Protocol Number: 0173

Official Title: A Phase 2 Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Induction Therapy with 2 Doses of TD-1473 in Subjects with Moderately-to-Severely Active Crohn's Disease

NCT Number: NCT03635112

Document Date: 09 June 2020

CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2 Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Induction Therapy with 2 Doses of TD-1473 in Subjects with Moderately-to-Severely Active Crohn's Disease
Study Short Title:	DIONE - Efficacy and Safety of TD-1473 in Crohn's Disease
Sponsor Study No.:	0173
Date:	09 June 2020, [redacted]
Test Product:	TD-1473
US IND:	139354
EudraCT No.:	2018-001272-37
Sponsor:	Theravance Biopharma Ireland Limited Connaught House 1 Burlington Road Dublin 4 D04 C5Y6 Ireland
Clinical Study Director:	[redacted] Theravance Biopharma US, Inc. [redacted]
CRO 24 Hour Study Support Center:	Telephone: [redacted] Facsimile: [redacted]

This study will be conducted according to the principles of Good Clinical Practice.

CONFIDENTIAL

PROTOCOL SYNOPSIS

Study Number and Title: Study 0173: A Phase 2 Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Induction Therapy with 2 Doses of TD-1473 in Subjects with Moderately-to-Severely Active Crohn's Disease

Study Short Title: DIONE - Efficacy and Safety of TD-1473 in Crohn's Disease

Estimated Number of Study Centers and Countries or Regions:

Background and Rationale:

[redacted]

PROTOCOL SYNOPSIS (CONTINUED)

[redacted]

Objectives:

The primary objectives of the study are as follows:

- To assess the effect of TD-1473 compared to placebo in improving Crohn's Disease Activity Index (CDAI) score at Week 12 in subjects with moderately-to-severely active CD
- To assess the safety and tolerability of TD-1473

The secondary objectives of the study are to assess the effects of TD-1473 given for 12 weeks compared to placebo as follows:

- To induce clinical remission
- To induce clinical response
- To induce endoscopic response
- To improve the Simplified Endoscopy Score for Crohn's Disease (SES-CD)

Study Design: This study includes 3 phases: Screening, Induction, and Active Treatment Extension (ATE). Screening is up to 5 weeks long. The Induction phase of the study is a multi-center, randomized, double-blind, placebo-controlled, parallel-group study evaluating 2 dose levels of TD-1473 (80 mg or 200 mg; approximately 60 subjects per dose level)

PROTOCOL SYNOPSIS (CONTINUED)

compared to placebo (approximately 40 subjects) for 12 weeks in subjects with moderately-to-severely active CD. Subjects who complete the Induction phase will continue to receive TD-1473 in ATE, either at 80 mg or 200 mg, for up to 48 additional weeks.

Screening:

To determine eligibility, subjects will undergo assessments during the Screening period (up to 35 days prior to Day 1 dosing) as outlined in the Schedule of Study Procedures (Table 1). Disease activity will be assessed by the clinical scores, based on symptoms reported on a daily diary, which will be captured electronically (or on a paper diary if electronic diary is not available) beginning the day after Screening Stage 1.

Subjects who meet all inclusion (with the exception of the endoscopic subscore criterion) and no exclusion criteria, as described in Section 4.1 and Section 4.2, respectively, will undergo ileocolonoscopy with biopsies to complete Screening Stage 2. The aim of this endoscopic exam is to assess the SES-CD score by central reading and to obtain biopsies.

Induction:

If the subject meets all eligibility criteria, the subject may be randomized into one of the following 3 treatment groups in a 3:3:2 ratio: TD-1473 80 mg, TD-1473 200 mg, or placebo.

The randomization will be stratified by prior biologics failure (as defined in Appendix 4) and CDAI score category (≤ 300, > 300) at the Screening Stage 2 visit. Approximately 40-60% of subjects randomized will have failed prior treatment with biologics. There will be a cap for enrollment of subjects once one of the biologics stratum reaches 60% (failure, not failure). Subjects will be treated for 12 weeks and assessed for the various endpoints, including those that incorporate findings from an ileocolonoscopy and biopsies at the Week 12 visit. Corticosteroids will start to be tapered at Week 8 with the tapering regimen described in Section 6.4.30.

Subjects will undergo clinic study visits every 4 weeks in accordance with Table 1. During this time, subjects will continue to fill out a daily diary.

Active Treatment Extension:

All subjects who complete Induction at the Week 12 visit will continue into ATE, where subjects will be treated with either 80 mg or 200 mg of TD-1473 for 48 weeks. Dose during ATE depends on treatment assignment during Induction (Figure 1 and Table 2): those who were dosed with TD-1473 during Induction will stay on the same dose; those who were dosed with placebo during Induction will be dosed with TD-1473 at 80 mg.

During ATE, subjects will undergo clinic study visits every 4-12 weeks in accordance with Table 1. Subjects will continue to complete a daily diary.

Corticosteroids will continue to be tapered during ATE with the tapering regimen recommended in Section 6.4.30. Subjects who have not shown clinical improvement (as assessed by the investigator) 16 weeks after initiation of ATE (i.e., ATE Week 16) will be discontinued from the study following completion of an End of Study (EOS) visit.

PROTOCOL SYNOPSIS (CONTINUED)

End of Study (EOS) Visit:

An EOS visit will be required for all subjects 4 weeks following their last dose of study drug. Subjects who complete an Early Study Drug Discontinuation visit during Induction or ATE will also be required to return for an EOS visit. Subjects will continue to complete a daily diary through the last day of the study participation.

Duration of Study Participation: Individual subject participation may require up to 69 weeks: including up to 5 weeks for Screening, 12 weeks of treatment (TD-1473 or placebo) in Induction, 48 weeks of TD-1473 treatment during ATE, and 4 weeks of follow-up.

Number of Subjects per Group: Approximately 160 subjects (approximately 60 in each of the two TD-1473 dose groups and approximately 40 in the placebo group).

Study Population:

Subjects with moderately-to-severely active CD [as defined by a CDAI score of 220-450 and SES-CD score of ≥ 6 (≥ 4 if isolated ileal disease) with ulceration (corresponding to a score of ≥1) in at least 1 of the 5 ileocolonic segments on the Presence of Ulcers subscore of the SES-CD] who are corticosteroid-dependent or have demonstrated inadequate response, or intolerance to conventional therapy (aminosalicylates, corticosteroids and immunomodulators such as azathioprine, 6-mercaptopurine, or methotrexate) or biologics (e.g., anti-TNF therapy, anti-IL-12/23, anti-integrin). A subset of subjects (up to approximately 10%) will have an SES-CD score between 3 and 5 points, inclusive.

Inclusion Criteria:

100. Subject is willing and able to provide written, signed informed consent at Screening Part 1 prior to start of any study-related procedures
101. Subject is a male or female at least 18 years of age at the time of Screening
102. Subject has a diagnosis of CD with involvement of at least the ileum or any portion of the colon at a minimum, diagnosed by radiology, endoscopy, and/or histology at least 3 months prior to Screening. The report of a previous diagnostic exam (endoscopy, radiology, and/or pathology) must be reviewed by the investigator and included in the source documents.
103. Subjects must have up-to-date colorectal cancer screening as per locally adopted guidelines (e.g., if subject has had ≥ 8 years of disease involving >30% of the colon, surveillance biopsies or chromoendoscopy should be performed if either is indicated as per locally adopted guidelines but has not been performed within the 12 months prior to Screening). If indicated, the surveillance biopsies (if ≥ 10) and chromoendoscopy need to be performed during Screening Stage 2 ileocolonoscopy after recording of a full ileocolonoscopy has been completed to avoid dye or biopsy-related bleeding artifact on the recorded images.

PROTOCOL SYNOPSIS (CONTINUED)

104. Subject has CDAI score ≥ 220 and ≤ 450

105. Subject has a SES-CD score of ≥ 3 with ulceration (corresponding to a score of ≥1) in at least 1 of the 5 ileocolonic segments on the Ulcerated Surface subscore of the SES-CD, as assessed by central reading, during Screening

    a. Up to approximately 10% of the study population will have SES-CD score of between 3 and 5, inclusive, with the presence of ulceration in any 1 of the 5 ileocolonic segments, all other subjects (approximately 90% of the study population) will require an SES-CD score of ≥ 6 (≥ 4 if isolated ileal disease) with ulceration (corresponding to a score of ≥1) in at least 1 of the 5 ileocolonic segments on the Ulcerated Surface subscore of the SES-CD

106. Subject is corticosteroid-dependent or had intolerance or inadequate response to any of the following: aminosalicylates, corticosteroids, immunomodulators (azathioprine, 6-mercaptopurine, or methotrexate), or biologics (anti-TNF anti-IL-12/IL-23 therapy, or anti-integrin) [Refer to Appendix 10]

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

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

    a. the subject has been on corticosteroid 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 budesonide 9 mg/day or beclomethasone at 5 mg/day ***AND***
    c. the dose is stable for at least 2 weeks prior to Screening Stage 2 ***AND***
    d. the subject is willing to continue on the same dose as warranted until Week 8

108. If subject is currently receiving oral aminosalicylate (including, but not limited to sulfasalazine or mesalamine), the subject is eligible provided the subject has been on a stable dose for ≥ 4 weeks prior to Day 1 and is willing to stay on the same dose as warranted until Week 12

109. If subject is on antibiotics or probiotics for CD, subject must have been on the same dose for at least 2 weeks before Screening Stage 2 with stable symptoms and is willing to remain on the same dose as warranted until Week 12

110. If subject has recently discontinued oral corticosteroids, these must have been stopped at least 2 weeks before endoscopy during Screening Stage 2 visit

111. During the Study and for 7 days after receiving the last dose of the Study drug, females of childbearing potential or males 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).

PROTOCOL SYNOPSIS (CONTINUED)

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

113. Subject has completed the daily diary at least 5 out of 7 days prior to Screening Stage 2

114. Subject is able to communicate effectively with the investigator, and willing and able to comply with the study procedures, requirements and restrictions, and directions of the clinic staff

Exclusion Criteria:

Exclusion Criteria Pertinent to GI:

300. Subject with current symptoms or signs suggestive of intestinal perforation, intra-abdominal or pelvic abscess, symptomatic internal fistulae, abdominal wall fistulae, or symptomatic stricture

301. Subject with a diagnosis of indeterminate colitis, ulcerative colitis, microscopic colitis, ischemic colitis, radiation colitis, diverticular disease associated with colitis, or suspected ulcerative colitis

302. Subject with a confirmed or suspected diagnosis or history of primary sclerosing cholangitis (PSC)

303. Subject is likely to require bowel surgery or any other type of major surgery (e.g., requiring general anesthesia) during the study duration

304. Subject has had extensive colonic resection (i.e., more than half of colon), subtotal or total colectomy, intestinal resection within 6 months of Screening, > 2 small bowel resections or carries a diagnosis of short bowel syndrome or currently has an ostomy

305. Subject has a history of unresected colonic mucosal dysplasia or history of resected high-grade colonic dysplasia within 3 years prior to Screening. Subjects will not be excluded from the study because of a pathology finding of indefinite dysplasia with reactive atypia or because of adenomas that have been completely resected

306. Subject has required enteral feeding via feeding tube or parenteral alimentation within 21 days prior to Day 1

Exclusion Criteria Pertinent to Medications:

400. Medications of exclusion ([redacted]) below must be discontinued within the timeframe specified (if applicable)

- azathioprine, 6-mercaptopurine, or methotrexate taken within the 14 days prior to Day 1

PROTOCOL SYNOPSIS (CONTINUED)

- 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
- intravenous corticosteroids within the 14 days prior to Day 1
- rectal mesalamine or corticosteroid (i.e., enemas or suppositories) taken within the 14 days prior to Day 1
- prior exposure to vedolizumab, ustekinumab, mycophenolic acid, tacrolimus, sirolimus, or cyclosporine taken within 60 days or 5 half-lives, whichever is longer, prior to Day 1
- any prior exposure to natalizumab, rituximab, efalizumab, fingolimod, cyclophosphamide, or thalidomide
- 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).
- anakinra or any other immune-modifying biologic agent taken within 90 days prior to Day 1
- A JAK inhibitor (e.g., tofacitinib) within 60 days prior to Day 1

Note: For anti-TNFs, vedolizumab, and ustekinumab, there is no requirement for a washout period if there is documented finding of undetectable drug level by a validated assay (e.g., through commercially available testing).

401. Prior exposure or potential exposure to a 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 or end of study)

402. Subject 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)

403. Subject had inadequate response (i.e., either primary or secondary non-response) to ≥ 3 biologic agents of 3 different mechanisms of action (i.e., anti-TNF, anti-integrin, and anti-IL12/23)

404. Subject is 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 CYP3A4 or is a substrate of P-gp or BCRP and has a narrow therapeutic index ([redacted] For

PROTOCOL SYNOPSIS (CONTINUED)

clarity, corticosteroids at doses not excluded elsewhere in the protocol are not considered potent inducers of CYP3A4, P-gp, or BCRP

405. Subject is taking non-CD concomitant prescription medications that have started or have had a dose adjustment within 4 weeks prior to Day 1 (with the exception of corticosteroids as discussed in inclusion criterion #107, antibiotics for recent infections, sedating agents for ileocolonoscopy, hormonal contraceptives, hormone replacement therapy, vitamin D, insulin therapy, and replacement thyroid hormone - see Section 6.4.29)

406. Subject is taking non-CD over-the-counter medications or dietary supplements that have started or have had a dose adjustment within 2 weeks 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 up to 325 mg per day for cardiovascular prophylaxis, and over-the-counter doses of vitamin D - see Section 6.4.29)

Exclusion Criteria Pertinent to Infections:

500. 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 completion of treatment regimen and b) viral load during Screening is undetectable
d. hepatitis E Immunoglobulin M (IgM) antibody
e. human immunodeficiency virus (HIV) antibody

501. 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, 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

502. The subject has or may have untreated active or latent TB as evidenced by any of the following:

a. Two indeterminate or two positive QuantiFERON®-TB Gold result within 90 days prior to screening or during the Screening Period, 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.
Refer to Section 6.4.15 for rationale and required documentation for repeat testing.

PROTOCOL SYNOPSIS (CONTINUED)

A subject who has a history of latent or active tuberculosis (TB) may be eligible for the study if criteria outlined in Section 6.4.15 are met.

503. Subject has:

a. an active, clinically significant bacterial, parasitic, fungal, mycobacterial (including atypical infection), or viral infection, except for local skin or nail bed infection, within 30 days prior to Day 1
b. any infection requiring hospitalization or intravenous antibiotics within 30 days prior to Screening
c. any infection requiring oral antimicrobial treatment within 2 weeks prior to Screening
d. a history of more than one episode of herpes zoster or one or more episodes of disseminated or complicated herpes zoster (complicated: multi-dermatomal, ophthalmic, or CNS involvement or post-herpetic neuralgia) or disseminated herpes simplex

504. Subject has had a chest X-Ray or equivalent chest imaging performed within the 90 days prior to Screening or at Screening that shows an abnormality suggestive of a malignancy or current active infection, including TB, chronic lung disease or a potentially active fungal, viral, or bacterial infection

505. Subject has C. difficile or other gastrointestinal infections (e.g., Salmonella, Shigella, Yersinia, Campylobacter, E. coli O157, etc.) on stool testing or cytomegalovirus [CMV] colitis suspected on endoscopic appearance during Screening. Subject may be treated, re-tested, and re-screened.

506. Subject has had a bone marrow transplant

507. Within 4 weeks of Screening or during Screening, subject has:

a. Confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (coronavirus disease 2019 [COVID-19]) (test positive), ***OR***

b. 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***

c. 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

Coexisting Medical Conditions or Past Medical History Exclusion Criteria:

600. Subject is a female who is pregnant, lactating, breastfeeding or planning to become pregnant during the study or within 7 days after the last dose of study drug

601. Subject is a male who is planning to father a child or donate semen during the study or within 7 days after the last dose of study drug

PROTOCOL SYNOPSIS (CONTINUED)

602. Subject has clinically significant abnormalities in the results of laboratory evaluations at Screening visit as determined by the investigator or Sponsor, including but not limited to:

- AST, ALT, or alkaline phosphatase ≥ 2x the upper limit of normal (ULN),
- total bilirubin > 2x ULN (unless diagnosed with Gilbert's syndrome, in which case, total bilirubin > 4x ULN),
- creatinine clearance as calculated by the Cockcroft-Gault formula < 30 mL/min (Appendix 1),
- total white blood cell count (WBC) < 3 x 10^9/L,
- absolute neutrophil count < 1.5 x 10^9/L,
- absolute lymphocyte count < 0.8 x 10^9/L,
- hemoglobin < 8 g/dL, or
- platelet count < 100 x 10^9/L.

603. Subject has a clinically significant abnormal ECG at Screening, including QTcF > 450 msec for males and > 470 msec for females

604. Subject 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 CD), genitourinary, psychiatric, oncologic or neurological disease or other medical disorder that would compromise subject safety or confound study safety assessments as determined by the investigator at Screening and Day 1. [redacted] 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.

605. Subject has known hypersensitivity to excipients or contents of the study drug

606. Subject has a history of alcohol or drug abuse within 1 year of Screening, per the judgment of the investigator

607. Subject with a current or history of malignancy within 5 years prior to Screening, except for completely resected basal cell carcinoma or squamous cell carcinoma in situ of the skin, or 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.

