Title: A Phase 1, Open-Label Study to Assess the Relative Bioavailability, Effect of Food, and Gastric pH Modification on the Pharmacokinetics of TAK-931 in Patients with Advanced Solid Tumors

NCT Number: NCT03708211

SAP Approve Date: Mar 5, 2020

Certain information within this Statistical Analysis Plan has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable (PPD) information or company confidential information (CCI).

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

STATISTICAL ANALYSIS PLAN

TAK-931

A Phase 1, Open-Label Study to Assess the Relative Bioavailability, Effect of Food, and Gastric pH Modification on the Pharmacokinetics of TAK-931 in Patients with Advanced Solid Tumors

Protocol #: 1003

SAP Version:	Date of Statistical Analysis Plan:
Final	Mar 5, 2020

CCI

Approval Signatures

Mar 31, 2020
Date

Date

Date

31-Mar-2020
Date

STATISTICAL ANALYSIS PLAN

TAK-931

A Phase 1, Open-Label Study to Assess the Relative Bioavailability, Effect of Food, and Gastric pH Modification on the Pharmacokinetics of TAK-931 in Patients with Advanced Solid Tumors

Protocol #: 1003

SAP Version:	Date of Statistical Analysis Plan:
Final	Mar 5, 2020

Approval Signatures

CCI

[redacted]

Date

Date

31 March 2020

Date

Date

TAK-931

A Phase 1, Open-Label Study to Assess the Relative Bioavailability, Effect of Food, and Gastric pH Modification on the Pharmacokinetics of TAK-931 in Patients with Advanced Solid Tumors

Protocol #: 1003

SAP Version:	Date of Statistical Analysis Plan:
Final	Mar 5, 2020

CCI

TABLE OF CONTENTS

1. LIST OF ABBREVIATIONS

%CV	coefficient of variation
AE	adverse event
ALT	alanine aminotransferase
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the plasma concentration-time curve
AUC_{∞}	area under the concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration
AUC_{24}	area under the plasma concentration-time curve from the time 0 to 24 hours
AUC_{last}	area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration
CDC7	cell division cycle 7
CL/F	apparent oral clearance
C_{max}	maximum observed plasma concentration
CNS	central nervous system
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CCI	[redacted]
CxDx	Cycle x, Day x
CV	cardiovascular
DCR	disease control rate
DDI	drug-drug interaction
DDR	DNA damage response
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	end-of-treatment (visit)
IC_{50}	the concentration producing 50% inhibition
IHC	immunohistochemistry
IRB	institutional review board
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
NCI	National Cancer Institute
ORR	overall response rate
PD	progression of disease
PFS	progression-free survival
PIC	powder-in-capsule (formulation)

PK	pharmacokinetic(s)
PPI	proton pump inhibitor
PR	partial response
QD	once daily
QTc	QT interval corrected for heart rate
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SD	stable disease
TEAE	treatment-emergent adverse event
$t_{1/2z}$	terminal disposition phase half-life
t_{max}	time to first occurrence of C_{max}
WHO	World Health Organization

2. INTRODUCTION

The purpose of the Statistical Analysis Plan (SAP) is to provide a framework that addresses the protocol objectives in a statistically rigorous fashion, with minimized bias or analytical deficiencies. Specifically, this plan has the following purpose:

To prospectively (a priori) outline the types of analyses and data presentations that will address the study objectives outlined in the protocol, and to explain in detail how the data will be handled and analyzed, adhering to commonly accepted standards and practices of biostatistical analysis in the pharmaceutical industry.

2.1 Study Design

This is an open-label, multicenter, phase 1 study designed to evaluate the relative bioavailability of TAK-931 tablet in reference to PIC (Part 1), the effect of food and esomeprazole, a PPI, on PK of TAK-931 as tablet (Part 2). For the purposes of this study, cycle 0 will be defined as the PK cycle.

