Statistical Analysis Plan

NCT Number: NCT03943446

Title: A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Phase 2a Study to Evaluate the Safety, Tolerability, and Early Proof of Concept of TAK-018 for the Prevention of Postoperative Crohn's Disease Recurrence

Study Number: TAK-018-2001

Document Version and Date: Version 2 (02-November-2022)

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STATISTICAL ANALYSIS PLAN

Study Number: TAK-018-2001

A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Phase 2a Study to Evaluate the Safety, Tolerability, and Early Proof of Concept of TAK-018 for the Prevention of Postoperative Crohn's Disease Recurrence

Phase 2a

TAKEDA DEVELOPMENT CENTER AMERICAS

Version: 2 (Amendment 1)

Date: 02 November 2022

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Based on:

Protocol Amendment 05, Protocol Date: 08 October 2021

Statistical Analysis Plan, Original Version, Date: 07 October 2022

1.1 APPROVAL SIGNATURES

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonization E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

Electronic signatures can be found on the last page of this document.

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3.0 LIST OF ABBREVIATIONS

AE	adverse event
AESI	adverse of special interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate aminotransferase
BID	twice daily
BLQ	below the limit of quantification
BMI	body mass index
BUN	blood urea nitrogen
CD	Crohn's disease
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CTCAE	common terminology criteria for adverse events
CV	coefficient of variation
eCRF	electronic case report form
D1	Day 1
ET	early termination
ERR	endoscopic recurrence rate
FAS	full analysis set
FCP	fecal calprotectin
FCS	fully conditional specification
GLMM	generalized linear mixed model
HHC	home health care
IBD	inflammatory bowel disease
ICH	International Conference on Harmonization
ICF	informed consent form
IMP	investigational medical product
LLN	lower limit of normal
LLOQ	lower limit of quantitation
LOCF	last observation carried forward
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MOA	mechanism of action
OC	observed case

PCS	potentially clinically significant
PE	physical examination
PK	pharmacokinetics
PPS	per protocol set
[redacted]	[redacted]
Q1	lower quartile
Q3	upper quartile
[redacted]	[redacted]
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
SD	standard deviation
SE	standard error
SI unit	international system of units
SOC	system organ class
TBILI	total bilirubin
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
VAS	visual analog score
WBC	white blood cell
WHO	World Health Organization
W3	Week 3
W6	Week 6
W12	Week 12
W18	Week 18
W26	Week 26
W30	Week 30

4.0 INTRODUCTION

This document describes the statistical analyses to be performed and data presentations to be produced for this randomized, double-blinded, placebo-controlled, phase 2a study to evaluate the safety, tolerability, and Early Proof of Concept of TAK-018 for the prevention of postoperative Crohn's Disease (CD) recurrence in subjects who are undergoing a planned laparoscopic ileocecal resection with primary anastomosis.

The purpose of this statistical analysis plan (SAP) is to ensure the credibility of the study findings by specifying the statistical approaches to the analyses of the double-blinded data prior to database lock. This SAP was developed based on the International Conference on Harmonization (ICH) E3 and E9 Guidelines and in reference to the following document:

- Protocol TAK-018-2001 Amendment 05 dated 08 October 2021.

Any deviations during the analysis and reporting process from the current statistical analysis plan will be described and justified in the final report. Analysis issues that suggest changes to the principal features stated in the protocol will be documented in a protocol amendment. Otherwise, the statistical analysis plan will be updated through an amendment in which the changes in the analysis will be documented.

5.0 OBJECTIVES

5.1 Primary Objective

- To evaluate the efficacy of TAK-018 in reducing endoscopic recurrence of intestinal inflammation in postoperative subjects with CD after planned laparoscopic ileocecal resection with primary anastomosis.

5.2 Safety Objective

- To assess the safety and tolerability of TAK-018 in postoperative subjects with CD after planned laparoscopic ileocecal resection with primary anastomosis.

5.3 Secondary Objectives

- To evaluate the effect of TAK-018 on intestinal inflammation based on serial fecal calprotectin measurements.
- To characterize the pharmacokinetics (PK) of TAK-018 in postoperative subjects with CD after planned laparoscopic ileocecal resection with primary anastomosis.

5.4 Exploratory Objectives

- [redacted]
- [redacted].

[redacted]

5.5 Study Design

This is a randomized, double-blind, placebo-controlled, multicenter, phase 2a study to evaluate the safety, tolerability, and efficacy of TAK-018 administered postoperatively to subjects with CD who have undergone a planned laparoscopic ileocecal resection with primary anastomosis to prevent postoperative recurrence of their disease. Of note, the laparoscopic ileocecal resection is not considered a study procedure and should be completed per institutional standard of care.

Initial eligibility will be determined during the screening period. Subjects will provide written informed consent at screening. Subjects who meet all eligibility criteria on D1, defined as the day within 72 hours after surgery on which the first dose of study drug is administered, will be randomized into this study. Randomization will be stratified by smoking status (active smokers versus nonsmokers/previous smokers). Approximately 96 subjects will be randomized in a 1:1:1 ratio to 3 treatment arms: TAK-018 low dose (0.30 g BID), TAK-018 high dose (1.5 g BID), or placebo (approximately 32 subjects per arm) and will be treated for a 26-week treatment period to begin on D1. Study drug is taken immediately after a meal (ie, breakfast and dinner) with water BID, approximately 8 to 12 hours apart. While on treatment, subjects will have study visits at W3, W6, W12, W18, and W26, with a final clinic visit at W30, 30 days after the W26 endoscopy. Study visits at D1 and W26 are clinic visits; study visits at screening, W3, W6, W12, W18, and W30 may be conducted as clinic or home health care (HHC) visits to provide flexibility for subjects.

