Title: An Open-Label, Phase 2, Parallel Arm Study to Evaluate the Safety, Tolerability, and Activity of TAK-931 Single Agent in Patients With Metastatic Pancreatic Cancer, Metastatic Colorectal Cancer, and Other Advanced Solid Tumors

NCT Number: NCT03261947

SAP Approve Date: 12 Apr 2021

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

STUDY NUMBER: TAK-931-2001

An Open-Label, Phase 2, Parallel Arm Study to Evaluate the Safety, Tolerability, and Activity of TAK-931 Single Agent in Patients with Metastatic Pancreatic Cancer or Metastatic Colorectal Cancer, and other Advanced Solid Tumors

PHASE 2

Version: 1.0 Final

Date: 12 Apr 2021

Prepared by:

PPD

Based on:

Protocol Version: Amendment 3

Protocol Date: 26 June 2018

1.1 Approval Signatures

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

Study Title: **An Open-Label, Phase 2, Parallel Arm Study to Evaluate the Safety, Tolerability, and Activity of TAK-931 Single Agent in Patients with Metastatic Pancreatic Cancer, Metastatic Colorectal Cancer, and Other Advanced Solid Tumors**

Approvals:

PPD

Date

13May2020
Date

Date

Date

Date

1.1 Approval Signatures

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

Study Title: **An Open-Label, Phase 2, Parallel Arm Study to Evaluate the Safety, Tolerability, and Activity of TAK-931 Single Agent in Patients with Metastatic Pancreatic Cancer, Metastatic Colorectal Cancer, and Other Advanced Solid Tumors**

Approvals:

PPD

May 14, 2020
Date

Date

Date

13 MAY 2020
Date

Date

1.1 Approval Signatures

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

Study Title: **An Open-Label, Phase 2, Parallel Arm Study to Evaluate the Safety, Tolerability, and Activity of TAK-931 Single Agent in Patients with Metastatic Pancreatic Cancer, Metastatic Colorectal Cancer, and Other Advanced Solid Tumors**

Approvals:

PPD

Date

Date

Date

Date

May 14, 2020
Date

1.1 Approval Signatures

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

Study Title: **An Open-Label, Phase 2, Parallel Arm Study to Evaluate the Safety, Tolerability, and Activity of TAK-931 Single Agent in Patients with Metastatic Pancreatic Cancer, Metastatic Colorectal Cancer, and Other Advanced Solid Tumors**

Approvals:

PPD

Date

Date

13 May 2020
Date

Date

Date

2.0 TABLE OF CONTENTS

3.0 LIST OF ABBREVIATIONS

AE	adverse event
AUC	area under the plasma concentration-time curve
AUC_{τ}	area under the plasma concentration-time curve over the dosing interval
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
C1D1	Cycle 1, Day 1
CDC7	cell division cycle 7
CI	Confidence Interval
CLr	renal clearance
CL_{ss}/F	steady state apparent oral clearance
C_{max}	maximum observed plasma concentration
CR	complete response
CRC	colorectal cancer
CRO	contract research organization
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
DCR	disease control rate
DDR	DNA damage response
DLT	dose-limiting toxicity
DOR	duration of response
ECHO	echocardiogram
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EORTC	European Organisation for Research and Treatment of Care
HRQOL	health-related quality of life
MCM2	minichromosome maintenance complex 2
MedDRA	Medical Dictionary for Regulatory Activities
NSCLC	non small-cell lung cancer
ORR	overall response rate
OS	overall survival
PD	progression of disease
PFS	progression-free survival
PK	pharmacokinetic(s)
pMCM2	phosphorylation of MCM2 at serine-40
PR	partial response
PRO	patient-reported outcome

QD	once daily
QLQ-C30	Core Quality of Life Questionnaire
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
$R_{ac(AUC)}$	accumulation ratio based on AUC_{τ}
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SD	stable disease
sqEC	squamous esophageal cancer
sqNSCLC	squamous non-small-cell lung cancer
TEAE	treatment-emergent adverse event
$t_{1/2z}$	terminal disposition phase half-life
t_{max}	time to first occurrence of C_{max}

4.0 OBJECTIVES

4.1 Primary Objectives

- To confirm the safety and tolerability of TAK-931 in a cohort of Western patients with metastatic solid tumors.
- To evaluate the anti-tumor activity of TAK-931 in patients with metastatic pancreatic cancer, colorectal cancer (CRC), sqEC, and sqNSCLC.

