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: 11 Nov 2021

STATISTICAL ANALYSIS PLAN

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)**
Protocol Number:	**0164**
Compound Number:	**TD-1473**
Short Title	**TD-1473 LTS UC Study**
Sponsor Name:	**Theravance Biopharma Ireland Limited**
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EudraCT No.	**2018-002135-19**

This study will be conducted in compliance with Good Clinical Practice.

SIGNATURE PAGE

TD-1473
0164

Author: [redacted]

12 November 2021 | 07:39 PST
Date

Theravance Biopharma US, Inc.

Reviewer: [redacted]

12 November 2021 | 08:24 PST
Date

Theravance Biopharma US, Inc.

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12 November 2021 | 07:39 PST
Date

Theravance Biopharma Ireland Limited

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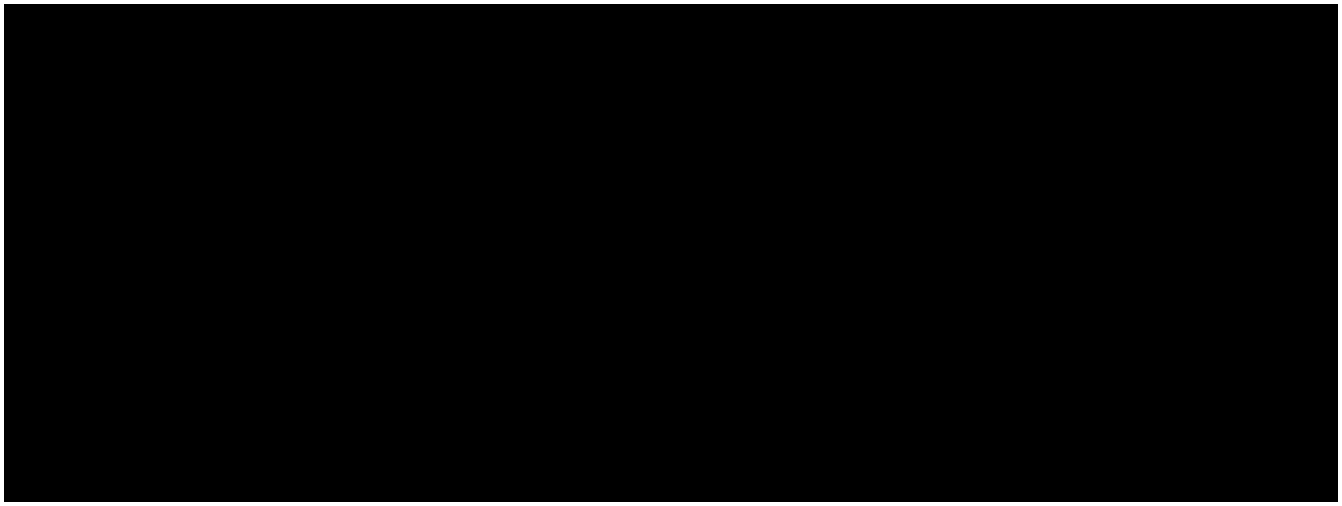
LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

Abbreviation	Term
AE	adverse event
AESI	adverse event of special interest
BMI	body mass index
CRF	case report form
[redacted]	[redacted]
CSR	clinical study report
DMC	data monitoring committee
LOD	limit of detection
LTS	Long-term safety
MedDRA	Medical Dictionary for Regulatory Activities
PT	preferred term
RTSM	randomization and trial supply management
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
TESAE	treatment emergent serious adverse event
UC	ulcerative colitis
WHODD	World Health Organization Drug Dictionary



1. INTRODUCTION

This statistical analysis plan (SAP) outlines the planned summarization and analysis of clinical data collected in the long-term safety (LTS) study of Protocol 0164 for TD-1473. Specifications for tables, figures, and data listings are contained in a separate document.

The results of the planned analyses will be presented in a synoptic clinical study report (CSR) which will include analyses of study subject data and safety endpoints. Inferential statistical tests will not be performed. The protocol-planned efficacy analyses will be excluded as they are not necessary for a synoptic CSR.

The 0164 study was terminated early due to lack of efficacy in the 0157 study, for all subjects the date of last dose occurred by 09SEP2021 and the end of study visit by 11OCT2021.

