance. Continued non-compliance may result in termination of the investigator's involvement in the Study. The IRB/IEC/REB and relevant regulatory authority will be informed.

9.9. Publication

The Sponsor recognizes the importance of communicating medical Study data and therefore encourages their publication in reputable scientific journals and presentation at seminars or conferences. The Sponsor will retain the ownership of the data collected in this Study. The investigator will provide any proposed manuscript or abstract to the Sponsor before submission for publication or presentation of any results or data obtained in this Study.

Additional details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this Study will be described in the Clinical Study Agreement between the Sponsor and the investigator.

10. REFERENCES

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References are available upon request.

APPENDIX 1. PROTOCOL SIGNATURE FORM

Protocol Signature Form

Protocol #:	0157
Protocol Title:	A Phase 2b/3 Multi-Center, Randomized, Double-Blind, Multi-Dose, Placebo-Controlled, Parallel-Group Set of Studies to Evaluate the Efficacy and Safety of Induction and Maintenance Therapy with TD−1473 in Subjects with Moderately-to-Severely Active Ulcerative Colitis
Study Short Title:	Rhea: Efficacy and Safety of TD-1473 in Ulcerative Colitis
Version:	Amendment 3
Version Date:	14 May 2020

I have read the protocol described above and agree to conduct this Study in accordance with procedures described therein. I also agree to conduct the Study in compliance with all applicable regulations.

Investigator's Name (print)

Investigator's Signature

Date

APPENDIX 2. COCKCROFT-GAULT CALCULATION

Creatinine clearance (mL/min) will be estimated using the Cockcroft-Gault equation as follows:

Estimated creatinine clearance =	$\frac{(140\text{-Age}) \times \text{Ideal Body Weight (kg)}}{72 \times \text{Serum Creatinine (mg/dL)}}$	, if male
Ideal body weight =	50 kg + 2.3 kg for each 2.54 cm over 152.4 cm	, if male
Estimated creatinine clearance =	$\frac{(140\text{-Age}) \times \text{Ideal Body Weight (kg)}}{72 \text{ x Serum Creatinine (mg/dL)}}$	× 0.85, if female
Ideal body weight =	45.5 kg + 2.3 kg for each 2.54 cm over 152.4 cm	, if female

APPENDIX 3. MAYO SCORING SYSTEM FOR ASSESSMENT OF ULCERATIVE COLITIS ACTIVITY

This is provided as an example only; electronic tablets will be provided by the Sponsor to capture this information.

Mayo Scoring Components for Assessment of Ulcerative Colitis Activity*
Stool Frequency (Each patient serves as his or her own control to establish the degree of abnormality of the stool frequency)
0 point: Normal number of stools for patient
1 point: 1 to 2 stools per day more than normal
2 points: 3 to 4 stools more than normal
3 points: >= 5 stools more than normal
Rectal Bleeding (The daily bleeding score represents the most severe bleeding of the day)
0 point: No blood seen
1 point: Streaks of blood with stool less than half the time
2 points: Obvious blood with stool most of the time
3 points: Blood alone passes
Endoscopic findings
0 point: Normal or inactive disease
1 point: Mild Disease (erythema, decreased vascular pattern)
2 points: Moderate Disease (marked erythema, lack of vascular pattern, friability, erosions)
3 points: Severe Disease (spontaneous bleeding, ulceration)
Physician's Global Assessment (acknowledges the three other criteria, the patient's daily recollection of abdominal discomfort and general sense of well-being, and other observations, such as physical findings and the patient's performance status.)
0 point: Normal
1 point: Mild disease
2 points: Moderate disease
3 points: Severe disease

Source: [11]

[redacted]

[redacted]

[redacted]

[redacted]

APPENDIX 7. DEFINITION OF INTOLERANCE OR INADEQUATE RESPONSE AND DEFINITION OF CORTICOSTEROID DEPENDENCE

A) Definition of intolerance or inadequate response:

Aminosalicylates:

- Signs and symptoms suggestive of persistence of active disease despite an 8-week regimen at the highest dose either defined by local guidelines or by subject's tolerance

