STATISTICAL ANALYSIS PLAN

NCT Number: NCT03827655

Study Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Dose Ranging Study to Evaluate the Efficacy and Safety of 2 Dose Regimens of Intravenous TAK-954 for the Prophylaxis and Treatment of Postoperative Gastrointestinal Dysfunction in Patients Undergoing Large- and Small-Bowel Resection

Study Number: TAK-954-2004

SAP Version and Date:

Version 3.0: 18-May-2021

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PHASE 2b

Version**: Final Version 3**

Date**:** 07 May 2021

Prepared by:

[redacted], Ph.D

[redacted], Statistical & Quantitative Sciences,
Takeda Development Center Americas, Inc.

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1.1 Approval Signatures

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

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LIST OF ABBREVIATIONS

AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AV	atrioventricular
BMI	body mass index
BP	blood pressure
bpm	beats per minute
CEC	cardiovascular endpoint committee
CI	Confidence interval
CNS	central nervous system
CRP	C-reactive protein
CV	cardiovascular
CYP	cytochrome P-450
DDI	drug-drug interaction
ECG	electrocardiogram
eCRF	case report form (electronic or paper)
EQ-5D	Euro Quality of Life-5 dimensional questionnaire
ERP	enhanced recovery pathway(s)
FAS	full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GIP	glucose-dependent insulinotropic peptide
HbA1c	glycosylated hemoglobin
hCG	human chorionic gonadotropin
IA	interim analysis
ICH	International Conference on Harmonisation
ID	identification
IEC	independent ethics committee
IL	interleukin
IMC	internal monitoring committee
IND	Investigational Drug Application
IRB	institutional review board
IRT	interactive response technology
IV	intravenous
LFT	liver function tests

LOCF	Last observation carried forward
LOS	length of stay
LS	Least squares
MCP	monocyte chemoattractant protein
MedDRA	Medical Dictionary for Regulatory Activities
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NG	nasogastric
NRS	numerical rating scale
PD	pharmacodynamic
PK	pharmacokinetic
POGD	postoperative GI dysfunction
PONV	postoperative nausea and vomiting
PTE	pretreatment event
QD	once daily
QTcF	QT interval with Fridericia correction method
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SF-12	12-Item Short Form Health Survey
SUSAR	suspected unexpected serious adverse reaction
SVT	supraventricular tachycardia
VT	ventricular tachycardia
Takeda	Takeda Development Center Americas, Inc
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

3.0 OBJECTIVES

3.1 Primary Objective

The primary objective of this study is to assess the efficacy and safety of IV TAK-954 for accelerating the recovery of GI function postsurgery in patients undergoing open or laparoscopic-assisted partial small- or large-bowel resection.

3.2 Secondary Objectives

The secondary objectives of this study are:

- To determine efficacy and safety of preoperative dosing of IV TAK-954 relative to preoperative and postoperative regimens of up to 10 days of IV TAK-954 for accelerating the recovery of GI function postsurgery.
- To determine the relative efficacy and safety of 0.1 and 0.5 mg IV TAK-954 given either preoperatively alone or preoperatively and postoperatively compared to placebo of up to 10 days or resolution of GI dysfunction postsurgery for accelerating the recovery of GI function postsurgery.
- To determine the PK of TAK-954 in patients undergoing major abdominal surgery.

3.3 Exploratory Objectives

The exploratory objectives are:

- To assess the effect of IV TAK-954 on circulating markers of inflammation, including but not limited to IL-6, IL-10, MCP-1 and CRP postsurgery.
- To assess the effect of IV TAK-954 on circulating markers associated with GI motility and/or nausea.
- To gain preliminary estimates of the incidence rate of postoperative complications and prolonged POGD (≥5 days) based on the type of surgery (laparoscopic vs open surgery), use of opioids, duration of surgical procedure, and ASA scores.
- To gain preliminary estimate of the effect of TAK-954 in preventing recurrence of GI dysfunction postsurgery.
- To gain preliminary estimate of the effect of TAK-954 in preventing POGD complications.

3.4 Study Design

This phase 2, randomized, placebo-controlled, parallel 5-group, double-blind study is designed to determine: (1) if TAK-954 decreases the duration of GI dysfunction in patients undergoing major abdominal open or laparoscopic-assisted surgeries that involve significant bowel manipulation, (2) whether preoperative dosing alone or a preoperative and postoperative dosing regimen is the most effective dosing regimen to decrease the duration of POGD and improve clinical outcomes, and (3) the most appropriate dose and dosing regimen to advance into phase 3.

Subjects will be randomized in a 1:1:1:1:1 ratio into 1 of 5 parallel treatment groups:

- Regimen 1: Placebo (NS 100 mL infusion over 60 minutes) preoperation and daily postoperation until return of upper and lower GI function (ie, resolution of POGD) or for up to 10 days.
- Regimen 2: TAK-954 (0.1 mg/100 mL infusion over 60 minutes) preoperation and daily postoperation until return of upper and lower GI function or for up to 10 days.
- Regimen 3: TAK-954 (0.5 mg/100 mL infusion over 60 minutes) preoperation and daily postoperation until return of upper and lower GI function or for up to 10 days.
- Regimen 4: TAK-954 (0.1 mg/100 mL infusion over 60 minutes) preoperation and daily placebo infusions postoperation until return of upper and lower GI function or for up to 10 days.
- Regimen 5: TAK-954 (0.5 mg/100 mL infusion over 60 minutes) preoperation and daily placebo infusions postoperation until return of upper and lower GI function or for up to 10 days.

Subject randomization will be stratified by laparoscopic and open surgery procedures.

With this Protocol Amendment 05, the planned total sample size is approximately 180 subjects. Two of the above TAK-954 regimens are discontinued based on internal monitoring committee (IMC) recommendations. As a result, eligible subjects will be equally randomized to into 1 of 3 of the remaining parallel treatment groups:

- Regimen 1: Placebo (NS 100 mL infusion over 60 minutes) preoperation and daily postoperation until return of upper and lower GI function (ie, resolution of POGD) or for up to 10 days
- Regimen 3: : TAK-954 (0.5 mg/100 mL infusion over 60 minutes) preoperation and daily postoperation until return of upper and lower GI function or for up to 10 days.
- Regimen 5: TAK-954 (0.5 mg/100 mL infusion over 60 minutes) preoperation and daily placebo infusions postoperation until return of upper and lower GI function or for up to 10 days.

It is standard of practice for the postoperative care of patients after colorectal surgery to implement an ERP to reduce the time to recovery of GI function (motility). To provide a consistent ERP as baseline therapy for all subjects, they will receive the same core features of an ERP for postoperative care as outlined below:

Core ERP:

