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STATISTICAL ANALYSIS PLAN

PT101-201

Version 02

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APPROVAL

STATISTICAL ANALYSIS PLAN

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[1] Author, signs for correctness and completeness

[2] Reviewer, signs for correctness and completeness

[3] Approver, signs for the release of the document

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DEFINITIONS AND ABBREVIATIONS

ADA	anti-drug antibody
AE	adverse event
ATC	anatomical therapeutic chemical
AUC	area under the curve
AUC_{0-inf}	area under the curve from time 0 to infinity
AUC_{0-t}	area under the curve from time 0 to time t
BLRM	Bayesian Logistic Regression Model
C_{max}	maximum concentration
CBT	continued blinded treatment
CRO	contract research organization
DLT	dose-limiting toxicity
DRC	data review committee
ECG	electrocardiogram
eCRF	electronic case report form
FAS	full analysis set
HCP	health care professional
IBDQ	Inflammatory Bowel Disease Questionnaire
IBT	initial blinded treatment
IL-5	interleukin 5
ITT	intent-to-treat analysis set
LOCF	last observation carried forward
LOQ	limit of quantitation
MCS	Mayo score
MedDRA	Medical Dictionary for Regulatory Activities
MES	Mayo endoscopic subscore
mMCS	modified Mayo score
MMRM	mixed-model-repeated measure
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NRI	non-responder imputation
OL	open-label
PD	pharmacodynamics
PGA	physician global assessment
PK	pharmacokinetics
pMCS	partial Mayo score
PP	per protocol analysis set
PT	preferred term
CCI [redacted]	CCI [redacted]
RB	rectal bleeding
RHI	Robarts Histopathology Index
RO	receptor occupancy
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SC	subcutaneous
sCD25	soluble form of IL2 receptor alpha chain
SF	stool frequency
SOC	system organ class

TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TMF	trial master file
Treg	regulatory T cell
UC	ulcerative colitis
ULN	upper limit of normal
WHODD	World Health Organization drug dictionary

1 INTRODUCTION

This is a Phase 1b, adaptive, randomized, double-blind, placebo-controlled, multiple-dose study. This study will evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of PT101 in subjects with active ulcerative colitis (UC) following multiple subcutaneous (SC) doses.

1.1 OBJECTIVE OF THE STATISTICAL ANALYSIS PLAN

This statistical analysis plan (SAP) describes in detail the statistical methods that will be applied to the data gathered in clinical trial protocol No. PT101-201. It will describe the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs), to assess the safety, PK, PD, and efficacy in patients with mildly to severely active UC. It will also outline the data analyses performed for the data review committee (DRC). This SAP will be finalized prior to database lock and the data analysis start. Any changes to the planned analyses (other than cosmetic) made after database lock will be documented in the clinical study report with rationales and details.

Safety, PK, PD, and efficacy analyses defined within this SAP will be periodically presented to the DRC to inform their recommendation on dose-escalation, opening of an optional cohort, continuing the study without changes, modifying the study, and/or dose/regimen selection to guide future clinical development of PT101 as outlined in the DRC charter. Roles and responsibilities of the DRC are also described in the DRC charter.

2 STUDY OBJECTIVES

This document will present analysis related to the primary (safety), secondary (PK, PD, immunogenicity), and exploratory clinical efficacy (assessment of improvement in disease activity) endpoints through CCI and applicable efficacy and safety endpoints CCI All primary, secondary, and exploratory endpoints are described in more detail in Table 1. All analyses specific to exploratory biomarkers will be described in a separate translational analysis plan.

2.1 OBJECTIVES AND ENDPOINTS

Table 1. Objectives and Endpoints

Objectives	Outcomes
Primary Objectives	***Primary Endpoint***
To evaluate the safety and tolerability of PT101 in subjects with active UC following multiple SC doses	• Safety and tolerability as assessed by incidence of TEAEs, TESAEs, and changes in laboratory values, ECGs, physical exam findings, and vital signs through CCI
Secondary Objectives	***Secondary Endpoint***
To assess the PK of PT101 in subjects with UC following multiple SC doses	• PK parameters of PT101 through CCI (as described in Table 7) • Change in serum concentration of PT101 over time
To assess the PD of PT101 in subjects with UC following multiple SC doses	• PD parameters of PT101 through CCI (as described in Table 8/Table 9)
To assess the immunogenicity of PT101 in subjects with UC following multiple SC doses	• Anti-drug antibodies to PT101 through CCI

To assess the PK/PD relationship of PT101 in subjects with UC following multiple SC doses	• The relationship between the PT101 PK and PD response
Exploratory Objectives	***Exploratory Endpoint***

To assess improvement in disease activity in subjects with UC following multiple SC doses of PT101	• Mean change from baseline in modified Mayo Score at CCI
	• Mean change from baseline in total Mayo Score at CCI
	• Mean change from baseline in partial Mayo Score at CCI CCI
	• Mean change from baseline in Robarts Histologic Index score at CCI CCI
	• Mean change from baseline in UC-100 score at CCI
	• Mean change from baseline in patient-reported outcome measures at CCI
	  ○ IBDQ
	  ○ SF-36
	• Proportion of subjects achieving clinical remission at CCI
	• Proportion of subjects achieving endoscopic improvement at CCI
	• Proportion of subjects achieving clinical response at CCI
	• Proportion of subjects achieving symptomatic remission at CCI CCI
	• Proportion of subjects achieving symptomatic response at CCI CCI
	• Proportion of subjects achieving endoscopic remission at CCI
	• Proportion of subjects achieving histologic remission at CCI
	• Proportion of subjects achieving histologic response at CCI
	• Proportion of subjects achieving mucosal healing at CCI
	• Change from baseline in partial Mayo Score beyond
	• Incidence and characterization of TEAEs and laboratory abnormalities beyond CCI

To evaluate changes in PT101- and UC-associated biomarkers following multiple SC doses of PT101	• Mean change from baseline in FC at CCI
	• Mean change from baseline in hs-CRP levels at CCI
	• Changes in PT101 and UC-associated biomarkers
	  ○ sCD25
	  ○ IL-5
	  ○ IFN-y, IL1-B, IL-2, IL-4, IL-6, IL-8, IL-10, IL12p70, IL-13, TNF-a
	  ○ TSDR FOXP3 Assay (Treg cells)
	  ○ TSDR CD4 Assay (CD4 T cells)

ECG = electrocardiograms; FC = fecal calprotectin; hs-CRP = high sensitivity C-reactive protein; IBDQ = Inflammatory Bowel Disease Questionnaire; IL-5 = interleukin 5; PD = pharmacodynamics; PK = pharmacokinetics; SC = subcutaneous; sCD25 = soluble form of IL2 receptor alpha chain; SF = Short Form-36; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event; TSDR = Treg-specific demethylated region; UC = ulcerative colitis

3 STUDY DESIGN

3.1 SUMMARY OF STUDY DESIGN

The study will enroll up to approximately 60 subjects with mildly to severely active UC in up to 6 cohorts of 10 subjects each (randomized 4:1 [PT101:placebo]) in a multiple ascending doses design. There will be 3 planned cohorts (Cohorts 1 to 3) and up to 3 optional cohorts (Cohorts 4 to 6). Subjects in Cohort 1 will receive PT101 or placebo CCI for a total of CCI Cohorts 2 and 3 will receive PT101 or placebo CCI for a total of CCI

period. Subject randomization will be stratified by prior advanced therapy use (yes or no). Enrollment of subjects with a prior history of inadequate response, loss of response, or intolerance to 2 advanced therapies as assessed by the Investigator will be capped at 20% of subjects per cohort.

Subjects who have achieved clinical response (based on the modified Mayo Score [mMCS] using the endoscopic subscore [MES] derived by the Investigator) at CCI will be eligible to enter the continued blinded treatment (CBT) phase of the study. Subjects in the CBT phase will receive the same treatment allocation (PT101 or placebo) as received during the initial blinded treatment (IBT) phase; subjects who received PT101 will continue receiving PT101 at the same dose/regimen. Corticosteroid tapering will be initiated at CCI of the IBT phase for subjects entering the CBT phase. Subjects who enter the CBT phase will receive their first dose of blinded study drug on CCI for both dosing regimens CCI CCI

Subjects who do not achieve clinical response at CCI will have the option to enter an open-label (OL) phase of the study. Subjects in the OL phase will receive PT101 at the same dose/regimen as received by subjects in their cohort during the IBT phase. Subjects participating in the OL phase who achieve a clinical response using the partial Mayo Score (pMCS) at CCI of the OL phase will also undergo corticosteroid tapering. Subjects who do not achieve a clinical response using the pMCS at CCI of the OL phase may continue on open-label treatment if it is considered in the best interest of the subject at the discretion of the investigator. Subjects who enter the OL phase will receive their first dose of PT101 on CCI for both dosing regimens CCI

Subjects with insufficient data to assess clinical response at CCI of IBT will not be eligible to enter the CBT or OL phases and will be discontinued from the study.

A DRC composed of unblinded members not involved in any way in the conduct of this trial will assess safety, PK, and PD data and provide recommendations on dose escalation/dosing regimen CCI study continuation, and enrollment of subjects into the 3 planned cohorts (Cohorts 1-3) and the 3 optional cohorts (Cohorts 4-6), as well as provide recommendations on dose and dosing regimen selection to inform future clinical development.

The schedules of assessments are presented in Appendix A.

3.2 TREATMENTS

Subjects in Cohorts 1 to 3 will receive placebo or PT101 at a dose of CCI CCI If optional cohorts are added based on a DRC review, no subject will receive a dose CCI

3.3 RANDOMIZATION AND BLINDING

3.3.1 RANDOMIZATION

The randomization schedule will be generated using an interactive web response system (IWRS). The investigator should assign the responsibility of unblinded health care professional (HCP) to a qualified person who will prepare the study drug and will not participate in the evaluation of any study subject. All randomization information will be stored in a secured area, accessible only by the unblinded HCP.

