Protocol Number: 0164

Official Title: A 3-Year, Multi-Center, Long-Term Safety (LTS) Study to Evaluate the Safety and Tolerability of TD-1473 in Subjects with Ulcerative Colitis (UC)

NCT Number: NCT03920254

Document Date: 15 Feb 2021

CLINICAL STUDY PROTOCOL

Study Title:	A 3-Year, Multi-Center, Long-Term Safety (LTS) Study to Evaluate the Safety and Tolerability of TD-1473 in Subjects with Ulcerative Colitis (UC)
Study Short Title:	TD-1473 LTS UC Study
Sponsor Study No.:	0164
Date:	15 Feb 2021 [redacted]
Test Product:	TD-1473
US IND:	128299
EudraCT number:	2018-002135-19
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: See contact list for most up to date numbers

JAPAN ONLY
[redacted]

Phone: [redacted]
Fax: [redacted]

ALL OTHER COUNTRIES
[redacted]

Phone: (Dial-in Numbers)
North America: [redacted]
EMEA: [redacted]
Asia-Pacific (not including Japan): [redacted]

Fax:
North America: [redacted]
Outside North America: [redacted]

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

PROTOCOL SYNOPSIS

Study Number and Title: Study 0164: A 3-Year Multi-Center, Long-Term Safety (LTS) Study to Evaluate the Safety and Tolerability of TD−1473 in Subjects with Ulcerative Colitis

Study Short Title: TD-1473 LTS UC Study

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

Background and Rationale

[redacted]

PROTOCOL SYNOPSIS (CONTINUED)

[redacted]

Objectives:

The primary objective of the study is as follows:

- To assess the safety and tolerability of TD-1473 administered up to 3 years in subjects with moderate to severe UC after participation in the Protocol 0157 Maintenance Study.

The additional objectives of the study are as follows:

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

Study Design: This is a multi-center, long-term safety study to evaluate the safety and tolerability of TD-1473 at doses up to 200 mg for up to 156 weeks (3 years) in subjects with moderate to severe UC exiting the preceding Maintenance Study. Subjects who:

a) demonstrate persistent loss of response (no improvement for approximately 6 to 8 weeks after meeting loss of response criteria despite more time on study drug and potentially concurrent rescue medication) OR

b) have repeated (two) Clinical Flares during the Maintenance Study after loss of response OR

c) complete the Maintenance Study

PROTOCOL SYNOPSIS (CONTINUED)

Treatment assignments upon entry to the LTS Study 0164 are dependent on both the subject's clinical status (remission or not) upon entry into LTS from Maintenance and prior dose assignment in Maintenance (Refer to Table 2).

Subjects will undergo clinic study visits initially at week 4, week 12 and thereafter, at a minimum of every 12 weeks for safety and laboratory evaluation. [redacted]

Four weeks following the last dose of study drug, subjects will return for an End of Study (EOS) visit to assess safety, laboratory evaluation and symptoms as described in the Schedule of Study Procedures.

Duration of Study Participation: Individual subject participation may be a maximum of 156 weeks (3 years) of treatment and 4 weeks of follow-up for a total of 160 weeks on study.

Total number of Subjects: up to 500 subjects

Study Population:

Subjects with moderate to severe UC, meeting all inclusion and none of the exclusion criteria.

Inclusion Criteria:

To be eligible for the study, subjects are required to enter the LTS Study within 14 days of exiting the Maintenance Study of Protocol 0157 and must meet all the following criteria:

1. One of the following:
   a. Those who demonstrated persistent (as confirmed by endoscopy) loss of response (no improvement approximately 6 to 8 weeks after meeting loss of response criteria)
   OR
   b. Two Clinical Flares after an episode of loss of response (as confirmed by endoscopy) during the Maintenance Study.
   OR
   c. Those who have completed the Maintenance Study (even if the subject declined endoscopy during a clinical flare assessment during the Maintenance Study of Protocol 0157) and have a confirmed clinical remission status (in remission or not in remission) with available results
2. During the study and for 7 days after receiving the last dose of the study drug, females of childbearing potential or men capable of fathering children must agree to use highly effective birth control measures (failure rate <1% when used consistently and correctly) or agree to abstain from sexual intercourse. Females of childbearing potential must test negative for pregnancy at Day 1 (Refer to Section 4.3).
3. All male subjects must agree to refrain from semen donation during the study and for 7 days after the last dose of study drug.

PROTOCOL SYNOPSIS (CONTINUED)

4. Must be able and willing to adhere to the study visit schedule and comply with other study requirements.

Exclusion Criteria:

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

Gastrointestinal:

1. Has current symptoms or signs suggestive of fulminant colitis, toxic megacolon, intestinal perforation
2. Has a high risk of requiring surgery for UC during the study
3. Has been diagnosed during Protocol 0157 with Crohn's disease, microscopic colitis, ischemic colitis, radiation colitis, diverticular disease associated with colitis, indeterminate colitis, or the subject has a current or past diagnosis of a fistula or abdominal abscess
4. Has dysplasia that was not completely resected or high-grade dysplasia detected during Protocol 0157; however, subjects with adenomas with low grade dysplasia that have been completely resected are eligible

Concomitant or previous medications /treatments:

5. Taking any medications/treatments listed in Appendix 4 currently or previously during Protocol 0157 Maintenance.

Coexisting medical conditions or past medical history:

6. Deemed by the investigator to be inappropriate for this study; or has any condition which would confound or interfere with the evaluation of the safety or tolerability of the study drug [e.g., developed unstable or uncontrolled and clinically significant allergic (except for untreated, asymptomatic, seasonal allergies), hematological, endocrine/metabolic, coagulation, immunologic, pulmonary, cardiovascular, hepatic (except hepatic steatohepatitis), GI (except UC), genitourinary, psychiatric, oncologic thrombotic (e.g., deep vein thrombosis or pulmonary embolism), or neurological disease or other medical disorder before, during, or after Protocol 0157]; or is unable or unwilling to comply with the study protocol.
7. Has developed hypersensitivity to excipients or contents of the study drug
8. Participating in or interested in participating in another investigational study (except Protocol 0157)
9. Has clinically significant abnormalities in the results of laboratory evaluations at the most recent laboratory evaluation prior to LTS Day 1 visit as determined by the investigator, including:
   - AST, ALT, or alkaline phosphatase ≥ 2x the upper limit of normal (ULN)
   - Total bilirubin > 2x ULN (unless diagnosis of Gilbert's syndrome)

PROTOCOL SYNOPSIS (CONTINUED)

- Creatinine clearance as calculated by the Cockcroft-Gault formula < 30 mL/min (Appendix 2)
- 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

10. Subject has had a live viral vaccine (e.g., MMR, varicella zoster, herpes zoster, oral polio virus, FluMist®, attenuated typhoid fever vaccine, attenuated rotavirus vaccine, yellow fever vaccine, or any investigational live vaccine) within 4 weeks prior to Day 1 and/or is unwilling or unable to avoid live viral vaccines during the Study and for 8 weeks following the last dose of study drug. 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.
11. Are pregnant, lactating, breastfeeding or planning to become pregnant during the Study or within 7 days after the last dose of Study Drug
12. Within 4 weeks of Day 1, has [1] confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (coronavirus disease 2019 [COVID-19]) (test positive), OR [2] suspected SARS-CoV-2 infection (clinical features without documented test results) unless has a negative test for SARS-CoV-2 two weeks after resolution of symptoms and remains asymptomatic until Day 1, OR [3] close contact with a person with known or suspected SARS-CoV-2 infection unless has a negative test for SARS-CoV-2 two weeks after contact and remains asymptomatic until Day 1.