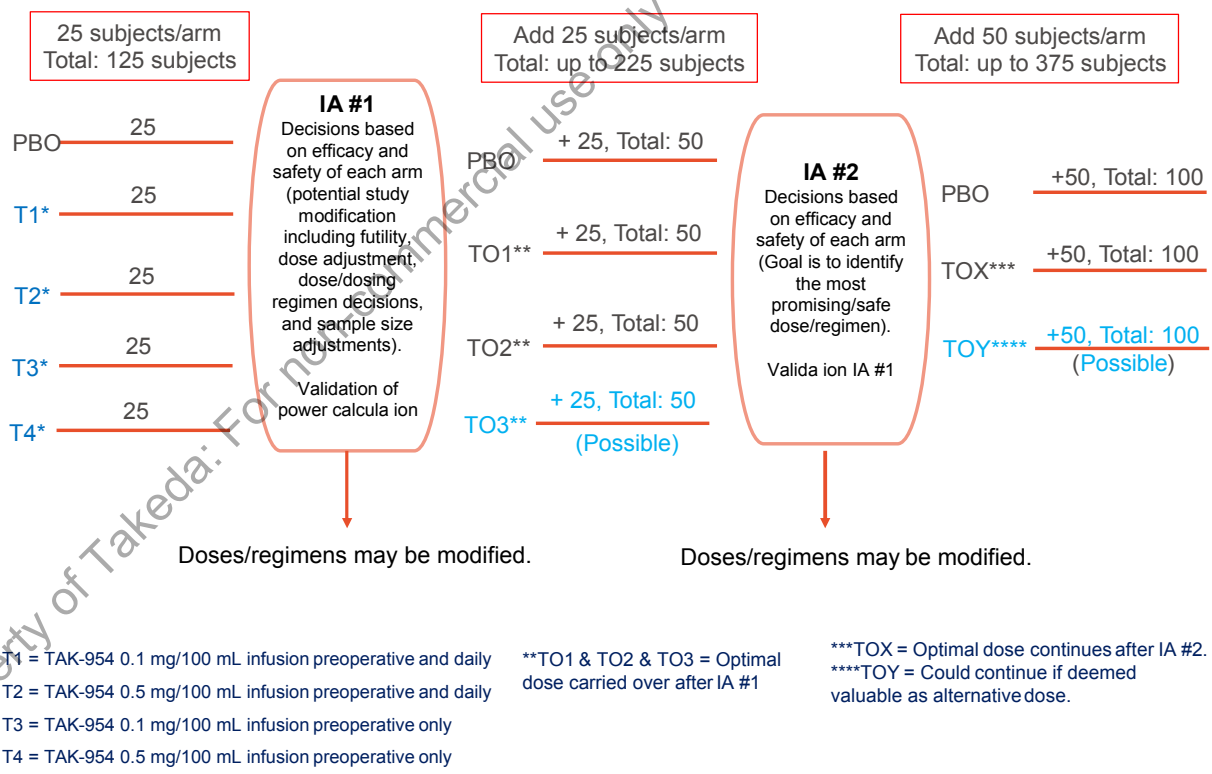
- Minimize opioid use while maintaining adequate pain control through use of multimodal analgesia. Suggested analgesics include opioid alternatives, such as nonsteroidal anti-inflammatory drugs (eg, ketorolac tromethamine IV), acetaminophen (paracetamol), or oral pregabalin, when possible. It is recommended that at least 2 different analgesics with different mechanism of action are tried and failed before prescribing opioids.

- Maintenance of euvolemia and normal salt and electrolyte state in perioperative period.
- No routine use of prophylactic NG tubes postsurgery. NG tubes should only be used if there is a documented medical reason to justify them.
- Use of a standardized risk-based strategy for PONV prophylaxis: use of preoperative antiemetic prophylaxis in patients with 1 or more risk factors of the simplified Apfel Score (female gender, planned postoperative use of opioids, nonsmokers, history of PONV/motion sickness).
- Early oral feeding postsurgery when possible. Clear liquids after the surgery on Day 1, advancing to soft diet on Day 2 if tolerant to liquids (no nausea or vomiting).
- Early mobilization starting after the surgery on Day 1 when possible.

The Schematics of the study design prior to Protocol Amendment 05 are included in Figure 3.a. and with the discontinuation of 2 treatment regimens and removal of the second IA in Figure 3.b

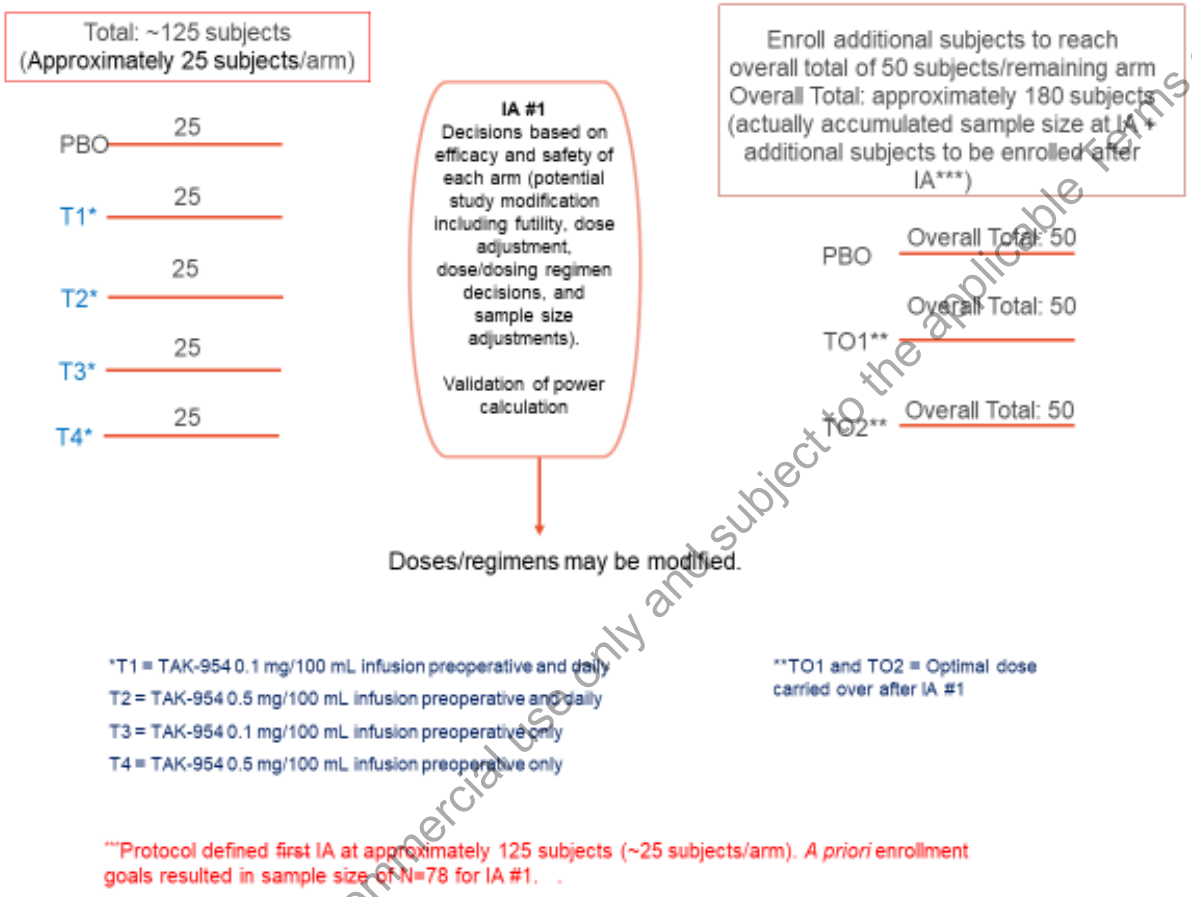
A schedule of assessments is listed in the protocol Appendix A.

Figure 3.a Schematic of Study Design Prior to Protocol Amendment 5



Abbreviations: IA, interim analysis; PBO, placebo.

Figure 3.b Schematic of Study Design by Protocol Amendment 05



Abbreviations: IA, interim analysis; PBO, placebo.

Criteria for resolution of upper and lower GI function is time to tolerance of solid food (defined as no vomiting or no clinically significant nausea for 1 calendar day after the first solid meal) and time to first spontaneous bowel movement (whichever occurs later), up to Day 10 postsurgery.

Following hospital discharge, subjects will be instructed to contact their physician if they have recurring symptoms suggestive of POGD to evaluate the need for hospital readmission in case of relapse. All subjects will return to the clinic 14 days post last dose (±4 days) for follow-up visits. Subjects will be contacted by phone 30 (±3 days) and 90 (±7 days) days posttreatment for a safety follow-up.

Two preplanned interim analyses (IAs) will be conducted when *a priori* enrollment goals have been achieved. Bayesian approach will be applied after these IAs for decision making for potential study modification including futility, dose and dosing regimen decision, and sample size adjustment. By the protocol amendment 05, the second IA is removed from the protocol.

4.0 ANALYSIS ENDPOINTS

4.1 Primary Endpoint

The primary efficacy endpoint is time from the end of surgery to resolution of upper and lower GI function (eg, time to tolerance of solid food [defined as first occurrence of no vomiting or no clinically significant nausea for 1 calendar day after a solid meal] and time to first spontaneous bowel movement, whichever occurs later) up to Day 10 postsurgery.