4.2 Secondary Objectives

- To characterize the PK of TAK-931 in a cohort of Western patients with metastatic solid tumors.
- To contribute to evaluation of population PK using a limited sampling strategy in tumor-specific cohorts.
- To assess additional measures of antitumor activity, including overall response rate (ORR), duration of response (DOR), progression free survival (PFS), and overall survival (OS).
- To further characterize the safety of TAK-931 as a single agent in patients with metastatic pancreatic cancer, CRC, squamous esophageal cancer (sqEC), and squamous non-small cell lung cancer (sqNSCLC).

CCI

[redacted]

CCI

[redacted]

4.4 Study Design

This is a phase 2, multicenter, single agent, uncontrolled, open-label, parallel arm trial in 4 advanced cancer indications. The study will also enroll a lead-in safety cohort of Western patients (United States [US] only) with locally advanced or metastatic solid tumors to determine the safety, tolerability and pharmacokinetics (PK) of TAK-931 50 mg QD for 14 days in 21-day cycles in this patient population.

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoints

- Frequency of TEAEs per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v. 4.03: DLTs, SAEs, TEAEs leading to dose modifications, and TEAEs leading to treatment discontinuation in the Western safety cohort.
- DCR per Response Evaluation Criteria in Solid Tumors (RECIST) v. 1.1 [22] in tumor-specific cohorts: complete response (CR) + partial response (PR) + stable disease (SD); SD has to be ≥6 weeks from treatment initiation to qualify for DCR.

5.2 Secondary Endpoints

- PK parameters after the first dose of TAK-931 on Cycle 1, Day 1 (C1D1): C_{max}, t_{max}; AUC_{24}, AUC from time 0 to the time of the last quantifiable concentration (AUC_{last}); and renal clearance (CLr). PK parameters following multiple doses of TAK-931 (C1D8): C_{max}, t_{max}, AUC_{24}, AUC_{last}, $t_{1/2z}$, steady-state apparent oral clearance (CL_{ss}/F), and accumulation ratio based on AUC over the dosing interval (AUC_{τ}) ($R_{ac(AUC)}$).
- ORR (CR+PR), DOR, PFS, and OS in tumor-specific cohorts. ORR, DOR, and PFS will be measured in the Western safety cohort.
- 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 in the tumor-specific cohorts.

CCI

[redacted]

6.0 DETERMINATION OF SAMPLE SIZE

Approximately 12 Western patients with metastatic solid tumors that progressed after appropriate prior therapy are expected to be enrolled in the US only to determine the safety, tolerability, and PK of TAK-931 in Western patients. Initially, 6 patients will be enrolled at US sites in the safety lead-in cohort for purposes of safety evaluation. If no more than 2 patients present with a DLT, the remaining 6 patients will be enrolled.

Sample size considerations for tumor-specific cohorts are based on a Bayesian predictive probability approach (ref 1) with 1 or 2 interim analyses for futility (Section 7.13) with the following parameters:

Assumptions	Pancreatic Cancer Cohort	Metastatic CRC Cohort	SqEC Cohort	sqNSCLC Cohort
Ineffective DCR (H_o)	13%	23%	30%	30%
Effective DCR (H_a)	30%	40%	50%	50%
Type 1 error	10%	10%	10%	10%
Power	80%	80%	80%	80%
Prior beta distribution parameters	a0=0.2, b0=0.8	a0=0.2, b0=0.8	a0=0.2, b0=0.8	a0=0.2, b0=0.8

CRC=colorectal cancer; DCR=disease control rate, H_o=null hypothesis, H_a=alternative hypothesis; sqEC=squamous esophageal cancer; sqNSCLC=squamous non-small cell lung cancer.

