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

Protocol Approve Date: 16 July 2018

Certain information within this protocol has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information (PPD) 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.

PROTOCOL

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

Sponsor: Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited
40 Landsdowne Street
Cambridge, MA 02139 USA
Telephone: +1 (617) 679-7000
Please note: Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, may be referred to in this protocol as "Millennium," "sponsor," or "Takeda."

Study Number: TAK-931-2001

IND Number: 127,176 **EudraCT Number:** Not applicable

Compound: TAK-931

Date: 16 July 2018 **Amendment Number:** 04

Amendment History:

Date	Amendment Number	Region
22 May 2017	Initial Protocol	Global
14 July 2017	01	Global
30 October 2017	02	Global
26 June 2018	03	Global
16 July 2018	04	Global

1.0 ADMINISTRATIVE

1.1 Contacts

A separate contact information list will be provided to each site.

Serious adverse event and pregnancy reporting information is presented in Section 10.0, as is information on reporting product complaints.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.1 and relevant guidelines provided to the site.

Contact Type/Role	Contact
Serious adverse event and pregnancy reporting	See Section 10.2

1.2 Approval

REPRESENTATIVES OF TAKEDA

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

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

SIGNATURES

The signature of the responsible Takeda medical officer (and other signatories, as applicable) can be found on the signature page.

Electronic Signatures may be found on the last page of this document.

PPD

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study patients in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.0 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.
- Responsibilities of the Investigator (Appendix B).

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix C of this protocol.

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Province)

Location of Facility (Country)

1.3 Protocol Amendment 04 Summary of Changes

Rationale for Amendment 04

This section describes the changes to the protocol incorporating Amendment 04. The primary reason for this amendment is change the method from SAE reporting from electronic data capture (EDC)-based to paper-based.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

For specific descriptions of text changes and where the changes are located, see Appendix F.

Changes in Amendment 04

1. SAE reporting requirements were changed from EDC-based reporting to paper/e-mail/fax-based reporting.

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2.0 STUDY SUMMARY

<table>
<tr><td colspan="2">Name of Sponsor:
Millennium Pharmaceuticals, Inc</td><td colspan="2">Compound:
TAK-931</td></tr>
<tr><td>Title of Protocol: 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</td><td>IND No.: 127,176</td><td>EudraCT No.:
Not applicable</td></tr>
<tr><td>Study Number: TAK-931-2001</td><td colspan="2">Phase: 2</td></tr>
<tr><td colspan="3">Study Design:
Phase 2, multicenter, single agent, uncontrolled, open-label, parallel arm trial in 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.</td></tr>
<tr><td colspan="3">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), squamous esophageal cancer (sqEC), and squamous non–small-cell lung cancer (sqNSCLC)</td></tr>
<tr><td colspan="3">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, sqEC, and sqNSCLC.</td></tr>
<tr><td colspan="3">Patient Population: Patients with one of the following diagnoses:
• Pathologically confirmed metastatic pancreatic adenocarcinoma that has progressed after, at least, a first line of standard systemic chemotherapy for metastatic disease.
• Pathologically confirmed metastatic adenocarcinoma of the colon or rectum who have progressed to at least 2 lines of standard systemic chemotherapy for the metastatic disease.
• Pathologically confirmed locally advanced or metastatic sqEC that has progressed after at least a first line of standard systemic therapy for metastatic disease. First-line patients can be enrolled if a platinum doublet is contraindicated or refused by the patient.
• Pathologically confirmed locally advanced or metastatic sqNSCLC that has progressed after at least 2 lines of standard systemic therapy for metastatic disease.</td></tr>
<tr><td colspan="2">Number of Patients:
It is expected that up to ~33 response-evaluable patients in the metastatic pancreatic cancer cohort and ~35 response-evaluable patients in the metastatic CRC cohort will be enrolled in the study in 3 stages, each with 2 futility evaluations. Additionally, up to 40 response-evaluable patients with locally advanced or metastatic sqEC and up to 40 response-evaluable patients with locally advanced or metastatic sqNSCLC may be enrolled in 2 stages, with 1 futility evaluation for each cohort.</td><td colspan="2">Number of Sites:
Approximately 2-4 sites for the Western safety cohort in the US; approximately 18 sites total (2-3 sites in Japan and approximately 15 in the US).</td></tr>
</table>

Dose Level:	**Route of Administration:**
TAK-931 50 mg QD 14 days on and 7 days off study drug in a 21-day cycle.	Oral.
Duration of Treatment:	**Period of Evaluation:**
Until a discontinuation criterion is met or 1 year of dosing. Patients with clinical benefit may continue after 1 year upon sponsor approval.	Patients will be followed for safety for approximately 30 days after their last dose of study drug or until the start of subsequent anticancer therapy, whichever occurs first. All patients will be followed for PFS and, in tumor-specific cohorts, for OS. It is anticipated that this study will last for approximately 24 months.

Main Criteria for Inclusion:

- Adult male or female patients aged ≥20 years (Japan) or ≥18 years (US).
- Eastern Cooperative Oncology Group (ECOG) performance status of 0-1.
- Patients with one of the following:
  - Pathologically confirmed metastatic pancreatic adenocarcinoma that has progressed after, at least, a first line of standard systemic chemotherapy for metastatic disease.
  - Pathologically confirmed metastatic adenocarcinoma of the colon or rectum who have progressed to at least 2 lines of standard systemic chemotherapy for the metastatic disease.
  - Pathologically confirmed locally advanced or metastatic sqEC that has progressed after at least a first line of standard systemic therapy for metastatic disease. First-line patients can be enrolled if a platinum doublet is contraindicated or refused by the patient.
  - Pathologically confirmed locally advanced or metastatic sqNSCLC that has progressed after at least 2 lines of standard systemic therapy for metastatic disease.
- For the Western safety cohort only: patients with locally advanced or metastatic solid tumor for whom no standard treatment with an established survival benefit is available or if the patient refuses other standard therapy.
- For disease-specific cohort patients: measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.
- Adequate bone marrow reserve and renal and hepatic function based on the following laboratory parameters:
- Absolute neutrophil count ≥1500/mm^3, platelet count ≥100,000/mm^3, and hemoglobin ≥9 g/dL.
- Total bilirubin ≤1.5× the institutional upper limit of normal (ULN).
- Serum alanine aminotransferase or aspartate aminotransferase ≤3.0× the institutional ULN (<5×ULN if liver enzyme elevations are due to hepatocellular cancer, biliary tract cancer, or metastatic disease in liver).
- Creatinine <1.5× the institutional ULN or estimated creatinine clearance using the Cockcroft-Gault formula ≥50 mL/minute for patients with serum creatinine concentrations above institutional limits.
- Left ventricular ejection fraction >50% as measured by echocardiogram or multiple gated acquisition scan within 4 weeks before receiving the first dose of study drug.
- Recovered to Grade 1 or Baseline from all toxic effects of previous therapy (except alopecia or neuropathy).
- For the Western safety cohort only: willingness to undergo serial skin tissue biopsies.
- For disease-specific cohort patients: Must have an archival (banked) tumor sample or agree to have a new (fresh) tumor biopsy during the screening period. If a new tumor sample is needed, the disease should, in the opinion of the investigator, be accessible. For patients in the Western safety cohort, this biopsy is optional.

Main Criteria for Exclusion:

- Patients who require continuous use of proton pump inhibitors (PPIs) or histamine-2 receptor antagonists and patients who are taking PPIs within 5 days before the first dose of study drug.
- Treatment with clinically significant enzyme inducers, such as phenytoin, carbamazepine, phenobarbital, rifampin, rifabutin, rifapentine, or Saint John's wort within 14 days before the first dose of study drug.
- Treatment with any systemic anticancer treatment (including investigational products) within 30 days or 5 half-lives, whichever is shorter, before the first dose of study drug.
- History of any of the following within the last 3 months before administration of the first dose of study drug:
  - Ischemic myocardial event including angina requiring therapy and artery revascularization procedures, myocardial infarction, and unstable symptomatic ischemic heart disease.
  - Ischemic cerebrovascular event, including transient ischemic attack and artery revascularization procedures.
  - Significant, uncontrolled cardiac arrhythmia (including atrial flutter/fibrillation, ventricular fibrillation, or ventricular tachycardia).
  - Placement of a pacemaker for control of cardiac rhythm.
  - New York Heart Association Class II to IV heart failure.
  - Any other cardiac condition that, in the opinion of the investigator, could pose an additional risk for participation in the study (eg, pericardial effusion or restrictive cardiomyopathy).
  - Baseline prolongation of the QT interval corrected for heart rate (HR) using Fridericia's formula ([QTcF] eg, repeated demonstration of QTcF interval >480 ms, history of congenital long QT syndrome, or torsades de pointes).
- Patients with hypertension that is unstable or not controlled by medication.
- History of uncontrolled brain metastasis unless:
  - Previously treated with surgery, whole-brain radiation, or stereotactic radiosurgery, AND
  - Stable disease (SD) for ≥30 days, without steroid use (or stable steroid dose established for ≥14 days before the first dose of TAK-931).
- Known history of human immunodeficiency virus infection.
- Known hepatitis B virus (HBV) surface antigen seropositive or detectable hepatitis C infection viral load. Note: Patients who have positive HBV core antibody or HBV surface antigen antibody can be enrolled but must have an undetectable HBV viral load.
- Known gastrointestinal (GI) disease or GI procedure that could interfere with the GI absorption of study drug, such as total gastrectomy or GI conditions that could substantially modify gastric pH.
- Prior treatment with radiation therapy involving ≥25% of the hematopoietically active bone marrow within 3 months before the first dose of study drug.
- Patients with known MSI-H genotype or known wild type *TP53* per local testing.

Western Lead-in Safety Cohort Only

- Patients with Japanese heredity.

Main Criteria for Evaluation and Analyses:

The primary endpoints for this study are:

- Frequency of treatment-emergent adverse events (TEAEs) per National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03: dose-limiting toxicities (DLTs), serious adverse events (SAEs), TEAEs leading to dose modifications, and TEAEs leading to treatment discontinuation in the Western safety cohort.
- Disease control rate (DCR) per RECIST version 1.1 in both disease-specific cohorts: complete response (CR) +

partial response (PR) + SD; SD has to be ≥6 weeks from treatment initiation to qualify for DCR.

Secondary endpoints for this study are:

- PK parameters after the first dose of TAK-931 on Cycle 1 Day 1 (C1D1): C_{max}, time to first occurrence of maximum (peak) concentration (t_{max}); AUC from time 0 to 24 hours (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}, terminal disposition phase half-life ($t_{1/2z}$), 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 disease-specific cohorts. ORR, DOR, and PFS will be measured in the Western safety cohort.
- Percentage of patients with TEAEs: Grade ≥3 TEAEs, serious AEs (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.

Statistical Considerations:

Sample size considerations for tumor-specific cohorts are based on a Bayesian predictive probability approach with interim analyses for futility (see Section 13.2) 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

Abbreviations: 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.

Metastatic Pancreatic and CRC Cohorts

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 disease control (CR, PR, or SD ≥6 weeks) 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 disease control, 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 disease control. Similarly, the 2 interim futility stopping bounds for DCR in the metastatic CRC cohort will be ≤1/15 and ≤4/25 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 disease control.

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 disease control in a total of 20 response-evaluable patients, and the null hypothesis will be rejected if there are more than 16 of 40 patients with disease control.

Sample Size Justification: 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.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the Clinical Study Supplier List or equivalent. The identified vendors for specific study-related activities will perform these activities in full or in partnership with the sponsor.

3.2 Principal Investigator/Coordinating Investigator

Takeda will select a signatory coordinating investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study medication, their expertise in the therapeutic area and the conduct of clinical research as well as study participation. The signatory coordinating investigator will be required to review and sign the clinical study report (CSR) and by doing so agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

%CV	coefficient of variation
5-FU	5-fluourouracil
5-HT_3	5-hydroxytryptamine 3 serotonin
AE	adverse event
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ATP	adenosine triphosphate
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
BP	blood pressure
C1D1	Cycle 1 Day 1
CA19-9	carbohydrate antigen 19-9
CDC7	cell division cycle 7
CEA	carcinoembryonic antigen
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
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
CxDx	Cycle x, Day x
CV	cardiovascular
CYP	cytochrome P-450
DCR	disease control rate
DDI	drug-drug interaction
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
EGFR	epidermal growth factor receptor
EORTC	European Organisation for Research and Treatment of Care
EOT	End-of-Treatment (visit)
EU	European Union
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
FIH	first-in-human
FOL	folinic acid
FOLFOX	folinic acid + 5-fluorouracil + oxaliplatin
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GI	gastrointestinal
GM-CSF	granulocyte-macrophage colony-stimulating factor
H_2	histamine-2 (receptor)
HBV	hepatitis B virus
HCV	hepatitis C virus
HR	heart rate
HRQOL	health-related quality of life
IC_{50}	the concentration producing 50% inhibition
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IHC	immunohistochemistry
IND	investigational new drug
IRB	institutional review board
MCM2	minichromosome maintenance complex 2
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	magnetic resonance imaging
MSI	microsatellite instability
MSI-H	microsatellite instability-high
MSS	microsatellite stability
MTD	maximum tolerated dose
MUGA	multiple gated acquisition scan
NA	nucleoside antagonist
NCI	National Cancer Institute
NGS	next generation sequencing
NSAID	nonsteroidal anti-inflammatory drug

NSCLC	non–small-cell lung cancer
ORR	overall response rate
OS	overall survival
PD	progression of disease
PD-L1	programmed death-ligand 1
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency of Japan
pMCM2	phosphorylation of MCM2 at serine-40
PO	*per os* (orally)
PPI	proton pump inhibitor
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}
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SD	stable disease
SUSAR	suspected unexpected serious adverse reaction
sqEC	squamous esophageal cancer
sqNSCLC	squamous non–small-cell lung cancer
TAS-102	LONSURF
TEAE	treatment-emergent adverse event
$t_{1/2z}$	terminal disposition phase half-life
t_{max}	time to first occurrence of C_{max}
ULN	upper limit of normal
US	United States
WBC	white blood cell
WHO	World Health Organization

3.4 Corporate Identification

Millennium	Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.
TDC Japan	Takeda Development Center Japan
TDC Asia	Takeda Development Center Asia, Pte Ltd
TDC Europe	Takeda Development Centre Europe Ltd.
TDC Americas	Takeda Development Center Americas, Inc.
TDC	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable
Takeda	Millennium Pharmaceuticals, Inc, TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable

4.0 INTRODUCTION

4.1 Background

TAK-931 is a highly potent and selective inhibitor of the cell division cycle 7 (CDC7) kinase. CDC7 is a serine/threonine kinase that contributes to initiation of DNA replication by phosphorylating the minichromosome maintenance complex 2 (MCM2) [1,2]. Kinase activity of CDC7 is controlled by its binding protein DBF4 in a cell cycle-dependent manner [3]. Recent studies revealed that CDC7 is also involved in DNA damage response (DDR) and DNA replication, suggesting that CDC7 plays important roles in both cell proliferation during the S phase and genomic stability in DDR [4-7].

Furthermore, elevated CDC7 expression has been reported in various cancers and correlates with poor prognosis, such as in diffuse large B-cell lymphoma, oral squamous carcinoma, and breast, colon, colorectal, ovarian, and lung tumors [8-11]. However, it is not clear to what extent this increased expression reflects proliferative potential [12].

In vitro inhibition of the CDC7/DBF4 kinase complex arrests cell proliferation and induces apoptosis in cancer cell lines [13]. The major reason why the inhibition of the CDC7/DBF4 kinase complex is highly relevant for cancer is that activation of diverse oncogenes and loss of some tumor suppressors evoke replication stress and consequent DNA damage that triggers the checkpoint responses of specific signaling cascades, as demonstrated in cell culture experiments and in analyses of clinical specimens from a range of human malignancies [14]. Taken together, these data suggest that CDC7 kinase inhibitors present a novel class of molecular targets for cancer therapy [15].

Given that CDC7 is responsible for two key functions of DNA replication and DDR, CDC7 appears to be a critical gene for proliferation and survival of cancer cells, and inhibition of CDC7 is expected to be antiproliferative and induce apoptosis in a broad range of cancers. Based on its dual mechanism of action, CDC7 inhibitors may also produce clinically meaningful efficacy both as a single agent and in combination with other DNA-damaging drugs.

4.1.1 Nonclinical Experience

4.1.1.1 Nonclinical Pharmacology

In vitro and in vivo pharmacology studies indicate that TAK-931 is a highly potent and selective inhibitor of CDC7 kinase with a concentration producing 50% inhibition (IC_{50}) of less than 0.3 nM. Time-dependent inhibition assays in the presence of high and low adenosine 5'-triphosphate (ATP) concentrations revealed that TAK-931 is an ATP-competitive inhibitor with slow-binding kinetics to CDC7 kinase. The specificity of TAK-931 was evaluated at 1 μM against a panel of kinases. Of the 308 kinases tested, TAK-931 at 1 μM inhibited 10 kinases by 80% or more. The IC_{50} values for these kinases—DAPK3, DAPK1, CDK9/Cyclin T1, DMPK, CDK8/Cyclin C, MAPK12, STK17A, CLK4, DYRK1A, and GSK3B—ranged from 36.9 to 338 nM. TAK-931 exhibited >120-fold selectivity for CDC7 kinase inhibition compared with the other kinases in this panel.

TAK-931 causes DNA replication stress by inhibiting the phosphorylation of MCM2 at serine-40 (pMCM2). In the colorectal adenocarcinoma cell lines COLO205, SW48, HCT116, and RKO, TAK-931 suppressed MCM2 phosphorylation in a dose dependent manner with IC_{50} values ranging from 18 to 170 nM.

The in vivo antitumor activity of TAK-931 administered orally as either a single agent or in combination (with irradiation, irinotecan, or topotecan) was evaluated in female BALB/c nude mice bearing COLO205 human colorectal adenocarcinoma or OC-11-JCK human primary ovarian adenocarcinoma xenografts. Single treatments with TAK-931 using either continuous or intermittent dosing schedules demonstrated significant dose-dependent antitumor activity against COLO205. In COLO205, TAK-931 combined with irradiation or irinotecan also exhibited additive antitumor activity compared with either single treatment alone. In the OC-11-JCK xenograft, the combination of TAK-931 and topotecan produced synergy compared with either treatment alone.