4.2 Secondary Endpoints

The secondary endpoints for this study will be:

- Time from the end of the surgery (time the incision is closed) until ready for discharge (defined as the time until the subject presents effective intestinal transit [spontaneous bowel movement], tolerates solids without vomiting or clinically significant nausea for 1 calendar day after a solid meal, has satisfactory pain control with oral analgesics, and is medically stable/free of complications).
- Time from the end of surgery until the discharge order is written.
- Time from the end of the surgery to discharge from hospital.
- Time from end of surgery to tolerance of solid food (defined as first occurrence of intake of solids without vomiting or clinically significant nausea for 1 calendar day after a solid meal), up to Day 10 postsurgery.
- Time from end of surgery to first spontaneous bowel movement (defined as a stool not induced by the use of enemas or laxatives) up to Day 10 postsurgery.
- Percent of subjects with POGD ≥5 days defined as subjects unable to tolerate solid foods, take anything by mouth, or requiring insertion or reinsertion of NG at or after 5 days postsurgery.
- Percentage of subjects requiring insertion of NG tube postsurgery, for drainage and symptom relief in case of persistent nausea and vomiting postsurgery up to Day 24 postsurgery (up to 10-day treatment period plus 14-day observation period post last dose for recurrence of symptoms).
- Time from end of surgery to first flatus up to Day 10 postsurgery.
- Observed plasma concentration of TAK-954 at the end of infusion on Day 1.

4.3 Safety and Tolerability Endpoints

Safety and tolerability will be evaluated based on the occurrence of AEs, physical examination findings, vital signs and weight, electrocardiograms, and clinical laboratory parameters (chemistry, hematology).

4.4 Exploratory Endpoints

The exploratory endpoints for this study will be:

- Change in circulating inflammatory markers including but not limited to IL-6, IL-10, MCP-1, and CRP, preoperatively compared with postoperatively across different treatment groups.
- Change in GIP and cortisol preoperatively compared with postoperatively across different treatment groups.
- Incidence rate of POGD recurrence for 14 days post last dose.
- Percentage of subjects with unplanned hospital readmissions due to recurrence of POGD.
- Percentage of subjects with postoperative complications, such as pneumonia, acute kidney failure, or documented anastomotic leak.
- Percentage of subjects requiring reoperation due to postoperative complications.
- Health-related quality of life as measured by 12-Item Short Form Health Survey (SF-12) and EuroQol 5-Dimensions Questionnaire (EQ-5D).
- Percentage of subjects with postoperative nausea and vomiting (PONV) within 24 hours after surgery, from Day 2 until discharge and at follow-up; defined as patients presenting with emetic events (nausea, vomiting, or retching) or requiring use of antiemetics.
- Peak nausea severity score from Day 1 until discharge using a numerical rating scale.
- Time from the end of the surgery to the first insertion of NG tube (for those requiring insertion of NG tube postsurgery).
- Percentage of subjects presenting complications or prolonged POGD (≥5 days) based on opioid use, type of surgery, duration of the surgical procedure, and ASA scores.

5.0 DETERMINATION OF SAMPLE SIZE

Assuming 80% of subjects will have resolution of POGD at the end of study in the placebo group and 92.5% of subjects will have resolution of POGD at the end of study in the active TAK-954 doses, a total of approximately 300 subjects (100 per treatment group) will provide 80% power with a 0.05 2-sided significance level under Protocol Amendment 04.

In order to mitigate the statistical, clinical, and operational risks to this study in light of the COVID-19 pandemic, the probability of success of the study is re-estimated by blinded assessments using efficacy assumptions of Protocol Amendment 04. Specifically, by the removal of the second IA per this amendment and changing the statistical significance level from 2-sided 5% to 1-sided 5%, the resulting sample size is an overall total of 50 subjects for each remaining arm (Figure 3.b). Under these revised assumptions and the dropping of 2 arms, an overall total of approximately 180 subjects for the study will provide approximately 80% probability, for at least 1 remaining TAK-954 treatment arm, that TAK-954 is superior to placebo in time to resolution of upper and lower GI function at 1-sided 5% significance level for the final analysis.

6.0 METHODS OF ANALYSIS AND PRESENTATION

6.1 General Principles

All tabulations of analysis results will include summaries for the following treatment groups:

- Placebo — Placebo preoperation and daily postoperation
- TAK-954 0.1mg DAILY — TAK-954 0.1mg preoperation and daily postoperation
- TAK-954 0.5mg DAILY — TAK-954 0.5mg preoperation and daily postoperation
- TAK-954 0.1mg PRE — TAK-954 0.1mg preoperation and daily placebo
- TAK-954 0.5mg PRE — TAK-954 0.5mg preoperation and daily placebo

Categorical data will be summarized as the number and percentage of subjects in each category. Percentages will be reported to 1 decimal place.

Continuous data will be summarized using descriptive statistics, including the number of subjects, mean, standard deviation (SD), median, minimum, and maximum. Arithmetic means, geometric means, and medians will be presented to 1 more decimal place than the recorded data, and SDs will be presented to 2 more decimal places than the recorded data, where appropriate.

All statistical tests will be 1-tailed at α=0.05 level for significance and 90% confidence intervals (CIs) will be reported for estimate of interest unless otherwise stated. Where applicable, confidence intervals about a parameter estimate will be presented using the same number of decimal places as the parameter estimate and p-values will be rounded to 3 decimal places prior to assessment of statistical significance.

Study-related raw data for enrolled subjects, including derived data, will be presented in data listings where indicated. The actual day relative to the first dose will be presented, where applicable.

All statistical analyses will be performed using the SAS System Version 9.4 or higher.

6.1.1 Definition of Study Day, Baseline and Study Visit Windows

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

Study Day 1 is defined as the date of the first dose of study drug, as recorded on the electronic case report form (eCRF). Other study days are defined relative to Study Day 1. Study days prior to the first dose of study drug will be calculated as: [date of interest – date of first dose of study drug]. Study days on or after the first dose of study drug will be calculated as: [date of interest – date of first dose of study drug + 1].

For each study visit, a window will be defined such that the lower and upper bounds of each window is generally the midpoint between 2 consecutive study visits. The visit windows and applicable study day ranges are presented below in Table 6.a.

More than 1 result for a parameter may be obtained in a 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 equidistant to the scheduled visit day, the later of the observations will be used.

In the safety data summary, the treatment period 'End of Treatment' values will be defined irrespective of falling in a particular window. Hence, the windowed Day 10 value may be different than the End of Treatment visit value.

Table 6.a Visit Windows

Nominal Visit Day	ECG	Labs	Vital Signs	ERP	EQ-5D, SF-12
Baseline (a)	≤1	≤1	≤1	≤1	≤1
1	1(b)		1(c)		
2	2(b)	≥2	2	≥2	
3			3		
4	3—4		4		
5			5		
6	5—6		6		
7			7		
8	7—8		8		
9			9		
10	≥9		10—12		2—12
16-24 Interim Follow-up (14 days post last dose)			≥13		≥13

(a) Some baseline evaluations are performed on Study Day 1 before study drug administration. While some other baseline evaluations are performed on Study Day -1.

(b) ECG will be collected prior to and at the end of the infusion on Day 1; approximately 1, 2, and 8 hours after the start of the 60-minute infusion on Day 2; and at the end of the infusion on every other day of treatment (Days 4, 6, 8, and 10).

(c) Vital signs will be collected before and after surgery on Day 1, at least every 12 hours on Days 2 to 10.

In general, the baseline value for a variable is defined as the last non-missing observation prior to the first dose of double-blind study medication (visit date/time ≤ first dose date/time), including the screening value, if necessary.

Adverse events that start more than 30 days after the last dose of double-blind study medication (start date – last dose date >30) will be listed, but excluded from the summaries and analyses. For other safety data, data that are obtained more than 14 days after the last dose of double-blind study medication (visit date – last dose date >14) will be listed, but excluded from summaries and analyses.