It is expected that the study will enroll up to ~33 response-evaluable patients in the metastatic pancreatic cancer cohort, ~35 response-evaluable patients in the metastatic CRC cohort, up to ~40 response-evaluable patients in the sqEC cohort, and up to ~40 response-evaluable patients in

the sqNSCLC cohort. With a potential drop-out rate of 10%, as many as approximately 76 patients may be enrolled in the pancreatic and CRC cohorts. Approximately 80 patients may be enrolled in the sqEC cohort and sqNSCLC cohorts.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

In general, summary tabulations will be presented to display the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percentage (of nonmissing) per category for categorical data, unless specified otherwise. Patients will be analyzed at the dose level to which they were originally assigned, unless specified otherwise, including those who receive subsequent treatment at a lower dose level or a higher dose level. Tables will be summarized by tumor-specific cohorts.

At the time of clinical study report(CSR) lock and/or final database lock, all relevant data will be queried and cleaned; a database snapshot will be taken and used for the CSR and/or CSR addendum. Additional treatment data will be entered into the database through study termination and/or by final database lock. Analyses may be updated based on additional information. An addendum to the CSR may be written if warranted based on these analyses.

In general, the baseline value is defined as the value collected at the time closest to, but prior to, the start of study drug administration.

Efficacy estimates including DCR and ORR will be reported as 2-sided 80% exact binomial confidence interval. Other confidence intervals. statistical tests, and resulting p-values will be reported as 2-sided 95% unless otherwise stated.

Means and medians will be presented to 1 more decimal place than the recorded data. The standard deviations (SDs) will be presented to 2 more decimal places than the recorded data. Confidence intervals about a parameter estimate will be presented using the same number of decimal places as the parameter estimate.

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. For quality of life data, missing data imputation will be based on published instrument specific methods. Missing data analysis for PRO data will be addressed in Section 7.11.

All statistical analyses will be conducted using SAS® version 9.2, or higher.

7.1.1 Study Definitions

7.1.2 Definition of Study Days

Study Day 1 (enrollment date) is defined as the date on which a subject is administered their first dose of the medication. Other study days are defined relative to the Study Day 1 with Day 1 being Study Day 1 and Day -1 being the day prior to Study Day 1.

7.1.3 Definition of Study Visit Windows

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

7.1.4 Conventions for Missing Adverse Event Dates

Every effort will be made to avoid missing/partial dates in on-study data.

7.1.4.1 Adverse events with start dates that are completely or partially missing will be analyzed as follows:

- If the start date has a month and year but the day is missing, the event will be considered treatment emergent if the month and year of the start date of the event are:
  - On or after the month and year of the date of the first dose of study drug

    and
  - On or before the month and year of the date of the last dose of study drug plus 30 days
- If the start date has a year, but the day and month are missing, the event will be considered treatment emergent if the year of the start date of the event is:
  - On or after the year of the date of the first dose of study drug

    and
  - On or before the year of the date of the last dose of study drug plus 30 days
- If the start date of an event is completely missing then the event is assumed to be treatment emergent.

However, if the end date is complete or partially missing but the end date is before the first dose of study drug, the event will not be considered treatment emergent.

7.1.5 Conventions for Missing Concomitant Medication Dates

Concomitant therapies with start dates that are completely or partially missing will be analyzed as follows:

1. If the start date has a month and year but the day is missing, the event will be considered concomitant if the month and year of the start date of the event are:
   - On or after the month and year of the date of the first dose of study drug

and

– On or before the month and year of the date of the last dose of study drug plus 30 days).

2. If the start date has a year, but the day and month are missing, the event will be considered concomitant if the year of the start date of the event is:
   – On or after the year of the date of the first dose of study drug

   and

   – On or before the year of the date of the last dose of study drug plus 30 days).
3. If the start date of an event is completely missing then the event is assumed to be concomitant.

