Title: An Open-Label, Phase 1, Dose-Escalation Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of TAK-931, a Cell Division Cycle 7 (CDC7) Inhibitor, in Adult Patients With Advanced Nonhematologic Tumors

NCT Number: NCT02699749

Protocol Approve Date: 23-FEB-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 or company confidential information.

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

- Named persons or organizations associated with the study.
- Patient identifiers within the text, tables, or figures or in by-patient data listings.
- 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.

If needed, certain appendices that contain a large volume of personally identifiable information or company confidential information may be removed in their entirety if it is considered that they do not add substantially to the interpretation of the data (eg, appendix of investigator's curriculum vitae).

PROTOCOL AMENDMENT

An Open-Label, Phase 1, Dose-Escalation Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of TAK-931, a Cell Division Cycle 7 (CDC7) Inhibitor, in Adult Patients With Advanced Nonhematologic Tumors

Sponsor: Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited
40 Landsdowne Street
Cambridge, MA USA 02139
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-931-1002

IND Number: 127,126 **EudraCT Number:** Not Applicable

Compound: TAK-931

Date: 23 February 2018 **Amendment Number:** 04

Date	Amendment Number	Amendment Type	Region
02 November 2015	Initial Protocol	Not applicable	Global
26 January 2016	01	Substantial	Global
30 June 2016	02	Substantial	Global
12 December 2016	03	Substantial	Global
23 February 2018	04	Substantial	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 11.0, 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 11.0

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 also 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, package insert, 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 subjects 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 11.0 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.
- Appendix B, Responsibilities of the investigator.

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 Rationale for Amendment 04

This document describes the changes in reference to the protocol incorporating Amendment 04. The primary reason for this amendment is to incorporate the exploration of 2 new dosing schedules, Schedule E and Schedule F.

As of 12 December 2017, the trial has been evaluating the safety, pharmacokinetic (PK), pharmacodynamic, and preliminary antitumor activity of TAK-931 in 3 dosing schedules (A, B, and D):

Schedule A: Twenty-five patients were treated in Schedule A (once daily [QD] 2 weeks on, 1 week off in a 21-day cycle): 30 mg (3 patients), 60 mg (3 patients), 40 mg (3patients) and 50 mg (16 patients: 7 patients during dose escalation and 9 patients in expansion cohort). Dose-limiting toxicities (DLTs) (Grade 4 neutropenia) were observed in 2 of 3 patients at 60 mg; 50 mg was considered the maximum tolerated dose (MTD) for this schedule. Preliminary PK data analysis demonstrated increased systemic exposure of TAK-931 in a dose-proportional manner between 30 mg and 60 mg, with minimal accumulation on Day 8 and a mean terminal elimination half-life between 4.3 and 6.3 hours. Dose-dependent inhibition of phosphorylation of minichromosome maintenance complex-2 (pMCM2), a direct substrate of cell division cycle 7 (CDC7), was observed in skin biopsies from patients treated with TAK-931, which correlated well with drug exposure. Partial responses were observed in 1 patient with duodenal cancer at 30 mg, 1 patient with esophageal cancer at 50 mg, and 1 patient with cervical cancer at 60 mg as well as prolonged stable disease of ~9.3 months in a patient with pancreatic cancer at 30 mg. One patient with cervical cancer, and 1 patient with thymic cancer at 50 mg continue on-treatment with stable disease beyond Cycle 9.

Schedule B: Nine patients were treated in Schedule B (QD 1 week-on 1 week-off in a 28-day cycle): 60 mg (3 patients), 80 mg (9 patients). At 60 mg, none of 3 DLT-evaluable patients had a DLT, and dosing was escalated to 80 mg. DLTs (Grade 3 febrile neutropenia) were observed in 2 out of 6 evaluable patients at 80 mg. One patient had Grade 3 neutropenia which lasted for >2 weeks and TAK-931 doses in the third week were skipped. The trial is enrolling 3 more patients at 80 mg in Schedule B to further assess the tolerability of 80 mg. CCI [redacted]

Schedule D: Twelve patients were treated in Schedule D (QD continuous in a 21-day cycle): 20 mg (6 patients), 30 mg (6 patients). Out of 6 DLT-evaluable patients at 20 mg, no patients had a DLT and dosing was escalated to 30 mg. All 6 patients in the 20-mg cohort discontinued treatment due to PD. As none of the 6 patients treated at 30 mg had a DLT, the dose was escalated to 40 mg. The trial is enrolling patients in Schedule D at 40 mg. CCI [redacted]

Based on these preliminary findings, this amendment was initiated to explore 2 additional TAK-931 dosing schedules.

- 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 H.