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

TD-1473 20 mg, 80 mg or 200 mg: given orally, once daily for up to 156 weeks (3 years) in the morning.

Study Evaluations

Safety Assessments:

Subject safety will be assessed throughout the study using standard measures, including vital signs, ECG, blood and urine safety laboratory tests, physical examinations, concomitant medication usage, and adverse event (AE) monitoring with emphasis on adverse events of special interest, such as suspected or confirmed intestinal perforation, complicated herpes zoster, malignancies, serious infection (e.g., that requires hospitalization or intravenous antibiotics), opportunistic infection, thromboembolic disease (e.g., deep vein thrombosis, pulmonary embolism), cardiovascular events or clinical laboratory abnormalities of concern.

PROTOCOL SYNOPSIS (CONTINUED)

[redacted]

Statistical Methods

Sample Size:

The sample size will depend on the number of subjects who are eligible and elect to enter from the Maintenance Study of Protocol 0157. It is anticipated that approximately 500 subjects will receive TD-1473 for up to 156 weeks (3 years).

Study Endpoints:

The primary study endpoint is:

- Incidence and severity of treatment-emergent adverse events, changes in laboratory safety tests, ECGs, and vital sign measurements.

Additional endpoints are:

[redacted]

PROTOCOL SYNOPSIS (CONTINUED)

[redacted]

Analysis: Safety data will be listed by subject and summarized using frequency of events or descriptive statistics, as appropriate.

Listings and descriptive summaries will be provided for demographics (age, sex, ethnicity, and race) and baseline characteristics (e.g., weight, BMI), adverse events, laboratory tests including vital signs, and ECG data. Concomitant medications will be listed and summarized.

[redacted]

Analysis Sets:

The Safety analysis set, comprising all subjects receiving at least one LTS dose of TD-1473, will be the analysis set for all summaries except some enrollment summaries.

Table 1: Schedule of Study Procedures

Study Procedures			WEEK VISITS +/- 5 Days								
	Day 1	Year 1	W4	W12		W24	W36	W48	W52	Early Study Drug Discontinuation[j] + 5 days from last dose	EOS 4 Weeks Post Last Dose[j] – 3 to + 5 days
		Year 2			W60	W72	W84	W96	W104		
		Year 3			W108	W120	W132	W144	W156		
Informed Consent	X										
Review Inclusion/Exclusion Criteria	X										
Physician Global Assessment (PGA)	X		X	X	X	X	X	X	X	X	X
Pregnancy Test (females of child-bearing potential)	X		X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]
FSH	X[a]										
[redacted]	[redacted]			[redacted]		[redacted]		[redacted]		[redacted]	[redacted]
In Clinic Dosing - Study Drug Dosing	X[k]										
Vital Signs (Temp, HR, BP, Respirations)	X[l]		X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X	X
Safety Laboratory (Chemistry, Hematology)	X[a, m]		X	X	X	X	X	X		X	X
Physical Exam	X[a]		X	X	X	X	X	X	X	X	X
Smoking Status	X[a]								X		X
Weight	X[a]								X		
Medical History / Demographics	X[a, b]										
Concomitant Medication /Adverse Event Review	X		X	X	X	X	X	X	X	X	X
Overnight Fasting Lipid Panel			X	X	X	X	X	X		X	X
[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]									[redacted]		
[redacted]									[redacted]		
12-Lead Electrocardiogram (ECG)	X[a]			X				X	X		
Study Drug Dispensing	X		X	X	X	X	X	X	X[g]		
Study Drug Accountability			X	X	X	X	X	X	X	X	
Subject eDiary Daily Compliance Review			X[h]	X[h]							
Subject Symptom Recall and Compliance Review					X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	
Dispense Subject eDiary	X[h]										
Return of Subject eDiary				X[h]							

Non-Site Study Procedures (Calculations for Programming/Statisticians and applicable suppliers)														
[redacted]														
[redacted]														

a. Subject will be enrolled into the Protocol 0164 (LTS) and undergo treatment-assignment on Day 1 after subject has signed informed consent and is confirmed to be eligible for the study. **Note**: the first visit of Protocol 0164 (LTS) is Day 1 and will include Study Drug intake. Subjects exiting Protocol 0157 who have already taken Study drug from Protocol 0157 will need to return to the Clinic on another day prior to consenting to LTS in order to ensure that they are able to take LTS Day 1 Study Drug in clinic. Subjects **should not** receive Protocol 0157 Study Drug AND Protocol 0164 (LTS) Study Drug on the same day. Day 1 of Protocol 0164 (LTS) should be within 14 days of subject exiting the Maintenance Study. If any listed study procedure has been completed in the last 14 days in the Protocol 0157 prior to Day 1, it does not need be repeated during Protocol 0164 (LTS) Day 1.

b. Medical history information, AE's and partial Demographic data will be collected from the Protocol 0157 database, if applicable. Additional demographic data may be required to be entered into the Protocol 0164 (LTS) database.

[redacted]

[redacted]

e. Urine b-hCG testing will be done before every visit for women of childbearing potential to confirm absence of pregnancy before dispensation of study drug. If the urine b-hCG test is positive, a serum b-hCG test must be performed.

[redacted]

g. Study drug will be dispensed for subjects to administer daily at home **with the exception** of Week 156 which is the last treatment visit.

h. Subjects will continue to complete the electronic diary **on a daily basis for the initial 12 weeks** of the LTS. Subjects will be instructed on daily diary completion, including symptom monitoring (rectal bleeding and stool frequency) as well as study drug dosing details from Day 1 through to Week 12. Subjects will be counseled on missed diary entries and missed study drug doses. Subjects will return the electronic diaries at Week 12.

i. After Week 12 subjects will be contacted approximately 10 days ±2 days preceding each clinic visit to be reminded that they will be asked to recall their symptoms (rectal bleeding, bowel movements and study drug dosing) for the 7 days prior to clinic visit.

j. Early Discontinuation is for subjects who prematurely discontinue the study drug. This visit will be conducted within 5 days after the last dose of study drug. Subjects will also return for the EOS visit for collection of safety data and assessment of disease activity.

k. Subjects **should not** receive Protocol 0157 Study Drug AND Protocol 0164 Study Drug on the same day.

l. Obtain blood pressure and heart rate anytime pre-dose at all visits.

m. If safety laboratory testing is required at Day 1, results from Safety Laboratory Test from Day 1 are not required to be received before enrolling the Subject into Protocol 0164 and dispensing Study Drug.

n. Required for any female that may have become or is suspected to be postmenopausal since enrolment in Protocol 0157

Note: See Appendix 7 for general guidance on study conduct during the coronavirus disease 2019 (COVID19) pandemic. Variations from planned assessments will still constitute protocol deviations.