Part I: in cycle 0 (PK cycle), approximately 20 patients (to ensure 14 to 16 patients evaluable for PK) will be randomized in a crossover fashion to receive a single dose of TAK-931 80 mg PIC or tablet on Day 1 and a single dose of TAK-931 80 mg with the alternate formulation on Day 3 (PIC to tablet, or tablet to PIC). There will be no TAK-931 dosing on Day 2 and Day 4. Starting on Day 5, patients will then continue to receive TAK-931 50 mg PIC once daily for 12 days followed by a 7-day rest period. Starting from cycle 1, patients will receive 50 mg PIC QD for 14 days followed by 7-day rest period in a 21-day treatment cycle until one of the discontinuation criteria is met.

Part 2: After the preliminary PK data from part 1 have been analyzed to estimate the relative bioavailability of the tablet formulation in reference to PIC, the dose of TAK-931 tablet will be calculated that provides total exposure (AUC) comparable to the 80-mg dose of PIC. In Part 2 cycle 0 (PK cycle), approximately 24 patients (to ensure 14 to 16 patients evaluable for PK) will be randomized in a crossover fashion to receive a single dose of TAK-931 tablet with or without a standard high-fat breakfast on Day 1, with the alternate food intake condition and dosing on Day 3 (fasted → fed or fed → fasted). Starting from Day 5, patients will receive esomeprazole 40 mg once daily through Day 13. On Day 12, each patient will receive a single dose of TAK-931 tablet (with a dose producing an equivalent exposure to 80 mg PIC), and PK samples will be collected up to 48 hours postdose (Day 14 predose). Starting on Day 14, patients will then continue to receive TAK-931 tablet at a dose expected

to achieve exposures comparable to 50 mg PIC once daily for 11 days followed by a 7-day rest period until a discontinuation criterion is met. Starting from Cycle 1, patients will receive TAK-931 tablet at a dose expected to achieve exposures comparable to 50 mg PIC QD for 14 days followed by 7-day rest period in a 21-day treatment cycle.

2.2 Study Objectives

2.2.1 Primary Objectives

The primary objectives are:

Part 1

- Estimate the relative bioavailability of a tablet formulation of TAK-931 in reference to a PIC formulation.

Part 2

- Assess the effect of high-fat meal on the single dose PK of TAK-931 administered as a tablet formulation.
- Assess the effect of esomeprazole, a PPI on the single dose PK of TAK-931 administered as a tablet formulation.

2.2.2 Secondary Objectives

The secondary objectives are:

Part 1

- To further characterize PK of TAK-931 administered as PIC or tablet formulations.
- To assess the safety and tolerability of TAK-931 administered as tablet and PIC formulations.
- To assess the antitumor activity of TAK-931 in patients with locally advanced or metastatic solid tumors.

Part 2

- To further characterize PK of TAK-931 as a tablet formulation under the fasting or fed conditions.
- To further characterize PK of TAK-931 administered as a tablet formulation in the presence or absence of esomeprazole, or PPI.

- To assess the safety and tolerability of TAK-931 administered as tablet under fed and fasted conditions.
- To assess the antitumor activity of TAK-931 in patients with locally advanced or metastatic solid tumors.

2.2.3 Exploratory Objectives

CCI

[redacted]

2.3 Endpoint

2.3.1 Primary endpoints

The primary endpoints are:

Part 1

- Ratio of geometric mean of following pharmacokinetic parameters for TAK-931 tablet in reference to PIC and associated 90% confidence intervals (Cis):
  C_{max}.
  AUC_{last}.
  AUC_{inf}.

Part 2

- Ratio of geometric mean of following pharmacokinetic parameters for TAK-931 tablet under fed in reference to fasting conditions and associated 90% CIs:
  C_{max}.
  AUC_{last}.
  AUC_{inf}.
- Ratio of geometric mean of following pharmacokinetic parameters for TAK-931 tablet in the presence versus in the absence of esomeprazole and associated 90% CIs:
  C_{max}.
  AUC_{last}.
  AUC_{inf}.
- Summary statistics of the following PK parameters for TAK-931:

C_{max}.

AUC_{last}.

AUC_{inf}.

2.3.2 Secondary endpoints

The secondary endpoints are:

Part 1

- PK parameters:

  t_{max}, CL/F, and $t_{1/2z}$ of TAK-931 following a single dose administration as PIC and tablet at 80 mg, respectively.