However, if the end date is complete or partially missing but the end date is before the first dose of study drug, the event will not be considered concomitant.

When the start date is complete and is before the first dose, and the concomitant medication is not ongoing but the end date is missing completely or partially, a similar algorithm should be used to assess whether the end date is before the last dose of study drug plus 30 days to be included.

7.2 Analysis Sets

The analysis sets used for analysis will include the following:

- Safety analysis set: The safety analysis set is defined as all patients who receive any amount of study drug. This analysis set will be used for safety and time to event analyses.
- Pharmacokinetic analysis set: The PK analysis set is defined as all patients for whom there are sufficient dosing and TAK-931 concentration-time data to reliably estimate the PK parameters. This analysis set will be used for analyses of PK parameters.
- DLT-evaluable analysis set: The DLT-evaluable analysis set is defined as all patients in the Western safety cohort who receive at least 1 of their planned TAK-931 doses during their first cycle of treatment (unless interrupted by related AEs) and who have sufficient follow-up data to allow the investigators and sponsor to determine whether a DLT occurred. Patients who receive <1 dose of TAK-931 in Cycle 1 for reasons other than related AEs are not eligible for DLT evaluation and may be replaced. This analysis set will be used for DLT analyses.
- Response-evaluable analysis set: The response-evaluable analysis set is defined as patients who receive at least 1 dose of study drug, have measurable disease at Baseline, and have at least 1 postbaseline response assessment. Patients who die (from any cause) and patients who discontinue due to clinical deterioration before a postbaseline assessment will be considered evaluable and as nonresponders. This analysis set will be used for response-related efficacy analyses.

7.3 Disposition of Subjects

Disposition of patients includes the number and percentage of patients in each cohort enrolled and total. The primary reasons for discontinuation of study drug as well as study termination will be summarized.

All percentages will be based on the number of patients in the safety analysis set.

7.3.1 Significant Protocol Deviations

Protocol deviations will be identified either through manual lists or using programmed algorithms. Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the patient, or confound interpretation of primary study assessment. Protocol deviations applicable to all study parts and protocol deviations specific to each study part will be identified. A listing will be generated for protocol deviations, which will include, but will not be limited to, at least 1 of the following:

- Any inclusion/exclusion criteria not met by an enrolled patient.
- Use of or administration of excluded and/or restricted medications, not in accordance with the study protocol.
- Study procedures not performed as per the clinical study protocol that may confound interpretation of primary clinical study objectives and/or affect patient safety.
- Dispensing of incorrect treatment and/or incorrect dose of clinical study medication.
- Any occasion that withdrawal criterion is met but the patient is not withdrawn.

7.4 Demographic

Baseline Demographic (age, sex, race, ethnicity, height, weight and other parameters as appropriate) will be summarized by cohorts. No inferential statistics will be carried out.

Age will be calculated from date of birth to date of informed consent.

7.4.1 Baseline Disease Characteristics

Baseline disease characteristics will be summarized by cohorts including, types of cancer, time since initial diagnosis to first dose, prior therapy, disease stage at study entry, ECOG performance status.

Initial diagnosis years from prior diagnosis to the first dose of TAK-931 is calculated by

$$\frac{\text{first dose date - date of initial diagnosis}}{365.25/12}$$

7.5 Medical History

General medical history will be presented in a by-patient listing, including the medical and surgical history, date of onset and the status (resolved or ongoing). Disease specific history will be summarized by cohorts. Separate by-patient listing will be presented as well.

7.6 Concomitant Medications

Concomitant medications will be coded by generic term using the World Health Organization (WHO) Drug Dictionary. The number and percentage of patients 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. Concomitant procedures will not be coded.

Concomitant medications and procedures will be presented in by-patient listings as well.

7.7 Study Drug Exposure and Compliance

A patient will be considered as treated in a cycle as long as this patient received any amount of study drug in that cycle. A treatment cycle is defined as a cycle in which the patient received any amount of study drug.

Relative dose intensity (%) is defined as 100 × (total amount of dose taken (mg)) / (sum of the planned dose over all treatment cycles).