3.3.2 BLINDING

The unblinded HCP will prepare and transfer study drug (PT101 and placebo) to the investigator or qualified designee for study drug administration. Contact between the unblinded HCP and study subjects should be avoided in order to protect the blind. Blinding is accomplished by the random, masked, assignment of allocation numbers to the treatment groups, and by ensuring the drug supplies administered in the treatment groups appear identical.

Information necessary to unblind a treatment assignment at the investigator's site is held by the unblinded HCP in the form of treatment codes. Should a situation arise which requires unblinding of the treatment assignment, the treatment code(s) will be provided according to the process defined in the clinical trial integrity plan. Upon unblinding, the subject should undergo the end of study (EOS) visit if possible and be followed for safety purposes. In the event of an accidental unblinding of treatment assignment, the medical monitor should be promptly notified. At the end of the study, all records for premature unblinding must be returned to the sponsor and filed in the trial master file (TMF).

Selected individuals from the sponsor, contract research organization (CRO), an independent statistician, and the DRC will be unblinded to treatment assignments. The purpose of having unblinded personnel is to monitor study conduct, prepare data for presentation to the DRC, and to facilitate planning for subsequent dosing cohorts. All unblinded personnel will be fire-walled from the operational study team at the sponsor and CRO to prevent inadvertent unblinding of treatment assignment and to minimize the risk of introducing bias into the study results. Designation of unblinded study personnel will be authorized by the sponsor's clinical director and the lead study biostatistician. A roster of unblinded personnel will be maintained in the TMF and in the clinical trial integrity plan. All unblinded personnel will be trained in steps necessary to maintain an adequate firewall.

4 GENERAL CONSIDERATIONS FOR DATA ANALYSIS

4.1 REPORTING CONVENTIONS

The summary tables, figures, and by-subject listings will be prepared using the following conventions:

- Unless otherwise specified, the baseline value is defined as the last non-missing assessment prior to the first dose of study treatment. The last non-missing evaluation includes unscheduled and repeat visits.
- If the date of interest occurs on or after the first dose/randomization date, the study day will be calculated as "date of interest – date of first dose/randomization + 1".
- If the date of interest occurred prior to the first dose/randomization date, then study day will be calculated as "date of interest – date of first dose/randomization".
- Both safety and efficacy analysis results will be presented using descriptive statistics. Depending on the parameter, the difference from baseline will either be computed using the original scale (raw change from baseline) or on the log scale and back transformed for reporting.
- Categorical data will be summarized by treatment group in terms of frequency counts and percentages.
- Continuous variables will be summarized by treatment group using descriptive statistics (the number of subjects [n], mean, median, SD, minimum, and maximum) of the values at each visit and the change from baseline to each visit. PK parameters and other laboratory analytes that are believed to follow an

approximate log-normal distribution will also be summarized by the geometric mean and coefficient of variation (expressed as a percent).

- CIs will be presented as 2-sided 95% CIs.
- All mean, median, and CI values will be formatted to one more decimal place than the measured values. SD values will be formatted to two more decimal places than the measured value. Minimum and maximum will be formatted to the same number of decimal places as the measured value. The maximum number of decimal places reported shall be four for any summary statistic.
- All percentages will be rounded to one decimal place. The number and percentage of responses will be presented in the form XX (XX.X), where the percentage is in the parentheses.
- Change from baseline is calculated as a post-baseline value minus the baseline value.
- All laboratory data will be reported using standard international units.
- All analyses and summary tables will include the analysis set sample size (i.e., number of subjects) in the column headings.
- Listing will include both the randomized treatment and actual treatment, if different.
- By-subject listings will be presented for all subjects in the relevant analysis sets, and sorted by treatment allocation, study site (if applicable), subject ID, date, and visit. Numeric data will be listed to the same number of decimal places as recorded on the electronic case report form (eCRF) or other data source. Data collected on log forms, such as adverse events (AEs), will be presented in chronological order within the subject.
- SAS® Software Version 9.4M5 (SAS Institute Inc., Cary, NC, USA.) is to be used for all analyses including tables, listings, and figures.
- Partial dates will be imputed as follows:
    - If day and month is missing but year is present, the 1st of July of the noted year will be used.
    - If day is missing but year and month are present, the 15th of the noted month and year will be used.
- Non-PK lab data that are continuous in nature but are less than the lower limit of quantitation (LOQ) or above the upper LOQ will be imputed as follows:
    - A value that is 1/10th unit less than the lower LOQ will be used for calculation of descriptive statistics if the datum is reported in the form of "< x" (where x is considered the lower LOQ). For example, if the values are reported as < 50 and < 5.0, values of 49 and 4.9, respectively, will be used for calculation of summary statistics. An exception to this rule is any value reported as < 1 or < 0.1, etc. For these, a value of 0.9 or 0.09, respectively, will be used for calculation of summary statistics.
    - A value that is 1/10th unit above the upper LOQ will be used for calculation of descriptive statistics if the datum is reported in the form of "> x" (where x is considered the upper LOQ). Values with decimal points will follow the same logic as above. The LOQ will be used for calculation of descriptive statistics if the datum is reported in the form of "≤ x" or "≥ x" (where x is considered the LOQ).
- PT101 plasma concentration values that are equal to or below the LOQ will be interpolated to 50% of the lower LOQ for the analytical assay throughout the dataset.

- Medical Dictionary for Regulatory Activities (MedDRA) version 24.0 or newest will be used to code AEs and medical history, World Health Organization drug dictionary (WHODD) version Sep 2021 or newest will be used for medication coding.

4.2 ANALYSIS SETS

The following analysis sets are defined for both the periodic safety reviews and the final study analysis. They will consist of all randomized subjects with data available at the time of analysis and will therefore change with each subsequent run.

4.2.1 INTENT-TO-TREAT ANALYSIS SET

The intent-to-treat analysis set (ITT) consists of all randomized subjects. Subjects will be included in the treatment group assigned at randomization regardless of the actual treatment received. All efficacy endpoints will be analyzed based on the ITT.

4.2.2 FULL ANALYSIS SET

The full analysis set (FAS) consists of all randomized subjects at the time of analysis who received any study drug (PT101 or placebo). Treatment groups will be determined using the actual treatment received, regardless of the randomization treatment assignment. If different from the ITT, efficacy endpoints will also be analyzed based on the FAS.

4.2.3 PER PROTOCOL ANALYSIS SET

This study will contain two per protocol analysis sets. The first per protocol analysis set (PP1) will include all subjects in the FAS who were not on concomitant corticosteroids during the treatment period. The second per protocol analysis set (PP2) set will consist of all subjects in the FAS who did not have any major protocol deviations that might impact the efficacy analyses. Exclusion of subjects from the PP will be determined in a final blinded data review meeting that will be held prior to unblinding the randomization list. Reasons for exclusion will be documented for each subject. All exploratory efficacy endpoints will be analyzed based on the PP for the final analysis.

4.2.4 SAFETY ANALYSIS SET

The safety analysis set (SAF) consists of all subjects who receive at least one dose of study drug. Treatment groups will be determined using the actual treatment received, regardless of the randomization treatment assignment. The SAF is the primary analysis set for safety analyses.

4.2.5 PK & BIOMARKER ANALYSIS SET

The PK & biomarker analysis set will include all randomized subjects who receive at least 1 dose of study drug and who have at least one valid analytical result at baseline, at least one post-dose analytical result and had no major relevant protocol or dosing deviations that could potentially affect the PK and/or PD profile. The PK & biomarker analysis set will be used for the summaries of all PK, PD, and biomarker data. All PK, PD, and biomarker parameters are summarized in Section 7.

4.3 HANDLING OF DATA

In general, missing data will not be imputed unless methods for handling missing data are specified. For purposes of the DRC safety assessment, all results will be presented 'as observed' with missing values not imputed. The handling of missing data in analyses of the efficacy endpoints is discussed in Section 6.2.4.

If multiple valid, non-missing, continuous measurements or visits (regardless if it's scheduled or unscheduled) occurring within a single visit, records will be chosen based on the following rules if a single value is needed:

- For baseline, the baseline value will be the last non-missing value prior to the first dosing of study drug; if multiple measurements occur on the same day, the last non-missing value prior to the time of first dosing of study drug will be considered as the baseline value. If these multiple measurements occur at the same time or the time is not available, the average of these measurements will be considered the baseline value.

- For post-baseline values:
  a. The record closest to the nominal day for that visit will be selected.
  b. If there are 2 records that are equidistant from the nominal day, the later record will be selected.
  c. If there is more than 1 record on the selected day, the average will be taken.

If multiple valid, non-missing, categorical observations exist for one visit, records will be selected as follow:

- For baseline, the last available record prior to the first dose of study drug will be selected. If there are multiple records at the same time or no time recorded on the same day, the worst value will be selected unless otherwise specified.
- For post-baseline values:
  a. The record closed to the nominal day for that visit will be selected.
  b. If there are 2 records that are equidistant from the nominal day, the later record will be selected.
  c. If there is more than 1 record on the selected day, the value with the worst severity will be used.

5 STUDY SUBJECTS

Unless otherwise specified, all available subject data will be listed and summary tables for disposition and protocol deviations will be presented for the SAF as described in Table 2.