Corticosteroids:

- Signs and symptoms suggestive of persistence of active disease despite a) a 4-week regimen that included ≥ 2 weeks of ≥ 0.75mg/kg/day of prednisolone or 40mg/day of prednisone or equivalent or b) budesonide ≥ 9mg/day or beclomethasone diproprionate (i.e., Clipper) at ≥ 5 mg/day given orally for ≥ 4 weeks ***OR***
- Intolerance: subject developed clinically significant adverse event(s) (including, but not limited to hyperglycemia, infection, Cushing's syndrome, anxiety, weight gain, blurry vision, corticosteroid-induced hypertension, intolerable insomnia, osteopenia/osteoporosis) unresponsive to dose reduction that preclude the use of corticosteroids to treat UC, in the PI's judgment, or subject has a medical condition that precludes use of corticosteroids to treat UC

Immunomodulators (azathioprine or 6-mercaptopurine):

- Signs and symptoms suggestive of persistence of active disease despite a) a regimen ≥ 12 weeks of oral azathioprine (≥ 2.0 mg/kg) or 6-mercaptopurine (≥ 1.0 mg/kg) or a lower dose of 6-MP or azathioprine if the local guidelines specify a different treatment regimen (included in the source document), b) a dose of 6-MP or azathioprine that is confirmed to be therapeutic by thioguanine nucleotide levels > 200 pmole/8 x 10^8 RBCs, or c) the highest dose with anything higher limited by leukopenia, elevated AST or ALT, or nausea ***OR***
- Intolerance to at least one immunomodulator (including, but not limited to nausea/vomiting, abdominal pain, pancreatitis, LFT abnormalities, lymphopenia, TPMT genetic mutation, infection) that is unresponsive to dose reduction that precludes the use of 6-MP or azathioprine to treat UC or the subject has a medical condition that precludes the use of 6-MP or azathioprine

Biologics (anti-TNF or anti-integrin; Refer to Appendix 8 for further detail):

- Signs and symptoms suggestive of persistence of active disease despite completing an Induction regimen ***OR***
- Symptom recurrence during maintenance dosing following previously demonstrating clinical benefit ***OR***

- Intolerance (including, but not limited to infusion-related reaction, rash, injection site reaction, demyelination, congestive heart failure, infection)

B) **Definition of corticosteroid dependence:** requiring prednisolone ≥10mg/d or ≥budesonide 3mg/d or equivalent for ≥3 months to control UC, or relapse within 3 months of stopping steroid therapy or unable to discontinue corticosteroids without flare within 3 months after initiating them.

APPENDIX 8. DEFINITION OF PRIOR BIOLOGICS FAILURE: PRIMARY AND SECONDARY NON-RESPONDER OR INTOLERANT TO PREVIOUS BIOLOGICS

Primary non-responder:

Subjects were to have received Induction doses of at least one of the following:

- Infliximab (3 doses of 5-10 mg/kg at Weeks 0, 2, and 6 or earlier)
- Adalimumab (dose of 160 mg at Week 0 followed by a dose of 80 mg at Week 2 or earlier)
- Vedolizumab 300 mg administered by intravenous infusion at Weeks 0, 2, and 6 or earlier
- Golimumab 100 mg administered by injection at Week 0 (2 100-mg injections), and Week 2 (1 100-mg injection) or earlier
- Ustekinumab single intravenous weight-based infusion 260 mg (< 55 kg), 390 mg (55-85 kg) or 520 mg (> 85 kg)

And did not respond to these induction doses as evidenced by at least 1 of the following signs or symptoms related to persistently active UC occurring within 2 weeks after receiving the last dose:

- Lack of improvement or worsening in stool frequency and/or consistency.
- Lack of improvement or worsening in bloody stools and/or rectal bleeding.
- Lack of improvement or worsening in daily abdominal pain.
- Occurrence, lack of improvement or worsening fever thought to be related to UC.
- Initiation or increase in antidiarrheal medication.