[redacted]

TABLE OF CONTENTS

[redacted]

LIST OF TABLES

LIST OF ABBREVIATIONS

Abbreviation	Description
AE	adverse event
ALT	alanine aminotransferase
[redacted]	[redacted]
AST	aspartate aminotransferase
BCRP	breast cancer resistance protein
BMI	body mass index
BP	blood pressure
CFA	Clinical Flare Assessment
CFR	(United States) Code of Federal Regulations
CRF	case report form
[redacted]	[redacted]
CYP	cytochrome P450
DNA	deoxyribonucleic acid
ECG	electrocardiogram
EDC	electronic data capture
EOS	End-of-Study
[redacted]	[redacted]
FDA	(United States) Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
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
[redacted]	[redacted]
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

Abbreviation	Description
IRB	Institutional Review Board
IUD	intrauterine device
JAK	Janus kinase
LTS	Long Term Safety Study
MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities (MedDRA®)
NK	natural killer
OTC	Over-the-Counter
PI	principal investigator
P-gp	p-glycoprotein
PK	pharmacokinetic(s)
[redacted]	[redacted]
PPI	proton pump inhibitor
PT	Preferred Term
QD	Once daily
QTc	corrected QT interval
QTcF	Fridericia-corrected QT interval
REB	Research Ethics Board
RTSM	randomization and trial supply management
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SAS	SAS® software for statistical analysis
SD	Standard Deviation
SOC	System Organ Class
SOP	standard operating procedure
STAT	signal transducer and activator of transcription
TEAE	Treatment-Emergent Adverse Event
TB	Tuberculosis
TBPH	Theravance Biopharma
[redacted]	[redacted]
TNF	tumor necrosis factor
UC	ulcerative colitis
USP	United States Pharmacopeia
WOCBP	Women of Childbearing Potential
[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

1. INTRODUCTION

1.1. Background and Rationale

[redacted]

profile. TD-1473 was generally well-tolerated at all doses. Rates of clinical response were [redacted]

1.2. Nonclinical Profile

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

1.3. Pharmacology

[redacted]

1.3.1. Toxicology

[redacted]

[redacted]

1.3.2. Pharmacokinetics

[redacted]

[redacted]

1.4. Clinical Experience

[redacted]

[redacted]

1.5. Risks and Benefits

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

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

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

The potential risks described in this section will be carefully assessed during the Study. Assessments include scheduled physical exams, and frequent monitoring of complete blood cell counts with differential, kidney and liver function, creatinine phosphokinase, and fasting cholesterol panel.

The clinical and laboratory observations planned for this clinical trial are sufficient to monitor for the key observations noted in the nonclinical evaluation of TD-1473 at doses relevant to this study, as well as many of the effects noted with use of tofacitinib.

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

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

2. OBJECTIVES

This is a multi-center, long-term safety study to evaluate the safety and tolerability of TD-1473 at doses up to 200 mg for up to 156 weeks (3 years) in subjects with moderate to severe UC entering from the Phase 3 Maintenance Study.

The primary objective of the study is as follows:

- To assess the safety and tolerability of TD-1473 administered up to 3 years in subjects with moderate to severe UC after participation in the Maintenance Study of Protocol 0157.

The additional objectives of the study are as follows:

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

3. STUDY DESIGN

3.1. Overview

This LTS Study 0164 is designed to evaluate the safety of long-term TD-1473 treatment in subjects with moderate to severe UC rolling over from Protocol 0157.

Subjects eligible for the study are those who are rolling over from Protocol 0157 Maintenance Study who meet all inclusion and no exclusion criteria, including having achieved clinical response during an Induction Study and during the Maintenance Study who:

a) demonstrate persistent [redacted] loss of response (no improvement for approximately 6 to 8 weeks after meeting loss of response criteria despite more time on study drug and potentially concurrent rescue medication
OR

b) have (two) Clinical Flares after an episode [redacted] of loss of response during the Maintenance Study
OR

c) complete the Maintenance Study and confirmation of clinical remission status results are available [redacted]

Refer to Protocol 0157 with regards to for additional information related to the Study design. Subjects are required to enter the LTS Study within 14 days of exiting the Maintenance Study of Protocol 0157.

3.2. Rationale for Study Design

[redacted]

3.3. Selection of Dose Ranges and Duration of Treatment

[redacted]

[redacted]

Study Endpoints:

The primary study endpoint is:

- Incidence and severity of treatment-emergent adverse events, changes in laboratory safety tests, ECGs, and vital sign measurements.

Additional endpoints are:

- [redacted]
- [redacted]

[redacted]

3.3.1. Safety Endpoints

Incidence and severity of treatment-emergent adverse events (defined in Section 7]); changes in laboratory safety test results, ECG intervals and abnormalities, and vital sign measurements.

3.3.2. Minimization of Bias

Bias in safety evaluation will be minimized through partial dose-blinding. In the case of subjects completing the Maintenance Study, the investigator will have firsthand observation of remission status but initially remain blinded to the precedent dose assignment in Maintenance. Thus, the specific dose assignment in LTS for Maintenance completers in remission will not be known to investigator, Sponsor, or subject. The dose assignment in LTS for subjects who enter without completing the Maintenance Study or who complete the Maintenance Study but are not in remission is also partially dose-blinded, as the consent form will include the treatment assignment scheme and all subjects will be assigned to an escalated dose from their preceding Maintenance TD-1473 dose. Once the database lock and unblinding have occurred in the precedent Maintenance Study Protocol 0157, the prior dose assignment may be disclosed.

3.3.3. Blinding

All TD-1473 tablets will be of the same shape, size, and color to ensure that the partial dose blind is maintained. All subjects will take two tablets per day.

Sponsor personnel involved in the conduct of the study will remain partially dose blinded (The dose will be blinded however it will be known to all parties that all subjects are on TD-1473) as described above until the database has been locked for final analysis.

A subject's treatment assignment will be unblinded only when knowledge of the treatment is essential for the further clinical management of the subject on this study or may potentially impact the safety of subjects currently enrolled or subjects in subsequent enrollment.

Unblinding at the study site for any other reason will be considered a protocol deviation. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a subject's treatment assignment is warranted and unblinding can be done through the RTSM system. Subject safety must always be the first consideration in making such a determination. Any investigator unblinding will be documented within the appropriate CRF and will be captured in the RTSM system.

Sponsor Drug Safety personnel may independently unblind cases for expedited reporting of suspected unexpected serious adverse reactions (SUSARs).

3.3.4. 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 determine the subject's treatment assignment and dispense Study drug.

Subject IDs will be carried over from the Protocol 0157 Induction/Maintenance Studies. Subject ID will be of format "164 - Site Number - Subject Number. The Site number and subject number will remain the same as Protocol 0157 Induction/ Maintenance Studies but Subject ID encompasses all these 3 elements.

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

3.3.5. End of Trial Definition

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

4. STUDY POPULATION

4.1. Inclusion Criteria

To be eligible for the study, subjects are required to enter the LTS Study within 14 days of exiting the Maintenance Study of Protocol 0157 and must meet all the following criteria:

Capable of providing informed consent, which must be obtained prior to any study-related procedures.

1. One of the following:
   a. Those who demonstrated persistent [redacted] loss of response (no improvement approximately 6 to 8 weeks after meeting loss of response criteria)
   OR
   b. Two Clinical Flares after an episode [redacted] of loss of response during the Maintenance Study.
   OR
   c. Those who have completed the Maintenance Study [redacted] and have a confirmed clinical remission status (in remission or not in remission) with available results.
2. During the study and for 7 days after receiving the last dose of the study drug, females of childbearing potential or men capable of fathering children must agree to use highly effective birth control measures (failure rate <1% when used consistently and correctly) or agree to abstain from sexual intercourse. Females of childbearing potential must test negative for pregnancy at Day 1. (Refer to Section 4.3).
3. All male subjects must agree to refrain from semen donation during the study and for 7 days after the last dose of study drug.
4. Must be able and willing to adhere to the study visit schedule and comply with other study requirements.

