Protocol Number: 0173

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

NCT Number: NCT03635112

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STATISTICAL ANALYSIS PLAN

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

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LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

Abbreviation	Term
AE	Adverse Event
ANCOVA	Analysis of Covariance
BMI	Body Mass Index
C	Continuous reporting format
CD	Crohn's Disease
CDAI	Crohn's Disease Activity Index
CI	Confidence interval
CMH	Cochran Mantel-Haenszel / CMH reporting format
CRF	Case Report Form
[redacted]	[redacted]
CSR	Clinical Study Report
DOB	Date of Birth
dy	Days
ECG	Electrocardiogram
[redacted]	[redacted]
F	Frequency reporting format
G	Geometric mean reporting format
GCP	Good Clinical Practices
ICF	Informed consent form
IRB	Institutional Review Board
ITT	Intent-to-Treat Population
LLN	Lower Limit of Normal
LOCF	Last Observation Carried Forward
LS	Least Square
LSM	Least Square mean
LSP	Least Square Proportion
MedDRA	Medical Dictionary for Regulatory Activities Terminology
MF	Multiple frequency reporting format
mITT	Modified Intent-to-Treat
mo	Months
N	Total Sample Size
NLSM	Normal Least Square Mean
NBLSM	Negative Binomial Least Square Mean
[redacted]	[redacted]
PK	Pharmacokinetics
pMS	Partial Mayo Score
PP	Per-Protocol Population
PRO	Patient-reported outcome
[redacted]	[redacted]
SD	Standard Deviation
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SES-CD	Simplified Endoscopy Score for Crohn's Disease
SOC	System Organ Class

Abbreviation	Term
TBPH	Theravance Biopharma, Inc.
TEAE	Treatment-emergent adverse event
ULN	Upper Limit of Normal
VAS	Visual Analogue Scale
WBC	White Blood Cell Count
WHO	World Health Organization
yr	Years

1. INTRODUCTION

This document describes the plan for the summarization and analysis of clinical data collected in Study 0173 for TD-1473.

[redacted]

This document describes the plan for analysis. Once the analyses are in progress, it may become apparent from the data that the planned analyses should be modified. Any substantial modification to the plan will be described in the clinical study report.

Due to the decision to terminate the study early, the exploratory ATE efficacy analyses will not be performed.

1.1. Objectives and Endpoints

1.1.1. Primary Objective(s)

The primary objectives of the study are as follows:

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

1.1.2. Secondary Objective(s)

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

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

1.1.3. Exploratory Objective(s)

[redacted]

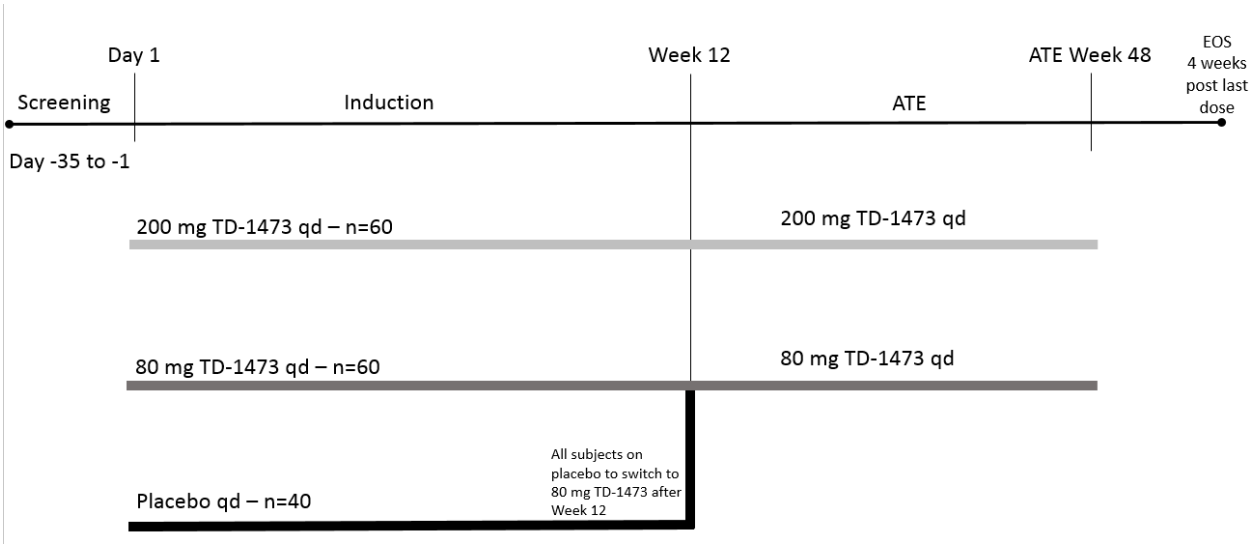
1.2. Study Design

1.2.1. Summary of Study Design

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

Subjects who complete the Induction phase will continue to receive TD-1473 in ATE, either at 80 mg or 200 mg, for up to 48 additional weeks.

Figure 1: Study Design Schematic



Screening:

To determine eligibility, subjects will undergo assessments during the Screening period (up to 35 days prior to Day 1 dosing) as outlined in the Schedule of Study Procedures (Section 1.4). Disease activity will be assessed by the clinical scores, based on symptoms reported on a daily diary, which will be captured electronically beginning the day after Screening Stage 1.

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

Induction

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

The randomization will be stratified by prior biologics failure and CDAI score category (≤ 300, > 300) at the Screening Stage 2 visit (using laboratory data from Screening Stage 1 for the score calculation). Approximately 40-60% of subjects randomized will have failed prior treatment with biologics. Subjects will be treated for 12 weeks and assessed for the various endpoints, including those that incorporate findings from an ileocolonoscopy and biopsies at the Week 12 visit. Corticosteroids will start to be tapered at Week 8. Subjects will undergo clinic study visits every 4 weeks in accordance with the Schedule of Assessments

(Section 1.4). During this time, subjects will continue to fill out a daily diary.

ATE:

All subjects who complete Induction at the Week 12 visit will continue into ATE, ATE Day 1 is scheduled for between 1 and 7 days after the Induction Week 12 visit where subjects will be treated with either 80 mg or 200 mg of TD-1473 for 48 weeks. Dose during ATE depends on treatment assignment during Induction (Figure 1 and Table 2): those who were dosed with TD-1473 during Induction will stay on the same dose; those who were dosed with placebo during Induction will be dosed with TD-1473 at 80 mg.

Table 2: Induction and Active Treatment Dose Assignment

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

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

Subjects who have not shown clinical improvement (as assessed by the investigator) 16 weeks after initiation of ATE (i.e., ATE Week 16) will be discontinued from the study following completion of an End of Study (EOS) visit.

End of Study (EOS) Visit:

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

1.2.2. Definition of Study Drugs

Study drug comprises the following (placebo and 2 doses of TD-1473):

- TD-1473 80 mg once daily: Taken orally for up to 60 (including ATE) weeks in the morning before eating. Subject must refrain from eating or drinking anything other than water and non-study medications for at least 30 minutes after dosing. Subjects from placebo arm will take from start of ATE Day 1 to ATE week 48.
- TD-1473 200 mg once daily: Taken orally for up to 60 (including ATE) weeks in the morning before eating. Subject must refrain from eating or drinking anything other than water and non-study medications for at least 30 minutes after dosing.

Placebo once daily: Taken orally for up to 12 weeks in the morning before eating. Subject must refrain from eating or drinking anything other than water and non-study medications for at least 30 minutes after dosing.

1.3. Treatment Assignment and Blinding

Central randomization for treatment allocation will be implemented. A computer-generated randomization schedule will be prepared for this study under the supervision of the sponsor.

The randomization will be stratified by history of biologic treatment failure (Yes, No) crossed with baseline CDAI category (≤ 300, > 300). A sequence of randomly permuted blocks will be used to centrally assign subjects in each stratum to TD-1473 at 80 mg, TD-1473 at 200 mg, or placebo in a 3:3:2 ratio. Enrollment targets are shown in Table 3:

Table 3: Randomization

Stratum\Treatment Group	All Treatment Groups	Placebo once daily	TD-1473 80 mg once daily	TD-1473 200 mg once daily
All Strata	160	40	60	60

Randomization caps will be placed on both prior biologics failure subgroups (no to biologic failure (up to 60%) and yes to biologic failure (up to 60%)) to ensure that neither subgroup is overrepresented. There will also be a cap at 10% for enrollment of subjects with an SES-CD score at screening in the range of 3 to 5.

1.4. Schedule of Assessments

The schedule of assessments is presented in Schedule of Assessments

.