Changes in Amendment 04

1. Added Dosing Schedules E and F.
2. Modified schedule for skin punch [redacted] biopsies.
3. Clarified method of calculation for the TAK-931 accumulation ratio.
4. Updated nonclinical data.
5. Added appendix of clinically significant strong metabolic enzyme inducers.
6. Revised criteria for beginning or delaying a subsequent treatment cycle.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

2.0 STUDY SUMMARY

Name of Sponsor: Millennium Pharmaceuticals, Inc	**Compound:** TAK-931	
Title of Protocol: An Open-Label, Phase 1, Dose-Escalation Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of TAK-931, a Cell Division Cycle 7 (CDC7) Inhibitor, in Adult Patients With Advanced Nonhematologic Tumors	**IND No.:** 127,126	**EudraCT No.:** Not Applicable
Study Number: TAK-931-1002	**Phase:** 1	

Study Design:

This is a phase 1, open-label, dose-escalation study designed to evaluate the safety, tolerability, and pharmacokinetics (PK), and to determine the maximum tolerated dose (MTD) or a maximum tested dose of TAK-931, a CDC7 inhibitor, in adult patients with histologically confirmed, nonhematologic (solid) tumors.

Eligibility will be determined during the screening period, which may last for up to 28 days before the Cycle 1, Day 1 (C1D1) visit. Patients who meet all eligibility criteria and provide written informed consent will be enrolled in this study.

Up to 4 schedules of TAK-931 will be tested in this study:

1. Dosing Schedule A: TAK-931 administered once daily (QD) (or twice daily [BID]) for 14 consecutive days followed by 7 days of rest in a 21-day cycle.
2. Dosing Schedule B: TAK-931 administered QD (or BID) for 7 consecutive days followed by another 7 days of rest and repeated for a 28-day cycle.
3. Dosing Schedule C: TAK-931 administered QD (or BID) for 7 consecutive days followed by 14 days of rest for a 21-day cycle.
4. Dosing Schedule D: TAK-931 will be administered QD (or BID) continuously in a 21-day cycle.
5. Dosing Schedule E: TAK-931 will be administered QD (or BID) for 2 consecutive days followed by 5 days of rest and repeated weekly for a 21-day cycle.
6. Dosing Schedule F: TAK-931 will be administered QD (or BID) for 1 day followed by 6 days of rest and repeated weekly for a 21-day cycle.

Subsequent cohorts may transition to a BID dosing schedule (by dividing the daily dose in 2) if C_{max}-related AEs are observed, or if it is recommended by the potential pharmacodynamic effect.

Patient assignment to a specific schedule will be decided jointly by the investigator and sponsor with the aim of maximizing enrollment efficiency in the study.

Approximately 100 patients will be enrolled into this study. A minimum of 3 patients will be enrolled in each cohort to support safety and PK-guided dose escalation. Once the MTD is determined, a safety expansion cohort of up to 16 patients may be initiated, including patients treated at the same dose during doses escalation, for all or some of the schedules, to better define the safety and tolerability of TAK-931 and to help in the selection of the schedule(s) for further development. The decision of whether to expand a specific schedule will be jointly considered by the investigators and the sponsor and based on the feasibility of the schedule to be further developed.

Study drug may be discontinued early if a patient experiences study drug-related toxicities, if a patient requires prolonged treatment interruption to recover from toxicity, or if the toxicity recurs upon retreatment. Patients will attend the End-of-Treatment (EOT) visit 30 to 40 days after receiving their last dose of study drug or before initiating new anticancer therapy (whichever comes first). Patients who discontinue study drug treatment for reasons other than progressive disease (PD) will undergo computed tomography/magnetic resonance imaging (CT/MRI) scans every 12 weeks from EOT until the occurrence of PD, the start of subsequent antineoplastic therapy, or until 6 months after the discontinuation of study treatment, whichever occurs first.

To ensure patient safety and to minimize the number of patients exposed to nonefficacious doses, dose escalation in Schedule A will consist of an initial accelerated escalation phase in which dose levels are increased by 100%. The accelerated escalation phase will transition to modified Fibonacci escalation steps after 1 patient experiences a DLT in Cycle 1 or when 2 patients experience Grade ≥2 hematologic or non-hematologic related or possibly related drug toxicity or when geometric mean plasma C_{max} for the cohort reaches or exceeds 800 ng/mL. Accelerated escalation is not applicable to Schedules B, C, D, E, and F. The dose escalation steps will be modified, as needed, based on clinical safety and PK results. The escalation steps for Schedules A, B, C, E, and F may also be modified based on accumulating PK data and Bayesian Logistic Regression Modeling (BLRM) that would provide narrower escalation steps and potentially decrease the number of patients exposed to doses above the MTD. In Schedule D, BLRM will not be applied. Clinical safety, PK, and pharmacodynamic information will drive escalation (or de-escalation) decisions.