For GI dysfunction and resolution related endpoints, specific rules for summary and analyses will be defined in Section 7.8.

The study window convention will not be applied to the data listings. The data listings will display the raw data as collected.

6.1.2 Grouping of Centers

In some statistical analysis, center effect will be investigated as a covariate in the statistical models. Before unblinding the data, centers that are considered small (<10 subjects) will be pooled with geographically similar centers to minimize artifacts in the statistical analyses from imbalances in subject counts within the centers.

Center(s) with less than 10 subjects enrolled will be pooled with the nearest center that enrolled more than 10 subjects. The pooling will start first within each country; if it is still small, other countries within the same geographical region (for example, Western Europe, Eastern Europe, and USA) will also be considered. The pooled centers within a region that still have less than 10 subjects will be kept as they are and will not be pooled with centers in other regions.

The pooling of the centers will be reviewed and approved by the clinical and statistical team for agreement prior to unblinding, and is then used in the appropriate analyses once the database is locked and unblinded.

6.2 Analysis Sets

Safety Set: The safety set will include all subjects who were randomized and received at least 1 dose of double-blind study medication. In safety summaries, subjects will be analyzed according to the treatment they received. If a subject receives more than 1 treatment, the actual treatment will be defined as the one that is used most frequently. If the 2 most common treatments are used with equal frequency, then the actual treatment will be defined as the one with highest dose level.

Full Analysis Set (FAS): The FAS will include all subjects who were randomized, received at least 1 dose of study drug, and have at least 1 valid postbaseline on-treatment primary efficacy evaluation (bowel movement or tolerating solid food). In efficacy summaries and analyses, subjects will be analyzed by the treatment to which they were randomized.

Per-Protocol Set (PPS): The PPS will include all FAS subjects who had no important protocol violations that could confound the interpretation of the primary analyses based on the FAS. The categories of these important protocol violations leading to subject's exclusion from FAS to form PPS include:

- No evaluable post-baseline on-treatment primary efficacy evaluation.
- Receiving incorrect study medication that leads to a treatment change.
- Low study drug compliance (<80%) or missed study drug for at least 3 consecutive days prior to resolution of upper and lower GI function.
- Violate ANY core features of ERP listed below.
    - Minimize opioid use while maintaining adequate pain control through use of multimodal analgesia. Suggested analgesics include opioid alternatives such as nonsteroidal anti-inflammatory drugs (eg, ketorolac tromethamine IV),

acetaminophen (paracetamol), or oral pregabalin when possible. It is recommended that at least 2 different analgesics with different mechanism of action are tried and failed before prescribing opioids.

- Maintenance of euvolemia and normal salt and electrolyte state in perioperative period.
- No routine use of prophylactic nasogastric (NG) tubes postsurgery. NG tubes should only be used if there is a documented medical reason to justify them.
- Use of a standardized risk-based strategy for postoperative nausea and vomiting (PONV) prophylaxis: use of preoperative antiemetic prophylaxis in patients with 1 or more risk factors of the simplified Apfel Score (female gender, planned postoperative use of opioids, nonsmokers, history of PONV/motion sickness).
- Early oral feeding postsurgery when possible. Clear liquids after the surgery on Day 1, advancing to soft diet on Day 2 if tolerant to liquids (no nausea or vomiting).
- Early mobilization starting after the surgery on Day 1 when possible.

Other important protocol violations leading to subject's exclusion from FAS will be identified during blinded data reviews and finalized prior to unblinding of subject's treatment assignment and database lock.

PK Analysis Set: The PK analysis set consists of all subjects who were randomized, received at least 1 dose of TAK-954 and have at least 1 measurable postdose plasma for TAK-954.

6.3 Disposition of Subjects

Study Information, including date of first subject signing Informed Consent Form (ICF), date of first/last study drug, date of last subject's last visit/contact, date of last subject's last procedure for collection of data for primary endpoint, Medical Dictionary for Drug Regulatory Activities (MedDRA) Version, World Health Organization Drug Dictionary (WHODrug) Version, and SAS Version, will be tabulated.

Disposition of all screened subjects will be summarized descriptively, including a summary of the number of screened subjects, the number of subjects eligible/not eligible for randomization, and the primary reason for ineligibility for randomization. The number of screen failures and primary reason of screen failures will also be summarized.

Disposition for all randomized subjects will be summarized by treatment group and overall. Disposition categories include:

- Number and percentage of subjects randomized but not dosed,
- Number and percentage of subjects completed study drug,
- Number and percentage of subjects prematurely discontinued study drug along with the primary reason for study drug discontinuation, and
- Number and percentage of subjects completed all study visits

- Number and percentage of subjects discontinued from the study along with the primary reason for discontinuation of study visits.

The number and percentage of randomized subjects by country and site will be summarized based on the Randomized Set. Important protocol deviations will be summarized based on the Randomized Set. Reasons for exclusion from the FAS to form PPS will be summarized based on the FAS.

The analysis sets defined in Section 7.2 will also be summarized.

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

6.4 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics including sex, age, age category (18-64 years, 65-84 years, 85 years and over), ethnicity, race, height, weight, BMI, substance abuse, surgery bowel (small and large), and subject surgery procedures (Laparoscopic and open) will be listed and summarized for each treatment group and overall. The demographic and baseline characteristics summary will be based on all randomized subjects.

Baseline values for the quality of life parameters (EQ-5D and SF-12) will also be presented for each treatment group and overall based on all randomized subjects.

Compliance with overall and individual core ERP recommendations will be summarized based on randomized subjects.

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

6.5 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 or 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. The table will include number and percentages of subjects, and will be sorted in alphabetical order by SOC. Within an SOC, preferred terms are sorted in decreasing frequency based on the total number of subjects. A subject will only be counted once within a particular class even if he/she has multiple conditions or symptoms. Summaries will be based on all randomized subjects.

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

6.6 Medication History and Concomitant Medications

The medication history and concomitant medications are defined as follows:

- Medication history refers to the medication that the study subjects stopped taking at or within 90 days prior to the Screening (time of informed consent).
- Concomitant medication is defined as medication that the study subjects continued taking or took from Screening (time of informed consent) through end of study:
  - Concomitant medication that started and stopped prior to baseline (ie, stop date ≥ first screening visit date, and stop date < first dose date).
  - Concomitant medication that started prior to and was ongoing at baseline (ie, start date < first dose date, and stop date ≥ first dose date).
  - Concomitant medication that started after baseline but before or at last dose (ie, start date ≥ first dose date, and start date ≤ last dose date).
  - Concomitant medication taken during the study (ie, start date ≤ last dose date, and stop date ≥ first dose date.

If start date and stop date are missing, medication will be assumed to occur both prior and concomitantly.

Medication history and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary and summarized by giving the number and percentage of subjects by preferred term within each therapeutic class, with therapeutic class sorted in alphabetical order and preferred term sorted in decreasing frequency based on the total number of subjects. The number of subjects with medications in each selected therapeutic class will also be presented. If a subject takes 2 drugs belonging to the same class, he/she will only be counted once within that class. Summaries of medication history and concomitant medication, including COVID-19 vaccination and medications, will be based on all randomized subjects.

Number and percentage of subjects who took opioid analgesics will also be documented.

In addition, number and percentage of subjects who took antiemetic prophylaxis for PONV will be summarized, including also information on the number of Apfel risk factors to justify this indication and the specific antiemetic prescribed.

All prior and concomitant medications will be listed by treatment, study center and subject number.

6.7 Study Drug Exposure and Compliance

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

Duration of exposure to double-blind study medication is defined as (date of last dose – date of first dose +1). Treatment duration will be summarized by duration category in days (1 to 4 days, ≥ 5 days) and the number of subjects in each duration category by treatment group. Treatment duration (days) will also be summarized as a continuous variable using descriptive statistics.

Percent of study drug compliance is defined as number of infusions administrated / (date of last dose – date of first dose +1)×100%.

For each treatment group, study medication compliance will be summarized by compliance category (<80% and ≥80%) and the number of subjects in each compliance category. Study medication compliance will also be summarized as a continuous variable using descriptive statistics for each treatment group.