Table 4: Schedule of Study Procedures

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

Dispense Electronic Diary [J]	X															
Corticosteroid Dosing Taper (if applicable) [K]					X		X	X	X							
Telephone Call [L]						X										
Concomitant Medications	----------X----------															
Adverse Event Assessment [M]	----------X----------															
Laboratory Assessments																
Pregnancy Test (females of childbearing potential only) [N]	X		X	X	X		X	X	X	X	X	X	X	X	X	X
FSH [O]	X															
Chemistry, Hematology	X		X	X	X		X		X	X	X	X	X	X	X	X
Urinalysis	X		X	X	X		X		X	X	X	X	X	X	X	X
Overnight Fasting Lipid Panel		X [P]	X	X	X		X		X	X	X	X	X	X	X	X
Viral hepatitis and HIV Serology Panel	X [Q]															
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tuberculosis Test (QuantiFeron)	X															
Ileocolonoscopy and Biopsies		X [R]					X [C]									
Fecal Sample for Infectious Studies [S]	X															
[redacted]			[redacted]				[redacted]					[redacted]		[redacted]	[redacted]	

[redacted]			[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]		[redacted]				
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]		[redacted]		[redacted]	[redacted]	[redacted]
Genetic Blood Sample (Optional – only collected for subjects who provide genetic testing consent)			X													
Disease Assessments																
CDAI Score		X [V]	X	X	X		X		X		X	X		X	X	X [A]
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
SES-CD Score		X					X									
Fistula Drainage Status (yes/no to active drainage), if fistula is present	X		X	X	X		X					X		X	X	X
[redacted]			[redacted]				[redacted]				[redacted]	[redacted]		[redacted]	[redacted]	
[redacted]			[redacted]				[redacted]				[redacted]	[redacted]		[redacted]	[redacted]	
Subject Diary Completion and Compliance Review [J]	X	X	X [W]	X	X		X	X	X	X	X	X	X	X	X	X [A]

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

A. This visit is for subjects who prematurely discontinue the study drug. This visit will be conducted within 5 days of the last dose of study drug, if possible. Subject will also return for the EOS visit for collection of safety data and assessment of disease activity. Subjects who discontinue study drug early due to AE are permitted to optionally complete their daily diary through to the EOS visit. Subjects who have not shown clinical improvement at ATE Week 16 should complete an Early Study Drug Discontinuation visit and be discontinued from study drug.

B. An EOS visit will be required for all subjects 4 weeks following their last dose of study drug, whether they completed the full duration of study drug treatment.
C. The Week 12 ileocolonoscopy and biopsies should be performed on the same day as the Week 12 visit, preferably in the early morning, to permit morning dosing with study drug. However, if not feasible to perform both the ileocolonoscopy and the clinic visit on the same day, the ileocolonoscopy could be performed within 3 days after the Week 12 clinic visit. If the study activities of this Week 12 visit are to be completed over two different visits, the study drug should be continued until the later of the two visits. The Week 12 endoscopy must be performed at least 1 day prior to ATE Day 1.
D. ATE Day 1 should occur between 1 and 7 days after the Week 12 clinic visit. No new study drug will be dispensed between the Week 12 clinic visit and ATE Day 1. ATE Day 1 must be performed at least 1 day after the Week 12 endoscopy has been conducted.
E. Subjects who have not shown clinical improvement, as deemed by the subject and investigator, 16 weeks after initiation of the ATE (i.e., ATE Week 16), should be discontinued from the study.
F. Physical exams (PEs) should be performed as per local standard practice.
G. Subjects who have had a documented chest X-ray or equivalent chest imaging or TB testing within 90 days prior to Screening do not require a repeat X-ray (or equivalent) or TB testing, respectively, unless subject is deemed by the investigator to be at high risk of recent pulmonary infection. If a chest X-ray is indicated, it may be performed anytime during Screening. Subjects with a history of latent TB should not have a TB test but must not live in a region with high prevalence of multidrug-resistant TB and have completed a well-accepted treatment regimen (e.g., a ≥ 9-month course of INH or equivalent therapy) within 5 years (3 years in countries where TB is endemic) prior to Screening, the documentation for which must be included in the source document and reviewed by the PI. Subjects who had treated active TB must still have a TB test. Subjects who has a history of latent or active tuberculosis (TB) may be eligible for the study if criteria are met.
H. Subject will be randomized on Day 1 after all pre-dose procedures (ECG, vital signs, and all labs [redacted]) have been completed and subject is confirmed to be eligible for the study.
I. Study drug administration will be in clinic on Day 1, Week 4, Week 8, Week 12, ATE Day 1, ATE Week 4, ATE Week 8, ATE Week 16, ATE Week 24, ATE Week 36, and ATE Week 48 on an empty stomach from the night before after all pre-dose assessments (with the exception of [redacted], which may be done post-visit on the same day) and procedures have been completed. Subject will take the study drug at home for the rest of the study. The last dose of Induction study drug will be taken at the Week 12 clinic visit. No new study drug will be dispensed between the Week 12 clinic visit and ATE Day 1.
J. Subjects will be provided with an electronic diary (or paper diary if electronic diary is not available) at the Screening Stage 1 visit and instructed on daily diary completion, including symptom monitoring and study drug dosing details. Diaries of symptoms will be collected daily from the Screening Stage 1 visit through the EOS visit. Study drug dosing details will be entered from Day 1 (Induction) through ATE Week 48 (or the last dose of study drug, if the subject prematurely withdraws from study drug). Diary completion will be monitored for completeness at each return study visit after the electronic diary is dispensed (i.e., Screening Stage 2 through the EOS visit). Subjects will be counseled on missed study drug doses and missed diary entries.
K. Corticosteroid taper, for those that are on corticosteroid at Screening Stage 1, should be initiated at the Week 8 visit.
L. Site personnel to call subjects approximately 2 weeks prior to Week 12 visit for reminder of compliance of diary completion. The site will also review compliance on corticosteroid taper (as applicable), review upcoming schedule for Week 12 and the reminders in preparation for the visit.
M. AE assessments are to include collection and reporting of AEs, SAEs, and AEs of Special Interest (AESIs).
N. Urine beta human chorionic gonadotropin (b-hCG) testing will be performed before dosing when dosing in-clinic and anytime during all other visits for females of childbearing potential to confirm absence of pregnancy. If urine b-hCG test is positive, confirm with serum b-hCG test.
O. Required for postmenopausal females.
P. Any Screening Stage 2 lab testing can be obtained from Day -35* to Day -1 during Screening. Overnight fasting lipid panel may be obtained on Day -35 if subjects are fasting as per institutions standard of care procedure, which must be clearly documented in the source documents. ***NOTE:** Subjects **must not**

be requested to come in fasting for study specific assessments prior to signing the informed consent. Results of these labs will not need to be reviewed before Screening Stage 2 or Day 1.

Q. Subjects with positive hepatitis B core antibody will undergo testing for hepatitis B DNA and hepatitis B surface antibody during Screening. Subjects with known hepatitis C will also undergo testing for hepatitis C RNA viral load (for details on Serology testing). During re-screening, if there is already a negative result from prior screening, the hepatitis B, C, or E or HIV serologies do not need to be repeated.

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

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

T. [redacted]

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

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

1.5. Sample Size Determination

Assuming that the less effective TD-1473 dose results in a 45-point improvement in placebo-adjusted CDAI change from baseline at Week 12, the more effective dose results in a 60-point improvement, and the residual SD is 100 points, 100,000 simulations performed using SAS/IML software yielded the following power estimates for 2-sided testing with the family-wise type 1 error rate for the primary efficacy endpoint controlled at 5% using the Hochberg step-up procedure[1]:

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

A more detailed rationale, including the basis for estimating the SD of CDAI change as 100 points, is given in "TD-1473 Study 0173 Sample Size Determination v1.0"

[1] The Hochberg step-up procedure is as follows: if both TD-1473 doses vs placebo p-values are < .05, reject both no-effect null hypotheses; otherwise, if the smaller p-value is < .025, reject the no-effect null hypothesis for that dose.

2. ANALYSIS SETS

Table 5: Analysis Sets

Analysis Set	Definition	Treatment Assignment
Screen Failures*	Subjects who give informed written consent but are not randomized are considered screen failures. Screen failure subjects and the main reason for screen fail will be captured in the EDC.	N/A
Randomized*	The randomized analysis set will include all subjects who were randomized into the study.	Randomized treatment
Safety*	The Safety analysis set will include all subjects who received at least one dose of study drug (or placebo). The Safety analysis set is the primary analysis set for safety analyses.	Actual Treatment received (see Section 3.1.6)
ITT*	The Intent-to-Treat (ITT) analysis set comprises all randomized subjects who receive at least one dose of study drug.	Randomized treatment
Modified ITT*	The modified Intent-to-Treat (mITT) analysis set comprises all randomized subjects who receive at least one dose of study drug and have at least one postbaseline CDAI score. Only include subjects randomized prior to the 23Aug2021. The mITT set is the primary analysis set for efficacy summaries and analyses.	Randomized treatment
PP*	The Per-Protocol (PP) analysis set comprises all subjects in the mITT analysis set who complete their Week 12 visit and have no major analysis protocol deviations	Randomized treatment
Active Draining Fistulae*	The active draining fistulae analysis set comprises all subjects in the mITT analysis set with at least one draining fistula at baseline.	Randomiznaed treatment

* Due to confirmed data integrity violations the data for site 36016 (deviation report GCP-XX) and site 38915 (deviation report GCP-11) will be excluded from all analysis sets.

3. STATISTICAL ANALYSES

3.1. General Considerations

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 variables will be summarized using an 8-point descriptive summary (number of subjects [n], mean, standard deviation [SD], median [Q2], interquartile range [25th percentile Q1, 75th percentile Q3], minimum, and maximum) unless otherwise indicated. Categorical variables will be summarized by frequency and percentage of subjects in each category. All summaries will be presented by treatment and visit when applicable.

For binary endpoint comparisons to placebo when the expected number of responders/non-responders are less than 5 per treatment groups being analyzed a fishers exact test will be performed. For safety assessments, summary statistics will be reported by treatment.