The analysis of pharmacokinetics data (derivation and summarization of individual PK parameters) is outside the scope of this document and is not addressed here.

This document describes the a priori plan for analysis. Any substantive modification to this analysis plan will be identified in the CSR.

Information in the appendices to the SAP are not considered a formal section of the signed SAP.

1.1. Objectives and Endpoints

1.1.1. Primary Objective

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 ulcerative colitis (UC) after participation in the Maintenance Study of Protocol 0157.

1.1.2. Secondary Objective

Not applicable for the synoptic CSR.

1.1.3. Exploratory Objectives

Not applicable for the synoptic CSR.

1.2. Study Design

This LTS Study 0164 will utilize a multi-center, parallel-group design to evaluate the safety of long-term TD-1473 treatment in subjects with moderate to severe UC rolling over from Protocol 0157 for up to 3 years.

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 repeated (two) Clinical Flares after an episode [redacted]

OR

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

All subjects will receive active drug at three dose levels of 20 mg, 80 mg and 200 mg, and thus, this study will not be placebo-controlled, but blinding as to the specific dose of TD-1473 will be maintained. The dosing regimen for subjects (Table 3) entering the Long-Term Study from the Maintenance Study will be based on:

1. The subject's clinical remission status from Protocol 0157 upon entry into the LTS Study
2. The subject's study drug assignment during the Protocol 0157 Maintenance Study.

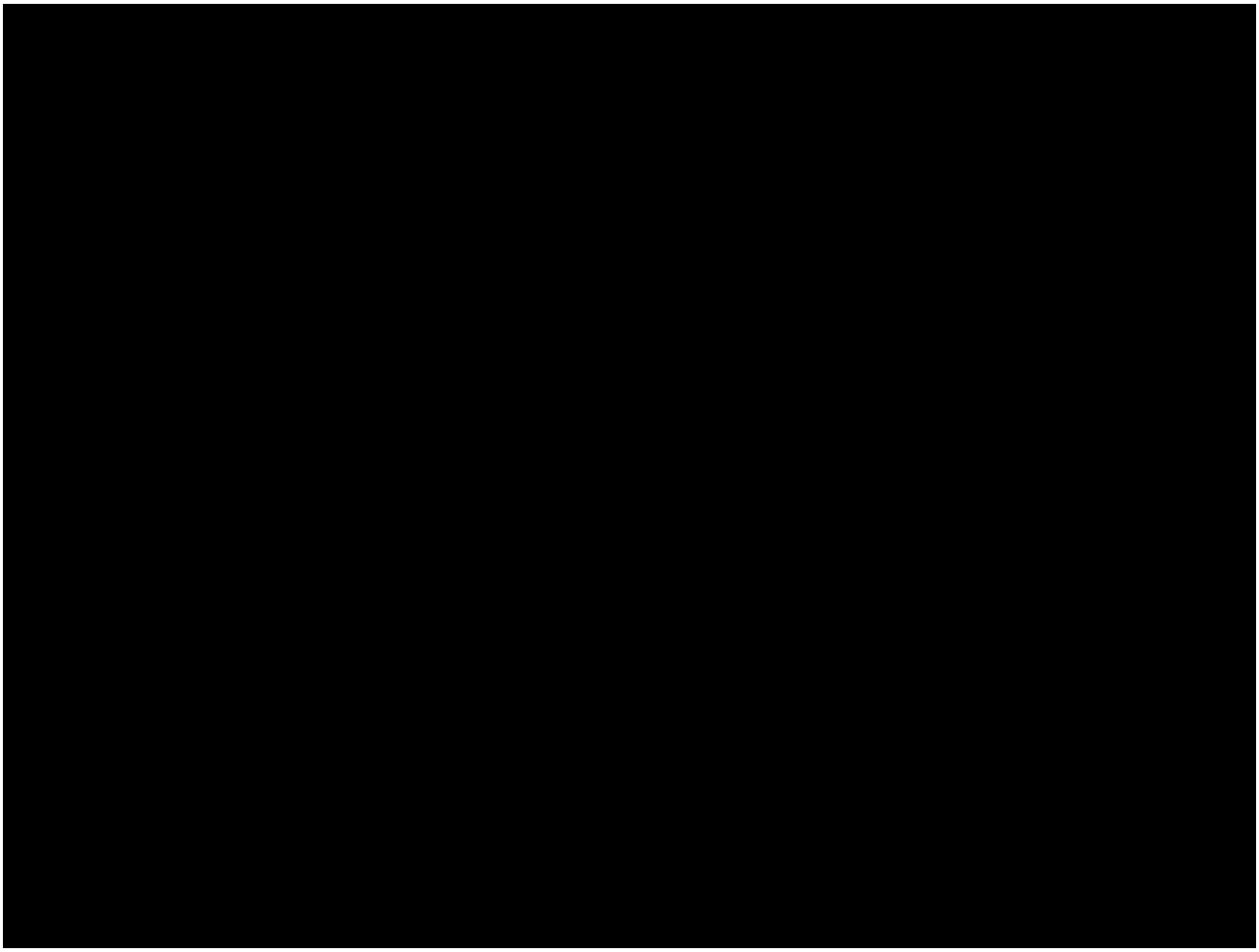
Subjects entering the LTS Study after completing the Maintenance Study in clinical remission on active drug will continue with the same dose of TD-1473. Subjects entering the LTS Study after completing the Maintenance Study in clinical remission on placebo will be placed on 20 mg.