  Safety: Percent of TEAEs, Grade ≥3 TEAEs, TEAEs producing discontinuation or dose modification, percent of laboratory abnormalities.

- Antitumor activity:

  ORR.

  PFS.

  DCR.

  DOR.

Part 2

- PK parameters:

  t_{max}, CL/F, and $t_{1/2z}$ of TAK-931 tablet following a single dose administration under fasting and fed conditions, respectively.

  t_{max}, CL/F, and $t_{1/2z}$ of TAK-931 tablet following a single dose administration in the absence and in the presence of esomeprazole, respectively.

- Antitumor activity:

  ORR.

  PFS.

  DCR.

  DOR.

2.3.3 Safety endpoints

The safety endpoints for parts 1 and 2 are:

- Frequency of TEAEs per National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0:
  - SAEs.
  - TEAEs leading to dose modifications.
  - TEAEs leading to treatment discontinuation.
- Percentage of patients with TEAEs:
  - Grade ≥3 TEAEs.

- SAEs.
- TEAEs leading to treatment discontinuation or dose modifications, and
- Clinically significant changes in laboratory values and vital sign measurements.

2.3.4 Exploratory endpoints

CCI

[redacted]

3. POPULATIONS FOR ANALYSIS

3.1 Safety population

The safety population is defined as all patients who receive at least one dose of study drug. All safety analyses will be based on the safety population.

3.2 Pharmacokinetic population

The PK population is defined as all patients who completed the protocol-specified dosing and PK sampling requirement to have sufficient plasma TAK-931 concentration-time data to reliably estimate the PK parameter(s).
PK analyses will be performed using the PK population.

3.3 Response-Evaluable Population

The response-evaluable population is defined as patients who receive at least 1 dose of study drug, have measurable disease at baseline, and at least 1 post-baseline response assessment. The response-evaluable population will be used for the analysis of ORR and DOR.

4. HYPOTHESES AND DECISION RULES

No formal hypothesis testing will be performed.

5. INTERIM ANALYSIS

An interim analysis will be conducted after completion of Part 1. The preliminary PK data from Part 1 will be analyzed to estimate the relative bioavailability of the tablet formulation in reference to PIC, the dose of TAK-931 tablet will be calculated that provides total exposure (area under the concentration-time curve [AUC]) comparable to the 80-mg dose of PIC. If for the purposes of clinical study report (CSR) writing the analysis is performed immediately after Part 1 completion, the interim analysis is not needed.

6. STATISTICAL METHODOLOGY

Analyses will be primarily descriptive in nature. No formal statistical tests will be performed. Summary tabulations will be presented that display the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percent (calculated using non-missing values) per category for categorical data, unless specified otherwise.

6.1 Sample Size Justification

The study is designed to assess the bioavailability of TAK-931 tablet formulation in reference to PIC and the effect of food and esomeprazole on PK of TAK-931 as tablet in patients with advanced solid tumors. It is anticipated that as many as 44 patients will be enrolled in this study.

The relative bioavailability study (Part 1) will use a crossover design to compare 2 formulations of TAK-931 (tablet and PIC). Approximately 20 patients will be randomized in a 1:1 ratio to 1 of 2 treatment sequences: single dose of 80 mg PIC or tablet TAK-931on Cycle 0 Day 1 and a single dose of TAK-931 80 mg with the alternate formulation on Day 3 (PIC to tablet or tablet to PIC). Approximately 14-16 PK-evaluable patients will be needed for this part. The sample size calculation is based on the expected 2-sided 90% confidence interval (CI) for difference in the paired, log transformed AUC (or Cmax) means on Day 1 and Day 3. According to preliminary data obtained from study TAK-931-1002, the within-subject CV was estimated to be 35% for AUC and 36.9% for Cmax respectively. Assuming the AUC ratio of the two formulations (tablet versus PIC) is 1, with a sample size of 14, the 90% CI for the AUC ratio is expected to be (0.795, 1.257) for AUC and (0.786, 1.272) for C_{max} based on the previously discussed variance assumptions. Patients who are not PK-evaluable may be replaced to ensure the availability of 14 to 16 PK-evaluable patients in the

final analysis of part 1. Assuming that up to 4-6 patients will be replaced, approximately 20 patients will be needed in Part 1.