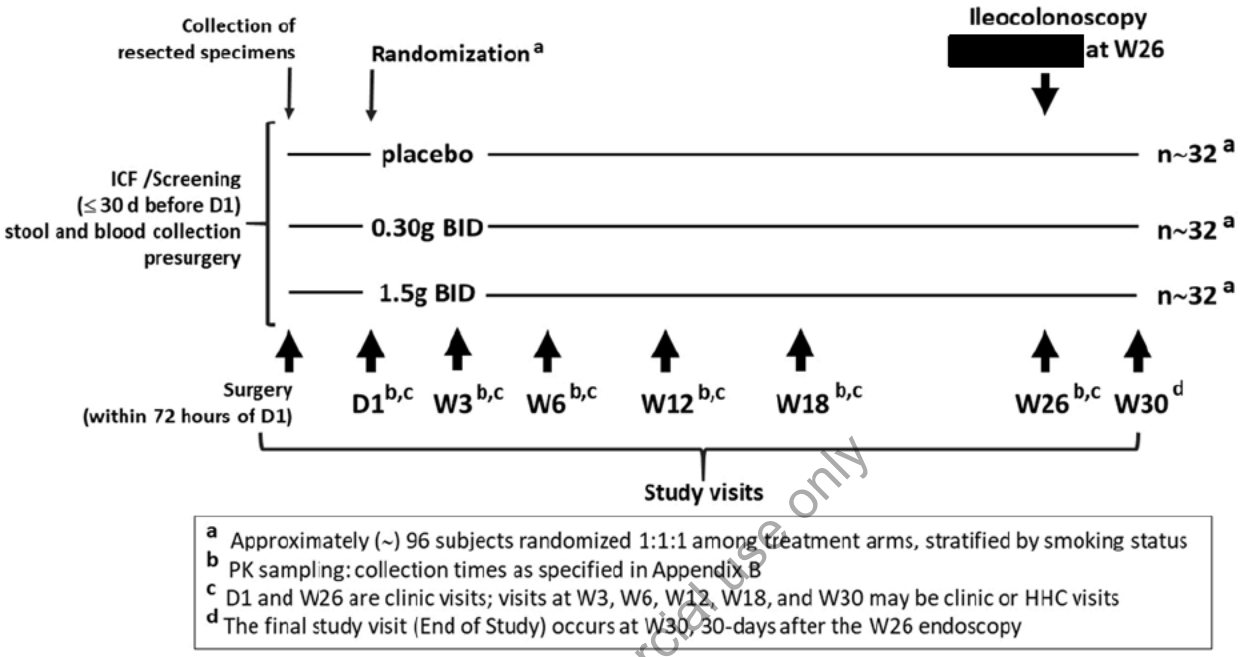
Blood samples will be collected presurgery and at all study visits after dosing starts to characterize disease progression, response to study drug, safety parameters, and the PK of TAK-018 (see Protocol Appendix B). Blood samples will be collected at all study visits not to exceed 425 mL per subject over the study period. Subjects will also provide stool samples before surgery during the screening period and at W3, W6, W12, W18, W26, and W30. Fecal calprotectin will be measured before surgery during the screening period and in every stool collection. Endoscopic assessment will be performed at the end of the 26-week treatment period (W26) and will be assessed by central readers.

The study consists of a screening period (up to 30 days before randomization), a 26-week treatment period that begins within 72 hours after surgery (starting when the subject arrives at the postsurgery recovery ward or unit), and a final study visit at W30, 30 days after the W26 endoscopy. The end of study visit will be the final study visit at W30 or, for subjects who discontinue early, will occur 30 days after their last dose of study drug.

Subjects who discontinue study drug treatment will complete an early termination (ET) visit upon discontinuation and a final safety visit 30 days after their last dose of study drug.

A schematic of the study design is depicted in Figure 5.a below. A schedule of assessments is listed in the protocol, Appendix A.

Figure 5.a Schematic of Study Design



BID: twice daily; D1: Day 1; HHC: home health care; ICF: informed consent form; PK: pharmacokinetic; W3: Week 3; W6: Week 6; W12: Week 12; W18: Week 18; W26: Week 26; W30: Week 30.

6.0 STUDY ENDPOINTS

6.1 Primary Endpoint

- The primary endpoint of this study is endoscopic recurrence defined as subject with Rutgeerts score of endoscopic lesions being graded equal to or higher than the ordinal Rutgeerts Grading Scale i2 (Appendix A) at Week 26 (W26).

6.2 Safety Endpoint

The treatment-emergent adverse events (TEAEs), defined as AEs that begin or worsen after the first dose of study treatment regardless of relationship to study drug, SAEs, and/or clinically significant changes in vital signs, standard laboratory tests and procedures (eg, clinical chemistry, hematology, urinalysis).

6.3 Secondary Endpoints

- Observed fecal calprotectin (FCP) level at Week 3 (W3), Week 6 (W6), Week 12 (W12), Week 18 (W18), Week 26 (W26), and Week 30 (W30).
- Observed plasma trough concentrations of TAK-018 at W3.