Table 2. Data Presentation for Study Subject Information

Data	Variables	Presentation
Subject Disposition	Subject, screen failures, reason for screen fail, subject study status by phase (e.g., in study, completed, discontinued, etc.), reason for discontinuation,	• n of subjects screened • n of subjects randomized • n and % of subjects included in each analysis set. • n of subjects treated • n and % of subjects who completed IBT phase • n and % of subjects discontinued by primary reason for discontinuation • n and % of subjects that had a protocol deviation in CBT/OL phase • n and % of subjects in clinical response at CCI • n and % of subjects in clinical remission at CCI • n and % of subjects who enter CBT phase • n and % of subjects who enter CBT phase and successfully taper off corticosteroids • n and % of subjects who completed CBT phase • n and % of subjects who enter OL phase • n and % of subjects who completed OL phase
Summary of Protocol Deviations	Subject, major/minor protocol deviations	• n and % of subjects that had a protocol deviation by treatment group. Both major and minor protocol deviations will be listed.
Summary of Demographics and Baseline Disease Characteristics	age, sex, race, ethnicity, height, weight, body mass index, duration of UC, prior advanced therapy use (yes/no), systemic corticosteroid use at baseline (yes/no) baseline disease characteristics (mMCS, MES, RB, SF, PGA)	• n and % of subjects for each demographic variable
Summary of Medical History	All medical events sorted by system organ class (SOC) and preferred term (PT)	• n and % of subjects for each medical event
Summary of Prior Medications	All medications taken prior to study drug administration.	• n and % of subjects for each concomitant medication listed by ATC Classification level 2 and preferred term
Summary of Concomitant Medications	All medications taken on or after the date of first study drug administration.	• n and % of subjects for each concomitant medication listed by ATC Classification level 2 and preferred term
Summary of Treatment Compliance	Duration of exposure, number of doses received, subjects with >= 1 missed dose, and	• n, mean, SD, median, min, and max number of days on treatment • n, mean, SD, median, min, and max number of doses given

	number of missed doses will be summarized.	• n and % of subjects who missed >=1 dose • n, mean, SD, median, min, and max missed doses •

ATC = anatomical therapeutic chemical; CBT = continued blinded treatment; IBT = initial blinded treatment; max = maximum; min = minimum; N = number of subjects in a group; OL = open-label; UC = ulcerative colitis; MCS = total mayo clinic score; MES = mayo endoscopic subscore; RB = rectal bleeding; SF = stool frequency; PGA = physician's global assessment

5.1 SUBJECT DISPOSITION

Subject disposition will be summarized for all subjects screened in this study. Total screened subjects and screen failed subjects will be expressed as overall counts. A summary and by-subject listing of subject disposition will be provided by treatment group for each phase in the study. This summary will present number and percentage of subjects randomized, discontinued, and completed for each study period. The number of subjects in each of the analysis sets will also be included. The reasons for premature discontinuation from treatment period as recorded in the eCRFs will be summarized. Number of subjects who reach clinical response and clinical remission at [CCI] will also be summarized.

The following by-subject listings will be provided by subject identification number in ascending order to support the above summary table:

- Reasons for premature study discontinuation
- Reasons for screen failure
- Reasons for re-screening

5.2 PROTOCOL DEVIATIONS

Protocol deviations will be summarized by type in each treatment group for each study phase. The number and percentage of subjects with protocol deviations will be summarized as major or minor by treatment group.

A by-subject listing will be provided for those subjects with any protocol deviations. A complete list of possible protocol deviations and how they are classified, tracked, and managed can be found in the PT101-201 protocol deviation plan.

5.3 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Subject demographic and baseline disease characteristics will be summarized for each treatment group and pooled across treatment groups. Demographic characteristics include age (years), sex (male/female), race/ethnicity, baseline body weight (kg), baseline height (cm), and baseline body mass index (BMI: kg/m^2). Baseline disease characteristics include duration of UC (years), tumor necrosis factor-alpha (TNF-α) exposure, prior advanced therapy use (yes/no), systemic corticosteroid use at baseline (yes/no), baseline disease measures (mMCS, RB, SF, MES, PGA). The summary of demographic data will be provided for the SAF and ITT.

Certain characteristics, that are collected at baseline or after baseline but not summarized in the demographic summary, will be reported as a listing.

5.4 MEDICAL, SURGICAL, AND MEDICATION HISTORY

Medical and surgical history will be coded using the most current available version of the MedDRA (version 25.1 or newer) and will include all relevant surgical and medical history including UC-related complications, other significant conditions or diseases relevant to the disease under study.

A summary table and by-subject listing will be provided for those subjects with any medical/surgical history for the SAF. No formal statistical testing is planned.

5.5 PRIOR AND CONCOMITANT MEDICATION

For the purposes of subgroup identification, prior and concomitant medications will be classified into anatomical therapeutic chemical (ATC) drug classes using the WHODD version September 2022 or newer.

Summaries of prior and concomitant medications will include the number and percentage of subjects by ATC classification level 2 and preferred term (PT). A subject will be counted only once within a given drug class and within a given drug name, even if he/she received the same medication at different times. If any prior or concomitant medication is classified into multiple ATC classes, the medication will be summarized separately under each of these ATC classes. The summary tables will be sorted by alphabetical order by drug class and drug name. In case any specific medication does not have ATC classification level 2 coded term, it will be summarized under "Unavailable ATC classification" category. Summaries will be based on the SAF.

All prior and concomitant medications will be provided in a by-subject listing with the relevant information collected by treatment group.

5.5.1 PRIOR MEDICATION

Prior medication is defined as any medication stopped before the date of study drug administration. If the stop date is unknown or incomplete and the medications cannot definitely be considered as stopped prior to first dosing date then the medications will be considered as concomitant medications (e.g., partial stop date is May 2021, first dosing date is 15 May 2021, medication will be considered as concomitant).

5.5.2 CONCOMITANT MEDICATION

Any medication with a start date prior to or on the first dosing date and continuing to take after the first dosing date or started after the first dosing date will be considered concomitant medications. If the start date of a medication is incomplete or missing, the medication will be assumed to be concomitant medication, unless the incomplete start date (month and/or year) or the stop date (complete or incomplete) clearly indicate that the medication stopped prior to first dosing date. Medication with completely missing start and stop dates will be included in the concomitant medication summary. Concomitant medications will be summarized for each study phase and listed. Additionally, a summary and listing of subjects who tapered off corticosteroids will be provided.

5.6 TREATMENT COMPLIANCE

Treatment exposure will be summarized and listed using descriptive statistics. Duration of exposure, number of doses, and cumulative total dose given (mg) will be summarized. Dose modifications, if any, will be included as a listing. Total duration of exposure to study treatment is defined as follows:

Duration of exposure during the IBT phase will be calculated as:

"Date of last study visit in IBT – Date of first dosing date +1"

Duration of exposure during the CBT phase will be calculated as:

"Date of last study visit in CBT phase – Date of the CBT Visit 1 dosing of study treatment + 1"

Duration of exposure during the OL phase will be calculated as:

"Date of last study visit in OL – Date of the OL Visit 1 dosing of study treatment + 1"

Frequency distributions and descriptive statistics for extent of exposure will be provided by treatment group for the SAF.

6 EFFICACY ANALYSES

Efficacy analyses will be primarily based on the ITT, and the FAS, if different. The efficacy analyses will also be performed on the PP for confirmatory purposes.

6.1 DERIVATION OF EFFICACY MEASUREMENTS

6.1.1 MAYO SCORE

The Mayo clinic score (MCS) is a composite index of 4 disease activity variables that measures disease severity in UC (Appendix B). This composite index consists of 2 subject-reported variables (stool frequency [SF] and rectal bleeding [RB]), a physician's global assessment (PGA) of disease severity and findings on endoscopy. The individual components of the MCS are scored on a 4-point scale (0 to 3 points). These individual variables are summed up to give a total disease activity score that ranges from 0 to 12.

6.1.1.1 Modified Mayo Score

The mMCS is defined as the total MCS without the PGA subscore and ranges from 0 to 9.

6.1.1.2 Partial Mayo Score

The pMCS includes 3 components of the total MCS (bowel frequency, RB, and PGA) and excludes the endoscopy subscore. The pMCS score ranges from 0 to 9 with higher scores representing more severe disease activity.

6.1.1.3 Mayo Endoscopic Subscore

The MES assesses disease activity on a 4-point scale (0 to 3 points), with higher scores representing more severe disease activity.

6.1.1.4 Calculation Rules

For the purpose of calculation of the MCS/pMCS/mMCS and component subscores, an anchor date is assigned and SF and RB records (from patient diary data) prior to the anchor date are used in the calculation of the subscores.

For screening and post-baseline calculation of MCS, mMCS, SF, and RB, the anchor date is considered the date of the endoscopy. As MES will be only evaluated during the screening visit and not on Day 1 (randomization visit), screening MCS and MES will be used as baseline evaluation.

For all calculations at other visits, including randomization, the anchor date is the date of the study visit. If a [redacted] endoscopy was not performed, the [redacted] study visit date will be used. Because the preparation for endoscopy procedure may impact the validity of the diary data, the patient reported daily SF and RB records collected the day of bowel preparation medication (if applicable) and on the day after endoscopy will not be used in the calculation of SF and RB subscores. Derivation of the SF and RB subscores based upon patient records is outlined in Appendix B.

6.1.1.5 Calculation of Screening and Post-baseline Mayo Score

To meet the entry criteria for the enrollment purpose, the calculation of the screening SF and RB subscores for the purpose of calculation of screening MCS is as follows (refer to eCRF completion guidelines):

1. SF subscore will be based on the average number of stools from the closest 3 days within the last 7 days prior to the endoscopic procedure date, excluding the date of bowel preparation (if applicable) compared to the number of stools per day during the patient UC remission.
2. RB subscore will be based on the average score from the closest 3 days within the last 7 days prior to the endoscopic procedure date, excluding the date of bowel preparation (if applicable).
3. PGA subscore used in the baseline MCS is recorded during the Screening visit.
4. MCS will be left as missing if any of four component subscores is missing.

Subjects who have less than 3 permitted days of diary data during screening are not eligible for randomization.

6.1.1.6 Calculation of Baseline Partial Mayo Score and Post-baseline Stool Frequency, Rectal Bleeding, and Partial Mayo Score

The calculation of baseline pMCS and post-baseline SF, RB, and pMCS use the study visit date as the anchor date. For baseline pMCS, the visit date is Day 1 (randomization visit). The calculation rules are described in Table 3 and Table 4 and are as follows:

1. SF and RB subscores will be based on the average score from the closest 3 days within the last 7 days prior to the visit day, excluding the date of bowel preparation (if applicable).
2. PGA subscore used in the calculation of baseline pMCS is the PGA subscore recorded on Day 1 (randomization visit). At subsequent visits, the PGA subscore used in calculation of pMCS is that recorded within the visit window.
3. pMCS will be considered as missing if any of three component subscores is missing.