The exposure to each study drug will be summarized including the number of cycles administered, total amount of TAK-931 taken (in mg), total number of doses taken, number and percentages of patients by treatment cycles, and relative dose intensity. An aggregate summary of numbers and percentages of patients who had 1-6, 7-13, 14-20, 21-26, and >26 treatment cycles will also be presented in the same table.

Exposure of TAK-931 will be presented by disease specific cohorts. The summary of each study drug exposure will be presented by each cohort and the total of safety patients in a similar format.

7.8 Efficacy Analysis

Response will be assessed according to RECIST version 1.1 for all patients at cycles where disease is assessed during the treatment period and subsequently every 12 weeks during the PFS follow-up period for patients not discontinued due to PD until the occurrence of PD, loss to follow up, consent withdrawal, death, the start of subsequent systemic antineoplastic therapy, study termination, the patient completes 1 year of treatment and continuation is not approved by the sponsor, or until 6 months after the patient discontinues treatment, whichever occurs first (protocol Section 9.4). Beside response, other efficacy parameters including, but not limited to, ORR and duration of response (DOR), PFS and OS will be presented in listings and summarized if appropriate.

Subgroup analysis by age, ECOG, molecular baseline characteristics, etc. may also be explored for some efficacy endpoints.

7.8.1 Primary Efficacy Endpoint(s)

The primary efficacy parameter is DCR per RECIST version 1.1 (CR+PR+SD; SD has to be ≥6 weeks from treatment initiation to qualify for DCR).

Estimate of DCR will be calculated based on 2-sided 80% exact binomial confidence interval by cohorts based on response-evaluable analysis set.

7.8.2 Secondary Efficacy Endpoint(s)

Secondary efficacy parameters are ORR, DOR, PFS, and OS.

ORR includes CR and PR per RECIST version 1.1. Estimate of ORR will be calculated based on 2-sided 80% exact binomial confidence interval by cohorts.

DOR is defined as the time from the date of first documentation of a response to the date of first documentation of PD. Patients without documentation of PD at the time of analysis will be censored at the date of their last response assessment that is SD or better. DOR will be analyzed using the Kaplan-Meier estimation. The DOR will be analyzed using the responders in the response-evaluable analysis set.

PFS is defined as the time from the date of first dose to the date of first documentation of PD (including clinical progression or clinical deterioration) 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% CIs and percentage of censored observations will be provided by cohorts. PFS will be analyzed using the safety analysis set. Patients without documentation of PD will be censored at the date of last response assessment that is SD or better. Patients without any post-baseline response assessment will be censored at first dose date.

OS is defined as the time from the date of first dose of study drug to death due to any cause. Patients without documentation of death at the time of analysis will be censored at the date last known to be alive. OS will be analyzed in the safety analysis set using Kaplan-Meier estimation for the tumor-specific cohorts only.

ORR and DOR, will not be analyzed if there are less than three responders.

Time to event parameters will be censored if patients withdraw, drop out, or are lost to follow-up before documentation of the events (progressive disease / death). Rules for censoring are detailed as above.

CCI

7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 Pharmacokinetic Analysis

For patients undergoing intensive PK sampling, PK parameters after the first dose of TAK-931 on C1D1: C_{max}, t_{max}; AUC_{24}, AUC from time 0 to the time of the last quantifiable concentration (AUC_{last}); and renal clearance (CL_R). PK parameters following multiple doses of TAK-931 (C1D8): C_{max}, t_{max}, AUC_{24}, AUC_{last}, $t_{1/2z}$, steady-state apparent oral clearance (CL_{ss}/F), and accumulation ratio based on AUC over the dosing interval (AUC_{τ}) ($R_{ac(AUC)}$). PK parameters in patients undergoing intensive PK sampling will be estimated by noncompartmental methods using Phoenix® WinNonlin® version 6.2 or higher (Pharsight Corp, Mountain View, California). The plasma PK parameters will be estimated from the concentration-time profiles for all PK analysis set patients that undergo intensive PK sampling. The plasma and urine PK of TAK-931 after the first dose on C1D1 and after multiple doses on C1D8 will be determined based on the PK parameters below, as permitted by data.