6.4 Exploratory Endpoints

[redacted]

7.0 DETERMINATION OF SAMPLE SIZE

This study is planned to randomize approximately 96 subjects stratified by smoking status (active smoker vs nonsmoker/previous smoker) in a 1:1:1 ratio to each of 3 treatment arms (approximately 32 subjects per arm).

Assuming the true recurrence rate in the placebo arm to be 50%, a total of 81 subjects will provide at least 75% power to detect a 25% or larger difference in recurrence rates between treatment and placebo arms using a 2-sided chi-squared test at a 0.2 level of significance.

To account for an assumed dropout rate of 15%, approximately 96 subjects will be randomized in this study.

8.0 METHODS OF ANALYSIS AND PRESENTATION

8.1 General Considerations

8.1.1 Statistics and Precision

For continuous variables, descriptive statistics will include the number of subjects (n), mean, standard deviation (SD), median, lower and upper quartiles (Q1 and Q3), minimum, and maximum. The number of decimal places displayed for each statistic will be determined as follows:

- Mean and median: 1 more than the number of decimal places allotted in the source data.
- SD: 2 more than the number of decimal places allotted in the source data.
- Q1 and Q3: 1 more than the number of decimal places allotted in the source data.

- Minimum and maximum: equal to the number of decimal places allotted in the source data.
- Confidence intervals (CIs) will be presented using the same number of decimal places as the parameters (eg, mean).
- p-values will be reported with three decimal places.

For categorical data, frequency counts and percentages will be presented. Percentages will be reported to 1 decimal place.

For plasma concentration data, descriptive statistics will be reported with three significant digits.

The data summaries will be accompanied by individual subject data listings sorted by treatment, study center and subject identifier. The actual day relative to the start of treatment will be determined and included in the listings.

8.1.2 Definition of Study Day and Visit Windows

A windowing convention will be used to determine the analysis value for a given study visit that applies to observed data.

Baseline values are defined as the last non-missing values collected during the time interval from the screening visit to the first dose date (time) of the study treatment.

Study Day 1 is defined as the date of the first dose of study drug, as recorded on the eCRF. Other study days are defined relative to Study Day 1. Relative day is calculated as (date of interest – date of first dose +1) for study days on or after the date of first dose, and as (date of interest – date of first dose) for study days prior to the first dose date.

For each visit, an analysis window will be defined such that the lower and upper bounds of each window is generally the midpoint between 2 consecutive study visits. Analysis windows for various parameters are specified in Table 8.a. More than 1 result for a parameter may be obtained in an analysis visit window. In such an event, the result with the date closest to the scheduled visit day will be used. In the event of 2 observations are equidistant to the scheduled visit day, the later of the observations will be used. [redacted]

The analysis window convention will not be applied to the eCRF data listings. The data listings for eCRF data will display the raw data as collected and entered in the eCRF.

8.2 Important Protocol Deviations

All subjects with important protocol deviations will be identified in the minutes of the subject evaluability assessment performed prior to unblinding and will be listed by study center and subject number.

Table 8.a Analysis Visit Window

Visit	Scheduled Day	Safety[a]	ECG	Endoscopy / [redacted]	FCP	[redacted]
Baseline	Day 1	≤1	≤1	≤1	≤1	
W3	Day 21	2-32	2-53	NA	2-32	
W6	Day 42	33-63	NA	NA	33-63	
W12	Day 84	64-105	54-133	NA	64-105	
W18	Day 126	106-154	NA	NA	106-154	
W26	Day 182	155-196	134-196	≥91	155-196	
W30	Day 212	≥197	≥197	NA	≥197	

[a] Safety analyses parameters including safety labs, vital signs, and urinalysis.

8.3 Analysis Sets

The following analysis sets will be used:

- Full analysis set (FAS) will include all subjects to whom study treatment have been assigned by randomization and received at least 1 dose of study drug. Subjects in this set will be analyzed by the treatment arm to which the subjects were randomized.
- Per protocol set (PPS) will include all FAS subjects who had no important protocol deviation that could confound the interpretation of the primary analyses based on the FAS. Subjects with any of the following protocol deviations will be excluded from the FAS to form the PPS.
  - Subject do not have a documented diagnosis of CD confirmed by endoscopic biopsy before resection or by tissue obtained at resection.
  - Non-evaluable ileocolonoscopic score at W26 (with the analysis visit window in Table 8.a applied).
  - Subjects received wrong treatment during study.

  The PPS will be used as a supplemental analysis for the primary efficacy endpoint.
- Response-evaluable set will include all randomized subjects who received at least 1 dose of study drug and had an evaluable ileocolonoscopic score at W26. Subjects in this set will be analyzed by the treatment arm to which the subjects were randomized.
- Safety analysis set (SAS) will include all randomized subjects who receive at least 1 dose of study drug. Subjects in this set will be analyzed according to the treatment received.
- PK analysis set: Subjects from the safety analysis set with at least 1 reported PK concentration. Subjects in this set will be analyzed according to the treatment received.

8.4 Disposition of Subjects

A subject disposition summary presented by treatment group and overall will be provided for all randomized subjects. The categories will include all subjects who were randomized, subjects who were not treated, subjects who discontinued from the study categorized by reason, and subjects who completed the study. Post-randomization discontinuation reasons will include all categories collected on the eCRF. A listing will be presented to describe study treatment, date of first dose, date of last dose, date of completion or early withdrawal, and the reason for early discontinuation for each subject.