For Mayo SF subscore, the excess SF is calculated as the difference between the 3-day average SF and the patient reported normal SF during remission. The average SF will be rounded to the nearest integer to match the following scorings:

0 Normal number of stools for this subject

1 1 to 2 stools more than normal

2 3 to 4 stools more than normal

3 5 or more stools than normal

Table 3. Example of Calculation of Stool Frequency Subscore at Post-baseline for Mayo Score[a]

		Diary Day Looking Back From Endoscopy Day[b]							Anchor Day	Validated Days for Calculation	Average Subscore	Average Subscore – Normal SF	Final SF Subscore
	Normal SF[c]	-7	-6	-5	-4	-3	-2	-1	V-Day 1				
		3 Jan	4 Jan	5 Jan	6 Jan	7 Jan	8 Jan	9 Jan	10 Jan				
Diary 1	15	16	20	17	**15**	**19**	**21**	18	X	-4, -3, -2,	18.3 ~18	18-15=3	2
Diary 2	18	M	M	M	M	15	18	M	X	-3, -2	Missing	Missing	Missing[d]
Diary 3	11	M	M	M	M	8	M	M	X	-3	Missing	Missing	Missing[d]
Diary 4	7	M	11	M	**11**	**15**	**10**	M	X	-4, -3, -2	12	12-7=5	3

M = missing; pMCS = partial Mayo score; SF = stool frequency; X = non-evaluable
[a] For the calculation of pMCS, consecutive days for SF are not required in the week prior to the visit.
[b] Days are named related to anchor day – Visit Day; The diary data collected prior/day of endoscopy will be discarded as endoscopy and its preparation may impact the validity of the diary data.
[c] Normal SF is defined as the average number of stools during patient remission
[d] Final subscore missing due to missing consecutive day(s) in the week prior to the endoscopy day (not including the bowel preparation day).

For Mayo RB Subscore, the RB average will be rounded to the nearest integer to match the following scorings:

0 No blood seen

1 Streaks of blood with stool less than half the time

2 Obvious blood (more than just streaks) or streaks of blood with stool most of the time

3 Blood alone passes

Table 4. Example of Calculation of Rectal Bleeding Subscore at Post-baseline for Mayo Score[a]

Examples	Diary Day Looking Back From Endoscopy Day[b]							Anchor Day	Validated Days for Calculation	Average Subscore	Final Subscore
	-7	-6	-5	-4	-3	-2	-1	V-Day 1			
	3 Jan	4 Jan	5 Jan	6 Jan	7 Jan	8 Jan	9 Jan	10 Jan			
Diary 1	M	M	2	2	1	2	2	X	-4, -3, -2,	1.67	2
Diary 2	M	M	M	M	0	1	M	X	-3, -2	Missing	Missing[c]
Diary 3	M	M	M	M	0	M	M	X	-3	Missing	Missing[c]
Diary 4	M	2	M	2	1	1	M	X	-4, -3, -2	1.33	1
Dairy 5	M	M	M	M	0	M	1	X	-3, -1	Missing	Missing[c]

M = missing; pMCS = partial Mayo score; RB = rectal bleeding; X = non-evaluable
[a] For the calculation of pMCS, consecutive days for RB are not required in the week prior to the visit.

[b] Days are named related to anchor day – Visit Day; The diary data collected prior/day of endoscopy will be discarded as endoscopy and its preparation may impact the validity of the diary data.
[c] Final subscore missing due to missing consecutive day (s) in the week prior to the endoscopy day (not including the bowel preparation day).

6.1.2 GEBOES SCORE

The Geboes scoring system is a stepwise ordinal grading system for histological assessment of disease severity in UC (Appendix C). The scoring system progressively grades disease severity by assessing 7 histological items. These 7 histological items are: architectural changes (Grade 0), chronic inflammatory infiltrate (Grade 1), lamina propria neutrophils and eosinophils (Grade 2), neutrophils in epithelium (Grade 3), crypt destruction (Grade 4), and erosions or ulcerations (Grade 5). Each grade of the score is divided in 4 subgrades, based upon the severity of tissue abnormalities or the extent of cell infiltration. The Geboes score ranges from 0 to 5.4, with higher scores indicating more severe inflammation; typically, UC is defined as active histological inflammation with a Geboes score of ≥ 2B.1. The overall Geboes score is calculated as the highest grade without a zero (i.e., absence) subscore, unless all grades are zero in which case the score will be 0.0. For example, if Grade 3: Neutrophils in lamina propria is checked as "< 50% crypts involved" (3.2), Grade 4: Crypt destruction is checked as "None" (4.0), and Grade 5: Erosions and ulcerations is checked as "No erosion, ulceration, or granulation tissue" (5.0), the subject will be assigned a final Geboes score of 3. If a subject has either abnormalities in lamina propria eosinophils or lamina propria neutrophils, they will be assigned a score of 2.

6.1.3 ROBARTS HISTOPATHOLOGY INDEX

The Robarts Histopathology Index (RHI) measures histological disease activity in patients with UC (Appendix D). The RHI is divided into 4 categories: 1) the extent of chronic inflammatory cell infiltration, 2) neutrophils in the lamina propria, 3) neutrophils in the epithelium, and 4) erosions and ulceration. Each item has 4 levels and is scored from 0 to 3 and multiplied by a weighting factor and summed to give the overall RHI score. The RHI score ranges from 0 to 33, with higher scores being indicative of more severe disease. If any one component of the RHI is found to be missing, then the overall RHI score will be set as missing. The equation used to calculate the RHI is shown below.

RHI =1 x chronic inflammatory infiltrate level + 2 x lamina propria neutrophils + 3 x neutrophils in epithelium + 5 x erosion or ulceration*

*A Geboes Grade 5 component score of >1 is reduced by 1 point prior to be incorporated into the RHI calculation.

6.1.4 UC-100

UC-100 is used to assess UC disease activity and is derived from the MCS and RHI variables. The UC-100 ranges from 1 (no disease activity) to 100 (severe disease activity). If any one component score of UC-100 is found to be missing, then the entire test score will be set as missing.

Composite UC-100 score: (1 + 16 × SF + 6 × MES+ 1 × RHI).

6.2 EFFICACY ENDPOINTS

6.2.1 DICHOTOMOUS EFFICACY ENDPOINTS

The definitions of the dichotomous efficacy endpoints are presented in Table 5.

Table 5. Definition of Binary Endpoints

Binary Endpoint	Measure	Definition	Analysis Timepoint
Clinical Remission	Modified MCS	Modified MCS (SF subscore ≤ 1 [with or without decrease], RB subscore of 0, and MES of ≤ 1 [where the definition of 1 does not include friability])	CCI [redacted]
Endoscopic Improvement	MES	MES of less than or equal to 1	
Clinical Response	Modified MCS	Decrease in modified MCS of ≥ 2 and a relative ≥ 30% from baseline, and a decrease of the Mayo RB subscore of at least 1 point or an absolute subscore for RB of 0 or 1	
Symptomatic Remission	SF, RB	SF subscore 0 or 1 with a decrease of ≥ 1 point from baseline, and RB subscore of 0	
Symptomatic Response	SF, RB	≥ 30% decrease from baseline in composite sum of SF and RB subscores	
Endoscopic Remission	MES	MES of 0	
Histologic Remission	GHI, RHI	Geboes index score < 2B.1 or RHI score ≤ 3, with subscores of 0 for lamina propria neutrophils and 0 for neutrophils in epithelium	
Histologic Response	RHI	Change from baseline RHI ≥ 7 points	
Mucosal Healing	GHI, MES	GHI < 2 and endoscopic remission (MES of 0)	

GHI = Geboes histologic index; MCS = Mayo score, MES = Mayo endoscopic subscore; RB = rectal bleeding; RHI = Robarts Histopathology Index; SF = stool frequency

6.2.1.1 Statistical Methods for Dichotomous Efficacy Endpoints

The proportion of subjects achieving each of the dichotomous efficacy endpoints defined in Table 5 will be summarized by treatment group using frequency distribution. To compare the proportion of subjects at a timepoint CCI [redacted] the Cochran-Mantel-Haenszel (CMH) method will be used, and an exact 95% CI will be estimated. Missing values in the categorical endpoints will be imputed as non-responders. All dichotomous efficacy endpoints will be listed in by-subject listings.

6.2.2 CONTINUOUS EFFICACY ENDPOINTS

The definitions of the continuous efficacy endpoints (mean change from baseline) are listed in Table 6.

Table 6. Definition of Continuous Efficacy Endpoints

Measure	Definitions	Analysis Timepoint
mMCS	Mean changes in mMCS from baseline	CCI [redacted]
MCS	Mean change in total MCS	
pMCS	Mean changes in pMCS from baseline	
RHI	Mean change in RHI from baseline	
UC-100	Mean change in UC-100 score from baseline	
pMCS	Mean changes in pMCS from baseline	

MCS = Mayo Score; mMCS = modified Mayo score; pMCS = partial Mayo Score; RHI = Robarts Histopathology Index; UC = ulcerative colitis

6.2.2.1 Statistical Methods for Continuous Efficacy Endpoints

Continuous endpoints will be summarized by treatment group using descriptive statistics of the values at each visit and the change from baseline to each post-baseline visit. For continuous endpoints at only one post-baseline visit, an analysis-of-covariance (ANCOVA) will be used for analysis. The changes from baseline will be compared between treatments adjusted for the baseline value.

For continuous data with repeated measures post-randomization, mixed-model-repeated measure (MMRM) will be used for analysis. The model will include fixed effects for treatment, visit, baseline value, and treatment-by-visit interaction. This analysis will be conducted by maximum likelihood methods using the SAS PROC MIXED procedure. Least squares means and 95% CIs will be provided for each assessment timepoint.

All collected efficacy data will also be presented in a by-subject listing.

6.2.3 Additional Analyses

In the event of controlling covariates, logistic regression will be used to compare the proportion of subjects achieving an endpoint in each group (PT101 or placebo). Covariates that may be included in the model are oral corticosteroid use, prior advanced therapy use, and baseline measures of mMCS, MES, SF, and RB scores.