608. Subject who, for any reason, is deemed by the investigator or Sponsor to be inappropriate for this study; or has any condition which would confound or

PROTOCOL SYNOPSIS (CONTINUED)

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 609. Subject with known moderate to severe hepatic impairment (e.g., known Child-Pugh Class B or C)
Test Product, Dose, and Route of Administration; Regimen; Duration of Treatment: **Induction:** • TD-1473 80 mg QD: given orally for up to 12 weeks in the morning before eating. Subject must refrain from eating or drinking anything other than water and non-study medications for at least 30 minutes after dosing. • TD-1473 200 mg QD: given orally for up to 12 weeks in the morning before eating. Subject must refrain from eating or drinking anything other than water and non-study medications for at least 30 minutes after dosing. **Active Treatment Extension:** • TD-1473 80 mg QD: given orally for up to 48 weeks in the morning before eating. Subject must refrain from eating or drinking anything other than water and non-study medications for at least 30 minutes after dosing • TD-1473 200 mg QD: given orally for up to 48 weeks in the morning before eating. Subject must refrain from eating or drinking anything other than water and non-study medications for at least 30 minutes after dosing.
Reference Therapy, Dose, and Route of Administration; Regimen; Duration of Treatment: **Induction:** • Placebo QD: given orally for up to 12 weeks in the morning before eating. Subject must refrain from eating or drinking anything other than water and non-study medications for at least 30 minutes after dosing.

PROTOCOL SYNOPSIS (CONTINUED)

Study Evaluations

Safety Assessments:

Subject safety will be assessed throughout the study using standard safety measures, including vital signs, 12-lead ECGs, blood and urine laboratory tests, physical examinations, concomitant medication usage, and adverse event (AE) monitoring.

Efficacy Assessments:

- CDAI score
- SES-CD
- [redacted]
- [redacted]
- Stool Frequency and Abdominal Pain (SFAP)
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

PROTOCOL SYNOPSIS (CONTINUED)

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:

Assuming that the less effective TD-1473 dose results in a 45-point improvement in placebo-adjusted CDAI score change at Week 12, the more effective dose results in a 60-point improvement, the residual SD is 100 points, and a sample size of 160 subjects with 60 subjects in each of the active dose groups and 40 subjects in the placebo group, 100,000 simulations performed using SAS/IML software yielded the following power estimates for 2-sided testing with the familywise Type I error rate controlled at 5% using the Hochberg -step-up procedure:

- 82% power to show at least one of the two doses effective
- 58% power to show both doses effective

The target effect size of 60 points was selected as predictive of a clinically significant increase in clinical response rate. Of note, the study is not powered for the secondary endpoints.

Study Efficacy Endpoints:

The primary endpoint is:

- CDAI score change from baseline at Week 12

The secondary endpoints are:

- CDAI clinical response (defined as reduction from baseline of ≥ 100 points or CDAI < 150) at Week 12
- CDAI clinical remission (defined as CDAI < 150) at Week 12
- SES-CD change from baseline at Week 12
- Endoscopic response (SES-CD reduction of ≥ 50% from baseline or endoscopic remission) at Week 12
- SFAP clinical remission defined as abdominal pain score ≤ 1 (on a scale of 0-3), stool frequency ≤ 2.8, and both not worse than baseline at Week 12

Study Safety Endpoints:

- Changes from baseline in vital signs, ECGs, and clinical laboratory results
- Incidence and severity of AEs

PROTOCOL SYNOPSIS (CONTINUED)

Analysis:

The primary analysis set for efficacy analyses will be a modified Intent-to-Treat (mITT) set: all randomized subjects who received study drug and had at least one postbaseline CDAI score. Efficacy data will be summarized by randomized treatment. The primary analysis set for general and safety analyses will be the Safety set: all randomized subjects who received study drug. Safety data will be summarized by treatment received.

Continuous endpoints including score change will be analyzed by fitting analysis of covariance (ANCOVA) models which include terms for treatment, stratification factors, and baseline score as covariate. Mixed effects model repeated measures analyses will be used to analyze efficacy endpoints assessed at multiple postbaseline time points. Confidence intervals for means and mean differences with nominal confidence level 95% will be calculated by methods which will be specified in the Statistical Analysis Plan (SAP).

Binary efficacy endpoint rates will be compared using stratified Cochran-Mantel-Haenszel tests, stratifying by randomization stratum. Subjects with missing binary outcome will be counted as treatment failures. Confidence intervals for rates and rate differences with nominal confidence level 95% will be calculated by methods which will be specified in the SAP. Logistic regression models may be fitted for selected endpoints to evaluate dose-response curves.

A Hochberg step-up procedure will be used for hypothesis testing of the primary efficacy endpoint and the family-wise Type I error rate will be controlled at 5%. All comparisons will be 2-sided.

Safety data will be listed by subject and summarized by received treatment, showing subject counts for event data and means, medians, etc. for measurements.

Listings and summaries will be provided for demographics (age, sex, ethnicity, and race), baseline characteristics including baseline disease characteristics (e.g., extent of disease, duration of disease, complications) and treatment history, adverse events, laboratory tests, vital signs, and ECG data. Concomitant medications will be listed and summarized by received treatment.

SCHEDULE OF STUDY PROCEDURES

Table 1: Schedule of Study Procedures

Procedures	Screening Period		Treatment Period												Early Study Drug Discontinuation [A]	End of Study [B] (4 weeks post last study drug dose)
			Induction (Day 1 to Week 12)					Active Treatment Extension (ATE Day 1 to ATE Week 48)								
Study Day/Week	**Day -35 to -1**		**Day 1**	**W4**	**W8**	**W10**	**W12 [C]**	**ATE Day 1 [D]**	**ATE W4**	**ATE W8**	**ATE W16 [E]**	**ATE W24**	**ATE W36**	**ATE W48**		
	Stage 1	**Stage 2**														
Hour Post-dose/Window				**- 3 to + 5 days**	**0 to + 7 days**	**0 to + 3 days**	**1 – 7 days after W12**	**- 3 to + 5 days**							**0 to + 5 days**	**- 3 to + 5 days**
General Procedures and Safety Assessments																
Informed Consent	X															
Review Inclusion/ Exclusion Criteria	X	X	X													
Medication/Medical History	X		X													
Tobacco Use Status			X				X							X	X	
Height	X															
Weight	X		X	X	X		X		X	X	X	X	X	X	X	X
Vital Signs	X		X	X	X		X	X	X	X	X	X	X	X	X	X
12-lead ECG	X		X				X			X	X	X	X	X	X	X
Physical Examination [F]	X		X	X	X		X		X	X	X	X	X	X	X	X
Chest X-ray [G]	X															
Randomization			X [H]													

SCHEDULE OF STUDY PROCEDURES (CONTINUED)

Table 1: Schedule of Study Procedures

Procedures	Screening Period		Treatment Period												Early Study Drug Discontinuation [A]	End of Study [B] (4 weeks post last study drug dose)
			Induction (Day 1 to Week 12)					Active Treatment Extension (ATE Day 1 to ATE Week 48)								
Study Day/Week	**Day -35 to -1**		**Day 1**	**W4**	**W8**	**W10**	**W12 [C]**	**ATE Day 1 [D]**	**ATE W4**	**ATE W8**	**ATE W16 [E]**	**ATE W24**	**ATE W36**	**ATE W48**		
	Stage 1	**Stage 2**														
Hour Post-dose/Window				**- 3 to + 5 days**		**0 to + 7 days**	**0 to + 3 days**	**1 – 7 days after W12**	**- 3 to + 5 days**						**0 to + 5 days**	**- 3 to + 5 days**
Study Drug Dispensing			X	X	X			X	X	X	X	X	X			
Study Drug Dosing [I]			X	X	X		X	X	X	X	X	X	X	X		
Dispense Electronic Diary [J]	X															
Corticosteroid Dosing Taper (if applicable) [K]					X		X	X	X							
Telephone Call [L]						X										
Concomitant Medications	----------X----------															
Adverse Event Assessment [M]	----------X----------															
Laboratory Assessments																
Pregnancy Test (females of childbearing potential only) [N]	X		X	X	X		X	X	X	X	X	X	X	X	X	X
FSH [O]	X															

SCHEDULE OF STUDY PROCEDURES (CONTINUED)

Table 1: Schedule of Study Procedures

Procedures	Screening Period		Treatment Period												Early Study Drug Discontinuation [A]	End of Study [B] (4 weeks post last study drug dose)
			Induction (Day 1 to Week 12)					Active Treatment Extension (ATE Day 1 to ATE Week 48)								
Study Day/Week	Day -35 to -1		Day 1	W4	W8	W10	W12 [C]	ATE Day 1 [D]	ATE W4	ATE W8	ATE W16 [E]	ATE W24	ATE W36	ATE W48		
	Stage 1	Stage 2														
Hour Post-dose/Window				- 3 to + 5 days		0 to + 7 days	0 to + 3 days	1 – 7 days after W12	- 3 to + 5 days						0 to + 5 days	- 3 to + 5 days
Chemistry, Hematology	X		X	X	X		X		X	X	X	X	X	X	X	X
Urinalysis	X		X	X	X		X		X	X	X	X	X	X	X	X
Overnight Fasting Lipid Panel		X [P]	X	X	X		X		X	X	X	X	X	X	X	X
Viral hepatitis and HIV Serology Panel	X [Q]															
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tuberculosis Test (QuantiFeron)	X															
Ileocolonoscopy and Biopsies		X [R]					X [C]									
Fecal Sample for Infectious Studies [S]	X															
[redacted]			[redacted]				[redacted]					[redacted]		[redacted]	[redacted]	

SCHEDULE OF STUDY PROCEDURES (CONTINUED)

Table 1: Schedule of Study Procedures

Procedures	Screening Period		Treatment Period												Early Study Drug Discontinuation [A]	End of Study [B] (4 weeks post last study drug dose)
			Induction (Day 1 to Week 12)					Active Treatment Extension (ATE Day 1 to ATE Week 48)								
Study Day/Week	Day -35 to -1		Day 1	W4	W8	W10	W12 [C]	ATE Day 1 [D]	ATE W4	ATE W8	ATE W16 [E]	ATE W24	ATE W36	ATE W48		
	Stage 1	Stage 2														
Hour Post-dose/Window				- 3 to + 5 days		0 to + 7 days	0 to + 3 days	1 – 7 days after W12	- 3 to + 5 days						0 to + 5 days	- 3 to + 5 days
[redacted]																
[redacted]																
Genetic Blood Sample (Optional – only collected for subjects who provide genetic testing consent)			X													
Disease Assessments																
CDAI Score		X [V]	X	X	X		X		X		X	X		X	X	X [A]
[redacted]																
SES-CD Score		X					X									
Fistula Drainage Status (yes/no to active drainage), if fistula is present	X		X	X	X		X					X		X	X	X
[redacted]																

SCHEDULE OF STUDY PROCEDURES (CONTINUED)

Table 1: Schedule of Study Procedures

Procedures	Screening Period		Treatment Period												Early Study Drug Discontinuation [A]	End of Study [B] (4 weeks post last study drug dose)
			Induction (Day 1 to Week 12)					Active Treatment Extension (ATE Day 1 to ATE Week 48)								
Study Day/Week	Day -35 to -1		Day 1	W4	W8	W10	W12 [C]	ATE Day 1 [D]	ATE W4	ATE W8	ATE W16 [E]	ATE W24	ATE W36	ATE W48		
	Stage 1	Stage 2														
Hour Post-dose/Window				- 3 to + 5 days		0 to + 7 days	0 to + 3 days	1 – 7 days after W12	- 3 to + 5 days						0 to + 5 days	- 3 to + 5 days
[redacted]			[redacted]				[redacted]				[redacted]	[redacted]		[redacted]	[redacted]	
Subject Diary Completion and Compliance Review [J]	X	X	X [W]	X	X		X	X	X	X	X	X	X	X	X	X [A]

Abbreviations: ECG, electrocardiogram; FSH, follicle stimulating hormone; [redacted]; CDAI, Crohn's Disease Activity Index; SES-CD, Simplified Endoscopy Score; [redacted] EOS, End-of Study, ATE, Active Treatment Extension

A. This visit is for subjects who prematurely discontinue the study drug. This visit will 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. Subjects who discontinue study drug early due to AE are permitted to optionally complete their daily diary through to the EOS visit. Subjects who have not shown clinical improvement at ATE Week 16 should complete an Early Study Drug Discontinuation visit and be discontinued from study drug.

B. An EOS visit will be required for all subjects 4 weeks following their last dose of study drug, whether they completed the full duration of study drug treatment.

C. The Week 12 ileocolonoscopy and biopsies should be performed on the same day as the Week 12 visit, preferably in the early morning, to permit morning dosing with study drug. However, if not feasible to perform both the ileocolonoscopy and the clinic visit on the same day, the ileocolonoscopy could be performed within 3 days after the Week 12 clinic visit. If the study activities of this Week 12 visit are to be completed over two different visits, the study drug should be continued until the later of the two visits. The Week 12 endoscopy must be performed at least 1 day prior to ATE Day 1.

D. ATE Day 1 should occur between 1 and 7 days after the Week 12 clinic visit. No new study drug will be dispensed between the Week 12 clinic visit and ATE Day 1. ATE Day 1 must be performed at least 1 day after the Week 12 endoscopy has been conducted.

E. Subjects who have not shown clinical improvement, as deemed by the subject and investigator, 16 weeks after initiation of the ATE (i.e., ATE Week 16), should be discontinued from the study.

SCHEDULE OF STUDY PROCEDURES (CONTINUED)

F. Physical exams (PEs) should be performed as per local standard practice (Section 6.4.9).

G. 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 equivalent) or TB testing, respectively, unless subject is deemed by the investigator to be at high risk of recent pulmonary infection. If a chest X-ray is indicated, it may be performed anytime during Screening. 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 and reviewed by the PI. 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 6.4.15 are met.

H. Subject will be randomized on Day 1 after all pre-dose procedures (ECG, vital signs, and all labs [redacted]) have been completed and subject is confirmed to be eligible for the study.

I. Study drug administration will be in clinic on Day 1, Week 4, Week 8, Week 12, ATE Day 1, ATE Week 4, ATE Week 8, ATE Week 16, ATE Week 24, ATE Week 36, and ATE Week 48 on an empty stomach from the night before after all pre-dose assessments [redacted] and procedures have been completed. Subject will take the study drug at home for the rest of the study. The last dose of Induction study drug will be taken at the Week 12 clinic visit. No new study drug will be dispensed between the Week 12 clinic visit and ATE Day 1.

J. Subjects will be provided with an electronic diary (or paper diary if electronic diary is not available) at the Screening Stage 1 visit and instructed on daily diary completion, including symptom monitoring and study drug dosing details. Diaries of symptoms will be collected daily from the Screening Stage 1 visit through the EOS visit. Study drug dosing details will be entered from Day 1 (Induction) through ATE Week 48 (or the last dose of study drug, if the subject prematurely withdraws from study drug). Diary completion will be monitored for completeness at each return study visit after the electronic diary is dispensed (i.e., Screening Stage 2 through the EOS visit). Subjects will be counseled on missed study drug doses and missed diary entries.

K. Corticosteroid taper, for those that are on corticosteroid at Screening Stage 1, should be initiated at the Week 8 visit. This taper will continue through ATE, as outlined in Section 6.4.30.

L. Site personnel to call subjects approximately 2 weeks prior to Week 12 visit for reminder of compliance of diary completion. The site will also review compliance on corticosteroid taper (as applicable), review upcoming schedule for Week 12 and the reminders in preparation for the visit.

M. 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.

N. Urine beta human chorionic gonadotropin (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.

O. Required for postmenopausal females.

P. Any Screening Stage 2 lab testing can be obtained from Day -35* to Day -1 during Screening. Overnight fasting lipid panel may be obtained on Day -35 if subjects are fasting as per institutions standard of care procedure, which must be clearly documented in the source documents. ***NOTE:** Subjects **must not** be requested to come in fasting for study specific assessments prior to signing the informed consent. Results of these labs will not need to be reviewed before Screening Stage 2 or Day 1.

Q. 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 6.4.14 for details on Serology testing). During re-screening, if there is already a negative result from prior screening, the hepatitis B, C, or E or HIV serologies do not need to be repeated.

SCHEDULE OF STUDY PROCEDURES (CONTINUED)

R. Ileocolonoscopy and biopsies will be performed after subject's eligibility is confirmed (upon review of CDAI score prior to the start of bowel preparation and no exclusionary criteria are met). Ileocolonoscopy does not need to be repeated for a rescreening if the ileocolonoscopy is within 28 days of Day 1 of the re-screen and if the SES-CD score is qualifying.

S. Stool infectious studies to include: C. difficile, other bacteria (including Shigella, Salmonella, Yersinia, Enterohemorrhagic or Enteropathogenic or Enterohemorrhagic E. coli O157, and Campylobacter), and ova and parasite.

T. [redacted]

U. [redacted]

V. Obtained prior to ileocolonoscopy (to assess eligibility criteria at Screening). Any time after Screening Stage 1 and once a minimum of 5 entries have been confirmed, the clinician assessments can be completed. Should be performed prior to the start of bowel preparation for the Screening Stage 2 endoscopy. The Screening Stage 1 weight and hematocrit result will be used to calculate this CDAI score.