All study drug administration and accountability data will be listed by treatment, study center, and subject number. The following variables will be listed: subject identifier, first and last dose dates, medication identification number, infusion date, and percent compliance.

6.8 Summary of the Impact due to COVID-19

All study data about the impact on study participants due to COVID-19 will be provided in by-subject listings for all randomized subjects.

6.9 Efficacy Analysis

The analyses and summaries for efficacy will be based on the FAS.

In the final analyses of efficacy endpoints, for the two discontinued TAK-954 arms, only the summary statistics (n, mean, SD, median, minimum, and maximum for continuous endpoints; number and percentage of subjects for categorical data; the number and percentages of events and censoring, median, minimum, and maximum for time to event endpoint) will be provided; for the remaining treatment groups after IA, the inferential statistics (point estimates of interest and 90% confidence intervals (CIs) and 1-sided p-values) for each treatment group and the TAK-954 doses/regimens in comparison with placebo will be provide along with summary statistics.

If more than 5% of the total subjects in the FAS have important protocol violations leading to subject's exclusion from FAS to form PPS, analyses based on the PPS will be performed for the primary efficacy endpoint and select secondary efficacy endpoints (i.e., Time from the end of the surgery until ready for discharge, Time from the end of surgery until the discharge order is written, Time from the end of the surgery to discharge from hospital, Time from end of surgery to tolerance of solid food up to Day 10 postsurgery, Time from end of surgery to first spontaneous bowel movement up to Day 10 postsurgery, and Time from end of surgery to first flatus up to Day 10 postsurgery). Otherwise, the analysis based on the PPS will be performed for the primary efficacy endpoint only.

If the inferential analyses of efficacy endpoints encounter either convergence issue or result in unstable estimation, the descriptive analysis method will be applied.

The primary, secondary, and exploratory variables for this study are presented in Table 6.b.

Table 6.b Primary, Secondary and Exploratory Variables

Parameter	Description	Variable Type (a)
TIME_RESO	Time from end of surgery to resolution of upper and lower GI function	1
TIME_FOOD	Time from end of surgery to tolerance of solid food	1
TIME_BOWL	Time from end of surgery to first spontaneous bowel movement	1
TIME_DIS_RD	Time from end of surgery until ready for discharge	1
TIME_DIS_OW	Time from end of surgery until discharge order is written	1
TIME_DIS_HP	Time from end of surgery to discharge from hospital	1
TIME_FLA	Time from end of surgery to first flatus	1
TIME_NGT	Time from end of surgery to the insertion of NG tube	1
POGD_5	Percent of subjects with POGD ≥5 days	3
NGT_INS	Percentage of subjects requiring insertion of NG tube postsurgery	3
POGD_RECU	Incidence rate of POGD recurrence for 14 days post last dose	3
HP_READ	Percentage of subjects with unplanned hospital readmissions due to recurrence of POGD	3
PO_COMP	Percentage of subjects with postoperative complications	3
PO_COMP_RO	Percentage of subjects requiring reoperation due to postoperative complications	3
PO_COMP_PRL	Percentage of subjects presenting complications or prolonged POGD (≥5 days) based onopioid use, type of surgery, duration of the surgical procedure, and ASA scores	3
PO_PONV	Percentage of subjects presenting with postoperative nausea and vomiting (PONV) within 24 hours after surgery, from Day 2 until discharge, and at follow-up	3
NRS_PEAK	Peak nausea severity score at Day 1, until discharge, and at follow-up by NRS	1
SF12_i	SF-36 sub-scale score i={physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role emotional, mental health}	1
EQ5D_TOT	EQ-5D index, sum of the 5 item scores for the EQ-5D-5L descriptive system	1
EQ5D_VAS	Score of EQ visual analogue scale, ranged from 0 to 100	1

(a) 1 = continuous; 2 = categorical; 3 = binary.

6.9.1 Analysis of Primary Efficacy Endpoint

The primary endpoint is the time from the end of surgery to resolution of upper and lower GI function (eg, time to tolerance of solid food [defined as first occurrence of no vomiting or no clinically significant nausea for 1 calendar day after a solid meal] and first spontaneous bowel movement, whichever occurs later) up to Day 10 postsurgery.

With respect to the primary endpoint, the null hypothesis to be tested is that there is no difference between TAK-954 dose level and placebo in the time to resolution of upper and lower GI function.

The primary endpoint will be analyzed using the Cox proportional hazard model with treatment group as a single covariate, with Efron's method of tie handling, stratified by randomization stratification factor. One-sided p-values for the pairwise comparisons between the remaining TAK-954 dose levels and the placebo will be calculated using Wald chi-square test from the Cox proportional hazards model. Hazard ratios of remaining TAK-954 dose levels to placebo and their 90% CIs will also be calculated from the Cox proportional hazards model.

The Wald chi-square test statistic formula is as follow:

$$W_T = \frac{\left[\hat{\theta} - \theta_0\right]^2}{1/I_n(\hat{\theta})} = I_n(\hat{\theta})\left[\hat{\theta} - \theta_0\right]^2$$

Where:

- $\hat{\Theta}$ is the maximum likelihood estimator (MLE)
- $I_n(\hat{\theta})$ is the expected Fisher information (evaluated at the MLE)

Median time to resolution of upper and lower GI function, which will also be used to express the magnitude of treatment effects in addition to hazard ratios, will be estimated by Kaplan-Meier survival analysis, and the difference (with 90% confidence intervals) between the TAK-954 dose levels and placebo will be provided. If an event does not occur for a patient during the study treatment period (maximum 10 days postoperatively), the patient will be assigned a censored time of 10 days postsurgery.

The overall type I error rate is set at 5% (one-sided), i.e., the trial is considered to have reached the primary efficacy objective if the two corresponding p-values (one-sided) based on the Cox proportional hazards model for testing the null hypothesis (TAK-954 0.5mg DAILY vs Placebo and TAK-954 0.5mg PRE vs Placebo) are less than 5% (one-sided) OR either one is less than 2.5% (one-sided).

For the primary endpoint, subgroup analyses by:

- Surgery procedures (Laparoscopic, open),
- Age (≤65, >65),
- Sex (female, male),
- Surgery Bowel (Small, large)

and other variables, if necessary, will be performed if each of the subgroups contains at least 20% of the total subjects in the study. The treatment groups will be compared within each subgroup. Additional exploratory analyses examining subgroup effect and treatment by subgroup interaction may be performed, if warranted.

6.9.2 Analysis of Secondary Efficacy Endpoints

The secondary endpoints time from end of surgery to tolerance of solid food, time from end of surgery to first spontaneous bowel movement, time from end of surgery until ready for discharge, time from end of surgery until discharge order is written, time from end of surgery to discharge from hospital, and time to first flatus will be analyzed similarly to the primary endpoint.

The percent of subjects with POGD ≥5 days and the percent of subjects requiring insertion of NG tube postsurgery will be analyzed using the Miettinen and Nurminen's method stratified by randomization stratification factor for risk difference.

The following rules will be applied for the summary and analyses of the secondary endpoints:

- For the analysis of time to tolerance of solid food and time to first spontaneous bowel movement, if a resolution does not occur for a patient during the study treatment period (maximum 10 days postoperatively), the patient will be assigned a censored time of 10 days postsurgery.
- For the analysis of time from end of surgery until ready for discharge, time from end of surgery until discharge orders are written, time from end of surgery to discharge from hospital, and time from end of surgery to first flatus, if an event does not occur for a patient during the study period, the patient will be assigned a censored time of 14 days post last dose.
- For the summary and analysis of percent of subjects requiring insertion of NG tube postsurgery, insertion of NG tube postsurgery until two weeks of follow-up (Insertion date ≤ last dose date + 14) will be counted.

6.9.3 Analysis of Exploratory Efficacy Endpoints

The time from the end of surgery to the insertion of NG tube will be analyzed similarly to the primary endpoint.