The food and Esomeprazole effect study (Part 2) will use a crossover design to assess the effects of food on a single dose PK of TAk-931. Approximately 14-16 PK-evaluable patients will be randomized into 1 of 2 treatment sequences: single dose of TAK-931 tablet formulation with or without a standard high-fat breakfast on Cycle 0 Day 1, with the alternate food intake and dosing on Day 3 (fasted to fed or fed to fasted). The planed sample size for the food effects assessment is similar to that discussed for the relative BA study design. Patients who are not PK-evaluable may be replaced to ensure the availability of 14 to 16 PK-evaluable patients in the final analysis of part 2. Assuming that up to 8-10 patients will be replaced, approximately 24 patients will be needed in Part 2.

If the ratio is X, the 90% CI of the ratio of geometric means is expected to be within (0.795X, 1.257X) for AUC and (0.786X, 1.272X) for C_{max}.

6.2 Randomization and Stratification

In the relative BA study (Part 1), patients will be randomized in a 1:1 ratio to receive TAK-931 in the tablet or PIC on Cycle 0 Day 1, and receive alternate formulation on Day 3. Patients will be replaced if they are considered not PK evaluable. Approximately 20 patients will be enrolled in Part 1 to ensure 14-16 PK-evaluable patients in the final analysis in Part 1.

In the food effect study (Part 2), patients will be randomly assigned in a 1:1 ratio to receive a single dose of TAK-931 in either the fasted state of the fed state on Cycle 0 Day 1. On Day 15, a single dose will be administered in the respective alternate food intake state. Patients may be replaced if they are considered not PK evaluable. Approximately 24 patients will be enrolled in Part 2 to ensure 14-16 PK-evaluable patients in the final analysis in Part 2.

6.3 Unblinding

Not applicable.

6.4 Data Handling

6.4.1 Methods for Handling Missing Data

All available efficacy and safety data will be included in data listings and tabulations. Data that are potentially spurious or erroneous will be examined under the auspices of standard data management operating procedures.

In general, missing data will be treated as missing and no data imputation will be applied, unless otherwise specified.

6.4.1.1 Missing/Partial Dates in Screening Visit

The following rules apply to dates recorded in the screening visits, with the exception of prior therapies (Section 6.4.1.2).

- If only the day-component is missing, the first day of the month will be used if the year and the month are the same as those for the first treatment. Otherwise, the 15th will be used.
- If only a year is present, and it is the same as the year of the first treatment, the 15th of January will be used unless it is later than the first treatment, in which case the date of the first of January will be used.
- If only a year is present, and it is not the same as the year of the first treatment, the 15th of June will be used, unless other data indicates that the date is earlier, in which case the 15th of January will be used.

6.4.1.2 Missing/Partial Dates in Adverse Events/Concomitant Therapies/Subsequent Therapies

Every effort will be made to avoid missing/partial dates in on-study data. If the resolution date of a resolved adverse event (AE) or the stop date of a concomitant therapy is missing, the following rules are to be used unless conflicting data exists: if month and year are present and the day of the month is missing, the last day of the month is imputed. If only a year is present, the 31st of December is used. After imputation, the imputed dates will be compared against the date of death, if available. If the date is later than the date of death, the date of death will be used as the imputed date instead.

In cases where the onset date of an adverse event is completely or partially missing, the following imputation rules will be used:

1. When month and year are present and the day of the month is missing,
    - If the onset month and year are the same as the month and year of first treatment with study drug, the day of first treatment or the day-component of the resolution date are imputed, whichever is earliest.
    - If the onset month and year are not the same as the month and year of first treatment with study drug, the first day of the month is imputed.
2. When only a year is present, or no components of the onset date are present,
    - If the resolution date is available, the earlier of the resolution date (possibly imputed) and the date of first treatment will be used.
    - If the resolution date is missing, and the onset-year is the same as the year of first treatment with study drug, then the date of first treatment with study drug is used.
    - Otherwise if only a year is present, the 1st of January of that year is imputed.
3. If none of the previous rules can be applied, then the date of first treatment with study drug is imputed as the onset date.