W. Subject must have completed their electronic diary (or paper diary if electronic diary is not available) at least 5 out of 7 days prior to Screening Stage 2.

Note: See Appendix 13 for general guidance on study conduct during the COVID-19 pandemic. Variations from planned assessments will still constitute protocol deviations.

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[redacted]

[redacted]

LIST OF TABLES

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Description
AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
Anti-IL-12/23	interleukin 12/23 inhibitor
Anti-TNF	tumor necrosis factor inhibitor
AST	aspartate aminotransferase
ATE	active treatment extension
BCG	Bacille Calmette Guerin
BCRP	breast cancer resistance protein
b-HCG	beta human chorionic gonadotropin
BMI	body mass index
BP	blood pressure
CD	Crohn's disease
CDAI	Crohn's disease activity index
CDAI Clinical Remission	defined as CDAI < 150
CDAI Clinical Response	defined as CDAI reduction from baseline of ≥ 100 or CDAI < 150
CEC	Clinical Events Committee
CFR	(United States) Code of Federal Regulations
COVID-19	coronavirus disease 2019
CRF	case report form
[redacted]	[redacted]
CSR	clinical study report
CYP	cytochrome P450
DDI	drug-drug interaction
DNA	deoxyribonucleic acid
DVT	deep vein thrombosis
ECG	Electrocardiogram
eCOA	electronic clinical outcome assessments
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
Endoscopic Remission	defined as SES-CD2
Endoscopic Response	defined as SES-CD reduction of ≥ 50% from baseline or endoscopic remission
EOS	End-of-Study
[redacted]	[redacted]
FDA	(United States) Food and Drug Administration
FSH	follicle stimulating hormone

Abbreviation	Description
GCP	Good Clinical Practice
GI	Gastrointestinal
H2 antagonists	Histamine H2 receptor antagonists
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HDPE	high-density polyethylene
HR	heart rate
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
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgM	immunoglobulin M
INH	Isoniazid
INR	international normalized ratio
IP	investigational product
IRB	Institutional Review Board
IUD	intrauterine device
JAK	Janus kinase
MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities (MedDRA®)
mITT	modified intent to treat
mRNA	messenger ribonucleic acid
Modified SFAP Clinical remission	defined as abdominal pain score ≤ 1, very soft/liquid stool frequency ≤ 1.5, and both not worse than baseline
Modified SFAP-e Remission	defined as abdominal pain score ≤ 1, stool frequency ≤ 1.5, neither abdominal pain score or stool frequency worse than baseline, and SES-CD ≤ 2
NK	natural killer
[redacted]	[redacted]
PA	posterior anterior
Pack years	number of packs per day times number of years smoked
PD	Pharmacodynamics(s)
PI	principal investigator
P-gp	p-glycoprotein

Abbreviation	Description
PIC	powder in capsule
PK	pharmacokinetic(s)
PP	Per-protocol
PPI	proton-pump inhibitor
PRO	Patient-reported outcome
[redacted]	[redacted]
PT	preferred term
QD	Once daily
QTc	corrected QT interval
QTcF	Fridericia-corrected QT interval
REB	Research Ethics Board
RNA	ribonucleic acid
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
SD	standard deviation
SES-CD	simplified endoscopy score for Crohn's disease
SFAP	Stool Frequency and Abdominal Pain
SFAP Clinical Remission	defined as abdominal pain score ≤ 1, stool frequency ≤ 2.8, and both not worse than baseline)
SFAP-e Remission	defined as abdominal pain score ≤ 1, stool frequency ≤ 2.8, neither abdominal pain score or stool frequency worse than baseline, and SES-CD ≤ 2
SOC	system organ class
SOP	standard operating procedure
STAT	signal transducer and activator of transcription
TB	Tuberculosis
TBPH	Theravance Biopharma, Inc.
TEAE	treatment-emergent adverse event
TNF	tumor necrosis factor
UC	ulcerative colitis
ULN	upper limit of normal
USP	United States Pharmacopeia

1. INTRODUCTION

1.1. Background and Rationale

[redacted]

[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.

1.2.1. Pharmacology

[redacted]

1.2.2. Toxicology

[redacted]

[redacted]

1.2.3. Pharmacokinetics

[redacted]

1.3. Clinical Experience

[redacted]

1.4. Risks and Benefits

TD-1473 is potentially effective for the treatment of inflammatory intestinal disorders. Tofacitinib, a systemic pan-JAK inhibitor, has demonstrated statistically significantly higher rates of induction of remission and higher rates of remission and response at Week 52 during maintenance therapy compared to placebo for UC.[5,6] Systemic JAK inhibitors filgotinib and upadacitinib have demonstrated efficacy in phase 2 trials in Crohn's disease.[7,8] 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. TD-1473 has not been studied in subjects with CD.

Some subjects 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, and infection (particularly herpes zoster and tuberculosis), cancer (including non-melanoma skin cancer), intestinal perforation, headache, diarrhea, rhinorrhea, nasopharyngitis, and sore throat. However, given the relatively low systemic exposure of TD-1473, these risks are anticipated to be lower in the current study compared to systemic JAK inhibitors.

In healthy volunteers, doses from 10 mg to 1000 mg as a single dose or 10 mg to 300 mg as a daily dose for 14 days were evaluated. TD-1473 was observed to be generally well tolerated up to 300 mg for 14 days without alterations to vital signs, electrocardiogram parameters, or laboratory evaluations relative to placebo. In the Phase 1 study in healthy volunteers, all treatment-emergent adverse events 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 event (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 day 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.

The current protocol requires pregnancy prevention measures for a duration of 7 days after the last dose of study medication for both male and female subjects. The 7 day duration for pregnancy prevention measures 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. For these reasons, 7 days after the last dose of study drug was chosen such that an adequate safety margin is established before implantation.

Pregnancy prevention measures in males 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).[10] 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.

The potential risks described in this section will be carefully assessed during the study. Assessments include adverse event collection and monitoring (including AEs of Special Interest), 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.

2. OBJECTIVES

The primary objectives of the study are as follows:

- To assess the effect of TD-1473 compared to placebo in improving Crohn's Disease Activity Index (CDAI) score at Week 12 in subjects with moderately-to-severely active CD
- To assess the safety and tolerability of TD-1473

The secondary objectives of the study are to assess the effects of TD-1473 given for 12 weeks compared to placebo as follows:

- To induce clinical remission
- To induce clinical response
- To induce endoscopic response
- To improve the Simplified Endoscopy Score for Crohn's Disease (SES-CD)

[redacted]

3. STUDY DESIGN

3.1. Overview

This study includes 3 phases: Screening, Induction, and Active Treatment Extension (ATE). Screening is up to 5 weeks long. The Induction phase of the study is a multi-center, randomized, double-blind, placebo-controlled, parallel-group study evaluating 2 dose levels of TD-1473 (80 mg or 200 mg; approximately 60 subjects per dose level) compared to placebo (approximately 40 subjects) for 12 weeks in subjects with moderately-to-severely active CD. Subjects who complete the Induction phase will continue to receive TD-1473 in ATE, either at 80 mg or 200 mg, for up to 48 additional weeks.

Screening:

To determine eligibility, subjects will undergo assessments during the Screening period (up to 35 days prior to Day 1 dosing) for CD signs and symptoms, electrocardiogram (ECG), tuberculosis (TB) test, chest X-ray, and laboratory testing, including infectious stool studies. Refer to Schedule of Study Procedures (Table 1) for a schedule of the Screening requirements. Disease activity will be assessed by the clinical scores, based on symptoms reported on a daily diary, which will be captured electronically (or on a paper diary if electronic diary is not available) beginning the day after Screening Stage 1.

Subjects who meet all inclusion (with the exception of the endoscopy subscore criterion) and no exclusion criteria, as described in Section 4.1 and Section 4.2, respectively, will undergo ileocolonoscopy with biopsies to complete Screening Stage 2. The aim of this endoscopic exam is to assess the SES-CD score by central reading and to obtain biopsies.

Induction

If the subject meets all eligibility criteria, the subject may be randomized into one of the following 3 treatment groups in a 3:3:2 ratio: TD-1473 80 mg, TD-1473 200 mg, or placebo.

The randomization will be stratified by prior biologics failure (as defined in Appendix 4) and CDAI score category (≤ 300, > 300) at the Screening Stage 2 visit. Approximately 40-60% of subjects randomized will have failed prior treatment with biologics. There will be a cap for enrollment of subjects once one of the biologics stratum reaches 60%. There will also be a cap at 10% for enrollment of subjects with an SES-CD score at screening in the range of 3 to 5. Subjects will be treated for 12 weeks and assessed for the various endpoints, including those that incorporate findings from an ileocolonoscopy and biopsies at the Week 12 visit. Corticosteroids will start to be tapered at Week 8 with the tapering regimen described in Section 6.4.30.

Subjects will undergo clinic study visits every 4 weeks in accordance with Table 1. During this time, subjects will continue to fill out a daily diary.

ATE:

All subjects who complete Induction at the Week 12 visit will continue into ATE, where subjects will be treated with either 80 mg or 200 mg of TD-1473 for 48 weeks. Dose during ATE depends on treatment assignment during Induction (Figure 1 and Table 2); those who were dosed with TD-1473 during Induction stay on the same dose; those who were dosed with placebo during Induction will be dosed with TD-1473 at 80 mg.

Table 2: Induction and Active Treatment Dose Assignment

Induction Dose (3:3:2 randomization)	**Active Treatment Extension (ATE) Dose**
80 mg	80 mg
200 mg	200 mg
Placebo	80 mg

During ATE, subjects will undergo clinic study visits every 4-12 weeks in accordance with Table 1. Subjects will continue to complete a daily diary.

Corticosteroids will continue to be tapered during ATE with the tapering regimen recommended in Section 6.4.30. Subjects who have not shown clinical improvement (as assessed by the investigator) 16 weeks after initiation of ATE (i.e., ATE Week 16) should be discontinued from the study following completion of an End of Study (EOS) visit.

End of Study (EOS) Visit:

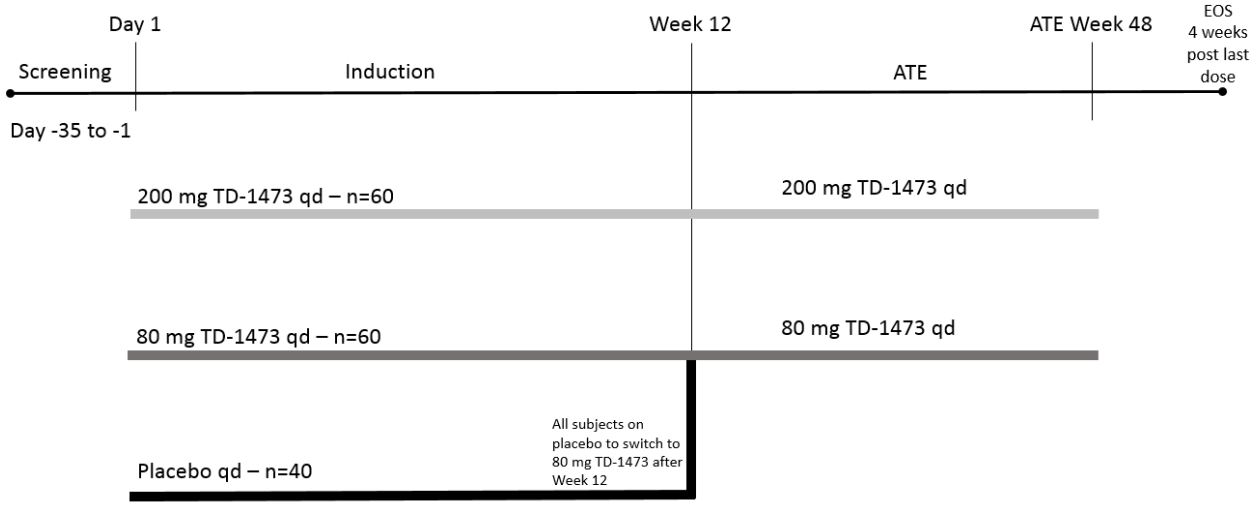
An EOS visit will be required for all subjects 4 weeks following their last dose of study drug. Subjects who complete an Early Study Drug Discontinuation visit during Induction or ATE will also be required to return for an EOS visit. Subjects will continue to complete a daily diary through the last day of the study participation.

Early Study Drug Discontinuation:

Subjects who prematurely discontinue the study drug due to adverse events (AEs), lack of response, or any other reason besides withdrawal of consent during Induction or ATE 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, if possible. Subjects will also return for the EOS visit for collection of safety data and assessment of disease activity 4 weeks after the Early Study Drug Discontinuation visit.

During ATE, subjects should be assessed for clinical benefit. If there is no clinical benefit, as deemed by the investigator, the subject should stop study drug treatment and be withdrawn from the study.

Figure 1: Study Design Schematic



3.2. Rationale for Study Design

[redacted]

3.3. Selection of Dose and Duration of Treatment

[redacted]

[redacted]

3.4. Study Endpoints

The primary endpoint is:

- CDAI score change from baseline at Week 12

The secondary endpoints are:

- CDAI clinical response (defined as reduction from baseline of ≥ 100 points or CDAI < 150) at Week 12
- CDAI clinical remission (defined as CDAI < 150) at Week 12
- SES-CD change from baseline at Week 12
- Endoscopic response (SES-CD reduction of ≥ 50% from baseline or endoscopic remission) at Week 12
- Stool Frequency and Abdominal Pain (SFAP) clinical remission defined as abdominal pain score ≤ 1 (on a scale of 0-3), stool frequency ≤ 2.8, and both not worse than baseline at Week 12

The safety endpoints are:

- Changes from baseline in vital signs, ECGs, and clinical laboratory results
- Incidence and severity of AEs

The exploratory endpoints include:

[redacted]

[redacted]

3.5. Minimization of Bias

This is a double-blind, placebo-controlled, randomized study. Treatments will be assigned centrally using a randomization and trial supply management (RTSM) system.

All persons involved in this study (i.e., physicians, nurses, participants, and site monitors) will remain blinded at all times, except in the event of a medical emergency as outlined in Section 3.5.1. The principal investigator may be unblinded to a subject's treatment to determine whether stopping criteria have been met, as outlined in Section 6.5.3.

3.5.1. Blinding

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 participant's treatment assignment is warranted. Participant 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). With these exceptions, Sponsor personnel involved in the conduct of the study, data cleaning, or data analysis will remain blinded to subject treatment assignments until the database has been locked for final analysis.

[redacted]

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. The randomization will be stratified, and the randomization schedule for each of the 4 strata defined by the stratification variables (i.e., prior biologics failure [Yes, No] crossed with CDAI category at Screening Stage 2 [≤ 300, >300]) will be a reproducible (through use of a pre-specified random number seed) sequence of randomly permuted treatment assignment blocks, generated or

reviewed by a Theravance Biopharma statistician not involved in the conduct of the study. 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 subjects have either completed the ATE or been withdrawn from the study. An induction analysis will be conducted after all subjects have either completed the induction period or been withdrawn from the study to inform the design of additional studies. However, no summary results or individual subject data will be disclosed to investigational site staff until the entire study including the ATE has been concluded and the database has been locked.

The RTSM system will implement modifiable enrollment caps designed to ensure that the prior biologic failure stratification variable category will be represented by at least a specified fraction of subjects enrolled (e.g., at least 40% will and at least 40% will not have had prior biologics failure). There will also be an enrollment cap implemented to include a maximum of approximately 10% of the total sample size in the study with an SES-CD score in the range 3 to 5 at screening. 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 when confirmation is received from the Sponsor.

For ATE dose assignment (noted in Table 2), the PI or their delegate will use the RTSM system to report whether the subject experienced clinical benefit at the Week 12 visit, as deemed by the investigator, and dispense study drug.

Further details regarding the randomization procedure and ATE dose assignment will be outlined in the RTSM system manual.

4. STUDY POPULATION

Subjects with moderately-to-severely active CD [as defined by a CDAI score of 220-450 and SES-CD score of ≥ 6 (≥ 4 if isolated ileal disease) with ulceration (corresponding to a score of 1) in at least 1 of the 5 ileocolonic segments on the Presence of Ulcers subscore of the SES-CD] who are corticosteroid-dependent or have demonstrated inadequate response or intolerance to conventional therapy (aminosalicylates, corticosteroids and immunomodulators such as azathioprine, 6-mercaptopurine, or methotrexate) or biologics (e.g., anti-TNF therapy, anti-IL-12/23, anti-integrin). A subset of subjects (up to approximately 10%) will have an SES-CD score between 3 and 5 points, inclusive.

4.1. Inclusion Criteria

100. Subject is willing and able to provide written, signed informed consent at Screening Part 1 prior to start of any study-related procedures

101. Subject is a male or female at least 18 years of age at the time of Screening

102. Subject has a diagnosis of CD with involvement of at least the ileum or any portion of the colon at a minimum, diagnosed by radiology, endoscopy, and/or histology at least 3 months prior to Screening. The report of a previous diagnostic exam (endoscopy, radiology, and/or pathology) must be reviewed by the investigator and included in the source documents.