A summary of screening failures and listings of inclusion/exclusion criteria responses for subjects with protocol deviations will also be provided.

8.5 Demographic and Baseline Characteristics

Demographic, baseline characteristics including sex, age, race, height, weight, body mass index (BMI), and smoking status will be listed and summarized for each treatment group and overall. These summaries will be based on FAS.

Height and weight values will be presented in metric units (cm and kg respectively). BMI is calculated as [weight (kg)/height (m) ^{2}], using the weight collected prior to first dose date.

All individual demographic and baseline data will be listed by treatment, study center and subject number.

8.6 Disease Characteristics

Crohn's Disease characteristics including family history of inflammatory bowel disease (IBD), time from diagnosis until randomization (months), number of acute exacerbations during the last 12 months, location and extent of the disease, prior interventions and prior therapies related to the disease will be summarized for each treatment group and overall. These summaries will be based on FAS.

All individual disease-related data will be listed by treatment, study center and subject number.

8.7 Medical History and Concurrent Medical Conditions

Medical history refers to significant conditions/diseases that stopped at or prior to Screening (time of informed consent). Concurrent medical conditions are those significant ongoing conditions/diseases present at Screening (time of informed consent).

Medical history and concurrent medical conditions will be coded using Medical Dictionary for Regulatory Activities (MedDRA) latest version and will be summarized by treatment group and overall using System Organ Class (SOC) and MedDRA preferred term based on FAS. The table will include number and percentages of subjects and will be sorted in alphabetical order by system organ class and preferred term. A subject will only be counted once within a particular class even if he/she has multiple conditions/symptoms.

All medical history and concurrent medical condition data will be listed by treatment, study center and subject number.

8.8 Medication/Procedure History and Concomitant Medications/Procedures

The medication/procedure history and concomitant medications/procedures are defined as follows:

- Medication/procedure history refers to the medication/procedure that the study subjects stopped taking within 30 days prior to randomization.
- Concomitant medication/procedure is defined as medication/procedure that the study subjects continued taking or started after randomization.

In the case of missing or partial dates, the rules of imputation are defined in Appendix C.

Medication history and concomitant medications will be coded using the latest version of the World Health Organization (WHO) Drug Dictionary and summarized by treatment group and overall using preferred term within each anatomical therapeutic class, with anatomical therapeutic class and medications in each class sorted in alphabetical order based on FAS. If a subject reports taking more than one drugs belonging to the same class, he/she will only be counted once within that class.

All prior and concomitant medications will be listed by treatment, study center and subject number. The listings will contain subject identifier, WHO Drug preferred term and reported term, dose, unit, route, frequency, the indication for which the medication was being taken, start date, whether start date was before or after signing informed consent, stop date, and whether the medication was ongoing.

All prior and concomitant procedures will be listed by treatment, study center, and subject number. The listings will contain subject identifier, category of procedure, procedure name, the indication for which the procedure was being taken, start date, whether start date was before or after signing informed consent, stop date, and whether the medication was ongoing.

8.9 Study Drug Exposure and Compliance

The summary of study drug exposure and compliance will be based on the safety analysis set.

The duration of exposure (weeks) to study medications is defined as (date of last dose – date of first dose +1)/7. Treatment duration will be summarized using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum). In addition, the number and percentage of subjects in each duration category (≤4 weeks, 4 - ≤8 weeks, 8 - ≤12 weeks, 12 - ≤16 weeks, 16 - ≤20 weeks, 20 - ≤26 weeks, and >26 weeks) will be summarized by treatment group and overall.

Percent of study drug compliance is defined as (number of tablets dispensed – number of tablets returned)/[(date of last dose – date of first dose +1)*6]*100%. If a value for the number of returned tablets is missing or the return date is missing, then 100% compliance will be assigned for each day up to number of tablets dispensed or up to the date of return whichever is earlier.

The number and percentage of subjects in each compliance category (<80% and ≥80%) will be summarized by treatment group and overall. Study medication compliance will also be summarized as a continuous variable using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) by treatment group and overall.

All study drug administration and accountability data will be listed by treatment, study site, and subject number. The following variables will be listed: subject identifier, visit number, first and last dose dates, medication identification number, date dispensed and returned, number of tablets dispensed and returned, and percent compliance.

8.10 Primary and Secondary Efficacy Analyses

All efficacy endpoints will be analyzed by placebo arm, TAK-018 dose arms, and TAK-018 pooled using the FAS.

8.10.1 Primary Efficacy Analyses

The number and percentage of subjects with evaluable ileocolonoscopic score at W26 will be summarized by the ordinal Rutgeerts score of endoscopic lesions (Appendix A) and treatment arm (ie, placebo arm, TAK-018 dose arms, and TAK-018 pooled) based on FAS.

The endoscopic recurrence is defined as a subject with Rutgeerts score of endoscopic lesions being graded equal to or higher than the ordinal Rutgeerts score i2 at W26. The Cochran-Mantel-Haenszel (CMH) test using the randomization stratification factor (smoking status) will be used for the comparison of the endoscopic recurrence rate (ERR) between TAK-018 dose arms (ie, two TAK-018 dose arms and TAK-018 pooled) and placebo arm. In the case of small cell sizes (ie, <5), the Fisher's exact test will be used instead of the CMH test. The estimate of ERR of each treatment arm and its 95% CI will be reported (the exact Clopper-Pearson CI will be reported if Fisher's exact test are used). The estimates of the difference in ERR between TAK-018 dose arms and placebo arm and their 80% and 95% CIs (the exact Clopper-Pearson CI will be reported if Fisher's exact test are used) will be provided as well. In addition, the nominal two-sided p-values for testing the differences in ERR between the TAK-018 dose arms (ie, two TAK-018 dose arms, and TAK-018 pooled) and placebo arm will be reported.