The incidence rate of POGD recurrence for 14 days post last dose, the percentages of subjects with unplanned hospital readmissions due to recurrence of POGD, the percent of subjects with postoperative complications, the percent of subjects presenting complications or prolonged POGD (≥5 days), percent of subjects requiring reoperation due to postoperative complications, and the percentages of subjects with postoperative nausea and vomiting (PONV) within 24 hours after surgery (from Day 2 until discharge and at follow-up; defined as patients presenting with emetic events [nausea, vomiting, or retching] or requiring use of antiemetics that will be identified during blinded data review and finalized prior to unblinding of subject's treatment assignment and database lock) will be compared between TAK-954 dose levels and placebo using the Miettinen and Nurminen's method stratified by randomization stratification factor for risk difference.

For the percent of subjects presenting complications or prolonged POGD (≥5 days), the treatment groups will also be compared to placebo within the following subgroups:

- Opioid use: Yes or no
- Type of surgery: open or laparoscopic
- Duration of the surgerical procedure: <2 hours, or >= 2 hours
- ASA Score: <=2 or >2

The change from baseline (Day 1) in NRS nausea severity score will be analyzed by study visit using analysis of covariance (ANCOVA), with treatment, stratum, and pooled center as fixed factors, baseline score as covariate.

The following rules will be applied for the summary and analyses of the exploratory endpoints:

- For the analysis of time from end of surgery to the insertion of NG tube, if an insertion of NG tube does not occur for a patient during the study period, the patient will be assigned a censored time of 14 days for the event.
- For the summary and analysis of incidence rate of POGD recurrence for 14 days post last dose, the percentages of subjects with unplanned hospital readmissions due to recurrence of POGD, the percent of subjects with postoperative complications, the percent of subjects presenting complications or prolonged POGD (≥5 days), percent of subjects requiring reoperation due to postoperative complications, and the percentages of subjects with postoperative nausea and vomiting (PONV) within 24 hours after surgery, events happen postsurgery until two weeks of follow-up (event date ≤ last dose date + 14) will be counted.

6.9.4 Analysis of Patient Reported Outcomes

The EQ-5D total score is the sum of the 5 item scores for the EQ-5D-5L descriptive system. Each item has 5 level score of perceived problem: 1 indicates no problem in relative health dimension, while 5 indicates extreme problems in relative health dimension.

The EQ-5D VAS is the score of the visual analogue scale, ranged from 0 to 100: 100 means the best health you can imagine, while 0 means the worst health you can imagine.

A detailed description of the SF-12 sub-scores calculation is found in Appendix A. The SF-12 self-rated questionnaire yields a health profile based on the following subscales:

- Physical Functioning: limitations in physical activities because of health problems.
- Role-Physical: limitations in usual role activities because of physical health problems.
- Bodily Pain.
- General Health: perception of general health.
- Vitality: energy and fatigue.
- Social Functioning: limitations in social activities because of physical or emotional problems.
- Role-Emotional: limitations in usual role activities because of emotional problems.
- Mental Health: general mental health (psychological distress and well-being.

Descriptive statistics in terms of score and change from baseline in the quality of life parameters (EQ-5D and SF-12) will be presented by visit and treatment group for each of the total and sub-scores.

The change from baseline in the quality of life parameters (EQ-5D and SF-12) total scores and sub-scores will also be analyzed by visits using analysis of covariance (ANCOVA), with treatment, stratum, and pooled center as fixed factors, baseline score as covariate.

6.9.5 Missing Items on Rating Scales

For some reasons, subjects may not complete the full task as requested, or subjects used irregular procedure and/or questionable effort. In such cases, the data may be considered missing, unreliable and/or invalid.

The general rule when individual items are missing from a multiple-item assessment is as follows:

- Total score will be calculated as (sum of non-missing item scores) x total number of items / (number of non-missing items).
- If more than 20% of the items are missing, the total score will be set to missing. The resulting calculated scores will be used in all analyses.

6.10 Pharmacokinetic/Pharmacodynamic Analysis

6.10.1 Pharmacokinetic Analysis

No formal noncompartmental PK analyses will be performed on concentration-time data. The observed plasma concentrations of TAK-954 will be summarized by dose/regimen at study scheduled day/time point where appropriate. The individual concentration-time data for TAK-954 and its metabolites will be included in listings. Details will be provided in the Clinical Pharmacology Analysis Plan (CPAP).

6.10.2 Pharmacodynamic Analysis

Not applicable.

6.11 Other Outcomes

Change in circulating inflammatory markers including but not limited to IL-6, IL-10, MCP-1, CRP and change in GIP and cortisol preoperatively compared to postoperatively will be analyzed by study visits using analysis of covariance (ANCOVA), with treatment, stratum, and pooled center as fixed factors, baseline value as covariate.

Considering that glucose-dependent insulinotropic peptide (GIP) is no longer collected under protocol amendment 05, if the ANCOVA of GIP results in convergence issue due to limited samples, the ANCOVA of GIP will be simplified (e.g., removing the pooled center and etc. until convergence issue is resolved) to ensure robust statistical estimate.

6.12 Safety Analysis

All safety summaries will be based on the safety set. Safety summaries will include descriptive statistics for values, changes, and incidence of events for all treatment groups combined in addition to summary by treatment.

6.12.1 Adverse Events

All adverse events will be coded using MedDRA latest version. In this dictionary, each verbatim term is coded to a lower level term, and then mapped to a preferred MedDRA term, which is then mapped to an SOC. All adverse events, including the COVID-19 related 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) will be defined as an AE or serious adverse event (SAE) that started or worsened after first study drug administration and within 30 days of last dose of study drug (AE onset date – date of last dose ≤30). AEs with missing onset dates will be summarized with TEAEs regardless of severity and relationship to study medication.

The following summaries will be presented:

- Overview of TEAEs during the study - number and percentage of subjects, number of events.
- TEAEs by SOC and PT - number and percentage of subjects.
- TEAEs by PT - number and percentage of subjects.
- Severity of TEAEs by SOC and PT - number and percentage of subjects.
- Relationship of TEAEs by SOC and PT - number and percentage of subjects.
- Drug-related TEAEs by SOC and PT - number and percentage of subjects.
- TEAEs Related to Study Procedure by SOC and PT - number and percentage of subjects.
- TEAEs leading to study discontinuation by SOC and PT - number and percentage of subjects.
- Serious treatment-emergent AEs by SOC and PT - number and percentage of subjects, number of events.
- Treatment-emergent Adverse Events of Special Interest by SOC and PT - number and percentage of subjects, number of events.
- Most Frequent (>=5%) Treatment-emergent Non-serious AEs by SOC and PT - number and percentage of subjects, number of events.
- Suspected MACE up to 90 days after last dose - number and percentage of subjects.

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

In the high-level adverse event summary tables, TEAEs will be summarized regardless of severity and relationship to study drug. Within each subject, multiple reports of events that map to a common MedDRA term will be counted only once.

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 (see above), adverse events will be summarized by the number of events reported in addition to the number and percentage of subjects with events.

For the summary of TEAEs by SOC, preferred term and maximum severity, 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 severity in that SOC.

TEAEs classified in the eCRF as possibly or probably related to the study medication will also be summarized by preferred term and SOC. If a subject experiences more than 1 episode of a particular coded adverse event, the subject will be counted only once by the most related report for the preferred term. Similarly, if a subject has more than 1 adverse event within an SOC, the subject will be counted only once by the most related report in that SOC. Adverse events with missing relationship will be classified as having the highest relationship to study drug.

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, whether the adverse event was an SAE and whether the event was an adverse event of special interest (AESI).

Special listings for TEAEs leading to study discontinuation, SAEs, deaths, and AE of special interest will also be presented.

6.12.2 Clinical Laboratory Evaluations

The local laboratory will perform laboratory tests for hematology and serum chemistries. The results of laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results. Any clinically significant laboratory result will be captured as an AE as per the CTCAE v5.0.

Descriptive statistics (N, mean, median, SD, minimum and maximum) of clinical safety laboratory variables will be summarized for baseline, postbaseline values, and change from

baseline by treatment group and overall at each measurement. Only the scheduled measurements will be included in the summary. No inferential analysis will be performed.