Secondary non-responder:

Initially responded to Induction therapy and received at least 2 of the following Maintenance doses:

- Infliximab (at a dose of ≥ 5 mg/kg)
- Adalimumab (at a dose of 40 mg every week or every other week)
- Vedolizumab 300 mg administered every 8 weeks or every 4 weeks
- Golimumab 100 mg injection at week 6 and every 4 weeks
- Ustekinumab subcutaneous 90 mg dose 8 weeks after the initial intravenous dose, then every 8-12 weeks thereafter or more frequently.

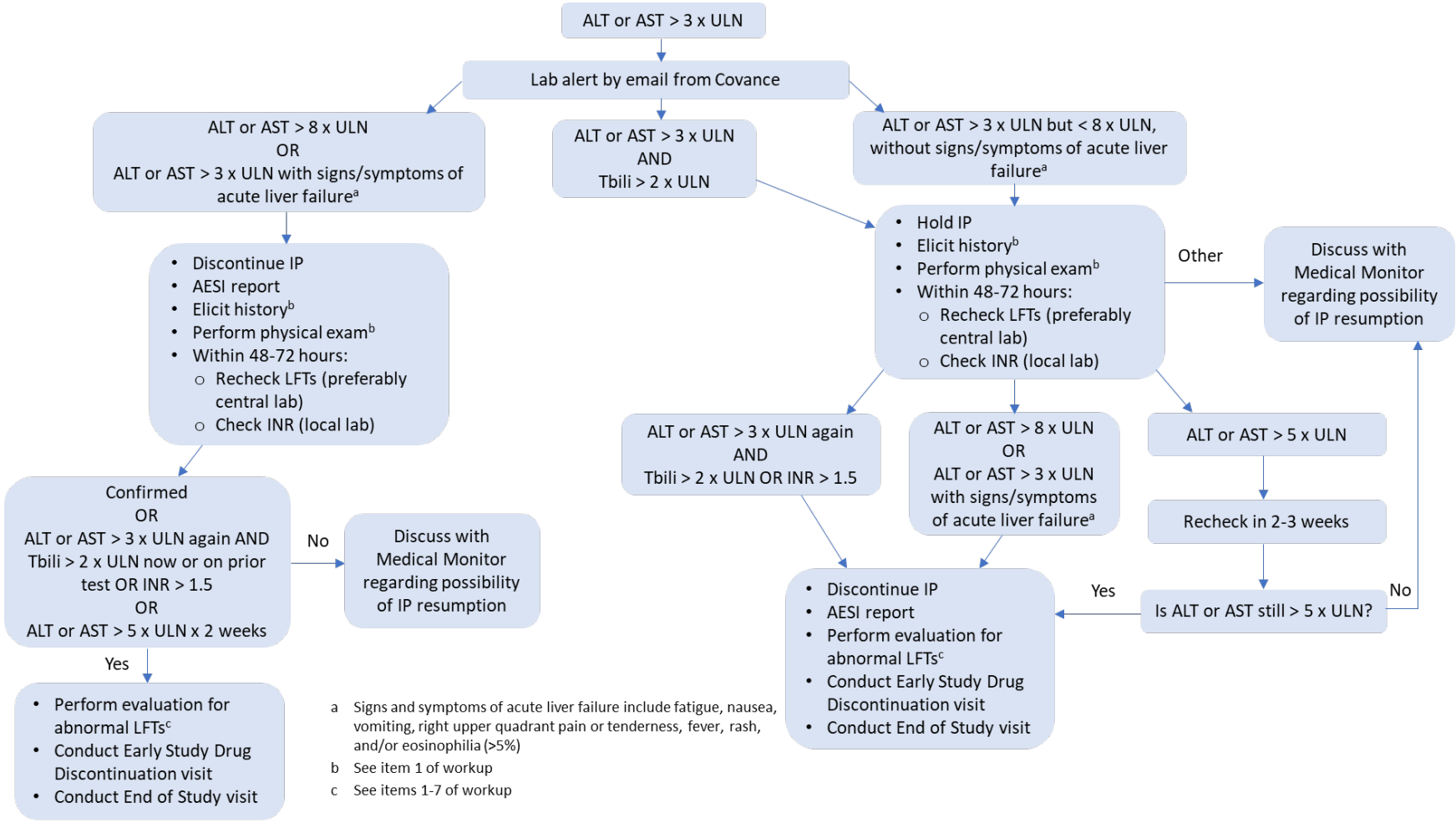
And had at least 1 of the following signs or symptoms related to recurrence of active UC occurring within 2 weeks after receiving the last dose:

- Lack of improvement or worsening in stool frequency and/or consistency.
- Lack of improvement or worsening in bloody stools and/or rectal bleeding.