The in vivo antitumor activity of TAK-931 was further characterized using 94 primary human xenograft tumors. In this nonclinical phase 2 like study, mice were treated with TAK-931 60 mg/kg orally (PO) with a 3 days on and 4 days off weekly schedule for 21 days. In this study, TAK-931 was more active in pancreatic and colorectal tumors (Figure 4.a and Figure 4.b).

In addition, microsatellite-instable (MSI) type of colorectal tumors appeared to show worse response to TAK-931 compared with microsatellite stable (MSS) type of CRC (Figure 4.b). These in vivo data were consistent with the in vitro cancer cell line screen results where the data suggested that the MSS group was more sensitive to TAK-931 than the MSI group in CRC cell lines.

Figure 4.a Kaplan-Meier Plot of TAK-931 Versus Vehicle in Pancreatic Cancer Xenografts (n=25)

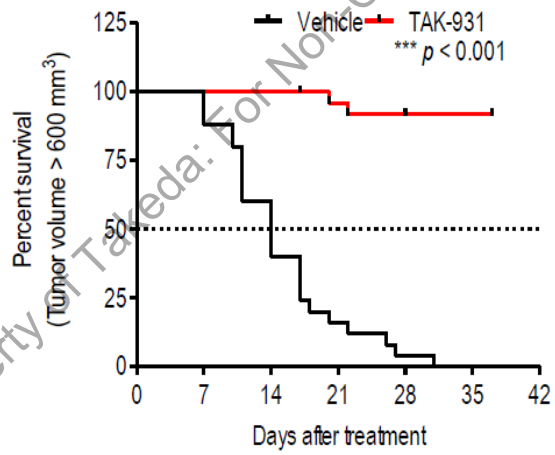
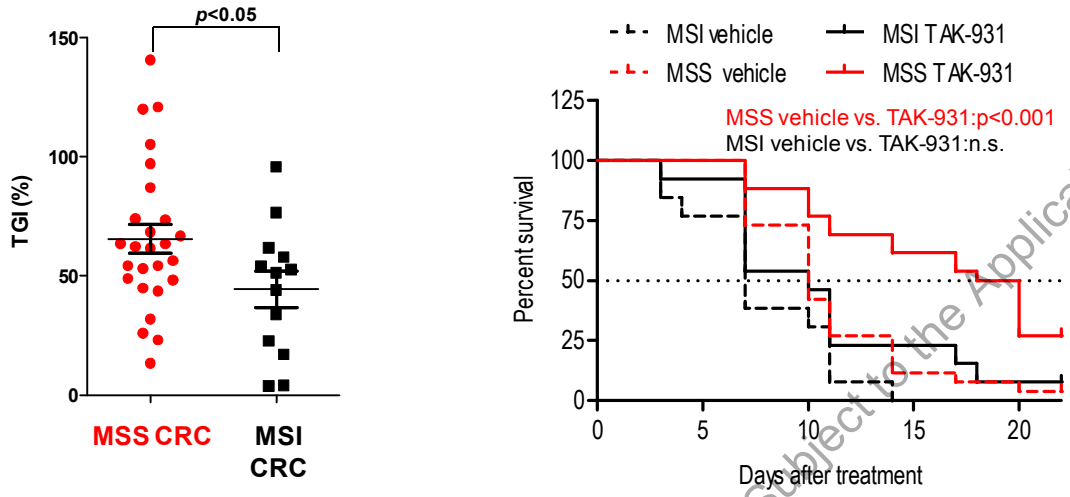


Figure 4.b Differential Activity of TAK-931 (n=26) in MSS CRC Versus MSI (n=13) Tumors



Abbreviations: CRC, colorectal cancer; MSI, microsatellite instable; MSS, microsatellite stable; PDX, patient-derived xenografts; TGI, tumor growth inhibition.

4.1.1.2 Nonclinical Pharmacokinetics and Pharmacodynamics

The pharmacokinetic (PK) and pharmacodynamic response of TAK-931 was evaluated after a single oral administration of 10, 20, 40, 60, and 80 mg/kg to female BALB/c nude mice bearing COLO205 human colorectal adenocarcinoma xenografts. Plasma and tumor samples were obtained and analyzed for TAK-931 concentrations and derived PK parameters. pMCM2, which CDC7 kinase phosphorylates directly, was used as a target-engagement pharmacodynamic marker. Pharmacodynamic analysis was performed using Western blot and immunohistochemistry (IHC). The plasma and tumor exposures of TAK-931 are increased in an approximately dose-proportional manner in female BALB/c nude mice bearing COLO205 xenografts. Both Western blot and IHC analysis detected modulations of the pharmacodynamic biomarker pMCM2 in xenograft tumors and mouse skin in a dose- and time-dependent manner. Furthermore, antitumor activity and duration of saturated pMCM2 suppression in tumor was well correlated in nude mice bearing COLO205 xenografts. These results indicate the potential utility of pMCM2 as clinical pharmacodynamic biomarkers to evaluate the pharmacodynamic response of TAK-931.

TAK-931 exposure after a single oral administration demonstrated that the compound is rapidly absorbed in vivo, with 35.1% and 21.6% oral bioavailability in Sprague-Dawley rats and beagle dogs, respectively. After a single intravenous dose, TAK-931 demonstrated high plasma clearance in rats (3260 mL/hr/kg) and dogs (2630 mL/hr/kg), and high volume of distribution at steady state in both species (rats: 2460 mL/kg; dogs: 3060 mL/kg). Both rats and dogs exhibited nonlinear oral PK.

TAK-931 exhibited nonlinear pharmacokinetics following oral dosing in rats and dogs with single-dose maximum observed concentration (C_{max}) and area under the plasma

concentration-time curve (AUC) from time 0 to 24 hours (AUC_{24}) increasing in a greater than dose-proportional manner at higher doses. No accumulation of TAK-931 was observed in either species.

TAK-931 has high permeability and is a substrate for breast cancer resistance protein, but is not likely a substrate for P-glycoprotein (P-gp) on the basis of transcellular transport investigations across Caco-2 cell monolayers. Additionally, TAK-931 may have a weak inhibitory effect on P-gp–mediated efflux activity (IC_{50}>100 μM). The drug-drug interaction (DDI) potential of TAK-931 with P-gp substrates and inhibitors is low.

In an in vitro study, plasma protein binding was 59% to 62% in mice, 73% to 74% in rats, 57% to 58% in dogs, and 73% to 74% in humans, with no concentration dependency observed from 0.01 to 1 μg/mL.

The in vitro oxidative metabolism of TAK-931 was evaluated using liver microsomes from CD-1 mice, Sprague-Dawley rats, beagle dogs, cynomolgus monkeys, and humans. TAK-931 was metabolized primarily to the unidentified metabolite UK-1 and, to a lesser extent, UK-2. There was no metabolite unique to human liver microsomes through oxidative metabolism.

Evaluation of the in vitro metabolism of TAK-931 in the presence of uridine-5'-diphosphateglucuronic acid showed that the compound is metabolized through glucuronidation by liver microsomes from all species except dogs (mice, rats, monkeys, and humans).

Investigations into cytochrome P450 (CYP) enzyme-mediated metabolism showed that CYP2D6 and CYP3A are the main CYPs involved in the metabolism of TAK-931. There is a DDI potential with UDP-glucuronosyltransferase inducers; however, the DDI potential with CYP inhibitors, though they are involved in metabolism, is unlikely. TAK-931 is unlikely to cause DDIs with concomitant medications metabolized via CYP isozymes at C_{max} values <800 ng/mL.

Details on these studies are provided in the current TAK-931 Investigator's Brochure (IB).

4.1.1.3 Nonclinical Toxicology

The toxicologic profile and systemic toxic potential of TAK-931 has been well defined in Sprague-Dawley rats and beagle dogs.

The primary dose-limiting toxicities (DLTs), particularly in the dog, appear to be associated with C_{max} and are closely associated with the observed cardiovascular (CV) changes. These CV effects were dose dependent and plasma compound concentration dependent, occurring in rats and dogs when TAK-931 plasma concentrations exceeded approximately 1000 ng/mL. It has been confirmed that the effects of TAK-931 on HR and BP are monitorable and reversible upon clearance of TAK-931.The CV effects may be related to TAK-931 inhibitory activity at off-target kinases. In addition, renal injury (obstructive nephropathy) was confirmed to be a DLT in rats, although similar changes were not observed in dogs. Renal effects of TAK-931 were monitorable with clinical and urine chemistry, and renal tubular damage is considered reversible.

The target organ toxicities after the repeated dosing of TAK-931 were largely similar in rats and dogs and were generally consistent with inhibition of CDC7 activity. Test article-related findings

included the hematopoietic and lymphoid systems, gastrointestinal (GI) mucosa, and reproductive organs. Decreased white blood cell (WBC) count or single cell necrosis in the GI mucosa appeared with minimal degree at lower doses and severity increased with dose level. All target organ toxicities observed in the repeated-dose studies were generally monitorable and reversible, except for the effect on germ cells.

Based on these results, the toxicology studies conducted with TAK-931 support the proposed clinical program in adult patients with advanced malignancies. The nonclinical toxicology profile demonstrated target organ toxicity that was generally considered to be monitorable and reversible. The primary C_{max}-related toxicity was CV effects (decreased BP with reflecting tachycardia). The DLTs related to total exposure were effects on the GI mucosa and lymphoid systems consistent with pharmacology-mediated CDC7 inhibition.

Details on these studies are provided in the current TAK-931 IB.

4.1.2 Clinical Experience

All prior clinical experience is from the first-in-human (FIH) phase 1 study (TAK-931-1002) in Japanese patients with advanced solid malignancies. The data cut-off used for the safety analysis and PK analysis was 04 January 2018 and included 49 patients who had received at least 1 dose of TAK-931 as a single agent. This trial in patients with advanced nonhematologic cancer has enrolled 16 patients in Schedule A (14 days on/7 days off in 21-day) in 4 dose levels (14 patients DLT-evaluable). The MTD was defined at 50 mg QD with this schedule. Twelve patients were enrolled into Schedule B (7 days on/7 days off twice in 28-day cycles), 3 patients at 60 mg QD and 9 patients at 80 mg. Currently this schedule is ongoing and enrolling patients at 100 mg QD. Twelve patients have been enrolled into Schedule D (continuous QD administration), 6 patients at 20 mg and 6 patients at 30 mg. Currently patients are being enrolled in this schedule at 40 mg.

4.1.2.1 Safety

The MTD has been defined per the protocol at 50 mg QD for Schedule A because there were no DLTs in the 14 DLT-evaluable patients receiving this dose in the escalation plus the expansion phases. Neutropenia has been the only reported DLT. Neutropenia was dose-dependent, noncumulative, and reversible, with the nadir usually occurring at the end of the dosing period. Neutropenia has not been accompanied by other toxicities such as thrombocytopenia, mucositis, or diarrhea.

Two of 3 patients receiving 60 mg QD in Schedule A had DLTs (Grade 4 neutropenia lasting longer than 3 days that, per the protocol, was considered a DLT). The first patient presented with an absolute neutrophil count (ANC) nadir of 190/mm^3 and low-grade fever that prompted the investigator to use prophylactic antibiotics and granulocyte-colony stimulating factor (G-CSF). The second patient's ANC nadir was 30/mm^3, and prophylactic antibiotics and G-CSF were also used. No Grade 4 neutropenia was observed at 50 mg. In Schedule B, 2 out of 9 patients in the 80-mg cohort had DLTs of Grade 3 febrile neutropenia; 1 of these 2 patients presented with concomitant ileus and the other with a peritoneal abscess. Both patients were discontinued as a consequence of the events. Escalation in this cohort is ongoing.

In the 49 patients treated with TAK-931 in the FIH study, nausea was reported in 24 (49%) patients. Other GI AEs included vomiting (n = 10 [20%]), diarrhea (n = 9 [18%]), constipation (n = 5 [10%]), abdominal pain (n = 4 [8%]), ileus (n = 2 [4%]), dysgeusia (n = 1 [2%]), and pancreatitis (n = 1 [2%]). In addition, 13 (27%) patients reported AEs of decreased appetite. Serious GI AEs included ileus (2 [4%]) and nausea (1 [2%]). Grade ≥3 GI AEs included decreased appetite (2 [4%]), abdominal abscess (1 [2%]), and ileus (1 [2%]). In general, GI tolerability was good with a low frequency of severe nausea, vomiting, and diarrhea, and there was no significant impact on treatment compliance. Nausea and vomiting were successfully managed with standard antiemetics.

Hypotension is considered a key nonclinical risk (Section 4.1.1.3). In the FIH trial, 2 patients presented with an AE of drug-related Grade 1 (asymptomatic, intervention not indicated) hypotension. One patient dosed with 40 mg in Schedule A presented with Grade 1 hypotension in Cycle 1 that started on Day 2 and lasted until the end of the dosing period in Cycle 1. No action was taken with study drug. Another patient treated at 50 mg QD presented with Grade 1 hypotension for 2 consecutive days (Cycle 1 Day 12 predose and Cycle 1 Day 13 predose); thus, TAK-931 doses were held for these 2 days. The low BP recovered without intervention. Both episodes of asymptomatic hypotension were not recorded as correlated with t_{max} (2 hours postdose). TAK-931 C_{max} in patients dosed with 50 mg QD in the FIH trial had a median concentration of 214 ng/mL with an interpatient CV of 39.6%. Hypotension in animals was observed with C_{max} above 1000 ng/mL. Based on clinical safety and PK, the risk of clinically relevant hypotension at a 50 mg dose is considered to be very low.

Alopecia has been reported in the study TAK-931-1002. As of 04 January 2017, 4 of the 12 patients who received treatment with TAK-931 reported Grade 1 or 2 alopecia. None of the reported TEAEs for alopecia were designated as serious.

The current study (TAK-931-2001) is the second trial with TAK-931. The enrollment of the Western cohort safety (n = 12) has been completed. One patient presented with Grade 3 neutropenia as a DLT. The PK profile on Days 1 and 8 is comparable to that obtained for the same dose in the previous FIH study in Japanese patients with solid tumors.

4.1.2.2 Pharmacokinetics

Absorption of TAK-931 was fast following single or multiple oral dose administrations, with a median time to first occurrence of C_{max} (t_{max}) of 1 to 4 hours. Systemic exposures (AUC) of TAK-931 increased in approximately a dose-proportional manner over the range of 30 to 60 mg QD. The C_{max} and AUC of TAK-931 had relatively low inter-patient variability (<50% for C_{max} and coefficient of variation [%CV] ≤30% for AUC). TAK-931 showed minimal accumulation following once-daily dosing with a mean terminal disposition phase half-life ($t_{1/2z}$) of 4.3 to 6.2 hours. These results suggested that TAK-931 showed PK properties that support routine oral administration.

4.1.3 Risks and Benefits

The safety of Schedule A at 50 mg QD has been adequately studied in the FIH trial in Japan. This dose and schedule have demonstrated safe and comparable in a similar cohort of Western patients with metastatic cancer (Section 4.1.2.1). The main clinical toxicity is neutropenia that is monitored routinely in this trial. The overall tolerability and safety of TAK-931 is adequate for an oral drug to be self-administered by the patient at home.

Early signs of clinical activity include PRs in duodenal cancer at 30 mg, squamous esophageal cancer at 50 mg, and squamous cervical cancer at 60 mg, prolonged SD (9 months) in 1 patient with pancreatic cancer at 30 mg, and biomarker response (CA125) in 1 patient with ovarian cancer at 60 mg.

In the nonclinical setting, TAK-931 suppressed MCM2 phosphorylation in a dose-dependent manner in various cancer cell lines. TAK-931 also demonstrated significant inhibition of pMCM2 in human xenograft tumors and mouse skin which correlated well with the plasma concentrations of TAK-931 observed in the nonclinical xenograft models. In the FIH study, strong pMCM2 inhibition in skin was observed in patients treated with TAK-931 (all dose levels) which correlated well with the drug exposures in these patients. Thus, pMCM2 appears to be a viable pharmacodynamic marker to monitor target engagement of TAK-931 in the clinic in skin tissue and possibly in tumors.

Based on these encouraging data, it is reasonable to continue the development of TAK-931 and test its initial activity in patients with metastatic CRC who have progressed after at least 2 lines of previous standard chemotherapy, patients with metastatic pancreatic cancer who have progressed after at least 1 line of standard chemotherapy, patients with metastatic sqNSCLC who have progressed after at least 2 lines of standard treatment, and patients with metastatic sqEC who have progressed after at least 1 line of standard chemotherapy. Enrollments in the CRC and pancreatic cohorts will follow a 3-stage design with 2 interim analyses for futility using disease control rate (DCR). Enrollments in sqNSCLC and sqEC will follow a 2-stage design with 1 interim futility analysis using DCR (see Sections 4.2 and 13.2 for details).

Trial participants are required to provide biopsies for predictive biomarker assessment. This activity is crucial for a successful patient selection in future trials.

- Patients in the Western safety cohort are requested to provide low-risk pretreatment and posttreatment skin tissue biopsies to demonstrate target engagement and to establish PK-pharmacodynamic relationships to further confirm the data obtained in the Japanese patient population from the FIH trial (TAK-931-1002). Skin tissue biopsies are optional for patients undergoing or scheduled to have pre and on-treatment tumor biopsies to establish a correlation between target engagement in skin and tumor.
- All patients in the disease-specific cohorts are required to provide a pretreatment tumor biopsy for predictive biomarker evaluation. It can be either a fresh tumor biopsy obtained during the screening period or an archival one. Because biopsy procedures have risks, the biopsy sampling plan and rationale are outlined in Section 9.3.16.4. If a fresh biopsy is required and the patient gives consent, the lesion should be accessible in the opinion of the investigator.

These tumor biopsies will be used to evaluate molecular biomarkers and their relationship with clinical response.