- $C_{max.}$
- $T_{max.}$
- AUC24 and AUClast after the first dose (C1D1) and after multiple-dose administration on C1D8.
- $t1_{/2z}$ (Day 8 only).
- CL_{ss}/F, Rac(AUC) (C1D8 only).
- Amount of TAK-931 excreted over 8 hours (C1D1 only) and CL_R (C1D1 only) for patients undergoing urine PK collection in the Western safety cohort.

PK parameters in patients undergoing intensive PK sampling will be summarized using descriptive statistics. Individual TAK-931 concentration-versus-time data and individual PK parameters will be presented in listings and tabulated using summary statistics by cohort. Individual and mean plasma concentration-time profiles will be plotted by cohort.

The sparse PK concentrations will be used in future integrated TAK-931 population PK analyses, which will be reported separately.

7.9.2 Pharmacodynamic Analysis

The posttreatment change from baseline of pMCM2 (Ser40) levels (% positive and H-score) in skin will be descriptively summarized for each individual patient and summarized for each cohort. The PD effect in skin in relation to the drug exposure (PK-PD relationship) will be assessed using statistics, graphical method, whichever is appropriate. The posttreatment change from baseline of pMCM2 (Ser40) levels (% positive and H-score) in tumor tissue biopsies may also be descriptively summarized for each individual patient.

- Posttreatment change from baseline of pMCM2 (Ser40) levels in skin in the Western safety cohort only.

- Posttreatment change from baseline of pMCM2 (Ser40) levels in the tumor in a subset of patients.

7.10 Biomarker Analysis

At the end of the study, tumor genetic alterations (mutations, amplification/deletions) in ctDNA and/or banked or fresh tumor tissues may be characterized by NGS. A retrospective correlative study of these genetic alterations in relation to clinical responses (ORR, best tumor size changes, DCR, PFS, OS etc) may be performed using descriptive statistics, graphical methods, and statistical modeling, whichever is appropriate. Preclinical study identified predictive biomarker signatures including but not limited to MSS status, DNA repair gene mutations and *TP53* mutations may be further validated in relation to the clinical responses to TAK-931.

The biomarker results will be reported separately.

7.11 Patient-Reported Outcome (PRO) Analysis

Analysis of PROs will be performed by cohorts using patients with baseline and at least one postbaseline measurements in the Safety analysis set.

Descriptive statistics of the actual value and change from baseline of the EORTC QLQ-C30 scale scores and summary score will be presented over time. Additionally, the descriptive statistics of the actual value and change from baseline of the EORTC QLQ-C30 scale scores and summary score will be presented over time by responders and non-responders.

The summary score of EORTC QLQ-C30 will be calculated from the mean of 13 of the 15 EORTC QLQ-C30 scales (the Global health status/quality of life and the Financial difficulties scale are not included).

Prior to calculating the mean, the symptom scales need to be reversed to obtain a uniform direction of all scales. The summary score should only be calculated if all of the required 13 scale scores are available.

Longitudinal analysis for the change from baseline of all the scale scores and summary score of the EORTC QLQ-C30 will be performed using linear mixed models, including visit and baseline score as covariates in the model. The estimated mean change from baseline scores with 95% CIs will be provided at each time point. Figures of estimated mean change from baseline scores with 95% CIs over time will be generated.

The proportion of patients who experience a clinically meaningful change from baseline in the scale scores and summary score of EORTC QLQ-C30 might be summarized over time.

Published scoring manuals and guidelines will be used to score EORTC QLQ-C30 scale scores, summary score and handle missing data. Further investigation of missing patterns, imputation, and subsequent sensitivity analyses may be conducted.

The compliance for EORTC QLQ-C30 will also be summarized by number of expected and number and percentage of received over time and overall.