4.2. Exclusion Criteria

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

Gastrointestinal:

1. Has current symptoms or signs suggestive of fulminant colitis, toxic megacolon, intestinal perforation
2. Has a high risk of requiring surgery for UC during the study
3. Has been diagnosed during Protocol 0157 with Crohn's disease, microscopic colitis, ischemic colitis, radiation colitis, diverticular disease associated with colitis, indeterminate colitis, or the subject has a current or past diagnosis of a fistula or abdominal abscess

4. Has dysplasia that was not completely resected or high-grade dysplasia detected during Protocol 0157; however, subjects with adenomas with low grade dysplasia that have been completely resected are eligible

Concomitant or previous medications / treatments:

5. Taking any medications / treatments listed in Appendix 4 currently or previously during Protocol 0157 Maintenance

Coexisting medical conditions or past medical history:

6. Deemed by the investigator to be inappropriate for this study; or has any condition which would confound or interfere with the evaluation of the safety or tolerability of the study drug [e.g., developed unstable or uncontrolled and clinically significant allergic (except for untreated, asymptomatic, seasonal allergies), hematological, endocrine/metabolic, coagulation, immunologic, pulmonary, cardiovascular, hepatic (except hepatic steatohepatitis), GI (except UC), genitourinary, psychiatric, oncologic thrombotic (e.g., deep vein thromboses (DVT) or pulmonary embolism or neurological disease or other medical disorder before during or after Protocol 0157]; or is unable or unwilling to comply with the study protocol.
7. Develops hypersensitivity to excipients or contents of the study drug as noted in Protocol 0157.
8. Participating in or interested in participating in another investigational study (exception Protocol 0157)
9. Has clinically significant abnormalities in the results of laboratory evaluations at the most recent laboratory evaluation prior to LTS Day 1 visit as determined by the investigator, including:
    - AST, ALT, or alkaline phosphatase ≥ 2x the upper limit of normal (ULN)
    - Total bilirubin > 2x ULN (unless diagnosis of Gilbert's syndrome)
    - Creatinine clearance as calculated by the Cockcroft-Gault formula < 30 mL/min (Refer to Appendix 2)
    - 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
    - Platelet count < 100 x 10^9/L.
10. Subject has had a live viral vaccine (e.g., MMR, varicella zoster, herpes zoster, oral polio virus, FluMist®, attenuated typhoid fever vaccine, attenuated rotavirus vaccine, yellow fever vaccine, or any investigational live vaccine) within 4 weeks prior to Day 1 and/or is unwilling or unable to avoid live viral vaccines during the Study and for 8 weeks following the last dose of study drug. 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.

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

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

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

Women of childbearing potential must have documentation of a negative pregnancy test at Day 1 and prior to dosing. All female subjects of childbearing potential must agree to abstain from sexual intercourse or to use a highly effective method of birth control during the study and for at least 7 days after completion of Study drug dosing.

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

Follicle-stimulating hormone (FSH) will be tested at Day 1 in post-menopausal females only to confirm post-menopausal state.

Highly effective birth control methods are defined as methods that can achieve a failure rate of less than 1% per year when used consistently and correctly. Such methods include: combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral/intravaginal/transdermal); progestogen-only hormonal contraception associated with inhibition of ovulation (oral/injectable/implantable); intrauterine device; intrauterine hormone-releasing system (IUS); bilateral tubal occlusion; vasectomised partner; sexual abstinence (if this is in line with the preferred and usual lifestyle). Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success. Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. More restrictive methods of birth control may be required as per local country requirements, and this will be defined in the IRB/IEC approved subject informed consent form.

5. STUDY DRUGS

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

5.1. Description of Study Drug

5.1.1. TD-1473

[redacted]

5.2. Dosage and Administration

Subjects will take TD-1473 tablets once daily for up to 156 weeks. Study drug will be self-administered orally. With the exception of the Day 1 visit, Subjects will be instructed to take two tablets once daily at approximately the same time each morning. Subjects will be required to take their first dose in clinic on Day 1. Study drug dispensation will occur at Scheduled Visits as per the Schedule of Study Procedures. Subjects will self-administer their Study drug at home. Subjects will initially utilize the electronic diary to enter Study drug compliance information daily for the first 12 weeks of the LTS Study; subsequently they shall be queried at scheduled visits to recall their UC symptoms and Study drug compliance.

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

5.3. Treatment Compliance

Compliance for the initial 12 weeks will be assessed by subject diary entry. Compliance will also be assessed in subjects when accountability is performed at visits where Study drug is dispensed to or returned by subjects. Treatment compliance will be assessed by reconciliation of used and unused tablets.

Subjects with poor dosing compliance (i.e., < 80% or > 120%), as assessed by tablet counts and/or missing entries on the Study drug administration diary (initial 12 weeks), should receive counseling or assistance, and re-training as appropriate.

5.4. Missed Dose(s)

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. If the subject does not take the Study drug within 12 hours after the usual time each day, the dose of Study drug should be skipped for that day and the subject should be instructed to take the Study drug on the following day..

5.5. Drug Accountability and Reconciliation

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

Subjects will be instructed to return all used and unused Study drug at each study visit.

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

6. STUDY PROCEDURES

6.1. Schedule of Study Procedures

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

The Schedule of Study Procedures is summarized in Table 1.

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

6.2. Total Blood Volume

The total estimated volume of blood to be drawn from each subject for safety laboratory assessments, lipid panel, FSH (If applicable) and [redacted] is approximately [redacted] Additional samples may be drawn for safety laboratory testing as considered necessary by the investigator.

6.3. Procedures by Visit

Refer to Section 6.4 for detailed description of each of the study assessments.

6.3.1. Day 1

Subjects meeting all eligibility criteria following exiting the preceding Protocol 0157 Maintenance Study will return to the clinic for enrollment assessments on Day 1.

The Schedule of Study Procedures is summarized in Table 1.

6.3.2. Week 4 and Week 12

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

The Schedule of Study Procedures is summarized in Table 1.

6.3.3. Weeks 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144

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

The Schedule of Study Procedures is summarized in Table 1.

6.3.4. Weeks 52, 104, and 156 (1 year, 2 year and 3 year)

The Schedule of Study Procedures is summarized in Table 1.

6.3.5. Early Study Drug Discontinuation

Subjects who prematurely discontinue the Study drug prior to 3 years completion due to AEs, loss of response, lack of efficacy or any other reason besides withdrawal of consent during the LTS Study will be asked to return for an Early Study Drug Discontinuation visit. This visit will be conducted within 5 days after the last dose of Study drug.

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

Subjects will also return for the End of Study visit for collection of safety data and assessment of disease activity.

The Schedule of Study Procedures is summarized in Table 1.

6.3.6. End of Study (EOS)

An EOS visit will be required for all subjects 4 weeks following their last dose of Study drug. Subjects should be instructed to fast from food and non-clear fluids on the evening prior to the EOS visit to ensure a minimum 8-hour fast prior to the fasted blood sample collection.

The Schedule of Study Procedures is summarized in Table 1.

6.4. Description of Study Assessments

6.4.1. Demographic and Baseline Assessments

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

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

Demographic data may be collected from the Protocol 0157, if applicable.

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

6.4.1.2. Medication History

On Day 1 of the LTS Study, all concomitant medications will be reviewed with the subject, if applicable. Protocol 0157 medications ongoing at the time of Day 1 of the Protocol 0164 LTS Study may be collected from the Protocol 0157, if applicable.