103. Subjects must have up-to-date colorectal cancer screening as per locally adopted guidelines (e.g., if subject has had ≥ 8 years of disease involving >30% of the colon, surveillance biopsies or chromoendoscopy should be performed if either is indicated as per locally adopted guidelines but has not been performed within the 12 months prior to Screening). If indicated, the surveillance biopsies (if ≥ 10) and chromoendoscopy need to be performed during Screening Stage 2 ileocolonoscopy after recording of a full ileocolonoscopy has been completed to avoid dye or biopsy-related bleeding artifact on the recorded images.

104. Subject has CDAI score ≥ 220 and ≤ 450

105. Subject has a SES-CD score of ≥ 3 with ulceration (corresponding to a score of ≥1) in at least 1 of the 5 ileocolonic segments on the Ulcerated Surface subscore of the SES-CD, as assessed by central reading, during Screening

    a. Up to approximately 10% of the study population will have SES-CD score of between 3 and 5, inclusive, with the presence of ulceration in any 1 of the 5 ileocolonic segments, all other subjects (approximately 90% of the study population) will require an SES-CD score of ≥ 6 (≥ 4 if isolated ileal disease) with ulceration (corresponding to a score of ≥ 1) in at least 1 of the 5 ileocolonic segments on the Ulcerated Surface subscore of the SES-CD

106. Subject is corticosteroid-dependent or had intolerance or inadequate response to any of the following: aminosalicylates, corticosteroids, immunomodulators (azathioprine, 6-mercaptopurine, or methotrexate), or biologics (anti-TNF anti-IL-12/IL-23 therapy, or anti-integrin) [Refer to Appendix 10]

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

107. If subject is currently receiving an oral corticosteroid, subject is eligible if:
    a. the subject has been on corticosteroid 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 budesonide 9 mg/day or beclomethasone at 5 mg/day ***AND***
    c. the dose is stable for at least 2 weeks prior to Screening Stage 2 ***AND***
    d. the subject is willing to continue on the same dose as warranted until Week 8
108. If subject is currently receiving oral aminosalicylate (including, but not limited to sulfasalazine or mesalamine), the subject is eligible provided the subject has been on a stable dose for ≥ 4 weeks prior to Day 1 and is willing to stay on the same dose as warranted until Week 12
109. If subject is on antibiotics or probiotics for CD, subject must have been on the same dose for at least 2 weeks before Screening Stage 2 with stable symptoms and is willing to remain on the same dose as warranted until Week 12
110. If subject has recently discontinued oral corticosteroids, these must have been stopped at least 2 weeks before endoscopy during Screening Stage 2 visit
111. During the Study and for 7 days after receiving the last dose of the Study drug, females of childbearing potential or males 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).
112. All male subjects must agree to refrain from semen donation during the study and for 7 days after the last dose of study drug
113. Subject has completed the daily diary at least 5 out of 7 days prior to Screening Stage 2
114. Subject is able to communicate effectively with the investigator, and willing and able to comply with the study procedures, requirements and restrictions, and directions of the clinic staff

4.2. Exclusion Criteria

Exclusion Criteria Pertinent to GI:

300. Subject with current symptoms or signs suggestive of intestinal perforation, intra-abdominal or pelvic abscess, symptomatic internal fistulae, abdominal wall fistulae, or symptomatic stricture
301. Subject with a diagnosis of indeterminate colitis, ulcerative colitis, microscopic colitis, ischemic colitis, radiation colitis, diverticular disease associated with colitis, or suspected ulcerative colitis

302. Subject with a confirmed or suspected diagnosis or history of primary sclerosing cholangitis (PSC)

303. Subject is likely to require bowel surgery or any other type of major surgery (e.g., requiring general anesthesia) during the study duration

304. Subject has had extensive colonic resection (i.e., more than half of colon), subtotal or total colectomy, intestinal resection within 6 months of Screening, > 2 small bowel resections or carries a diagnosis of short bowel syndrome or currently has an ostomy

305. Subject has a history of unresected colonic mucosal dysplasia or history of resected high-grade colonic dysplasia within 3 years prior to Screening. Subjects will not be excluded from the study because of a pathology finding of indefinite dysplasia with reactive atypia or because of adenomas that have been completely resected

306. Subject has required enteral feeding via feeding tube or parenteral alimentation within 21 days prior to Day 1

Exclusion Criteria Pertinent to Medications:

400. Medications of exclusion [redacted] below must be discontinued within the timeframe specified (if applicable)

- azathioprine, 6-mercaptopurine, or methotrexate taken within the 14 days prior to Day 1
- 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
- intravenous corticosteroids within the 14 days prior to Day 1
- rectal mesalamine or corticosteroid (i.e., enemas or suppositories) taken within the 14 days prior to Day 1
- prior exposure to vedolizumab, ustekinumab, mycophenolic acid, tacrolimus, sirolimus, or cyclosporine taken within 60 days prior to Day 1
- any prior exposure to natalizumab, rituximab, efalizumab, fingolimod, cyclophosphamide, or thalidomide
- 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).
- anakinra or any other immune-modifying biologic agent taken within 90 days prior to Day 1
- A JAK inhibitor (e.g., tofacitinib) within 60 days prior to Day 1

Note: For anti-TNFs, vedolizumab, and ustekinumab, there is no requirement for a washout period if there is documented finding of undetectable drug level by a validated assay (e.g., through commercially available testing).

401. Prior exposure or potential exposure to a 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 or end of study)

402. Subject 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)

403. Subject has had inadequate response (i.e., either primary or secondary non-response) to ≥ 3 biologic agents of 3 different mechanisms of action (i.e., anti-TNF, anti-integrin, and anti-IL12/23)

404. Subject is 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 CYP3A4 or is a substrate of P-gp or BCRP and has a narrow therapeutic index [redacted]). For clarity, corticosteroids at doses not excluded elsewhere in the protocol are not considered potent inducers of CYP3A4, P-gp, or BCRP

405. Subject is taking non-CD concomitant prescription medications that have started or have had a dose adjustment within 4 weeks prior to Day 1 (with the exception of corticosteroids as discussed in inclusion criterion #107, antibiotics for recent infections, sedating agents for ileocolonoscopy, hormonal contraceptives, hormone replacement therapy, vitamin D, insulin therapy, and replacement thyroid hormone - see Section 6.4.29)

406. Subject is taking non-CD over-the-counter medications or dietary supplements that have started or have had a dose adjustment within 2 weeks 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 up to 325 mg per day for cardiovascular prophylaxis, and over-the-counter doses of vitamin D - see Section 6.4.29)

Exclusion Criteria Pertinent to Infections:

500. 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 completion of treatment regimen and b) viral load during Screening is undetectable
   d. hepatitis E Immunoglobumin M (IgM) antibody
   e. human immunodeficiency virus (HIV) antibody

501. 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, 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

502. The subject 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 or during the Screening Period, 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.
    Refer to Section 6.4.15 for rationale and required documentation for repeat testing.

    A subject who has a history of latent or active tuberculosis (TB) may be eligible for the study if criteria outlined in Section 6.4.15 are met.

503. Subject has:

    a. an active, clinically significant bacterial, parasitic, fungal, mycobacterial (including atypical infection), or viral infection, except for local skin or nail bed infection, within 30 days prior to Day 1
    b. any infection requiring hospitalization or intravenous antibiotics within 30 days prior to Screening
    c. any infection requiring oral antimicrobial treatment within 2 weeks prior to Screening
    d. a history of more than one episode of herpes zoster or one or more episodes of disseminated or complicated herpes zoster (complicated: multi-dermatomal, ophthalmic, or CNS involvement or post-herpetic neuralgia) or disseminated herpes simplex

504. Subject has had a chest X-Ray or equivalent chest imaging performed within the 90 days prior to Screening or at Screening that shows an abnormality suggestive of a malignancy or current active infection, including TB, chronic lung disease or a potentially active fungal, viral, or bacterial infection.

505. Subject has C. difficile or other gastrointestinal infections (e.g., Salmonella, Shigella, Yersinia, Campylobacter, E. coli O157, etc.) on stool testing or cytomegalovirus [CMV] colitis suspected on endoscopic appearance during Screening. Subject may be treated, re-tested, and re-screened.

506. Subject has had a bone marrow transplant.

507. Within 4 weeks of Screening or during Screening, subject has:

    a. Confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (coronavirus disease 2019 [COVID-19]) (test positive), ***OR***

b. 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***

c. 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

Coexisting Medical Conditions or Past Medical History Exclusion Criteria:

600. Subject is a female who is pregnant, lactating, breastfeeding or planning to become pregnant during the study or within 7 days after the last dose of study drug.

601. Subject is a male who is planning to father a child or donate semen during the study or within 7 days after the last dose of study drug.

602. Subject has clinically significant abnormalities in the results of laboratory evaluations at Screening visit as determined by the investigator or Sponsor, including but not limited to:

- AST, ALT, or alkaline phosphatase ≥ 2x the upper limit of normal (ULN),
- total bilirubin > 2x ULN (unless diagnosed with Gilbert's syndrome, in which case, total bilirubin > 4x ULN),
- creatinine clearance as calculated by the Cockcroft-Gault formula < 30 mL/min (Appendix 1),
- total white blood cell count (WBC) < 3 x 10^9/L,
- absolute neutrophil count < 1.5 x 10^9/L,
- absolute lymphocyte count < 0.8 x 10^9/L,
- hemoglobin < 8 g/dL, or
- platelet count < 100 x 10^9/L.

603. Subject has a clinically significant abnormal ECG at Screening, including QTcF > 450 msec for males and > 470 msec for females.

604. Subject 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 CD), genitourinary, psychiatric, oncologic or neurological disease or other medical disorder that would compromise subject safety or confound study safety assessments as determined by the investigator at Screening and Day 1. [redacted] 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.

605. Subject has known hypersensitivity to excipients or contents of the study drug

606. Subject has a history of alcohol or drug abuse within 1 year of Screening, per the judgment of the investigator

607. Subject with a current or history of malignancy within 5 years prior to Screening, except for completely resected basal cell carcinoma or squamous cell carcinoma in situ of the skin, or 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.

608. Subject who, for any reason, is deemed by the investigator or Sponsor 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

609. Subject with known moderate to severe hepatic impairment (e.g., known Child-Pugh Class B or C)

4.3. Females of Childbearing Potential and Acceptable Birth Control

Females 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 to be 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 postmenopausal females only to confirm postmenopausal state.

A highly effective method of birth control is defined as one that results in a low failure rate (i.e., <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; vasectomized partner; sexual abstinence. Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the women of childbearing potential trial participant and that the vasectomized 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. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. 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

During Induction, subjects will take TD-1473 tablets or placebo once daily for up to 12 weeks. During ATE, subjects will take TD-1473 tablets once daily for up to 48 weeks. For Induction and ATE, subjects will be instructed to take two tablets once daily at approximately the same time each morning before eating and to refrain from eating or drinking anything other than water and non-study medications for at least 30 minutes after dosing.

The 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 nominal dosing time, as long as the subject has fasted for at least 4 hours before. After 12 hours post-nominal dosing time, 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 before the first meal of the day.

[redacted]

5.4. 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. Details of receipt, distribution or dispensing, and destruction of the material(s) will be recorded in the study medication accountability record according to the clinical site's standard operating procedures. Subjects will be instructed to return all used and unused study medication at each study visit.

Unused and expired study drugs will be disposed of in accordance with written instructions from the Sponsor. Copies of the study medication accountability records will be provided to the Sponsor at completion of the study and will be made available for review by the site monitor during the course of the study.

6. STUDY PROCEDURES

Study procedures will be performed only after written informed consent is obtained. The Screening visits (i.e., Stage 1 and Stage 2) will be performed within 35 days before dosing. One repeat Screening Stage 1 visit is allowed for each subject per the investigator's discretion. No more than one repeat Screening Stage 1 visit or repeat visit-specific procedure/assessment is allowed for each subject, unless prior written approval has been provided by the Sponsor. If the subject does not begin Induction treatment within this 35-day window, 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, depending on the reason for the initial screening failure, per consultation with and approval from the Sponsor.

During the study, every effort should be made to perform study procedures as listed in the Schedule of Study Procedures (Table 1). Assessments will be made and biological samples will be taken in the following recommended order at those study visits at which they coincide: fecal sample collection, adverse event assessment, ECG, vital signs, [redacted] clinical laboratory safety samples, [redacted] and ileocolonoscopy with biopsies (although ileocolonoscopy should be done within 3 days prior to the Week 12 clinic visit). Study drug administration will be in-clinic on Day 1, Week 4, Week 8, Week 12, ATE Week 16, ATE Week 24, ATE Week 36, and ATE Week 48 after all pre-dose assessments [redacted] and procedures have been completed.

Throughout the study, the acceptable window for scheduled assessments is as follows:

- - 3 to + 5 days from the nominal visit date for Week 4, Week 8, ATE Week 4, ATE Week 8, ATE Week 16, ATE Week 24, ATE Week 36, ATE Week 48 and the EOS visits
- -1 to +3 days from the nominal Week 12 clinic visit for the Week 12 ileocolonoscopy with biopsies. The Week 12 ileocolonoscopy and biopsies should be performed on the same day as the Week 12 visit, preferably in the early morning, to permit morning dosing with study drug. However, if not feasible to perform both the ileocolonoscopy and the clinic visit on the same day, the ileocolonoscopy could be performed within 3 days after the Week 12 clinic visit. However, the Week 12 endoscopy must be performed at least 1 day prior to ATE Day 1.
- + 3 days from the nominal visit date for the Week 12 clinic visit
- 1-7 days after the Week 12 clinic visit for ATE Day 1. The Week 12 endoscopy must be conducted at least 1 day prior to ATE Day 1.
- Within 5 days following last dose of study drug for Early IP Discontinuation visit (during Induction or ATE)
- [redacted]
- [redacted]
- Screening CDAI score is to be obtained prior to starting the bowel preparation for ileocolonoscopy (to assess eligibility criteria).

[redacted]

6.1. Schedule of Study Procedures

The schedule of study procedures is summarized in Table 1.

Additional safety tests, such as vital signs (blood pressure [BP], heart rate, respiratory rate, and body temperature), physical exams, ECGs, and laboratory safety tests, may be obtained during the course of the study on the basis of newly available data 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, serum pregnancy test (if applicable), FSH (if applicable), [redacted], QuantiFERON®-TB Gold test, [redacted], and genetic testing (if applicable) is [redacted] For subjects who consent to the optional genetic testing, [redacted] Additional samples may be drawn for safety laboratory testing as considered necessary by the investigator.

6.3. Procedures by Visit

6.3.1. Screening

6.3.1.1. Screening Stage 1

Screening Stage 1 visit assessments will be performed between 35 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 following procedures will be performed at Screening Stage 1:

- Written informed consent (signed and dated) after the nature of the study has been explained and before any study procedure is performed
- Review of inclusion and exclusion criteria
- Medication and medical history
- Vital signs
  - Heart rate (HR) and systolic and diastolic blood pressure (BP)
  - Respiratory rate

  - Body Temperature
- 12-lead ECG
- Physical examination (including fistula exam to determine drainage status if the subject has a fistula) to be conducted according to local practice
- Height and weight
- Chest X-ray (unless one has been performed within 3 months of Screening, documented to be negative, and reviewed by investigator. Subjects who have had a chest X-ray within 3 months prior to Screening will not require a repeat X-ray unless subject is deemed to be at high risk of recent pulmonary infection)
- Blood collection
  - Hematology
  - Serum chemistry
  - FSH (postmenopausal females)
  - Viral hepatitis and human immunodeficiency virus [HIV] serology panel (Refer to Section 6.4.14 for additional details)
  - QuantiFERON®-TB Gold [unless an exam has been done with negative findings within 90 days prior to Screening or subject has a history of latent TB that has been adequately treated within the prior 5 years (Refer to Section 6.4.15 for additional details)] - If the QuantiFERON®-TB Gold result is indeterminate, a repeat QuantiFERON®-TB Gold will be performed.
  - Labs required for Screening Stage 2 can be collected during this visit if the subject happens to be fasting during this visit. Subjects should not be instructed to come in fasting.
- Urine collection
  - Urinalysis
  - Pregnancy test for females of childbearing potential – If urine b-hCG test is positive, confirmation with serum b-hCG test is required
- Fecal collection
  - Fecal infectious studies [C. difficile, other bacteria (including Shigella, Salmonella, Yersinia, E. coli O157, and Campylobacter), and ova and parasite]
- Review concomitant medications
- Adverse event assessment (AEs, SAEs, Adverse Events of Special Interest)
- Electronic diary dispensation (or paper diary if electronic diary is not available) and review of daily diary completion instructions, including symptom monitoring

6.3.1.2. 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.

Subjects should be instructed to fast from food and non-clear fluids on the evening prior to the visit (which could be Screening Stage 2 visit) to ensure a minimum 8-hour fast prior to the fasted blood sample collection for lipid level measurement.