- Paired baseline predose and postdose tumor biopsies in Cycle 1 after exposure to TAK-931 to evaluate target engagement in the tumor tissues by measuring pMCM2 levels are optional in this trial. Patients undergoing paired biopsies will specifically consent to the procedure, which must be considered of nonsignificant risk in the opinion of the investigator (see Section 9.3.16.4). The predose Cycle 1 Day 1 (C1D1) fresh tumor biopsy can be replaced by banked tumor tissues obtained at the time of the last PD if there has been no intervening anticancer treatment. For these patients, a skin tissue biopsy may also be collected (optional).

4.2 Rationale for the Proposed Study

This trial has 2 principal objectives:

- To confirm the dose and schedule of 50 mg QD for 14 days in 21-day cycles in Western patients of non-Japanese ethnicity. This objective has been achieved.
- To evaluate the antitumor activity of TAK-931 in patients with metastatic pancreatic adenocarcinoma, patients with metastatic CRC, patients with locally advanced or metastatic squamous esophageal cancer, and patients with locally advanced or metastatic sqNSCLC. The selection of the 2 additional indications is based in the identification of an enrichment signature that it is described in Section 4.2.1.

The trial will enroll patients at sites in the United States (US) and in Japan. To achieve the objectives, the study is divided into 2 parts. In the first part, a limited safety cohort of ~12 patients with metastatic solid tumors that progressed after appropriate prior therapy were enrolled only in the US. Safety, PK, and skin pharmacodynamic information was used to confirm the 50 mg QD dose in Western patients. To achieve this, a descriptive comparison with a similar population with a Japanese ethnicity treated in the FIH study (TAK-931-1002, NCT02699749) was performed. In this cohort of 12 patients, the number of patients with DLTs had to be 3 or fewer to consider the dose safe. However, to accept that the 50 mg QD dose is therapeutically sufficient in Western patients, other factors, including the TEAE rate, PK parameters, antitumor activity, and pMCM2 changes in skin, were considered. If there had been potential clinically meaningful differences from the Japanese patients, the tumor-specific cohorts would not have started enrolling and the trial could have been amended to evaluate other dosing alternatives. This objective has been already achieved and 50 mg QD is considered comparable between Japanese and Western cancer patients.

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4.2.2 Colorectal Cancer

The second part of the study will assess in a noncontrolled manner the anticancer activity of TAK-931 in patients with metastatic pancreatic adenocarcinoma that progressed after at least a first line of chemotherapy and in patients with metastatic CRC progressing after at least 2 lines of standard chemotherapy. Based on nonclinical research, TAK-931 is expected to be more active in MSS colorectal tumors. For this reason, the trial excludes patients with known MSI-H genotype. The selection of these indications is based on nonclinical efficacy models as described in Section 4.1.1.1.

The FIH study TAK-931-1002 has confirmed 50 mg QD as the MTD for 21-day cycle dosing (14 days on followed by 7 days of rest). For this reason, Japanese sites will enroll patients directly in the tumor-specific cohorts. If the same dose is confirmed in the US, US sites will begin to enroll patients with pancreatic cancer and CRC with the characteristics specified in the inclusion criteria (Section 7.1).

The selection of DCR as the primary endpoint for activity is based on the recent phase 3 registration trial in CRC and pancreatic cancer. In these trials, ORR (CR+PR) per RECIST was minimal in a similar pretreated patient population; however, there were differences in DCR (defined as the sum of CR+PR+SD ≥6 weeks) (see Sections 13.2 and 13.3).

Regorafenib (STIVARGA) single agent was approved by the US Food and Drug Administration (FDA) in patients with metastatic CRC previously treated with 2 lines of chemotherapy. The phase 3 placebo-controlled trial enrolled 760 patients with a 2:1 randomization scheme. The trial demonstrated benefits in OS and PFS (hazard ratios of 0.77 and 0.49, respectively). Only 1% of patients achieved a PR status per RECIST; however, DCR (defined as PR+SD assessed at least 6

weeks after randomization) was achieved in 207 patients (41%) assigned to regorafenib and in 38 (15%) patients assigned to placebo (p<0.0001) [16]. Similarly, TAS-102 (LONSURF) was approved in Japan and the European Union (EU) in a similar patient population with a placebo-controlled phase 3 trial (N = 800, 2:1 randomization). The trial demonstrated a significant OS and PFS advantage (hazard ratios of 0.69 and 0.48, respectively). PR was achieved in only 1.6% of patients with TAS-102; however, DCR was reached in 221 patients (44%) in the TAS-102 group and in 42 patients (16%) in the placebo group (p<0.0001) [17].

4.2.3 Pancreatic Cancer

Liposomal irinotecan (Onivyde) single agent was initially compared with 5-fluorouracil/folinic acid (5-FU/FOL) for treatment of patients with metastatic pancreatic cancer that had progressed after gemcitabine (liposomal irinotecan n = 151; 5-FU/FOL n = 149). The trial was amended once started to include an arm using triplet liposomal irinotecan/5-FU/FOL, which was approved in the US in 2015 and in the EU in 2016. Nine patients (6%) allocated to liposomal irinotecan monotherapy achieved an objective response compared with one patient (1%) assigned to 5-FU/FOL (difference of 5.3%, 95% CI 1.3 to 9.3; p = 0.02). Forty-one percent of patients in the irinotecan arm achieved a PR or SD versus 24.2% treated with 5-FU/FOL. Twenty-nine of 123 patients (24%) allocated to liposomal irinotecan monotherapy had a carbohydrate antigen 19-9 (CA19-9) response versus 12 of 105 patients (11%) assigned to 5-FU/FOL (p = 0.024) [18,19].

The DCR endpoint was selected over PFS or OS because it can be used as an early indicator of futility in a multistage design; however, for future studies other time-to-event indicators will be considered.

4.2.4 Squamous Esophageal Cancer

sqEC is the most common histological subtype of esophageal cancer and is of particularly high incidence in Japan. There are no systemic treatments approved specifically for the metastatic squamous indication. With few exceptions (HER2-positive adenocarcinomas), the same treatments are recommended for esophageal adenocarcinoma, sqEC, gastroesophageal junction carcinoma (GEJC), and gastric cancer. The standard first-line therapy is a doublet containing a platinum plus a fluoropyrimidine. After recurrence, single-agent chemotherapy with a taxane or irinotecan is indicated in patients with a good performance status [18] [20].

Seven patients with esophageal cancer have been dosed in the FIH trial TAK-931-1002, 1 at 20 mg, 4 at 30 mg, 1 at 40 mg using a continuous QD administration schedule, and 1 patient at 50 mg QD with a 2 weeks on/1 week off schedule. One patient presented a RECIST 1.1 PR until progressing at Cycle 7. Three patients presented with PD in Cycle 3, 2 stayed on treatment until Cycle 6 (1 had a target lesion reduction of -20%), and 1 is ongoing in Cycle 10+.

There are no published clinical trials evaluating the effect of any single-agent chemotherapy as second-line treatment in sqEC. As a reference, we used the control arm in the RAINBOW trial: paclitaxel plus ramucirumab versus paclitaxel plus placebo in patients with gastric cancer or GEJC in second line (n = 665). In this trial, computed tomography (CT) scans were done every 6 weeks

[3]. The ORR in the paclitaxel arm was 16% (95% CI:13-20%), and the DCR was 64% (95% CI: 58-69) with a median duration of response of 2.8 months (interquartile range 1.4 to 4.4).

4.2.5 Squamous NSCLC

There are many approved options for patients with metastatic NSCLC in the first 2 lines of treatment. However, most patients with metastatic disease will eventually progress after available therapies. Approximately 30% of NSCLC patients are fit enough to receive further treatment, which is typically monotherapy with either chemotherapy or a targeted agent [21]. Although targeted agents are a valid option for some patients whose tumors express anaplastic lymphoma kinase (*ALK*), epidermal growth factor receptor (*EGFR*), B Raf-proto-oncogene, serine/threonine kinase (*BRAF*), c-ros oncogene 1 or programmed death-ligand 1 (*PD-L1*), many of these patients fail to respond to targeted agents. In this context, a clinical trial with an oral single-agent drug is a reasonable option for sqNSCLC in third-line treatment and beyond.

There are no specific published references of clinical trials in the sqNSCLC third-line setting and beyond. Establishing an acceptable comparator to retrospectively evaluate activity is even more complicated because of the recent introduction of several checkpoint inhibitors in first- and second-line treatment.

In a single-arm phase 2 trial, 444 patients with metastatic NSCLC that progressed after at least 2 previous lines of standard treatment received durvalumab as a single agent. The trial enrolled 3 cohorts of patients, depending on *ALK*, *EGFR* and *PD-L1* expression. The subset of patients of interest as a reference for this trial were enrolled in cohort 2: tumors *EGFR−/ALK−* with <25% cells expressing *PD-L1*. In this group of patients (n = 93), ORR was 7.5% (95% CI: 3.1-14.9) with a DCR at 6 months of 20.4% (95% CI: 12.8-30.1).

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objectives

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

5.1.2 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 ORR, duration of response (DOR), PFS, and OS.
- To further characterize the safety of TAK-931 as a single agent in patients with metastatic pancreatic cancer, CRC, sqEC, and sqNSCLC.

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5.2 Endpoints

5.2.1 Primary Endpoints

- 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.
- DCR per RECIST version 1.1 [22] in disease-specific cohorts: CR+PR +SD; SD has to be ≥6 weeks from treatment initiation to qualify for DCR.

5.2.2 Secondary Endpoints

- 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 (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.

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6.0 STUDY DESIGN

6.1 Overview of Study Design

This is a phase 2, multicenter, single-agent, uncontrolled, open-label, parallel-arm trial in patients with metastatic cancer (CRC, pancreas cancer, sqNSCLC and sqEC). The study will also enroll a safety cohort of ~12 Western patients of non-Japanese ethnicity with metastatic solid tumors with locally advanced or metastatic solid tumors for whom no standard treatment with an established survival benefit is available or if the patient refuses other standard therapy to determine the safety, tolerability, and PK of 50 mg QD for 14 days followed by a 7-day rest period in 21-day cycles. In this cohort, initially 6 patients will be enrolled for safety and PK evaluation. These 6 patients can be enrolled concurrently. If no more than 2 patients present with a DLT (Section 8.2), the remaining 6 patients will be enrolled. If the final number of patients with a DLT is 4 or more, the 50 mg QD dose will be considered unsafe for Western patients and enrollment of the disease-specific cohorts will not start in the US until the protocol is amended and a safe path to evaluate the dose and schedule is identified. Before deciding that the 50 mg QD dose is adequate to proceed into the disease-specific cohorts in Western patients, a complete review of available safety, PK, and antitumor activity will be performed. These results will be compared with those from Japanese patients who were treated in the FIH study TAK-931-1002 (NCT02699749). Dose comparability will not be established using formal statistical methods. If TAK-931 exposures at 50 mg QD in Japanese and Western populations are considered comparable, the trial will start enrolling patients with metastatic pancreatic adenocarcinoma and CRC in the US. In Japan, the proposed dose has been considered the MTD of 50 mg QD for the 14 days on/7 days off schedule; therefore, Japanese sites will enroll disease-specific cohorts from the beginning. The comparability of dose and schedule between Japanese and Western patients was achieved at the time of Protocol Amendment 03.

AEs will be assessed according to CTCAE, version 4.03, effective date 14 June 2010 [20], and laboratory values, vital signs, and ECGs will be obtained to evaluate the safety and tolerability of TAK-931.

HRQOL will be evaluated using the patient-reported outcome (PRO) measure, the EORTC QLQ-C30.

Serial blood samples for determination of the plasma concentration of TAK-931 will be obtained at prespecified time points as described in the Pharmacokinetic Sampling Schedule (Appendix A). An intensive PK collection with time-matched triplicate ECGs will be performed in the Western safety cohort and first 10 patients in the pancreatic cancer and CRC cohorts in the US to allow comparison with a similar Japanese population. All other patients, including all patients in the sqEC and sqNSCLC cohorts, will undergo sparse PK sampling.

Serial blood samples will be collected in the Western safety cohort for tumor-specific markers (CEA in the CRC cohort and CA19-9 in the pancreatic cancer cohort).

An evaluation of disease response using the modified RECIST version 1.1 [22] will be performed at Baseline and every other cycle of treatment.

In the Western safety cohort only, predose and postdose skin biopsies will be collected in Cycle 1 for pharmacodynamic biomarker (pMCM2) assessment and PK-pharmacodynamic relationships for target engagement evaluation and comparison with similar data obtained in the FIH trial.

Relationships between plasma exposures of TAK-931 and pMCM2 (Ser40) levels in pretreatment and posttreatment tumor biopsies will be explored to evaluate PK/pharmacodynamic-efficacy relationships. Paired baseline predose and postdose tumor biopsies in Cycle 1 after exposure to TAK-931 are optional for patients in the disease-specific cohorts to evaluate target engagement in the tumor tissues by measuring pMCM2 levels. Other potential biomarkers (to be determined) will be assessed in the same way.

Serial plasma samples will be collected for NGS characterization of ctDNA in patients to identify molecular determinants of TAK-931 efficacy.

For the discovery of other potential predictive biomarkers, the trial requires all patients in the disease-specific cohorts to provide a pretreatment tumor biopsy, either fresh (during the screening period) or archival (obtained at any time since the initial diagnosis). A fresh biopsy or an archival one obtained after last tumor progression is preferred.

6.2 Number of Patients

Initially, ~12 Western patients with metastatic solid tumors are expected to be enrolled in the US to confirm the dose of 50 mg QD for 14 days in 21-day cycles based on the safety, tolerability, and PK of TAK-931 in Western patients of non-Japanese ethnicity.

It is expected that up to ~33 response-evaluable patients in the metastatic pancreatic cancer cohort and ~35 response-evaluable patients in the metastatic CRC cohort will be enrolled in the study in 3 stages, each with 2 futility evaluations. Additionally, up to 40 response-evaluable patients with locally advanced or metastatic sqEC and up to 40 response-evaluable patients with locally advanced or metastatic sqNSCLC may be enrolled in 2 stages, with 1 futility evaluation for each cohort (see Sections 13.2 and 13.3).

6.3 Duration of Study

6.3.1 Duration of an Individual Patient's Study Participation

Patients may receive TAK-931 until they experience PD or unacceptable toxicity or until any other discontinuation criterion is met (Section 8.3.3). The maximum scheduled duration of treatment will be 1 year; however, patients with clinical benefit (per investigator and as agreed by the sponsor's medical monitor) can continue treatment beyond 1 year with the explicit approval of the sponsor's medical monitor.

All patients will attend an End-of-Treatment (EOT) visit 30 days (+10 days) after receiving their last dose of study drug or before the start of subsequent systemic anticancer therapy, whichever occurs first, to permit detection of any delayed TEAEs and resolution of ongoing events. Patients with unresolved TEAEs will continue the periodic safety follow-up until complete resolution or stabilization (established as sequelae) occurs.

Patients who discontinue study treatment for reasons other than PD will continue PFS follow-up every 12±1 weeks from the EOT visit until the occurrence of PD, loss to follow-up, consent withdrawal, death, the start of subsequent systemic antineoplastic therapy, study termination (Section 9.4), or until 6 months after the discontinuation of study treatment, whichever occurs first. Patients in tumor-specific cohorts will be followed for OS every 12±1 weeks until death, loss to follow-up, consent withdrawal, study termination, or any of the circumstances described in Section 9.7.

6.3.2 End of Study/Study Completion Definition and Planned Reporting

The final data cutoff for the CSR will be conducted after all patients have been discontinued from treatment or transferred to a long-term safety study, a single-patient investigational new drug application, or a similar program.

The estimated time frame for study completion is 18 to 24 months. Alternatively, if futility criteria are met for any disease-specific cohort(s), the study will be considered complete (see Section 13.2).

Refer to Table 6.a for disclosure information for all primary and secondary endpoints.

Table 6.a Primary and Secondary Endpoints for Disclosures

Endpoint	Definition	Maximum Time Frame
Primary: Frequency of TEAEs.	Includes DLTs, SAEs, TEAEs leading to dose modifications, and TEAEs leading to treatment discontinuation in the Western safety cohort (see Section 5.2.1).	1 year
Primary: DCR	See Section 5.2.1	1 year
Secondary: PK of TAK-931	See Section 5.2.2	1 year
Secondary: ORR	See Section 5.2.2	1 year
Secondary: DOR	See Section 5.2.2	1 year
Secondary: PFS	See Section 5.2.2	1 year
Secondary: OS	See Section 5.2.2	1 year
Secondary: Percentage of patients with TEAEs	Includes 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 (see Section 5.2.2)	1 year

6.3.3 Total Study Duration

It is anticipated that this study will last approximately 18 to 24 months. Alternatively, if futility criteria are met for any disease-specific cohort(s), the study will be considered complete (see Section 13.2).

7.0 STUDY POPULATION

7.1 Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study:

1. Adult male or female patients aged ≥20 years (Japan) or ≥18 years (US).
2. Eastern Cooperative Oncology Group (ECOG) performance status of 0-1.
3. Patients with one of the following diagnoses:
   - Pathologically confirmed metastatic pancreatic adenocarcinoma that has progressed after, at least, a first line of standard systemic chemotherapy for metastatic disease.
   - Pathologically confirmed metastatic adenocarcinoma of the colon or rectum who have progressed to at least 2 lines of standard systemic chemotherapy for metastatic disease.
   - Pathologically confirmed locally advanced or metastatic sqEC that has progressed after at least a first line of standard systemic therapy for metastatic disease. First-line patients can be enrolled if a platinum doublet is contraindicated or refused by the patient.
   - Pathologically confirmed locally advanced or metastatic sqNSCLC that has progressed after at least 2 lines of standard systemic therapy for metastatic disease.
4. For the Western safety cohort only: patients with locally advanced or metastatic solid tumor for whom no standard treatment with an established survival benefit is available or the patient refuses other standard therapy.
5. For disease-specific cohort patients: measurable disease per RECIST version 1.1. [22]
6. Adequate bone marrow reserve and renal and hepatic function based on the following laboratory parameters:
   - ANC ≥1500/mm^3, platelet count ≥100,000/mm^3, and hemoglobin ≥9 g/dL.
   - Total bilirubin ≤1.5 × the institutional upper limit of normal (ULN).
   - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≤3.0 × the institutional ULN (<5 × ULN if liver enzyme elevations are due to hepatocellular cancer, biliary tract cancer, or metastatic disease in liver).
   - Creatinine <1.5 × the institutional ULN or estimated creatinine clearance using the Cockcroft-Gault formula ≥50 mL/minute for patients with creatinine concentrations above institutional limits.
7. Left ventricular ejection fraction >50% as measured by echocardiogram (ECHO) or multiple gated acquisition (MUGA) scan within 4 weeks before receiving the first dose of study drug.
8. Recovered to Grade 1 or Baseline from all toxic effects of previous therapy (except alopecia or neuropathy).