Please refer to Inclusion/ Exclusion Criteria and Appendix 4 for Prohibited Medications.

6.4.1.3. Medical History

Medical history and adverse events may be collected from the Protocol 0157, if applicable.

6.4.1.4. Body Weight

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

6.4.1.5. Smoking Status

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

6.4.1.6. 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 manual or automatic blood pressure device. Heart rate will be recorded by palpation of the radial pulse over at least a 30-second period or by the automated blood pressure device.

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

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

6.4.1.7. 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.

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

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

If at a particular post dose time point, the QTcF is > 500 msec and/or 60 msec longer than the value at Day 1 or the mean QRS interval is > 130 msec, a decision on Study drug discontinuation should be made by the investigator with input from the Study Medical Monitor, if feasible. The investigator should also consider evaluating the subject for potential concurrent risk factors (e.g., electrolyte abnormalities, concomitant medications known to prolong the QT interval, severe bradycardia).

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

6.4.1.8. Physical Examination

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

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

6.4.1.9. Concomitant Medications / Treatments

All concomitant medications (i.e., prescription and over-the-counter medications, herbals, vitamins, and supplements) will be reviewed throughout the Study as described in the Schedule of Study Procedures (Table 1). Details such as name of medication, date started and stopped, route of administration, indication, and dose will be recorded. Medical therapy may be altered during the study however administration of a prohibited medication/ treatments listed in Appendix 4 should result in the subject being discontinued from the Study.

Refer to Section 6.5 for further details.

6.4.1.10. Adverse Events (AEs)

Adverse events, including serious adverse events (SAEs) and adverse events of special interest (AESI) will be reviewed and recorded following the time the subject signed the Informed Consent Form through the follow-up visit. AEs may be observed by the site Study personnel or spontaneously reported by the subject or reported in response to standard questions from site Study personnel. Subjects will be reminded to call the site to report AEs that occur between visits. Refer to Section 6 for definition, assessment, and reporting of AEs.

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

Urine b-hCG testing will be performed during specified visits, as listed in the Schedule of Study Procedures (Table 1), 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.

6.4.1.12. Follicle-Stimulating Hormone (FSH)

Follicle-stimulating hormone (FSH) will be tested at Day 1 in any female that may have become or is suspected to be post-menopausal since enrolment in Protocol 0157. The FSH test is to confirm post-menopausal state. FSH will be performed as specified in Schedule of Study Procedures in Table 1.

6.4.1.13. Chemistry and Hematology

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

From Day 1 onwards, 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.

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.

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

6.4.1.14. 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.

[redacted]

[redacted]

[redacted]

[redacted]

6.4.3. Safety Assessments

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

6.4.3.1. Adverse Events

Refer to Section 6.4.1.10

6.4.3.2. Medical History

Refer to Section 6.4.1.3

6.4.3.3. 12-Lead Electrocardiograms

Refer to Section 6.4.1.8

6.4.3.4. Physical Examination

Refer to Section 6.4.1.8

6.4.3.5. Vital Signs

Refer to Section 6.4.1.6

6.4.3.6. Laboratory Tests

Refer to Section 6.4.1.13 – Section 6.4.1.15

6.5. Concomitant Medications

Refer to Section 6.4.1.9.

6.5.1. Prohibited Medications / Treatments

The use of the following are restricted during Study participation as specified:

[redacted]

6.5.2. Permitted Medications

Subjects entering the LTS due to loss of response would have been eligible for treatment with permitted rescue medications in the Maintenance Study. It is advisable for these doses to be tapered or adjusted according to the clinical judgment of the Principal Investigator. Rescue medications should not be withheld if, in the opinion of the investigator, failure to prescribe them would compromise subject safety. A subject's medical therapy can be adjusted as deemed appropriate by the investigator except for prohibited medications; prohibited medication use must be followed per Appendix 4.

6.5.3. Restrictions on Alcohol Consumption and Illicit Drug Use

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

6.6. Discontinuation

6.6.1. Subject Discontinuation

Any subject may withdraw his/her consent to participate in the Study at any time without prejudice. The investigator must withdraw from the study any subject who requests to be withdrawn. A subject's participation in the study may be discontinued at any time at the discretion of the investigator and in accordance with his or her clinical judgment. Subjects must also be discontinued on study drug for any AESI (except non-melanoma skin cancer, mono-dermatomal herpes zoster, and certain laboratory abnormalities that are deemed by the investigator to not place subjects at immediate safety risk) or if the subject becomes pregnant. When possible, the tests and evaluations listed for the Early Study Drug Discontinuation visit should be carried out. If a subject withdraws before completing the Study, the reason for withdrawal is to be documented on the CRF.

The Sponsor will be notified of all subject withdrawals.

Reasons for which the investigator or the Sponsor may withdraw a subject or a subject may choose to terminate participation before completion include, but are not limited to, the following:

- Adverse event
- Subject choice/Withdrawal of consent
- Major violation of the protocol
- Termination of the Study by the Sponsor
- Initiation of medication / treatments that are prohibited as listed in Appendix 4
- Investigator's assessment of lack of clinical benefit
- Pregnancy
- Colectomy
- Lost-to follow-up

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.

Subjects with laboratory abnormalities as outlined in Section 7.2 (i.e., two sequential occurrences of renal, leukocyte, leukocyte subset, or hepatic panel abnormalities or hepatic panel abnormalities with clinical sign or symptom of acute liver failure) should discontinue the study drug. Any non-laboratory-related AE considered an AESI defined in Section 7.1.4, except for non-melanoma skin cancer and mono-dermatomal herpes zoster, should also lead to study drug discontinuation.

Four weeks following the last dose of study drug, subjects will return for an End of Study (EOS) visit to assess safety, laboratory evaluation and symptoms as described in the Schedule of Study Procedures.

6.6.2. Subject Replacement

There will be no subject replacement in the LTS Study.

6.6.3. Study Discontinuation

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

Periodic reviews of accumulating data by the IDMC may lead to the committee's recommendation of pausing dosing or terminating the 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 IRB/IEC/REBs and the Regulatory Authorities will be informed.

6.7. Pregnancy

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

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

7. ADVERSE EVENTS

7.1. Definitions

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

7.1.1. Adverse Events (AE)

An AE on Protocol 0164 (LTS) is any AE that occurs after the first dose of study drug. An AE prior to the first dose of study drug on Protocol 0164 (LTS) will be documented in the 0157 Study and if continuing at the time of consent to Protocol 0164 (LTS), the AE will be documented in the Protocol 0164 (LTS) database as an ongoing event.

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 [redacted]
- 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 drug.

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

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

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

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

- Death
- Life-threatening situation. "Life-threatening" refers to a situation in which the patient was at risk of death at the time of the event; it does not refer to an event which might have caused death if it were more severe.
- Inpatient hospitalization or prolongation of existing hospitalization

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

7.1.3. Additional Considerations for Serious Adverse Events

- Death is an outcome of an adverse event and not an adverse event in itself. Deaths of unknown cause for which the investigator cannot identify a cause of death will be captured as death of unknown cause or death not otherwise specified.

- All deaths, regardless of cause, must be reported for subjects if the death occurs while the subject is participating in the Study.
- "Occurring at any dose" does not imply that the subject is receiving Study drug at the time of the event; dosing may have been given as treatment cycles or interrupted temporarily before the onset of the SAE, but may have contributed to the event.

