Protocol Number: 0157

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

NCT Number: NCT03758443

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Induction Phase - 01 July 2021
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STATISTICAL ANALYSIS PLAN

Protocol Title:	**A Phase 2b/3 Multi-Center, Randomized, Double-Blind, Multi-Dose, Placebo-Controlled, Parallel-Group Set of Studies to Evaluate the Efficacy and Safety of Induction and Maintenance Therapy with TD-1473 in Subjects with Moderately-to-Severely Active Ulcerative Colitis**
Protocol Number:	**0157**
Compound Number:	**TD-1473**
Short Title:	**Rhea: Efficacy and Safety of TD-1473 in Ulcerative Colitis**
Sponsor Name:	**Theravance Biopharma Ireland Limited**
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LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

Abbreviation	Term
AE	Adverse Event
ALT	Alanine Aminotransferase
aMS	Adapted Mayo Score
ANCOVA	Analysis Of Covariance
ANOVA	Analysis Of Variance
C	Continuous Reporting Format
CMH	Cochran Mantel-Haenszel
CRF	Case Report Form
[redacted]	[redacted]
CSR	Clinical Study Report
DOB	Date Of Birth
dy	Days
[redacted]	[redacted]
F	Frequency Reporting Format
G	Geometric Mean Reporting Format
GCP	Good Clinical Practices
[redacted]	[redacted]
IRB	Institutional Review Board
ITT	Intent-To-Treat Population
KM	Kaplan-Meier
LLN	Lower Limit Of Normal
LOCF	Last Observation Carried Forward
LS	Least Square
LSM	Least Square Mean
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
OTC	Over The Counter Medication
PGA	Physician Global Assessment
PLSM	Poisson Least Square Mean
pMS	Partial Mayo Score
PP	Per-Protocol Population
PRO2	PRO 2 Score
[redacted]	[redacted]
SD	Standard Deviation
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
tMS	Total Mayo Score
UC	Ulcerative Colitis
ULN	Upper Limit Of Normal

VAS	Visual Analogue Scale
WBC	White Blood Cell Count
WHO	World Health Organization
[redacted]	[redacted]
yr	Years

1. INTRODUCTION

This document outlines the plan for the summarization and analysis of clinical data collected in the Phase 2b Induction Study of Protocol 0157 for TD-1473.

Protocol 0157 comprises 3 separate studies within a single protocol. The purpose of multiple studies within a single protocol is to increase operational efficiency and reduce operational costs.

The analyses and summarization of clinical data is divided into 3 separate SAPs corresponding to the separate studies within the protocol:

- Phase 2b Dose-Finding Induction SAP (this document)
- Phase 3 Dose-Confirming Induction SAP
- Phase 3 Maintenance SAP

Each study set of analyses will control Type I error < 0.05. As such, study analyses (Phase 2b Induction Study, Phase 3 Induction Study, Phase 3 Maintenance Study) are considered independent and no control of multiplicity will occur across the 3 sets of analyses.

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 clinical study report (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 Phase 2b Dose-Finding Induction is:

- Assess the effect of TD-1473 taken once daily for 8 weeks at doses of 20 mg, 80 mg, and 200 mg on the change from baseline in the total Mayo score

1.1.2. Key Secondary Objective

- Assess the effect of TD-1473 on rates of clinical remission at Week 8

1.1.3. Additional/Exploratory Objectives

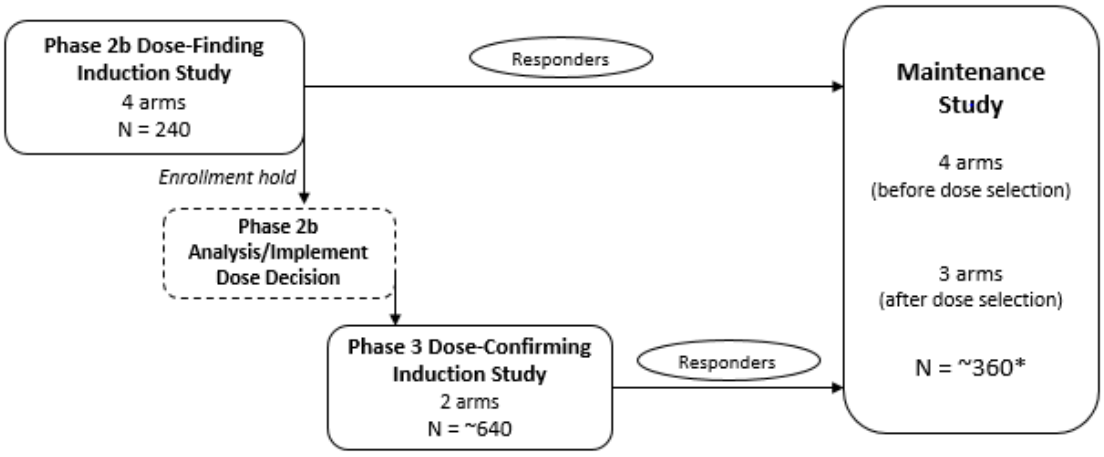
[redacted]

1.2. Study Design

1.2.1. Summary of Study Design

This single protocol includes three studies: a Phase 2b dose-finding Induction Study, a Phase 3 dose-confirming Induction Study, and a Phase 3 randomized-withdrawal Maintenance Study (Figure 1).

Figure 1: Protocol Schema



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

Each of the three studies will utilize a multi-center, randomized, double-blind, placebo-controlled, parallel-group design to evaluate various doses of TD-1473 compared to placebo in subjects with moderately-to-severely active ulcerative colitis (UC).

The Induction Studies will target subjects with moderately-to-severely active UC who demonstrate an inadequate response or failure to tolerate conventional or biologic therapy.

The Maintenance Study will be a randomized withdrawal study targeting subjects with moderately-to severely-active UC who demonstrate a clinical response to induction treatment with TD-1473.

Phase 2b Dosing-Finding Induction Study:

To determine initial eligibility, subjects will undergo assessments during the Screening Stage 1 period. Disease activity will be assessed by the total, adapted, and partial Mayo scores and PRO2 score. Subjects who meet inclusion and no exclusion criteria will undergo an endoscopic exam (i.e., sigmoidoscopy or colonoscopy) with biopsies to complete screening Stage 2. If the subject meets all eligibility criteria, including a Mayo endoscopic subscore ≥ 2 from central review of the Screening Stage 2 endoscopy and an adapted Mayo score between 4 and 9, inclusive, on Day 1, the subject may be randomized.

The randomization will be stratified by prior biologic failure status and corticosteroid use at enrollment into the Induction Study. Biologic failure is defined as having demonstrated primary or secondary non-response or intolerance to one or more biologics (i.e., anti-TNF-therapy, anti-integrin, or anti-IL-12/23).

The Induction Study will consist of treatment for

a. 8 weeks for those who demonstrate clinical response by adapted Mayo Score at Week 8, and,

b. 16 weeks for those who do not demonstrate a clinical response by adapted Mayo score at Week 8,

Subjects who do not demonstrate clinical response at Week 8 will receive an additional 8 weeks of treatment during an extended induction period as follows,

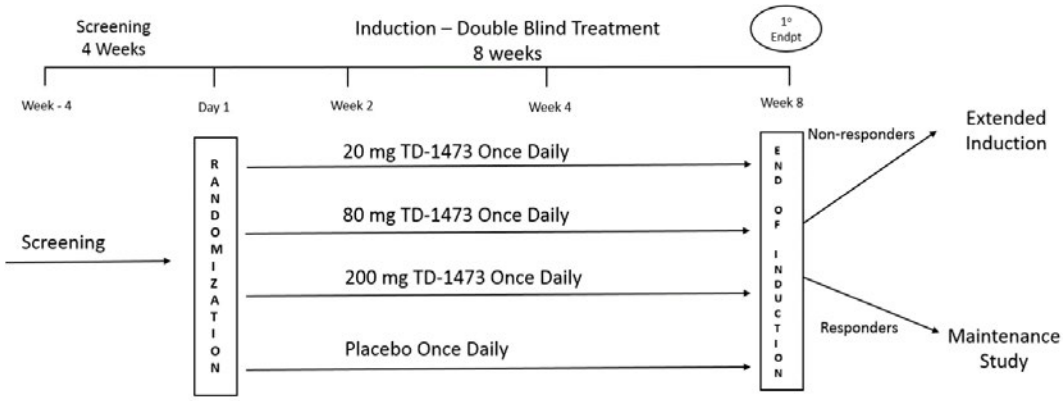
a. Subjects randomized to TD-1473 during the first 8 weeks will remain on the same dose of TD-1473;
b. Subjects who received placebo during the first 8 weeks will receive TD-1473 80 mg.

This portion of the Induction Study will not be placebo-controlled, but blinding as to the specific dose of TD-1473 will be maintained. Those who demonstrate clinical response at Week 16 will enter the Maintenance Study; those who do not exit the study.

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

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

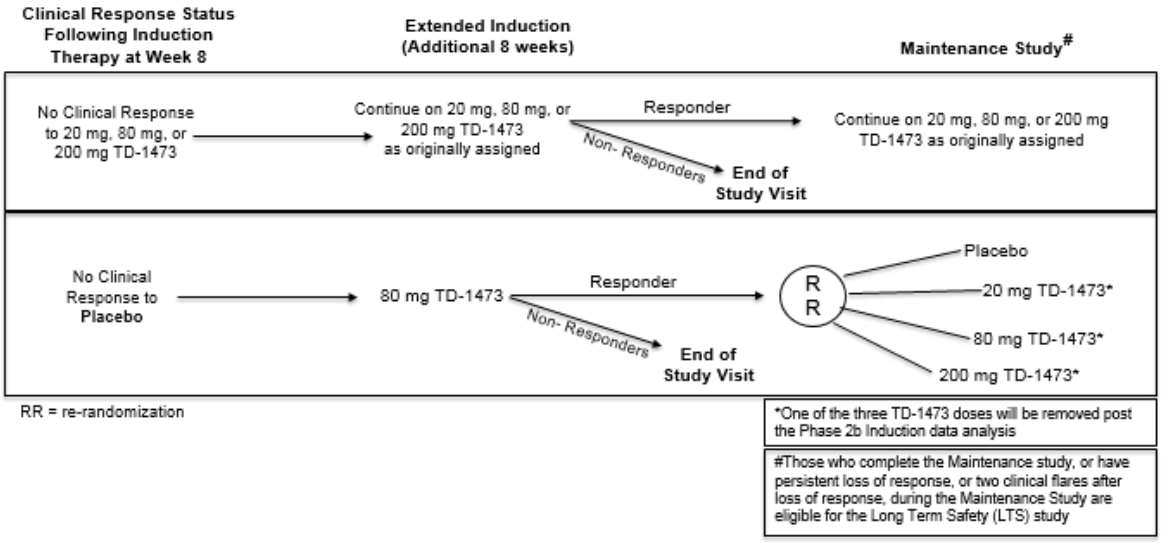
Figure 2: Phase 2b Dose-Finding Induction Study



Subjects who do not demonstrate clinical response by adapted Mayo score at Week 8 with active drug will receive an additional 8 weeks of treatment staying on the same dose of TD-1473 as the first 8 weeks, and those who had received placebo during the first 8 weeks will now receive TD-1473 at 80 mg (Figure 3).