9. Female patients who:
   - Are postmenopausal for at least 1 year before the screening visit, OR
   - Are surgically sterile, OR
   - If they are of childbearing potential, agree to practice one highly effective method of contraception and one additional effective (barrier) method at the same time, from the time of signing the informed consent through 30 days after the last dose of study drug, OR
   - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)
10. Male patients, even if surgically sterilized (ie, status postvasectomy), who:
   - Agree to practice effective barrier contraception during the entire study treatment period and through 120 days after the last dose of study drug, OR
   - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)
   - Agree not to donate sperm during the course of this study and for 120 days after receiving their last dose of study drug.
11. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.
12. Suitable venous access for the study-required blood sampling.
13. For the Western safety cohort only: willingness to undergo serial skin tissue biopsies.
14. For disease-specific cohort patients: Must have an archival (banked) tumor sample or agree to have a new (fresh) tumor biopsy during the screening period. If a new tumor sample is needed, the disease should, in the opinion of the investigator, be accessible. For patients in the Western safety cohort, this biopsy is optional.

7.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study.

1. Patients who require continuous use of proton pump inhibitors (PPIs) or histamine-2 (H_2) receptor antagonists and patients who are taking PPIs within 5 days before the first dose of study drug.
2. Treatment with clinically significant enzyme inducers, such as phenytoin, carbamazepine, phenobarbital, rifampin, rifabutin, rifapentine, or Saint John's wort within 14 days before the first dose of study drug.

3. Treatment with any systemic anticancer treatment (including investigational products) within 30 days or 5 half-lives, whichever is shorter, before the first dose of study drug.
4. History of any of the following within the last 3 months before administration of the first dose of study drug:
    - Ischemic myocardial event including angina requiring therapy and artery revascularization procedures, myocardial infarction, and unstable symptomatic ischemic heart disease.
    - Ischemic cerebrovascular event, including transient ischemic attack and artery revascularization procedures.
    - Significant, uncontrolled cardiac arrhythmia (including atrial flutter/fibrillation, ventricular fibrillation, or ventricular tachycardia).
    - New York Heart Association Class III to IV heart failure.
    - Any other cardiac condition that, in the opinion of the investigator, could pose an additional risk for participation in the study (eg, pericardial effusion or restrictive cardiomyopathy).
    - Baseline prolongation of the QT interval corrected for HR using Fridericia's formula ([QTcF], eg, repeated demonstration of QTcF interval >480 ms, history of congenital long QT syndrome, or torsades de pointes).
5. Hypertension that is unstable or not controlled by medication.
6. History of uncontrolled brain metastasis unless:
    - Previously treated with surgery, whole-brain radiation, or stereotactic radiosurgery, AND
    - SD for ≥30 days, without steroid use (or stable steroid dose established for ≥14 days before the first dose of TAK-931).
7. Known history of human immunodeficiency virus infection.
8. Known hepatitis B virus (HBV) surface antigen seropositive or detectable hepatitis C virus (HCV) infection viral load. Note: Patients who have positive HBV core antibody or HBV surface antigen antibody can be enrolled but must have an undetectable HBV viral load.
9. Known GI disease or GI procedure that could interfere with the GI absorption of study drug, such as total gastrectomy or GI conditions that could substantially modify gastric pH.
10. Female patients who are lactating and breastfeeding or who have a positive serum pregnancy test during the screening period or a positive urine pregnancy test on Day 1 before the first dose of study drug.
11. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.
12. Prior treatment with radiation therapy involving ≥25% of the hematopoietically active bone marrow within 3 months before the first dose of study drug.

13. Patients with known MSI-H genotype or known wild type *TP53* per local testing.

Western Safety Cohort Only

14. Patients with Japanese heredity.

8.0 STUDY DRUG

8.1 Study Drug Administration

All protocol-specific criteria for administration of study drug must be met and documented before drug administration. Study drug will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s).

TAK-931 will be administered to patients on an empty stomach. Patients should not eat for 2 hours before taking the study drug with at least 8 ounces (230 mL) of water. Patients should be instructed to eat a meal or snack >1 hour after taking the study drug.

Patients should be instructed to take their study medication at approximately the same time each day and not to take more than the prescribed dose at any time. Patients should swallow the study medication whole and not chew it, open it, or manipulate it in any way before swallowing. If a patient fails to take the TAK-931 dose within the time frame specified (±12 hours), that dose should be skipped. Patients should record any skipped doses in their dosing diary (see Study Manual) and resume dosing at the next scheduled time with the prescribed dosage.

If severe emesis or mucositis prevents the patient from taking a TAK-931 dose, that dose will be skipped. If emesis occurs after study medication ingestion and if whole capsule(s) are visible in the vomitus, replacement capsule(s) should be taken; otherwise the dose will not be re-administered and patients should simply adhere to the dosing schedule and resume dosing at the next scheduled time with the prescribed dosage. Patients should record the time of the emesis in their dosing diary (see Study Manual). Except for the case of emesis with visible capsules in the vomitus as described above, patients should never repeat a dose or double-up on doses.

TAK-931 will be administered only during Days 1 to 14 of each 21-day cycle of study participation. TAK-931 doses missed due to any reason, including treatment interruption due to toxicity, will not be made up by extending the 14-day treatment period during the 21-day cycle.

8.2 Definitions of Dose-Limiting Toxicity

In this study, DLTs will be evaluated only in patients enrolled in the safety cohort of Western patients with metastatic solid tumors. Initially, up to 6 evaluable Western patients will be dosed. These patients can be enrolled concurrently. If 2 or fewer patients have DLTs, then 6 more patients will be enrolled to complete the safety cohort of 12 evaluable patients. If the final number of patients with DLTs is 4 or more, enrollment will be interrupted until the clinical, PK, and pharmacodynamic data are evaluated. In this cohort, the number of patients with DLTs should be 3 or fewer for the dose of 50 mg QD to be considered safe.

Toxicity will be evaluated according to the NCI CTCAE, version 4.03, effective 14 June 2010. A DLT will be defined as any of the following events occurring during Cycle 1 that are considered by the investigator to be at least possibly related to therapy with TAK-931:

- Nonfebrile Grade 4 neutropenia (ANC <500 cells/mm^3) lasting more than 7 consecutive days. If myeloid growth factors are used, the event will be considered a DLT irrespective of the duration.

- Febrile neutropenia: Grade ≥3 neutropenia (ANC <1000 cells/mm^3) with fever and/or infection, where fever is defined as a single temperature >38.3°C or sustained temperature of ≥38°C for more than 1 hour.
- Grade 4 thrombocytopenia.
- Grade ≥3 thrombocytopenia of any duration accompanied by Grade 2 bleeding or requiring transfusion.
- Delay in the initiation of Cycle 2 by more than 14 days due to a lack of adequate recovery of treatment-related hematological or nonhematologic toxicities.
- Grade 2 ejection fraction decreased by ECHO or MUGA scan.
- Grade 4 laboratory abnormalities—even if asymptomatic—of any duration.
- Other Grade 2 nonhematologic toxicities that are considered by the investigator to be related to study drug and dose-limiting.
- Patients receiving <50% of doses (<7 doses) of the planned TAK-931 dosing in Cycle 1 due to study drug-related AEs.
- Grade ≥3 nonhematologic toxicity with the following exceptions:
  - Grade 3 arthralgia/myalgia that responds to nonsteroidal anti-inflammatory drugs (NSAIDs) within 1 week.
  - Grade 3 fatigue that lasts less than 1 week.
  - Asymptomatic Grade 3 laboratory abnormalities, if improved to Grade ≤2 in ≤48 hours. Adequate test(s) must be repeated at least every 2 days until the event is Grade ≤2. Grade 3 nausea and/or emesis that can be controlled to Grade <3 in ≤3 days with the use of optimal antiemetics (defined as an antiemetic regimen that employs both a 5-hydroxytryptamine 3 serotonin [5-HT$_3$] receptor antagonist and a corticosteroid given in standard doses and according to standard schedules).
  - Grade 3 diarrhea that can be controlled to Grade <3 in ≤3 days with appropriate treatment.

Patients not receiving at least 11 daily doses of TAK-931 in Cycle 1 for reasons other than drug-related AEs will be replaced within the cohort.

8.3 Dose Modification Guidelines

Dose modification guidelines for toxicities are described below for TAK-931 based on the type and severity of AEs and causality determination by investigators. Further clarification can be obtained in consultation with the sponsor clinician (or designee).

Table 8.a TAK-931 Dose Reductions

Dose Reduction Levels	TAK-931
Standard dose	50 mg
–1 dose level	40 mg
–2 dose levels	30 mg

8.3.1 Criteria for Beginning or Delaying a Subsequent Treatment Cycle

Before starting a new treatment cycle, TAK-931 related AEs or laboratory abnormalities must have returned to Grade ≤1 or baseline levels.

If there is a delay of a subsequent cycle longer than 2 weeks because of an AE, the patient may be withdrawn from treatment unless there is clinical benefit as assessed by the investigator, with agreement by the sponsor's medical monitor. TAK-931 dosing may be continued at a reduced dose level.

Treatment with TAK-931 will use a cycle length of 21 days. For a new cycle of treatment to begin, the patient must meet the following criteria:

- ANC must be ≥1500/mm^3.
- Platelet count must be ≥100,000/mm^3.

For therapy to resume, toxicity considered to be related to treatment with TAK-931 must have resolved to Grade ≤1, to the patient's baseline values, or to a level considered acceptable by the physician (eg, hypophosphatemia that can be managed by oral replacement).

If the patient fails to meet the above-cited criteria for retreatment, initiation of the next cycle of treatment should be delayed until the criteria for retreatment have been met. The patient must be retested or re-evaluated at least once a week at the investigator's discretion. The patient can be retreated once recovery is achieved.

Only for Western patients in the safety lead-in cohort: Should the start of the next cycle need to be delayed for more than 2 weeks because of incomplete recovery from treatment-related toxicity, this will be considered a DLT. If the patient is to receive additional treatment with TAK-931 despite this DLT, the dose will be reduced by one dose level when treatment resumes (see Section 8.3).

8.3.2 Criteria for Treatment Interruption and Dose Reduction

All toxicities that occur during the study will be actively managed following the standard of care unless otherwise specified in the protocol. Patients experiencing AEs attributed to TAK-931 may continue study treatment with the same dose, may have TAK-931 treatment held, may have their dose reduced, or may be permanently discontinued from the study. Patients who have study drug held because of treatment-related or possibly related AEs may resume study drug treatment after resolution of the AE at the same dose level or at a reduced dose depending on the nature and severity of the AE and whether it is the first occurrence or it is recurrent.

Refer to Table 8.b for general dose modification recommendations. When the dose of TAK-931 is withheld based on these criteria, clinical and laboratory reevaluation should be repeated at least weekly or more frequently, depending on the nature of the toxicity observed until the toxicity resolves to Grade ≤1 or Baseline. For transient laboratory abnormalities that, based on investigator assessment, are not clinically significant or drug-related, continuation of therapy without dose modification is permissible upon discussion with the sponsor. See details for the management of specific TEAEs in Section 8.4.

Table 8.b Dose Modification Recommendations for TAK-931 Toxicities

Criteria	Action
Grade 1 AEs	No dose reductions or interruptions
Grade 2 AEs	Treat according to local practice. Whether to hold treatment or continue it at the same or at a reduced dose is at the discretion of the investigator. Patients experiencing Grade 2 AEs considered related to study treatment that are not easily managed or corrected and are not tolerable to the patient, or AEs that are not acceptable in the investigator's judgment, should have study treatment interrupted until the AE resolves to Grade ≤1 or Baseline and then restarted at the same dose or, depending on the toxicity, at a reduced dose level.
Grade 3 AEs	Hold TAK-931 until resolution to Grade ≤1 or Baseline, then resume treatment at either the same dose or a reduced dose level at the discretion of the investigator.
Grade 4 (life-threatening) AEs	Consider permanently withdrawing the patient from the study, except when the investigator determines that the patient is receiving clinical benefit and has discussed this with the sponsor, then treatment may be restarted at a reduced dose level or below when toxicity recovers to Grade ≤1 or Baseline.
AEs of all grades	If treatment has been held for >14 consecutive days without resolution of the toxicity (to Baseline or Grade ≤1), consider permanently discontinuing study treatment unless there is clinical benefit for the patient as assessed by the investigator and with sponsor's approval. Treatment can be resumed at a reduced dose level after resolution of AEs to Grade ≤1 or Baseline.

Dose reductions are shown in Table 8.a. If initial dose adjustment does not provide sufficient relief, the dose of TAK-931 can be further reduced by an additional dose level if the treating physician considers that the patient is receiving benefit. In general, after a dose is reduced it should not be re-escalated even if there is minimal or no toxicity with the reduced dose. However, if further evaluation reveals that the AE that led to the dose reduction was not study drug-related, the dose may be re-escalated to the original dose level. Up to 2 dose level reductions of TAK-931 due to AE are generally recommended. If a third dose reduction is needed, it must first be discussed with and approved by the sponsor's medical monitor.

Only for the safety cohort in Western patients: The dose of TAK-931 will not be reduced for an individual patient during Cycle 1 unless a DLT has been declared and it is still possible for the patient to receive treatment within the 2-week dosing period scheduled. In this case, the patient can complete the remainder of Cycle 1 at a reduced dose level.

8.3.3 Criteria for Discontinuation of TAK-931

TAK-931 should be discontinued in patients experiencing an AE meeting the criteria for a DLT (see Section 8.2) for which the investigator considers that retreatment of the patient could be dangerous. For Grade 4 life-threatening TEAEs, consider permanently withdrawing the patient from the study; however, if the investigator determines that the patient is receiving clinical benefit and has discussed this with the sponsor, treatment may be restarted at a reduced dose level when toxicity recovers to Grade ≤1 or baseline.

If more than 2 dose reductions are required, or if the next cycle of TAK-931 is delayed for >14 days because of TAK-931–related toxicities, study treatment should be discontinued unless the investigator considers that the patient will benefit from continuing in the study. Further dose reduction must be discussed with, and approved by, the sponsor's medical monitor. If the patient is discontinued from treatment, the end-of-treatment visit should be completed within 30 to 40 days of the last administration of TAK-931 or before initiation of new anticancer therapy (whichever comes first).

8.4 Management of Specific Adverse Events

Therapies that are required to manage AEs and control cancer symptoms are allowed based on standard clinical practice, unless specifically excluded. Supportive care agents, such as erythropoietin and G-CSF are permitted as needed per the American Society of Clinical Oncology (ASCO) guidelines.[23] Blood products (red blood cell [RBC] and platelet transfusions) and pain medications are permitted per local institutional practice. For patients enrolled in the Western safety cohort, these agents (excluding NSAIDs) should be avoided at Baseline to meet inclusion criteria or to mitigate toxicity during Cycle 1 before DLT declaration. Each treatment intervention should be clearly documented.

8.4.1 Hematologic Toxicities

Refer to Table 8.c for dose delay and reduction recommendations for hematologic toxicities. Dosing with TAK-931 should be held if significant treatment-emergent cytopenia or bleeding is suspected to be related to, or can be worsened by, study treatment. Precautionary measures should be taken to prevent bleeding and overwhelming infections. Blood transfusions (RBC or platelets) and hematopoietic or thrombopoietic stimulating factors may be used to treat cytopenia/ thrombocytopenia at the discretion of the investigator per standard clinical practice. It should be noted that use of myeloid growth factors (eg, G-CSF and granulocyte-macrophage colony-stimulating factor [GM-CSF]) are not allowed in Cycle 1 before DLT confirmation. For a first event, a dose reduction is preferred over the use of myeloid growth factors [3].

Table 8.c TAK-931 Dose Adjustments for Hematologic Toxicities

Criteria	Action
Neutropenia (ANC)	
Grade 1 (ANC <LLN to 1500 cells/mm^3)	Continue TAK-931 at the same dose level.
Grade 2 (ANC 1000-1499 cells/mm^3)	Continue TAK-931 at the same dose level.
Grade 3 (ANC 500-999 cells/mm^3) without fever	Withhold dose until resolved to Grade ≤1 or Baseline, then: If resolved in ≤7 days, resume treatment at the same dose level; If resolved in >7days, resume treatment at a reduced dose level; If it is a repeat occurrence, resume treatment at a reduced level.
Grade 4 (ANC <500 cells/mm^3)	Withhold dose until resolved to Grade ≤1 or Baseline, then resume treatment at a reduced dose level.
Febrile neutropenia (ANC <1000 cells/mm^3, with a single temperature of >38.3°C or sustained temperature of ≥38°C for more than 1 hour)	Withhold dose until fever/infection have recovered, then resume treatment at a reduced dose level.
Thrombocytopenia (PLT)	
Grade 1 (PLT <LLN to 75,000 cells/mm^3)	Continue TAK-931 at the same dose level.
Grade 2 (PLT 50,000-74,999 cells/mm^3)	Continue TAK-931 at the same dose level.
Grade 3 (PLT 25,000-49,999 cells/mm^3) without bleeding	Withhold dose until resolved to Grade ≤1 or Baseline, then: If resolved in ≤7 days, resume treatment at the same dose level; If resolved in >7 days, resume treatment at a reduced dose level.
Grade 4 (PLT <25,000 cells/mm^3) without bleeding	Withhold dose until resolved to Grade ≤1 or Baseline, resume treatment at a reduced dose level.
Platelets <10,000 cells/mm^3, thrombocytopenia Grade ≥3 associated clinically significant bleeding	Consider permanently withdrawing the patient from the study, except when the investigator determines that the patient is obtaining clinical benefit and has discussed this with the sponsor.

Abbreviations: ANC, absolute neutrophil count; LLN, lower limit of normal; PLT, platelets.