The imputation rules for missing/partial start dates of concomitant therapies will be the same as the above with the exception as follows:

For prior therapy data, no imputation will be done for start dates.

The imputation rules for missing/partial start dates of subsequent therapies recorded as concomitant medications will be the same as the above with exceptions as follows.

1. When month and year are present and the day of the month is missing,
    a. If the month and year of the start date are the same as the month and year of treatment termination, the day of treatment termination or the day-component of the stop date is imputed, whichever is earliest.
    b. If the start month and year are not the same as the month and year of treatment termination, the first day of the month is imputed.

2. When only a year is present, or no components of the start date are present, the date will not be imputed.

6.4.2 Definition of Baseline Values

Unless otherwise specified, the baseline value is defined as the value collected at the time closest to, but prior to, the start of study drug administration. For the ECG summaries, the baseline is defined as the average of the triple 12-lead ECG measurements at the time closest to, but prior to, the start of TAK-931 administration.

6.4.3 Windowing of Visits

All data will be categorized based on the scheduled visit at which they were collected. These visit designators are pre-defined values that appear as part of the visit tab in the eCRF.

6.4.4 Justification of Pooling

All data from all sites will be pooled. Study center or treatment-by-center interaction will not be included in any statistical analysis.

6.5 Patient Disposition

A disposition of patients includes the number and percentage of patients for the following categories: patients in each of the study population, primary reason to discontinue from the treatment, patients discontinued from the study, and primary reason to discontinue from the study. All percentages will be presented based on the number of patients in the safety population.

A listing will present data concerning patient disposition.

6.6 Demographics and Baseline Disease Characteristics

6.6.1 Demographics

Demographics and baseline characteristics will be summarized by treatment group (randomization arm) in a descriptive fashion for the safety population. Baseline demographic data to be evaluated will include age, sex, race, ethnicity, height, weight, and other parameters as appropriate.

Demographic data will also be presented in a by-patient listing.

6.6.2 Medical History

Medical history will be presented in a by-patient listing, including the medical and surgical history, date of onset and the status (whether it is resolved or ongoing).

6.6.3 Baseline Disease Status

Baseline disease characteristics will be summarized by the number and percentage of patients by treatment group and total if there is sufficient data for analysis. Eastern Cooperative Oncology Group (ECOG) performance status will be summarized similarly in the same table.

Separate by-patient listing will be presented for baseline disease and ECOG performance status.

6.7 Treatments and Medications

6.7.1 Concomitant Medications

Concomitant medications will be coded by preferred term using the World Health Organization (WHO) Drug Dictionary for patients in the safety population. The number and percentage of subjects taking concomitant medications will be tabulated by WHO drug generic term, from the first dose of study treatment through 30 days after the last dose of study medication or until the start of subsequent antineoplastic therapy, whichever occurs first. Concomitant medications will also be presented in a by-patient listing.

Concomitant procedures will not be coded, but will be presented in a by-patient listing.

6.7.2 Study Treatments

In Part 1 relative BA study, patients will be randomized in a crossover fashion to receive a single dose of TAK-931 80 mg PIC or tablet on Day 1 and a single dose of TAK-931 80 mg with the alternate formulation on Day 3 of Cycle 0. There will be no TAK-931 dosing on Day 2 and Day 4. Patients will then continue to receive TAK-931 50 mg PIC once daily for 12 days followed by a 7-day rest period. Starting from Cycle 1, patients will take 50 mg PIC QD for 14 days followed by 7-day rest period in a 21-day treatment cycle until one of the discontinuation criteria is met.