All subjects who undergo extended induction treatment will receive active drug, and thus, this portion of the Induction Study will not be placebo-controlled, but blinding as to the specific dose of TD-1473 will be maintained. During this time, at the discretion of the investigator, subjects are permitted but are not required to begin corticosteroid taper. Those who demonstrate clinical response at Week 16 will enter the Maintenance Study; those who do not demonstrate clinical response at Week 16 will have an EOS visit and exit the study.

Figure 3: Extended Induction Treatment Regimen



1.2.2. Definition of Study Drugs

Study drug comprises the following (placebo and 3 doses of TD-1473):

- TD-1473 20 mg (2 x 10 mg tablets) once daily: Taken orally for up to 16 (including Extended Induction when applicable) weeks 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 16 (including Extended Induction when applicable) weeks 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 16 (including Extended Induction when applicable) weeks 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.
- Placebo once daily: Taken orally for up to 8 (Induction period only) weeks 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. Note: Subjects who do not respond on placebo during Induction Period will be switched to TD-1473 80 mg (2 x 40 mg tablets) once daily for the Extended Induction period.

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.

Subjects will be randomized at Day 1 to 1 of 4 treatment groups (placebo QD, TD-1473 20 mg QD, TD-1473 80 mg QD or TD-1473 200 mg QD) using permuted block randomization with

biologic failure status (yes/no) and corticosteroid use at baseline (yes/no) as stratification variables. Separate randomization lists will also be created for subjects enrolled in Asia and the rest of the world.

Randomization caps will be placed on both prior biologics failure subgroups (no to biologic failure (60%) and yes to biologic failure (60%)) to ensure that neither subgroup is overrepresented.

At Week 8, subjects who are in clinical response will exit the Induction Study and will be re-randomized into the Phase 3 Maintenance Study with the exception of placebo responders who will continue placebo in a blinded fashion during the Maintenance Study. Subjects who do not achieve clinical response at Week 8 will enter Extended Induction: those who received TD-1473 treatment during induction will continue their current randomized treatment for an additional 8 weeks. Placebo subjects who do not exhibit clinical response at Week 8 will receive TD-1473 80 mg for 8 weeks during Extended Induction).

Maintenance of the Blind

In order to maintain the blind in subjects whose treatment is known once database lock has occurred for the Phase 2b Induction 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 Week 44 analyses for the Maintenance 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 2: Schedule of Study Procedures – Induction and Extended Induction Studies

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

Table 2: Schedule of Study Procedures – Induction and Extended Induction Studies

Procedures	Screening Period		INDUCTION VISITS				EXTENDED INDUCTION VISITS[33]			Early Study Drug D/C[5]	End of Study (4 weeks post last study dose)
			Day 1	Week 2	Week 4	Week 8a [1]	Week 8b[2],[3]	Week 12 [2]	Week 16 [2][4]		
Study Day/Week	**Day -28 to – 1**										
	Stage 1	**Stage 2**									
Window				± 3 days	± 3 days	-3 to + 5 days	+ 1 to 7 days from week 8a visit[6]	-3 to + 5 days	-3 to + 7 days	+ 5 days	-3 to + 5 days
Plasma PK Samples [13]			X		X		X	X	X		
Overnight Fasting Lipid Panel	X[19]		X		X	X[29]		X	X	X	X
[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
Fecal Sample for stool infectious analysis[14]	X										
[redacted]			[redacted]			[redacted]			[redacted]	[redacted]	
[redacted] [16][19]	X										
Pregnancy Test (females of child-bearing potential only)[17]	X[19]		X	X	X		X	X	X	X	X
FSH[18] [19]	X										
Chemistry, Hematology	X[19]		X	X	X	X[29]		X	X	X	X
Urinalysis	X[19]		X			X[29]			X	X	X

Table 2: Schedule of Study Procedures – Induction and Extended Induction Studies

Procedures	**Screening Period**		**INDUCTION VISITS**				**EXTENDED INDUCTION VISITS[33]**			**Early Study Drug D/C[5]**	**End of Study** (4 weeks post last study dose)
			Day 1	**Week 2**	**Week 4**	**Week 8a [1]**	**Week 8b[2],[3]**	**Week 12 [2]**	**Week 16 [2][4]**		
Study Day/Week	**Day -28 to – 1**										
	Stage 1	**Stage 2**									
Window				± 3 days	± 3 days	-3 to + 5 days	+ 1 to 7 days from week 8a visit[6]	-3 to + 5 days	-3 to + 7 days	+ 5 days	-3 to + 5 days
Whole Blood and Serum Biomarker Samples	X		X		X	X[29]		X	X	X	X
Genetic Blood Sample *(optional – only collected for subjects who provide genetic testing consent)*			X								
Endoscopy and Biopsies		X [20]				X[21]			X[21]		
Concomitant Medication review [22]	X		X	X	X	X	X	X	X	X	X
Adverse Events Assessment [23]	X	X	X	X	X	X	X	X	X	X	X
Physician Global Assessment (PGA)	X[24]		X	X	X	X		X	X	X	X
Partial Mayo score		X									
Adapted Mayo score			X[31]			X[31]			X[31]		

Table 2: Schedule of Study Procedures – Induction and Extended Induction Studies

Procedures	Screening Period		INDUCTION VISITS				EXTENDED INDUCTION VISITS[33]			Early Study Drug D/C[5]	End of Study (4 weeks post last study dose)
			Day 1	Week 2	Week 4	Week 8a [1]	Week 8b[2],[3]	Week 12 [2]	Week 16 [2][4]		
Study Day/Week	**Day -28 to – 1**										
	Stage 1	**Stage 2**									
Window				± 3 days	± 3 days	-3 to + 5 days	+ 1 to 7 days from week 8a visit[6]	-3 to + 5 days	-3 to + 7 days	+ 5 days	-3 to + 5 days
Dispense Subject Diary[25]	X										
Subject Diary Completion and Compliance Review [26]		X	X	X	X	X	X	X	X	X	X
[redacted]			■			■			■	■	
[redacted]			■			■			■	■	
[redacted]			■			■			■	■	
[redacted]			■			■			■	■	
Randomization			X[27]								
Study Drug Dispensing			X	X	X		X				
In Clinic Dosing - Study Drug Dosing[28]			X		X		X		X		
Non-Site Study Procedures (Calculations for Programming/Statisticians and applicable suppliers)											
partial Mayo score and PRO2 scores calculation		X	X	X	X	X		X	X	X	X

Table 2: Schedule of Study Procedures – Induction and Extended Induction Studies

Procedures	Screening Period		INDUCTION VISITS				EXTENDED INDUCTION VISITS[33]			Early Study Drug D/C[5]	End of Study (4 weeks post last study dose)
			Day 1	Week 2	Week 4	Week 8a [1]	Week 8b[2],[3]	Week 12 [2]	Week 16 [2][4]		
Study Day/Week	**Day -28 to – 1**										
	Stage 1	**Stage 2**									
Window				± 3 days	± 3 days	-3 to + 5 days	+ 1 to 7 days from week 8a visit[6]	-3 to + 5 days	-3 to + 7 days	+ 5 days	-3 to + 5 days
adapted and total Mayo score calculations			X			X			X		

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

Induction Studies:

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

- **Week 8b** visit if subject **did not achieve clinical response**, or
- **Maintenance Week 0** (mWeek 0) if subject **achieved clinical response**

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

2. Week 8b, Week 12, and Week 16 visits pertain only to subjects who undergo extended induction (i.e., who do not demonstrate clinical response based on the adapted Mayo score from Week 8a visit)
3. Subject should be instructed not to take study drug from their Induction study drug bottles at home to allow for re-randomization and to receive the first dose of extended induction in the clinic.

4. Week 16 visit may be done over a period of 1 to 3 visits to complete: a) the Week 16 endoscopy, b) Week 16 clinical assessments (e.g., vital signs, weight, laboratory testing, and Quality-of-Life assessments), and c) an optional visit to bring subjects back (or could be done over the phone) to inform them that they should stop study drug and proceed to EOS visit if they did not achieve clinical response (those who achieve clinical response will proceed to mWeek 0 visit). The Week 16 clinical response will be determined using the adapted Mayo score utilizing the centrally read endoscopic subscore from the Week 16 endoscopy.
5. Early Study Drug Discontinuation visit is for subjects who prematurely discontinue the Study drug during the Induction Study. Visit to be conducted within 5 days of the last dose of Study drug, if possible. Subject will also return for the EOS visit for collection of safety data and assessment of disease activity four weeks after last study drug. An EOS visit will be required for all subjects 4 weeks following their last dose of study drug, regardless if they completed the full duration of study drug treatment.
6. Seven-day window provided to allow time to receive results from the central reading of endoscopy performed at Week 8a.
7. Blood pressure and heart rate will be measured after the subject has been resting for at least 5 minutes in the seated or supine position. Vital sign measurements should be obtained prior to scheduled blood draws.
8. Obtain blood pressure and heart rate pre-dose and approximately 1-hour post-dose on Day 1.
9. ECGs should be performed after the subject has been resting in a supine position for at least 10 minutes.
10. Physical Exam will be performed as per local standard practice.
11. A chest X-ray will be performed at screening to assess for signs of latent or active TB or other active viral, fungal or bacterial infections unless one has been performed within 90 days of screening, documented to be negative, and reviewed by investigator. Posterior anterior (PA) and lateral views (lateral view may not be necessary if PA view is deemed adequate by the investigator) will be obtained. Subjects who have had a chest X-ray or equivalent chest imaging within 90 days prior to screening will not require a repeat X-ray unless subject is deemed to be at high risk of recent pulmonary infection. If a chest X-ray is indicated, it may be performed anytime between Screening Stage 1 and Screening Stage 2 visits.
12. Subjects who have had a documented chest X-ray or equivalent chest imaging or TB testing within 90 days prior to Screening do not require a repeat X-ray or TB testing, respectively, unless subject is deemed by the investigator to be at high risk of recent pulmonary infection. Subjects with a history of latent TB should not have a TB test but must not live in a region with high prevalence of multidrug-resistant TB and have completed a well-accepted treatment regimen (e.g., a ≥ 9-month course of INH or equivalent therapy) within 5 years (3 years in countries where TB is endemic) prior to Screening, the documentation for which must be included in the source document. Subjects who had treated active TB must still have a TB test. Subjects who has a history of latent or active tuberculosis (TB) may be eligible for the Study if criteria outlined in protocol are met.
13. PK sampling will be performed in subjects at the following time points:

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

- **Week 12** (n= 1 sample): One sample to be collected **anytime between 0.5 to 6 hours post-doses**
- **Week 16** (n=2 samples): one **pre-dose** and one **post-dose** sample collected **anytime between 0.5 to 6 hours**. The Week 16 sample may be obtained -3 to + 7 days from the endoscopy visit

NOTE: Post-dose sampling times are defined relative to the time of Study drug administration on the day of collection. All PK sampling times will be accurately recorded by collection date, hour, and minute. Study drug dosing time on the day before each PK collection will also be accurately recorded by dosing date, hour, and minute by the subject; Study drug dosing time on the day of each PK collection will be accurately recorded by dosing date, hour, and minute by the Study staff.