The primary efficacy analysis will be conducted using both local and central reads of the endoscopic results. Analysis results based on local and central reads will be reported separately.

In the primary efficacy analysis, missing data will be handled using non-responder (worst-case) imputation, ie, subjects will be classified as endoscopic recurrence (ie, ordinal Rutgeerts score is i2 or higher) at W26 if no endoscopy was performed at W26 or if the ileocolonoscopic score was unevaluable at W26.

8.10.1.1 Sensitivity Analyses

To assess the robustness of the primary efficacy analysis, the following additional sensitivity analyses will be performed for the primary efficacy endpoint:

- The primary efficacy analysis described in section 8.10.1, will be repeated using the response-evaluable set.
- The primary efficacy analysis described in section 8.10.1, will be repeated using the PPS.

The sensitivity analysis will be conducted using both local and central reads of the endoscopic results. Analysis results based on local and central reads will be reported separately.

8.10.2 Secondary Efficacy Analyses

The actual values of fecal calprotectin (FCP) in stool sample will be summarized by treatment arms (ie, placebo arm, TAK-018 dose arms, and TAK-018 pooled) and scheduled visits (ie, Baseline, W3, W6, W12, W18, W26, and W30) using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) based on FAS. In addition, the number and percentage of subjects with FCP level >135 µg/g, >250 µg/g, and <100 µg/g will be summarized respectively by treatment arms (ie, placebo arm, TAK-018 dose arms, and TAK-018 pooled) and scheduled visits (ie, Baseline, W3, W6, W12, W18, W26, and W30) based on FAS.

The generalized mixed-effects model (GLMM) will be applied to analyze the secondary efficacy endpoints (ie, rates of FCP level >135 µg/g, >250 µg/g, and <100 µg/g, respectively) observed at visits of W3, W6, W12, W18, and W26 to assess the treatment difference between TAK-018 dose arms and placebo. In GLMM, the missing continuous values of FCP at visits of W3, W6, W12, W18, and W26 will be handled using multiple imputation (MI), ie, the missing FCP value (based on log-10 transformation) will be imputed by treatment group, smoking status at randomization, and baseline FCP value (on a log-10 transformation) via a multivariate step-wise approach using fully conditional specification (FCS) regression method. Twenty-five (25) complete datasets will be computed and analyzed by using GLMM, as the relative efficiency is sufficiently high with the expected fraction of missing information is 65%.The results from the 25 complete datasets will be combined for the GLMM inference following Rubin's rule.

The GLMM will have FCP level >135 µg/g, >250 µg/g, and <100 µg/g as response variable, respectively, with treatment group, visit, treatment and visit interaction, smoking status at randomization, and baseline FCP value (on log-10 transformation) as fixed effects, and subject as random effect. The estimate of the FCP rate of each treatment arm at each visit (ie, W3, W6, W12, W18, and W26) and its 95% CI will be reported. The estimates of the difference in FCP rates and the odds ratio between TAK-018 dose arms and placebo at each visit, and its associated 95% CIs and nominal two-sided p-values based on the GLMM will be reported as well.

Among the 25 complete datasets from MI procedure, if less than 15 (<60%) datasets analyzed by using GLMM converge after database lock, other analyses, such as the GLMM without adjusting for smoking status at randomization, the chi-squared test or the Fisher's exact test in the case of small cell sizes at each scheduled visits, will be explored.

For visualization purpose of the FCP data over time, the following plots will be generated: (1) spaghetti plot of FCP levels (log-10 transformed) for individual subject by scheduled visits and treatment arms; (2) box plot with mean, median, Q1, and Q3 of actual values of FCP by scheduled visits and treatment arms; (3) percentage of subjects with actual value of FCP >135 µg/g or >250 µg/g or <100 µg/g by scheduled visits and treatment arms; (4) the estimated FCP rates for levels >135 µg/g, >250 µg/g, and <100 µg/g with corresponding 95% CI from GLMM by scheduled visits and treatment arms, if the convergence criterion for GLMM specified above has been met.

8.11 Pharmacokinetic Analyses

Concentrations of TAK-018 will be determined from pharmacokinetic samples collected and listed by treatment, study site and subject number.

The PK analysis set will be used for all PK analyses. Approximately one-third of subjects may participate in the PK subgroup for relatively more intensive collections at D1 and W3. All other subjects will be required to provide sparse PK samples as outlined in the SOE (see protocol Appendix A) and PK SOE (see protocol Appendix B). Missing PK data will not be imputed. Plasma concentration below the limit of quantification (BLQ) will be treated as zero in the summary of concentration values.

Plasma concentrations of TAK-018 will be summarized using descriptive statistics (n, mean, SD, CV[%], median, minimum, and maximum) by treatment group, nominal visit (W0/Day 1 and W3/Day 21) and time (Predose, 1, 2, 3, 4, 6, 8, and 12 hours) based on the PK subgroup (subjects in PK analysis set with intensive collections at D1 and W3). The observed plasma trough concentrations of TAK-018 at W3/Day 21 will be summarized using descriptive statistics (n, mean, SD, CV[%], median, minimum, and maximum) by treatment group based on the PK analysis set (including both subjects with intensive and sparse sample collections).