- Lack of improvement or worsening in daily abdominal pain.
- Occurrence, lack of improvement or worsening fever thought to be related to UC.
- Initiation or increase in antidiarrheal medication.

[redacted]

APPENDIX 10. GUIDELINE ALGORITHM FOR MONITORING, ASSESSMENT, AND EVALUATION OF ABNORMAL LIVER TESTS IN PARTICIPANTS WITH NO UNDERLYING LIVER DISEASE



Abbreviations: AESI, adverse event of special interest; ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; IP, investigational product; LFT, liver function test; Tbili, total bilirubin; ULN, upper limit of normal

Item 1 should be performed where "b" appears above; however, the complete work-up below (Items 1-5) should be performed in every situation where "c" appears above. Items 6-7 are optional, to be considered on case-by-case basis. All tests should be reported with appropriate source documentation. The study medical monitor should be notified when the abnormalities are detected and provided with an update of the results of the diagnostic work-up.

The following definition of patterns of Drug Induced Liver Injury (DILI) is used when directing the work-up for potential DILI based on elevations of common laboratory tests (LT):

Histopathology	LT	Ratio (ALT/ULN)/(Alk Phos/ULN)
Hepatocellular	**ALT ≥ 3 × ULN**	**≥ 5**
Cholestatic	**ALT ≥ 3 × ULN**	**≤ 2**
Mixed	**ALT ≥ 3 × ULN and AP ≥ 2 × ULN**	**> 2 to < 5**

1. Obtain detailed history of present illness (abnormal LTs) including (if not already obtained at baseline) height, weight, body mass index (BMI). Assess for abdominal pain, nausea, vomiting, scleral icterus, jaundice, dark urine, pruritus, rash, fever, and lymphadenopathy. Assess for history of prior abnormal liver tests, liver disease including viral hepatitis, obesity, metabolic syndrome, congestive heart failure (CHF), occupational exposure to hepatotoxins, diabetes mellitus (DM), gallstone disease or family history of gallstone or liver disease. Specifically record history of alcohol use, other medications including acetaminophen, non-steroidal anti-inflammatory drugs (NSAID), over the counter (OTC) herbal supplements, vitamins, nutritional supplements, traditional Chinese medicines, and street drugs; and document whether or not there has been any recent change in any other prescription drugs and start-stop dates. Obtain travel history to endemic areas for hepatitis A, hepatitis E. Ask for history of any prior blood transfusions and when they were performed. Perform physical exam, obtain vital signs and BMI, and document presence or absence of scleral icterus, palpable liver including size, degree of firmness or tenderness, palpable spleen including size, ascites, and stigmata of chronic liver disease (spider angiomata, gynecomastia, palmar erythema, testicular atrophy). Allow free text in case report form for other relevant history and physical information.
2. Mandatory liver ultrasound with consideration of further imaging (eg, computerized tomography [CT], magnetic resonance imaging [MRI], magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), Doppler studies of hepatic vessels, etc., if indicated based on ultrasound findings or clinical situation).
3. If total bilirubin (Tbili) is > 2 x ULN, request fractionation to document the fraction that is direct bilirubin and to rule out indirect hyperbilirubinemia indicative of Gilbert's syndrome, hemolysis or other causes of indirect hyperbilirubinemia. Complete blood count (CBC) with white blood count (WBC) and eosinophil count platelet count, international normalized ratio (INR), and total protein and albumin (compute globulin fraction) should also be documented.