14. For stool infectious analysis: Including C. difficile, other bacterial pathogens (including Shigella, Salmonella, Yersinia, E. coli O157, and Campylobacter), and ova and parasite. This can be done **any time after written consent and prior to Screening Stage 2 visit, and results reviewed before Screening Stage 2 visit**.
15. [redacted]
16. Serology testing: Subjects with positive hepatitis B core antibody will undergo testing for hepatitis B DNA and hepatitis B surface antibody during Screening. Subjects with known hepatitis C will also undergo testing for hepatitis C RNA viral load. Serologies do not need to be repeated during re-screening if results from the first screening were negative and within 90 days of re-screening.
17. B-hCG testing (serum for Screening and urine for all other visits) will be performed for females of childbearing potential to confirm absence of pregnancy. If urine b-hCG test is positive, confirm with serum b-hCG test.
18. Required for postmenopausal females.
19. Screening Labs including urinalysis may be obtained anytime during the 28-day window for Screening, but results must be available before Screening Stage 2 endoscopy with the exception of [redacted] and fasting lipid panel. ***NOTE:** Subjects **must not** be requested to come in fasting for study specific assessments prior to signing the informed consent. Exception: The overnight fasting lipid panel may be obtained on Day -28 if subjects are fasting as per institutions standard of care procedure, which must be clearly documented in the source documents.
20. Endoscopy with biopsies will be performed at the Screening Stage 2 visit after subject's eligibility from Screening Stage 1 is confirmed. This screening endoscopy must occur at **≥ 5 days before Day 1 to allow ≥ 3 days of symptom reporting for adapted Mayo score calculation on Day 1**. This Screening Stage 2 endoscopic subscore, determined by central reading, will be used to calculate any clinical score for Day 1 that requires the endoscopic subscore. The centrally read endoscopic subscore will be used for all endpoints and for eligibility criteria to enroll a subject into the Induction and Maintenance Studies. Local reading of the endoscopic subscore will also be collected. The aMS will be calculated by the electronic tablet at all applicable visits.
21. Centrally read endoscopic subscore from Week 8a visit will used to calculate adapted Mayo score to determine whether subject should undergo extended induction or continue into Maintenance Study depending on whether the subject meets criteria for clinical response at Week 8a. Centrally

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

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

23. AE assessments are to include collection and reporting of AEs, SAEs, and AEs of Special Interest (AESIs).

24. PGA from Screening Stage 1 visit will be used for the partial Mayo score calculation as a guide to assess if subject should proceed with endoscopy at Screening Stage 2 visit. It is suggested that subjects with a partial Mayo score ≥ 3 (reflecting disease that is **at least moderate in severity**) should proceed with endoscopy screening. This partial Mayo Score can be assessed at any time between Screening Stage 1 visit and Screening Stage 2 visit as long as there are **≥ 3 days of symptom reporting.** The pMS is calculated by the electronic tablet at the Screening Stage 2 visit page and it is recommended that this is completed before the subject proceeds with the Screening Stage 2 visit endoscopy.

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

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

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

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

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

30. [redacted]

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

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

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

1.5. Sample Size Determination

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

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

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

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

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

2. ANALYSIS SETS

Table 3: 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
Safety*	The Safety analysis set will include all subjects who received at least one dose of study drug (TD-1473 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 into the Phase 2b study.	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. The mITT set is the primary analysis set for efficacy summaries and analyses.	Randomized treatment
Modified ITT-16w*	The modified Intent-to-Treat for extended induction (mITT-16w) analysis set comprises all randomized into the Phase 2b study, who did not meet the criteria for clinical response by adapted Mayo score at Week 8, and, continued dosing during extended induction.	Randomized treatment
PP*	The Per-Protocol (PP) analysis set comprises all subjects in the mITT analysis set who complete their Week 8 visit and have no major analysis protocol deviations	Randomized treatment

- Due to confirmed data integrity violations the data for site 36044 (deviation report GCP-23) 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 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 predose.

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 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.

3.1.3. Visit Windows

All assessments (including unscheduled assessments) will be summarized using analysis windows. The exception is the End of Study 4 week follow up visit which will not be windowed.

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 4: Visit Analysis Windows

Nominal Visit	Nominal Day	Start (days)	Stop (days)
Screening	NA	-28	-1
Day 1	1	1	1
Week 2	14	7	21
Week 4	28	22	35
Week 8a/8b	56	46	Minimum of: • Day 71, or • 8 Week Induction period end date
Week 12	Extended Induction day 28	Extended Induction day 22	Extended Induction day 35
Week 16	Extended Induction day 56	Extended Induction day 46	Minimum of: • Extended Induction day 71, or • Extended Induction period end date

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

Unless stated otherwise the following are the definitions for Induction and Extended Induction treatment periods for analysis and summaries.

3.1.5.1. Induction Treatment Period

All data collected for each subject from first dose up until the earliest event between first dose at Week 8b, first dose at mWeek 0 or End of Treatment + 5 days will be presented.

3.1.5.2. Extended Induction Treatment Period

All data collected for each subject from first dose at Week 8b up until the End of Treatment + 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 (Induction, Extended Induction or overall) that the incorrect treatment was dispensed and returned.

Mean Dose	Actual Treatment
>0 mg and <=50 mg	20mg
>50 mg and <=140 mg	80mg
>140 mg	200mg

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

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. Where specified additional summaries on the mITT-16w will also be presented.

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 on all randomized subjects and mITT-16w analysis set separately 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 disposition summary will be provided on the ITT set for Induction period:

- Number of subjects who completed the Week 8a Visit
- Number of subjects who discontinued prior to the Week 8a Visit
  - Primary reasons for discontinuation prior to the Week 8a Visit, with frequencies

A listing of subject disposition will include analysis set flags (ITT, Safety, mITT, mITT-16w, PP [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.

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

Unless otherwise stated all Demographic and Baseline Characteristic tables will be summarized on the both the ITT and the mITT-16w analysis set. All listings will be presented for the Safety analysis set.

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.

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.

Ulcerative Colitis Disease State Clinical Characteristics

A summary of Ulcerative Colitis Clinical Characteristics taken at baseline or screening will be provided. A listing will also be provided.

Parameter	**Units/Response category**
Severity of Disease	Moderate: 6≤ tMS ≤ 10, Severe: tMS >10
Time Since Diagnosis	Years
Time Since Diagnosis categories	≤ 5years; >5 to <=15 years; > 15 years
Time since start of symptoms	Years
Extent or location of Disease	Proctosigmoiditis, Left-sided colitis, Extensive, Unknown
Presence of Complications	Yes, No
Normal stool count in remission or prior to diagnosis	Stools
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Prior Ulcerative Colitis Therapy Characteristics

A summary of Prior Ulcerative Colitis 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
Inadequate Response 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, non-response or intolerance	Yes, No
Prior immunomodulator use	Yes, No
History of immunomodulator non-response or intolerance	Yes, No
Prior aminosalicylate use	Yes, No
Aminosalicylate use at enrolment	Yes, No
History of aminosalicylate non-response	Yes, No
Prior Jak-inhibitor use	Yes, No

Complications of Ulcerative Colitis at Baseline

A summary of complications of ulcerative colitis at Baseline will be provided, the number and percentage of subjects with each complication collected on the Ulcerative Colitis History page will be presented. A listing will also be provided.

Baseline Mayo Scores

A summary of baseline Mayo scores and components will include the following items. A listing will also be provided.

Parameter	**Units/Response category**
Baseline tMS	Points
Baseline pMS	Points
Baseline aMS	Points
Baseline PRO2	Points
Baseline Mayo Stool Frequency subscore	0, 1, 2, 3
Baseline Mayo Rectal Bleeding subscore	0, 1, 2, 3
Baseline Mayo Endoscopy Findings subscore	0, 1, 2, 3
Baseline Mayo Physician Global Assessment subscore	0, 1, 2, 3

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.

Major analysis protocol deviations include:

1. Subjects who received the wrong treatment prior to Week 8a visit,

2. Study drug compliance defined as compliance < 80% or ≥ 120% during 8 Week Induction study,
3. Subject did not meet efficacy-related inclusion criteria (inclusion criterion 4 and 5),
4. Subject took a prohibited medication prior to Day 1 (exclusion criteria 7a-j),
5. Subject required prohibited concomitant medications that are deemed to have an impact on the efficacy outcomes

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 # 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. Medications that stopped more than 60 days prior to screening will not be included in the prior medication summaries. The number and percentage of subjects who have taken each medication will be provided by study treatment.

On-going Ulcerative Colitis Medications of Interest at Baseline will also be presented. Ulcerative Colitis Medications of Interest include aminosalicylates and corticosteroids. 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 medications to treat UC or AE of worsening UC and are categorized as :

- Initiation of oral corticosteroids or aminosalicylates

- Increase in oral corticosteroids or aminosalicylates dose 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 Total Mayo score at Week 8.

3.3.2. Total Mayo Score (tMS)

The Total Mayo score (0-12 points) (Table 5) is the sum of four components: stool frequency (0-3 pts), rectal bleeding (0-3 pts), Mayo endoscopic (0-3 pts) and Physician Global Assessment (0-3 pts) subscores.

Additional information on derivation of stool frequency and rectal bleeding components from diary data can be found in Section 5.4.

If at least one component of the Total Mayo score is available then the score will be calculated. Missing components will be imputed through last observation carried forward (LOCF).

Table 5: Components of Total Mayo Score

Stool Frequency
0 point: Normal number of stools for patient
1 point: 1 to 2 stools per day more than normal
2 points: 3 to 4 stools more than normal
3 points: ≥ 5 stools more than normal
Rectal Bleeding
0 point: No blood seen
1 point: Streaks of blood with stool less than half the time
2 points: Obvious blood with stool most of the time
3 points: Blood alone passes
Endoscopic Findings
0 point: Normal or inactive disease
1 point: Mild Disease (erythema, decreased vascular pattern)
2 points: Moderate Disease (marked erythema, lack of vascular pattern, friability, erosions)

3 points: Severe Disease (spontaneous bleeding, ulceration)
Physician's Global Assessment (PGA)
0 point: Normal
1 point: Mild disease
2 points: Moderate disease
3 points: Severe disease

3.3.3. Statistical Hypotheses

The primary estimate of interest, change from baseline in total Mayo score at Week 8, is used to evaluate the effectiveness of TD-1473 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 TD-1473 (active) and the mean response on the placebo treatment in the change from baseline in total Mayo score at Week 8.

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 3 active treatment groups versus placebo for the primary endpoint, a multiplicity procedure is planned.

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 patients regardless of use of rescue medication.

Population:

The study population consists of treated subjects with moderately-to-severely active UC as defined by an adapted Mayo score between 4 and 9 with a Mayo endoscopic subscore ≥ 2 who are corticosteroid-dependent or had intolerance or demonstrate an inadequate response or loss of response to conventional therapy (aminosalicylates, corticosteroids or immunomodulators) [i.e., as azathioprine or 6-mercaptopurine] or biologics [i.e., anti-TNF-therapy, anti-integrin, or anti-IL-12/23]. Randomized and treated subjects with inclusion or exclusion protocol deviations will be included in the analysis.