6.2.4 Missing Data Handling

6.2.4.1 Non-responder Imputation

For the responder analyses described in Table 5, subjects who do not have sufficient measurements to determine the endpoint will be considered as non-responders (i.e., non-responder imputation [NRI]). Specifically, all subjects who discontinue from the study at any time prior to the assessment timepoint or fail to have an adequate efficacy assessment at the timepoint will be considered a non-responder. The NRI may be applied at any time point specified for analysis.

6.2.5 Sensitivity Analyses

6.2.5.1 Per-Protocol Analysis

To evaluate the robustness of the efficacy analysis, the binary endpoint based on the NRI in the PP will use the same analysis methods for ITT as described in Section 6.2.1.

7 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

7.1 PHARMACOKINETIC ASSESSMENTS

Blood samples for PK assessment will be collected as outlined in the protocol and outlined in Appendix A. The PK endpoints will include change in serum concentration of PT101 over time and analysis of PK parameters.PK parameters for PT101 will be estimated using noncompartmental analysis (NCA) methods. PK parameters that will be assessed are shown in Table 7. The maximum concentration (C_{max}) for each subject will be determined along with the actual time it occurs (T_{max}). As there are multiple doses given prior to complete elimination, the terminal elimination constant (K_{el}) will be estimated from the concentrations observed following the final concentration peak. If there exists at least one observed concentration following the final peak, log-linear regression will be used to estimate the slope of the

concentration-time curve, the absolute value of which will be the K_{el}. From this, the terminal elimination half-life ($t_{1/2}$) will be estimated using the formula:

$$t_{1/2} = ln\ 2/\ K_{el}.$$

The area under the concentration-time curve (AUC) from zero to infinity will be estimated in two parts: (1) AUC from zero to last observed concentration; and (2) AUC from last observed to infinity.

$$AUC_{0-\infty} = AUC_{0-t_{last}} + AUC_{t_{last}-\infty}.$$

The portion of the AUC up to the last observed concentration will be estimated using the log-linear trapezoidal method. The incremental portions of the AUC between each observed concentration will be estimated individually and summed to give the AUC across the period. The absorption phase will use a linear interpolation.

$$AUC_i = \frac{1}{2}(C_1 + C_2)(t_2 - t_1).$$

While the elimination phase will use a logarithmic interpolation, following the equation below.

$$AUC_i = \frac{C_1 - C_2}{\ln C_1 - \ln C_2}(t_2 - t_1).$$

The portion of the AUC following the last observed concentration will be assumed to follow an exponential elimination dictated by the terminal elimination constant. It will be estimated as follows:

$$AUC_{t_{last}-\infty} = \int_{t_{last}}^{\infty} C_{last} \cdot e^{-K_{el} \cdot t}\, dt = \frac{C_{last}}{K_{el}}.$$

Table 7. Standard Pharmacokinetics Parameters

Name	Description
C_{max}	Maximum concentration in a dosing interval
C_{min}	Minimum concentration in a dosing interval
T_{max}	Time of occurrence of C_{max} within a dosing interval
$t_{1/2}$	Terminal elimination half-life
AUC_{0-t}	Area under the concentration-time curve from time 0 to the last measurable concentration in a dosing interval
AUC_{0-inf}	Area under the concentration-time curve from time 0 extrapolated to infinity
CL/F	Apparent total body clearance following administration
V_d/F	Apparent volume of distribution following administration

Serum concentrations of PT101 will be listed and summarized by treatment group using descriptive statistics. PK parameters will be calculated using the actual time of sample collection whereas nominal time will be used for graphical presentations. Summary statistics including arithmetic mean, geometric mean, % coefficient of variation, SD, median, minimum, and maximum of the PK parameters listed in Table 7 will

be summarized. All individual PK parameters will be listed in a by-subject listing. PK parameters will be analyzed for the PK & Biomarker analysis set.

Graphical presentations will use the nominal time of sample collection. Mean and median concentration time profiles will be calculated by dose-level (cohort) and nominal time and plotted on linear and semi-log transformed scales. The mean profiles will include SD error bars to indicate precision in the observed mean concentration; median profiles will include the minimum and maximum observed values. Individual and mean PT101 concentration time profiles will also be produced on linear and semi-log transformed scales for each cohort at CCI [redacted] Mean and median trough concentration time profiles will be calculated by cohort and nominal time and plotted on linear and semi-log transformed scales. Individual and mean trough concentration time profiles will be plotted on linear and semi-log transformed scales for each cohort.

Dose-proportionality of CCI [redacted] will be assessed using a linear regression fit of ln(AUC/C_{max}) versus ln(Dose) to estimate slope and confidence interval of slope. Natural log-transformed exposures versus natural log-transformed dose relationship for both $AUC_{0\text{-}inf}$ and C_{max} will also be presented.

7.2 IMMUNOGENICITY ASSESSMENTS

For all dosing cohorts (refer to Appendix A for dosing schedule), blood samples for immunogenicity / anti-drug antibody (ADA) analyses will be collected. ADA to PT101 will be assessed using a standard 3-tier approach to measure binding antibody with a screening assay, ADA titer using a confirmatory assay, and neutralizing antibody to PT101 in subjects with confirmed positive titers. Summary statistics including number and percentage of subject ADA status and titer by dose for each cohort will be presented. A by-subject listing of ADA status and titers by dose will also be provided.

To assess the impact of ADA on the concentration of PT101, individual PK profiles from ADA positive and ADA negative subjects will be plotted on both a linear scale and log scale at their relevant dose levels and for each dosing regimen CCI [redacted] evaluated. Impact of ADA on the PD markers that will be the most affected by PT101 may also be graphically investigated via e.g., box plots of PT101 PK parameters by ADA status or ADA titer versus time profiles. Immunogenicity assessments will be analyzed for the PK & Biomarker analysis set.

7.3 PHARMACODYNAMIC ASSESSMENTS

Blood samples for PD analyses will be collected at baseline and at the timepoints specified in the schedule of events tables in Appendix A. Whole blood will be collected for immunophenotyping and analyzed by flow cytometry to enumerate immune cell subsets.. All immunophenotypic PD data will be summarized by dose and sampling times. Summary statistics in each table will include arithmetic mean, geometric mean, % coefficient of variation, SD, median, minimum, and maximum. All PD assessments will be analyzed for the PK & Biomarker analysis set.

7.3.1 IMMUNOPHENOTYPING OF CELL POPULATIONS ASSESSMENT

Whole blood will be collected for flow cytometry analysis to evaluate and quantify T, B, natural killer, and Tregs cells. Only data from Immunophenotyping flow cytometry samples that pass Merck sample quality review (Pass/Fail criteria documented in Merck ELN) will be transferred from PPD for analysis. All reportable cell populations and calculations that will be performed are defined Table 8.

Immunophenotyping PD analyses listed in Table 8 will be summarized by dose group at each timepoint, except for maximum fold change from baseline. The maximum absolute change from baseline and maximum fold-change from baseline may be calculated for each cell population. Individual subject level immunophenotypic PD data will be provided in supplemental by-subject listings. Supplemental time course immunophenotyping profile figures will be developed for each cell population type assessed showing mean immunophenotyping parameter level with SD error bars versus time (actual day of collection), doses and dosing regimen. Baseline used in calculations will be defined as the average level of the screening sample and the Day 1 pre-dose sample. If in the event only one sample was available, that sample would be utilized to determine baseline. CD25 mean fluorescence intensity on Tregs will be analyzed at each timepoint.

Table 8. Parameters and Analyses to be Reported From the Immunophenotyping Panel

Cell Population	Antigen Markers	Parameter	Absolute Count (cell/µl)	Percentage of Lymphocytes	Percent of Parent Cell Type[a]	Absolute Change From Baseline[b]	Fold Change From Baseline[c]	AUC of Absolute Change From Baseline[d]
Total T lymphocytes	$CD45^+$ $CD14^-$ $CD3^+$	Absolute counts and relative percentage of cell subsets of interest	Output from PPD Inc	Output from PPD Inc	no	yes	yes	yes
Helper T lymphocytes	$CD45^+$ $CD14^-$ $CD3^+$ $CD4^+$ $CD8^-$		Output from PPD Inc	Output from PPD Inc	no	yes	yes	yes
Cytotoxic T lymphocytes	$CD45^+$ $CD14^-$ $CD3^+$ $CD4^-CD8^-$		Output from PPD Inc	Output from PPD Inc	no	yes	yes	yes
B lymphocytes	$CD45^+$ $CD14^-$ $CD3^+$ $CD20^+$ $CD56^-$		Output from PPD Inc	Output from PPD Inc	no	yes	yes	yes
Natural killer cells	$CD45^+$ $CD14^-$ $CD3^+$ $CD20^-$ $CD56^+$		Output from PPD Inc	Output from PPD Inc	no	yes	yes	yes
Tregs	$CD45^+$ $CD14^-$ $CD3^+$ $CD4^+$ $CD8^-$ $CD127^{-/dim}$ $FoxP3^+$		Output from PPD Inc	Output from PPD Inc	yes[c]	yes	yes	yes
CD25 Total Tregs	CD45+ CD14- CD3+ CD4+ CD8- FoxP3+CD25+		Output from PPD Inc	Output from PPD Inc	yes[c]	yes	yes	yes

AUC = area under the curve; N/A = not applicable; Tconv = conventional T cell; Treg = regulatory T cell

Equations:

[a] Percent of Parent Cell Type: $\frac{Abolute\ number\ of\ Tregs}{Absolute\ number\ of\ helper\ T\ lymphocytes}$

Cell Population	Antigen Markers	Parameter	Absolute Count (cell/µl)	Percentage of Lymphocytes	Percent of Parent Cell Type[a]	Absolute Change From Baseline[b]	Fold Change From Baseline[c]	AUC of Absolute Change From Baseline[d]
[b] Absolute Change in Cell Count from Baseline: $Absolute\ number\ of\ Cell\ Type\ at\ Time\ x - Absolute\ number\ of\ Cell\ Type\ at\ Baselin$ [c] Fold Change from Baseline: $\frac{Abolute\ number\ of\ cell\ type\ at\ Time\ x}{Absolute\ number\ of\ cell\ type\ at\ Baseline}$ [d] Calculated from absolute change in cell count from baseline time course profile								

8 BIOMARKER ANALYSES

Relationships of biomarker parameters (e.g., baseline values, changes from baseline) to efficacy, safety, and PK parameters will be explored. Relationships and associated data that are determined to be of interest will be summarized. Biomarker analysis will be analyzed for the PK & Biomarker analysis set.