Individual plasma concentration data versus time will be presented in a data listing based on the PK analysis set.

Further analysis may be performed as deemed necessary for the interpretation of the data and will not be reported in the clinical study report and reported as part of a separate report.

8.12 Exploratory Endpoints Analyses

[redacted]

8.12.1 [redacted]

[redacted]

[redacted]

8.12.2 [redacted]

[redacted]

8.12.3 [redacted]

[redacted]

8.12.4 [redacted]

[redacted]

[redacted]

8.12.5 [redacted]

[redacted]

8.12.6 [redacted]

[redacted]

8.13 Safety Analyses

Safety summaries will be based on the safety analysis set. Conventions for the definition of baseline values and visit windowing are given in Section 8.1.2. Clinical laboratory evaluations and vital signs will be summarized by study visit and treatment groups.

8.13.1 Adverse Events

All adverse events will be coded using MedDRA latest version. All adverse events will be included in the data listings but only treatment-emergent adverse events will be included in the summary tables.

A treatment-emergent adverse event (TEAE) is defined as an adverse event with an onset that occurs after receiving study drug (AE start date ≥ first dose date) and within 30 days after

receiving the last dose of study drug (AE start date - last dose date ≤30). A TEAE may also be a pretreatment adverse event or a concurrent medical condition diagnosed prior to the date of first dose of study drug that increases in severity after the start of dosing. Adverse events data with onset occurring more than 30 days after last dose of study drug (AE start date - last dose date >30) will be listed, but not included in the summary tables. In the case of missing or partial dates, the rules of imputation are defined in Appendix C.

Serious adverse events (SAEs) with onset that occurs after receiving study drug (AE start date ≥ first dose date) and within 30 days after receiving the last dose of study drug (AE start date - last dose date ≤30) will be summarized.

At the adverse event level, the summary tables will present the number of subjects reporting each of these MedDRA events, ie, the number of subjects reporting 1 or more events that map to the given MedDRA term.

At the SOC level, the summary tables will present the number of subjects reporting 1 or more events that map to the given SOC. That is, the number of subjects reported at the SOC level will be less than or equal to the sum of the subject counts across all adverse events within that SOC.

In selected summaries (TEAEs overview, and TEAEs by SOC and preferred term), adverse events will be summarized by Placebo, TAK-018 dose arms, TAK-018 pooled, and Overall using the number and percentage of subjects with events.

For the summary of TEAEs by SOC, preferred term and maximum intensity, if a subject experiences more than 1 episode of a particular coded adverse event, the subject will be counted only once by the maximum intensity of the episode (preferred term). Similarly, if a subject has more than 1 adverse event within an SOC, the subject will be counted only once by the maximum intensity in that SOC. Adverse events with missing severity will be classified as having the highest severity. Similarly, adverse events with missing relationship will be classified as having the highest relationship to study drug.

The following summaries will be presented:

- Overview of TEAEs during the study - number and percentage of subjects.
- TEAEs by SOC and preferred term - number and percentage of subjects.
- TEAEs by SOC and preferred term by sex (male and female) - number and percentage of subjects.
- TEAEs by SOC and preferred term by age group (≤65, >65) - number and percentage of subjects.
- TEAEs with grade 3 or higher by SOC and preferred term - number and percentage of subjects.
- Treatment-related TEAEs by SOC and preferred term - number and percentage of subjects.
- Treatment-related TEAEs with grade 3 or higher by SOC and preferred term - number and percentage of subjects.

- TEAEs leading to study discontinuation by SOC and preferred term - number and percentage of subjects.
- Treatment-emergent SAEs by SOC and preferred term - number and percentage of subjects.
- Treatment-related treatment-emergent SAEs by SOC and preferred term - number and percentage of subjects.
- Most frequent non-serious TEAEs (>5% in any treatment arm) by preferred term - number and percentage of subjects

SOCs will be sorted by alphabetical order. Within a SOC, adverse events will be sorted in descending order of total number of subjects with preferred term among all the treatment groups.

All adverse events will be listed by treatment, study center, subject number and onset date of the adverse event. The listing will contain subject identifier, age, sex, body weight, race, adverse event (preferred term and reported term), SOC, onset date, end date or whether the event was ongoing, duration, frequency, intensity (mild, moderate or severe), action taken concerning study drug, causality to study drug, the outcome, and whether the adverse event was an SAE.

8.13.2 Clinical Laboratory Evaluations

The summaries will include all clinical laboratory assessments collected no later than 30 days after the last administration of study treatment. All laboratory assessments will be listed and those collected later than 30 days after the last treatment date will be flagged in the listings.

Laboratory data will be classified into CTC grades according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) v5.0. For laboratory tests where grades are not defined by CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

For each laboratory parameter, the following will be displayed for each scheduled time point (each visit and end of study).

- Summary statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) by Placebo, TAK-018 dose arms, TAK-018 pooled, and Overall for the actual values and change from Baseline values.
- Shift tables using CTCAE grades to compare baseline to the worst post-baseline value will be produced for hematology and chemistry laboratory parameters with CTCAE grades.
- Shift tables for the change from Baseline to each post-baseline time point will be presented. For these tables each subject will be categorized as low, normal, or high for the baseline value, and low, normal, or high for each post-Baseline time point, according to the central laboratory reference ranges. The number of subjects in each of the combinations of shifts will be presented.
- Potentially clinically significant (PCS) laboratory values, as defined in Appendix A, will be summarized by treatment group and overall. The number and percentage of subjects with

PCS values observed post-Baseline in each of the applicable laboratory parameters will be presented.