Variable:

Change from baseline in Total Mayo Score at Week 8.Subjects with any of the following intercurrent events (ICE) prior to Week 8 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 UC or adverse event of worsening UC
2. Documented ostomy, colectomy or any other major intestinal resection for UC during the treatment period
3. Increase in dose of oral corticosteroids or aminosalicylates above baseline dose
4. Initiation of oral corticosteroids or aminosalicylates where they were not ongoing at baseline
5. Discontinuation of study treatment due to lack of clinical benefit or AE of worsening UC

Other ICE:

6. Discontinuation of study treatment due to COVID-19
7. Discontinuation of study treatment due to reasons other than COVID-19, lack of clinical benefit or AE of worsening UC

Population-level summary:

The mean difference in change from baseline in Total Mayo Score at Week 8 between each TD-1473 group and placebo.

3.3.4.2. Analysis Methods

The primary endpoint of change from baseline in Total Mayo Score at Week 8 will be analyzed based on the Primary Estimand by fitting an ANCOVA model incorporating the change from baseline tMS measurement at Week 8 as the dependent variable in the model. The model will include fixed-effect class terms for treatment group, prior biologic failure status (yes/no), corticosteroid use at baseline (yes/no). A covariate for baseline tMS will be included.

Summaries will be on the mITT population and include observed values, change from baseline values, and least square (LS) means estimate. 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. Unadjusted p-values will also be reported.

A 4-group forest plot will summarize the LS mean change from baseline in Total Mayo Score at Week 8 with 95% confidence interval. An additional 3-group forest plot will summarize the difference from placebo in LS mean change from baseline in Total Mayo Score at Week 8 with 95% confidence interval. The 3-group 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 equal slopes, linearity of regression, equal variances and the independence and normality of errors. In the event that the ANCOVA 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

After accounting for intercurrent events and individual missing components (outlined in Section 3.3.2) all missing data (including data missing due to COVID-19) will be assumed missing completely at random (MCAR) and not imputed.

3.3.5. Sensitivity Analyses

A sensitivity analysis of the MCAR assumption for the primary endpoint will be performed where missing data will be assumed Missing at Random (MAR). Missing components of the Total Mayo Score will be imputed through multiple imputation. Details on the multiple imputation methodology are outlined in Section 5.9.

3.3.6. Supplementary Analyses

3.3.6.1. Supplementary Estimand 1

This estimand uses a hybrid strategy where subjects meeting intercurrent events for treatment failure follow a composite strategy and subjects meeting intercurrent events other than treatment failure follow a hypothetical strategy.

Population:

The study population consists of treated subjects with moderately-to-severely active UC as defined by an adapted Mayo score between 4 and 9 with a Mayo endoscopic subscore ≥ 2 who are corticosteroid-dependent or had intolerance or demonstrate an inadequate response or loss of response to conventional therapy (aminosalicylates, corticosteroids or immunomodulators) [i.e., as azathioprine or 6-mercaptopurine] or biologics [i.e., anti-TNF-therapy, anti-integrin, or anti-IL-12/23]. Randomized and treated subjects with inclusion or exclusion protocol deviations will be included in the analysis.

Variable:

Change from baseline Total Mayo Score at Week 8. Subjects meeting intercurrent events (1-5) will have their change from baseline in Total Mayo Score at Week 8 equal to zero.

Intercurrent events:

Intercurrent events outlined in Section 3.3.4.1.

Population-level summary:

The mean difference in change from baseline in Total Mayo Score at Week 8 between each TD-1473 group and placebo.

Analysis Methods:

Subjects meeting intercurrent events (1-5) follow a composite strategy with baseline observation carried forward (BOCF). Subjects affected by remaining intercurrent events follow a hypothetical strategy where data following the intercurrent event is set to missing and assumed MAR. All other missing data following application of intercurrent event strategies will be also be assumed to be MAR. For all data assumed MAR multiple imputation will be performed to a generate a group of imputed datasets (n=20 imputed datasets per Mayo subscore component). Details on the multiple imputation are outlined in Section 5.9.

The following covariates will be included in the imputation model to impute the missing components: treatment group, prior biologic failure status (yes/no), corticosteroid use at baseline (yes/no) and the individual baseline Total Mayo subscore components. The tMS will then be calculated by summing together the individual components for each imputation.

The change from baseline in Total Mayo Score at Week 8 will be analyzed after applying multiple imputation using the same ANCOVA model as outlined for the primary estimand on each imputed dataset. The SAS procedure MIANALYZE is then used to combine the results from the ANCOVA analysis of each imputation.

3.3.6.2. Supplementary Estimand 2

This estimand has the same variable, analysis, ICE and population level summary as primary estimand however the population differs and is defined below.

Population:

Treated subjects who reach the Week 8 visit without any major protocol deviations and who enter the study with moderately-to-severely active UC as defined by an adapted Mayo score between 4 and 9 with a Mayo endoscopic subscore ≥ 2 who are corticosteroid-dependent or had intolerance or demonstrate an inadequate response or loss of response to conventional therapy (aminosalicylates, corticosteroids or immunomodulators) [i.e., as azathioprine or 6-mercaptopurine] or biologics [i.e., anti-TNF-therapy, anti-integrin, or anti-IL-12/23].

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 an interaction term of treatment*subgroup category and baseline*subgroup category into the primary analysis model. If a subgroup determines the level of a class effect included in the primary analysis model, the redundant term will be omitted (e.g., prior biologic failure status subgroup analyses will not include the status term). Treatment group LS means for each subgroup will be calculated by setting the baseline score to the subgroup mean (for the subjects included in the analysis).

The following subgroups are pre-defined:

- Biologic Failure Status: [a] Yes, [b] No

- Biologics experience categories: [a] Primary non-responder, Secondary non-responder or intolerant, [b] naïve, [c] bio-experienced [but not documented failure]
- Number of prior biologics failed [a] 0 [b] 1 [c] ≥2
- Number of biologic classes failed [a] 0 [b] 1 [c] ≥2
- Inadequate response to at least one biologic: [a] Yes, [b] No
- Intolerant to at least one biologic: [a] Yes, [b] No
- Steroid use status at enrollment: [a] Yes, [b] No
- Baseline Tobacco use Status: [a] no use [b] prior use [c] current use
- Extent of disease: [a] Proctosigmoiditis,[b] Left-sided colitis, [c] extensive
- Duration of disease: [a] ≤ 5 years, > 5 to ≤ 15 years, > 15 years
- [redacted]
- [redacted]
- Baseline total Mayo score: [a] ≤ 10 [b] > 10
- Baseline adapted Mayo score: [a] ≤ 7 [b] > 7
- Baseline Mayo Endoscopy subscore [a] 2 [b] 3
- Baseline Rectal Bleeding subscore [a] 0 [b] ≥1
- Geographic Region: [a] North America [b] Eastern Europe [c] Europe (excluding Eastern Europe)[d] Asia/Pacific [e] Other;
- Country: [a] Japan [b] United States [c] Rest of the world
- Refractory or intolerant to 6-MP/AZA: (yes, no)
- Refractory, dependent or intolerant to oral or IV corticosteroids: (yes, no)
- Evidence of inadequate response, recurrent disease or relapse 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

3.3.6.4. Total Mayo Score Component Analysis

Summaries of each individual Total Mayo Score component will be presented by treatment group and visit over time. The components will be presented as both a continuous and categorical variables separately, displaying summary statistics and then a shift table for percentage of subjects with each score (0, 1, 2, 3) at baseline and Week 8.

3.3.6.5. Total Mayo Score Completeness and Intercurrent Event Summaries

Summaries of the completeness of Total Mayo Score components at Week 8 will be performed where the number of patients missing 1, 2, 3 or all components will be presented. For subjects with all components missing the summary will be further broken down by those of discontinue prior to Week 8 and those who missed the Week 8 visit.

The number of subjects who experience an intercurrent event prior to Week 8 and those who don't will also be presented for the subset of subjects with at least one Total Mayo Score component missing at Week 8.

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. Key Secondary Endpoint

The key secondary endpoint is:

- Clinical remission by adapted Mayo score components at Week 8

3.4.2. Statistical Hypotheses

The key secondary estimate of interest, clinical remission by adapted Mayo score components at Week 8, 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 secondary endpoint:

The null hypothesis for the treatment comparison will be that there is no difference between the proportion of subjects in remission at a given dose level of TD-1473 (active) and the proportion of subjects in remission on the placebo treatment.

The alternative hypothesis will be that there is a difference.

Symbolically, this is expressed as follows:

$$H_0: P_{Active} = P_{\text{placebo}}$$

$$H_1: P_{Active} \neq P_{\text{placebo}}$$

In order to control for the comparison of 3 active treatment groups versus placebo for the secondary endpoint, a multiplicity procedure is planned (See Section 3.6).

3.4.3. Definition of Key Secondary Endpoint

The adapted Mayo score (0-9 points) is the sum of three components: stool frequency (0-3 pts), rectal bleeding (0-3 pts), and Mayo endoscopic (0-3 pts) subscores.

Clinical remission by Adapted Mayo Score requires each of the subscores to meet the criteria defined in Table 6. If at least one component of the adapted Mayo score (aMS) is available then the score will be calculated. Missing components will be imputed through last observation carried forward.

Table 6: Clinical Remission by aMS Definition

Mayo Definition	Stool Frequency	Rectal Bleeding	Endoscopic Findings
Adapted Mayo Score (aMS)	0 or 1	0	0 or 1

3.4.4. Key Secondary Efficacy Analyses

3.4.4.1. Estimands

Clinical remission by adapted Mayo Score 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). Subjects meeting criteria for ICE, with the exception of ICE criteria 6, will have their remission status at Week 8 set to not in remission.
- Intercurrent Events: Intercurrent events outlined in Section 3.3.4.1.
- Population-level summary: The difference in proportion in clinical remission by adapted Mayo Score between each TD-1473 group and placebo.

3.4.4.2. Analysis Methods

Subjects meeting criteria for ICE, with the exception of ICE criteria 6, will follow a composite strategy with their remission status at Week 8 set to not in remission. Subjects meeting ICE criteria 6 will have their Week 8 remission status missing and not imputed and assumed MCAR. The proportions of subjects with clinical remission by aMS definitions will be compared between each TD-1473 treatment group and the placebo group using a Cochran-Mantel-Haenszel (CMH) chi-square test stratified by biologic failure status (yes or no) and corticosteroid use at baseline (yes or no). In order to derive the weighed difference in proportions, CMH weights (w_j) will be used:

$$\widehat{w}_j = \frac{\left(\frac{n_{1j}n_{2j}}{n_{1j}+n_{2j}}\right)}{\sum_{j=1}^{4}\left(\frac{n_{1j}n_{2j}}{n_{1j}+n_{2j}}\right)} \text{ For j=1…4 stratum}$$

To derive the difference in proportions within a stratum, the standard difference in proportions is used, $\hat{d}_j = \hat{p}_{2j} - \hat{p}_{1j}$ where the difference over all strata is $\hat{d}_{CMH} = \sum_{j=1}^{4} \widehat{w}_j \hat{d}_j$.

A Wald-type CI is constructed as follows:

$$\hat{d}_{CMH} \pm (z\alpha_{/2} \times \hat{\sigma}(\hat{d}_{cmh}))$$

Where $\hat{\sigma}(\hat{d}_{cmh})$ is estimated with the Sato variance estimator (Sato, 1989).

Summaries of the proportion of subjects in remission will be presented by treatment group, the adjusted treatment difference in proportions between each TD-1473 group and placebo will also be presented along with associated 95% CIs calculated based on the Wald method outlined above. P-values from the CMH Chi-square test for the comparison of each dose of TD-1473 versus placebo will also be presented.