7.1.4. Adverse Events of Special Interest (AESI)

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

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

All AESIs, except for non-melanoma skin cancers and mono-dermatomal herpes zoster, must be reported to TBPH Clinical Safety and Pharmacovigilance within 24 hours of the time the Investigator or his/her designee becomes aware of an AESI (Refer to Section 7.1.4). 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 AESI, an additional targeted questionnaire needs to be completed to assess for risk factors. For thromboembolic events in particular, the subject should undergo evaluation for hypercoagulable state (e.g., with clinically relevant investigations, such as referral to a specialist and/or blood testing for a predisposition to a hypercoagulable state) and repeat imaging to assess resolution of the finding.

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

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

Abnormal laboratory findings (such as clinical chemistry, hematology, or urinalysis) or other abnormal assessments (such as electrocardiograms [ECGs], X-rays, or vital signs) that are associated with signs and/or symptoms or are considered clinically significant in the judgment of the investigator must be recorded as AEs or SAEs if they meet the definition of an adverse event (or serious adverse event), as described in Section 7.1.1 (Adverse Event) and Section 7.1.2 (Serious Adverse Event).

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

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

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

- moderate or severe neutropenia (e.g., absolute neutrophil count of $< 1.0 \times 10^9$/L) on two sequential laboratory reports
- moderate or severe leukopenia (e.g., white blood cell count of $< 2.0 \times 10^9$/L) on two sequential laboratory reports
- moderate or severe lymphocytopenia (e.g., absolute lymphocyte count of $< 0.5 \times 10^9$/L) on two sequential laboratory reports
- a reduction by ≥ 50% from baseline in creatinine clearance on two sequential laboratory reports
- ALT or AST >8x ULN on a single laboratory report. Note: See Appendix 6 for an algorithm of evaluating and managing subjects with ALT or AST > 3x ULN.
- Abnormal AST or ALT > 3x ULN on two sequential laboratory visits with bilirubin > 2x ULN on at least one of the two laboratory reports, or international normalized ratio (INR) > 1.5 on at least one of the two reports (INR will be checked locally)
- AST or ALT > 5x ULN on two sequential laboratory reports, least 2 weeks apart

- AST or ALT > 3x ULN associated with signs or symptoms suggestive of acute liver injury.

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

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.

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 drug.

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 Drug

The Investigator's assessment of causality is based on clinical judgment regarding the reasonable possibility that the Study drug 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 drug.
- Whether the AE resolved or improved with decreasing the dose or stopping the Study drug ("dechallenge") or recurred or worsened upon re-exposure to the Study drug ("rechallenge").

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

7.4. AE Reporting and Recording

7.4.1. AE Reporting

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

7.4.2. AE, SAE and AESI Recording

All AEs, regardless of seriousness, severity, or causal relationship to Study drug, 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 drug 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 drug 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 drug:

The Investigator will make an assessment of the causal relationship of the Study drug to the AE using the guidelines in Section 7.3.2.

Severity:

The severity of the AE will be assessed using the guidelines in Section 7.3.1.

Outcome:

The outcome of AEs will be recorded.

Therapeutic measures:

Measures taken for the treatment or management of the AEs will be recorded.

7.4.3. SAE and AESI Reporting Timeline

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

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

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

Theravance Biopharma Clinical Safety and Pharmacovigilance

[redacted]

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

Sponsor Medical Monitor Contact Information:

[redacted]

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

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

7.5. Adverse Event Follow-up

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

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

8. STATISTICAL CONSIDERATIONS

8.1. General Considerations

All individual data will be listed as measured. All statistical summaries and analyses will be performed using [redacted]

Continuous data will be summarized using an 8-point descriptive summary (*n*, mean, standard deviation, median, interquartile range [25% quartile, 75% quartile]), minimum, and maximum) or a 7-point descriptive summary (*n*, mean, SD, coefficient of variation [CV], median, minimum, and maximum) unless otherwise specified.

Categorical data will be summarized using counts and percentages. Percentages will be shown to 1 decimal place and percentages for zero counts will be omitted.

The Statistical Analysis Plan (SAP) and the table, figure, and listing shells will be finalized prior to database lock. Any changes to protocol-specified analyses will be described in the SAP.

8.2. Sample Size

The sample size will depend on the number of subjects who are eligible and elect to enter from the Maintenance Study of Protocol 0157. It is anticipated that approximately 500 subjects will receive TD-1473 for up to 156 weeks (3 years).

8.3. Analysis Sets

8.3.1. Analysis Sets

The Safety analysis set, comprising all subjects receiving at least one LTS dose of TD-1473, will be the analysis set for all summaries except some enrollment summaries.

8.3.2. Examination of Subgroups

Subgroups to be defined in detail in the SAP for safety analysis purposes will include the following:

- Males, females
- Subgroups defined by age category, e.g., under 40 years of age, 40 to 64, 65 and over
- Subgroups defined by geographic region, e.g., North America, Europe, other
- Subgroups defined by steroid use

Subgroups may also be defined in the SAP for efficacy endpoint summaries.

8.3.3. Major Protocol Analysis Deviations

The following protocol deviations are considered major and as having (unless rare) a substantial effect on the interpretation of efficacy or safety results:

[redacted]

Additional criteria may be specified in the SAP. Listings of all protocol deviations and of major analysis protocol deviations, as defined above and in the SAP, will be provided.

8.4. General Analyses

8.4.1. Demographics and Baseline Characteristics

Demographic and baseline characteristics including age, sex, race, ethnicity, creatinine clearance, weight, body mass index (BMI), UC characteristics, current UC medications by category, and other medical history will be summarized.

8.4.2. Disposition

An enrollment summary will be provided showing the following counts by previous study treatment and clinical status at enrollment:

- Number of subjects eligible to enroll
- Number who elected to enroll
- Number who received at least one LTS dose

Enrollment will also be summarized for subjects in the Safety analysis set by region and country, and by site, ordering sites by descending number of subjects dosed.

For subjects in the Safety analysis set, a disposition summary will present the following counts:

- Number of subjects who completed the Week 4 visit
- Number who completed the Week 12 visit
- Number who completed the Week 52 (1-yr) visit
- Number who completed the Week 104 (2-yr) visit
- Number who completed the Week 156 visit
- Number who discontinued from the study prior to the Week 156 visit, overall and by reason for discontinuation