The following procedures will be performed at Screening Stage 2:

- Review of inclusion and exclusion criteria
- Blood collection (if not collected at Screening Stage 1)
  - Overnight fasting lipid panel
  - [redacted]
  - [redacted]
- Disease Assessments
  - CDAI Score (must be obtained prior to Screening Stage 2 ileocolonoscopy to assess eligibility criteria; must be performed prior to starting the bowel preparation for the endoscopy; CDAI score ≥ 220 and ≤ 450 is required for continued eligibility)
  - Abdominal Pain and Total Stool Frequency Scores
  - SES-CD Score (to be provided by central reading)
- Ileocolonoscopy and Biopsies (Refer to Section 6.4.18);
- Review concomitant medications
- Adverse event assessment (AEs, SAEs, Adverse Events of Special Interest)
- Review of diary completion, compliance, and symptom monitoring; counsel subject, as needed.

6.3.2. Day 1 (Induction)

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.

Prior to dosing on Day 1, the results of the clinical and laboratory evaluations (as described in Table 1) must be reviewed by the investigator to confirm the continued eligibility of each subject to participate in the study.

The following procedures will be performed on the Day 1 visit:

- Review of inclusion and exclusion criteria
- Review of diary completion and compliance
- Medication and medical history
- Tobacco use status
- Vital signs
  - Heart rate (HR) and systolic and diastolic blood pressure (BP)
  - Respiratory rate
  - Body Temperature
- 12-lead ECG
- Physical examination (including fistula exam to determine drainage status if the subject has a fistula) is to be conducted according to local practice
- Weight
- Blood collection
  - Hematology
  - Serum chemistry
  - Overnight fasting lipid panel
  - [redacted]
  - Genetic blood sample (Optional – only collected for subjects who provide genetic testing consent. Refer to Section 6.4.23)
  - [redacted]
- Urine collection
  - Urinalysis
  - Pregnancy test for females of childbearing potential – If urine b-hCG test is positive, the subject does not meet eligibility criteria and cannot proceed with the Day 1 visit. A serum b-hCG would need to be performed and confirmed by central laboratory testing in order to proceed with randomization.

- Fecal collection (may be collected within 72 hours before Day 1 through the end of day on Day 1; however, it is preferable that the stool sample be collected during the first bowel movement in the morning)
  - [redacted]
- Disease Assessments
  - CDAI Components
  - Abdominal Pain and Total Stool Frequency Scores
  - [redacted]
  - [redacted]
- Randomization via RTSM (after all pre-dose procedures have been completed and subject is confirmed to be eligible for the study)
- Subject dosing in clinic (in the morning before eating)
- Review concomitant medications
- Adverse event assessment (AEs, SAEs, Adverse Events of Special Interest)
- Study drug dispensation and review of subject instructions for dosing
- Re-review diary completion instructions, including symptom monitoring and study drug dosing details.

6.3.3. Week 4 (Induction)

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 following procedures will be performed on the Week 4 visit:

- Vital signs
  - Heart rate (HR) and systolic and diastolic blood pressure (BP)
  - Respiratory rate
  - Body Temperature
- Physical examination is to be conducted according to local practice
- Fistula drainage assessment (if applicable) to determine the number of fistula and confirm draining is occurring.
- Weight
- Blood collection
  - Hematology
  - Serum chemistry
  - Overnight fasting lipid panel

- [redacted]
- Urine collection
  - Urinalysis
  - Pregnancy test for females of childbearing potential – If urine b-hCG test is positive, confirmation with serum b-hCG test is required
- Disease Assessments
  - CDAI Components
  - Abdominal Pain and Total Stool Frequency Scores
- Perform drug accountability and review subject's compliance with study drug dosing
- Subject dosing in clinic (in the morning before eating)
- Review concomitant medications
- Adverse event assessment (AEs, SAEs, Adverse Events of Special Interest)
- Study drug dispensation and re-review of subject instructions for dosing
- Review diary completion and compliance; counsel subject as needed

6.3.4. Week 8 (Induction)

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

The following procedures will be performed on the Week 8 visit:

- Vital signs
  - Heart rate (HR) and systolic and diastolic blood pressure (BP)
  - Respiratory rate
  - Body Temperature
- Physical examination is to be conducted according to local practice
- Fistula drainage assessment (if applicable) to determine the number of fistula and confirm draining is occurring.
- Weight
- Blood collection

  - Hematology
  - Serum chemistry
  - Overnight fasting lipid panel
  - [redacted]

- Urine collection
  - Urinalysis
  - Pregnancy test for females of childbearing potential – If urine b-hCG test is positive, confirmation with serum b-hCG test is required
- Disease Assessments
  - CDAI Components
  - Abdominal Pain and Total Stool Frequency Scores
- Perform drug accountability and review subject's compliance with study drug dosing
- Subject dosing in clinic (in the morning before eating)
- Review concomitant medications
- Adverse event assessment (AEs, SAEs, Adverse Events of Special Interest)
- Study drug dispensation and re-review of subject instructions for dosing
- Review diary completion and compliance; counsel subject as needed
- Initiate corticosteroid taper by 2.5 mg per week (Section 6.4.30), for subjects who entered the study on corticosteroids

6.3.5. Week 10 Telephone Call (Induction)

Subjects should be called approximately 14 days to 7 days prior to the Week 12 visit.

The following procedures will be performed at the Week 10 visit:

- Review concomitant medications
- Continue corticosteroid taper by 2.5 mg per week (Section 6.4.30), for subjects who entered the study on corticosteroids (as applicable)
- Adverse event assessment (AEs, SAEs, Adverse Events of Special Interest)

- Review diary completion and compliance; counsel subject as needed and remind of the importance of completion prior to Week 12
- Review schedule of upcoming Week 12 visit. Remind the subject not eat anything prior to the next visit or take study drug on the morning of their next visit. Review bowel preparation activities.

6.3.6. Week 12 (Induction)

Subjects should be instructed to fast from food and non-clear fluids on the evening prior to the Week 12 visit to ensure a minimum 8-hour fast prior to the fasted blood sample collection.

The Week 12 ileocolonoscopy and biopsies should be performed on the same day as the Week 12 visit, preferably in the early morning, to permit morning dosing with study drug. However, if not feasible to perform both the ileocolonoscopy and the clinic visit on the same day, the ileocolonoscopy could be performed anytime within 3 days after the Week 12 clinic visit. If the study activities of this Week 12 visit are to be completed over two different visits, the study drug should be continued until the later of the two visits.

<u>The following procedures will be performed at the Week 12 visit</u>:

- Tobacco use status
- Vital signs
  - Heart rate (HR) and systolic and diastolic blood pressure (BP)
  - Respiratory rate
  - Body Temperature
- 12-lead ECG
- Physical examination is to be conducted according to local practice
- Weight
- Blood collection
  - Hematology
  - Serum chemistry
  - Overnight fasting lipid panel
  - [redacted]
    - [redacted]
    - [redacted]
    - [redacted]
    - [redacted]
    - [redacted]

- Urine collection
  - Urinalysis
  - Pregnancy test for females of childbearing potential – If urine b-hCG test is positive, confirmation with serum b-hCG test is required
- Fecal collection [may be collected within 3 full days (approximately 72 hours) prior to the visit but must precede the start of a bowel preparation if it is to be collected during the same day as the bowel preparation; however, it is preferable that the stool sample be collected during the first bowel movement in the morning]
  - [redacted]
- Ileocolonoscopy and Biopsies (Refer to Section 6.4.18)
- Disease Assessments
  - CDAI Components
  - Abdominal Pain and Total Stool Frequency Scores
  - SES-CD Score
  - [redacted]
  - [redacted]
- Perform drug accountability and review subject's compliance with study drug dosing
- Subject dosing in clinic (in the morning before eating; last dose of Induction study drug)
- Review concomitant medications
- Continue corticosteroid taper by 2.5 mg per week (Section 6.4.30), for subjects who entered the study on corticosteroids (as applicable)
- Adverse event assessment (AEs, SAEs, Adverse Events of Special Interest)
- Review diary completion and compliance; counsel subject as needed

6.3.7. ATE Day 1

Subjects should be instructed to fast from food and non-clear fluids on the evening prior to the ATE Day1 visit to ensure a minimum 8-hour fast prior to the fasted blood sample collection.

ATE Day 1 may be performed 1 to 7 days following the Week 12 (Induction) visit. However, it must be conducted at least 1 day following the Week 12 ileocolonscopy and biopsies.

The following procedures will be performed at the ATE Day 1 visit:

- Vital signs
  - Heart rate (HR) and systolic and diastolic blood pressure (BP)
  - Respiratory rate

  - Body Temperature
- Blood collection
  - [redacted]
  - [redacted]
    - [redacted]
    - [redacted]
    - [redacted]
- Urine collection
  - Pregnancy test for females of childbearing potential – If urine b-hCG test is positive, confirmation with serum b-hCG test is required
- Assignment of ATE dose (Refer to Table 2 and Section 3.3)
- Subject dosing in clinic (in the morning before eating)
- Review concomitant medications
- Continue corticosteroid taper by 2.5 mg per week (Section 6.4.30), for subjects who entered the study on corticosteroids (as applicable)
- Adverse event assessment (AEs, SAEs, Adverse Events of Special Interest)
- Study drug dispensation and re-review of subject instructions for dosing
- Review diary completion and compliance; counsel subject as needed

6.3.8. ATE Week 4

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

The following procedures will be performed at the ATE Week 4 visit:

- Vital signs
  - Heart rate (HR) and systolic and diastolic blood pressure (BP)
  - Respiratory rate
  - Body Temperature
- Physical examination is to be conducted according to local practice
- Weight
- Blood collection
  - Hematology
  - Serum chemistry

  - Overnight fasting lipid panel
  - [redacted]

- Urine collections
  - Urinalysis
  - Pregnancy test for females of childbearing potential – If urine b-hCG test is positive, confirmation with serum b-hCG test is required
- Disease Assessments
  - CDAI Components
  - Abdominal Pain and Total Stool Frequency Scores
- Perform drug accountability and review subject's compliance with study drug dosing
- Subject dosing in clinic (in the morning before eating)
- Review concomitant medications
- Continue corticosteroid taper by 2.5 mg per week (Section 6.4.30), for subjects who entered the study on corticosteroids (as applicable)
- Adverse event assessment (AEs, SAEs, Adverse Events of Special Interest)
- Study drug dispensation and re-review of subject instructions for dosing
- Review diary completion and compliance; counsel subject as needed

6.3.9. ATE Week 8

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

The following procedures will be performed at the ATE Week 8 visit:

- Vital signs
  - Heart rate (HR) and systolic and diastolic blood pressure (BP)
  - Respiratory rate
  - Body Temperature
- 12-lead ECG
- Physical examination is to be conducted according to local practice
- Weight

- Blood collection
  - Hematology
  - Serum chemistry
  - Overnight fasting lipid panel
  - [redacted]
- Urine collections
  - Urinalysis
  - Pregnancy test for females of childbearing potential – If urine b-hCG test is positive, confirmation with serum b-hCG test is required
- Disease Assessments
  - Abdominal Pain and Total Stool Frequency Scores
- Perform drug accountability and review subject's compliance with study drug dosing
- Subject dosing in clinic (in the morning before eating)
- Review concomitant medications
- Confirm corticosteroid taper by 2.5 mg per week (Section 6.4.30) is complete, for subjects who entered the study on corticosteroids (as applicable)
- Adverse event assessment (AEs, SAEs, Adverse Events of Special Interest)
- Study drug dispensation and re-review of subject instructions for dosing
- Review diary completion and compliance; counsel subject as needed

6.3.10. ATE Week 16

Subjects should be instructed to fast from food and non-clear fluids on the evening prior to the ATE Week 16 visit to ensure a minimum 8-hour fast prior to the fasted blood sample collection.

The following procedures will be performed at the ATE Week 16 visit:

- Vital signs
  - Heart rate (HR) and systolic and diastolic blood pressure (BP)
  - Respiratory rate
  - Body Temperature
- 12-lead ECG

- Physical examination is to be conducted according to local practice
- Weight
- Blood collection
  - Hematology
  - Serum chemistry
  - Overnight fasting lipid panel
  - [redacted]
- Urine collections
  - Urinalysis
  - Pregnancy test for females of childbearing potential – If urine b-hCG test is positive, confirmation with serum b-hCG test is required
- Disease Assessments
  - CDAI
  - Abdominal Pain and Total Stool Frequency Scores
  - [redacted]
  - [redacted]
- Perform drug accountability and review subject's compliance with study drug dosing
- Subject dosing in clinic (in the morning before eating)
- Review concomitant medications
- Adverse event assessment (AEs, SAEs, Adverse Events of Special Interest)
- Study drug dispensation and re-review of subject instructions for dosing
- Review diary completion and compliance; counsel subject as needed

The investigator should consider discontinuation for any subject who has not responded to treatment by ATE Week 16. Subjects who have not shown clinical improvement at ATE Week 16 should complete an Early Study Drug Discontinuation visit and be discontinued from study drug. They will need to return to complete an EOS visit 4 weeks after their last dose.

6.3.11. ATE Week 24

Subjects should be instructed to fast from food and non-clear fluids on the evening prior to the ATE Week 24 visit to ensure a minimum 8-hour fast prior to the fasted blood sample collection.

The following procedures will be performed at the ATE Week 24 visit:

- Tobacco use status
- Vital signs

  - Heart rate (HR) and systolic and diastolic blood pressure (BP)
  - Respiratory rate
  - Body Temperature
- 12-lead ECG
- Physical examination is to be conducted according to local practice
- Fistula drainage assessment (if applicable) to determine the number of fistula and confirm draining is occurring.
- Weight
- Blood collection
  - Hematology
  - Serum chemistry
  - Overnight fasting lipid panel
  - [redacted]
- Urine collection
  - Urinalysis
  - Pregnancy test for females of childbearing potential – If urine b-hCG test is positive, confirmation with serum b-hCG test is required
- Fecal collection [may be collected within 3 full days (approximately 72 hours) prior to the visit; however, it is preferable that the stool sample be collected during the first bowel movement in the morning]
  - [redacted]
- Disease Assessments
  - CDAI Components
  - Abdominal Pain and Total Stool Frequency Scores
  - [redacted]
  - [redacted]
- Perform drug accountability and review subject's compliance with study drug dosing
- Subject dosing in clinic (in the morning before eating)
- Review concomitant medications

- Adverse event assessment (AEs, SAEs, Adverse Events of Special Interest)
- Review diary completion and compliance; counsel subject as needed

6.3.12. ATE Week 36

Subjects should be instructed to fast from food and non-clear fluids on the evening prior to the ATE Week 36 visit to ensure a minimum 8-hour fast prior to the fasted blood sample collection.

The following procedures will be performed at the ATE Week 36 visit:

- Vital signs
  - Heart rate (HR) and systolic and diastolic blood pressure (BP)
  - Respiratory rate
  - Body Temperature
- 12-lead ECG
- Physical examination is to be conducted according to local practice
- Weight
- Blood collection
  - Hematology
  - Serum chemistry
  - Overnight fasting lipid panel
  - [redacted]
- Urine collection
  - Urinalysis
  - Pregnancy test for females of childbearing potential – If urine b-hCG test is positive, confirmation with serum b-hCG test is required
- Disease Assessments
  - CDAI Components
  - Abdominal Pain and Total Stool Frequency Scores
- Perform drug accountability and review subject's compliance with study drug dosing
- Subject dosing in clinic (in the morning before eating)
- Review concomitant medications
- Adverse event assessment (AEs, SAEs, Adverse Events of Special Interest)
- Review diary completion and compliance; counsel subject as needed

6.3.13. ATE Week 48

Subjects should be instructed to fast from food and non-clear fluids on the evening prior to the ATE Week 48 visit to ensure a minimum 8-hour fast prior to the fasted blood sample collection.

The following procedures will be performed at the ATE Week 48 visit:

- Tobacco use status
- Vital signs
  - Heart rate (HR) and systolic and diastolic blood pressure (BP)
  - Respiratory rate
  - Body Temperature
- 12-lead ECG
- Physical examination to be conducted according to local practice
- Fistula drainage assessment (if applicable) to determine the number of fistula and confirm draining is occurring.
- Weight
- Blood collection
  - Hematology
  - Serum chemistry
  - Overnight fasting lipid panel
  - [redacted]
  [redacted]
- Urine collection
  - Urinalysis
  - Pregnancy test for females of childbearing potential – If urine b-hCG test is positive, confirmation with serum b-hCG test is required
- Fecal collection [may be collected within 3 full days (approximately 72 hours) prior to the visit; however, it is preferable that the stool sample be collected during the first bowel movement in the morning]
  - [redacted]
- Disease Assessments
  - CDAI Components
  - Abdominal Pain and Total Stool Frequency Scores
  - [redacted]

  - [redacted]
- Perform drug accountability and review subject's compliance with study drug dosing
- Subject dosing in clinic (in the morning before eating; last dose of ATE study drug)
- Review concomitant medications
- Adverse event assessment (AEs, SAEs, Adverse Events of Special Interest)
- Review diary completion and compliance; counsel subject as needed

6.3.14. End of Study

An EOS visit will be required for all subjects 4 weeks following their last dose of study drug. Subjects who complete an Early Study Drug Discontinuation visit during Induction or ATE 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 following procedures will be performed at the EOS visit:

- Vital signs
  - Heart rate (HR) and systolic and diastolic blood pressure (BP)
  - Respiratory rate
  - Body Temperature
- 12-lead ECG
- Physical examination is to be conducted according to local practice
- Fistula drainage assessment (if applicable) to determine the number of fistula and confirm draining is occurring.
- Weight
- Blood collection
  - Hematology
  - Serum chemistry
  - Overnight fasting lipid panel
  - [redacted]
  - [redacted]
- Urine collections
  - Urinalysis
  - Pregnancy test for females of childbearing potential – If urine b-hCG test is positive, confirmation with serum b-hCG test is required

- Disease Assessments
  - CDAI Components
  - Abdominal Pain and Total Stool Frequency Scores
- Review concomitant medications
- Adverse event assessment (AEs, SAEs, Adverse Events of Special Interest)
- Review diary completion and compliance and collect diary from subject

6.3.15. Early Study Drug Discontinuation

Subjects who prematurely discontinue the study drug due to adverse events (AEs), lack of response, or any other reason besides withdrawal of consent during Induction or ATE 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, if possible. Subjects will also return for the EOS visit for collection of safety data and assessment of disease activity.