Separate 3-group forest plots for the difference in proportion versus placebo at Week 8 will display the CMH weighted difference in proportions and associated 95% CI.

3.4.4.3. Missing Data Handling

Following the application of ICE strategy, missing data will be imputed as not in remission .

3.4.5. Sensitivity Analyses

No sensitivity analysis will be performed for secondary endpoints.

3.4.6. Supplementary Analyses

3.4.6.1. Change in aMS

Change in aMS at Week 8 will be analyzed by fitting an ANCOVA model incorporating the change from baseline aMS measurement at Week 8 as the dependent variable in the model. The model will include independent fixed-effect class terms for treatment group, prior biologic failure status (yes/no), corticosteroid use at baseline (yes/no). A covariate for baseline aMS will also be included.

The analysis population, intercurrent events and missing data will be analyzed in the same way as for the primary estimand. Summaries will 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 4-group forest plot will summarize the LS mean change from baseline in aMS at Week 8 with 95% confidence interval. An additional 3-group forest plot will summarize the difference from placebo in LS mean change from baseline in aMS at Week 8 with 95% confidence interval.

3.4.6.2. Subgroup Analyses

All subgroup analyses outlined for the primary endpoint will be performed on clinical remission by aMS at Week 8 and change from baseline in aMS at Week 8.

3.4.6.3. Adapted Mayo Score Completeness

Summaries of the completeness of Adapted Mayo Score components at Week 8 will be performed where the number of patients missing 1, 2 or all components will be presented. For subjects with all components missing the summary will be further broken down by those of discontinue prior to Week 8 and those who missed the Week 8 visit.

The number of subjects who experience an intercurrent event prior to Week 8 and those who don’t will also be presented for the subset of subjects with at least one Adapted Mayo Score component missing at Week 8.

3.5. Multiplicity Adjustment

Adjustment for multiplicity on the primary endpoint will follow the step-down Hochberg procedure. The resulting nominal p-values for the primary endpoint will be ordered, largest to smallest.

- If the largest p-value < 0.05, then all treatment groups will be declared as statistically significant.
- If the largest p-value is > 0.05, then the next largest p-value will be compared to 0.025. If this p-value is < 0.025, then the last 2 treatment groups will be declared as statistically significant.
- If the second largest p-value is > 0.025 and the largest is > 0.05, the smallest p-value will be compared to 0.0167. If this p-value < 0.0167, then the last treatment group 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 will be considered not met.

The key secondary endpoint will only be tested if all three active treatment groups are declared statistically significant for the primary endpoint, if that occurs then adjustment for multiplicity of the key secondary endpoint will also follow the step-down Hochberg procedure.

3.6. Exploratory Endpoint(s) Analyses

3.6.1. Exploratory Endpoint(s)

[redacted]

[redacted]

3.6.2. Definition of Exploratory Endpoint(s)

[redacted]

[redacted]

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

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3.6.3. Exploratory Efficacy Analyses

[redacted]

[redacted]

[redacted]

3.6.4. Supplementary Analyses

3.6.4.1. Subgroup analysis

To characterize the consistency of the treatment effect for clinical response by aMS and tMS, endoscopic healing, and endoscopic remission, subgroup analyses will be performed for each of the subgroups in Section 3.3.6.3.

3.7. 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.

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 phase 2b induction study overall, data will be presented separately for the following groups:

1. Subjects treated with placebo in induction period
2. Subjects treated with TD-1473 20mg in Induction period and Extended Induction period if they enter
3. Subjects treated with TD-1473 80mg in Induction period and Extended Induction period if they enter
4. Subjects treated with TD-1473 80mg in Extended Induction period who were randomized to placebo in Induction period
5. Combined data on TD-1473 80mg from groups (2) and (3)

   Subjects treated with TD-1473 200mg in Induction period and Extended Induction period if they enter

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 the Week 8 visit dose administration date for those that reach the Week 8 visit or equal to date of last study drug return for those who discontinue prior to Week 8 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 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:

Label
≥ 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.

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

- 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.

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 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
- 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.

3.7.3. 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. 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
- Leukoocytes
- Lymphocytes
- Hemoglobin
- Lipids [LDL cholesterol, HDL cholesterol, Cholesterol, and Triglyceride]
- Liver Function Test's [ALT, AST, Bilirubin]
- Creatinine
- Creatinine Kinase

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 x 109/L
- white blood cell count of < 2.0 x 109/L
- absolute lymphocyte count of < 0.5 x 109/L

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 8 and through Week 16.

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 9 will be flagged in the listing.

Table 9: 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 correction.

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 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 10 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.

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 10: 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

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)
					≥ 450	
					≥ 470	
					≥ 480	
					≥ 500	
					Females:	
					< 450	
					≥ 450	
					≥ 470	
					≥ 480	
					≥ 500	

3.8. Other Analyses

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

3.9. Interim Analyses

The study will have an interim freeze to perform the primary analysis after the last subject ongoing in induction period reaches the Week 8b/mWk0 timepoint or discontinues.

3.9.1. Maintenance of blind following interim analysis

Study team members with access to subject level data during the interim analysis that reveals a subjects dose (i.e. 20mg, 80mg or 200mg) during the Extended Induction period cannot participate in study-related activities that involve direct site interaction from Week 8 unblinding onwards.

3.9.2. Data Monitoring Committee

[redacted]

4. REFERENCES

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5. SUPPORTING DOCUMENTATION

5.1. Appendix 1: Changes to Protocol-Planned Analyses

The endpoints and analysis have been updated follow the advice in **ICH E9 (R1**) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. As a result, endpoints following a treatment policy strategy no longer omit data meeting treatment failure criteria as outlined in the protocol section 8.9.

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:

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

5.2.1.4. 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.

5.2.1.5. **QTcF**

QTcF is calculated as:

$$QTcF = \frac{QT}{\left(\frac{RR}{1sec}\right)^{\frac{1}{3}}}.$$

5.2.1.6. Time Since Ulcerative Colitis Diagnosis

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

5.2.1.7. Prior Biologic Failure

Subjects who have entered primary non-response, secondary non-response or intolerant to at least one biologic treatment are defined as failing prior biologic treatment. All other subjects regardless of receiving prior biologic treatment are not considered failures.

Subjects who have not received a biologic are considered “biologic-naïve”.

Subjects who have received a biologic but have not met the criteria for failure above are considered “bio-experienced [but not documented failure]”.

5.2.1.8. Prior Biologic Mechanism of Actions

Anti-tumor necrosis factor-alpha therapies:

- Adalimumab
- Golimumab
- Infliximab

Anti-integrin therapy:

- Vedolizumab

Anti-interleukin-12 and interleukin-23 therapy

- Ustekinumab

5.2.1.9. Creatinine Clearance

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

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

Ideal body weight =	50 kg + 2.3 kg for each 2.54 cm over 152.4 cm	, if male
Ideal body weight =	45.5 kg + 2.3 kg for each 2.54 cm over 152.4 cm	, if female
Serum Creatinine (mg/dL) =	Serum Creatinine (umol/L)/88.4	

5.2.2. Missing Date 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 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 injection 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 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.

5.2.2.3. 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".

5.2.3. 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, 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"; 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 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";

5.2.4. 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.

5.3. 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".

5.4. Diary Data derivations

5.4.1. Selection of diary days to use in calculation

Derivation of rectal bleeding and stool frequency subscores will consider the 7 days prior to:

- Treatment start date for calculation Baseline score.
- Start date of study visit for Week 2, 4, 8a, 12 and 16.

Days of endoscopy prep, days of endoscopy and the day after endoscopy are set to missing as endoscopy affects rectal bleeding (and stool frequency)

To select the appropriate 3 days in the calculation:

- Find 3 most recent consecutive days in 7 day period
- If 3 days of consecutive diary data are not available then use 3 most recent days
- If there are not 3 days of data available then missing

5.4.2. Rectal Bleeding

Score calculated by averaging the 3 days and rounding to closest whole number i.e. scores of 1, 2, 2, then average= 1.67, round to score of 2

5.4.3. Stool Frequency

Score calculated through the following steps:

- Average stool score calculated by taking average of the 3 days selected scores and rounding to closest whole number (from Evening Diary)
- Average stool score then has the subjects normal stool count subtracted (from Normal Stool Frequency) from it to give number of stools above normal
- Then this new score (number of stools above normal) is mapped as follows