Subjects who enter the LTS Study not in clinical remission on TD-1473 upon completion of the Maintenance Study and subjects who exit the Maintenance study prematurely due to persistent loss of response or recurrent clinical flare with loss of response (also not in clinical remission) will receive an escalated dose in the LTS Study, based on their Maintenance Dose. Subjects on 20 mg and 80 mg of TD-1473 will be dose-escalated one level up to 80 mg and 200 mg, respectively. Subjects on the highest dose (200 mg) will remain on the highest dose. Placebo subjects entering the LTS Study not in remission will be dose escalated to 80 mg.

The dose assigned to subjects entering the LTS is thus partially dependent on the clinical remission status upon entry. For subjects completing the Maintenance Study in remission on active drug, continuing on the same dosing regimen will potentially allow for maintenance of clinical benefit and continued assessments for maintenance of response/remission. For subjects on TD-1473 entering LTS with persistent loss of response or recurrent clinical flare after loss of response, dose escalation in LTS may allow for the possibility of achieving clinical benefit and even recapture of clinical response at a potentially higher dose than that administered during the Maintenance Study. For placebo subjects entering LTS not in clinical remission, dose escalation to 80 mg would potentially allow for achievement of clinical response or remission. For placebo subjects entering LTS in clinical remission, escalation to 20 mg would potentially allow for a higher likelihood of maintenance of clinical remission.

After the global, last subject study visit (including the 4 week follow up visit), an analysis of safety data will be performed.

No interim analyses are planned for this study.



1.3. Treatment Assignment and Blinding

The dosing regimen and schedule for this study are as follows:

- TD-1473 20 mg (2 x 10 mg tablets) once daily: Taken orally for up to 3 years in the morning. With the exception of clinic visit days, subjects will be instructed to take two tablets once daily at approximately the same time each morning.
- TD-1473 80 mg (2 x 40 mg tablets) once daily: Taken orally for up to 3 years in the morning. With the exception of clinic visit days, subjects will be instructed to take two tablets once daily at approximately the same time each morning.
- TD-1473 200 mg (2 x 100 mg tablets) once daily: Taken orally for up to 3 years in the morning. With the exception of clinic visit days, subjects will be instructed to take two tablets once daily at approximately the same time each morning.

Maintenance of the Blind

In order to maintain the blind in subjects whose treatment is known once database lock has occurred for the Maintenance Study, a firewall will be maintained ensuring that Sponsor employees who are aware of treatment assignments will not have contact with site personnel.

In order to maintain the study blind, the study medications will have a label containing the study name, Kit ID number, and reference number. The KIT ID number will be automatically entered in the case report form (CRF) when the drug is dispensed. The study medications will be identical in appearance and packaging.