- For liver function tests, the number and percentages of subjects with the worst post-baseline values that fall in each of the listed categories will be summarized by Placebo, TAK-018 dose arms, TAK-018 pooled, and Overall:
  - ALT:
    - >3 × upper limit of normal (ULN);
    - >5 × ULN;
    - >8 × ULN;
    - >20.0 × ULN.
  - AST:
    - >3 × ULN;
    - >5 × ULN;
    - >8 × ULN;
    - >20 × ULN.
  - ALT or AST:
    - ALT >3 × ULN or AST >3 × ULN;
    - ALT >5 × ULN or AST >5 × ULN;
    - ALT >8 × ULN or AST >8 × ULN;
    - ALT >20 × ULN or AST >20 × ULN.
  - ALT/AST and Total Bilirubin (TBILI):
    - ALT >3 × ULN AND TBILI >2 × ULN;
    - AST >3 × ULN AND TBILI >2 × ULN;
    - (ALT >3 × ULN or AST >3 × ULN) AND TBILI >2 × ULN.

A listing of all laboratory data will be provided. Laboratory data outside of the normal reference range will be flagged on the listing along with values meeting PCS criteria. The listing will also include the age (at consent) and sex of the subject. Listings of PCS laboratory values will also be presented.

Summaries and listings of laboratory data will be presented in conventional units.

8.13.3 Vital Signs and Weight

Vital signs and weight at scheduled visits and their changes from Baseline will be summarized by Placebo, TAK-018 dose arms, TAK-018 pooled, and Overall using descriptive statistics by visit and end of study. The number and percentage of subjects with at least one post-Baseline

PCS vital sign value during the double-blind treatment period will be presented by Placebo, TAK-018 dose arms, TAK-018 pooled, and Overall for each variable over all visits. A listing of PCS vital signs values will also be presented. The criteria for identification of PCS vital signs values are given in Appendix A.

8.13.4 Physical Examinations

All physical examination findings, if applicable, will be listed by treatment, study center and subject number. The following variables will be listed: subject identifier, age, sex, study visit, visit date, body system, whether there was an abnormality, and, a description of the abnormality.

8.13.5 Pregnancy Test, Urine Drug and Alcohol Screen Test

For females, pregnancy test results will be listed by treatment, study center and subject number.

8.13.6 12-lead ECG

The investigator's ECG interpretation (ie, with normal limits, abnormal but not clinically significant, abnormal and clinically significant, and not evaluable) will be summarized by Placebo, TAK-018 dose arms, TAK-018 pooled, and Overall using descriptive statistics by visit (Baseline, W3, W12, W26) and end of study based on safety analysis set.

All ECG data will be presented in the by-subject listing based on safety analysis set.

8.14 Interim Analysis

Not applicable.

8.15 Changes in the Statistical Analysis Plan

8.15.1 Changes From the Protocol Analysis Plan

Version	Protocol Version	Changes	Justifications
1	Amendment 04, Protocol Date: 30 July 2020	Rephrase the definition of the primary endpoints	To make the endpoint more clearly defined.
		Rephrase the definitions of some binary secondary [redacted] endpoints	To make these endpoints to become variables defined at a subject level instead of summary statistics at a population level.
		Add the definition of per protocol set.	To provide a sensitivity analysis of the primary endpoint based on the per protocol set.
		Add the option of using the Fisher's exact test as an alternative to the CMH test in the case of small cell sizes (ie, the expected values of any of the cells of the contingency table are below 5).	To make the analysis method more robust in case of small cell sizes.

Version	Protocol Version	Changes	Justifications
		Add the method of analyzing longitudinal binary secondary endpoint of fecal calprotectin response observed at visits of W3, W6, W12, W18, W26, and W30 using the generalized mixed-effects model (GLMM).	To make the analysis method more efficient than simple descriptive summary statistics
		[redacted]	[redacted]
2	Amendment 05, Protocol Date: 08 October 2021	Rephrase the definitions of some secondary [redacted] endpoints.	To improve clarity on endpoint definitions.
		Add the additional efficacy endpoints for FCP to include categories of >250 µg/g and <100 µg/g.	To provide comprehensive analysis on both higher and lower levels of FCP.

8.15.2 Revision History

Version	Approval Date	Primary Rationale for Revision
1.0	07 October 2020	Not Applicable
2.0		Updated the texts for objectives and study design in Section 5.0 and endpoints in Section 6.0 to be consistent with Protocol Amendment 5 dated 08 October 2021. Added the definition of Baseline and the table of analysis visit window for various endpoints in Section 8.1.2. Added the description of the descriptive analyses for primary and secondary endpoints in Section 8.10.1 and Section 8.10.2, respectively. Added the option of using the Fisher's exact test as an alternative to the CMH test in the case of small cell sizes in Section 8.10.1. Clarified the primary endpoint analyses will be performed using both central and local reading results in Section 8.10.1. Updated the missing data imputation method for FCP to be MI in Section 8.10.2 to support the secondary endpoint analyses with multiple FCP related binary outcomes. Added the option of using the Chi-squared test or Fisher's exact test as an alternative to the GLMM in Section 8.10.2 in the case of model convergence issue due to small sample size. Clarified the analysis set used for PK summary tables and listings and the method to handle the values below LLOQ in Section 8.11. [redacted]. Added the visualization plan for secondary [redacted] endpoints in Section 8.10.2 and Section 8.12 respectively. Updated the summaries and listings of laboratory data to be presented in conventional units in Section 8.13.2. Added the analysis plan for 12-lead ECG data in Section 8.13.6. [redacted]. Removed the position for vital signs in Appendix E to make it consistent with data collection in EDC.