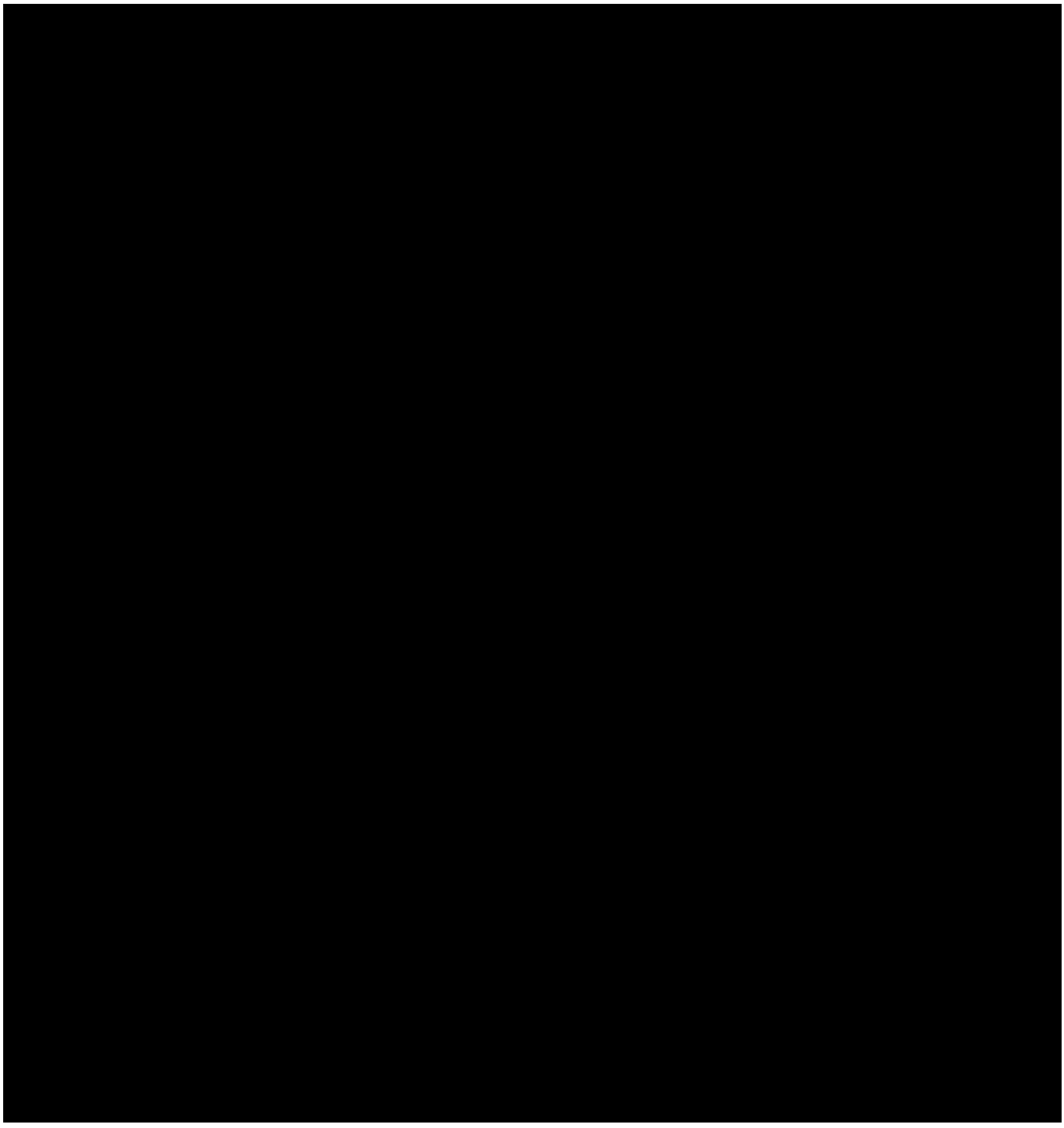
5.4.4. Diary Weeks

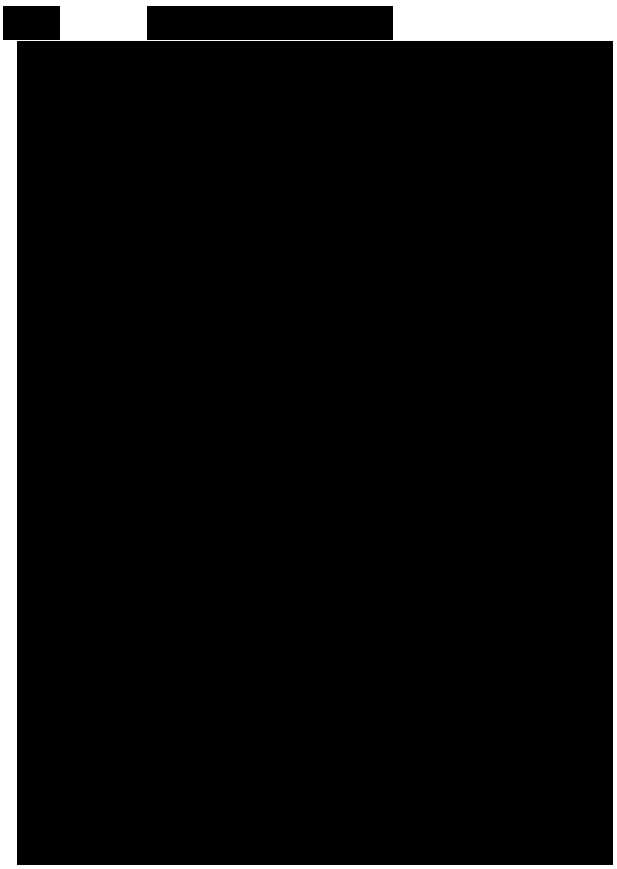
Analysis of endpoints by diary weeks will be mapped according to the table below:

Table 11: Diary Weeks

Nominal Period	Start (days)	Stop (days)
Diary Week 1	1	7
Diary Week 2	8	14
Diary Week 3	15	21
Diary Week 4	22	28
Diary Week 5	29	35
Diary Week 6	36	42
Diary Week 7	43	49
Diary Week 8	50	56
Diary Week 9	57	63
Diary Week 10	64	70
Diary Week 11	71	77
Diary Week 12	78	84
Diary Week 13	85	91
Diary Week 14	92	98
Diary Week 15	99	105
Diary Week 16	106	112

[redacted]





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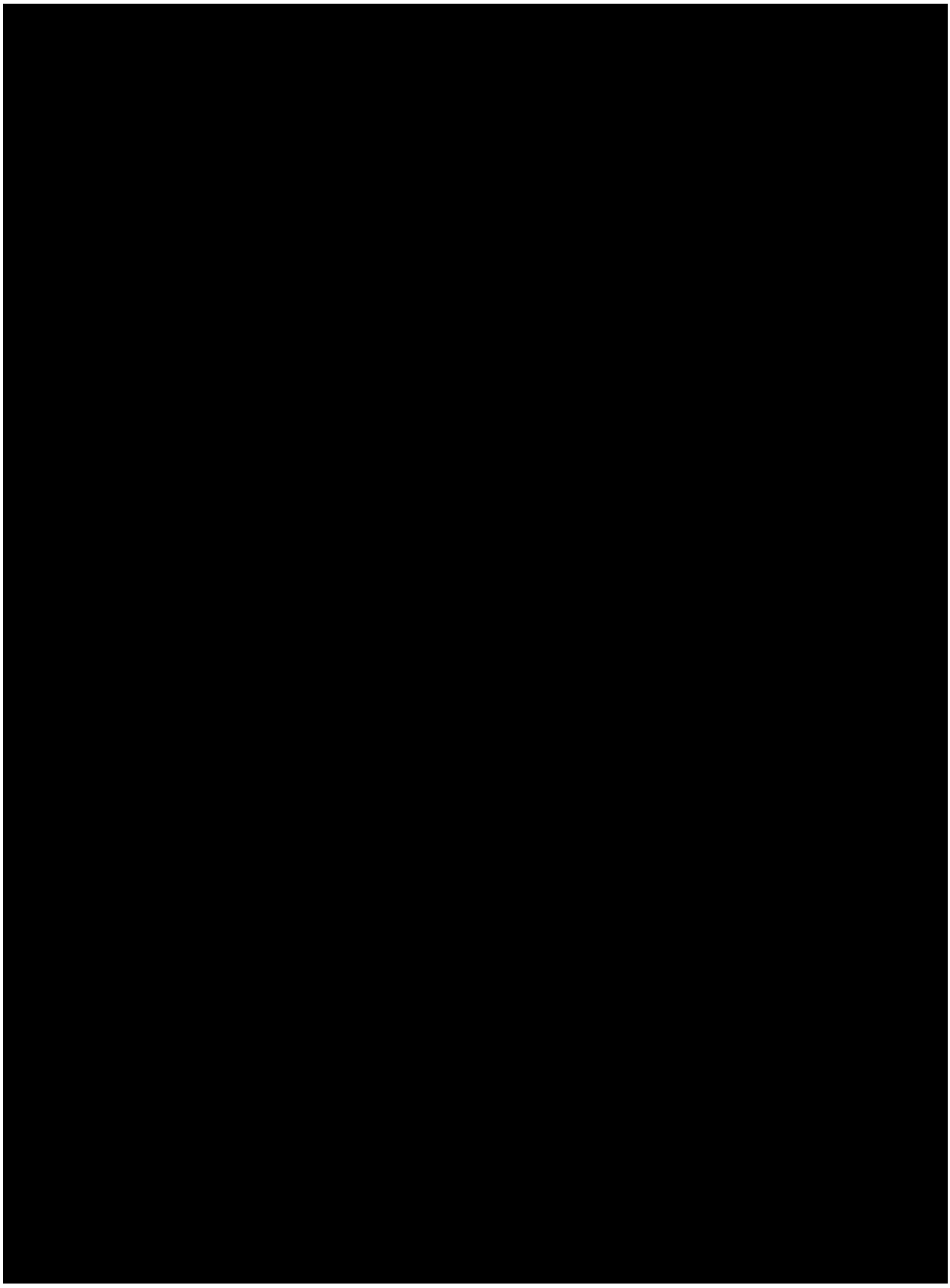
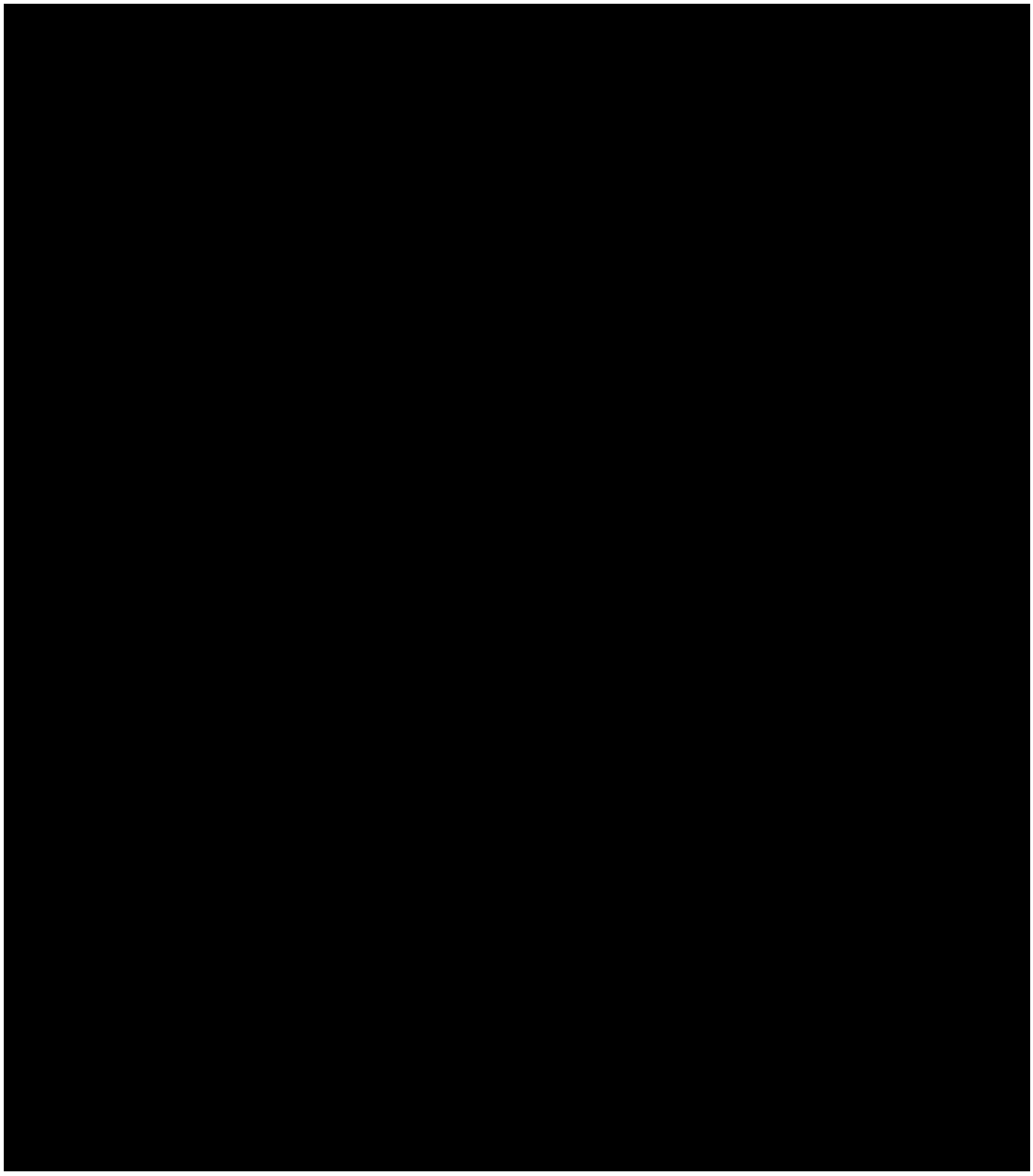
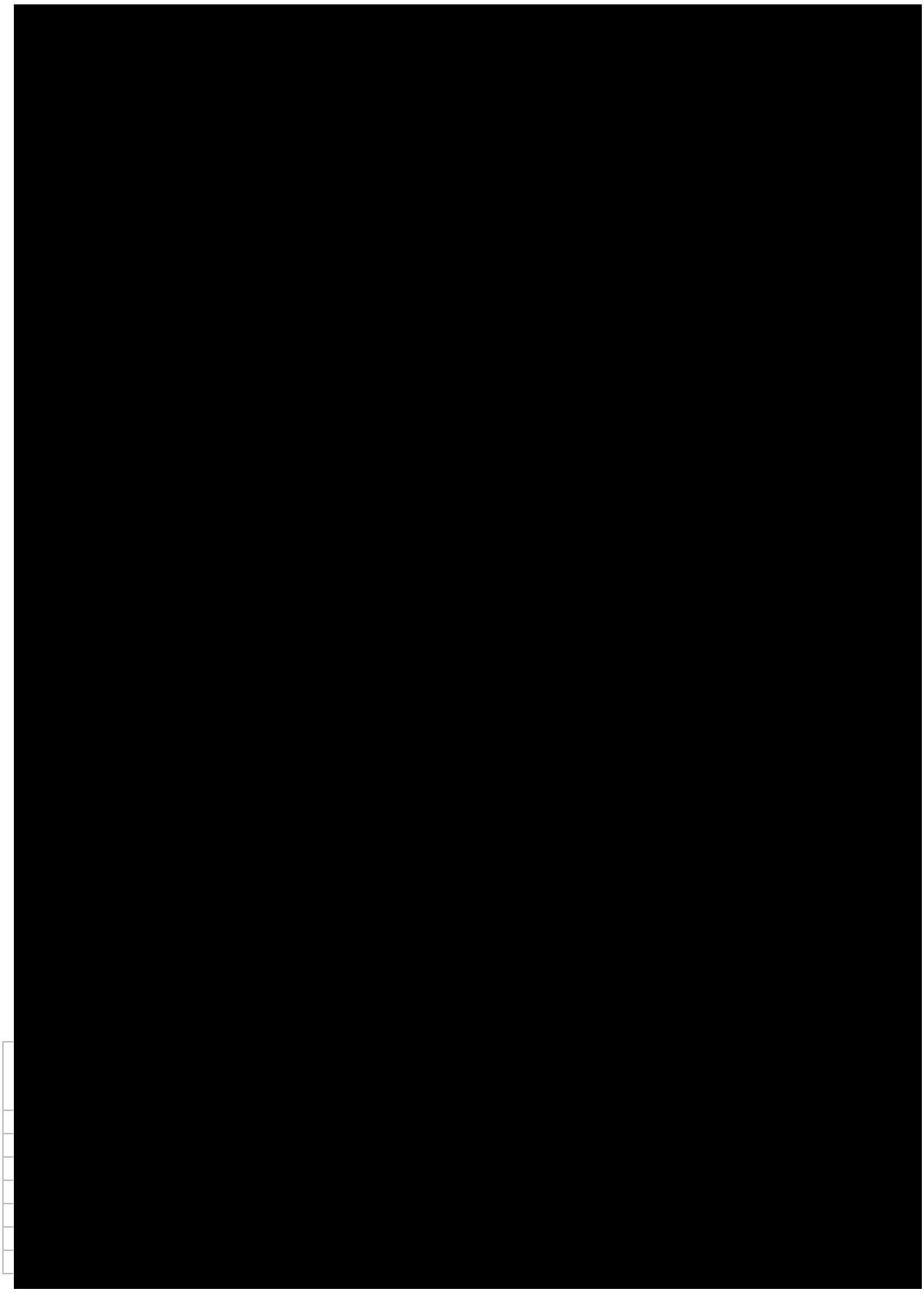