The investigator will not be provided with randomization codes. The codes will be maintained within the Randomization and Trial Supply Management System (RTSM), which has the functionality to allow the investigator to break the blind for an individual subject. The date and reason for the unblinding will be documented in the appropriate section of the CRF and in the source document. The documentation received from the RTSM indicating the code break will be retained with the subject's source documents in a secure manner. Subjects who had their treatment assignment unblinded by the investigator will be discontinued from study medications.

Data that may potentially unblind the treatment assignment (i.e., study medication, plasma concentrations and treatment allocation) will be handled by the use of subject aliases at the Bioanalytical Lab that conducts initial data analyses to ensure that the integrity of the blind is maintained and the potential for bias is minimized when transferring said information to the Sponsor.

[redacted]

Treatment assignment blinding will be maintained for investigative sites, site monitors, and subjects participating in this protocol until the analyses for the study have been completed.

An independent DMC will regularly review unblinded safety data. The committee and its statistical support group will have access to unblinded treatment information. They will not divulge any information to the Sponsor that may potentially unblind an individual subject’s treatment group.

1.4. Schedule of Assessments

Table 4: 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]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[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

1.5. Sample Size Determination

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

2. 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.

3. STATISTICAL ANALYSES

3.1. General Considerations

All individual data will be listed as measured. All statistical summaries and analyses will be performed using SAS software (SAS Institute, Cary, North Carolina, USA).

All data from scheduled and unscheduled visits will be presented in the subject listings. However, unless noted otherwise, only data from scheduled/windowed visits will be included in the summaries, statistical analysis, and calculation of derived parameters.

Summary tables and listings (e.g., post text tables and individual subject data listings are prepared according to ICH Guideline E3) include a "footer" providing explanatory notes.

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) 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.

For safety assessments, summary statistics will be reported by treatment.

3.1.1. Baseline Definition

In general, the baseline value for efficacy variables and for safety variables is the value associated with the last available pre first dose visit/time point at which the variable was to be collected according to the schedule of study procedures, and must have been collected pre-dose.

3.1.2. Study Day

If the date of interest occurs on or after the first dose/randomization date, then study day will be calculated as (date of interest – date of first dose) + 1.

If the date of interest occurs prior to the first dose/randomization date, then study day will be calculated as (date of interest – date of first dose).

3.1.3. Visit Windows

The visit indicated on the CRF will be used in summaries of the data.

3.1.4. Multiple Assessments

In general, if multiple, valid, non-missing observations exist at a visit or collection time point then records will be chosen based on the following:

• The record closest to the nominal time point in question.

If 2 records are equidistant:

• The later record of the two visits.

If 2 records with same date/time

• Average (generally applies to assessments done in triplicate).

There is a special rule for laboratory test results: if there are multiple valid records within the visit window for the same visit or time point, the record(s) with the latest collection time will be selected rather than the record(s) with collection time closest to the nominal time. The protocol states that:

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.

Hence, the latest laboratory test result associated with a visit or time point will be selected for summarization. All results will be provided in listings.

3.1.5. Actual Treatment

Data will be summarized by actual treatment group which will be determined by the treatment that was dispensed at the Day 1 visit.

3.2. Study Subjects

3.2.1. Enrollment

Not applicable for the synoptic CSR.

3.2.2. Subject Disposition and Completion Status

A summary of study disposition will be provided by study treatment on the Safety analysis set showing the following:

- Number of subjects enrolled
- Number of subjects treated
- Number of treated subjects who completed the study
- Number of treated subjects who discontinued early from the study
- Primary reasons for early study discontinuation, with frequencies
- Number of treated subjects who completed treatment
- Number of treated subjects who discontinued treatment early
- Primary reasons for early treatment discontinuation, with frequencies

A listing of subject disposition will include Safety analysis set flag [Yes/No], dates of first and last dose of study drug, primary reason for subject discontinuation of study treatment, study completion status, primary reason for study termination, and date of last contact.

3.2.3. Demographic and Baseline Characteristics

Demographic data including age, sex, race, ethnicity, weight, height, and body mass index (BMI) will be summarized overall and by treatment group. Sex, race, and ethnicity frequency distributions will be provided.

3.2.4. Protocol Deviations

The number and percentage of subjects reporting important protocol deviations will be summarized overall and by treatment group for the Safety analysis set. Important protocol deviations are defined in the protocol deviation plan.