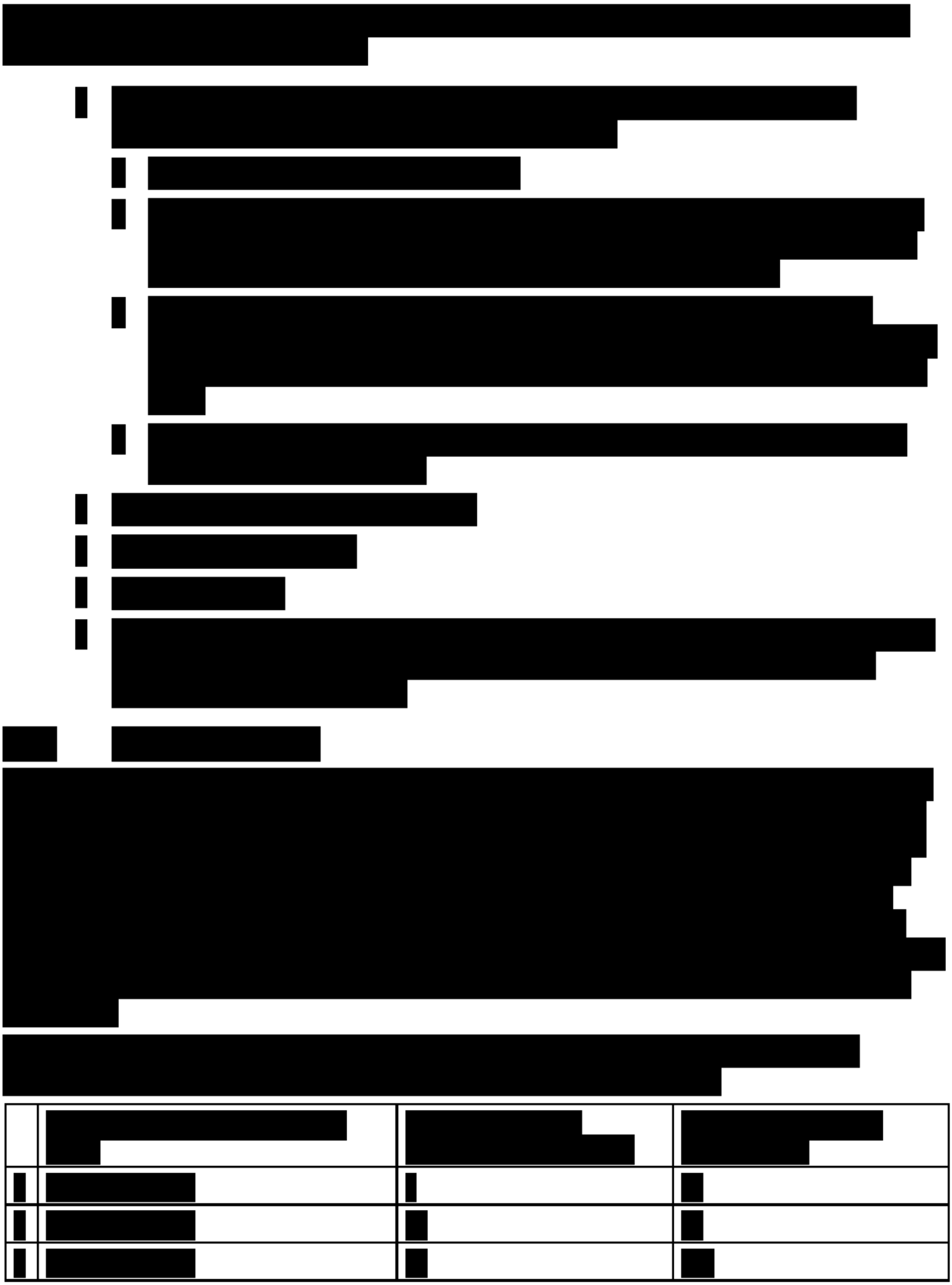
Subjects who discontinue study drug prior to the Week 156 visit will complete an End of Study visit 4 weeks after their last dose of study drug.

8.4.3. Compliance and Exposure

For each interval between visits, the number of tablets dispensed and the number returned will be recorded in the study drug administration and study drug accountability eCRF pages and used to calculate the number of tablets taken. Compliance (%) over the interval from first to last dose and over the interval from first dose to a specified visit will be calculated as $100 \times 0.5 \times$ (number of tablets dispensed - number of tablets returned)/(interval end date - date of first dose + 1). Compliance over each interval will be summarized overall and by dose group both as a continuous variable and using the following disjoint categories: $\geq 120\%$, $\geq 100\%$ to $< 120\%$, $\geq 90\%$ to $< 100\%$, $\geq 80\%$ to $< 90\%$, and $< 80\%$.

[redacted]

[redacted]



[redacted]

	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

8.6. Safety Analyses

Safety variables to be summarized include vital signs, adverse events, clinical laboratory results (hematology, chemistry, overnight fasting lipid panel), and 12-lead ECG intervals, including QT interval corrected for heart rate using Fridericia's formula (QTcF).

8.6.1. Adverse Event Data

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®). Summaries will present by system organ class (SOC), preferred term (PT), and severity, the number and percentage of subjects reporting each observed event.

A treatment-emergent adverse event (TEAE) is defined as any AE with a recorded start date on or after the date of the first dose of LTS study drug up through 4 weeks after the last dose of study drug. Treatment-emergent status of AEs with a partial start date will be determined using available date information. If the available date information is inconclusive or no date information was recorded, the AE will be classified as LTS treatment-emergent.

All TEAEs will be listed by subject, and a separate listing of AEs classified as not LTS treatment-emergent (i.e., ongoing at entry) will be provided. Numbers of subjects who experienced TEAEs will be summarized overall and by arm. TEAEs will also be summarized by relationship to treatment (study drug) and severity, and by duration of exposure categories to be specified in the SAP.

A listing will be provided for all subjects who experience an SAE. Listings will also be provided for subjects who discontinued study treatment because of AEs, subjects who temporarily interrupted study treatment because of AEs, and subjects who experienced AESIs.

8.6.1.1. Adverse Events of Special Interest

A summary will be provided showing, overall and by arm, numbers of subjects who experienced events in each of the following categories:

- 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., deep vein thrombosis, pulmonary embolism)
- Clinical laboratory abnormalities of concern (Refer to Section 7.2)
- Major cardiovascular event (e.g., myocardial infarction or cerebrovascular accident)

For events in each category for which at least one event was reported, a time-to-event plot will be provided. Time 0 will be the time of the first TD-1473 dose, rather than the time of the first LTS TD-1473 dose.

8.6.2. Concomitant Medications

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

- UC medications ongoing at LTS study entry
- Medications with indications other than UC ongoing at LTS study entry
- Medications started or restarted during the LTS study, including those with indication for UC

8.6.3. Laboratory Data

Safety laboratory values and C-reactive protein values, changes from baseline, values relative to normal ranges, and clinical laboratory abnormalities of concern will be summarized by visit, overall and by arm. C-reactive protein, [redacted] total cholesterol, LDL, HDL, and triglycerides levels will be log-transformed for summarization.

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. Clinical laboratory abnormalities of concern will be listed in a separate listing. A listing of pregnancy test results will be provided.

8.6.4. Vital Signs Data

For each scheduled visit, vital signs summaries will include summary statistics for observed values and changes from baseline. Values above or below the following thresholds will be flagged.

Table 3: Vital Signs Thresholds

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

8.6.5. 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 in Table 4.

Table 4: Thresholds for ECG

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	

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

8.7. Missing Data Handling

[redacted]

8.8. Independent Data Monitoring Committee (IDMC)

[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 01572 and, if applicable, a financial disclosure form. For applicable studies, financial disclosure forms must also be completed for all sub-investigators who will be directly involved in the treatment or evaluation of research subjects in this Study. (A sub-investigator is defined in ICH E6 as any individual member of the clinical Study team designated and supervised by the investigator at a Study site to perform critical Study-related procedures and/or to make important Study-related decisions [e.g., associates, residents, research fellows].)