Analyses and tabulations will generally be prepared using SAS®, version 9.4 or later.

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 prior to first dose.

The exceptions are for fecal samples and electronic tablet data that can be submitted within 3 days of first dose.

3.1.2. Study Day

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

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

There is no induction study day 0.

ATE study day will calculated in a similar manner with first dose in ATE period used to calculate the day (expected to be ATE Day 1).

3.1.3. Visit Windows

All assessments will be summarized using analysis windows.

The terminology of unscheduled will be applied to assessments that are outside an analysis window regardless of the nominal label associated with the assessments in the EDC system.

The following visit windows will be used in the summary of clinical data.

Table 6: Visit Analysis Windows

Nominal Visit	Nominal Day	Start (days)	Stop (days)
Screening	NA	-28	-1
Baseline	1	1	Induction Day 1
Week 4	Induction Day 28	Induction Day 21	Induction Day 35
Week 8	Induction Day 56	Induction Day 49	Induction Day 63
Week 12	Induction Day 84	Induction Day 77	Earliest of: • ATE Day 1 dose date • Induction Day 98 (Induction Day 112 for SES-CD score)
ATE Week 4	ATE Day 28	ATE Day 21	ATE Day 35
ATE Week 8	ATE Day 56	ATE Day 49	ATE Day 63
ATE Week 16	ATE Day 112	ATE Day 105	ATE Day 126
ATE Week 24	ATE Day 168	ATE Day 161	ATE Day 182
ATE Week 36	ATE Day 252	ATE Day 245	ATE Day 266
ATE Week 48	ATE Day 336	ATE Day 329	ATE Day 350

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. Repeat laboratory testing of abnormal potentially clinically significant or clinically significant results for Screening evaluation of the subject may be repeated at the discretion of the investigator.

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. Study Period Definitions

3.1.5.1. Induction Period

For analysis and summaries of the induction period, only data collected for each subject from first dose up until the earliest event between the ATE Day 1 dose or date of last dose + 5 days will be presented.

3.1.5.2. Active Treatment Extension Period

Active Treatment Extension is the period from first dose at ATE Day 1 until date of last dose + 5 days.

3.1.5.3. Overall Study Period

For analysis and summaries of the overall study period, only data collected for each subject from first dose up until date of last dose + 5 days will be presented.

3.1.6. Actual Treatment

In the event that a subject is dispensed incorrect treatment the following rules will be used to decide actual treatment during the period that the incorrect treatment was dispensed and returned:

Mean Dose	Actual Treatment
<=140 mg	80mg
>140 mg	200mg

Mean dose is calculated over a period as the summation of each tablet taken (where placebo is considered 0mg) and divided by total number of days on treatment in the period.

3.2. Study Subjects

Unless otherwise noted, the ITT analysis set is the main analysis set used in the summarization of general (Study Population) analyses.

3.2.1. Subject Disposition and Completion Status

The number of subjects screened for the study will be provided. A summary of study disposition will be provided by study treatment showing the following:

- Number of subjects randomized
- 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

The following additional disposition summary will be provided:

- Number of subjects who completed the Week 12 Visit
- Number of subjects who discontinued prior to the Week 12 Visit
  - Primary reasons for discontinuation prior to the Week 12 Visit, with frequencies

A listing of subject disposition will include analysis set flags (ITT, Safety, mITT, PP [Yes/No], Active Draining Fistula), 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.

A listing of subject eligibility (inclusion or exclusion criteria exceptions) and a listing of subjects randomized but not treated will be provided.

3.2.2. Demographic and Baseline Characteristics

Demographics

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. Age will be further categorized as 18 to 64 vs. ≥ 65 years.

Tobacco Consumption

A summary of Tobacco Consumption taken at baseline or screening will be provided summarizing:

Parameter	Units/Response category
Tobacco Consumption Status	Never, Current, Former
Number of Tobacco Units Per Day	Converted Units
Number of Years With Tobacco Use	Years
Total Number Of Pack Years	Pack Years
Type of Tobacco Product Used	Cigarettes, Cigars, Pipe, Smokeless Tobacco

The following conversion process is used to standardize a unit of tobacco consumption:

1 unit = 1 pack (20 cigarettes) = 5 cigars = 8 pipes = 8 pinches

Number of years of tobacco use is calculated as follows where current smokers use the Day 1 Visit date as end date:

$$\frac{(Tobacco\ use\ end\ date - Tobacco\ use\ start\ date\ +\ 1)}{365.25}$$

Pack Years is calculated as number of years of tobacco use multiplied by number of tobacco units per day (converted units).

A listing will also be provided.

Crohn's Disease Clinical Characteristics

A summary of Crohn's Disease Clinical Characteristics taken at baseline or screening will be provided. A listing will also be provided.

Parameter	Units/Response category
Time since diagnosis of Crohn's disease	Years
Time Since Diagnosis categories	≤ 5years; >5 to <=15 years; > 15 years
Extent of disease	Ileal, Colonic, Ileocolonic
Baseline CDAI score	Points
Baseline CDAI score categories	≤300 points, >300 points
Baseline Abdominal Mass	None, Questionable, Definite
Baseline average daily Abdominal Pain	None, Mild, Moderate, Severe
Baseline average daily liquid or very soft Stool Frequency	Stools
Baseline average daily total Stool Frequency	Stools
Baseline SES-CD score	Points
Upper GI Crohn's	Yes, No
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Prior Crohn's Disease Therapy Characteristics

A summary of Prior Crohn's Disease Therapy Characteristics will be provided. A listing will also be provided.

Parameter	Units/Response category
Prior biologic failure	Yes, No
Prior biologic experience	Failed, Naïve, Experienced but no documented failure

Number of prior biologics failed	0, 1, 2, ≥3
Biologic classes failed	0, 1, 2, 3
Primary Non-responder to at least 1 Biologic	Yes, No
Secondary Non-responder to at least 1 Biologic	Yes, No
Intolerant to at least 1 Biologic	Yes, No
Oral corticosteroid use at enrollment	Yes, No
History of steroid non-response	Yes, No
History of steroid dependence	Yes, No
History of steroid dependence or non-response	Yes, No
Prior immunomodulator use	Yes, No
Prior immunomodulator non-response or intolerance	Yes, No
Prior aminosalicylate use	Yes, No
Aminosalicylate use at baseline	Yes, No
Prior aminosalicylate non-response	Yes, No
Prior Jak-inhibitor use	Yes, No

Complications of Crohn's Disease at Baseline

A summary of complications at Baseline will be provided. A listing will also be provided.

A summary of complications of Crohn's Disease at Baseline will be provided, the number and percentage of subjects with each complication collected on the Crohn's Disease History page will be presented. A listing will also be provided.

Fistula Drainage at Baseline

A summary of Fistula Drainage at Baseline will be provided. A listing of Fistula drainage over time will also be provided.

Parameter	**Units/Response category**
Fistula	Yes, No
Location	Small Intestine to Small Intestine, Small Intestine to Colon, Small Intestine to Bladder, Small Intestine to Skin On Abdominal Wall, Colon to Skin on Abdominal Wall, Small Intestine to Vagina, Colon to Vagina, Colon or Rectum to Skin in Pelvic Area, Small Intestine to Skin in Pelvic Area, Other
Active Drainage	Yes, No

3.2.3. Protocol Deviations

Unique subjects reporting major protocol deviations that have significant impact on primary efficacy analyses (major analysis protocol deviations) will be summarized overall and by treatment group for the ITT set.

[redacted]

[redacted]

A subject listing with all protocol deviations identified prior to database lock will be provided. Moreover, a listing of all major analysis protocol deviations will be provided. All subject listings will be based on the randomized analysis set.

A summary and listing of COVID-19 protocol deviations will also be presented, along with a listing of COVID-19 impacts.

3.2.4. Medical History

Medical history data will be coded using the Medical Dictionary for Regulatory Activities, version 23.0 or later. The number and percentage of subjects with medical history coded to each system organ class and preferred term will be summarized by treatment group for the safety analysis set.

3.2.5. 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 non-study 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 not be included in summaries but will be included in the listing of concomitant medications, with a flag.

Recorded prior and concomitant medication names from the Prior and Concomitant Medications eCRF page will be mapped according to the [redacted]

Prior and concomitant medication use will be tabulated separately. The number and percentage of subjects who have taken each medication will be provided by study treatment.

On-going Crohn's Disease Medications of Interest at Baseline will also be presented. Crohn's Disease Medications of Interest include aminosalicylates, corticosteroids and antibiotics for Crohns Disease. Should a subject enter the study on prohibited biologics and immunomodulators these medications will also be presented.

On-treatment rescue medication use will be summarized. Rescue medications are defined as the following medications if used to treat CD or AE of worsening CD:

- Addition of oral corticosteroids, aminosalicylates or antibiotics
- Increase in oral corticosteroids dose up to or above baseline
- Prohibited medications

3.3. Primary Endpoint(s) Analysis

3.3.1. Definition of Primary Endpoint(s)

The primary efficacy endpoint is defined as the change from baseline in CDAI score at Week 12.

3.3.2. CDAI Score

CDAI score is calculated as sum of a Subscore x Multiplier from Appendix 5.2. The following subscores are calculated based on the most recent evaluable 7 days.