A listing of all important protocol deviations will be provided.

3.2.5. Medical History

Medical and surgical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 24.0 or later. A listing of medical history coded to each system organ class and preferred term for each subject will be provided.

3.2.6. Prior/Concomitant Medications

Prior medications include all medications taken prior to the first dose of study drug, regardless of when they were stopped. Concomitant medications include all nonstudy medications that the subject was taking prior to the Day 1 visit that were ongoing at the visit, in addition to all medications with a start date on or after the first dose date and no later than the last dose date + 28 days. Medications with a start date after the last dose date + 28 days will be included in a listing of concomitant medications with a flag.

Recorded prior and concomitant medication names will be mapped according to [redacted]

3.3. Primary Analyses

The primary objective is 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 analyses for this objective are outlined in Section 3.4 Safety Analyses. No efficacy endpoints are considered primary endpoints.

3.4. Safety Analyses

The analysis of safety data includes an overall summary of adverse event preferred terms by body/organ system, drug exposure (duration of treatment), dosing information/compliance, clinical laboratory results, vital signs and ECGs. Tables summarizing the adverse events reported by subjects who died, experienced non-fatal serious adverse events (SAE), or prematurely discontinued the study due to adverse event (AEs) will be prepared. Summaries of potentially clinically notable laboratory results and vital sign abnormalities are presented.

Inferential statistical tests will not be performed for adverse event incidence rates.

For all safety analyses, the safety analysis population will be used.

3.4.1. Extent of Exposure

Study drug exposure will be summarized using the 8-point descriptive summary presenting number of doses and duration of treatment for the study.

Duration of treatment will be displayed in days and calculated as:

$$date\ of\ last\ dose\ -first\ dose\ date\ +\ 1$$

Calculated values will be rounded to 1 significant digit in the analysis datasets.

3.4.1.1. Treatment Compliance

Study drug compliance will be calculated as:

$$\frac{100\ \times\ 0.5\ \times\ (number\ of\ capsules\ dispensed\ -\ number\ of\ capsules\ returned)}{(date\ of\ last\ dose\ -\ date\ of\ first\ dose\ +\ 1)}$$

Study drug compliance over the interval from first to last dose will be summarized as a continuous variable and by rounding to the nearest 0.1% and showing counts and percentages for the following disjoint categories: ≥ 120%; 110% to 120%; 90% to 110%; 80% to 90%; < 80%.

Study drug administration information (date/time and study day) will be provided in a data listing. Study drug accountability information and study drug exposure and compliance will also be provided in data listings.

Study drug discontinuations and reasons for study drug discontinuation will be listed.

3.4.2. Adverse Events

Adverse events (AEs) will be coded to the preferred terms (PT) of the Medical Dictionary for Regulatory Activities (MedDRA®). Summaries will be presented by system organ class (SOC), preferred term, and severity and/or relatedness, the number and percentage of subjects for whom events were reported.

Adverse events (AEs) are recorded from signing of the informed consent form through the final follow-up assessment. Adverse events observed prior to first dose are non-treatment emergent.

Treatment emergent adverse events are defined as follows:

- TEAEs are AEs with onset on or after the first initiation of study drug up to the date of last dose of study drug + 28 days.

Only treatment-emergent AEs will be summarized in the tables. A listing of all TEAEs by subject will be provided.

An AE will be considered a treatment emergent serious AE (TESAE) if it is a TEAE that additionally meets any SAE criteria.

If more than 1 AE is coded to the same preferred term for the same subject, the subject will be counted only once for that preferred term using the most severe and most related occurrence for the summarizations by severity and by relationship to study drug.

Summary tables will also be provided for subjects with:

- TESAEs by SOC and PT
- TEAEs leading to discontinuation of study drug by SOC and PT
- TEAEs leading to temporary interruption of study drug by SOC and PT

- TEAEs by severity and by SOC and PT
- Drug related TEAEs by severity and by SOC and PT

Listings of all AEs, SAEs, AEs resulting in death, and AEs leading to discontinuation by subject will be presented.