If INR is abnormal, prothrombin time (PT), partial thromboplastin time (PTT) should be obtained and these values should be followed until normal, along with documentation of whether parenteral vitamin K was given along with the effect of such treatment on INR.

4. If initial LTs and ultrasound do not suggest Gilbert's syndrome, biliary tract disease or obstruction, viral hepatitis serology should be obtained including anti-hepatitis A virus immunoglobin M (anti-HAV IgM), anti-HAV total, hepatitis B surface antigen (HBsAg), anti-HBs, anti-HB core total, anti-HB core IgM, anti-hepatitis C virus (anti-HCV), anti-hepatitis E virus IgM (anti-HEV IgM) (even if has not traveled to an endemic area for hepatitis E), Epstein-Barr virus (EBV) and Cytomegalovirus (CMV) screen.
   - If patient is immunosuppressed, test for HCV RNA and HEV RNA.
   - If HBsAg or anti-HB core IgM or anti-HB core IgG positive, also get HBV DNA to detect active HepB, especially in patients who are immunosuppressed.
   - If all other hepatitis B serologic tests are negative and anti-HBc total is the only positive test, HBV DNA should be obtained to detect reactivation of hepatitis B.
5. Assuming that the history, physical, and initial imaging and laboratory has not revealed a cause of elevated LTs, screen for other causes of liver disease including: Total protein and albumin (estimate globulin fraction and obtain quantitative immunoglobulins if elevated), antinuclear antibody (ANA), anti-liver kidney microsomal antibody type 1 (anti-LKM1), anti-liver-kidney microsomal antibodies (anti-LKM antibodies), anti-smooth muscle antibodies (ASMA), erythrocyte sedimentation rate (ESR), and [redacted]). If the pattern of laboratory abnormalities is not hepatocellular, but cholestatic or a mixed pattern (see definitions in table above), then gamma-glutamyl transferase (GGT), anti-mitochondrial antibody (AMA) and anti-neutrophil cytoplasmic antibody (pANCA) should also be tested. If there is an indication by history or elevated baseline LTs that there may be an underlying chronic liver disease possibly exacerbated by exposure to the study intervention in the clinical trial or making the participant more susceptible to DILI, test iron/Total iron binding capacity (TIBC) and ferritin (hemochromatosis), and alpha-1-antitrypsin level. If patient is < 50 years of age, ceruloplasmin should also be tested to screen for Wilson's disease. If patient is sick enough to be hospitalized and is under age 50, a slit lamp examination to detect Kayser-Fleischer rings and a 24-hour urine collection for copper should be measured. Consider serum ethanol and/or acetaminophen level and urine drug screen as clinically appropriate.
6. A liver biopsy should be considered if autoimmune hepatitis remains a competing etiology and if immunosuppressive therapy is contemplated.

   A liver biopsy may be considered:

   - if there is unrelenting rise in liver biochemistries or signs of worsening liver function despite stopping the suspected offending agent.
   - if peak ALT level has not fallen by > 50% at 30-60 days after onset in cases of hepatocellular DILI, or if peak Alk P has not fallen by > 50% at 180 days in cases of cholestatic DILI despite stopping the suspected offending agent.
   - in cases of DILI where continued use or re-exposure to the implicated agent is expected.

– if liver biochemistry abnormalities persist beyond 180 days to evaluate for the presence of chronic liver diseases and chronic DILI.