Listings and descriptive statistics (n, mean, median, SD, CV%, minimum, and maximum) will be provided by treatment group for each biomarker specified in **Table 9** as follows:

- Baseline values
- Values at each post-baseline visit
- Absolute change from baseline at each post-baseline visit
- Fold Change from baseline at each post-baseline visit

In addition, the following figures will be generated for sCD25, IL-5, IFN-y, IL1-B, IL-2, IL-4, IL-6, IL-8, IL-10, IL12p70, IL-13, TNF-a, and FOXP3, and CD4:

- Mean plot of absolute level aggregated and separated by treatments
- Mean plot of fold change from baseline aggregated and separated by treatments
- Mean plot of absolute change from baseline aggregated and separated by treatments

All other biomarker analysis will be included in a separate Translational SAP.

Table 9. Definition of Biomarker Endpoints

Measure	Definitions	Analysis Timepoint
FC	Mean change from baseline in fecal calprotectin	CCI
hs-CRP	Mean change from baseline in high sensitivity C-reactive protein levels	
sCD25	Mean change from baseline in sCD25	
IL-5	Mean change from baseline in IL-5	
IFN-y	Mean change from baseline in IFN-y	
IL-1	Mean change from baseline in IL-1	
IL-2	Mean change from baseline in IL-2	
IL-4	Mean change from baseline in IL-4	
IL-6	Mean change from baseline in IL-6	
IL-8	Mean change from baseline in IL-8	
IL-10	Mean change from baseline in IL-10	
IL12p70	Mean change from baseline in IL12p70	
IL-13	Mean change from baseline in IL-13	
TNF-a	Mean change from baseline in TNF-a	
FOXP3	Mean change from baseline in TSDR FOXP3 Assay (Treg cells) (% and cells/ul)	
CD4	Mean change from baseline in TSDR CD4 Assay (CD4 T cells) (% and cells/ul)	

9 SAFETY ANALYSES

The safety analyses will be performed using the SAF. The safety parameters will include treatment-emergent AEs (TEAEs) and treatment-emergent serious AEs (TESAEs), vital sign measurements, electrocardiogram (ECG) findings, physical examination findings, and clinical laboratory values. The primary safety analysis will include all data available for all subjects at the time of the primary efficacy analysis data snapshot at [redacted] Safety will be evaluated via descriptive statistics. No inferential testing for statistical significance will be performed.

9.1 ADVERSE EVENTS

9.1.1 ADVERSE EVENT CODING

All AEs will be listed and classified according to the MedDRA, including system organ class (SOC) and PT.

9.1.2 ADVERSE EVENT SEVERITY

The severity of AEs will be graded according to the National Cancer Institute Common Terminology Criteria for AEs (NCI CTCAE) version 5.0 (27 November 2017). The general categories for each grade are presented in **Table 10**.

Table 10. Adverse Event Severity Grading

Grade	Severity	Alternate Description
1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate	Minimal; local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living
3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
4	Very severe, life-threatening, or disabling	Life-threatening consequences; urgent intervention indicated
5	Death related to adverse event	Death related to adverse event

9.1.3 Relationship of Adverse Event to Study Treatment

The relationship of the AE to study treatment will be assessed by the investigator to be not related or related. If the investigator's opinion of not related to study drug for an SAE is given, an alternative cause of the event such as underlying disease(s), concomitant therapy, and other risk factors must be provided.

9.1.4 Serious Adverse Events

SAEs will be identified and captured as SAEs if AEs met the definitions of SAEs that were specified in the study protocol (protocol section 7.6.1.1).

9.1.5 Treatment-emergent Adverse Events

AEs will be defined as treatment-emergent if they are newly occurring or worsen following exposure to study treatment. All AEs reported following exposure to study treatment are considered TEAEs.

TEAE are defined as 1 or both of the following:

- AE onset date ≥ 1st study treatment start date/time; or
- AE onset date < 1st study treatment start date/time and either:
    - The severity worsened on or after the 1st study treatment start date/time; or
    - The event became serious on or after the 1st study start treatment date/time

If the onset date of AE is later than the last dosing date of study treatment, then the event is considered AE in follow-up period.

If the onset date of AE is incomplete and the AE stop date is not prior to the first dosing date of study treatment, then the month and year (or year alone if month is not recorded) of onset determine whether an AE is treatment-emergent. The event is considered treatment-emergent if both of the following 2 criteria are met:

- The AE onset/severity worsened is the same as or after the month and year (or year) of the first dosing date of study treatment, and

- The AE onset/severity worsened is the same as or before the month and year (or year) of the last dosing date of study treatment

An AE with completely missing onset and stop dates, or with the onset date missing and a stop date later than the first dosing date of study treatment, will be considered to be treatment-emergent. In addition, an AE with onset date missing and incomplete stop date with the same or later month and year (or year alone if month is not recorded) as the first dosing date of study treatment will be considered treatment-emergent. All AEs that occur after the safety reporting period and are considered study treatment-related in the opinion of the investigator will also be included. All non-treatment-emergent AEs will be included in the listing.

9.1.6 SUMMARIES OF TREATMENT-EMERGENT ADVERSE EVENTS

TEAEs will be summarized by period based on the SAF.

A brief, high-level summary table will be presented to provide the number and percentage of subjects experiencing any TEAEs, any severe TEAEs, any drug-related TEAEs, any TESAEs, any drug-related TESAEs, any TEAEs leading to study drug interruption or discontinuation, and death.

In addition to the above summary table, summary tables and listings of AE described below will be provided by period.

- Summary of TEAEs by SOC and PT
- Summary of TEAEs by SOC, PT and maximum severity
- Summary of severe (CTCAE Grade ≥ 3) TEAEs by SOC and PT
- Summary of related TEAEs to Study Treatment by SOC and PT
- Summary of TEAEs of Clinical Interest by SOC and PT
- Summary of related AEs to Study Procedure by SOC and PT
- Summary of serious TEAEs by SOC and PT
- Summary of TEAEs Leading to Premature Discontinuation by SOC and PT
- Summary of related TEAEs to Study Treatment by SOC and PT
- Summary of related Serious AEs to Study Procedure by SOC and PT
- Listing of all AEs
- Listing of serious TEAEs and death
- Listing of TEAEs leading to study drug interruption or discontinuation

9.2 PHYSICAL EXAMINATION

A complete physical examination is performed at the screening visit and end of treatment visits. An abbreviated or targeted interim physical exam may be done to assess areas with previously noted abnormalities and/or that are associated with any new complaints from the subject. All abnormal findings will be presented in a by-subject listing.

9.3 VITAL SIGNS

Descriptive statistics will be provided by treatment group for vital signs (blood pressure (mm Hg), heart rate (bpm), respiratory rate, temperature, and weight (kg), as follows:

- Baseline values
- Values at each post-baseline visit
- Change from baseline at each post-baseline visit

A by-subject listing of vital signs will be provided by treatment group, subject ID number, and visit in chronological order.

9.4 CLINCAL LABORATORY TESTS

Descriptive statistics will be provided by treatment group for each laboratory test (hematology, chemistry, coagulation, and urinalysis) specified in the study protocol as follows:

- Baseline values
- Values at each post-baseline visit
- Change from baseline at each post-baseline visit

Shift tables will be presented by showing change in lab normal range (low, normal, and high) for clinical laboratory values by treatment group.

Laboratory values will be listed in by-subject listings. Laboratory values which fall outside the reference ranges and have clinically significant and abnormal findings will be provided in a separate by-subject listing. These listings will include treatment group, subject ID, laboratory collection date/time, analyte name, analyte finding, and reference range.

9.5 ELECTROCARDIOGRAMS

Triplicate ECG measurements will be obtained at the screening visit and on Day 1. On Day 1 only, triplicate ECGs will be performed ~ 12 hours after study drug administration. The median of these measurements will be used to calculate change from baseline for safety evaluations. The ECG assessment values at each visit and change from baseline to each visit will be summarized and shift tables using the normal/abnormal classification to compare baseline to the post-baseline visit values will be provided. In addition, a by-subject listings, which includes treatment group, subject ID, ECG date/time, test name, test result, and ECG interpretation (e.g., clinical interpretation such as normal, abnormal – not clinically significant, abnormal – clinically significant) will be presented. If any clinically significant ECG measurement occurs, it will be recorded as an AE.

9.6 EVENTS OF CLINICAL INTEREST

The number and percentages of subjects with the following elevations in hepatic laboratory tests and drug overdoses will be summarized between treatment groups and included in a by-subject listing.

- An overdose of study product, defined as any dose of any drug administered as part of the study exceeding the dose prescribed by the protocol.
- ALT ≥ 3x upper limit of normal (ULN)

- AST ≥ 3x ULN
- Total bilirubin level (TBL) ≥ 2xULN and alkaline phosphatase value < 2xULN

10 QUALITY OF LIFE ANALYSIS

10.1.1 INFLAMMATORY BOWEL DISEASE QUESTIONNAIRE

The Inflammatory Bowel Disease Questionnaire (IBDQ) is a psychometrically validated patient-reported outcome instrument for measuring the disease-specific quality of life in patients with inflammatory bowel disease, including UC. The IBDQ comprises of 32 items that are grouped into 4 dimensions: bowel function, emotional study (loose stools, abdominal pain), emotional status (anger, depression, irritability), systemic symptoms (fatigue, altered sleep pattern) and social function (work attendance, need to cancel social events). See Appendix E.