An overall summary of adverse events will also be presented and will include the following summary lines: Any AE, Moderate or Severe AEs, AEs Related to Study Drug, Moderate or Severe AEs Related to Study Drug, Serious AEs, Serious AEs Related to Study Drug, AEs Leading to Premature Study Drug Discontinuation, AEs Leading to Temporary Interruption of Study Drug, and Deaths During Study.

3.4.2.1. Adverse Events of Special Interest

An AE of special interest (AESI) is one of scientific and medical interest specific to understanding the investigational product and may require close monitoring and rapid communication by the investigator to the sponsor. The following are the AESI's defined for the 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, pulmonary embolism)
- Clinical Laboratory Abnormalities of Concern
- Major Cardiovascular Event (e.g. myocardial infarction or cerebrovascular accident)

The incidence of AESI's will be summarized overall and by AESI category and preferred term.

3.4.3. Additional Safety Assessments

3.4.3.1. Clinical Laboratory Parameters

Laboratory data, hematology, serum chemistry and urinalysis, will be summarized in terms of observed values and changes from baseline. In addition, changes from baseline relative to normal ranges from the central lab (e.g., shifts from normal to abnormal high/low) will be summarized.

The number and percentage of subjects with clinically abnormal lab values will also be summarized by timepoint for the following criteria:

- absolute neutrophil count of $< 1.0 \times 10^9$/L

- white blood cell count of $< 2.0 \times 10^9$/L
- absolute lymphocyte count of $< 0.5 \times 10^9$/L

A listing of all abnormal lab values will be provided.

3.4.3.2. Vital Signs

Descriptive statistics for vital signs (heart rate, systolic and diastolic blood pressures, respiratory rate, and body temperature) and changes from baseline values at each visit and at the end of study will be presented by treatment group.

The number and percentage of subjects with marked abnormalities as defined in Table 5 will be summarized and flagged in a listing of all vital signs values.

Table 5: Criteria for Marked Abnormalities in Vital Signs

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

3.4.3.3. Electrocardiogram

Descriptive statistics for ECG parameters (heart rate, PR interval, QRS interval, QT interval, and QTcF) and changes from baseline values at each assessment time point to the end of study will be presented by treatment group. The QTcF will be calculated using the Fridericia correction.

All recorded values for the standard 12 lead electrocardiogram parameters will be presented in a by-subject listing.

Categorical Analyses

The number and percentage of subjects with absolute ECG values and change from baseline in the ranges shown in Table 6 will be presented in Electrocardiogram Categorical Summary by Visit and Time Point.

Subjects without a postbaseline measurement for a given treatment period will be excluded from the summary statistics (e.g., denominator of the summary statistic) for that time point.

In addition, in the same summary, QTcF will also be summarized by the following categories, Normal (males < 430, females ≤ 450), Borderline (males (> 430, ≤ 450); females (> 450, ≤ 470)) and Prolonged (males > 450, females > 470).

Individual ECG data collected during the study will be presented in a listing. A separate listing of subjects with values of QTcF > 500 msec or an increase > 60 msec will be provided, as necessary.

Table 6: ECG Interval Categories

Heart Rate (bpm)	Heart Rate Change from Baseline (bpm)	PR Interval (msec)	PR Percentage 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
					≥ 430	> 60
					≥ 450	
					≥ 470	
					≥ 480	
					≥ 500	
					Females:	
					< 450	
					≥ 450	
					≥ 470	
					≥ 480	
					≥ 500	

3.5. Other Analyses

Not applicable for the synoptic CSR.

3.5.1. Other Variables and/or Parameters

Not applicable for the synoptic CSR.

3.5.2. Subgroup Analyses

Not applicable for the synoptic CSR.

3.6. Interim Analyses

No interim analysis is planned for this study but the database lock for the Maintenance Study Protocol 0157 will occur prior to the end of the study.

Blinding

Bias in safety evaluation will be minimized through partial dose-blinding. The dose will be blinded however it will be known to all parties that all subjects are on TD-1473. 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.

3.6.1. Data Monitoring Committee

[redacted]

4. REFERENCES

SAS Institute Inc. 2017. *Base SAS® 9.4 Procedures Guide, Seventh Edition*. Cary, NC: SAS Institute Inc.