Appendix A Rutgeerts Grading Scale for Endoscopic Recurrence at the Ileocolonic Anastomosis and Pre-anastomotic Ileum

Rutgeerts Score	Endoscopic Description of Lesions
i0	No lesions.
i1	≤5 aphthous ulcers.
i2	>5 aphthous ulcers with normal mucosa between lesions or lesions are confined to the anastomosis.
i3	Diffuse aphthous ileitis with diffusely inflamed mucosa.
i4	Diffuse inflammation with larger ulcers, nodules, and/or narrowing.

Source: Adapted from Rutgeerts P, Geboes K, Vantrappen G, et al. Predictability of the postoperative course of Crohn's disease. Gastroenterology. 1990;99(4):956-63.

Appendix B [redacted]

[redacted]

Appendix C Missing/Partial Dates for Adverse Event/Concomitant Medication/Procedures

Missing Data Imputation for Start Dates

If the stop date is non-missing and the imputed start date is after the stop date, the stop date will be used as the start date.

(1) Missing day only

- If the month and year are the same as the month and year of the first dose date, the first dose date will be used.
- If the month and year are before the month and year of the first dose date, the last day of the month will be assigned to the missing day.
- If the month and year are after the month and year of the first dose date, the first day of the month will be assigned to the missing day.

(2) Missing day and month

- If the year is the same as the year of the first dose date, the first dose date will be used.
- If the year is prior to the year of the first dose date, December 31 will be assigned to the missing fields.
- If the year is after the year of the first dose date, January 1st will be assigned to the missing fields.

(3) Missing day, month, and year

- The first dose date will be used.

Missing Data Imputation for Stop Date

If the start date is non-missing and the imputed stop date is before the start date, the start date will be used. If the death date is available and the imputed stop date is after the death date, the death date will be used.

(1) Missing day only

- The last day of the month will be assigned as the missing day.

(2) Missing day and month

- December 31 will be assigned to the missing fields.

(3) Missing day, month and year

- The event will be regarded as ongoing.

Appendix D Criteria for Identification of Potentially Clinically Significant Laboratory Values

Parameter	Unit Type	Unit (a)	PCS Definition
Sodium	SI	mmol/L	High: ≥155, Low: ≤125
	conventional	mEq/L	High: ≥155, Low: ≤125
Potassium	SI	mmol/L	High: ≥5.5, Low: ≤3.0
	conventional	mEq/L	High: ≥5.5, Low: ≤3.0
Calcium (total)	SI	mmol/L	High: ≥3.0, Low: ≤1.75
	conventional	mg/dL	High: ≥12.0, Low: ≤7.0
Creatinine	SI	µmol/L	High: ≥175
	conventional	mg/dL	High: ≥2.0
Creatine phosphokinase (CPK)	both	U/L	High: ≥2×ULN
Uric acid	SI	µmol/L	High: ≥1.3×ULN, Low: ≤0.7×LLN
	conventional	mg/dL	High: ≥1.3×ULN, Low: ≤0.7×LLN
Glucose (non-fasting)	SI	mmol/L	High: ≥13.9, Low: ≤2.8
	conventional	mg/dL	High: ≥250, Low: ≤50
Cholesterol (total)	SI	mmol/L	High: ≥7.8
	conventional	mg/dL	High: ≥302
Triglycerides	SI	mmol/L	High: ≥3.40
	conventional	mg/dL	High: ≥301
High density lipoproteins (HDL) cholesterol	SI	mmol/L	Low: <0.9
	conventional	mg/dL	Low: <35
Low density lipoproteins (LDL) cholesterol	SI	mmol/L	High: ≥5.0
	conventional	mg/dL	High: ≥193
Urinalysis			
Glucose			N/A
Protein			N/A
Occult Blood			N/A
Pregnancy			N/A

(a) Systeme International (SI) units, conventional units and conversion factors were obtained from Laposata, Michael. SI Unit Conversion Guide. Boston: NEJM Books, 1992.
LLN=lower limit of normal range; N/A=not applicable; PCS=potentially clinically significant; ULN=upper limit of normal range.

Appendix E Criteria for Identification of Potentially Clinically Significant Vital Signs

Parameter	Unit	PCS Definition (a)
Systolic Blood Pressure	mmHg	≥180 mmHg and an increase of ≥20 mmHg or ≤90 mmHg and a decrease of ≥20 mmHg
Diastolic Blood Pressure	mmHg	≥105 mmHg and an increase of ≥15 mmHg or ≤50 mmHg and a decrease of ≥15 mmHg
Pulse	bpm	≥120 bpm and an increase of ≥15 bpm or ≤50 bpm and a decrease of ≥15 bpm
Weight	kg	Change of ≥7% body weight

(a) PCS criteria are applied to postbaseline values and changes relative to Baseline values, as appropriate.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Biostatistics Approval	05-Nov-2022 02:09 UTC