The 4 domains are scored as follows:

- Bowel symptoms: 10 to 70
- Systemic symptoms: 5 to 35
- Emotional function: 12 to 84
- Social function: 5 to 35

The total IBDQ score ranges from 32 to 224. For the total score and each domain, a higher score indicates better quality of life. A score of at least 170 corresponds to clinical remission and an increase of at least 16 points indicates a clinically meaningful improvement.

IBDQ scores will be collected based on the schedule of assessments. Summary statistics of the absolute and change from baseline scores for IBDQ total score and each subscale score will be displayed by treatment group and visit. A by-subject listing of all IBDQ scores and the subcomponents will be provided.

IBDQ scores will be calculated as follows:

- The question on the same day of measurement will be used for calculation of each subscore and total score.
- For each subscore, sum of the questions will be round off to the first decimal place.
- IBDQ total score: sum of all questions and round off to the first decimal places.
- The value of each question after imputing missing data will be used for the calculation of each subscore.

The instructions on how the IBDQ score is calculated in the presence of missing or incomplete information is provided below.

Rules for handing missing data:

1. If no response is given for a particular question and only one response per dimensional score is missing, impute the missing value to be equal to the mean score for that other item of the subscore
2. If two or more questions are unanswered for a particular domain, then the subscore will be set to missing.

3. If after steps 1 and 2, more than 4 questions are missing for the full IBQD, then the total IBDQ will be set to missing.

10.1.2 SHORT-FORM QUESTIONNAIRE

The SF-36 is a widely used general health status questionnaire that assesses 8 domains of functional health and well-being: Physical Functioning, Role Limitations due to Physical Health Problems, Bodily Pain, Social Functioning, Mental Health, Role Limitations due to Emotional Problems, Vitality, and General Health Perceptions. Scales are scored from 0 to 100, with higher scores indicating a better health-related quality of life. A Physical Health component summary score and Mental Health component summary score are calculated from the 8 domain scores. The SF-36 is a psychometrically valid and reliable instrument. The concepts measured by the SF-36 are not specific to any age, disease, or treatment group, allowing comparison of relative burden of different diseases and the relative benefit of different treatments.

11 SUBGROUP ANALYSIS

No subgroup analysis is planned.

12 CONTINUED BLINDED TREATMENT AND OPEN-LABEL ANALYSIS

Any efficacy, safety, PK, and PD data assessments that are completed during safety follow-up, CBT and OL phase will be analyzed and summary tables will be provided.

Safety data will be analyzed based on the methods described in Section 9 PK and PD data will be analyzed based on the methods described in Section 7. Immunogenicity assessments outlined in Section 7.2 may also be further analyzed during the CBT and OL phase. Efficacy endpoints that are assessed in the CBT and OL phase will be analyzed based on the methods described in Section 6.2. All data for the CBT and OL phase will be summarized up until CCI or until subject's discontinuation from the study.

13 DRC REVIEW

For the planning of dose-escalation, opening of an optional cohort, continuing the study without changes, modifying the study, and/or dose/regimen selection, a review of safety, PK, PD, and efficacy data will be performed by an external DRC throughout the course of the study as described in detail in the DRC Charter.

Progression from Cohort 1 to Cohort 2 per protocol will be based on DRC recommendations from all available unblinded safety, PK, and PD data reviewed from Cohort 1 along with all available unblinded safety data (all 10 subjects [PT101: placebo 4:1] up to CCI CCI in a concurrent PT101 study conducted in young adult healthy volunteers population (MK-6194-003). Dose escalation from Cohort 2 to Cohort 3 will be determined only after the CCI in CCI reach CCI CCI Up to 3 optional cohorts may be added following DRC review of all available data from the previous planned cohorts (Cohorts 1 to 3) to (a) assess additional dose levels of PT101 CCI dosing regimen, and/or (b) repeat a previously studied dose level/dosing regimen.

At each DRC meeting, the committee will review cumulative AE and safety data, as well as available PK, PD, UC disease activity, and biomarker data from all treated patients. The analysis will be presented blinded for the open sessions and unblinded for the closed sessions. The study may be stopped at the discretion of the sponsor based on recommendations of the DRC. All necessary measures will be taken to ensure appropriate safety follow-up for all subjects in the trial.

The following analysis may be provided:

- Section 5.1: Disposition and Subject Characteristics
- Section 5.3: Demographic and baseline characteristics
- Section 6.2.1: Dichotomous Efficacy Endpoints; clinical remission, clinical response, symptomatic remission, symptomatic response, endoscopic improvement, endoscopic remission, mucosal healing, histologic remission, histologic response.
- Section 6.2.2: Continuous Efficacy Endpoints; MCS, pMCS, mMCS, RHI, UC-100.
- Section 7.1: Pharmacokinetic Assessments: Descriptive statistics for available PK data
- Section 7.2/7.3: Pharmacodynamic Assessments: Descriptive statistics for available PD data
- Section 8: Biomarker Analyses: Descriptive statistics for available biomarker data
- Section 9: Safety Analyses: Overall summary of TEAEs, TEAEs by SOC and PT, TEAEs by SOC, PT and maximum severity, severe (CTCAE Grade >=3) TEAEs by SOC and PT, Related TEAEs by SOC and PT, TESAEs by SOC and PT, descriptive statistics for ECGs, vital signs, clinical laboratory parameters.
- Section 13.1: Assessment of Dose-Limiting Toxicity: Overall listing of dose-limiting toxicity (DLT) AE's.

13.1 ASSESSMENT OF DOSE-LIMITING TOXICITY

A dose-limiting toxicity (DLT) is defined as any treatment-related AE reported within CCI from dosing that meets both the following criteria:

- Grade 3 or higher in severity according to the NCI CTCAE, Version 5.0
- A shift of ≥ 2 NCI CTCAE grades from baseline (initial presentation of the AE)

The safety of each dose level will be evaluated by examining the probability of experiencing a DLT based on a Bayesian Logistic Regression Model (BLRM) (Neuenschwander, 2008) and the incidence of TEAEs, TESAEs, treatment-related TEAEs, and treatment-related TESAEs.

A dose will be considered safe if the estimated probability (posterior median) of overdosing CCI The maximum tolerated dose (MTD) will be determined according to the following rules:

CCI

CCI [redacted]

To support the dose selection decision, results from dose toxicity modeling using a 2-parameter BLRM will also be considered. The model parameters ($\log f_0(\alpha)$,$\log f_0(\beta)$) are given a weakly informative bivariate normal prior distribution, with prior means (-1.912, 0.167), prior standard deviations (2.424, 1.139), and prior correlation of 0.486. The target probability of toxicity is under 10% [Neuenschwander et al, 2014].

For Cohort 1, the model will be run using all available safety data from subjects that have completed CCI [redacted] and subsequently at the same timepoint for the 3 potential optional cohorts. The analysis will be performed (using appropriate software, such as East Software [Cytel Inc, v6.4]) based on estimation of the posterior median. The selected dose may not exceed the escalation with overdose control (EWOC) threshold: the posterior probability of overdosing is 0.25. The dose level(s) and dosing regimen with the best benefit/risk profile based on the totality of safety and efficacy data at CCI [redacted] will inform selection for future clinical development.

14 CHANGES FROM PROTOCOL

- Last observation carried forward (LOCF) was dropped from the SAP as an MMRM analysis planned and LOCF would not be efficient in this case.
- Protocol stated that the SAP would be finalized prior to the DRC review of Cohort 1 data, but the SAP will not be finalized until prior to the final database lock.
- Physical exam findings will only be included in a by-subject listing and no change from baseline calculations will be done..
- Removed receptor occupancy (RO) as a secondary objective along with corresponding analysis. Upon thorough investigation of the assay and data generated on production samples, technical issues related to the assay remained unresolved resulting in failure to obtain acceptable quality data and deeming the RO assay an assay failure for MK-6194-002. The assay main concerns were loss of CD4 resolution in the majority of production samples, lack of dynamic range between background and maximal MK-6194 signal to accurately calculate RO, and lack of true MK-6194 and Ki-67 production sample gating controls resulting in variable/subjective gate placement and erroneous data.

15 REVISION HISTORY

Version	Effective Date	Reason
V01	06DEC2022	New
V02	23FEB2024	Updated FAS definition and removed analysis related to receptor occupancy. Added additional biomarkers to the analyses in Section 8.


CCI

CCI

[redacted]


CCI


CCI


CCI


CCI

CCI


CCI

CCI

CCI


CCI

APPENDIX B: MAYO SCORE

Note: The partial MCS is calculated using only the stool frequency, rectal bleeding, and physician's global assessment subscores from the table below.