5. SUPPORTING DOCUMENTATION

5.1. Appendix 1: Changes to Protocol-Planned Analyses

The protocol-planned efficacy analyses are not required for the synoptic CSR.

5.2. Appendix 2: Data Conventions and Transformations

5.2.1. Derived and Transformed Data

5.2.1.1. Study Day

If the date of interest occurs on or after the first dose/randomization date, then study day will be calculated as (date of interest – date of first dose/randomization) + 1.

If the date of interest occurs prior to the first dose/randomization date, then study day will be calculated as (date of interest – date of first dose/randomization).

There is no Study Day 0.

5.2.1.2. Change from Baseline

Change from baseline is calculated as (postbaseline result – baseline result).

Percent change from baseline is calculated as (change from baseline/baseline result) × 100 or equivalently as 100 × (postbaseline value/baseline value - 1).

If either the baseline or the postbaseline result is missing, the change from baseline and percentage change from baseline values are missing.

5.2.1.3. BMI

BMI is calculated as:

$$BMI\left(kg/m^2\right)=\frac{weight\left(kg\right)}{height\left(m\right)^2}.$$

5.2.2. Missing Data Imputation

5.2.2.1. Missing/Incomplete AE/Start Date

Imputation of dates with missing day and/or month is only applied to TEAEs. TEAE start dates with missing day or month will be imputed as follows:

- If day and month are missing but year is available, then the imputed day and month will be 01 Jan [with a time of 00:00 if applicable] or first study drug dose date if they have the same year, whichever is later (because TEAE onset is not expected prior to administration of study treatment)
- If day is missing but the month and year are available, then the imputed day will be the first day of the month [with a time of 00:00 if applicable] or the first study drug dose date if they have the same month and year, whichever is later.

5.2.2.2. Missing/Incomplete AE/Medication End Date/Time

Imputation of dates with missing day and/or month is only applied to TEAEs when AE duration is calculated. TEAE end dates with missing day or month will be imputed as following:

- If day and month are missing but year is available, then the imputed day and month will be 31 Dec [with a time of 23:59 if applicable] or the date and time of last study drug dose if they have the same year, whichever is earlier
- If day is missing but the month and year are available, then the imputed day will be the last day of the month [with a time of 23:59 if applicable] or the date and time of the last study dose if they have the same month and year, whichever is earlier.

5.2.2.3. Missing/Incomplete Start for Medication

To determine whether medications were used prior to initiation of dosing and whether they were used after initiation of dosing, missing or partial dates for medications will be imputed according to the following rule:

Missing medication start date/time:

- If day and month are missing but year is available, then the imputed day and month will be 31 Dec [with a time of 23:59 if applicable] or the study exit date if they have the same year, whichever is earlier.
- If day is missing but the month and year are available, then the imputed day will be the first day [or 1 minute after midnight if applicable] of the month or the first dose date if they have the same month and year, whichever is later.
- If day, month and years are completely missing, impute as date and time of first dose if 1) end date is not missing and occurs on and after date of first dose, or 2) end date is missing but marked as “ongoing”.

5.2.2.4. Laboratory Data

For non-efficacy laboratory data, a missing baseline value will be replaced with the last available assessment, generally the screening assessment. A retest value will be used if the original test result is invalid, e.g., specimen hemolyzed.

Laboratory data that are continuous in nature but are less than the lower limit of quantitation/limit of detection (LOD) will be, in general, imputed as follows:

- A value that is 1 unit less than the LOD will be used for calculation of descriptive statistics if the data are reported in the form of “< x” (x is considered as the LOD). More specifically, x−1 is used for data summarization if the data are reported in the form of “< x”; and x.e where e = d−1, will be used for analysis if the data are reported in the form of “< x.d”.

Laboratory data that are continuous in nature and above the upper limit of quantitation/limit of detection (LOD) will be, in general, imputed as follows:

- A value that is 1 unit more than the LOD will be used for calculation of descriptive statistics if the data are reported in the form of “> x” (x is considered as the LOD).

More specifically, x+1 is used for data summarization if the data are reported in the form of "> x"; and x.e where e = d+1, will be used for analysis if the data are reported in the form of "< x.d".

5.2.2.5. AE Severity

For graded adverse event summaries, AEs with no grade reported will be graded as severe.