The PI will ensure the following:

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

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

9.2. Institutional Review Board/Independent Ethics Committee

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

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

9.3. Informed Consent

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

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

9.4. Data Recording and Quality Assurance

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

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

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

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

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

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

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

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

9.5. Document Retention

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

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

9.6. Confidentiality

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

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

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

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

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

9.7. Access to Data and Documents

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

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

9.8. Quality Control: Study Monitoring and Auditing

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

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

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

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. Crohn's and Colitis Foundation of America, About the Epidemiology of IBD. http://www.ccfa.org/resources/epidemiology.html, Accessed on 19 October 2015

2. Johnston RD, Logan RF, What is the peak age for onset of IBD? Inflamm Bowel Dis, 2008. 14 Suppl 2: p. S4-5.

3. Ng SC, Shi HY, Hamidi N, Underwood FE, Tang W, Benchimol EI, Panaccione R, Ghosh S, Wu JCY, Chan FKL, Sung JJY, Kaplan GG. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet. 2018 Dec 23;390(10114):2769-2778. doi: 10.1016/S0140-6736(17)32448-0. Epub16 Oct. 2017

4. Dyson JK and Rutter MD, Colorectal cancer in inflammatory bowel disease: what is the real magnitude of the risk? World J Gastroenterol, 2012. 18(29): p. 3839-48.

5. 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.

6. Kappelman MD, 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.

7. Navarro F, SB Hanauer, Treatment of inflammatory bowel disease: safety and tolerability issues. Am J Gastroenterol, 2003. 98(12 Suppl): p. S18-23.

8. Sandborn WJ, et al., Tofacitinib as Induction and Maintenance Therapy for Ulcerative Colitis. N Engl J Med, 2017. 376(18): p. 1723-1736.

9. Banholzer ML, et al., Clinical trial considerations on male contraception and collection of pregnancy information from female partners. J Transl Med, 2012. 10: p. 129.

10. Jairath V, et al., Development of interim patient-reported outcome measures for the assessment of ulcerative colitis disease activity in clinical trials. Aliment Pharmacol Ther, 2015. 42(10): p. 1200-10.

11. Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, Travers S, Rachmilewitz D, Hanauer SB, Lichtenstein GR, de Villiers WJ, Present D, Sands BE, Colombel JF. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2005 Dec 8;353(23):2462-76.

APPENDIX 1. PROTOCOL SIGNATURE FORM

Protocol Signature Form

Protocol #:	0164
Protocol Title:	A 3-Year, Multi-Center, Long-Term Safety (LTS) Study to Evaluate the Safety and Tolerability of TD-1473 in Subjects with Ulcerative Colitis (UC)
Version:	Amendment 2
Version Date:	15 February 2021

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

Investigator's Name (print)

Investigator's Signature Date

APPENDIX 2. COCKCROFT-GAULT CREATININE CLEARANCE CALCULATION

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

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

[redacted]

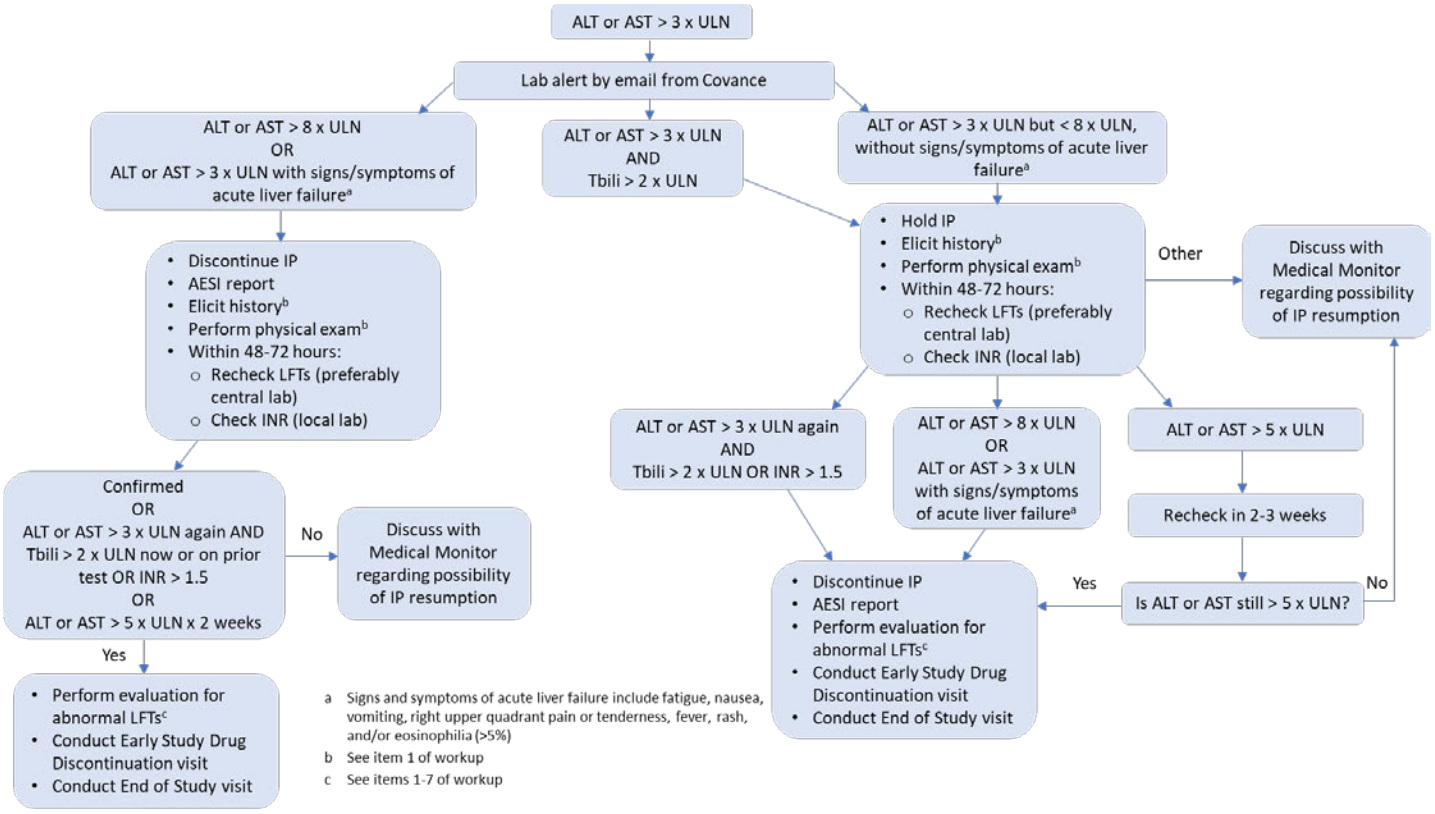
[redacted]

[redacted]

[redacted]

[redacted]

APPENDIX 6. 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 (e.g., computerized tomography [CT], magnetic resonance imaging [MRI], magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), Doppler studies of hepatic vessels, etc., if indicated based on ultrasound findings or clinical situation).
3. If total bilirubin (Tbili) is > 2 x ULN, request fractionation to document the fraction that is direct bilirubin and to rule out indirect hyperbilirubinemia indicative of Gilbert's syndrome, hemolysis or other causes of indirect hyperbilirubinemia. Complete blood count (CBC) with white blood count (WBC) and eosinophil count platelet count, international normalized ratio (INR), and total protein and albumin (compute globulin fraction) should also be documented. If INR is abnormal, prothrombin time (PT), partial thromboplastin time (PTT) should be

obtained and these values should be followed until normal, along with documentation of whether parenteral vitamin K was given along with the effect of such treatment on INR.

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

   A liver biopsy may be considered:

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

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

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

Abbreviations

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

APPENDIX 7. 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.
  - [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 Day 1 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.