The number and percentage of subjects with abnormal values observed post-Baseline will be presented.

Individual results for hematology laboratory tests and serum chemistry tests will be evaluated against the Takeda predefined laboratory markedly abnormal value (MAV) criteria (Appendix B). All subjects that meet the MAV criteria will be presented in a data listing. If a subject has a MAV for a particular laboratory test, all values for that subject and for that parameter will be listed. The number and percentage of subjects with at least 1 postbaseline markedly abnormal laboratory test result will be presented by treatment group and overall. All postbaseline clinical lab results within 7 days of the last dose, including scheduled and unscheduled measurements will be included in the MAV summaries. The mapping of the subjects with postbaseline results which meet the MAV criteria will be listed as a table.

Summaries and listings of laboratory data will be presented in Systeme International (SI) unit. Laboratory data outside of the normal reference range will be flagged on the listing along with values meeting MAV criteria

6.12.3 Vital Signs and Weight

Vital signs and weight at scheduled visits and their changes from Baseline will be summarized for each treatment group and overall using descriptive statistics by visit and end of treatment.

All individual vital signs that meet Takeda's predefined criteria for markedly abnormal values (Appendix C) will be listed. The number and percentage of subjects with at least 1 postbaseline markedly abnormal vital sign measurement will be summarized. All postbaseline vital signs within 7 days of the last dose, including both scheduled and unscheduled measurements, will be included in the MAV summaries. The mapping of the subjects with postbaseline results which meet the MAV criteria will be listed as a table.

All vital sign data will be presented in the listings. Vital sign MAVs will be flagged in the listings.

6.12.4 12-Lead ECGs

The ECG parameters include heart rate, PR interval, QRS duration, QT interval, and QT interval with Fredericia's corrections (QTcF).

ECG variables at scheduled visits and their changes from Baseline will be summarized for each treatment group and overall using descriptive statistics by study visit and end of treatment.

A shift table for the investigator's ECG interpretation will provide the number of subjects in each of the appropriate categories (Normal, Abnormal but not clinically significant, or Abnormal and clinically significant) at the scheduled visit relative to the Baseline status.

All individual ECGs that meet Takeda's predefined criteria for markedly abnormal values (Appendix D) will be listed. The number and percentage of subjects with at least one markedly

abnormal ECG measurement will be summarized. All post dose ECGs within 7 days of the last dose, including both scheduled and unscheduled measurements, will be included in the MAV summaries. The mapping of the subjects who meet the MAV criteria will be listed as a table.

All ECG data will be presented in the listings. ECG MAVs will be flagged in the listings.

6.12.5 Other Observations Related to Safety

Not applicable.

6.13 Interim Analysis

Two preplanned interim analyses will be conducted when a priori enrollment goals have been achieved. Additional interim analyses may be added if deemed appropriate based on study findings from preplanned interim analyses. The first interim analysis will be conducted after approximately 125 subjects (25 per arm) have completed or withdrawn from the study. The second interim analysis will be conducted after approximately 50 subjects per arm have completed or withdrawn from study. The interim analyses will include the key safety and efficacy data available for subjects identified at the time of the interim analysis data cut.

Following each interim analysis, Bayesian approach for decision making will be implemented for the potential study modification including futility, dose and regimen decision, and sample size adjustment. An internal monitoring committee within Takeda composed of a senior clinician, a senior statistician, a senior clinical pharmacologist, and a senior pharmacovigilance scientist not involved in the study will review the unblinded interim analysis results and make recommendations for changes to the study based on the prespecified decision criteria.

At each interim analysis, the decision criteria based on Bayesian approach with a non-informative prior and safety consideration are as follow:

- For each TAK-954 dose and dose regimen, the posterior probability will be calculated based on an expectation of at least 5% increase over placebo in resolution of upper and lower GI function given the observed interim data:
  - **GO**: if the posterior probability ≥ 70%. At this case, the relative dose or dose regimen will continue to be studied.
  - **No-Go**: if the posterior probability < 30%. At this case, the relative dose or dose regimen will be dropped.
  - **Gray Zone**: if the posterior probability is between 30% and 70%. At this case, information from other doses or dose regimens will be taken into consideration. A decision will be made based on overall evaluation.
- The study will be terminated if all doses and dose regimens reach a "No-Go" criterion based on the posterior probability.
- Any dose or dose regimen with clinically significantly higher incidence of serious adverse events compared to placebo will be terminated regardless of the efficacy assessment.

- The assumptions for sample size justification will be reviewed based on the interim data:
  - After the second interim analysis, sample size for remaining treatment groups may be adjusted to ensure at least 80% power to detect a 10% difference between TAK-954 and placebo at end of study, however the sample size for each treatment arm will be capped at 150 subjects.

Due to lack of good prior distributions, a frequentist approach instead of Bayesian approach was implemented for interim analysis. The details about the interim analysis were documented in the TAK-954-2004 Internal Monitoring Committee Charter (Version 2.0, Amendment 1.0, dated on 04Dec2020) that was approved prior to the data cut (09Dec2020) for interim analysis.

6.14 Changes in the Statistical Analysis Plan

The changes in the statistical analysis plan for protocol amendment 05 are summarized in the table below.

Statistical Analysis Plan (SAP) Amendment 02			
Summary of Changes Since the Last Version of the Approved SAP			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	**Description**	**Rationale**
1	Section 4.2 Secondary Objectives	Clarified the secondary objective related to relative efficacy and safety was for accelerating the recovery of gastrointestinal (GI) function postsurgery. Specified time window of up to 10 days for study drug dosing for the secondary objective of determining efficacy and safety of preoperative dosing of intravenous TAK-954 relative to preoperative and postoperative regimens.	Changes were made to reflect the corresponding changes in Protocol Amendment 05.

Statistical Analysis Plan (SAP) Amendment 02			
Summary of Changes Since the Last Version of the Approved SAP			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	**Description**	**Rationale**
2	Section 4.4 Study Design	Randomizations into 2 treatment groups (TAK-954 0.1 mg/100 mL preoperative and daily and TAK-954 0.1 mg/100 mL preoperative only) have been discontinued based on the IA results. Removed the second IA. Revised the language to reflect these changes.	Changes were made to reflect the corresponding changes in Protocol Amendment 05.
3	Figure 4.b Schematic of Study Design by Protocol Amendment 05 Section 6.0 Determination of Sample Size	Added new figure to indicate study design after Protocol Amendment 5. Revised sample size of remaining arms based on blinded assessments that were conducted using efficacy assumptions of the original protocol before the interim analysis (IA).	Changes were made to reflect the corresponding changes in Protocol Amendment 05.
4	Section 5.1 Primary Endpoint Section 5.2 Secondary Endpoints Section 5.4 Exploratory Endpoints	Refined the definition of the primary efficacy endpoint time to resolution of upper and lower GI function by specifying "from the end of surgery", defined tolerance to solid food as "first occurrence" of absence of vomiting or clinically significant nausea for 1 calendar day after a solid meal, and clarified that the follow-up time for the primary endpoint is up to Day 10 postsurgery.	Changes were made to reflect the corresponding changes in Protocol Amendment 05.
5	Section 7.1 General Principle Analysis Sets Section 7.9	Statistical tests will be 1-tailed at α=0.05 level for significance and 90% confidence intervals (CIs) will be reported for estimate of interest. Removed 'received protocol specified	Changes were made to reflect the changes of significance level from two-sided α = 0.05 to one-sided α = 0.05 and removing

Statistical Analysis Plan (SAP) Amendment 02			
Summary of Changes Since the Last Version of the Approved SAP			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	**Description**	**Rationale**
	Efficacy Analysis Section 7.10.1 Pharmacokinetic Analysis	surgery' in safety set and Used conservative principle for safety evaluation to determine the actual treatment when most frequently used treatment with tied frequency. Removed 'received protocol-specified surgeries' and 'a valid baseline' in the definition for FAS. Clarified the definition for PPS; the term 'major protocol violation' was changed to 'important protocol violation'. Added PK analysis set and provided details for the summary analysis of observed plasma concentration of TAK-954.	'received protocol specified surgery' in Protocol Amendment 05. Changes were made to the definition of safety set to match the definition in protocol and used conservative principle for safety evaluation to determine the actual treatment when most frequently used treatment with tied frequency. Changes were made to the definition of FAS to match the definition in protocol. Clarified the definition for PPS and the term 'major protocol violation' was changed to 'important protocol violation'. Added PK analysis set and provided details for the summary analysis of observed plasma concentration of TAK-954.