8.4.2 Gastrointestinal Adverse Events

Nausea and/or Vomiting

This study will not initially employ prophylactic antiemetics; however, a patient who develops nausea and/or vomiting will be actively managed by employing optimal antiemetic treatment per local standard practice. Additionally, antiemetics may be used prophylactically as clinically indicated following the occurrence of the first event of TAK-931–related or possibly related nausea and/or vomiting. An optimal antiemetic regimen is defined as one that employs both a 5-HT_3 antagonist and a corticosteroid given in standard doses and according to standard schedules. PPIs and histamine H_2 receptor antagonists are not allowed during treatment.

Diarrhea

Prophylactic antidiarrheals will not be used in this study; however, diarrhea should be managed according to clinical practice, including the administration of antidiarrheals once infectious causes are excluded. Fluid intake should be maintained to avoid dehydration. Fluid deficit should be corrected before initiation of treatment and during treatment.

8.4.3 Hepatobiliary Disorders

Liver function tests should be monitored throughout participation in the study (AST, ALT, alkaline phosphatase, and bilirubin). If abnormalities are observed, the patient should be assessed for causes other than the TAK-931. Transaminase elevations should be managed according to locally accepted clinical practice including frequent monitoring of appropriate laboratory functions (2 to 3 times per week). If possible, hepatotoxic concomitant medications should be discontinued in patients who develop elevated transaminases.

Dose interruption should be considered in any patient who develops Grade 2 elevated transaminases lasting longer than 2 weeks or at any time if patient develops Grade ≥3. Treatment should be restarted at a reduced dose level (after transaminase levels resolve to Grade ≤1 or Baseline), provided that this occurs within 14 days of dose interruption.

Patients who develop AST or ALT >3 × ULN in conjunction with bilirubin >1.5 × ULN must be permanently discontinued from study treatment, unless a correctable non–drug-related cause of hepatic injury is identified.

8.4.4 Cardiac Toxicities

A MUGA scan or ECHO will be performed at the time points indicated in the Schedule of Events (Appendix A). An ECHO or MUGA scan will also be performed if symptoms of heart failure are noted. Patients with significant abnormalities should be treated per standard of care at their institution and the treatment should be documented in the electronic case report forms (eCRFs). If Grade ≥2 decrease in cardiac ejection fraction occurs, treatment should be discontinued until resolution to Grade ≤1, then the study drug will be resumed at a reduced dose level.

If Grade 3 QTcF prolongation or arrhythmia occur, treatment should be discontinued until resolution to Grade ≤1. An evaluation by a cardiologist must be performed and adequate patient management and follow-up (including hospitalization if necessary) should be put in place immediately after observation of a QTcF prolongation or arrhythmia. Review of concomitant medications and electrolyte abnormalities for QT effects is also required. Upon resolution of the event to Grade ≤1, the study drug will be resumed at a reduced dose level. For Grade 4 QTcF prolongation or arrhythmia, treatment should be permanently discontinued. If the patient shows a clinically significant benefit and is willing to resume treatment, treatment can be resumed at a reduced dose level after consultation with a cardiologist and approval from the sponsor (see Section 8.3.3).

8.4.5 Hypotension

Transient hypotension with reflex tachycardia was observed in toxicology studies with dogs at t_{max}. This risk has not been substantiated in Japanese patients dosed up to 80 mg QD in the FIH trial. With the current experience of patients being dosed at 50 mg QD, the risk of clinically meaningful hypotension can be reasonably discharged (Section 4.1.2.1). However, guidance on the event of hypotension is maintained as follows.

Patients should be advised of the possibility of orthostatic hypotension and recommended to lie down and seek assistance if symptoms occur, and, if possible, to measure HR and BP. The patient also should be advised not to perform dangerous activities or to drive an automobile during t_{max} (1 to 3 hours after administration). If the hypotensive event recurs, the patient should be advised to contact the site for instructions. BP and HR monitoring should be performed at home, if indicated by the investigator, and values recorded in the patient's diary.

If a hypotensive event occurs at the site, the patient can be discharged only if no clinically relevant BP or HR changes occurred during the observation period. If the investigator notes changes in BP/HR and/or symptoms of concern, subsequent doses of TAK-931 should be administered at the site with the same monitoring as for Cycle 1, Day 1 until the risk is confirmed or discharged.

- Grade 1 hypotension: Hypotension (at least 20 mmHg systolic BP drop and/or at least 10 mmHg diastolic BP drop versus individual patient's baseline BP) without symptoms and no reflex tachycardia at rest. No treatment modification or monitoring is indicated.
- Grade 2 hypotension: Hypotension with compatible symptoms and/or reflex tachycardia (or Grade 2 presyncope). BP, HR, ECG, and blood draw for TAK-931 concentration will be performed promptly. Repeated assessments should be performed as clinically indicated. Treatment should follow local practice. After recovery and normalization to Baseline, the patient can continue receiving treatment at the same dose if it is the first occurrence or at a reduced dose if it is a reoccurrence.
- Grade ≥3 hypotension: Stop treatment. Treatment for the event should follow local practice. Consider continuous electronic monitoring of HR, BP, and ECG until complete normalization of vital signs. Take a blood sample for measurement of TAK-931 concentration. Depending on the seriousness of the event, associated pathologies and recovery, consider either discontinuing the patient's treatment or continuing treatment at a reduced dose level.

8.5 Excluded Concomitant Medications and Procedures

All prescription and over-the-counter medications, including influenza vaccines, taken by a patient as of the first study drug administration through the EOT visit or initiation of new anticancer therapy (whichever comes first) will be recorded in the designated eCRF. Patients must be instructed not to take any medications, including over-the-counter medications and herbal supplements, without first consulting with the investigator.

The following medications and procedures are prohibited during the study:

Patients currently on chronic erythropoietin support for anemia may continue to receive erythropoietin, but initiation of new erythropoietin therapy is not allowed during the first cycle [3]. Note: erythropoietin has not been approved for the treatment of anemia associated with cancer chemotherapy in Japan.

- Any investigational agent other than TAK-931.

- Any concurrent antineoplastic therapy (eg, chemotherapy, hormonal therapy, immunotherapy, radiation therapy except for palliative radiation therapy and once PD is ruled out), or standard or investigational agents for treatment of cancer.
- Clinically significant CYP enzyme inducers, such as the enzyme-inducing antiepileptic drugs phenytoin, carbamazepine, or phenobarbital, or rifampin, rifabutin, rifapentine, or Saint-John's wort within 14 days before the first dose of TAK-931 and during the study.
- Chronic concomitant administration of any PPI is not allowed during the study. Patients receiving PPI therapy must stop using the PPI for 5 days before their first dose of TAK-931. Examples of PPIs include omeprazole, esomeprazole, pantoprazole, lansoprazole, vonoprazan, and rabeprazole. During study participation, patients who develop new clinical symptoms that may require treatment with PPIs should be discussed with the sponsor to determine the dose, schedule, and suitability of the patient for continued study participation.
- H_2 receptor antagonists (eg, cimetidine, nizatidine, and ranitidine) are not permitted from the day before the first dose (Day -1) through the last day of TAK-931 dosing in the treatment cycle. Intermittent use may be considered especially during the 1-week rest period if needed. Patients who require additional therapy with H_2 receptor antagonists during the active treatment period with TAK-931 should be discussed with the sponsor to determine the dose, schedule, and suitability of the patient for continued study participation.

8.6 Permitted Concomitant Medications and Procedures

Other medications considered necessary for the safety and wellbeing of the patient may be administered at the discretion of the investigator. Any concomitant medications added or discontinued during the study should be recorded in the eCRF. Use of myeloid growth factors (eg, G-CSF, GM-CSF) may be administered to manage patients who experience severe and/or febrile neutropenia if clinically indicated in accordance with ASCO guidelines and/or institutional practices. For the first episode of neutropenia, dose reduction is preferred [24].

Over-the-counter antacid preparations such as calcium carbonate are allowed, but should not be taken from 2 hours before and until 2 hours after administration of TAK-931. They are allowed as needed on non-dosing days.

8.7 Precautions and Restrictions

Patients should be advised of the possibility of orthostatic hypotension and recommended to lie down and seek assistance if symptoms occur, and, if possible, to measure HR and BP. The patient also should be advised not to perform dangerous activities or to drive an automobile between 1 and 3 hours from intake. If the hypotensive event recurs, the patient should be advised to contact the site for instructions. In these cases, BP and HR monitoring should be instituted at home and values recorded in the patient's diary.

Because of the risk of neutropenia, the patient should be instructed to measure axillary temperature at least daily and to follow local procedures if their body temperature reaches 38ºC.

8.7.1 Pregnancy and Contraception

It is not known what effects TAK-931 has on human pregnancy or development of the embryo or fetus; therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of reproductive age and male patients should use effective methods of contraception throughout defined periods during and after study treatment as specified below.

Female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit, OR
- Surgically sterile, OR
- If they are of childbearing potential, agree to practice one highly effective method of contraception and one additional effective (barrier) method at the same time, from the time of signing of the informed consent form (ICF) through 30 days after the last dose of study drug, OR
    - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

Male patients, even if surgically sterilized (eg, status postvasectomy) must agree to one of the following:

- Agree to practice effective barrier contraception during the entire study treatment period and through 120 days after the last dose of study drug, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods for the female partner], withdrawal spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)
- Agree not to donate sperm during the course of this study and for 120 days after receiving their last dose of study drug.

8.7.2 Females Who Are Lactating or Breastfeeding

Female patients who are lactating must refrain from breastfeeding from the start of study participation (Section 7.2, exclusion criterion #10) through 30 days after the last dose of study drug.

8.7.3 Patients With Prior Exposure to Hepatitis B or Hepatitis C

Patients who have detectable HBV or HCV viral loads are excluded from study participation (see Section 7.2, exclusion criterion 8). Patients with prior exposure to HBV or HCV who have subsequently cleared the infection (based on a negative viral load) are allowed on study, but should

be monitored for reactivation every 2 months. Patients who develop detectable HBV or HCV levels will have TAK-931 treatment held with administration of a nucleoside antagonist (NA) per institutional guidelines and a consultation with a hepatologist should be considered.

Restarting TAK-931 after HBV or HCV is no longer detected may be considered in the setting of continued NA prophylaxis and after a discussion with the Takeda medical monitor to review the potential benefit versus risk to the patient in the setting of a controlled HBV or HCV infection.

8.7.4 Photosafety

In the photoabsorption spectrum, TAK-931 exhibits a peak at 294 nm, which is within the zone of concern for potential phototoxicity and/or photoallergy. A photosafety assessment of TAK-931 has not yet been performed; therefore, patients should be cautioned to take protective measures (eg, avoidance of exposure to direct sunlight, use of sunglasses and long sleeves).

8.8 Blinding and Unblinding

Not applicable. This is an open-label study.

8.9 Description of Investigational Agents

TAK-931 will be supplied as capsules for oral administration. TAK-931 is available in 2 dose strengths, 10 and 25 mg of TAK-931 in addition to the following inactive ingredients: mannitol (filler), colloidal silicon dioxide (flow aid), and hard gelatin capsule.

The dose strength in each capsule is differentiated by size and color, as listed in the following:

- 10-mg TAK-931 capsules: white opaque color, size 4 capsule.
- 25-mg TAK-931 capsules: Swedish orange opaque color, size 4 capsule.

Refer to the TAK-931 Investigational Brochure for full details.

8.10 Preparation, Reconstitution, and Dispensation

TAK-931 dosage forms will be provided in labeled bottles in accordance with all applicable regulations. Materials provided by the sponsor should be dispensed to patients with clear administration instructions from the investigator.

TAK-931 is an anticancer drug, and as with other potentially toxic compounds, caution should be exercised when handling TAK-931 capsules.

8.11 Packaging and Labeling

TAK-931 will be provided by Takeda and will be handled at the investigative site as open-label material.

TAK-931 will be provided in high-density polyethylene bottles with polypropylene, child-resistant caps, and an induction seal.

TAK-931 is packaged and labeled in accordance with all applicable regulations.

8.12 Storage, Handling, and Accountability

Upon receipt at the investigative site, TAK-931 should be stored in the original bottles until use and stored at 2°C to 8°C (refrigerated). The study drug should be stored at home in a refrigerator. All temperature excursions at the site pharmacy will be reported to the sponsor for assessment and authorization for continued use. All investigational supplies must be stored in a secure area with controlled access and will be stored in original packaging. All TAK-931 should be used before the retest expiry date.

A drug dispensing log, including records of drug received from the sponsor and drug dispensed to the patients, will be provided and kept at the study site. Storage area temperature conditions must be monitored and recorded daily. A daily temperature log will also be kept at the study site.

Because TAK-931 is an investigational agent, it should be handled with due care. In case of contact with broken capsules, raising dust should be avoided during the clean-up operation. The product may be harmful if inhaled, ingested, or absorbed through the skin. Gloves and protective clothing should be worn during the clean-up operation. The area should be ventilated and the spill site washed after material cleanup is complete. The spilled material should be disposed of as hazardous medical waste in compliance with federal, state, and local regulations. In case of contact with the powder (eg, from a broken capsule), skin should be washed immediately with soap and copious amounts of water for at least 15 minutes. In case of contact with the eyes, copious amounts of water should be used to flush the eyes for at least 15 minutes. Medical personnel should be notified.

Patients will receive instructions for home storage and administration of TAK-931.

Patients will be instructed to return any unused study drug in the original packaging along with their completed diary cards at the appropriate visits.

Please refer to the Study Manual for additional instructions.

8.13 Other Protocol-Specified Materials

Not applicable.

9.0 STUDY CONDUCT

This trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP), applicable regulatory requirements, and International Conference on Harmonisation (ICH) guidelines.

9.1 Study Personnel and Organizations

The contact information for the Takeda project clinician for this study, the central laboratory and any additional clinical laboratories, the coordinating investigator for each member state/country (where applicable), and the contract research organization (CRO) team may be found in the Study Manual. A full list of investigators is available in the sponsor's investigator database.

9.2 Arrangements for Recruitment of Patients

Recruitment and enrollment strategies for this study may include recruitment from the investigator's local practice or referrals from other physicians. If advertisements become part of the recruitment strategy, they will be reviewed by the institutional review board (IRB)/ independent ethics committee (IEC).

9.3 Study Procedures

Refer to the Schedule of Events (Appendix A) for timing of assessments. Additional details are provided as necessary in the sections that follow. Evaluations during the screening period are to be conducted within 28 days before administration of the first dose of study drug. Unless otherwise noted, evaluations during the treatment period must occur before study drug administration. Tests and procedure should be performed on schedule for all visits. The timing of PK assessments is specified in Appendix A, Table C. All end-of-study evaluations should occur 30 to 40 days after the last dose of study drug.

Note: Tests and procedures should be performed on schedule; patients may remain on study with occasional changes (±3 days) for holidays, vacations, and other administrative reasons.

9.3.1 Informed Consent

Each patient must provide written informed consent before any study-required procedures are conducted, unless those procedures are performed as part of the patient's standard care.

9.3.2 Patient Demographics

The date of birth, race, ethnicity, and sex of the patient are to be recorded during screening.

9.3.3 Medical History

During the Screening period, a complete medical history will be compiled for each patient. The history will emphasize the background and progress of the patient's malignancy and include a description of prior therapies with a breakdown by treatment intention (neoadjuvant, adjuvant, or metastatic), line of therapy for metastatic disease, regimen, and drug(s). Treatment start and stop

dates (including at least month and year), best response and PD date. Known genetic and blood tumor biomarkers previously analyzed at the site should be recorded. In addition, concomitant medications will be recorded as specified in Section 9.3.8. Tobacco smoking history should be collected for patients in the sqEC and sqNSCLC cohorts.

Patients followed by CT scans (rather than magnetic resonance imaging [MRI]): CT scans acquired for disease assessment in addition to the most recent prescreening CT scan, if available, will be submitted to an imaging core laboratory vendor for tumor growth rate determination (see Section 13.1.3). The date of the scan should be indicated. Availability of the prescreening scan is not a prerequisite for study eligibility.

9.3.4 Physical Examination

A physical examination will be completed per standard of care at the times specified in the Schedule of Events (Appendix A).

9.3.5 Patient Height and Weight

Height will be measured only once, during screening (within 28 days before the first dose of TAK-931). Body weight will be measured at the visits specified in the Schedule of Events (Appendix A).

9.3.6 Vital Signs

Standard vital signs should be obtained at least once during each visit specified in the Schedule of Events (Appendix A, Tables A and B) and will include temperature (oral or axillary), BP, and heart rate (HR).

9.3.7 Pregnancy Test

A serum pregnancy test will be performed for women of childbearing potential at screening and within 4 days before the first dose of study drug.

Women of childbearing potential will be defined as sexually mature females who meet the following criteria:

- Those who have not undergone hysterectomy or bilateral oophorectomy, and
- Those who have not had natural menopause for 12 consecutive months or longer (eg, follicle-stimulating hormone >40 IU/L and no menopausal period for at least 12 consecutive months). Note that a loss of menopausal periods following chemotherapy may not rule out childbearing potential.

The results from these tests must be available and negative before the first dose of study drug is administered. If Cycle 1, Day 1 serum pregnancy results will not be available before dosing, a urine pregnancy test may be performed.

Pregnancy tests may also be repeated during the study if requested by an IEC/IRB or if required by local regulations.

9.3.8 Concomitant Medications and Procedures

Medications used by the patient and therapeutic procedures completed by the patient will be recorded in the eCRF from the ICF signature through the EOT visit or before initiation of new anti-cancer therapy, whichever comes first. See Sections 8.5 and 8.6 for a list of medications and therapies that are prohibited and/or allowed during the study.

9.3.9 Adverse Events

Monitoring of AEs, serious and nonserious, will be conducted throughout the study as specified in the Schedule of Events (Appendix A). Refer to Section 10.0 for details regarding definitions, documentation, and reporting of AEs and SAEs.

9.3.10 Enrollment

Enrollment is defined as when the written informed consent has been obtained and the patient's eligibility has been confirmed per the inclusion and exclusion criteria (Section 7.0). Procedures for completion of the enrollment information are described in the Study Manual. Information regarding patients who do not meet the study entry criteria will be collected in a separate log.