In Part 2 for the effect of food and esomeprazole study, patients will be randomized to receive a single dose of TAK-931 tablet with or without a standard high-fat breakfast on Day 1, with the alternate food intake condition and dosing on Day 3. Starting from Day 5, patients will receive esomeprazole 40 mg once daily through Day 13. On Day 12, each patient will receive a single dose TAK-931 tablet and continue to receive TAK-931 tablet at dose expected to achieve exposures comparable to 50 mg PIC once daily for 11 days followed by a 7-day rest period until a discontinuation criterion is met. Starting from cycle 1, patients will receive TAK-931 tablet at a dose expected to achieve exposures comparable to 50 mg PIC QD for 14 days followed by 7-day rest period in a 7-day treatment cycle.

6.7.2.1 Extent of Exposure

Extent of exposure to TAK-931 will be characterized by total amount of dose taken in mg, total number of dose taken, number of treated cycles, numbers and percentages of patients who had ≥1, ≥2, …, and ≥12 treated cycles, and relative dose intensity (%). Duration of treatment (days), and number and percentages of patients who had >=3, >=6, … weeks of treatment will be summarized for patients in the safety population by arms.

A treated cycle is defined as a cycle in which the patient received any amount of any treatment drug.

Relative dose intensity (%) is defined as 100 x (total dose received in mg) / (sum of prescribed dose over all treated cycles).

Dosing data will also be presented in a by-patient listing.

6.7.2.2 Treatment Modifications

The actions on TAK-931 (reduce prescribed, reduce non-prescribed, increased prescribed, increased non-prescribed, held, missed, interrupted, delayed, discontinued permanently) will be summarized over all treatment periods, and by each of Cycle by randomization arms. Reasons for dose modification may also be tabulated similarly.

6.7.3 Pharmacokinetic Analyses

The plasma PK parameters will be estimated from the concentration-time profiles for all PK population patients. In estimating the PK parameters, BQL values at the beginning of the profile will be set to zero. BQL values that occur after the first quantifiable point will be considered missing. Values that are embedded between BQLs, or quantifiable values

occurring after two or more BQLs, will be set to missing at the discretion of the pharmacokineticist. Actual sampling timeswill be used in deriving TAK-931 PK parameters. Concentration data that are identified as anomalous may be excluded from the concentration summaries and plots and will not be used in the calculation of PK parameters. Evidence or explanations will be provided to justify the exclusion of data.

Descriptive statistics (number of patients, arithmetic mean, arithmetic standard deviation, arithmetic coefficient of deviation, geometric mean, median, minimum value, and maximum value) will be used to summarize TAK-931 PK parameters. For T_{max}, only median, minimum value, and maximum value will be calculated only if quantifiable and/or reportable values are available for at least 50% of the observations. A minimum of 2 patients are required to show the mean and geometric mean, and at least 3 patients are required to show the standard deviation and CV. The number of observations above the limit of quantification will be shown for plasma concentration-time data.

Part 1

For the relative bioavailability estimation of tablet vs. PIC, at least the ratios of geometric mean AUC_{last}, AUC_{inf} and C_{max} (tablet vs. PIC) associated 2-sided 90% CIs will be calculated, based on the within-patient variance calculated via analysis of Variance (ANOVA). Following log-transformation, AUC_{last}, AUC_{inf} and C_{max} will be separately will be analyzed by ANOVA fitting terms for treatment (formulation) group (TAK-931 tablet and PIC), sequence and period. Subject within sequence will be treated as a random effect in the model. Point estimates and adjusted 90% confidence intervals for the difference in treatment (tablet or PIC) will be constructed. The point estimate and adjusted 90% confidence intervals will then be exponentially back transformed to provide point and confidence interval estimates for the ratios of interest appropriately (eg, $AUC_{0\text{-}last}$ of the TAK-931 in PIC vs. $AUC_{0\text{-}last}$ of the TAK-931 in Tablet).