7. If pertinent, copies of hospital discharge summary, radiology, pathology and autopsy reports should be obtained.

Abbreviations

Abbreviation	Definition
AlkP	alkaline phosphatase
ALT	alanine aminotransferase
AMA	anti-mitochondrial antibody
ANA	antinuclear antibody
Anti-LKM1	anti-liver kidney microsomal antibody type 1
ASMA	anti-smooth muscle antibodies
AST	aspartate aminotransferase
BMI	body mass index
CBC	complete blood count
CHF	congestive heart failure
CMV	cytomegalovirus
[redacted]	[redacted]
CT	computerized tomography
DM	diabetes mellitus
DNA	deoxyribonucleic acid
EBV	Epstein-Barr virus
ERCP	endoscopic retrograde cholangiopancreatography
ESR	erythrocyte sedimentation rate
EOI	end of intervention
GGT	gamma-glutamyltransferase
HAV	hepatitis A virus
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HepB	hepatitis B virus
HEV	hepatitis E virus
IgM	immunoglobin M
INR	international normalized ratio
LT/LFT	liver tests/liver function tests
MRI	magnetic resonance imaging
MRCP	magnetic resonance cholangiopancreatography
NSAID	nonsteroidal anti-inflammatory drug
OTC	over the counter
PT	prothrombin time
PTT	partial thromboplastin time
RNA	ribonucleic acid
Tbili	total bilirubin
TIBC	total iron binding capacity
ULN	upper limit of normal
WBC	white blood count

APPENDIX 11. SPONSOR GUIDANCE ON STUDY CONDUCT DURING THE CORONAVIRUS DISEASE 2019 (COVID-19) PANDEMIC

Every effort should be made to adhere to protocol-specified assessments for participants on study drug including follow-up, to the extent possible. However, the sponsor recognizes that the COVID-19 pandemic may have an impact on the conduct of this clinical study including, but not limited to: self-isolation or quarantine by study participants and study-site personnel, travel restrictions and limited access to public places (including hospitals), and study site personnel being reassigned to critical tasks. Thus, while aligning with recent health authority guidances, the sponsor is providing options for managing study participants in the event of a disruption to the conduct of the study due to the COVID-19 pandemic. This sponsor guidance does not supersede local or government guidelines, requirements, or the clinical judgement of the investigator. Protecting the safety, welfare, and rights of study participants must be of utmost priority. If a participant's safety is at risk, study drug should be discontinued at the discretion of the investigator, and study follow-up should be conducted. The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance. If a participant has confirmed or suspected COVID-19, the investigator should contact the Medical Monitor to discuss plans for study drug and follow-up and report as an AE.

Measures Considered

Protocol-required visits to the clinical site may not be possible during the COVID-19 pandemic. Hence, temporary measures may be implemented, if deemed appropriate by the sponsor and investigator, to maintain continuity of participant care and study integrity. Certain measures, including but not limited to, those listed below, may be necessary and should be taken in accordance with applicable laws, regulations, guidelines, and procedures:

- Virtual or remote (e.g., by phone/telemedicine) and/or off-site (e.g., in-home) interactions between site staff (or designees) and participants for study procedures such as those related to safety monitoring, efficacy evaluation, and study drug administration (including training where pertinent).
  - Conduct interview with participants to collect safety data and include questions regarding general health status.
  - Perform key efficacy endpoint assessments (endoscopy, Quality-of-Life questionnaires, [redacted], [redacted], PGA) in-person as required, and if feasible. If an in-person visit is not feasible, the minimum assessment to be performed remotely include obtaining information for the PGA.
- Procurement of study drug by participants (or designee) from the site or shipment of study drug directly to participants for at home administration.
- Laboratory assessments using a suitably accredited local laboratory; for selected assessments such as urine pregnancy, home testing may be conducted.

COVID-19-Related Exclusion

The field of COVID-19-related testing (for presence of, and immunity to, the SARS-CoV-2 virus) is rapidly evolving. Additional testing may be performed as part of screening and/or during the study if deemed necessary by the investigator and in accordance with current regulations or guidance from authorities and standards of care.

Documentation

Document what relevant contingency measures are implemented, how restrictions related to COVID-19 led to changes to the study conduct, and how the study participant was impacted. Related documentation, either in source or systems (e.g. eCRF), should be labelled with the prefix "CV19." Protocol deviations related to the pandemic should also be labeled as such with the "CV19" prefix.

Activities that require the appropriate documentation include, but are not limited to, the following:

- Missed, delayed, or modified visits and/or assessments;
- Study drug dosing modification, dosing interruptions, and discontinuation and withdrawal from the study;
- Other temporary measures such as those listed in this appendix;
- If a participant is excluded from the study due to recent COVID-19-related elements, the reason for screen failure should be documented in the CRF.