During ATE, subjects should be assessed for clinical benefit and if there is no clinical benefit, as deemed by the investigator, the subject should stop study drug treatment and be withdrawn from the study.

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

The following procedures will be performed at the Early Study Drug Discontinuation visit:

- Tobacco use status
- Vital signs
  - Heart rate (HR) and systolic and diastolic blood pressure (BP)
  - Respiratory rate
  - Body Temperature
- 12-lead ECG
- Physical examination to be conducted according to local practice
- Fistula drainage assessment (if applicable) to determine the number of fistula and confirm draining is occurring.
- Weight
- Blood collection
  - Hematology
  - Serum chemistry
  - Overnight fasting lipid panel
  - [redacted]

[redacted]

- Urine collection
  - Urinalysis
  - Pregnancy test for females of childbearing potential – If urine b-hCG test is positive, confirmation with serum b-hCG test is required
- Fecal collection [may be collected within 3 full days (approximately 72 hours) prior to the visit; however, it is preferable that the stool sample be collected during the first bowel movement in the morning]
  - [redacted]
- Disease Assessments
  - CDAI Components
  - Abdominal Pain and Total Stool Frequency Scores
  - [redacted]
  - [redacted]
- Perform drug accountability and review subject's compliance with study drug dosing
- Review concomitant medications
- Adverse event assessment (AEs, SAEs, Adverse Events of Special Interest)
- Review diary completion and compliance; counsel subject as needed Description of Study Assessments

6.4. Description of Study Assessments

6.4.1. 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: date or year of birth, gender, race, and ethnicity.

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 the inclusion and none for exclusion criteria.

6.4.2. Medication History

All medications (i.e., prescription and over-the-counter medications, herbals, vitamins, and supplements) used within 60 days of the Screening visit will be recorded. All CD medications since diagnosis will be collected, and subjects will be asked at Screening as to whether they ever had been or are currently on aminosalicylates, immunomodulators, corticosteroids, biologics, or alternative therapies, the names, treatment duration, and the reasons for discontinuation (lack of efficacy, loss of efficacy, intolerance, or other).

6.4.3. 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 CD, diagnosis date, extent of disease (categorized as ileal, colonic, ileocolonic), presence of complications (fistula [including number, location, and drainage status], abscess [including location], oral manifestations, arthralgia), documented in the appropriate eCRF. 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 CD) will be recorded in the eCRF.

6.4.4. Tobacco Use Status

Subject's current use of tobacco, number of years used, and annual pack years used will be obtained at designated study visits according to the Schedule of Study Procedures (Table 1) and recorded in the appropriate eCRFs.

6.4.5. Height Measurements

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

6.4.6. Body Weight

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

6.4.7. 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).

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 calibrated 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.

Vital sign measurements should be obtained prior to scheduled blood draws.

6.4.8. 12-Lead Electrocardiograms

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

Lead placement should be as consistent as possible for all ECG recordings. ECGs must be performed after the subject has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws). Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, phone, conversation), should be avoided during the pre-ECG resting period and during ECG recording.

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 time point during study drug treatment, the QTcF is > 500 msec and/or 60 msec longer than the value at Screening or the mean QRS interval is > 130 msec, a repeat ECG should be performed for confirmation, and a decision on study drug discontinuation should be made by the investigator. 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).

Of note, it is not necessary to perform more frequent ECG monitoring given an exposure-response analysis comparing the systemic exposure of TD-1473 with heart rate-corrected QT interval (QTcF) was conducted on data collected from performed during the Phase 1 healthy volunteer study. At exposures achieved after single doses of up to 1000 mg and steady-state exposures following daily doses of up to 300 mg, no concentration-related effect on any cardiac intervals was observed. This analysis and preclinical data were used in considering frequency and replicate ECGs required for this study.

6.4.9. Physical Examination

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

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.

6.4.10. Pregnancy Test (females of childbearing potential only)

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

6.4.11. Follicle-Stimulating Hormone (FSH)

Follicle-stimulating hormone (FSH) will be tested at Screening in postmenopausal females only to confirm postmenopausal state.

6.4.12. Chemistry, Hematology, and Urinalysis

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

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. 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.

6.4.13. 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). 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.

6.4.14. Viral Hepatitis and HIV 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 (hepatitis B DNA, hepatitis B surface antibody, and hepatitis C RNA, if appropriate) may be done at Screening Stage 1 or subsequent to it during Screening.

During rescreening, if there is already negative result from the first screening within 90 days, the viral hepatitis B, C, or E or HIV serologies do not need to be repeated.

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

6.4.15. Tuberculosis (TB) Test

A subject with a history of latent TB or signs of latent TB on chest X-ray 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 in countries where TB is endemic) years 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.
3. A subject 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.

A subject with history of active TB may be eligible for the Study if:

- He or she has completed an adequate course of treatment 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 and reviewed by the PI),
- The QuantiFERON®-TB Gold within 90 days of screening is negative, and
- The subject has not lived in a region with high prevalence of multidrug-resistant 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 prior to 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 the subject should be excluded.

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.

6.4.16. Chest X-ray

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 investigator. Posterior anterior (PA) and lateral views (lateral view may not be necessary if PA view is deemed adequate) will be obtained. Subjects who have had a chest X-ray within 3 months prior to Screening will not require a repeat X-ray unless subject is deemed to be at high risk of recent pulmonary infection.

[redacted]

6.4.18. Ileocolonoscopy and Biopsies

Ileocolonoscopy and biopsies will be performed after subject's eligibility is confirmed (CDAI score within inclusion/exclusion criteria upon review prior to the start of bowel preparation, and no exclusionary criteria are met). Subjects who meet locally adapted guidelines for colon cancer surveillance should undergo the locally adapted method of surveillance.

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 endoscopy reading team, 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 the same bowel preparation.

All procedures can be performed by the investigator or qualified designee using the institution's standard procedure with or without sedation (e.g., conscious sedation, monitored anesthesia, or general anesthesia) for endoscopic assessment of disease activity using the SES-CD (Appendix 5) and for biopsies. The Week 12 ileocolonoscopy and biopsies should be performed on the same day as the Week 12 visit, preferably in the early morning, to permit morning dosing with study drug. However, if not feasible to perform both the Week 12 ileocolonoscopy and the clinic visit on the same day, the ileocolonoscopy could be performed within 3 days after the Week 12 clinic visit. The Week 12 endoscopy must be performed at least 1 day prior to ATE Day 1. All procedures will be recorded and the images will be uploaded to the central endoscopy reading platform. The SES-CD score will be evaluated by central reading. An endoscopic imaging video instruction manual will be provided separately.

Up to six biopsies per site will be taken at up to three biopsy sites at Screening and Week 12. [redacted] During the Week 12 visit, every effort should be made to take biopsies in the same areas as done during the Screening ileocolonoscopy regardless of area of worst inflammation in the current ileocolonoscopy. Subjects may undergo a total of up to three endoscopic procedures during their participation on the study. In subjects who re-screen, ileocolonoscopy does not need to be repeated for a rescreening if the ileocolonoscopy is within 28 days of Day 1 of the re-screen and if the SES-CD score is qualifying.

Ileal and colonic tissue samples may be preserved and stored in the central laboratory for future analysis for up to 20 years or as required by applicable law. A system to ensure optimal confidentiality to protect the subjects' personal information as well as standard processes for sample and data collection, storage, analysis, and destruction have been established. Subjects who provided tissue samples can withdraw their consent and request disposal of stored samples at any time.

A biopsy manual will be provided with detailed instructions for biopsy site identification, sample collection, handling, and shipping. The biopsy sites will be recorded in the eCRF. Biopsy sample collection kits will be provided.

[redacted]

[redacted]

6.4.21. Infections

Infections will be defined as non-treated or treated. Treated infections are infections that require anti-microbial therapy. Any infection requiring parenteral anti-microbial treatment resulting in hospitalization for treatment or meeting criteria for a SAE is considered to be a serious infection. Subjects who experience a serious infection should be discontinued from study drug.

[redacted]

6.4.23. 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 [redacted] of TD-1473 and/or to provide further knowledge of inflammatory bowel disease. This sample should be collected at the 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 genetic specimen will be stored for up to 20 years after the end of the study for possible future analyses.

6.4.24. Subject Daily Diary

Subjects will report on a daily basis the time of study drug administration (should be in the morning); the use of anti-diarrheal treatments, including opiates if used for anti-diarrheal treatment; general well-being; presence of fever; the number of very soft to loose and of normal stools; and the severity of the average and of the worst abdominal pain on 4-point (0-3) and 11-point (0-10) abdominal pain scales, respectively, over the preceding 24-hour period (Appendix 7).

6.4.25. Disease Activity Assessments

The disease activity indices SES-CD and CDAI will be assessed as specified in the Schedule of Study Procedures (Table 1). In addition to the patient-reported questions in the CDAI questionnaire, subjects will also be asked to rate their worst abdominal pain of the day on a [redacted] and provide the total number of normal stools that occurred within the past 24 hours.

6.4.25.1. SES-CD

The SES-CD incorporates 4 descriptors: the ulcer size, the proportion of surface covered by ulcer, the proportion of surface covered by other lesions, and the presence of stenosis. Each descriptor is graded from 0-3 and is scored in 5 segments (ileum, right colon, transverse colon, left colon, and rectum). The total score is calculated as the sum of all the items in each segment and can range from 0 to 56. Please see Appendix 5 for the SES-CD calculation.[11] SES-CD data will be collected as specified in the Schedule of Study Procedures (Table 1).

6.4.25.2. CDAI

The CDAI score is generated using regression coefficients for eight different predictors of disease activity: severity of abdominal pain, general well-being, very soft/liquid stool frequency, extra-intestinal symptoms, need for antidiarrheal drugs, presence of an abdominal mass, body weight and hematocrit. The subject will be provided the Bristol Stool Form Scale as a reference for what to consider very soft/liquid stool. See Appendix 6 for the questions that will be asked on a daily basis to calculate the CDAI. The subscores of abdominal pain (0-3), general well-being, and number of very soft or liquid stools are then summed over the 7 days prior to each visit.

CDAI scores should be calculated using the closest previous 7 days not impacted by the colonoscopy and/or its preparation. Note that symptoms on the day prior, the day of, and the day following a colonoscopy should not be counted as part of the 7 days to avoid effect of the bowel preparation or the procedure on symptoms. Additionally, the remaining predictors are also noted and weighted to create the total CDAI score. See Appendix 6 for the CDAI calculation.[12] Benchmarks for disease activity as measured by the CDAI are: <150, clinical remission; 150 to 219, mildly active disease; 220-450, moderately active disease; and >450, very severe disease. CDAI data will be collected as specified in the Schedule of Study Procedures (Table 1). Subjects will enter the 4 subjective parameters daily from Screening Stage 1 to the last day of study participation.

[redacted]

6.4.25.4. Fistula Drainage Assessment

Subjects will also undergo fistula exam at Screening, Day 1, and Week 12 as part of the complete physical exam. At every visit during Induction, at ATE Week 24, at ATE Week 48 or Early Study Drug Discontinuation visit (if applicable), and at the EOS visit, subjects will be inquired about any existing fistula. If they have at least one fistula, the subject will confirm whether each of the fistula are draining.

[redacted]

[redacted]

6.4.27. Adverse Events (AEs)

Adverse events, including serious adverse events (SAEs) and adverse events of special interest (AESIs) 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 communicate with the site to report AEs that occur between visits. Refer to Section 7 for definition, assessment, and reporting of AEs.

6.4.28. Concomitant Medications

All concomitant non-CD 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 in the source documentation and on the CRF. Doses of non-CD 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. All CD medications the subject has ever used should be documented in the eCRF. Medications to be used with clinical discretion are listed in Appendix 3.

[redacted]

[redacted]

6.4.30. Permitted Medications

Permitted medications include, but are not limited to:

- Doses of oral aminosalicylate, probiotics, or antibiotics prescribed for CD should be stable during the Screening and Induction, after which dose may be adjusted up or down during ATE or during the 4 weeks between last dose of study drug and EOS visit.
- Oral corticosteroids for CD are permitted at a stable dose ≤ 25mg/day of prednisone or beclomethasone 5 mg/day or equivalent or ≤ 9mg/day budesonide during Day 1 through Week 12 but need to start to be tapered slowly at Week 8. The required tapering regimen is as follows: prednisone (or equivalent) dose should be tapered by 2.5 mg/day every week until completely off by ATE Week 6. If subject is on budesonide, budesonide MMX, or beclamethasone, then the dose should be tapered according to clinical practice. Oral, topical, or intranasal corticosteroids for non-CD indications are permitted during ATE.

- The only rescue medication permitted (i.e., that allows subjects to stay in the study and continue study drug) is the addition or increase in oral corticosteroid dose up to or above the dose at baseline.
  - If a subject requires one increase of the corticosteroid dose up to baseline dose (defined as dose at Day 1) during the taper, he/she can continue study as usual.
  - If subject requires during Induction a) use of a higher corticosteroid dose than the baseline dose, or b) de novo initiation of corticosteroids of any route of administration for CD symptoms, the subject can continue study drug (but may be deemed as meeting treatment failure definition). The subject would need to taper the steroid dose within two weeks after initiation using the tapering regimen as outlined above.
  - If subject requires during ATE a) use of a higher corticosteroid dose than the baseline dose, or b) de novo initiation of corticosteroids of any route of administration for CD symptoms after ATE Week 16, the subject should discontinue study drug treatment and return for an EOS Visit. For those who initiate or increase corticosteroid dose before ATE Week 16, consider tapering the steroids within two weeks after initiation using the tapering regimen as outlined above.
- Addition of, cessation of, or dose adjustments for the following are allowed during the study:
  - Hormonal therapy for postmenopausal females
  - Oral contraception for females of childbearing potential
  - Aspirin for cardio protection at a maximum dose of 325 mg/day
- Any medication used on a long-term basis at a stable dose (e.g., oral contraceptive pill, multivitamins); doses of non-CD prescription and over-the-counter medications may be altered or new medications may be added during the study only if they are medically indicated and do not confound safety assessment, as deemed by the investigator or Medical Monitor; however, such changes should be minimized during Weeks 1-12.

6.4.31. Restrictions on Alcohol Consumption and Illicit Drug Use

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

6.5. Discontinuation

6.5.1. 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.

When possible, the tests and evaluations listed for the Early Study Drug Discontinuation visit and EOS visit should be carried out, as noted in Sections 6.3.12 and 6.3.15. 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 study or a subject may choose to terminate participation before completion of the study include the following:

- Adverse event
- Subject choice / Withdrawal of consent
- Major violation of the protocol
- Termination of the study by the Sponsor
- Need for a new prohibited medication for CD or surgery
- Lost to follow-up
- Subject demonstrates lack of clinical benefit (e.g., ATE Week 16 visit)
- Pregnancy
- Other

Subjects with laboratory abnormalities must recheck lab values or discontinue study drug as outlined in Section 7.2. Any non-laboratory-related AE considered an AESI defined in Section 7.1.4, except for non-melanoma skin cancer, 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.

6.5.2. 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.

6.5.3. Study Discontinuation

The Sponsor reserves the right to discontinue this study at any time for any reason. Periodic review of unblinded safety data by an external Independent Data Monitoring Committee (IDMC) (Section 8.10) may lead to the board's recommendation of pausing dosing or terminating the study. 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 IRBs and the Regulatory Authorities will be informed.

6.6. Pregnancy

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

All pregnancies whether of a subject participating in the study or in the female partner of a 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 study from the time of consent until 7 days after the subject's last dose of study drug, Theravance Biopharma, Inc. (TBPH) will be notified according to the procedures for SAE reporting as

outlined in Section 7.4.3. 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

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 preexisting 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 of 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 (AESIs)

At each study visit, the Investigator (or designee) will specifically query for any adverse events of special interest (AESIs). 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 (Section 7.2)
- cardiovascular event (e.g., myocardial infarction or cerebrovascular accident)

All AESIs, except for non-melanoma skin cancers, must be reported to TBPH Clinical Safety and Pharmacovigilance within 24 hours of awareness by the Investigator or his/her designee (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 AESIs should lead to discontinuation of the study drug. For each of these AESIs, 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.

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 considered clinically significant in the judgment of the investigator may be recorded as AEs or SAEs if they meet the definition of an adverse event (or serious adverse event), as described in Sections 7.1.1 (Adverse Event) and 7.1.2 (Serious Adverse Event). 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.