- Number of liquid or very soft stools subscore
- Average Abdominal pain subscore
- General well-being subscore

Evaluable days are defined as any non-missing diary days during the 10 days prior to the study visit. The day prior to endoscopy, day of endoscopy and the day following endoscopy will be treated as non-evaluable and treated as missing.

If fewer than 5 evaluable days data are available for any of the above subscores then the subscore is set to missing for that timepoint. If only 5 or 6 evaluable days' data are available for the above mentioned subscores then the subscore total is calculated as:

(Total score over available days/Number of available days)*7

The weight component of the CDAI will be based on ideal weight (see Section 5.3.1.4).

The CDAI score should be calculated for a visit only if ≥ 4 subscores are available at a visit, with missing subscores imputed by carrying forward the last non-missing subscore. If <4 subscores are available at a visit then the CDAI score will be set to missing.

3.3.3. Statistical Hypotheses

The primary estimate of interest, change from baseline in CDAI score at Week 12, is used to evaluate the effectiveness of therapy relative to the placebo comparator in the mITT population.

The following hypothesis testing schema will be employed to assess the primary endpoint: The null hypothesis for the treatment comparison will be that there is no difference between the mean responses at a given dose level of 1473 (active) and the mean response on the placebo treatment in change from baseline CDAI score at Week 12. The alternative hypothesis will be that there is a difference. Symbolically, this is expressed as follows:

$$H_0 : \mu_{Active} = \mu_{\text{placebo}}$$
$$H_1 : \mu_{Active} \neq \mu_{\text{placebo}}$$

In order to control for the comparison of 2 active treatment groups versus placebo for the primary endpoint, a multiplicity procedure is planned.

Only the primary endpoint is covered under multiplicity control and all other endpoints will be presented with nominal p-values.

A step-up Hochberg procedure will be used. The resulting nominal p-values for the primary endpoint will be ordered, largest to smallest.

If the largest p-value < 0.05, then both treatment groups will be declared as statistically significant.

If the largest p-value is > 0.05, then the smaller p-value will be compared to 0.025. If this p-value is < 0.025, then the treatment group with the smaller p-value will be declared as statistically significant.

If no p-values meet the above conditions, the primary endpoint will be considered not statistically significant and the primary objective of the study was not met.

3.3.4. Primary Efficacy Analyses

3.3.4.1. Primary Estimand

The primary estimand uses a treatment policy strategy that considers the efficacy response in subjects regardless of use of rescue medication.

Population:

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

Variable:

Change from baseline in CDAI score at Week 12. Subjects with any of the following intercurrent events (ICE) prior to Week 12 will have data analyzed as collected following ICE under Treatment Policy approach.

Intercurrent events:

The following are the intercurrent events considered for this study:

Treatment Failure ICE:

1. Prohibited medication for AE of worsening CD (Section 5.7)
2. Any gastrointestinal resection
3. Increase in dose of oral corticosteroids for CD above baseline dose

4. Initiation of oral corticosteroids or aminosalicylates for CD where they were not ongoing at baseline
5. Discontinued study intervention due to AE of worsening CD or lack of clinical benefit

Other ICE:

6. Discontinued study intervention due to COVID-19
7. Discontinued study intervention for reasons other than COVID-19, AE of worsening CD or lack of clinical benefit
8. No attempt to taper steroids from Week 8

Population-level summary:

The mean difference in change from baseline CDAI score at Week 12 between each TD-1473 group and placebo.

3.3.4.2. Analysis Methods

The primary endpoint of CDAI score change from baseline at Week 12 will be analyzed based on the Primary Estimand by fitting a mixed effects repeated measures model using the change from baseline values at Weeks 4, 8, and 12 as the dependent variable. The model will include baseline CDAI score as a covariate and independent fixed effects for treatment group and prior biologics failure status (yes, no). The time effect of visit, the interaction of baseline CDAI score with visit and treatment with visit will also be included. Within-subject correlation will be modelled using an unstructured covariance structure. The Kenward and Roger method for approximating the denominator degrees of freedom will be used.

Summaries will be on the mITT population and include observed values, change from baseline values and least square (LS) means estimates. For testing of the primary endpoint, each TD-1473 dose versus placebo will be compared by displaying the LS mean difference estimate to placebo and associated 95% confidence interval. Nominal p-values will also be reported.

A CDAI score figure will also be presented with the LS mean change from baseline in CDAI score over time to Week 12 displayed. A placebo-adjusted figure will be also be provided displaying the LS mean difference to placebo in CDAI score over time to Week 12.

A 2-group forest plot will summarize the LS mean difference from placebo in CDAI at Week 12 with 95% confidence interval. The forest plot will also display the differences from placebo for Supplementary Estimand 1 (Section 3.3.6.1) and Supplementary Estimand 2 (Section 3.3.6.2).

Graphical inspection of the model assumptions on the primary analysis will be performed and will include inspection of linearity of regression, equal variances and the independence and normality of errors. In the event that the assumptions are not met then p-values will be generated from the nonparametric randomization-based analysis of covariance methodology of Koch et al. (1998).

3.3.4.3. Missing Data Handling

Missing data (including data missing due to COVID-19) will be assumed missing at random (MAR) and accounted for through correlation of repeated measures.

3.3.5. Sensitivity Analyses

3.3.5.1. Sensitivity Analyses 1

To assess the impact of the MAR assumption on missing data a sensitivity analysis be performed assuming data is missing completely at random (MCAR) and not imputed. An analysis of covariance (ANCOVA) on change from baseline in CDAI score at Week 12 will be performed fitting an equal-slopes model with terms for prior biologics failure status, baseline CDAI score, and treatment.

3.3.5.2. Sensitivity Analyses 2

To assess the sensitivity of the treatment effect to the stool frequency component of the CDAI score, the primary analysis will be repeated where the CDAI score is calculated without the stool frequency component.

3.3.6. Supplementary Analyses

3.3.6.1. Supplementary Estimand 1

This estimand will follow a composite strategy and has the same components as the Primary Estimand except for the handling of the intercurrent events. Here subjects who have any intercurrent event under treatment failure (ICE 1-5) will have their change from baseline set equal to zero following the ICE. Subjects experiencing intercurrent events (6, 7 and 8) will have their data following the intercurrent event set to missing.

Analysis will follow the same methodology to the primary estimand with missing data after the adjustment for intercurrent events assumed to be MAR.

3.3.6.2. Supplementary Estimand 2

This estimand has the same variable, intercurrent events and population level summary as the primary estimand; however, this estimand has a different population and is defined as below.

Population:

Subjects who reach the Week 12 visit without any major protocol deviations and who enter the study with moderately-to-severely active CD [as defined by a CDAI score of 220-450 and SES-CD score of ≥ 6 (≥ 4 if isolated ileal disease) with ulceration (corresponding to a score of 1) in at least 1 of the 5 ileocolonic segments on the Presence of Ulcers subscore of the SES-CD] who are corticosteroid-dependent or have demonstrated inadequate response or intolerance to conventional therapy (aminosalicylates, corticosteroids and immunomodulators such as azathioprine, 6-mercaptopurine, or methotrexate) or biologics (e.g., anti-TNF therapy, anti-IL-12/23, anti-integrin). A subset of subjects (up to approximately 10%) will have an SES-CD score between 3 and 5 points, inclusive.

Analysis:

An ANCOVA model incorporating the change from baseline in CDAI score at Week 12 as the dependent variable in the model will be used to assess this supplementary estimand.

The model will include independent fixed-effect class terms for treatment group, prior biologic failure status (yes, no) and baseline CDAI score as a covariate.

3.3.6.3. Subgroup Analysis

To characterize the consistency of the treatment effect for the primary and supplementary estimands, the primary endpoint analysis will be repeated for each examination group specified below.

The subgroups will be analyzed with the inclusion of a 3-way interaction term treatment*visit*subgroup category into the primary analysis model. The exceptions are, (1) baseline CDAI category (≤ 300, > 300) where along with the inclusion of the of a 3-way interaction term treatment*visit*[baseline CDAI category (≤ 300, > 300)], the baseline continuous CDAI score is replaced in the primary analysis model with the baseline CDAI category and (2) subgroups listed (2-5) below where prior biologic failure in the model is replaced with the subgroup along with the addition of the 3 way interaction term.