Table 7.a Definition of Subscale Scores of EORTC QLQ-C30

Scale/Subscale	Individual Items
Global health status/quality of life	29-30
Physical functioning	1-5
Role functioning	6-7
Emotional functioning	21-24
Cognitive functioning	20, 25
Social functioning	26-27
Fatigue	10, 12, 18
Nausea and vomiting	14-15
Pain	9, 19
Dyspnea	8
Insomnia	11
Appetite loss	13
Constipation	16
Diarrhea	17
Financial difficulties	28

7.12 Safety Analysis

Primary safety endpoint

Frequency of TEAEs per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03: DLTs, SAEs, TEAEs leading to dose modifications, and TEAEs leading to treatment discontinuation in the Western safety cohort.

Secondary safety endpoints

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 in the tumor-specific cohorts.

The incidence of DLTs in the lead-in safety cohort in Western patients will be tabulated. In addition, to assess the relationship between toxicities and TAK-931 dose, the preferred term of individual toxicities will be summarized by their frequency and intensity. The DLT-evaluable analysis set will be used for the analysis of DLT.

Safety will be evaluated by the incidence of TEAEs (defined as any AEs that occur after administration of the first dose of study drug through 30 days after the last dose of study drug), severity, and by changes from baseline in the patient's vital signs and clinical laboratory results in the safety analysis set. Exposure to study drug will be summarized, and reasons for discontinuation and modification will be tabulated. Safety will be summarized by cohort.

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

7.12.1 Adverse Events

Adverse events (AE) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be reported from the first dose of study drug through 30 days after administration of the last dose of study drug. All AEs will be presented in a by-patient listing. AEs will be tabulated according to the MedDRA by system organ class, high level terms, preferred terms, and by cohorts. Treatment-emergent adverse events (TEAE) is defined as any AE that occurs after administration of the first dose of any study treatment through 30 days after the last dose of any study treatment.

Summary tabulations will include the following categories:

- TEAEs.
- Drug-related TEAEs.
- Grade ≥3 TEAEs.
- Grade ≥3 drug-related TEAEs.
- Most common TEAEs (≥10% of all patients).
- SAEs.
- TEAEs resulting in study drug discontinuation.

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 and worst grade.

Drug-related treatment-emergent AEs will also be summarized by the National Cancer Institute Common Toxicity Criteria (NCI CTCAE) version 4.03 AE(1). Patients with the same AE more than once will have the maximum intensity of that event counted once within each body system, once within each high level term, and once within each preferred term.

Most commonly reported (at least 10% of all patients) treatment-emergent AEs will be presented by preferred term only. Patients with the same AE more than once will have that event counted only once within each preferred term.

Most commonly reported (at least 5% of all patients) non-serious TEAEs will be presented by system organ class and preferred term. Patients with the same AE more than once will have that event counted only once within each body system, and once within each preferred term.

An overall summary AE table by cohorts will include numbers and percentages of patients who had any AE, drug-related AE, grade 3 or higher AE, grade 3 or higher drug-related AE, serious AE (SAE), drug-related SAE, AE resulting in any drug discontinuation, AE resulting in any dose reduction, AE resulting in any dose modification (defined as delay, reduction or discontinuation), and on-study deaths.

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

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

A by-patient listing of the on-study deaths will be presented. On-study death is defined as the death that occurs between the first dose of study drug up to 30 days after the last dose of study drug.

The number and percentage of patients experiencing at least one adverse event resulting in discontinuation of study drug by cohorts will be summarized by MedDRA system organ class, high level term, and preferred term.

A by-patient listing of treatment-emergent AEs resulting in discontinuation of study drug will be presented. All AEs resulting in discontinuation of any study drug occurring on-study will be displayed.

The number and percentage of patients experiencing at least one adverse event resulting in any dose modification including dose reduction, treatment interruption, and treatment delay by cohorts will be summarized by MedDRA system organ class, high level term, and preferred term.

A by-patient listing of AEs resulting in dose modification of study drug will be presented. All AEs resulting in dose modification of any study drug occurring on-study will be displayed.