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

- clinically significant reduction in leukocytes or leukocyte subsets that may place subjects at higher risk for infection such as:
  - moderate neutropenia (e.g., absolute neutrophil count of $< 1.0 \times 10^9$/L)

  - moderate leukopenia (e.g., white blood cell count of < 2.0 x 10^9/L)
  - moderate lymphocytopenia (e.g., absolute lymphocyte count of < 0.5 x 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, pre-dose)

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 neutropenia (e.g., absolute neutrophil count of < 1.0 x 10^9/L) on two sequential lab results
- moderate leukopenia (e.g., white blood cell count of < 2.0 x 10^9/L) on two sequential lab results
- moderate lymphocytopenia (e.g., absolute lymphocyte count of < 0.5 x 10^9/L) on two sequential lab results
- a reduction by ≥ 50% from baseline in creatinine clearance on two sequential lab results
- Abnormal AST or ALT > 3x ULN on two sequential lab results with associated bilirubin > 2x ULN on at least one of the two lab results or international normalized ratio (INR) >1.5 on at least one of the two reports (INR will need to be checked locally),
- ALT or AST > 8x ULN **on a single lab result**
- AST or ALT > 5x ULN on two sequential lab results at least 2 weeks apart, or
- AST or ALT > 3x ULN **on a single lab result 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%).

Appendix 12 presents an algorithm for evaluating and managing subjects with ALT or AST > 3x ULN

The first occurrence of these laboratory abnormalities may not trigger the definition of an AESI and study drug discontinuation until the second sequential abnormality (except for the two bolded circumstances above). If there are any questions as to whether a laboratory abnormality should be reported as an AE or an AESI, the investigator is encouraged to contact the Medical Monitor 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 who 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 describe the membership, 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 patients 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 (except for non-melanoma skin cancer) 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 appropriate Case Report Form to the following:

Theravance Biopharma Clinical Safety and Pharmacovigilance

[redacted]

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

Medical Monitor Contact Information:

[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, 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, 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

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

Continuous data will be summarized using an 8-point summary (n, mean, standard deviation [SD], median, interquartile range [25% quartile, 75% quartile], minimum, and maximum) unless otherwise specified in the SAP or table shell. Categorical data will be summarized using counts and percentages.

Study Day 1 is defined as the day of the first study drug dose. The preceding day is Study Day -1.

Baseline is the last assessment (scheduled or unscheduled) obtained before start of study drug dosing, unless otherwise specified in the SAP (e.g., for fecal sample assessments). Baseline for endpoints that have more than one component is calculated from the individual component baselines, whether or not they were assessed during the same visit.

The study will include 2 formal database locks, one after all 160 subjects have either completed or withdrawn from the Induction phase, and one after all subjects have completed or withdrawn from the ATE phase. Separate SAPs will be prepared for the following unblinded analyses, and finalized before the database are locked for analysis:

Database lock after the Induction Phase is completed:

- Analyses of induction data, to include specifications for [redacted] SAP, when not otherwise specified, refers to this SAP)
- [redacted]

Database lock after the ATE phase is completed:

- Analyses of ATE data

Any changes to the data summaries and analyses outlined in this section will be described in the applicable SAP. Any major changes to the definition of the primary endpoint will also be included in a protocol amendment.

8.2. Sample Size and Power

Assuming that the less effective TD-1473 dose results in a 45-point improvement in placebo-adjusted CDAI score change at Week 12, the more effective dose results in a 60 point improvement, the residual SD is 100 points, and a sample size of 160 subjects with 60 subjects in each of the active dose groups and 40 subjects in the placebo group, 100,000 simulations performed using SAS/IML software yielded the following power estimates for 2-sided testing with the familywise Type I error rate controlled at 5% using the Hochberg step-up procedure:

- 82% power to show at least one of the two doses effective
- 58% power to show both doses effective

The target effect size of 60 points was selected as predictive of a clinically significant increase in clinical response rate. Of note, the study is not powered for the secondary endpoints.

8.3. Analysis Sets

The modified Intent-to-Treat (mITT) analysis set comprises all randomized subjects who receive at least one dose of study drug and have at least one postbaseline CDAI score. The mITT set is the primary analysis set for efficacy summaries and analyses.

The Per-Protocol (PP) analysis set comprises all subjects in the mITT analysis set with no major analysis protocol deviations (Section 8.3.2). If the number of mITT subjects excluded from the PP analysis set is ≤ 5 per treatment group, PP analyses will not be performed. Otherwise, both the mITT and the PP analysis set will be used for selected efficacy summaries and analyses.

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 both general (baseline, exposure, and compliance) and safety analyses.

[redacted]

Except for the [redacted] Analyses using the mITT analysis set will be by randomized treatment. Analyses using the PP analysis set and the Safety analysis set will be by actual treatment.

8.3.1. Examination of Subgroups

Predefined subgroups will include the following:

- Prior biologics failure (Yes, No)
- CDAI score at Screening Stage 2 (≤ 300 or > 300)

Others will be defined in the applicable SAP. For analysis purposes, prior biologics failure status and baseline CDAI score will be determined using the information captured in the clinical database rather than the information in the RTSM database.

For selected efficacy endpoints, results will be provided by subgroup.

8.3.2. Major Analysis Protocol Deviations

The following protocol deviations are considered major and as affecting analyses of efficacy data:

- [redacted]
- [redacted]
- [redacted]

Additional categories may be specified in the applicable SAP.

8.4. General Analyses

8.4.1. Demographics and Other Baseline Characteristics

Demographics and baseline characteristics including age, sex, race, ethnicity, creatinine clearance, weight, body mass index, CD characteristics, previous and current CD medications by category, and other medical history will be summarized.

8.5. Efficacy Analyses

8.5.1. Efficacy Endpoints

The primary endpoint is:

- CDAI score change from baseline at Week 12

The secondary endpoints are:

- CDAI clinical response (defined as reduction from baseline of ≥ 100 points or CDAI < 150) at Week 12
- CDAI clinical remission (defined as CDAI < 150) at Week 12
- SES-CD change from baseline at Week 12
- Endoscopic response (SES-CD reduction of ≥ 50% from baseline or endoscopic remission) at Week 12
- Stool Frequency and Abdominal Pain (SFAP) clinical remission defined as abdominal pain score ≤ 1 (on a scale of 0-3), stool frequency ≤ 2.8, and both not worse than baseline at Week 12

8.5.2. Primary Efficacy Evaluations

The primary analysis of CDAI score change at Week 12 will be performed by fitting a mixed effects repeated measures model to values at Weeks 4, 8, and 12, with baseline CDAI score as a covariate, using SAS procedure MIXED to fit a model with random subject effects, an unstructured covariance matrix, and including terms for prior biologics failure status, visit, and baseline CDAI score by visit and treatment by visit interactions.

The effect of each TD-1473 dose on reduction in CDAI at Week 12 (and also at Week 4 and at Week 8) will be estimated. These estimates are unbiased if missing data are missing at random (MAR). This assumption will be assessed with a missing data sensitivity analysis if at least one TD-1473 dose is shown to reduce Week 12 CDAI more than placebo.

As a sensitivity analysis, CDAI score change at Week 12 will also be analyzed by fitting the equivalent analysis of covariance (ANCOVA) model, using SAS procedure MIXED to fit an equal-slopes model with terms for prior biologics failure status, baseline CDAI score, and treatment.

8.5.3. Secondary and Exploratory Efficacy Evaluations

Binary efficacy endpoint rates will be compared using stratified Cochran-Mantel-Haenszel tests, stratifying by randomization stratum as determined from information in the clinical database. Selected binary endpoints will also be analyzed by fitting logistic regression models. Confidence intervals for treatment effects with nominal confidence level 95% will be calculated by methods specified in the SAP.

[redacted] and other efficacy endpoints assessed only at baseline and Week 12 will be analyzed by fitting an ANCOVA model like the one given for CDAI score change at Week 12. The covariate in each model will be the baseline value of the endpoint. [redacted]

[redacted] and other efficacy endpoints assessed at baseline and Weeks 4, 8, and 12 will be analyzed by fitting a mixed effects repeated measures model like the one given for CDAI score change at Week 12. The covariate in each model will be the baseline value of the endpoint. [redacted]

8.5.4. Multiplicity Adjustment

A Hochberg step-up procedure will be used for testing hypotheses associated with the primary efficacy endpoint (mean change in CDAI at Week 12):

Each TD-1473 dose will be compared with placebo. The null hypothesis will be that there is no difference between the TD-1473 dose level mean and the placebo mean, and the alternative hypothesis will be that they differ. To control the family-wise type 1 error rate at 5%, the Hochberg step-up procedure will be used:

Step 1. If both p-values are ≤ 0.05, reject both no-effect null hypotheses and conclude that both TD-1473 doses reduce the CDAI score at Week 12, compared to placebo; otherwise

Step 2. If the smaller p-value is ≤ 0.025, reject the no-effect null hypothesis for that dose; otherwise

Step 3. Fail to reject both no-effect null hypotheses and conclude that TD-1473 does not reduce the CDAI score compared to placebo.

[redacted]

8.7. Pharmacodynamic Analyses

Tissue markers of inflammation and whole blood and serum samples will be collected as described in the Schedule of Study Procedures tables (Table 1). PD analyses will be detailed as appropriate. [redacted]

8.8. Safety Analyses

Safety data will be summarized by treatment received; specifically, induction safety data will be summarized by treatment received during induction and ATE safety data by treatment received during the ATE. Summaries will be provided by nominal visit and time point or for the entire treatment period, as appropriate for the type of data. 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.

[redacted]

8.8.2. Adverse Events

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 for whom events were reported.

In general, a treatment-emergent adverse event (TEAE) will be defined as any AE that begins on or after the date and time of the first dose of study drug and up to the date of last dose of study drug plus the number of days in the follow-up period.

TEAEs will be summarized separately for the Induction and ATE phases. Assignment of TEAEs to different phases of the study (Induction or ATE) will be detailed in the SAPs.

All AEs will be listed by subject. The number and percentage of subjects who experience TEAEs will be summarized. Summaries of TEAEs will include the following types of summaries:

- All AEs, by SOC and PT and also by PT (by descending overall frequency)
- All AEs, by SOC, PT, and severity
- All study drug-related AEs, by SOC and PT
- All study drug-related AEs, by SOC, PT, and severity
- All AEs leading to premature discontinuation of study drug, by SOC and PT
- All AEs leading to temporary interruption of study drug, by SOC and PT
- All SAEs, by SOC and PT
- All study drug-related SAEs, 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. AEs of Special Interest, as described in Section 7.1.4, will be listed and summarized.

8.8.3. Concomitant Medications

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

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

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

Concomitant medication use during the ATE will be summarized separately.

8.8.4. Laboratory Data

Laboratory values, changes from baseline, values relative to normal ranges, and values and changes meeting specified criteria, including the numeric criteria given as examples in Section 7.2, will be summarized.

Clinical laboratory test results will be listed by subject. 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. Abnormalities in clinical laboratory test results will be listed in a separate listing.

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 3.

Table 3: 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 the following categories:

Table 4: ECG Interval Ranges

Heart Rate (bpm)	Heart Rate Change from Baseline (bpm)	PR Interval (msec)	PR Percent Change From Baseline (%)	QRS Interval (msec)	QT_cF (msec)	QT_cF 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	

In addition, QTcF (msec) will also be summarized by the following categories: Normal (males ≤ 430, females ≤ 450), Borderline (males [> 430, ≤ 450], females [> 450, ≤ 470]), and Prolonged (males > 450, females > 470).

All recorded ECG interval values and ECG assessments will be presented in a by-subject listing. A separate listing of subjects with extreme values or changes, as specified in the SAP (e.g., values of QTcF > 450 msec if male or > 470 msec if female, QTcF increases from baseline > 60 msec) will be provided.

8.9. Handling of Missing Data

For the primary analysis of score change endpoints (e.g., CDAI score change, SES-CD score change), missing values will not be imputed. Sensitivity analyses for the primary endpoint will be specified in the SAP, and will be performed if one or both TD-1473 doses are shown to reduce Week 12 CDAI more than placebo.

Subjects with missing data for binary efficacy endpoints will be counted as treatment failures. Alternative approaches may be specified in the SAP.

In addition, subjects who had nonmissing data for a binary efficacy endpoint meeting the criterion for success but met one of the following criteria prior to the visit will be counted as treatment failures:

- Received rescue medication, defined as any medication given to treat CD symptoms, other than antidiarrheal medication for control of chronic diarrhea, if started postbaseline or if the dose was increased postbaseline to a dose higher than at baseline (both induction and ATE; ATE baseline is Week 12)
- Experienced disease worsening, defined as an increase in CDAI score from baseline of ≥ 100 points at consecutive visits (ATE only; ATE baseline is Week 12)

[redacted]

8.10. Independent Data Monitoring Committee

There will be an external independent data monitoring committee (IDMC) comprising four [redacted]

[redacted]

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 subinvestigators 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 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 diary, electronic laboratory data transfer. Study site personnel will enter (in English) study data into the CRFs for each subject that is screened. Training on systems used by site personnel (e.g., EDC) or study subjects (e.g., electronic diary) 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, electronic clinical outcome assessments (eCOA), and electronic diary 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.

Noncompliance 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 noncompliance 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

1. Behzadi, Payam, Elham Behzadi, and Reza Ranjbar. "The incidence and prevalence of Crohn's disease in global scale." SOJ Immunol 3.2 (2015): 1-6.
2. Ng, S.C., et al., Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet, 2017.
3. Gunnarsson, C., et al., The employee absenteeism costs of inflammatory bowel disease: evidence from US National Survey Data. J Occup Environ Med, 2013. 55(4): p. 393-401.
4. Kappelman, M.D., et al., Direct health care costs of Crohn's disease and ulcerative colitis in US children and adults. Gastroenterology, 2008. 135(6): p. 1907-13.
5. Longobardi, T., P. Jacobs, and C.N. Bernstein, Work losses related to inflammatory bowel disease in the United States: results from the National Health Interview Survey. Am J Gastroenterol, 2003. 98(5): p. 1064-72.
6. Sandborn, William J., et al. OCTAVE Induction 1, OCTAVE Induction 2, and OCTAVE Sustain Investigators. N Engl J Med. 2017 May 4;376(18):1723-1736.
7. Vermeire et al. Clinical remission in patients with moderate-to-severe Crohn's disease treated with filgotinib (the FITZROY study): results from a phase 2, double-blind, randomized, placebo-controlled trial. Lancet 2016.
8. Sandborn, William J., et al. Safety and Efficacy of ABT-494 (Upadacitinib), an Oral Jak1 Inhibitor, as Induction Therapy in Patients with Crohn's Disease: Results from Celest. Gastroenterology 152.5, 2017. S1308-S1309.
9. Molnar T., Annaházi A. (2014) Pathogenesis of Ulcerative Colitis and Crohn's Disease: Similarities, Differences and a Lot of Things We Do Not Know Yet. J Clin Cell Immunol 5: 253. doi:10.4172/2155-9899.1000253
10. Banholzer, M.L., et al., Clinical trial considerations on male contraception and collection of pregnancy information from female partners. J Transl Med, 2012. 10: p. 129.
11. Koutroumpakis E, Katsanos KH. Implementation of the simple endoscopic activity score in Crohn's disease. Saudi J Gastroenterol. 2016;22(3):183-191.
12. Best, W.R., Becktel, J.M., Singleton, J.W. and Kern, F., 1976. Development of a Crohn's disease activity index. Gastroenterology, 70(3), pp.439-444.

[redacted]

APPENDIX 1. COCKCROFT-GAULT CALCULATION

The estimated creatinine clearance (mL/min) will be calculated 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 2. PROTOCOL SIGNATURE FORM

Protocol Signature Form

Protocol #:	**0173**
Protocol Title:	A Phase 2 Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Induction Therapy with 2 Doses of TD-1473 in Subjects with Moderately-to-Severely Active Crohn's Disease
Version:	[redacted]
Version Date:	09 June 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

APPENDIX 3. MEDICATIONS TO USE WITH CLINICAL DISCRETION

In vitro metabolism data indicate that CYP3A4/5 and CYP2D6 are the primary human CYP enzymes involved in the metabolism of TD-1473. Since TD-1473 is expected to have a low fraction absorbed, the potential for a CYP-mediated drug-drug interaction (DDI) with inhibitors/inducers of the CYP450 enzymes (i.e., the impact of other drugs on TD-1473) is considered to be low. However, limited data exist in humans at this time. Due to the potential for interaction with TD-1473, strong CYP3A4 inducers and inhibitors should be avoided.

In vitro CYP450 inhibition and induction metabolism data suggest that TD-1473 has a low potential to inhibit or induce CYP450 enzymes. TD-1473 did not induce the expression or activity of CYP enzymes (CYP1A2, CYP2B6, CYP3A4) in cultured human hepatocytes and is not expected to achieve free plasma concentrations high enough to activate hepatic PXR. TD-1473 showed competitive inhibition of CYP3A4 (IC50 = 4.5 μg/mL) and CYP2D6 (IC50 = 6.0 μg/mL), but the maximum unbound TD-1473 plasma concentrations observed in healthy subjects dosed up to 1000 mg were > 500-fold lower than the CYP3A4 IC50. Therefore, it is unlikely that TD-1473 would impact the exposure of any concomitantly administered CYP substrates.