The following subgroups at baseline are pre-defined:

1. Biologic Failure Status: [a] Yes, [b] No

(definition see section 5.3.1.7)

2. Biologics experience categories: [a] Failed, [b] naïve, [c] bio-experienced [but not failed]
3. Number of prior biologics failed [a] 0 [b] 1 [c] 2 [d] >=3
4. Number of biologic mechanism of actions failed [a]0 [b] 1 [c] 2 [d] 3
5. Intolerant to at least one biologic: [a] Yes, [b] No
6. Baseline CDAI category: [a] ≤ 300 pts, [b] > 300 pts
7. Tobacco use Status: [a] no use, [b] prior use, [c] current use
8. Extent of disease: [a] Ileal, [b] Colonic, [c] Ileocolonic
9. Age: [a] ≤ 40 years, [b] > 40 years
10. Duration of disease: [a] ≤ 5 years, [b] > 5 to ≤ 15 years, [c] > 15 years
11. Age at diagnosis: [a] ≤ median, [b] > median
12. Baseline Fistula: [a] Yes, [b] No

[redacted]

[redacted]

15. Baseline SES-CD score: [a] ≤ median, [b] > median
16. Presence of extra-intestinal manifestations at baseline: [a] Yes, [b] No

17. Corticosteroid-use at baseline: [a] Yes, [b] No
18. Refractory or intolerant to 6-MP/AZA: (yes, no)
19. Refractory or dependent to oral or IV corticosteroids: (yes, no)
20. Refactory, intolerant or dependent to to 6-MP/AZA OR corticosteroids: [a] yes to both, [b] No to 6-MP/AZA and yes to steroids, [c] yes to 6-MP/AZA and no to steroids, [d] No to both
21. History of intestinal resection: [a] Yes, [b] No
22. Geographic Region: [a] North America [b] Eastern Europe [c] Europe (excluding Eastern Europe)[d] Other;

3.3.6.4. CDAI Component Analysis

Descriptive summaries of each individual CDAI component will be presented by treatment group and visit over time. Summaries will be presented as follows:

- Change from baseline by visit in:
    - Average daily liquid or very soft stools over last 7 evaluable days
    - Haematocrit
    - Percent deviation from ideal body weight
- Shift tables of change from baseline in:
    - Average daily abdominal pain over last 7 evaluable days
    - Average general well-being over last 7 evaluable days
    - Abdominal mass
- Number and percentage of subjects by visit with:
    - [redacted]
    - Requiring anti-diarrheal medication in last 7 days

3.3.6.5. Liquid or very soft stool definition analysis

The primary endpoint analysis will be repeated with the definition of liquid and very soft updated to include Type 5 stools from the Bristol Stool Scale (Perez et al, 2009).

3.3.6.6. CDAI Completeness and Intercurrent Event Summaries

Summaries of the completeness of CDAI subscores at Week 12 will be performed where the number of subjects missing 1, 2, 3, 4 or >=5 subscores will be presented. For subjects with >=5 subscores missing the summary will be further broken down by those who discontinue prior to Week 12 and those who missed the Week 12 visit.

The number of subjects who experience an intercurrent event prior to Week 12 and those who don't will also be presented for the subset of subjects with at least five CDAI component missing at Week 12.

An analysis of all subjects who experience an intercurrent event will also be performed where the number of subjects overall who experience an ICE and the number who experience each specific ICE criteria will be presented.

3.4. Secondary Endpoint(s) Analyses

3.4.1. Secondary Endpoint(s)

The secondary endpoints are:

- CDAI clinical response (defined as reduction from baseline of ≥ 100 points or CDAI < 150) at Week 12
- CDAI clinical remission (defined as CDAI < 150) at Week 12
- SES-CD change from baseline at Week 12
- Endoscopic response (SES-CD reduction of ≥ 50% from baseline or SES-CD ≤ 4, a reduction of ≥ 2 from baseline, and no subscore ≥ 2) at Week 12
- Stool Frequency and Abdominal Pain (SFAP) clinical remission defined as abdominal pain score ≤ 1 (on a scale of 0-3), stool frequency ≤ 2.8, and both not worse than baseline at Week 12

3.4.2. Statistical Hypotheses

There is no hypothesis testing of secondary endpoints.

3.4.3. Definition of Secondary Endpoint(s)

3.4.3.1. CDAI Clinical Response

CDAI score reduction from baseline of ≥ 100 or CDAI score < 150

3.4.3.2. CDAI Clinical Remission

CDAI score < 150

3.4.3.3. Simplified Endoscopy Score for Crohn's Disease (SES-CD)

The SES-CD incorporates 4 descriptors: the ulcer size, the proportion of surface covered by ulcer, the proportion of surface covered by other lesions, and the presence of stenosis. Each descriptor is graded from 0-3 as shown in Table 7 and is scored in 5 segments (ileum, right colon, transverse colon, left colon, and rectum). The total score is calculated as the sum of all the items in each segment and can range from 0 to 56. The SES-CD score will be performed by a central reader.

Table 7. SES-CD Scoring

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

To calculate the SES-CD score at a visit, the sum of the segments that were present at baseline will be used. For segments that were present at baseline but missing post-baseline, the baseline score for the missing segment(s) will be carried forward. In the event that a segment is missing at baseline but non-missing at post-baseline, the non-missing post-baseline score is not used in the calculation of SES-CD.

3.4.3.4. Endoscopic Response

Endoscopic response is met when a subject meets either of the following two criteria:

- SES-CD reduction from baseline of ≥ 50%
- SES-CD ≤ 4, a reduction of ≥ 2 from baseline, and no subscore ≥ 2

3.4.3.5. Stool Frequency and Abdominal Pain (SFAP) Clinical Remission

To achieve SFAP clinical remission a subject needs to have average daily abdominal pain score ≤1 (on a scale of 0 to 3), average daily stool frequency ≤ 2.8, and neither worse than baseline.

A subject's electronic diary records the total number of different stool types they pass each day as defined by the Bristol Stool Form Scale which classifies stools from Type 1 (hard lumps and hard to pass) to Type 7 (watery and entirely liquid). A subject's daily stool total is calculated for a given day by summing the total number of Type 1 to Type 7 stools entered by the subject in the electronic diary.

The average daily stool frequency is the mean of daily stool total from the stool diary over the most recent 7 evaluable days prior to endpoint visit. A minimum of 5 evaluable days data are required to calculate average score.

Abdominal pain (CDAI) score is derived as the mean of abdominal pain subscore from the CDAI questionnaire over the most recent 7 evaluable days prior to endpoint visit. The abdominal pain question scores pain on a scale of 0 (mild) to 3 (severe) and a minimum of 5 days evaluable data are required to calculate average score.

3.4.4. Secondary Efficacy Analyses

3.4.4.1. Estimands

The treatment policy strategy that was used for the primary estimand for the primary endpoint analysis will be used for change from baseline in SES-CD Score at Week 12.

The remaining secondary endpoints of response/remission will be analyzed through a composite strategy as follows:

- Population: Same as primary estimand
- Variable: Endpoints(Section 3.4.1) and Definition (3.4.3)
- Intercurrent Events: For this estimand, meeting the criteria of an ICE (1-5) is considered an unfavorable outcome and subjects who meet these criteria prior to Week 12 will be considered not to be in response/remission.

3.4.4.2. Analysis Methods

The proportion of subjects at Week 12 with CDAI clinical response, CDAI clinical remission, Endoscopic Response and SFAP clinical remission will be analyzed separately using a stratified Cochran-Mantel-Haenszel (CMH) test, stratifying by prior biologic status (yes, no) and CDAI baseline score category (≤ 300, >300) as determined from information in the clinical database. Summaries of the proportion of subjects in response/remission will be presented by treatment group, the adjusted treatment difference in proportions between each TD-1473 and placebo will also be presented along with associated 95% CIs calculated based on the Wald method. P-values from the CMH Chi-square test for the comparison of each dose of TD-1473 versus placebo will also be presented.

Separate 2-group forest plots for the difference in proportion of each secondary endpoint of response/remission versus placebo at Week 12 will display the CMH weighted difference in proportions and associated 95% CI.

Analysis of change from baseline in SES-CD at Week 12 will be performed using an ANCOVA model. The model will include independent fixed-effect class terms for treatment group, prior biologic failure status (yes, no) and CDAI baseline score category (≤ 300, >300) with baseline SES-CD as a covariate.

Summaries will be on the mITT population and include observed values, change from baseline values and least square (LS) means estimates. Each TD-1473 dose versus placebo will be compared by displaying the LS mean difference estimate to placebo and associated 95% confidence interval. Nominal p-values will also be reported.

A 3-group forest plot will summarize the LS mean change from baseline in SES-CD at Week 12 with 95% confidence interval.

3.4.4.3. Missing Data Handling

For change in SES-CD at Week 12, missing data will be assumed MCAR there will be no imputation of missing data.

For binary endpoints missing data will be imputed with non-responder imputation with the exception of data missing due to COVID-19, in these instances the data will be assumed missing completely at random and not analyzed.

3.4.5. Sensitivity Analyses

No sensitivity analysis will be performed for secondary endpoints.

3.4.6. Supplementary Analyses

All subgroup analyses outlined in section 3.3.6.3 will be performed on the secondary endpoints.

Descriptive summaries of change in each SES-CD segment at Week 12 will also be presented.

3.5. Multiplicity Adjustment

There will be no hypothesis testing of secondary endpoints. Adjustment of multiplicity on the primary endpoint is outlined in Section 3.3.3.

3.6. Exploratory Endpoint(s) Analyses

3.6.1. Exploratory Endpoint(s)

[redacted]

[redacted]

3.6.2. Definition of Exploratory Endpoint(s)

[redacted]

[redacted]

3.6.3. Exploratory Efficacy Analyses

[redacted]

3.6.4. Supplementary Analyses

3.6.4.1. Subgroup analysis

To characterize the consistency of the treatment effect for endoscopic remission each of the subgroups in Section 3.3.6.3 will be performed.

3.7. Safety Analyses

The analysis of safety and tolerability data includes an overall summary of tolerability, 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.

In general, inferential statistical tests are not performed for adverse event incidence rates.