9.3.11 Electrocardiogram

9.3.11.1 Safety ECGs

Standard 12-lead ECGs will be administered at the time points specified in the Schedule of Events (Appendix A, Tables A and B). All machine-generated tracings should be acquired in the supine position after patients have been resting for 5 minutes. Additional ECGs may be obtained as clinically indicated (see Section 8.4.5).

9.3.11.2 Triplicate ECGs

Patients in the Western safety cohort and the first 10 US patients in the CRC and pancreatic cancer cohorts will undergo triplicate ECGs matching PK sampling for QTc assessment during Cycle 1 on Days 1 and 8 (Appendix A, Table C). **Triplicate ECGs are not required for all other patients, including all patients in the sqEC and sqNSCLC cohorts.**

Before each nominal triplicate ECG sampling time point, patients must maintain a supine position for 15 minutes. A Holter monitoring device will be used for triplicate ECG assessment. Three ECGs (approximately 1 minute apart) will be extracted at prespecified time points at times that match the times of Day 1 and Day 8 postdose PK/ECG sampling. For these matched PK/ECG collections, the PK blood sample should be collected only after completion of the triplicate ECG collection as described below. It is recommended that patients refrain from eating or limit themselves to bland food for 1 hour before and until completion of the 4-hour triplicate ECG measurements. Before each nominal triplicate ECG time point listing in Appendix A, Table C, the patient must be maintained at supine bed rest for 15 minutes. The triplicate ECGs will be performed during the final 10 minutes of that rest period (the ECG extraction 10-minute window).

The PK blood draws will occur immediately following the completion of the ECG extractions on Cycle 1, Days 1 and 8.

9.3.12 Eastern Cooperative Oncology Group Performance Status

The ECOG performance status (Appendix D) will be assessed at the times specified in the Schedule of Events.

9.3.13 Echocardiogram or Multiple Gated Acquisition Scan

A MUGA scan or ECHO will be administered at the time points specified in the Schedule of Events (Appendix A).

9.3.14 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed locally. Handling of clinical laboratory samples will be outlined in the Study Manual. Clinical laboratory evaluations will be performed as outlined below.

Blood samples for analysis of the clinical chemistry and hematological parameters shown in Table 9.a and urine samples for analysis of the parameters shown in Table 9.b will be obtained as specified in the Schedule of Events (Appendix A).

Table 9.a Clinical Chemistry and Hematology Tests

Hematology	Chemistry	
Hematocrit	Alanine aminotransferase	Creatinine
Hemoglobin	Albumin	Glucose
Leukocytes with differential	Alkaline phosphatase	Lactate dehydrogenase
Neutrophils	Aspartate aminotransferase	Magnesium
Platelets	Bicarbonate	Phosphate
	Bilirubin (total)	Potassium
	Blood urea nitrogen	Sodium
	Calcium	Urate
	Chloride	

Table 9.b Clinical Urinalysis Tests

Urinalysis	
Bilirubin	pH
Glucose	Protein
Ketones	Specific gravity
Leukocytes	Turbidity and color
Nitrite	Urobilinogen
Occult blood	

9.3.15 Disease Assessment

Patients will undergo CT scan, with contrast as appropriate, or MRI scan to monitor and assess disease progression, using RECIST, version 1.1 [20] as outlined in the Schedule of Events (Appendix A).

Primary determination of disease status will be based on local investigator assessment. The collection and central storage of scans are planned in the event that more detailed analysis of imaging data, as determined by the sponsor, is needed. More details can be found in the Imaging Review Charter.

A blood sample will be collected during screening for measurement of CEA (CRC) or CA19-9 (pancreatic adenocarcinoma) and analyzed locally. Tests will be repeated at the frequency specified in the Schedule of Events. Other tumor biomarkers that are increased at Baseline should be collected and followed at the time points used for CEA and CA19-9 measurement.

CCI

[redacted]

9.3.16 Biomarker and Pharmacodynamic Samples

9.3.16.1 Fresh Skin Tissue Biopsy Sample

pMCM2 will be detected semiquantitatively by IHC in histologic sections of formalin-fixed, paraffin-embedded (FFPE) fresh skin tissue biopsies. Fresh skin tissue biopsies (2 to 4 mm) will be obtained from patients in the Western safety cohort either during screening or predose on C1D1

and postdose on Day 8 in Cycle 1. If the skin biopsy cannot be taken during Day 8 visit, it can be scheduled at any other day from Day 9 to Day 14 while the patient is still taking TAK-931. It is strongly recommended that the postdose skin biopsies are collected 4 to 9 hours after study drug administration. For patients who consent to paired tumor biopsies (Section 9.3.16.4), it is optional to collect a skin tissue biopsy simultaneously with the tumor biopsy.

For sample retention, refer to Section 9.3.16.7.

9.3.16.2 Archival (Banked) Tumor Tissue Sample

All patients enrolled in the disease-specific cohorts must have an FFPE pretreatment tumor tissue biopsy to assess TAK-931 efficacy in relation to various biomarkers. It is acceptable to use archival tumor tissues collected before study enrollment. An archival sample obtained at the time of the last progression, if available, is preferred; however, an archival FFPE sample obtained at the time of the initial diagnosis (eg, surgical specimen) is acceptable. An FFPE block or a minimum of 10 unstained slides is required.

For sample retention, refer to Section 9.3.16.7.

9.3.16.3 Fresh Tumor Tissue Biopsy Sample

If FFPE tumor tissue is not available, a fresh biopsy must be obtained. If a new biopsy is performed, it should be obtained during the screening period with a nonsignificant risk procedure per the treating physician as described in Section 9.3.16.4.

9.3.16.4 Paired Fresh Tumor Tissue Biopsy Sample for Pharmacodynamics

Paired tumor biopsies are optional from patients in each disease-specific cohort to demonstrate TAK-931 target engagement and to evaluate possible changes of other potential biomarkers related to CDC7. The predose biopsy can be collected any time before the first dose of TAK-931. The postdose biopsy can be collected 4 to 9 hours postdose on any dosing day after completion of 3 consecutive days of TAK-931 treatment (Day 4 and later). It is recommended that the postdose biopsy be taken from the same lesion or, at least, from the same organ as at Baseline.

The investigator should preselect patients for this procedure and the patient must consent specifically to undergoing paired biopsies. Biopsies should meet the characteristics of nonsignificant risk as assessed by the investigator. Failure to obtain a follow-up biopsy (eg, if the patient declines to undergo the second procedure) will not be considered a reason to discontinue a patient from the trial.

Refer to Section 9.3.16.7 for sample retention.

9.3.16.5 Plasma Sample for Circulating Tumor DNA

Plasma should be collected at the time points specified in the Schedule of Events (Appendix A) and will be used for isolation of ctDNA and NGS analysis of ctDNA to identify potential predictive biomarkers. A retrospective correlative study may be performed to assess the association of the tumor genetic alterations with clinical responses to TAK-931.

Refer to Section 9.3.16.7 for sample retention.

9.3.16.6 Blood Sample for DNA

Whole blood samples will be collected at screening to isolate genomic DNA for NGS analysis in parallel with tumor DNA to identify potential predictive biomarkers.

9.3.16.7 Sample Retention

Tumor tissues, skin tissues, plasma samples for DNA measurements, and blood samples for genomic DNA analyses will be stored at BioStorage Technologies (Indiana USA) for up to 15 years after the date of study completion as identified in the CSR and will be destroyed by a third-party vendor identified by BioStorage Technologies per company standard operating procedures. Tumor tissues and skin tissues will be stored at ambient temperature and plasma will be stored at -70°C. If a patient withdraws consent, the samples will be discarded following local procedures. Test results should not be discussed with patients unless required by local law. The tests performed with these samples are not intended to make determinations about a patient's health or the likelihood that a patient will develop any disease, so no test results will be provided to the investigator or put into a patient's medical record.

9.3.17 Pharmacokinetic Measurements

Serial blood and urine specimens for PK analysis of TAK-931 will be collected at the time points specified in the Schedule of Events (Appendix A, Table C). The dates and exact times of administration of TAK-931 before collection of the blood or urine sample for PK analysis and the dates and exact times of the postdose PK sample collection will be recorded in the eCRF.

Detailed instructions on the procedure for collection, processing, storage, and shipment of the urine samples will be provided in the Study Manual. Plasma and urine samples may be stored for possible future analysis of TAK-931 metabolites and to test for inversion of the single chiral center within TAK-931.

Intensive PK measurements, as described in Section 5.2.2, will be obtained for the first 10 patients in the Western safety cohort and for the first 10 patients from US sites in the CRC and pancreatic cohorts. Sparse PK concentrations will be obtained for all other patients, including patients in the sqEC and sqNSCLC cohorts, for use in future integrated TAK-931 population PK analyses, which will be reported separately.

Across the Western cohort and the CRC and pancreatic cancer cohorts, a total of approximately 32 US patients will be expected to contribute time-matched PK/triplicate ECG data in this study to contribute to future PK/QTc analyses. If these patients do not complete the protocol-specified data collections, the PK/ triplicate ECG sampling may be performed in additional US patients as needed to ensure availability of these data in a total of approximately 32 patients.

If the timing of PK and ECGs coincide, the ECGs should be acquired first followed by the PK sample collection.

9.3.18 EORTC QLQ-C30

HRQOL assessment using the EORTC QLQ-C30 will be collected from patients in the disease-specific cohorts at the time points specified in the Schedule of Events (Appendix A, Table C). The patient should be given the paper version of the questionnaire to complete at the scheduled visit before other clinical assessments are conducted. The questionnaire should be completed in the language most familiar to the patient, at the scheduled visit, before the patient sees the investigator for clinical assessments. The patient should be given sufficient space and time to complete the questionnaire. The patient should complete the questionnaires on their own without any assistance from site staff or a caregiver. The questionnaire is intended to be self-reported and should not be interviewer-administered.

The questionnaire should be checked for completeness and the patient is encouraged to complete any missing response. Detailed instructions relating to the administrative procedures of the questionnaire will be provided to the sites. Patient's refusal to complete all or any part of a questionnaire should be documented in the eCRF.

The EORTC QLQ C30 was designated to assess HRQOL in a wide range of cancer patient populations and contains 30 items which incorporates 5 functional scales (physical, role, cognitive, emotional, and social), 9 symptom scales (fatigue, nausea and vomiting, pain, dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial difficulties), and a global quality of life/health status scale. Most of the 30 items have 4 response levels (not at all, a little, quite a bit, and very much), with 2 questions relying on a 7-point numeric rating scale. Raw scores are converted into scale scores ranging from 0 to 100. For the functional scales and the global health status scale, higher scores represent better HRQOL; whereas for the symptom scales lower scores represent better HRQOL. All items in this questionnaire relate to a recall period of 1 week.

9.4 Completion of Study Treatment (for Individual Patients)

Patients will be considered to have completed study treatment if they discontinue study drug for any of the reasons outlined in Section 9.6.

9.5 Completion of Study (for Individual Patients)

Patients will be considered to have completed the study if they withdraw from the study for any of the reasons outlined in Section 9.7.

9.6 Discontinuation of Treatment With Study Drug and Patient Replacement

Treatment with study drug may be discontinued for any of the following reasons:

- Adverse event.
- Protocol deviation.
- Progressive disease.
- Withdrawal by patient.

- Lost to follow-up.
- Initiation of another systemic anticancer treatment.
- Treatment completion: the patient completes 1 year of treatment and continuation is not approved.
- Study terminated by sponsor.

Once study drug has been discontinued, all study procedures outlined for the End-of-Treatment, PFS, and OS visits will be completed as specified in the Schedule of Events (Appendix A). The primary reason for study drug discontinuation will be recorded on the eCRF.

Note that some patients may discontinue study drug for reasons other than PD before completing the full treatment course; these patients will remain in the study for posttreatment assessments as outlined in the Schedule of Events (Appendix A) until PD occurs.

Patients in the Western safety cohort who receive <11 daily doses of TAK-931 in Cycle 1 for reasons other than study drug-related AEs may be replaced. In the disease-specific cohorts, patients not evaluable for response (Section 13.1.1) may be replaced.

9.7 Withdrawal of Patients From Study

A patient may withdraw from the study at any time or be withdrawn from the study for any of the following reasons:

- Lost to follow-up.
- Consent withdrawal.
- Death.
- Study terminated by sponsor.
- Transfer of patient to a long-term safety study, single-patient investigational new drug application, or similar program.

The consequence of study withdrawal is that no new information will be collected from the withdrawn patient and added to the existing data or any database.

9.8 Study Compliance

Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified subinvestigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing.

Patients are responsible for taking TAK-931 as instructed by site personnel and will receive a sufficient quantity of study drug for 1 cycle of treatment. Patients will be given a diary to record study drug dosing and associated events (eg, time of intake, doses missed, vomiting, symptoms). The study center staff will check the patient's drug diary versus the patient's supply of TAK-931 capsules to assess compliance.

9.9 Posttreatment Follow-up Assessments (Progression-Free Survival and Overall Survival)

Patients in the disease-specific cohorts who stop treatment for any reason other than PD will continue to have PFS and OS follow-up visits. Patients in the Western safety cohort will be followed only for PFS. The PFS follow-up visit should be conducted at the site every 12±1 weeks from the EOT visit until the occurrence of PD, loss to follow up, consent withdrawal, death, the start of subsequent systemic antineoplastic therapy, study termination (Section 9.4), or until 6 months after the patient discontinues treatment, whichever occurs first.

After the occurrence of PD or the start of subsequent anticancer therapy, all patients in the disease-specific cohorts will continue to have OS follow-up visits. The OS visits should be conducted every 12±1 weeks until death, loss to follow-up, consent withdrawal, study termination, or any of the circumstances described in Section 9.7. The duration of follow-up for OS will be up to 1 year after the last patient discontinues treatment, or until 50% of patients have died, whichever occurs first.

Survivor information and death details may be collected by methods that include, but are not limited to, telephone, e-mail, mail, or retrieved from online or other databases (eg, social security indexes). In addition, the start of another anticancer therapy for the disease under study will be collected.

The end-of-study visit is to be completed when the patient discontinues from the follow-up period. See the Schedule of Events (Appendix A) for appropriate assessments during follow-up.

NOTE: Only study drug-related SAEs must be reported to the Global Pharmacovigilance department or designee after the EOT visit. Refer to Section 10.0 for details regarding definitions, documentation, and reporting of SAEs.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 Adverse Event Definition

AE means any untoward medical occurrence in a patient administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from Baseline.

10.1.2 Serious Adverse Event Definition

SAE means any untoward medical occurrence that at any dose:

- Results in **death.**
- Is **life-threatening** (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient **hospitalization or prolongation of an existing hospitalization** (see clarification in the paragraph in Section 10.2 on planned hospitalizations).
- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**.
- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

In this study, intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, version 4.03, effective date 14 June 2010 [20]. Clarification should be made

between an SAE and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a WBC count of 1000/mm^3 to less than 2000/mm^3 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

10.2 Procedures for Recording and Reporting Adverse Events and Serious Adverse Events

All AEs spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF (see Section 10.3 for the period of observation). Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event.

Regardless of causality, SAEs (as defined in Section 10.1.2) must be reported (see Section 10.3 for the period of observation) by the investigator to the Takeda Global Pharmacovigilance department or designee (contact information provided below). This should be done by faxing the SAE Form within 24 hours after becoming aware of the event. The SAE Form, created specifically by Takeda, will be provided to each clinical study site. A sample of the SAE Form may be found in the Study Manual. Follow-up information on the SAE may be requested by Takeda. SAE report information must be consistent with the data provided on the eCRF.

SAE Reporting Contact Information

CCI [redacted]

Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the trial are not to be considered AEs unless the condition deteriorated in an

unexpected manner during the trial (eg, surgery was performed earlier or later than planned). Prolongation of hospitalization as a matter of practical convenience is not to be considered an AE unless the patient's condition deteriorated.

For both serious and nonserious AEs, the investigator must determine both the severity (toxicity grade) of the event and the relationship of the event to study drug administration.

Severity (toxicity grade) for each AE, including any laboratory abnormality, will be determined using the NCI CTCAE, v. 4.03, effective date 14 June 2010 [25]. The criteria are provided in the Study Manual.

Relationship of the event to study drug administration (its causality) will be determined by the investigator responding yes (related) or no (unrelated) to this question: "Is there a reasonable possibility that the AE is associated with the study drug?"

10.3 Monitoring of Adverse Events and Period of Observation

AEs, both nonserious and serious, will be monitored throughout the study as follows:

- AEs will be reported from the signing of the ICF through 30 days after administration of the last dose of study drug or before initiation of new anticancer therapy (whichever comes first) and recorded in the eCRF.
- SAEs will be reported to the Takeda Global Pharmacovigilance department or designee from the signing of the ICF through 30 days after administration of the last dose of study drug or before initiation of new anticancer therapy (whichever comes first) and recorded in the eCRF. After this period, only related SAEs must be reported to the Takeda Global Pharmacovigilance department or designee. SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor must also be contacted immediately by sending a completed Pregnancy Form to the Takeda Global Pharmacovigilance department or designee (see Section 10.2). The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor must also be contacted immediately by sending a completed Pregnancy Form to the Takeda Global Pharmacovigilance department or designee (see Section 10.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

10.5 Procedures for Reporting Product Complaints or Medication Errors (Including Overdose)

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who

identify a potential product complaint situation should immediately report this via the phone numbers or e-mail addresses provided below.

A medication error is a preventable event that involves an identifiable patient and that leads to inappropriate medication use, which may result in patient harm. Whereas overdoses and underdoses constitute medication errors, doses missed inadvertently by a patient do not. Individuals who identify a potential medication error (including overdose) situation should immediately report this via the phone numbers or e-mail addresses provided below.

Call center	Phone number	E-mail	Fax
CCI			

Product complaints, in and of themselves, are not AEs. If a product complaint results in an SAE, the SAE should be reported (refer to Section 10.2).

10.6 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, including investigators and IRBS and IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited reports within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues that might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the trial.