Part 2

For the estimation of food effect, the ratios of geometric mean $AUC_{0\text{-}last}$, AUC_{inf} and C_{max} (TAK-931 administered with and without food intake) and associated 2-sided 90% CIs will be calculated, based on the within-patient variance calculated via ANOVA. Following log-transformation, AUC_{last}, AUC_{inf} and C_{max} will be separately analyzed by ANOVA fitting terms for treatment groups (fed: fasted). Subject will be treated as a random effect in the model. Point estimates and adjusted 90% confidence intervals for the difference in treatment will be constructed. The point estimate and adjusted 90% confidence intervals will then be

exponentially back transformed to provide point and confidence interval estimates for the ratios of interest appropriately (eg, AUC_{last} of fed vs. AUC_{last} of fasted). For evaluating the effect of esomeprazole on TAK-931 PK, the ratio of geometric mean $AUC_{0\text{-}last}$, AUC_{inf} and C_{max} (presence of esomeprazole : absence of esomeprazole) and associated 2-sided 90% CIs will be calculated, based on the within-patient variance estimated by analysis of variance. The PK population will be used for these analyses.

Descriptive statistics for TAK-931 plasma concentrations and PK parameters will be tabulated by formulation (part 1), food intake state (fed or fasted, part 2) and the use of esomeprazole (in the presence or absence of esomeprazole, part 2):

Individual comparison of AUC_{last}, AUC_{inf} and C_{max} will be plotted by formulation, food intake and the use of esomeprazole, respectively. Individual and mean plasma concentration-time profiles will be plotted by formulation, food intake state, and the use of esomeprazole, respectively.

TAK-931 plasma concentration-time data will be listed using the PK-Evaluable population.

6.7.4 Efficacy Analysis

The secondary efficacy parameters include ORR (CR + PR), PFS, DCR and DOR.

The ORR is defined as the proportion of patients who achieved PR or CR. The estimate of the ORR will be presented with 2-sided 95% exact binomial confidence intervals by treatment groups. ORR will be analyzed using the response-evaluable population.

Progression-free survival is defined as the time from the date of first dose to the date of first documentation of progressive disease or death due to any cause, whichever occurs first. The Kaplan-Meier survival curves, 25th, 50th (median), and 75th percentiles (if estimable), along with their 2-sided 95% confidence intervals will be provided for each treatment group if there is sufficient data. PFS will be analyzed using safety population. The details regarding the handling of missing assessments and censoring for the PFS analysis are presented in the table below.

Handling of Missing Assessments and Censoring for PFS
Primary Analysis Based on FDA guidance

Situation	Date of Progression or Censoring	Outcome
No baseline and/or no post baseline assessment, no subsequent anticancer therapy after study treatment, no death	Date of Randomization	Censored
Disease progression documented between scheduled visits	Date of next scheduled visit	Progressed
No documented death or disease progression	Date of last adequate assessment[a]	Censored
Lost to follow-up, withdraw consent before any documented death or disease progression	Date of last adequate assessment[a]	Censored
Death or progression after more than 1 missed visit[b]	Date of last adequate assessment[a]	Censored
Alternate antineoplastic therapy started prior to disease progression	Date of last adequate assessment prior to starting alternate antineoplastic therapy	Censored
Death before first assessment	Date of death	Progressed
Death between adequate assessment visits	Date of death	Progressed

a Adequate disease assessment is defined as there is sufficient data to evaluate a patient's disease status.
b Death or progression occur more than 90 days from previous adequate assessment.

DCR will be assessed by investigator per RECIST version 1.1 [1] (CR + PR + SD; SD must be ≥1 post baseline CT scan evaluation from treatment initiation to qualify for DCR).

The DOR is defined as the time from the date of first documentation of a response (PR or better) to the date of first documentation of progressive disease. Patients without documentation of progressive disease at the time of analysis will be censored at the date of their last response assessment that is stable disease or better. The DOR will be analyzed using the Kaplan-Meier method based on the responders in the response-evaluable population if there is sufficient data (at least 3 responders).

If there are less than 3 responders in the Response-Evaluable population, only the secondary efficacy analysis for disease control rate and PFS will be conducted if applicable and disease response will be presented in listings only.

6.7.5 CCI

CCI [redacted]

CCI [redacted]

6.7.6 Safety Analyses

Safety evaluations will be based on the incidence, severity, type of AEs, clinically significant changes, or abnormalities in the subject's physical examination, vital signs, ECG, and clinical laboratory results. Reasons for discontinuation and modification will be tabulated. Safety will be summarized by different dose sequence of different formulation, food intake state, and the use of esomeprazole by randomization arms.