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

For summaries on exposure, compliance and adverse events for the study overall (Induction and ATE),

3.7.1. Extent of Exposure

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

Duration of treatment will be displayed in weeks and calculated for the induction period as:

$$\frac{(last\ induction\ phase\ dose\ date\ -\ first\ dose\ date\ +\ 1)}{7}$$

*Last induction phase dose date is considered to be the Week 12 visit dose administration date for those that reach the Week 12 visit or equal to date of last study drug return for those who discontinue prior to Week 12 visit.

Duration of treatment for the entire study period will also be displayed in weeks and calculated as:

$$\frac{(last\ study\ drug\ return\ date\ -\ first\ dose\ date\ +\ 1)}{7}$$

Calculated values will be rounded to 1 significant digit in the analysis datasets and summary statistics will be presented to the follow significant digits:

- Mean, median, Q1, Q3: 1 significant digit
- Standard deviation: 2 significant digits
- Minimum, maximum: 1 significant digit

3.7.1.1. 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 in the induction period and the study overall 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.

3.7.2. Adverse Events

Adverse events (AEs) will be coded to the preferred terms (PT) of the Medical Dictionary for Regulatory Activities (MedDRA®). Summaries for induction period and for the complete study period will be presented separately and 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.

All summaries will be presented for both the Induction Period and the overall study period separately.

Treatment emergent adverse events are defined as follows for induction period and overall:

- Induction period TEAEs are events with a start date/time after the first dose date/time in Induction period up to the date/time of ATE Day 1 dose or date of last dose of study drug + 28 days, whichever is earlier.
- TEAEs for the whole study and listings are defined as AEs with onset on or after the first initiation of study drug up to the date of last dose study drug + 28 days.

Only treatment-emergent AEs will be summarized in the tables. Separate by-subject listings of all TEAEs and all non-TEAEs 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 Induction period and overall for subjects with:

- TESAEs by SOC and PT
- TEAEs leading to discontinuation of study drug by SOC and PT
- Drug related TEAEs by SOC and PT
- TEAEs by severity and by SOC and PT
- TEAEs resulting in death by PT

Listings of all AEs, SAEs, and AEs leading to premature study drug 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.

3.7.2.1. 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 antibiotics)
- 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 will be summarized overall and by AESI category and preferred term.

3.7.3. Additional Safety Assessments

3.7.3.1. Clinical Laboratory Parameters

Laboratory data, hematology, serum chemistry and urinalysis, will be summarized in terms of observed values and changes from baseline for Induction period and overall separately. 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.

Summaries for laboratory parameters of special interest will also be presented, these will include:

- Neutrophils
- Leukocytes
- Lymphocytes
- Hemoglobin
- Lipids [LDL cholesterol, HDL cholesterol, Cholesterol, and Triglyceride]
- Liver Function Test's [ALT, AST, Bilirubin]
- Creatinine
- Creatinine Kinase

A summary of maximum National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) toxicity grade (Appendix 5.8) for postbaseline laboratory values through Week 12 and ATE Week 48.

Listings will flag laboratory values that are outside of normal range.

A listing of all abnormal lab values will be provided. Listings of subjects with any abnormal postbaseline laboratory values of CTCAE grade ≥2 will also be provided.

3.7.3.2. Vital Signs

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

For each nominal time point, vital signs will be summarized in terms of observed values and changes from baseline. Marked abnormalities as defined in Table 8 will be flagged in the listing.

Table 8: 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

3.7.3.3. Electrocardiograms

Descriptive statistics for ECG parameters (heart rate, RR interval, 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 corrections.

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.

All recorded values by central reader at ECG core lab for the standard 12-lead electrocardiogram parameters will be presented in a by-subject listing.

Categorical Analyses

The number (percentage) of subjects with absolute ECG values and change from baseline in the ranges shown in Table 9 will be presented in Electrocardiogram Categorical Summary by Visit and 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.

Figures

Cumulative distribution plots will be provided for maximum change in QTcF at Week 8.

Investigator Assessment of ECG Readings

The investigators' assessment of ECGs as normal, abnormal and clinically significant, or abnormal but not clinically significant will be summarized for baseline and for each visit.

Table 9: 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	

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)
					> 480	
					> 500	
					Females:	
					≤ 450	
					> 450	
					> 470	
					> 480	
					> 500	

3.8. Other Analyses

3.8.1. Patient Reported Outcomes

[redacted]

total number with problems at baseline

[redacted]

3.9. Interim Analyses

The study will have an interim freeze to perform the primary analysis after the last subject reaches the Week 12 timepoint or discontinues prior to Week 12.

3.9.1. Maintenance of blind following interim analysis

Study team members with access to subject level during the interim analysis that reveals a subjects dose (i.e. 80mg or 200mg) during the ATE period cannot participate in study-related activities from that point on. Full details on maintenance of the blind and who has access to subject level data are detailed in the study unblinding plan.

3.9.2. Data Monitoring Committee

[redacted]

4. REFERENCES

Devine, B.J. (1974). Gentamicin therapy. *Drug Intelligence and Clinical Pharmacy* **8**:650-655.

[redacted]

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

5. SUPPORTING DOCUMENTATION

5.1. Changes to Protocol-Planned Analyses

5.2. CDAI Questionnaire

Subscore	Definition	Multiplier
Number of liquid or very soft stools	Number of liquid or very soft stools (7 day total) Note: Liquid or very soft stools are entered as Type 6 and Type 7 in the patient diary	x 2
Abdominal pain	Abdominal pain (7 day total) Daily scores calculated as (0=none, 1=mild, 2=moderate, 3=severe)	x 5
General well-being	General well-being (7 day total) Daily scores calculated as (0=generally well, 1=slightly under par, 2=poor, 3=very poor, 4=terrible)	x 7
Extra-intestinal maifestations	Arthritis/arthralgia (yes=1, no=0)	x 20
	Iritis/uveitis (yes=1, no=0)	x 20
	Erythema nodosum, pyoderma gangrenosum, aphthous stomatitis (yes=1, no=0)	x 20
	Anal fissure, fistula, or abscess (yes=1, no=0)	x 20
	Other fistula (yes=1, no=0)	x 20
	Fever over 37.8C (100F) during past 7 days (yes=1, no=0)	x 20
Any anti-diarrhea	Any anti-diarrhea medication in the last 7 days (yes=1, no=0)	x 30
Abdominal mass	Abdominal mass (None=0, Questionable=2, Definite=5)	x 10
Haematocrit (%)	If male, (47 – local hematocrit) [note: if negative impute with 0] If female, (42 – local hematocrit) [note: if negative impute with 0]	x 6

Body Weight	[(ideal weight – current weight) x 100]/ ideal weight [note: if < -10 impute with -10]	x 1
Final Score	Add totals:	

5.3. Data Conventions and Transformations

5.3.1. Derived and Transformed Data

5.3.1.1. 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.

5.3.1.2. 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.

5.3.1.3. BMI

BMI is calculated as:

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

5.3.1.4. Ideal Body Weight

Ideal body weight is calculated as follows (Devine 1974):

- 50 kg + 2.3 kg for each 2.54 cm (1 in) over 152.4 cm (5 ft), if male
- 45.5 kg + 2.3 kg for each 2.54 cm (1 in) over 152.4 cm (5 ft), if female

This is a conversion to metric units of the following simple rule:

- For women, allow 100 lb for the first 5 feet and 5 lb for each additional inch.
- For men, allow 110 lb for the first 5 feet and 5 lb for each additional inch.

5.3.1.5. Creatinine Clearance

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

$$\text{Estimated creatinine clearance (mL/min)} = \begin{cases} \dfrac{(140\text{-Age}) \times \text{Ideal Body Weight (kg)}}{72 \times \text{Serum Creatinine (mg/dL)}}, & \text{if male} \\ \dfrac{(140\text{-Age}) \times \text{Ideal Body Weight (kg)}}{72 \times \text{Serum Creatinine (mg/dL)}} \times 0.85, & \text{if female} \end{cases}$$

Creatinine clearance will also be estimated using actual body weight in the Cockcroft-Gault equation above. In tables, figures, and listings, estimates using actual body weight (ABW) will be labeled "Creatinine Clearance - ABW."

5.3.1.6. Time Since Crohn's Disease Diagnosis

Time since CD diagnosis (years) as of the first dose date is calculated as (diagnosis date - first dose date)/365.25. It is left unrounded for calculation of summary statistics but rounded to 1 decimal place for display.

5.3.1.7. Prior Biologic Failure

Subjects who have entered primary or secondary non-response and/or intolerance to a biologic treatment on the Prior Crohn's Disease Medications page are defined as failing prior biologic treatment. All other subjects regardless of receiving prior biologic treatment are not considered failures.

5.3.1.8. Prior Biologic Classes

Anti-tumor necrosis factor-alpha therapies:

- Adalimumab
- Certolizumab
- Infliximab

Anti-integrin therapy:

- Vedolizumab

Anti-interleukin-12 and interleukin-23 therapy

- Ustekinumab

5.3.1.9. Presence of extra-intestinal manifestations

Subjects who have any extra-intestinal manifestations ongoing at baseline as collected in the electronic tablet at site will be categorized as having a presence of extra-intestinal manifestations.

5.3.2. Missing Date Imputation

5.3.2.1. 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 or the initial treatment 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 or the initial dosing date if they have the same month and year, whichever is later.

5.3.2.2. 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 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 last day of the month or the study exit date if they have the same month and year, whichever is earlier.

5.3.2.3. 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".