5.8. CTCAE Grading

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	≥65 - <80	<65
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]
Creatine Kinase	Increase	>ULN - ≤2.5 xULN	>2.5 xULN - ≤5.0 xULN	>5.0 xULN - ≤10.0 xULN	>10.0 xULN
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; 120-124 mmol/L regardless of symptoms	<120
Triglycerides (mmol/L)	Increase	1.71 - ≤3.42	>3.42 - ≤5.7	>5.7 - ≤11.4	>11.4

5.9. Multiple Imputation

Missing data after application of the appropriate intercurrent event strategy for (a) the primary estimand sensitivity analysis and (b) all supplementary estimand 1 analyses, is assumed missing

at random (MAR). A Multiple Imputation (MI) method will be used to impute missing data where the MI procedure will be used.

The MI procedure in the SAS Software is a multiple imputation procedure that creates multiply imputed data sets for incomplete p-dimensional multivariate data. It uses methods that incorporate appropriate variability across the m number of imputations. Once the m complete data sets are analyzed by using standard procedures, the MIANALYZE procedure can be used to generate valid statistical inferences about these parameters by combining results from the m complete data sets.

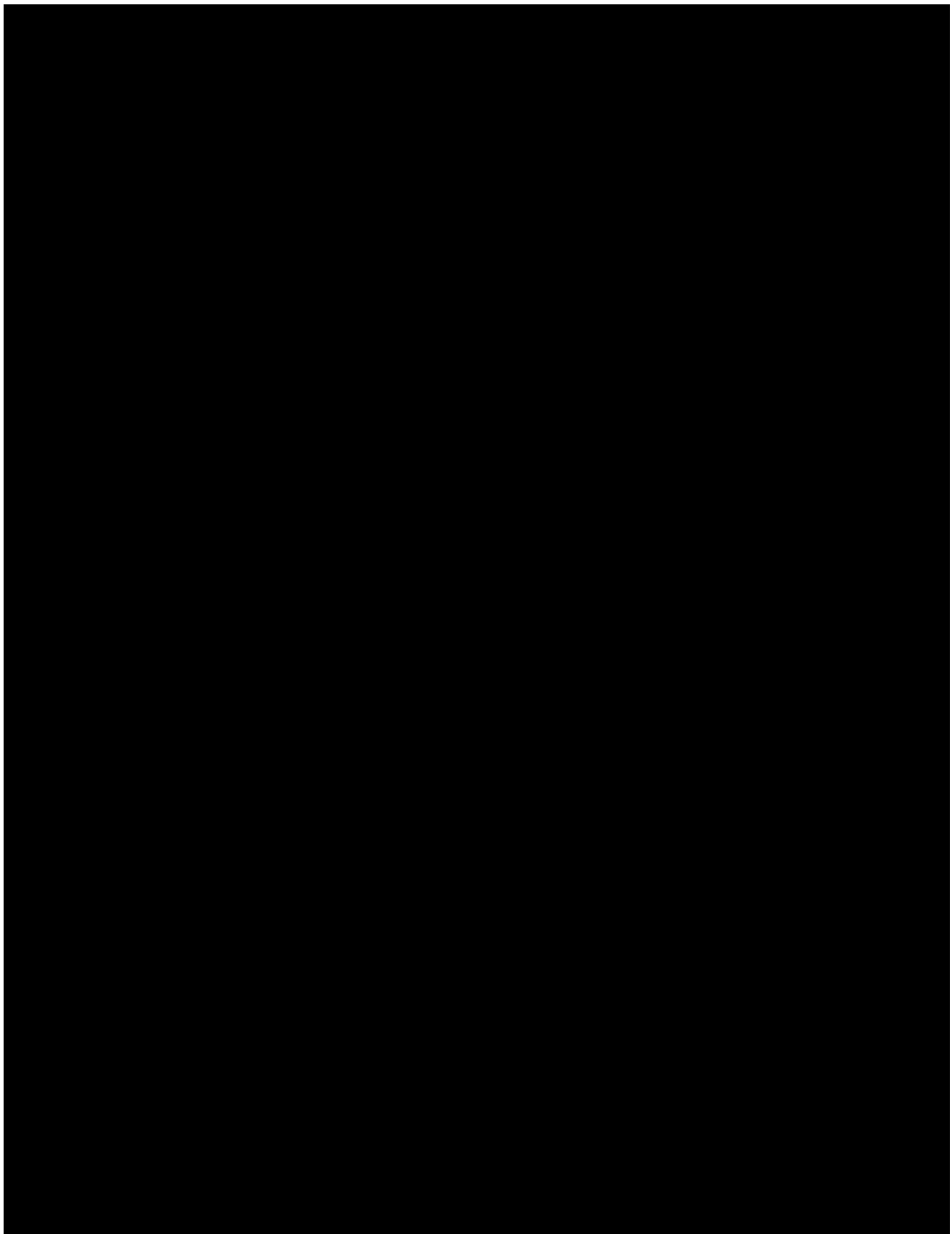
- The missing data are filled in m times to generate m complete data sets.
- The m complete data sets are analyzed by using standard procedures.
- The results from the m complete data sets are combined for the inference.

The following 5 step process will be followed for the primary estimand sensitivity analysis and all supplementary estimand 1 analyses:

1. To explore missing data patterns the MI procedure will be performed with 0 imputations and presented by treatment group for the following list of variables:
    a. Prior biologic failure,
    b. Corticosteroid use at enrolment,
    c. Stool frequency, Rectal Bleeding and PGA scores at Baseline, Week 2, Week 4 and Week 8
    d. Endoscopy score at Baseline and Week 8.

[Note: stratification factors and baseline variables are expected to be non-missing due to study eligibility criteria]

2. Generate 20 sets of imputed datasets separately for each treatment group using a fully conditional specification (FCS) with the logistic method (i.e. FCS LOGISTIC). The FCS statement will specify each of the total Mayo score components at Week 8 and both the CLASS and VAR statements will specify all variables listed in step 1.
3. The total Mayo score and respective change from baseline score will be calculated for each subject on each set of imputed datasets.
4. The statistical analysis plan specified ANCOVA model will be performed on each of the 20 imputed datasets.
5. Finally, the MIANALYZE procedure combines the results and provides valid statistical inferences.



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STATISTICAL ANALYSIS PLAN

PHASE II-III

Protocol Title:	A Phase 2b/3 Multi-Center, Randomized, Double-Blind, Multi-Dose, Placebo-Controlled, Parallel-Group Set of Studies to Evaluate the Efficacy and Safety of Induction and Maintenance Therapy with TD-1473 in Subjects with Moderately-to-Severely Active Ulcerative Colitis
Protocol Number:	0157
Compound Number:	TD-1473
Short Title	Rhea: Efficacy and Safety of TD-1473 in Ulcerative Colitis
Sponsor Name:	Theravance Biopharma Ireland Limited
Legal Registered Address:	Connaught House 1 Burlington Road Dublin 4 D04 C5Y6 Ireland
EudraCT No.	2018-002136-24

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

CONFIDENTIAL

SIGNATURE PAGE

TD-1473

0157

Author: [redacted] 11 November 2021 | 05:49 PST
Date

Theravance Biopharma Ireland Limited.

Reviewer: [redacted] 11 November 2021 | 09:18 PST
Date

Theravance Biopharma US, Inc.

Reviewer: [redacted] 12 November 2021 | 07:40 PST
Date

Theravance Biopharma Ireland Limited.

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LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

Abbreviation	Term
AE	adverse event
BMI	body mass index
CI	confidence interval
CSR	clinical study report
DMC	data monitoring committee
ITT	intent-to-treat
LLoQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
SD	standard deviation
SAE	serious adverse event
SAP	statistical analysis plan
SMQs	standardized MedDRA queries
ULN	upper limit of normal

1. INTRODUCTION

This document outlines the plan for the summarization and analysis of clinical data collected in the Phase 3 Maintenance Study of Protocol 0157 for TD-1473.