The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

11.0 STUDY-SPECIFIC COMMITTEES

For the Western safety cohort, patient information will be discussed in regularly scheduled meetings with investigators, other site personnel, and sponsor representatives. The main outcomes of these meetings are DLT evaluation, patient allocation, and dose confirmation. Meetings will be documented in minutes that will be distributed to members.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. If selected for coding, AEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 21.0. Drugs will be coded using the World Health Organization (WHO) Drug Dictionary.

All available safety, tolerability, efficacy, PK, and pharmacodynamic data will be included in data listings and tabulations. No imputation of values for missing data will be performed. The relevance of missing sample data will be assessed.

Data that are potentially spurious or erroneous will be examined according to standard data management operating procedures.

12.1 eCRFs

Completed eCRFs are required for each patient who signed an ICF.

The sponsor or its designee will supply investigative sites with access to eCRFs and will train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor, CRO partners, and regulatory authorities. Investigative sites must complete eCRFs in English.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

Any change of, modification of, or addition to the data on the eCRFs should be made by the investigator or appropriate site personnel. Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change.

The principal investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the principal investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the patient's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The following procedures apply to all countries except Japan.

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all

participating patients, medical records, temporary media such as thermal-sensitive paper, source worksheets, all original signed and dated ICFs, patient authorization forms regarding the use of personal health information (if separate from the ICFs), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal-sensitive paper should be photocopied by the site and filed with the original in the patient's chart to ensure long-term legibility. Furthermore, ICH E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

Refer to the Clinical Study Site Agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

The following procedures apply to Japanese sites only:

The investigator and the head of the institution agree to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating patients, medical records, temporary media such as thermal-sensitive paper, source worksheets, all original signed and dated ICFs, patient authorization forms regarding the use of personal health information (if separate from the ICFs), electronic copy of eCRFs including audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal-sensitive paper should be photocopied by the site and filed with the original in the patient's chart to ensure long-term legibility. Furthermore, ICH E6 Section 4.9.5 requires the investigator and the head of the institution to retain essential documents specified in ICH E6 (Section 8) until at least 3 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 3 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and/or the head of the institution and sponsor.

Refer to the Clinical Study Site Agreement for the sponsor's requirements on record retention. The investigator and the head of the institution should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan will be prepared and finalized before database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

13.1.1 Analysis Sets

The populations used for analysis will include the following:

- Safety population: The safety population is defined as all patients who receive any amount of study drug.
- Pharmacokinetic population: The PK population is defined as all patients for whom there are sufficient dosing and TAK-931 concentration-time data to reliably estimate the PK parameters. This population will be used for analyses of PK parameters.
- DLT-evaluable population: The DLT-evaluable population 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.
- 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 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.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographic (age, sex, and other parameters as appropriate) and baseline disease characteristics (weight, height, and other parameters as appropriate) will be summarized by cohort.

13.1.3 Efficacy Analysis

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). DCR will be analyzed using the response-evaluable population in both tumor-specific cohorts and in the Western safety cohort.

Secondary efficacy parameters are ORR, DOR, PFS, and OS. OS will be evaluated only in the tumor-specific cohorts.

The DCR and ORR will be estimated with 2-sided 95% exact binomial CIs using the response-evaluable population (Section 13.1.1).

PFS is defined as the time from the date of first dose to the date of first documentation of PD 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 for each disease cohort and for the Western safety cohort. PFS will be analyzed using the safety population.

OS is defined as the time from the date of first dose of study drug to death due to any cause. OS will be analyzed in the safety population using Kaplan-Meier estimation.

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. The DOR will be analyzed using the Kaplan-Meier estimation. The DOR will be analyzed using the responders in the response-evaluable population.

The most recent prescreening CT scans (see Section 9.3.15.1) collected from patients (if available) may facilitate estimation of those patients' pretreatment tumor growth rates to isolate the antitumor effect of TAK-931. These exploratory analyses will be reported separately from the final CSR for this study.

13.1.4 Pharmacokinetic Analysis

PK parameters in patients undergoing intensive PK sampling will be estimated using noncompartmental methods with WinNonlin Phoenix 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 population 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}.
- AUC_{24} and AUC_{last} after the first dose (C1D1) and after administration of multiple doses on C1D8.
- $t_{1/2z}$ (Day 8 only).
- CL_{ss}/F, $R_{ac(AUC)}$ (C1D8 only).
- Amount of TAK-931 excreted over 8 hours (C1D1 only) and CLr (C1D1 only) for patients undergoing urine PK collection in the Western safety cohort.

PK parameters 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.

13.1.5 Safety Analysis

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 population 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 population. Exposure to study drug will be summarized, and reasons for discontinuation and modification will be tabulated. Safety will be summarized by cohort.

TEAEs will be tabulated according to the MedDRA by system organ class, high level term, and preferred term and 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.

A listing of TEAEs resulting in study drug discontinuation will be provided.

Descriptive statistics for the actual values of clinical laboratory parameters (and/or change from Baseline in clinical laboratory parameters) will be presented for all scheduled measurements over time. Mean laboratory values over time will be plotted for key laboratory parameters.

Descriptive statistics for the actual values (and/or the change from Baseline) of vital signs, weight, ECHO, or MUGA scans over time will be tabulated by scheduled time point.

Shift tables for laboratory parameters and other safety parameters deemed appropriate will be generated to show changes in NCI CTCAE grade from Baseline to the worst postbaseline value. Graphical displays of key safety parameters, such as scatter plots of baseline versus worst postbaseline values, may be used to understand the TAK-931 safety profile.

Concomitant medications collected from the first dose of study drug through the study period will be coded using the WHO Drug Dictionary. The number and percentage of patients taking concomitant medications will be tabulated by WHO drug generic term using the safety population.

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

Electrocardiogram Analysis

ECG intervals (QT and QTcF, and PR interval), QRS duration, and ventricular rate will be summarized at each scheduled time point, along with mean change from Baseline to each posttreatment time point. The number and percentage of patients with ECG abnormalities will be summarized at each time point. Patients in the disease-specific cohorts will undergo ECGs as specified in the Schedule of Events (Appendix A, Tables A and B). Patients in the Western safety cohort and the first 10 US patients in each disease-specific cohort will undergo PK time-matched triplicate ECGs during Cycle 1 on Days 1 and 8 (Table C). **Triplicate ECGs are not required for all other patients, including patients in the sqEC and sqNSCLC cohorts.** The results of the PK-pharmacodynamic ECG analysis will be reported separately.

13.1.6 Pharmacodynamic Analysis

The change from Baseline of pMCM2 (Ser40) levels in skin will be descriptively summarized by cohort. The change from Baseline of pMCM2 (Ser40) levels in tumor tissue biopsies may also be descriptively summarized.

13.1.7 Biomarker Analysis

At the end of the study, tumor genetic alterations (mutations, amplification/deletions) in ctDNA and/or banked tumor tissues may be characterized by NGS and a retrospective correlative study of these genetic alterations in relation to clinical responses may be performed using descriptive statistics, graphical methods, and statistical modeling, whichever is appropriate. MSS status and *TP53* mutations may be confirmed in participating patients. CRC molecular subtypes may be characterized and their relationship to clinical efficacy may be retrospectively evaluated.

13.1.8 Analysis of Patient-Reported Outcomes

The PRO analysis will be performed based on subscale scores from EORTC QLQ-C30 (disease-specific cohorts only). The actual value and change from baseline of the subscale scores for EORTC QLQ-C30 will be summarized using descriptive statistics by disease-specific cohort over time. The EORTC QLQ-C30 subscale scores will also be analyzed using linear mixed models by incorporating the measurements across different time points.

13.2 Interim Analyses and Criteria for Early Termination

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 disease control (CR, PR, or SD ≥6 weeks) 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 disease control, 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 disease control. 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 disease control.

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 disease control in a total of 20 response-evaluable patients, and the null hypothesis will be rejected if there are more than 16 of 40 patients with disease control.

13.3 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 with interim analyses for futility (see Section 13.2) 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

Abbreviations: 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.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or designee, including but not limited to the Investigator's Binder, study medication, patient medical records, informed consent documentation, documentation of patient authorization to use personal health information (if separate from the ICFs), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The following procedures apply to all countries except Japan.

> The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study patients. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.
>
> The site should document all protocol deviations in the patient's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or EC, as required). 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. A Protocol Deviation Form should be completed by the site and signed by the sponsor or designee for any significant deviation from the protocol.

The following procedures apply to Japanese sites only.

> The investigator can deviate and change from the protocol for any medically unavoidable reason, for example, to eliminate an immediate hazard to study patients, without a prior written agreement with the sponsor or a prior approval from IRB. In the event of a deviation or change, the principal investigator should notify the sponsor and the head of the site (when applicable) of the deviation or change as well as its reason in a written form, and then retain a copy of the written form. When necessary, the principal investigator may consult and agree with the sponsor on a protocol amendment. If the protocol amendment is appropriate, the amendment proposal should be submitted to the head of the site as soon as possible and an approval from IRB should be obtained.

The investigator should document all protocol deviations.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the US FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency [MHRA], the Pharmaceuticals and Medical Devices Agency of Japan [PMDA]). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, patients) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those American sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the informed consent form, and, if applicable, patient recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and patient ICF must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the sponsor-supplied drug or study-specific screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, ICF) reviewed; and state the approval date. The sponsor will notify site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the trial. Until the site receives notification, no protocol activities including screening may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the ICF, recruitment materials intended for viewing by patients, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Patient incentives should not exert undue influence for participation. Payments to patients must be approved by the IRB or IEC and the sponsor.

15.2 Patient Information, Informed Consent, and Patient Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The ICF, patient authorization form (if applicable), and patient information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the patient's personal and personal health information for purposes of conducting the study. The ICF and the patient information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The ICF will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the ICF and if applicable, the patient authorization form. The ICF, patient authorization form (if applicable), and patient information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor before use.

The ICF, patient authorization form (if applicable), and patient information sheet (if applicable) must be written in a language fully comprehensible to the prospective patient. It is the responsibility of the investigator to explain the detailed elements of the ICF, patient authorization form (if applicable), and patient information sheet (if applicable) to the patient. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the patient is not capable of rendering adequate written informed consent, then the patient's legally acceptable representative may provide such consent for the patient in accordance with applicable laws and regulations.

The patient, or the patient's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the patient, or the patient's legally acceptable representative, determines he or she will participate in the study, then the ICF and patient authorization form (if applicable) must be signed and dated by the patient, or the patient's legally acceptable representative, at the time of consent and before the patient entering into the study. The patient or the patient's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the ICF and patient authorization (if applicable) at the time of consent and before the patient enters into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original ICF, patient authorization form (if applicable), and patient information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the patient signs the informed consent in the patient's medical record. Copies of the signed ICF, the signed patient authorization form (if applicable), and patient information sheet (if applicable) shall be given to the patient.

All revised ICFs must be reviewed and signed by relevant patients or the relevant patient's legally acceptable representative in the same manner as the original informed consent. The date the

revised consent was obtained should be recorded in the patient's medical record, and the patient should receive a copy of the revised ICF.

15.3 Patient Confidentiality

The sponsor and designees affirm and uphold the principle of the patient's right to protection against invasion of privacy. Throughout this study, a patient's source data will be linked to the sponsor's clinical study database or documentation only via a unique identification number. As permitted by all applicable laws and regulations, limited patient attributes, such as sex, age, or date of birth, and patient initials may be used to verify the patient and accuracy of the patient's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, US FDA, MHRA, PMDA), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the patient's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a patient's study participation, and autopsy reports. Access to a patient's original medical records requires the specific authorization of the patient as part of the informed consent process (see Section 15.2).

Copies of any patient source documents that are provided to the sponsor must have certain personally identifiable information removed (eg, patient name, address, and other identifier fields not collected on the patient's eCRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

15.4.2 Clinical Trial Registration

To ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register interventional

clinical trials it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites on or before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for American investigators), country, and recruiting status will be registered and available for public viewing.

As needed Takeda and Investigator/site contact information may be made public to support participant access to trials via registries. In certain situations/registries, Takeda may assist participants or potential participants to find a clinical trial by helping them locate trial sites closest to their homes by providing the investigator name, address, and phone number via email/phone or other methods callers requesting trial information. Once patients receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established patient screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to Takeda providing this information to callers must provide Takeda with a written notice requesting that their information not be listed on the registry site.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov or other publicly accessible websites (including the Takeda corporate site) and registries, as required by Takeda Policy/ Standard, applicable laws, and/or regulations.

Data Sharing

The sponsor is committed to responsible sharing of clinical data with the goal of advancing medical science and improving patient care. Qualified independent researchers will be permitted to use data collected from patients during the study to conduct additional scientific research, which may be unrelated to the study drug or the patient's disease. The data provided to external researchers will not include information that identifies patients personally.

15.5 Insurance and Compensation for Injury

Each patient in the study must be insured in accordance with the regulations applicable to the site where the patient is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study patients. Refer to the Clinical Study Site Agreement regarding the sponsor's policy on patient compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

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Appendix A Schedule of Events

Table A Schedule of Events for Cycle 1

		Day														
	Screening [a]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Informed consent	X															
Inclusion/exclusion criteria	X															
Demographics	X															
Medical history [b]	X	X														
Physical examination [b]	X	X							X							X
Height	X															
Weight	X															
Vital signs [c]	X	X							X							X
ECOG performance status	X															
12-Lead Safety ECG [d]	X	X							X							X
Triplicate ECG [e]		X							X							
ECHO/MUGA	X															
Disease assessment [f]	X															
Monitoring of concomitant medications and procedures	Recorded from ICF signature through the EOT visit or initiation of new anticancer therapy (whichever comes first).															
Adverse event reporting	Recorded from ICF signature through 30 days after administration of the last dose of study drug or before initiation of new anticancer therapy (whichever comes first).															
	Serious adverse events [g] will be reported from signing of the ICF through the EOT visit or initiation of new anticancer therapy (whichever comes first).															
TAK-931 administration [h]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	

See footnotes on the last table page.

Table A Schedule of Events for Cycle 1 (continued)

	Screening [a]	Day 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Samples/Laboratory Assessments																
Pregnancy test [i]	X	X														
Hematology/chemistry [j]	X	X							X							X
CA-19-9 (pancreatic cancer patients only) [k]	X															
CEA (CRC patients only) [k]	X															
Urinalysis [l]	X	X														
Plasma sample for ctDNA [n]		X														
Whole blood sample [o]	X	X														
Archival (banked) tumor tissue sample [p]	X															
Fresh skin tissue biopsy sample [q]	X (or C1D1)								(X)							
Fresh tumor tissue biopsy sample [r]	X (or C1D1)															
Fresh tumor tissue biopsy pairs for pharmacodynamics [s]	X (or C1D1)				X	→										
EORTC QLQ-C30 [t]	X	X														
Plasma sample for TAK-931 PK	See Table C, below.															
Urine sample for TAK-931 PK	See Table C, below.															

See footnotes on the following page.

Abbreviations: C1D1, Cycle 1 Day 1; CEA, carcinoembryonic antigen; CRC, colorectal cancer; CT, computed tomography; ctDNA, circulating tumor DNA; CxDx, Cycle x Day x; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organisation for Research and Treatment of Care Core Quality of Life Questionnaire; EOT, end of treatment; FFPE, formalin-fixed, paraffin-embedded; HRQOL, health-related quality of life; IEC/IRB; independent ethics committee/institutional review board; ICF, informed consent form; MRI, magnetic resonance imaging; MUGA, multiple gated acquisition (scan); PK, pharmacokinetic(s); QD, once daily; sqEC, squamous esophageal cancer; sqNSCLC, squamous non–small-cell lung cancer.

[a] Unless otherwise noted, the Screening visit must occur within 28 days before administration of the first dose of study drug (C1D1). The ICF may be signed more than 28 days before C1D1.

[b] The C1D1 medical history should focus on study disease and changes since the screening medical history. For patients in sqEC and sqNSCLC cohorts, collect tobacco smoking history. The C1D1 physical examination is not required if the screening physical examination was conducted within 4 days before administration of the first dose of study drug (C1D1).

[c] Perform vital sign measurements, including HR and BP measurements, before dosing on C1D1, C1D8, and on C1D15. Also, for all patients in Western safety cohort and the first 10 US patients in CRC and pancreatic cancer cohorts, repeat HR and BP measurements on C1D1and C1D8 at 2, 4, and 6 hours postdose just before PK sampling.

[d] All 12-lead safety ECG recordings should be made with the patient in a supine position. On C1D1, C1D8, and C1D15, a 12-lead safety ECG should be recorded after vital sign measurements and before any specified predose PK sampling.

[e] Triplicate ECGs: Refer to Table C in this appendix for triplicate ECG/PK collection on C1D1 and C1D8. Patients in the Western safety cohort and the first 10 US patients in the pancreatic cancer and CRC cohorts will undergo triplicate ECGs matching PK sampling for QTc assessment during Cycle 1 on Days 1 and 8. **Triplicate ECGs are not required for all other patients, including patients in the sqEC and sqNSCLC cohorts.** Before each nominal triplicate ECG sampling time point, patients must maintain at supine position for 15 minutes. A Holter monitoring device will be used for triplicate ECG assessment. Three ECGs (approximately 1 minute apart) will be extracted at prespecified time points at times that match the times of Day 1 and Day 8 postdose PK/ECG sampling.

[f] Baseline CT (with contrast) or MRI scan of the chest, abdomen, and pelvis must be obtained within 4 weeks before the first dose of TAK-931, according to standard of care. Bone scans may be performed rather than CT or MRI on patients with bone metastases. See Section 9.3.15 for more details

[g] Including serious pretreatment events; see Section 10.1.1.

[h] TAK-931 will be administered orally daily for 14 days of a 21-day cycle followed by 7 days of rest. Study drug will be administered to patients on an empty stomach. Patients should not eat for 2 hours before taking the study drug with 8 ounces of water. See Section 8.1.

[i] A serum β-human chorionic gonadotropin pregnancy test will be performed only for women of childbearing potential during screening and again at C1D1 (Baseline) if the screening test was performed more than 4 days before the first dose of study drug. The results must be negative within 4 days before the first dose of TAK-931 is administered (within the 4 days before C1D1), or as otherwise required by local regulations. If C1D1 serum pregnancy results will not be available before dosing, a urine pregnancy test may be performed. Additional pregnancy testing may be performed during the study at the discretion of the investigator, upon request of an IEC/IRB, or if required by local regulations.