5.3.3. 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, eg, 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"; Note:

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 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";

5.3.4. AE Severity

Instructions:

- AE severity should be provided through data cleaning process as much as possible. If AE severity is not available because a subject was lost to follow-up, sample text for the data imputation is provided below.

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

5.4. Adverse Event Start and End Date/Time Imputation Rules

Missing start date and times will be handled as follows:

- AE onset date completely missing:
    - If AE is not ongoing and AE onset date missing and AE end date missing, then impute AE onset as date/time of first dose.
    - Else if AE is not ongoing and AE onset date missing and AE end date not missing and date/time of first dose <= AE end date, then impute AE onset as date/time of first dose of study drug.
    - Else if AE is not ongoing and AE onset date missing and AE end date not missing and AE end date is BEFORE first dose of study drug, then impute AE onset as AE end date YEAR and MONTH with 01 as the day and 00:00 as time.

    - Else if AE IS ongoing and AE onset date missing, then impute AE onset as date/time of first study drug dose.

- AE onset date has year and month only:
    - If AE onset date has year and month only and they are the year and month of first dose of study drug, then impute AE onset as date/time of first dose:
    - Else if AE onset date has year and month only and date/time of first dose is not missing, then impute AE onset as AE onset year and month with 01 as the date and 00:00 as the time.

- AE onset date has year only:
    - If AE onset date has year only and it is year of first dose of study drug, then impute AE onset as date/time of first dose of study drug.
    - Else if AE onset date has year only and date of first study drug dose is not missing and year of AE onset is NOT the year of first dose of study drug, then impute AE onset as Jan. 1 of the AE onset year and 00:00 as the time.

- AE onset missing (where it was not handled by the above cases):
    - If AE onset date is missing, then impute AE onset as date/time of first study drug dose.

- AE onset has complete date but missing time:
    - If AE onset date is a date only and is same as date of first study drug dose, then impute AE onset as date/time of first study drug dose:
    - Else if AE onset date is a date only and is NOT = date of first study drug dose, then impute AE onset as AE onset date with 00:00 as the time:

Missing end date and times will be handled as follows:

- AE end date - completely missing:
    - If AE if not ongoing and both AE onset and AE end dates are missing, then impute AE end date as date/time of last study drug dose.
    - Else if AE is not ongoing and AE onset date not missing and AE end date missing AND AE onset date <= date/time of last dose, then impute AE end date as date/time of last study drug dose.
    - Else if AE is not ongoing and AE onset date is not missing and AE end date is missing and date of last dose is not missing and AE onset is AFTER date of last dose, then impute AE end date as the last day of the month of AE onset date, with 23:59 as time.

- AE end date = year and month only:
    - If AE is NOT ongoing and AE end date consists of year and month only, then impute AE end date as the last day of the month of AE end date month and year, with 23:59 as time.

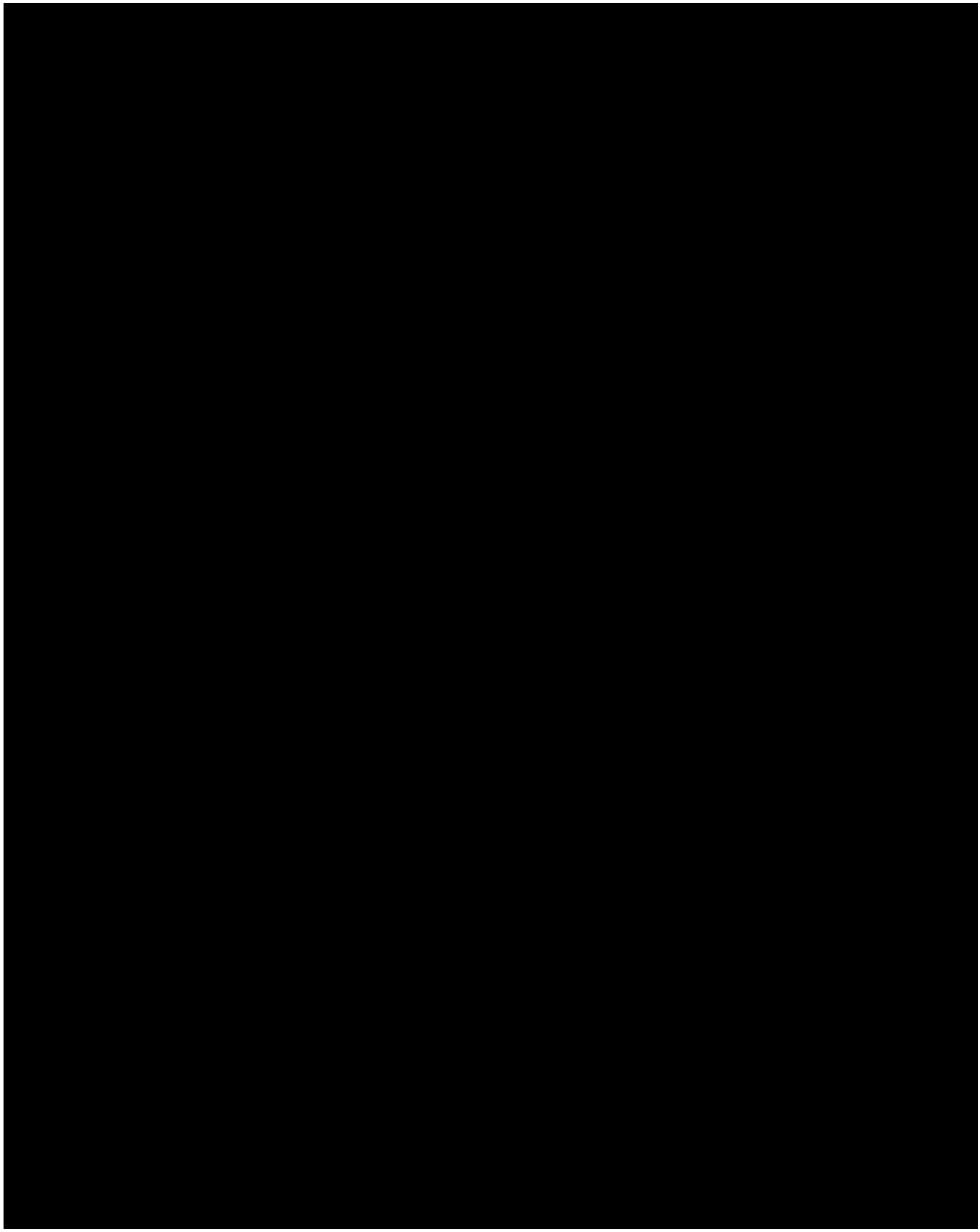
- AE end date = year only:

- If AE is NOT ongoing and AE end date consists of a year only, and year = year of AE onset and AE onset date <= date of last study drug dose, then impute AE end date as the date of last study drug dose.
- Else if AE is NOT ongoing and AE end date consists of a year only, and year = year of AE onset and AE onset date > date of last study drug dose, then impute AE end date as the year and month of AE onset, with the last day of the month as the day, and 23:59 as the time.

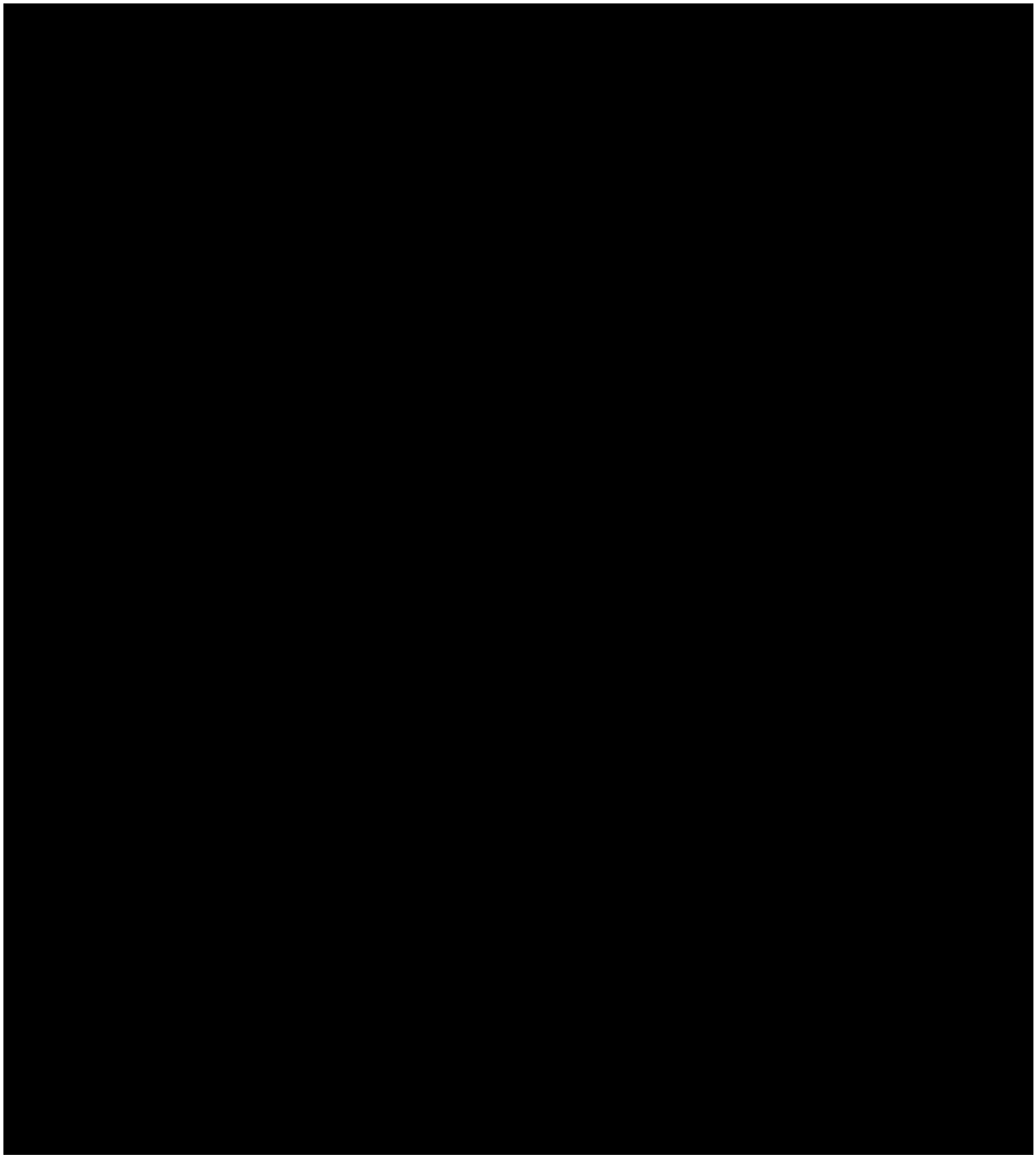
- AE end date = complete date but no time:

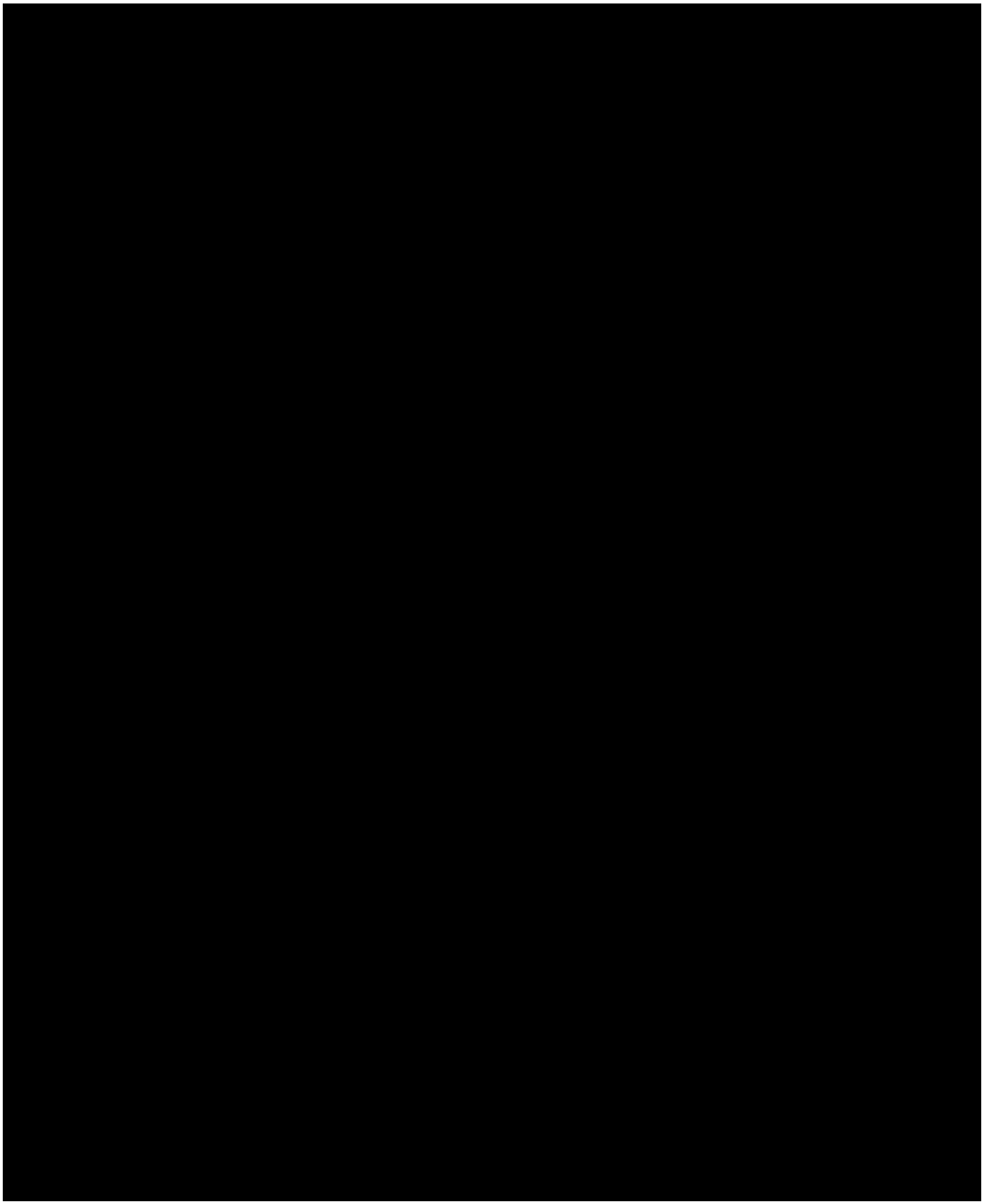
If AE is NOT ongoing and AE end date consists of a complete date but no time, then impute AE end date = trim(AE end date) || "T23:59".

[redacted]



[redacted]





[redacted]

[redacted]

5.8. CTCAE Grading

Grading Criteria for Clinical Laboratory Tests [CTCAE Version 5.0]					
Hematology Tests		**Criteria**			
Test	**Direction**	**1**	**2**	**3**	**4**
Hemoglobin (g/L)	Decrease	≥100 - <LLN	≥80 - <100.0	<80	
Leukocytes (WBC) (10^9/L)	Decrease	≥3.0 - <LLN	≥2.0 - <3.0	≥1.0 - <2.0	<1.0
Lymphocytes (10^9/L)	Decrease	≥0.8 - <LLN	≥0.5 - <0.8	≥0.2 - <0.5	<0.2
Neutrophils (10^9/L)	Decrease	≥1.5 - <LLN	≥1.0 - <1.5	≥0.5 - <1.0	<0.5
Platelets (10^9/L)	Decrease	≥75.0 - <LLN	≥50.0 - <75.0	≥25.0 - <50.0	<25.0
Chemistry Tests		**Criteria**			
Test	**Direction**	**1**	**2**	**3**	**4**
ALT	Increase	>ULN - ≤3.0 Xuan if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 xULN - ≤5.0 xULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 xULN - ≤20.0 xULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 xULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Albumin (g/L)	Decrease	≥30 - <LLN	≥20 - <30	<20	
Alkaline Phosphatase	Increase	>ULN - ≤2.5 xULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 xULN - ≤5.0 xULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 xULN - ≤20.0 xULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 xULN if baseline was normal; >20.0 x baseline if baseline was abnormal

AST	Increase	>ULN - ≤3.0 xULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 xULN - ≤5.0 xULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 xULN - ≤20.0 xULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 xULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Bilirubin	Increase	>ULN - ≤1.5 xULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 xULN - ≤3.0 xULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	>3.0 xULN - ≤10.0 xULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	>10.0 xULN if baseline was normal; >10.0 x baseline if baseline was abnormal
Calcium (mmol/L)	Increase	>ULN - ≤2.9	>2.9 - ≤3.1	>3.1 - ≤3.4	>3.4
Calcium (mmol/L)	Decrease	[Albumin ≥40 g/L or missing and calcium ≥2.0 - <LLN]; or [Albumin < 40 g/L and (calcium – 0.8 x (albumin – 40)) ≥2.0 - <LLN]	[Albumin ≥40 g/L or missing and calcium ≥1.75 - <2.0]; or [Albumin < 40 g/L and (calcium – 0.8 x (albumin – 40)) ≥1.75 - <2.0]	[Albumin ≥40 g/L or missing and calcium ≥1.5 - <1.75]; or [Albumin < 40 g/L and (calcium – 0.8 x (albumin – 40)) ≥1.5 - <1.75]	[Albumin ≥40 g/L or missing and calcium <1.5]; or [Albumin < 40 g/L and (calcium – 0.8 x (albumin – 40)) <1.5]
Creatinine	Increase	>ULN - ≤1.5 xULN	>1.5 xULN - ≤3.0 xULN	>3.0 xULN - ≤6.0 xULN	>6.0 xULN
GGT	Increase	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Phosphate (mmol/L)	Decrease	≥0.8 - <LLN	≥0.6 - <0.8	≥0.3 - <0.6	<0.3
Potassium (mmol/L)	Increase	>ULN - ≤5.5	>5.5 - ≤6.0	>6.0 - ≤7.0	>7.0
Potassium (mmol/L)	Decrease	≥3.0 - <LLN		≥2.5 - <3.0	<2.5
Sodium (mmol/L)	Increase	>ULN - ≤150	>150 - ≤155	>155 - ≤160	>160
Sodium (mmol/L)	Decrease	≥130 - <LLN		125-129 mmol/L symptomatic; 120-	<120

				124 mmol/L regardless of symptoms	