In vitro evaluation indicate that TD-1473 is a substrate for both the efflux transporters P-gp and BCRP. The potential for a transporter-mediated DDI with inhibitors of P-gp or BCRP (i.e., impact to TD-1473 systemic exposure due to a change in fraction absorbed) is considered to be moderate.

TD-1473 is an inhibitor of BCRP (IC50 = 1.2 μg/mL), P-gp (IC50 = 32 μg/mL), and OATP2B1 (IC50 <4.0 μg/mL). Due to the low systemic exposure observed in the Phase 1 healthy subject study and Phase 1b study in subjects with UC (detailed in Section 1.3 and Section 1.4, respectively), hepatic inhibition of these transporters is not expected. However, based on fecal and intestinal tissue concentrations observed in clinical studies, inhibition of intestinal BCRP and OATP2B1 by TD-1473 may occur at doses above 30 mg. For medications with limited bioavailability due to BCRP-mediated restriction to the GI tract, caution should be exercised if concurrent therapy with TD-1473 is required since TD-1473 may result in a change in systemic exposure (e.g., sulfasalazine). All medications that are substrates of P-gp or BCRP with a narrow therapeutic index (e.g., digoxin and dabigatran) should be avoided. Although limited clinical evidence exists to assess the impact of OATP2B1 inhibition on concomitantly administered drugs which are OATP2B1 substrates, the potential for TD-1473 to have a clinically meaningful impact is considered to be low.

Due to the potential for interaction with TD-1473, medications that are strong P-gp or BCRP inhibitors should be avoided. A non-exhaustive list of CYP3A4, P-gp, and BCRP inducers and inhibitors is provided. A non-exhaustive list of examples is provided. Examples: amiodarone, carbamazepine, carvedilol, clarithromycin, curcumin, cyclosporine, daclatasvir, dronedarone, eltrombopag, fostamatinib, grapefruit or grapefruit juice, itraconazole, ketoconazole, lapatinib, ledipasvir, paritaprevir, phenytoin, posaconazole, propafenone, ombitasvir, quinidine, ranolazine, rifampin, ritonavir, sofosbuvir, St. John's wort, telaprevir, velpatasvir, verapamil, and voriconazole. For clarity: 1) any amount of grapefruit in the diet is prohibited; 2) curcumin is prohibited as a concentrated supplement, but dietary intake is allowed; 3) corticosteroids at doses not excluded elsewhere in the protocol are not considered strong CYP3A4/P-gp/BCRP inducers.

APPENDIX 4. DEFINITION OF PRIOR BIOLOGICS FAILURE: PRIMARY AND SECONDARY NON-RESPONSE OR INTOLERANCE TO PREVIOUS BIOLOGICS

Primary non-response:

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

- Infliximab (3 doses of 5 mg/kg or 10 mg/g 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)
- Certolizumab pegol (3 doses of 400 mg at Weeks 0, 2, and 4 or earlier)
- Vedolizumab 300 mg administered by intravenous infusion at Weeks 0, 2, and 6 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 Crohn's disease occurring within 2 weeks after receiving the last dose:

- Lack of improvement or worsening in stool frequency.
- Lack of improvement or worsening in daily abdominal pain.
- Occurrence, lack of improvement or worsening fever thought to be related to Crohn's disease.
- Recurring drainage from a previously non-draining fistula or development of a new draining fistula.
- Lack of improvement or worsening in rectal bleeding.
- Initiation or increase in antidiarrheal medication.

Secondary non-response:

Initially responded to induction therapy and received at least 2 of the following maintenance doses:

- Infliximab (at a dose of ≥ 5 mg/kg every 8 weeks or more frequently)
- Adalimumab (at a dose of 40 mg every week or every other week)
- Certolizumab pegol (at a dose of 400 mg every four weeks or more frequently)
- Vedolizumab 300 mg administered every 8 weeks or more frequently
- 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 Crohn's disease occurring within two weeks of receiving the last dose:

- Worsening in stool frequency.
- Worsening in daily abdominal pain.
- Occurrence or worsening in fever thought to be related to Crohn's disease.
- Recurring drainage from previously non-draining fistula or development of a new draining fistula.
- Worsening rectal bleeding.
- Initiation or increase in antidiarrheal medication.

APPENDIX 5. SES-CD

The SES-CD incorporates 4 descriptors: the ulcer size, the proportion of surface covered by ulcer, the proportion of surface covered by other lesions, and the presence of stenosis. Each descriptor is graded from 0-3 and is scored in 5 segments (ileum, right colon, transverse colon, left colon, and rectum). The total score is calculated as the sum of all the items in each segment and can range from 0 to 56.[11]

Simple Endoscopic Score (SES-CD)

Variable	**0**	**1**	**2**	**3**
Size of ulcers (cm)	None	Aphthous ulcers (diameter 0.1-0.5)	Large ulcers (diameter 0.5-2)	Very large ulcers (diameter >2)
Ulcerated surface	None	< 10%	10-30%	> 30%
Affected surface	Unaffected segment	< 50%	50-75%	> 75%
Presence of narrowings	None	Single, can be passed	Multiple, can be passed	Cannot be passed

SES-CD score equals the sum of all variables for the 5 bowel segments. Values are given to each variable for every examined bowel segment.[11]

APPENDIX 6. EXAMPLE OF THE CDAI

Crohn's Disease Activity Index (CDAI)[12]										
Variable	Day							7 Day Total	Weighting Factor	Total
	1	2	3	4	5	6	7		x2=	
1. Number of liquid or very soft stools										
2. Abdominal pain 0=none, 1=mild, 2=moderate, 3=severe									x5=	
3. General well-being 0=generally well, 1=slightly under par, 2=poor, 3=very poor, 4=terrible									x7=	
4. Extra-intestinal manifestations, Current									Check all that Apply	
a. Arthritis/arthralgia										
b. Iritis/uveitis										
c. Erythema nodosum, pyoderma gangrenosum, aphthous stomatitis										
d. Anal fissure, fistula, or abscess										
e. Other fistula										
f. Fever over 37.8C (100F) during past 7 days										
									Total number of checked boxes=	
									x20=	
5. Lomitil, Imodium, Opiates for diarrhea in the last 7 days									No=0, Yes=1	
									x30=	
6. Abdominal mass									None=0, Questionable=2, Definite=5	
									x10=	
7. Local Haematocrit (%, rounded to whole)									If Male, 47-_____= If Female, 42-_____= If negative, enter 0	
									x6=	
8. Body weight calculation									Percentage deviation from standard weight x1= If value is less than -10, enter -10	
									CDAI TOTAL=	

APPENDIX 7. EXAMPLE OF THE SUBJECT DAILY DIARY

The following questions will be assessed daily in the subject daily diary. The first 6 pertain to the CDAI:

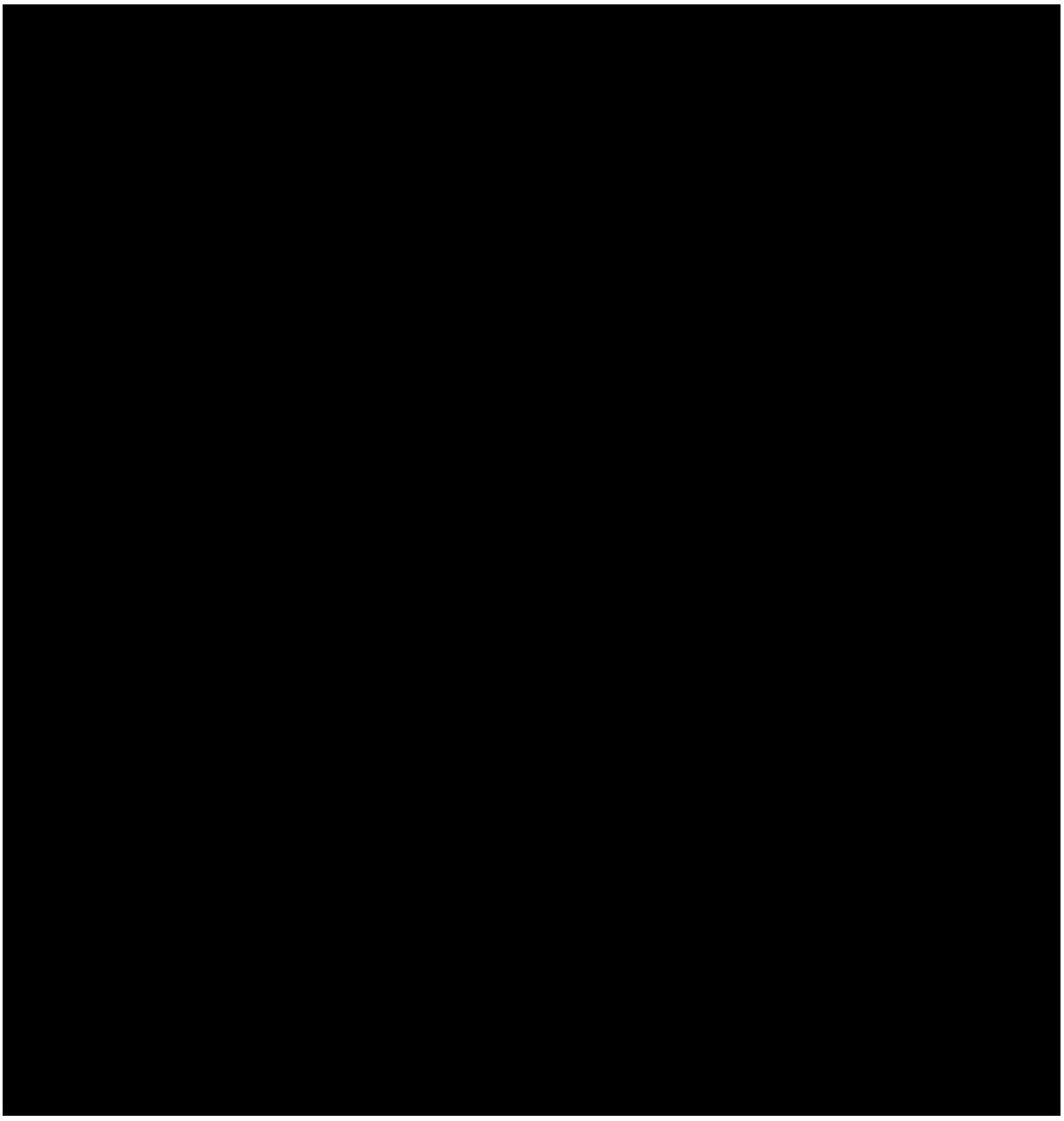
Variable	Day						
	1	2	3	4	5	6	7
1. Number of liquid or very soft stools (collected via the Bristol Stool Form Scale)							
2. Number of normal stools (collected via the Bristol Stool Form Scale)							
3. Average abdominal pain 0=none, 1=mild, 2=moderate, 3=severe							
4. Fever (yes/no)							
5. Use of Imodium, Lomotil, or opiates for diarrhea (yes/no)							
6. Well-being 0=generally well, 1=slightly under par, 2=poor, 3=very poor, 4=terrible							
7. Worst abdominal Pain of the day [redacted]							

Additionally, there will be daily information collected on the timing of dosing.

[redacted]

[redacted]

[redacted]



APPENDIX 10. DEFINITION OF CD MEDICATION INTOLERANCE OR INADEQUATE RESPONSE AND OF CORTICOSTEROID DEPENDENCE

1. **Definition of intolerance or inadequate response:**
   a. 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

   b. Corticosteroids:
      - Signs and symptoms suggestive of persistence of active disease despite a 4-week regimen that included ≥ 2 weeks of ≥ 25 mg/day of prednisone or beclomethasone diproprionate (i.e., Clipper) at 5 mg/day or equivalent
      - Intolerance (including, but not limited to hyperglycemia, infection, Cushing's syndrome, anxiety, weight gain, blurry vision, corticosteroid-induced hypertension, intolerable insomnia, osteopenia/osteoporosis)

   c. Immunomodulators (azathioprine, 6-mercaptopurine or methotrexate):
      - Signs and symptoms suggestive of persistence of active disease despite a regimen ≥ 8 weeks of oral azathioprine (≥ 1.5 mg/kg) or 6-mercaptopurine (≥ 0.75 mg/kg)
      - Signs and symptoms suggestive of persistence of active disease despite a history of at least one 12-week regimen of methotrexate of 12.5 mg/week
      - Intolerance of at least one immunomodulator (including, but not limited to nausea/vomiting, abdominal pain, pancreatitis, LFT abnormalities, lymphopenia, TPMT genetic mutation, infection)

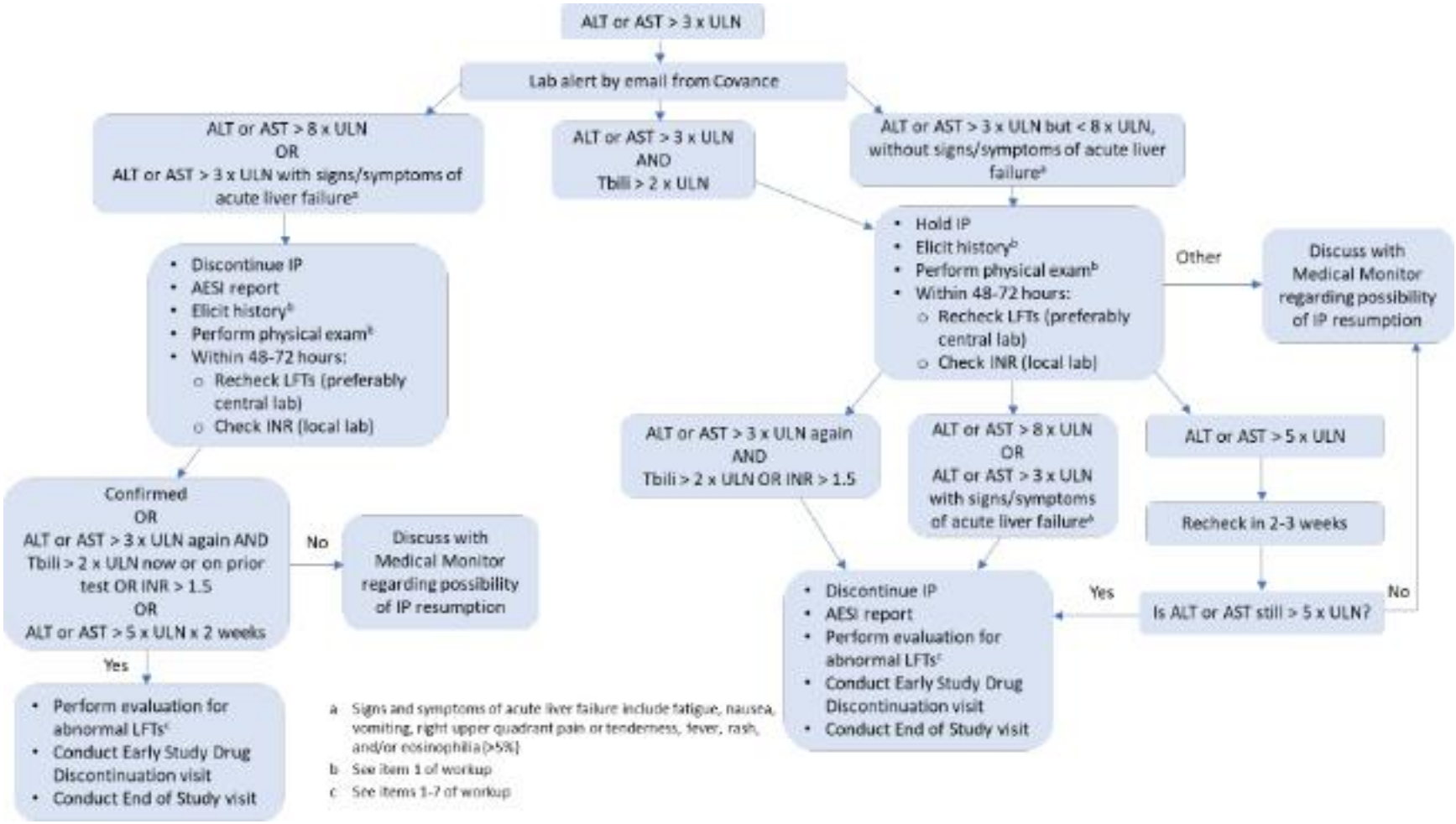
   d. Biologics (anti-TNF or anti-integrin; Refer to Appendix 4 for further detail):
      - Signs and symptoms suggestive of persistence of active disease despite completing an Induction regimen
      - Symptom recurrence during Maintenance dosing following previously demonstrating clinical benefit
      - Intolerance (including, but not limited to infusion-related reaction, rash, injection site reaction, demyelination, congestive heart failure, infection)

2. **Definition of corticosteroid dependence:**
   a. Requiring prednisolone ≥10mg/d (or equivalent) or ≥budesonide 3mg/d for ≥3 months to control CD, ***OR***
   b. Relapse within 3 months of stopping steroid therapy, ***OR***
   c. Unable to discontinue corticosteroids without flare within 3 months after initiating them

[redacted]

[redacted]

APPENDIX 12. 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.

Abbreviation	Description
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

Abbreviation	Description
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 13. 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, [redacted] 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 [redacted]
- 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.