Component	Mayo Score (MCS)
Stool Frequency[a, d]	
Normal number of stools for this subject	0
1 to 2 stools more than normal	1
3 to 4 stools more than normal	2
5 or more stools than normal	3
Subscore, 0 to 3	
Rectal bleeding[b, d]	
No blood seen	0
Streaks of blood with stool less than half the time	1
Obvious blood (more than just streaks) or streaks of blood with stool most of the time	2
Blood alone passes	3
Subscore, 0 to 3	
Findings on endoscopy	
Normal or inactive disease	0
Mild disease (erythema, decreased vascular pattern, no friability)	1
Moderate disease (marked erythema, absent vascular pattern, friability, erosions)	2
Severe (spontaneous bleeding, ulceration)	3
Subscore, 0 to 3	
Physician's global assessment[c]	
Normal	0
Mild disease	1
Moderate disease	2
Severe disease	3
Subscore, 0 to 3	
Total score	**0-12**
a Each subject serves as his or her own control to establish the degree of abnormality of the stool frequency	

b The daily bleeding score represents the most severe bleeding of the day

c The physician's global assessment acknowledges the 3 other criteria, the subject's recollection of abdominal discomfort and general sense of wellbeing, and other observations, such as physical findings and the subject's performance status

d The modified Mayo score calculated at the CCI visits must use the SF and RB Mayo subscores recorded on the eDiary (or paper diary) over the **3 consecutive days prior to the endoscopy** (excluding the bowel preparation day)

APPENDIX C: GEBOES SCORING

Grade 0	**Structural (architectural change)**
Subgrades	
0.0	No abnormality
0.1	Mild abnormality
0.2	Mild or moderate diffuse or multifocal abnormalities
0.3	Severe diffuse or multifocal abnormalities
Grade 1	**Chronic inflammatory infiltrate**
Subgrades	
1.0	No increase
1.1	Mild but unequivocal increase
1.2	Moderate increase
1.3	Marked increase
Grade 2	**Lamina propria eosinophils and neutrophils**
2A Eosinophils	
2A.0	No increase
2A.1	Mild but unequivocal increase
2A.2	Moderate increase
2A.3	Marked increase
2B Neutrophils	
2B.0	None
2B.1	Mild but unequivocal increase
2B.2	Moderate increase
2B.3	Marked increase
Grade 3	**Neutrophils in epithelium**
3.0	None
3.1	< 5% crypts involved
3.2	< 50% crypts involved
3.3	> 50% crypts involved
Grade 4	**Crypt destruction**
4.0	None
4.1	Probable – local excess of neutrophils in part of crypt
4.2	Probable – marked attenuation

4.3	Unequivocal crypt destruction
Grade 5	**Chronic inflammatory infiltrate**
5.0	No erosion, ulceration, or granulation of tissue
5.1	Recovering epithelium + adjacent inflammation
5.2	Probable erosion – focally stripped
5.3	Unequivocal erosion
5.4	Ulcer or granulation tissue

APPENDIX D: ROBARTS HISTOPATHOLOGY INDEX SCORING

Histological Variable	Grading	Multiplication Factor
Chronic inflammatory infiltrate	0=No increase 1=Mild but unequivocal increase 2=Moderate increase 3=Marked increase	X1
Lamina propria neutrophils	0=None 1=Mild but unequivocal increase 2=Moderate increase 3=Marked increase	X2
Neutrophils in epithelium	0=None 1= < 5% crypts involved 2= < 50% crypts involved 3= > 50% crypts involved	X3
Erosion or ulceration	0=No erosion, ulceration, or granulation tissue 1=Recovering epithelium + adjacent inflammation 1=Probably erosion-focally stripped 2=Unequivocal erosion 3=Ulcer or granulation tissue	X5

APPENDIX E: QUALITY OF LIFE IN INFLAMMATORY BOWEL DISEASE QUESTIONNAIRE (IBDQ)

INSTRUCTIONS FOR SELF-ADMINISTERED IBDQ

This questionnaire is designed to measure the effects of your inflammatory bowel disease on your daily function and quality of life. You will be asked about symptoms you have been having as a result of your bowel disease, the way you have been feeling in general, and how your mood has been.

There are two versions of this questionnaire, the IBDQ and IBDQ-Stoma. If you have a colostomy or ileostomy, you should complete the IBDQ-Stoma. Questions 1, 5, 17, 22, 24 and 26 are slightly different in each version. Be sure you have the correct questionnaire.

On this questionnaire there are 32 questions. Each question has a graded response numbered from I through 7. Please read each question carefully and circle/mark the number which best describes how you have been feeling in the past 2 weeks.

EXAMPLE

How often have you felt unwell as a result of your bowel problem in the past 2 weeks?

(1) ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

If you are having trouble understanding a question, **STOP** for a moment! Think about what the question means to you. How is it affected by your bowel problem? Then answer the question as best you can. You will have the chance to ask the research assistant questions after completing the questionnaire. This takes only a few minutes to complete.

QUALITY OF LIFE IN INFLAMMATORY BOWEL DISEASE QUESTIONNAIRE (IBDQ)

This questionnaire is designed to find out how you have been feeling during the last 2 weeks. You will be asked about symptoms you have been having as a result of your inflammatory bowel disease, the way you have been feeling in general, and how your mood has been.

1. How frequent have your bowel movements been during the last two weeks? Please indicate how frequent your bowel movements have been during the last two weeks by picking one of the options from

1 BOWEL MOVEMENTS AS OR MORE FREQUENT THAN THEY HAVE EVER BEEN
2 EXTREMELY FREQUENT
3 VERY FREQUENT
4 MODERATE INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
5 SOME INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
6 SLIGHT INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
7 NORMAL, NO INCREASE IN FREQUENCY OF BOWEL MOVEMENTS

2. How often has the feeling of fatigue or of being tired and worn out been a problem for you during the last 2 weeks? Please indicate how often the feeling of fatigue or tiredness has been a problem for you during the last 2 weeks by picking one of the options from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

3. How often during the last 2 weeks have you felt frustrated, impatient, or restless? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

4. How often during the last 2 weeks have you been unable to attend school or do your work because of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

5. How much of the time during the last 2 weeks have your bowel movements been loose? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

6. How much energy have you had during the last 2 weeks? Please choose an option from

1 NO ENERGY AT ALL
2 VERY LITTLE ENERGY
3 A LITTLE ENERGY
4 SOME ENERGY
5 A MODERATE AMOUNT OF ENERGY
6 A LOT OF ENERGY
7 FULL OF ENERGY

7. How often during the last 2 weeks did you feel worried about the possibility of needing to have surgery because of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

8. How often during the last 2 weeks have you had to delay or cancel a social engagement because of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

9. How often during the last 2 weeks have you been troubled by cramps in your abdomen? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

10. How often during the last 2 weeks have you felt generally unwell? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

11. How often during the last 2 weeks have you been troubled because of fear of not finding a washroom? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

12. How much difficulty have you had, as a result of your bowel problems, doing leisure or sports activities you would have liked to have done during the last 2 weeks? Please choose an option from

1 A GREAT DEAL OF DIFFICULTY; ACTIVITIES MADE IMPOSSIBLE
2 A LOT OF DIFFICULTY
3 A FAIR BIT OF DIFFICULTY
4 SOME DIFFICULTY
5 A LITTLE DIFFICULTY
6 HARDLY ANY DIFFICULTY
7 NO DIFFICULTY; THE BOWEL PROBLEMS DID NOT LIMIT SPORTS OR LEISURE ACTIVITIES

13. How often during the last 2 weeks have you been troubled by pain in the abdomen? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

14. How often during the last 2 weeks have you had problems getting a good night's sleep, or been troubled by waking up during the night? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

15. How often during the last 2 weeks have you felt depressed or discouraged? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

16. How often during the last 2 weeks have you had to avoid attending events where there was no washroom close at hand? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

17. Overall, in the last 2 weeks, how much of a problem have you had with passing large amounts of gas? Please choose an option from

1 A MAJOR PROBLEM
2 A BIG PROBLEM
3 A SIGNIFICANT PROBLEM
4 SOME TROUBLE
5 A LITTLE TROUBLE
6 HARDLY ANY TROUBLE
7 NO TROUBLE

18. Overall, in the last 2 weeks, how much of a problem have you had maintaining or getting to, the weight you would like to be at? Please choose an option from

1 A MAJOR PROBLEM
2 A BIG PROBLEM
3 A SIGNIFICANT PROBLEM
4 SOME TROUBLE
5 A LITTLE TROUBLE
6 HARDLY ANY TROUBLE
7 NO TROUBLE

19. Many patients with bowel problems often have worries and anxieties related to their illness. These include worries about getting cancer, worries about never feeling any better, and worries about having a relapse. In general, how often during the last 2 weeks have you felt worried or anxious? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

20. How much of the time during the last 2 weeks have you been troubled by a feeling of abdominal bloating? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

21. How often during the last 2 weeks have you felt relaxed and free of tension? Please choose an option from

1 NONE OF THE TIME
2 A LITTLE OF THE TIME
3 SOME OF THE TIME
4 A GOOD BIT OF THE TIME
5 MOST OF THE TIME
6 ALMOST ALL OF THE TIME
7 ALL OF THE TIME

22. How much of the time during the last 2 weeks have you had a problem with rectal bleeding with your bowel movements? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

23. How much of the time during the last 2 weeks have you felt embarrassed as a result of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

24. How much of the time during the last 2 weeks have you been troubled by a feeling of having to go to the bathroom even though your bowels were empty? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

25. How much of the time during the last 2 weeks have you felt tearful or upset? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

26. How much of the time during the last 2 weeks have you been troubled by accidental soiling of your underpants? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

27. How much of the time during the last 2 weeks have you felt angry as a result of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

28. To what extent has your bowel problem limited sexual activity during the last 2 weeks? Please choose an option from

1 NO SEX AS A RESULT OF BOWEL DISEASE
2 MAJOR LIMITATION AS A RESULT OF BOWEL DISEASE
3 MODERATE LIMITATION AS A RESULT OF BOWEL DISEASE
4 SOME LIMITATION AS A RESULT OF BOWEL DISEASE
5 A LITTLE LIMITATION AS A RESULT OF BOWEL DISEASE
6 HARDLY ANY LIMITATION AS A RESULT OF BOWEL DISEASE
7 NO LIMITATION AS A RESULT OF BOWEL DISEASE

29. How much of the time during the last 2 weeks have you been troubled by nausea or feeling sick to your stomach? Please choose an option. from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

30. How much of the time during the last 2 weeks have you felt irritable? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

31. How often during the past 2 weeks have you felt a lack of understanding from others? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

32. How satisfied, happy, or pleased have you been with your personal life during the past 2 weeks? Please choose one of the following options from

1 VERY DISSATISFIED, UNHAPPY MOST OF THE TIME
2 GENERALLY DISSATISFIED, UNHAPPY
3 SOMEWHAT DISSATISFIED, UNHAPPY
4 GENERALLY SATISFIED, PLEASED
5 SATISFIED MOST OF THE TIME, HAPPY
6 VERY SATISFIED MOST OF THE TIME, HAPPY
7 EXTREMELY SATISFIED, COULD NOT HAVE BEEN MORE HAPPY OR PLEASED

PT101-201-StatisticalAnalysisPlan-V02

Final Audit Report 2024-02-14

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