[j] The hematology and chemistry blood samples for C1D1 may be collected within 4 days before dosing to ensure patient eligibility on C1D1. If screening clinical laboratory testing was performed within 4 days before the C1D1 dose, then testing does not need to be repeated on C1D1. See Section 9.3.14 for an analyte listing. For patients in the DLT observation window (C1, safety lead-in cohort), any symptomatic or asymptomatic Grade 3 laboratory abnormalities need to be retested every 2 days until the event is ≤Grade 2. For patients in the disease specific cohorts in Cycle 1, new clinically significant Grade ≥3 laboratory results should be repeated a minimum of every 3 days until recovered to Grade ≤2. Safety laboratory measurements outside C1D1 can be collected up to 2 days before the actual visit date.

[k] If another biomarker is elevated, it must be followed and collected according to the schedule for CEA (CRC) and CA-19-9 (pancreatic cancer) measurements.

[l] Complete urinalysis with qualitative analysis for protein at Screening and C1D1. Refer to Section 9.3.14 for required clinical urinalysis tests. If screening urinalysis was performed within 4 days before the C1D1 dose, urinalysis does not need to be repeated on C1D1.

[n] A blood sample will be obtained before administration of TAK-931 at C1D1, C3D1, C5D1, and EOT/relapse for plasma and subsequent ctDNA isolation.

[o] The whole blood sample can be taken at Screening OR before dosing on C1D1. This sample will be used as reference DNA for tumor mutation detection.
[p] All patients enrolled in disease-specific cohorts must have an archival/banked FFPE pretreatment tumor biopsy to assess TAK-931 efficacy in relation to various biomarkers. An archival sample obtained at the time of the last progression, if available, is preferred; however, an archival FFPE sample obtained at the time of the initial diagnosis (eg, surgical specimen) is acceptable. An FFPE blocks or ≥10 unstained slides are required.
[q] A fresh skin tissue biopsy sample (2 to 4 mm) will be obtained from all patients in the Western safety cohort either during screening or predose on C1D1 and postdose on Day 8 in Cycle 1. In the event that the skin biopsy cannot be taken on the Day 8 visit, it can be scheduled on any other day from Day 9 to Day 14 while the patient is still receiving TAK-931. It is strongly recommended that postdose skin biopsies are collected from 4 to 9 hours after study drug administration. For all patients in the Western safety cohort and for those in the disease-specific cohorts who consent to have paired (predose and on-treatment) tumor biopsies, an **optional** skin tissue biopsy will be collected simultaneously, if possible, with the tumor collection.
[r] If FFPE tumor tissue is not available (see footnote p), a fresh tumor tissue biopsy sample must be obtained. If a new biopsy is performed, it should be obtained during the screening period with a nonsignificant risk procedure in the opinion of the investigator. For patients in the Western safety cohort, this biopsy is optional.
[s] Paired tumor biopsies (predose and postdose on any dosing day after the completion of 3 consecutive days in Cycle 1 [Day 4 and after]) are optional and the patient needs to consent specifically for them (see Section 9.3.16.4). The predose biopsy can be collected any time before the first dose of TAK-931. The postdose biopsy can be collected 4 to 9 hours postdose on any dosing day after completion of 3 consecutive days of TAK-931 treatment (Day 4 and later). It is recommended that the postdose biopsy be taken from the same lesion or, at least, from the same organ as at Baseline. Fresh tumor biopsies are optional for patients enrolled in the Western safety cohort. Fresh biopsies should meet the characteristics of nonsignificant risk, in the opinion of the investigator.
[t] Patient-reported outcomes (HRQOL) should be completed before any other study procedures are performed.
Note: Tests and procedures should be performed on schedule; patients may remain on study with occasional changes (±3 days) for holidays, vacations, and other administrative reasons.

Table B Schedule of Events for Treatment Cycle 2 Through PFS Follow-up

	Cycle 2 and Subsequent Cycles								
	Day 1		**Day 8**		**Day 15**	**Day 18**	**EOT [a]**	**PFSFU**	**OSFU [a]**
Symptom-directed physical examination [b]	X						X		
Weight	X [c]						X		
Vital signs [d]	X		X [d]		X [d]		X		
ECOG performance status [f]	X						X		
12-Lead ECG [g]	X						X		
ECHO/MUGA [h]	X						X		
Disease assessment [i]						X (±4 days starting C2 and every other cycle thereafter)	X [j]	X [k] (Q 12 weeks)	
Monitoring of concomitant medications and procedures	Recorded from ICF signature through the EOT visit or initiation of new anticancer therapy (whichever comes first).								
Adverse event reporting	Recorded from ICF signature through 30 days after administration of the last dose of study drug or before initiation of new anticancer therapy (whichever comes first).								
	Serious adverse events [l] will be reported from signing of the informed consent form through 30 days after the last dose of study drug or before initiation of new anti-cancer therapy (whichever comes first).							X [m]	
TAK-931 administration [n]	Days 1 through 14 of each treatment cycle								
Samples/Laboratory Assessments									
Pregnancy test [o]							X		
Hematology/chemistry [e,p]	X				X [e]		X		
CA-19-9 (pancreatic patients only) [q]	X						X		
CEA (CRC patients only) [q]	X						X		
Urinalysis [r]	X								
Plasma sample for DNA [s]	X						X		
EORTC QLQ-C30 [t]	X						X		
Blood samples for PK [d]	See Table C, below.								

Footnotes are on the following page.

Abbreviations: BP, blood pressure; C, cycle; CEA, carcinoembryonic antigen; CRC, colorectal cancer; CxDx, Cycle x Day x; CT, computed tomography; ctDNA, circulating tumor DNA; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organisation for Research and Treatment of Care Core Quality of Life Questionnaire; EOT, end of treatment; FIT, fusion-inferred threshold; HR, heart rate; HRQOL, health-related quality of life; IEC/IRB; independent ethics committee/institutional review board; MRI, magnetic resonance imaging; MUGA, multiple gated acquisition (scan); OSFU, overall survival follow-up; PD, progression of disease; PFS, progression-free survival; PFSFU, progression-free survival follow-up; Q, every; QD, once daily; SAE, serious adverse event.

[a] For patients in disease-specific cohorts, survival status is to be assessed every 12±1 weeks after the occurrence of PD or the start of subsequent anticancer therapy. These OS visits should continue until death, loss to follow-up, consent withdrawal, study termination, or any of the circumstances described in Section 9.7.

[b] The symptom-directed physical examination will be conducted within 3 days prior to dosing on Day 1 of each treatment cycle and at the EOT visit. The symptom-directed physical examination may be performed at other visits during the treatment cycle at the discretion of the investigator.

[c] Weight will be measured every other cycle beginning with Cycle 3, and at EOT.

[d] Perform vital sign measurements prior to dosing. For all patients in the Western safety cohort and first 10 US patients in the pancreatic cancer and CRC cohorts, BP will be measured predose and at 2 and 4 hours postdose on Days 1 and 8 of Cycle 2 only and before the PK blood draw. From Cycle 3 to Cycle 5 if the investigator considers that there is no hypotension risk based on previous determinations, only standard vital signs will be performed (BP, HR, and temperature) on Day 1. For the remaining patients, collect BP, HR, and temperature only on Day 1 of each cycle and at EOT.

[e] Safety laboratory values can be collected up to 2 days before the actual visit date. From Cycle 6 and beyond, hematology and chemistry tests will only be conducted on Day 1 of each cycle if, in the opinion of the investigator, this is safe.

[f] ECOG performance status will be performed within 3 days before the beginning (Day 1) of each treatment cycle and at the EOT visit.

[g] Predose, single safety ECGs will be collected on Day 1 of Cycle 2 and at the EOT visit. Additional ECGs may be obtained as clinically indicated at the discretion of the investigator. ECG assessments are to be performed with the patient supine and rested for 5 minutes.

[h] ECHO and/or MUGA should be performed predose on C2D1, C3D1, every 3rd cycle thereafter (C6D1, C9D1, etc.), and at the EOT visit. From Cycle 3 (inclusive) onwards, a window of ±2 weeks is allowed for the ECHO and/or MUGA procedures. The same modality should be used as on the Screening visit.

[i] Contrast-enhanced baseline CT or MRI scan of the chest, abdomen, and pelvis must be acquired at Screening, after which contrast-enhanced CT or MRI should be acquired starting on C2D18 (±4 days) and every other cycle thereafter or as clinically indicated. The same imaging modality (CT or MRI) should be used on a patient as at the Screening visit and throughout the study. Additional bone scans may be performed on patients with bone metastases rather than CT or MRI. See Section 9.3.15 for more details.

[j] At EOT, tumor assessments will be done only on patients who have not previously demonstrated disease progression in the study unless completed within the previous 4 weeks.

[k] Patients who discontinue study treatment for reasons other than PD will undergo CT/MRI scans every 12±1 weeks from EOT until the occurrence of PD, loss to follow-up, consent withdrawal, death, the start of subsequent systemic antineoplastic therapy, study termination (Section 9.4), or until 6 months after the patient discontinued study treatment, whichever occurs first.

[l] Including serious pretreatment events; see Section 10.2.

[m] After EOT, only study drug-related SAEs must be reported to the sponsor's Department of Pharmacovigilance or designee.

[n] TAK-931 will be administered orally daily for 14 days of a 21-day cycle followed by 7 days of rest. Study drug will be administered to patients on an empty stomach. Patients should not eat for 2 hours before taking the study drug with 8 ounces of water. Patients should be instructed to eat a meal or snack >1 hour after taking study drug. See Section 8.1.

[o] Additional pregnancy testing may be performed at the discretion of the investigator, upon request of an IEC/IRB, or if required by local regulations. See Section 8.7.1.

[p] Any new Grade ≥3 results should be repeated at investigator discretion until recovered to Grade ≤2.

[q] If another biomarker is elevated, it has to be followed and collected according to the schedule for CEA (CRC) and CA-19-9 (pancreatic cancer) measurements.

[r] Complete urinalysis with qualitative analysis for protein will be performed at C2D1 and every other cycle thereafter. Positive results may require quantitative analysis (assessment of urine protein–to-creatinine ratio). Refer to Section 9.3.14 for the required clinical urinalysis tests.

[s] A blood sample will be obtained before administration of TAK-931 at C1D1, C3D1, C5D1, and EOT/relapse for plasma and subsequent ctDNA isolation.
[t] Patient-reported outcomes (HRQOL) should be completed before any other study procedures are performed.
Note: Tests and procedures should be performed on schedule; patients may remain on study with occasional changes (±3 days) for holidays, vacations, and other administrative reasons.

Table C Pharmacokinetic Sampling Schedule

	Cycle 1					Cycle 2	
	Day 1			Day 8		Day 1	Day 8
	Plasma	Triplicate ECG [a]	Urine	Plasma	Triplicate ECG [a]	Plasma	Plasma
Intensive PK Sampling							
Predose (within 1 hour before study drug)	X	X	X [b,c]	X	X		X [d]
30 min postdose (±5 min)	X			X			
1 hour postdose (±10 min)	X	X		X [e]	X		
2 hours postdose (±20 min)	X	X		X	X		
4 hours postdose (±30 min)	X	X		X	X		
6 hours postdose (±1 hr)	X	X		X	X		
8 hours postdose (±1 hr)	X	X		X [e]	X		
24 hours postdose (±3 hr) (f)	X			X			
Sparse PK Sampling (All patients enrolled from Amendment 03 onward)							
Predose	X			X		X	X
1 hour postdose (±10 min)	X						
2 hours postdose (±20 min)	X			X		X	X
4 hours postdose (±30 min)	X						

Footnotes are on the following page.

Abbreviations: AE, adverse event; ECG, electrocardiogram; hr, hour(s); min, minute(s); PK, pharmacokinetic(s); sqEC, squamous esophageal cancer; sqNSCLC, squamous non–small-cell lung cancer; US, United States.

[a] Limited to all patients in Western safety cohort and the first 10 US patients in the pancreatic cancer and CRC cohorts (target a total of ~32 patients). **Triplicate ECGs are not required for all other patients, including patients in the sqEC and sqNSCLC cohorts.** A Holter device will be used for collecting triplicate ECGs. Collection of PK time-matched triplicate ECGs begins after the patient has rested in the supine position for approximately 15 minutes. It is recommended that patients refrain from eating or limit themselves to bland food for 1 hour before and until completion of the 4-hour triplicate ECG measurements. Three Holter ECGs (approximately 1 minute apart) will be extracted at prespecified time points. Before each nominal triplicate ECG time point, the patient must be maintained at supine bed rest for 15 minutes. The triplicate ECGs will be extracted during the final 10 minutes of that rest period (the ECG extraction 10-minute window). The PK blood draws will occur immediately following the completion of the ECG extractions on Cycle 1, Days 1 and 8.

Note: For any patient who experiences hypotension or other AEs on non-PK sampling days considered to be possibly related to study drug, an additional PK plasma specimen should (if feasible) be collected at the time of the event.

[b] The first 10 patients from US sites in the CRC and pancreas cancer cohorts do not require urine collection.

[c] The 8-hour urine collection begins on Day 1 at the time of TAK-931 administration and ends 8 hours later. For the timed 8-hour urine collection on C1D1 in the Western safety cohort, patients should be asked to void completely in a container approximately 30 minutes before administration of the first dose of study drug. An aliquot of this spot urine specimen will be a predose sample. The volume of the urine collected during the 8-hour period on C1D1 will be recorded.

[d] The scheduling of the time of the study visit and PK sample on Cycle 2, Day 8 should be encouraged to occur at approximately the same time as dosing on Days 1 to 7.

[e] These plasma samples from Western safety cohorts may also be used for TAK-931 protein binding measurement.

[f] The PK plasma sample is collected before administration of the morning dose of TAK-931.

Note: Further details about sample collection, processing, storage, and shipment can be found in the Study Manual.

Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are patient to ICH GCP and all the applicable local laws and regulations.

The investigator agrees to assume the following responsibilities:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study-related procedures, including study-specific (nonroutine/nonstandard panel) screening assessments are NOT performed on potential patients before the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56, ICH, and local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to patients. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH, and local regulations, are met.
8. Obtain valid informed consent from each patient who participates in the study, and document the date of consent in the patient's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each ICF should contain a patient authorization section that describes the uses and disclosures of a patient's personal information (including personal health information) that will take place in connection with the study. If an ICF does not include such a patient authorization, then the investigator must obtain a separate patient authorization form from each patient or the patient's legally acceptable representative.
9. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc., and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor. This responsibility lies on the appropriate individual, designated by the site in Japan.

12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix C Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, United States, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study medication.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Appendix D Eastern Cooperative Oncology Group (ECOG) Scale for Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction.
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Source: [26]

Appendix E Cockcroft-Gault Equation

For men:

$$\text{Creatinine Clearance} = \frac{(140\text{-age [years]}) \times \text{weight [kg]}}{72 \times (\text{serum creatinine [mg/dL]})}$$

OR

$$\text{Creatinine Clearance} = \frac{(140\text{-age [years]}) \times \text{weight [kg]}}{0.81 \times (\text{serum creatinine [µmol/L]})}$$

For women:

$$\text{Creatinine Clearance} = \frac{0.85\ (140\text{-age [years]}) \times \text{weight [kg]}}{72 \times (\text{serum creatinine [mg/dL]})}$$

OR

$$\text{Creatinine Clearance} = \frac{0.85\ (140\text{-age [years]}) \times \text{weight [kg]}}{0.81 \times (\text{serum creatinine [µmol/L]})}$$

Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41 [27].

Appendix F Detailed Description of Amendments to Text

The primary section(s) of the protocol affected by the changes in Amendment 04 are indicated. The corresponding text has been revised throughout the protocol.

Change 1: SAE reporting requirements were changed from EDC-based reporting to paper/e-mail/fax-based reporting.

The primary change occurs in Section 10.2 Procedures for Recording and Reporting Adverse Events and Serious Adverse Events:

Initial wording:

…

Regardless of causality, SAEs must be reported (see Section 10.3 for the period of observation) by the investigator to the Takeda Global Pharmacovigilance department or designee within 24 hours of becoming aware of the event. Investigators should transmit an electronic data capture (EDC) SAE report; however, if transmission of an EDC SAE report is not feasible, a facsimile of the completed Takeda paper-based SAE form may be sent. A sample of the paper-based SAE form and processing directions are found in the Study Manual. Information in the SAE report or form must be consistent with the data provided on the eCRF.

If information not available at the time of the first report becomes available at a later date, the investigator will transmit a follow-up EDC SAE report (or a paper-based SAE form if an EDC SAE report is not feasible) or provide other documentation immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

…

Amended or new wording:

…

Regardless of causality, SAEs **(as defined in Section 10.1.2)** must be reported (see Section 10.3 for the period of observation) by the investigator to the Takeda Global Pharmacovigilance department or designee **(contact information provided below). This should be done by faxing the SAE Form** within 24 hours ~~of~~ **after** becoming aware of the event. ~~Investigators should transmit an electronic data capture (EDC) SAE report; however, if transmission of an EDC SAE report is not feasible, a facsimile of the completed Takeda paper-based SAE form may be sent. A sample of the paper-based SAE form and processing directions are found in the Study Manual. Information in the SAE report or form must be consistent with the data provided on the eCRF.~~ **The SAE Form, created specifically by Takeda, will be provided to each clinical study site. A sample of the SAE Form may be found in the Study**

Manual. Follow-up information on the SAE may be requested by Takeda. SAE report information must be consistent with the data provided on the eCRF.

SAE Reporting Contact Information

~~If information not available at the time of the first report becomes available at a later date, the investigator will transmit a follow-up EDC SAE report (or a paper-based SAE form if an EDC SAE report is not feasible) or provide other documentation immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.~~

~~All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.~~

…

Prolongation of hospitalization as a matter of practical convenience is not to be considered to be an AE unless the patient's condition deteriorated.

…

Rationale for Change: EDC SAE reporting is intended for new studies. EDC systems are not in place yet for this study.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Statistical Approval	18-Jul-2018 14:01 UTC
	Clinical Pharmacology Approval	18-Jul-2018 14:16 UTC
	Clinical Approval	18-Jul-2018 16:06 UTC