Statistical Analysis Plan (SAP) Amendment 02			
Summary of Changes Since the Last Version of the Approved SAP			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	**Description**	**Rationale**
6	Section 7.3 Disposition of Subjects	Clarified the display of disposition summary and listing.	Clarified the display of disposition summary and listing.
7	Section 7.4 Demographic and Other Baseline Characteristics	Simplified the analysis of demographic and baseline characteristics by removing the ANOVA for continuous variable and CMH for categorical variables.	Simplified the analysis of Demographic and Other Baseline Characteristics.
8	Section 7.6 Medication History and Concomitant Medications Section 7.8 Summary of the Impact due to COVID-19 Section 7.12.1 Adverse Events	Included COVID-19 vaccination and medications as part of the analysis of medication history and concomitant medications. Added the details that COVID-19 impact data will be provided in by-subject listings. Included COVID-19 related adverse events as part of the analysis of adverse events.	Included COVID-19 vaccination and medications as part of the analysis of medication history and concomitant medications. Added the details that COVID-19 impact data will be provided in by-subject listings. Included COVID-19 related adverse events as part of the analysis of adverse events.

Statistical Analysis Plan (SAP) Amendment 02			
Summary of Changes Since the Last Version of the Approved SAP			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	**Description**	**Rationale**
9	Section 7.9 Efficacy Analysis Section 7.9.1 Analysis of Primary Efficacy Endpoint Section 7.9.2 Analysis of Secondary Efficacy Endpoints Section 7.9.3 Analysis of Exploratory Efficacy Endpoints	Added general principles for analyzing and reporting the efficacy analyses of the two dropped arms and three remaining arms in the final analyses. Added the rules for performing sensitivity analysis of efficacy endpoints based on PPS. Added default analyses of efficacy endpoints to deal with either convergence issue or unstable estimation. Specified the Efron's method for handling ties in Cox model. Specified the principles for evaluating primary efficacy objective. Used the stratified Miettinen and Nurminen's method for the analysis binary endpoints and calculating risk difference. Clarified the endpoint of percentages of subjects with postoperative nausea and vomiting (PONV) within 24 hours after surgery.	Clarified the analysis and reporting strategies for two dropped arms and three remaining arms in the final efficacy analyses. Added the rules for performing sensitivity analysis of efficacy endpoints based on PPS. Specified method for handling ties. Specified the principles for evaluating primary efficacy objective. Changed the method for the analysis of binary endpoints and calculating risk difference to reflect the corresponding changes in Protocol Amendment 05. Clarified the endpoint of percentages of subjects with postoperative nausea and vomiting (PONV) within 24 hours after surgery.

Statistical Analysis Plan (SAP) Amendment 02			
Summary of Changes Since the Last Version of the Approved SAP			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	**Description**	**Rationale**
10	Section 7.13 Interim Analysis	Clarified the Interim Analysis that was conducted in accordance with the approved protocol amendment 04.	Clarified the Interim Analysis that was conducted in accordance with the approved protocol amendment 04.

7.0 REFERENCES

1. Bruce G. Wolff, MD, et al. Alvimopan, a Novel, Peripherally Acting μ Opioid Antagonist. Results of a Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase III Trial of Major Abdominal Surgery and Postoperative Ileus.
2. Irinel Popescu, et al. The Ghrelin Agonist TZP-101 for Management of Postoperative Ileus After Partial Colectomy: A Randomized, Dose-Ranging, Placebo-Controlled Clinical Trial.
3. Grant Bochicchio, et al. Ghrelin Agonist TZP-101/Ulimorelin Accelerates Gastrointestinal Recovery Independently of Opioid Use and Surgery Type: Covariate Analysis of Phase 2 Data.
4. Justin T Brady, et al. The use of alvimopan for postoperative ileus in small and large bowel resections.
5. Conor P. Delaney, et al. Postoperative upper and lower gastrointestinal recovery and gastrointestinal morbidity in patients undergoing bowel resection: pooled analysis of placebo data from 3 randomized controlled trials.

Appendix A The 12-Item Short Form Health Survey (SF-12)

Eight sub-scores are derived from the 12-item short-form survey (SF-12) as follow:

Sub-score	Items (I, BP, GH)	Formula
Physical Functioning	I2a, I2b	100*(I2a+I2b-2)/(6-2)
Role-Physical	I3a, I3b	100*(I3a+I3b-2)/(10-2)
Bodily Pain	I5	100*(6-I5-1)/(5-1)
General Health	I1	100*(6-I1-1)/(5-1)
Vitality	I6b	100*(6-I6b-1)/(5-1)
Social Functioning	I7	100*(I7-1)/(5-1)
Role-Emotional	I4a, I4b	100*(I4a+I4b-2)/(10-2)
Mental Health	I6a, I6c	100*(6-I6a-I6c-2)/(10-2)

Appendix B Criteria for Identification of Markedly Abnormal Laboratory Values

Hematology—Criteria for Markedly Abnormal Values

Parameter	Unit	Low Abnormal	High Abnormal
Hemoglobin	SI	<0.8 × LLN	>1.2 × ULN
Hematocrit	SI	<0.8 × LLN	>1.2 × ULN
RBC count	SI	<0.8 × LLN	>1.2 × ULN
WBC count	SI	<0.5 x LLN	>1.5 x ULN
Platelet Count	SI	<7100x 10^9/L	>450 x 10^9/L

LLN=lower limit of normal, RBC=red blood cell, ULN=upper limit of normal, WBC=white blood cell.

Serum Chemistry—Criteria for Markedly Abnormal Values

Parameter	Unit	Low Abnormal	High Abnormal
ALT	SI	--	>3x ULN
AST	SI	--	>3x ULN
GGT	SI	--	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal
Alkaline phosphatase	SI	--	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal
Total Bilibrubin	SI	--	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal
Albumin	SI	<30 g/L	--
Total protein	SI	<0.8x LLN	>1.2x ULN
Creatinine	SI		>177 μmol/L
Blood urea nitrogen	SI		>10.7 mmol/L
Sodium	SI	<130 mmol/L	>150 mmol/L
Potassium	SI	<3.0 mmol/L	>5.5 mmol/L
Blucose	SI	<3 mmol/L	>10 mmol/L*
Chloride	SI	<75 mmol/L	>126 mmol/L
Calcium	SI	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	
Bicarbonate	SI	<8.0 mmol/L	

ALT=alanine aminotransferase, AST=aspartate aminotransferase, GGT=γ-glutamyl transferase, LLN=lower limit of normal, ULN=upper limit of normal.

Appendix C Criteria for Abnormal Changes from Baseline of Vital Signs

Parameter	Unit	Lower Criteria	Upper Criteria
Heart Rate	bpm	<60	>120
Systolic blood pressure	mm Hg	<90	>140
Diastolic blood pressure	mm Hg	<60	>90
Body temperature	^{o}C	<35.6	>37.7
	^{o}F	<96.1	>99.9

Appendix D Criteria for Markedly Abnormal Values for the 12-Lead ECG Parameters

Parameter	Lower Criteria	Upper Criteria
Heart rate	<50 beats per minute	>120 beats per minute
PR	≤120 milliseconds	≥200 milliseconds
QTcF Interval		≥500 milliseconds OR ≥30 milliseconds change from baseline and ≥450 milliseconds
QRS	≤60 milliseconds	≥120 milliseconds

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Biostatistics Approval	18-May-2021 15:40 UTC