These analyses will be performed using the safety population.

6.7.6.1 Adverse Events

AEs will be coded using the MedDRA dictionary, version 21.0. All AEs will be presented in a by-patient listing. Treatment-emergent AEs will be tabulated where treatment-emergent is defined as any AE that occurs after administration of the first dose of study treatment and up through 30 days after the last dose of study medication or until the start of subsequent antineoplastic therapy, whichever occurs first, any event that is considered drug related regardless of the start date of the event, or any event that is present at baseline but worsens in severity after baseline or is subsequently considered drug-related by the investigator. Treatment-emergent AEs will be tabulated according to the MedDRA by system organ class, high level terms and preferred terms and will include the categories listed below. Patients with the same AE more than once will have that event counted only once within each body system, once within each high level term, and once within each preferred term.

- Treatment-emergent AEs
- Drug-related treatment-emergent AEs
- Grade 3 or higher treatment-emergent AEs
- Grade 3 or higher drug-related treatment-emergent AEs

The most commonly reported treatment-emergent AEs (ie, those events reported by ≥10% of all patients in the safety population) will be tabulated by system organ class and preferred term. Patients with the same AE more than once will have that event counted only once within each system organ class and once within each preferred term.

6.7.6.2 Serious Adverse Events

The number and percentage of patients experiencing at least one treatment emergent serious AE (SAE) will be summarized by MedDRA primary system organ class, high level term, and preferred term. Drug-related SAE will be summarized similarly.

In addition, a by-patient listing of the SAEs will be presented (the patient listing will contain all SAEs regardless of treatment emergent AE status).

6.7.6.3 Deaths

A by-patient listing of the deaths will be presented. All deaths occurring on-study and during follow-up will be displayed (regardless of treatment emergent AE status). An on-study death is defined as a death that occurs between the first dose of study drug and 30 days of the last dose of study drug.

6.7.6.4 Adverse Events Resulting in Discontinuation of Study Drug

A by-patient listing of treatment-emergent AEs resulting in discontinuation of study drug will be presented.

Additional safety analyses may be performed to more clearly enumerate rates of toxicities and to further define the safety profile of TAK-931.

6.7.7 Laboratory Data

For the purposes of summarization in both the tables and listings, all laboratory values will be converted to standardized units. If a laboratory value is reported using a non-numeric qualifier (e.g., less than (<) a certain value, or greater than (>) a certain value), the given numeric value will be used in the summary statistics, ignoring the non-numeric qualifier.

If a patient has repeated laboratory values for a given time point, the value from the last evaluation will be used. In case more than one assessment is available on the same date, the later assessment will be used.

Laboratory test results will be summarized descriptively according to the scheduled sample collection time points by treatment groups. Actual values and change from baseline will be summarized over time. Laboratory data will also be presented in listings. Unscheduled laboratory test results will be listed and included in laboratory shift tables.

Shift tables will be constructed for laboratory parameters to tabulate changes in NCI CTCAE for toxicity from baseline to post baseline worst CTCAE grade. Parameters to be tabulated will include:

- Hematology: hemoglobin, hematocrit, platelets, absolute neutrophil counts (ANC), lymphocytes, eosinophils, and WBC
- Clinical chemistry: ALT/SGPT, AST/SGOT, alkaline phosphatase, bilirubin (total), calcium, creatinine, glucose, hemoglobin A1c, magnesium, phosphate, potassium, and sodium

By-patient listings to be presented include hematology and clinical chemistry.

6.7.8 Electrocardiograms

A summary of ECG abnormalities will be presented by visit and treatment groups. ECG intervals (QT, QTc and PR) will be summarized by treatment groups at each scheduled time point, along with mean change from baseline at each scheduled time point. The number and percentage of patients with ECG abnormalities will be summarized at each time point.

7. PROGRAMMING CONSIDERATIONS

7.1 Statistical Software

SAS version 9.2 (or higher) will be used for all analyses.

7.2 Rules and Definitions

Subject populations are defined in Section 3.

Baseline values are defined in Section 6.4.2.

8. REFERENCES

1. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47.