Protocol 0157 comprises 3 separate studies within a single protocol. The purpose of multiple studies within a single protocol is to increase operational efficiency and reduce operational costs.

The 0157 maintenance study was terminated early due to lack of efficacy in the 0157 Phase 2b Induction study, all subjects date of last dose occurred by 11 September 2021 date and end of study visit by 20 October 2021 date.

The 0157 CSR will be an abbreviated CSR incorporating data from the Phase 2b Induction and Phase 3 Maintenance study and as a result all protocol defined analyses will not be performed.

1.1. Objectives and Endpoints

1.1.1. Primary Objective(s) and Endpoint(s)

The primary objectives of the study are as follows:

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

The primary endpoint is clinical remission by adapted Mayo score components at mWeek 44

1.1.2. Secondary Objective(s) and Endpoint(s)

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

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

As the study was terminated early only the following secondary endpoints will be analyzed:

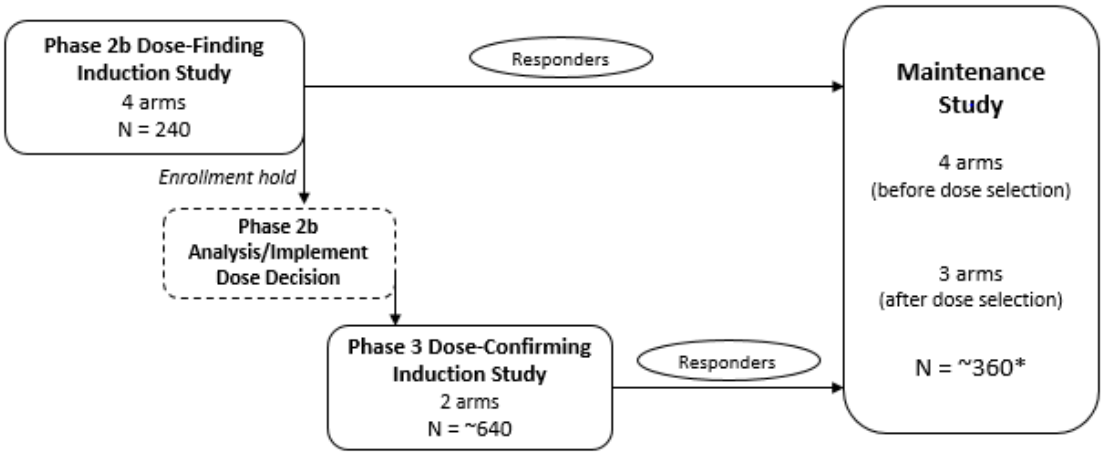
- Clinical response by adapted Mayo score at mWeek 44
- Endoscopic healing at mWeek 44
- Symptomatic remission at mWeek 44
-

[redacted]

1.2. Study Design

This single protocol includes three studies: a Phase 2b dose-finding Induction Study, a Phase 3 dose-confirming Induction Study, and a Phase 3 randomized-withdrawal Maintenance Study (Figure 1).

Figure 1: Protocol Schema



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

Each of the three studies will utilize a multi-center, randomized, double-blind, placebo-controlled, parallel-group design to evaluate various doses of TD-1473 compared to placebo in subjects with moderately-to-severely active ulcerative colitis (UC).

The Induction Studies will target subjects with moderately-to-severely active UC who demonstrate an inadequate response or failure to tolerate conventional or biologic therapy.

The Maintenance Study will be a randomized withdrawal study targeting subjects with moderately-to severely-active UC who demonstrate a clinical response to induction treatment with TD-1473.

Maintenance Study

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

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

1.3. Treatment Assignment and Blinding

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

1.4. Schedule of Assessments

The schedule of assessments is presented in the protocol.

1.5. Sample Size Determination

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

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

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

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

2. ANALYSIS SETS

Table 3: Analysis Sets

Analysis Set	Definition	Treatment Assignment
Safety	The Safety analysis set will include all subjects who received at least one dose of study drug (TD-1473 or placebo) in the Maintenance study. The Safety analysis set is the primary analysis set for safety analyses.	Actual Treatment received
ITT	The ITT set comprises all randomized into the Phase 3 Maintenance study. Note: Subjects who demonstrate clinical response to a total of 8 weeks of TD-1473 induction therapy, either at Week 8 or Week 16 are eligible to be re-randomized into the maintenance study.	Randomized treatment
mITT	The mITT set comprises all randomized into the Phase 3 Maintenance study who were also treated. Note: Subjects who demonstrate clinical response to a total of 8 weeks of TD-1473 induction therapy, either at Week 8 or Week 16 are eligible to be re-randomized into the maintenance study.	Randomized treatment

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 visits will be included in the summaries, statistical analysis, and calculation of derived parameters. All assessments will be summarized using CRF visits.

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

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

3.2. Study Subjects

Unless otherwise noted, the safety analysis set is the main analysis set used in the summarization of general (Study Population) analyses. Disposition and Demographics tables will be presented also on the ITT population.

3.2.1. Subject Disposition and Completion Status

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 subjects who completed treatment
  - Number of subjects who discontinued treatment early
  - Primary reasons for early treatment discontinuation, with frequencies

3.2.2. 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.

3.2.3. Protocol Deviations

A listing of important protocol deviations will be presented.

3.2.4. Medical History

A listing of subjects medical history will be provided.

3.2.5. Prior/Concomitant Medications

A listing of all concomitant medications will be presented.

3.3. Primary Endpoint(s) Analysis

3.3.1. Definition of Primary Endpoint

The primary endpoint is:

- Clinical remission by adapted Mayo score components at mWeek 44

The adapted Mayo score (0-9 points) is the sum of three components: stool frequency (0-3 pts), rectal bleeding (0-3 pts), and Mayo endoscopic (0-3 pts) subscores.

Clinical remission by adapted Mayo score requires each of the subscores to meet the criteria defined in Table 4. There will be no imputation of missing components, if a component is missing then the endpoint is missing.

Table 4: Clinical Remission by aMS Definition

Mayo Definition	Stool Frequency	Rectal Bleeding	Endoscopic Findings
Adapted Mayo Score (aMS)	0 or 1	0	0 or 1

3.3.2. Statistical Hypotheses

The primary estimate of interest, clinical remission by adapted Mayo score components at mWeek 44, is used to evaluate the effectiveness of therapy relative to the placebo comparator in the mITT population.

As the 0157 maintenance study was terminated early the study is not powered to detect a difference between the active groups and placebo, all analysis and p-values will be interpreted in a purely descriptive manner.

3.3.3. Main Analysis Methods

The proportions of subjects with clinical remission by aMS definitions will be compared between each TD-1473 treatment group and the placebo group using a fishers exact test.

Summaries of the proportion of subjects in remission will be presented by treatment group and p-values from the fishers exact test for the comparison of each dose of TD-1473 versus placebo.

3.3.3.1. Missing Data Handling

There will be no imputation of missing data.

3.3.4. Sensitivity Analyses

There will be no sensitivity analyses performed.

3.3.5. Supplementary Analyses

There will be no supplementary analyses performed.

3.4. Secondary Endpoint(s) Analyses

3.4.1. Definition of Secondary Endpoint(s)

As the study was terminated early only the following secondary endpoints will be analyzed:

- Endoscopic healing at mWeek 44
- Clinical response by adapted Mayo at mWeek44
- Symptomatic remission at mWeek44

Endoscopic Healing

Mayo endoscopic findings subscore ≤ 1.

Symptomatic Remission

Symptomatic remission is defined as stool frequency subscore ≤ 1 and rectal bleeding subscore = 0.

Clinical Response by adapted Mayo score

Clinical response is defined as a reduction from baseline in adapted Mayo score of ≥ 2 points and ≥ 30% relative to baseline. It also requires ≥ 1 reduction in the rectal bleeding subscore or an absolute subscore ≤ 1.

3.4.2. Statistical Hypotheses

As the study was terminated early there will be no hypothesis testing of secondary endpoints, all p-values will be interpreted in a purely descriptive manner.

3.4.3. Main Analysis Methods

Analysis for the secondary endpoints will be performed similar to the primary endpoint outlined in Section 3.3.3.

3.4.3.1. Missing Data Handling

Refer to Section 3.3.3.1.

3.4.4. Sensitivity Analyses

Refer to Section 3.3.4.

3.4.5. Supplementary Analyses

There will be no supplementary analyses.

3.5. Multiplicity Adjustment

As the study was terminated early there will be no hypothesis testing and associated multiplicity adjustment.:

[redacted]

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.

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

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 for the study will 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 100 × 0.5 × (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 assessed using the following categories:

- ≥ 100%
- ≥ 90% to < 100%
- ≥ 80% to < 90%
- < 80%

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 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.

Treatment emergent adverse events are defined as AEs with onset on or after the first initiation of study drug up to the date of study follow visit. Subjects who do not complete study follow-up visit will include AE's up to date of last dose study drug + 28 days.

Only treatment-emergent AEs will be summarized in the tables. Listings of both 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.

The number and percentage of subjects with TEAEs [in each study drug group/during the study] will be tabulated separately by

- Preferred term
- System organ class and preferred term
- System organ class, preferred term, and severity

The number and percentage of subjects with treatment-related TEAEs [in each study drug group/during the study] will be tabulated by system organ class and preferred term.

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:

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

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
- Cardiovascular Event (e.g. myocardial infarction or cerebrovascular accident)

The incidence of AESI's will be summarized overall and by SOC and PT.

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. 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 x 109/L
- white blood cell count of < 2.0 x 109/L
- absolute lymphocyte count of < 0.5 x 109/L

A summary of maximum National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) toxicity grade (Appendix 5.3) for postbaseline laboratory values.

A listing of all abnormal lab values will 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 below and will be flagged in the listing.

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

3.7.3.3. Electrocardiogram

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 correction.

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 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 below 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.

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 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	

3.8. Other Analyses

3.8.1. Subgroup Analyses

Not applicable due to early termination of study.

3.9. Interim Analyses

There is no interim analysis planned.

3.9.1. 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 major changes to the analyses specified in the protocol, dated 14 May 2020, are as follows due to early termination of the study:

- deletion of secondary efficacy parameters corticosteroid free remission, maintenance of clinical remission and mucosal healing. The only exploratory efficacy parameter to be displayed is endoscopic remission.
- Changes in the statistical methodology for the primary, secondary efficacy and exploratory parameters from CMH to fishers exact test due to small sample size

5.2. Appendix 3: Date Conventions and Transformations

5.2.1.1. Derived and Transformed Data

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.

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.

5.2.2. 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 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 injection 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 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.

5.2.2.3. 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 1 Jan [with a time of 01-01T00:01 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).

5.2.2.5. AE Severity

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

5.3. 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	≥65 - <80	<65
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]

Creatine Kinase	Increase	>ULN - ≤2.5 xULN	>2.5 xULN - ≤5.0 xULN	>5.0 xULN - ≤10.0 xULN	>10.0 xULN
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; 120-124 mmol/L regardless of symptoms	<120
Triglycerides (mmol/L)	Increase	1.71 - ≤3.42	>3.42 - ≤5.7	>5.7 - ≤11.4	>11.4