A by-patient listing of DLTs that occur during Cycle 1 of treatment in Western safety cohort will be presented.

7.12.2 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed locally. 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.

Laboratory test results (and/or change from baselines) will be summarized according to the scheduled sample collection time point. Shift tables for the change in CTCAE grade will be constructed for hematology and chemistry laboratory parameters which have corresponding CTCAE grades to tabulate changes in NCI CTCAE (version 4.03)[1] from baseline to worst post baseline on study CTCAE grade. All the data from both scheduled and unscheduled time points are to be included in the shift table.

The mean and median estimates over time may be graphed for a selected list of lab parameters.

Parameters to be tabulated will include:

- Hematology: hemoglobin, hematocrit, platelets, absolute neutrophil counts (ANC), leukocytes
- Clinical chemistry: Alanine aminotransferase, albumin, alkaline phosphatase, bicarbonate, bilirubin (total), calcium, chloride, creatinine, glucose, lactate dehydrogenase, magnesium, phosphate, potassium, sodium, urate.

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

7.12.3 Vital Signs, Echocardiogram and Multiple Gated Acquisition Scan

Descriptive statistics for the actual values (and or/changes from baseline) of vital signs, weight, ECHO, or MUGA scans over time will be tabulated by scheduled time point. A by-patient listing will also be presented.

7.12.4 12-Lead ECGs

ECG intervals (QT, QTcF, and PR interval), and any other clinically meaningful -in the opinion of the investigator-ECG abnormalities will be summarized at each scheduled time point, along with mean change from baseline to each posttreatment time point.

Patients in the Western safety cohort and the first 10 US patients in each tumor-specific cohort will undergo PK time- matched triplicate ECGs during Cycle 1 on Days 1 and 8.

Standard ECGs, including abnormalities, will be listed in a by-patient listing.

Triplicate ECGs in the Western safety cohort and the first 10 US patients in the CRC and pancreatic cancer will be listed in a by-patient listing.

The results of the PK-pharmacodynamic ECG analysis will be reported separately.

7.12.5 Other Observations Related to Safety

Pregnancy testing results will be presented in a by-patient listing.

Additional safety analyses may be determined at any time to enumerate rates of toxicities and to further define the safety profile of the study drugs.

7.13 Interim Analysis

Interim analysis for futility will be conducted to inform whether continuation of enrollment is warranted. The disease control rate (DCR, including CR, PR, or SD ≥6 weeks) will be used as the endpoint for the interim analysis.

Metastatic Pancreatic Cohort and CRC Cohort

Two interim futility analyses will be conducted for both cohorts.

In the metastatic pancreatic cancer cohort, the first interim futility analysis will be carried out after the first 16 response-evaluable patients. If no patients with DCR are observed in the first stage, the study will be stopped for futility; otherwise, the study will continue to the second

stage. The second interim futility analysis will be carried out after 25 response-evaluable patients. If ≤2 patients have achieved DCR, the study will be stopped for futility; otherwise, the study will continue into the third stage to more fully characterize the DCR in a total of 33 response-evaluable patients and the null hypothesis will be rejected if there are more than 7 patients with DCR.

Similarly, the 2 interim futility stopping bounds for DCR in the metastatic CRC cohort will be ≤1 of 15 and ≤4 of 25 in a total of 35 response-evaluable patients, and the null hypothesis will be rejected if there are more than 11 of 35 patients with DCR.

Squamous Esophageal Cancer and Squamous Non–Small-Cell Lung Cancer Cohorts

One interim futility analysis will be conducted for both cohorts. The interim futility stopping bound for DCR will be ≤6 patients with DCR in a total of 20 response-evaluable patients, and the null hypothesis will be rejected if there are more than 16 DCR patients of 40 patients.

7.14 Changes in the Statistical Analysis Plan

{Not applicable}

8.0 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.
2. Lee JJ, Liu DD. A predictive probability design for phase II cancer clinical trials. Clin Trials 2008;5(2):93-106.
3. Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03. U.S. Department of Health and Human Services National Cancer Institute. 14 June 2010.