There will be a minimum of 1-week interval between C1D1 of the first patient dosed and C1D1 of the second patient dosed for each dose escalation cohort for Schedules A, B, and C. Subsequent patient dosing (third patient per cohort and beyond) may occur at a shorter interval (eg, <7 days from previous patient's C1D1 dosing) but no more than 1 patient will undergo C1D1 dosing within a 1-day period. These intervals are not applicable to patients enrolled in Schedule D, to cases of dose de-escalation and patients enrolled in the safety expansion cohorts. For schedules E and F, it is necessary to wait at 24 hours from the last dose administered in the first week of treatment of the first patient to the C1D1 of the second and third patients in each escalation cohort.

Vital signs, physical examinations, adverse event (AE) assessments, laboratory values (chemistry, hematology, and urinalysis), and 12-lead electrocardiograms (ECGs) will be obtained to evaluate the safety and tolerability of TAK-931. There are specific Schedules of Events for each dosing schedule to be tested in this study. Patients will have their blood pressure and heart rhythm monitored starting on their first day of dosing (C1D1) and during dosing days in the Cycle 1 inpatient observation. Patients enrolled in Schedule D will not have intensive heart rate and blood pressure monitoring during Cycle 1 although they will be hospitalized for the duration of Cycle 1. Baseline blood pressure will be determined for each individual patient during the screening period, calculated as the median value of at least 3 separate measurements. Each patient's cardiac function will be assessed by either echocardiogram (ECHO) or multiple gated acquisition scan (MUGA) at the screening visit and on the first day of Cycle 2 (C2D1). Additional assessments during the study will include measurement of cardiac enzymes in serum that are predictive of acute injury (ie, troponin I or T) and chronic or progressive failure (ie, B-type natriuretic peptide [BNP] or N-terminal pro-brain natriuretic peptide [NT-proBNP]).

CCI [redacted]

Phosphorylation of minichromosome maintenance complex-2 (pMCM2) (Ser40) will be detected semiquantitatively by immunohistochemistry of histologic sections of formalin-fixed, paraffin-embedded (FFPE) skin CCI [redacted] CCI [redacted] The finding of inhibition of phosphorylation of MCM2 (Ser40) in the on-treatment specimen compared with pre-treatment specimen will demonstrate that TAK-931 is reaching and affecting the target in surrogate tissue and the tumors at the tested dose. This information may be used to refine the dose escalation steps and to define a future recommended Phase 2 dose(s) (RP2D). Banked tumor tissue (preferably FFPE) tumor tissues, blocks, or ≥10 unstained slides, whichever are available) will be requested to assess whether predictive biomarkers revealed from nonclinical studies correlate with clinical responses to TAK-931 in patients.

Skin punch biopsies will be obtained for all patients either during screening or predose on C1D1, and for patients in Schedules A to D postdose on any dosing day after the completion of 3 consecutive dosing days (eg, Day 4 or after) in Cycle 1. A postdose skin biopsy will be obtained on Day 9 in Schedule E and on Day 8 in Schedule F. CCI [redacted]
CCI [redacted]

CCI are collected between 4 to 9 hours after study drug administration (simultaneously if possible).

If skin biopsy CCI is taken on a non-PK sampling day, sparse PK plasma samples should be collected at predose, 1 to 3 hours postdose, and 4 to 9 hours postdose on the day of biopsy. The exact dosing, biopsy, and PK sampling date and times will be recorded.

Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03, effective date 14 June 2010.

Primary Objectives:

- To evaluate the safety and tolerability of TAK-931.
- To identify the MTD or maximum tested dose of TAK-931 in adult patients with nonhematologic tumors.

Secondary Objectives:

- To characterize the PK of TAK-931 in adult patients with nonhematologic tumors.
- To assess the pharmacodynamic effect of TAK-931 by measuring basal and postdose levels of phosphorylated MCM2 (Ser40), a CDC7 substrate, in skin.
- To assess preliminary clinical activity of TAK-931.

CCI

CCI

Subject Population: Adult patients (≥20 years old) with advanced nonhematologic tumors.

Number of Subjects:	**Number of Sites:**
Approximately 100 patients	Approximately 2 to 4 sites in Japan
Dose Levels: TAK-931: Schedule A: Starting at 30 mg QD (or BID) for 14 consecutive days followed by 7 days of rest in a 21-day cycle. Schedule B: Starting at 60 mg QD (or BID) for 7 consecutive days followed by 7 days of rest and repeated in a 28-day cycle. Schedule C: Maximum administered dose in Schedule B administered QD (or BID) for 7 consecutive days and followed by 14 days of rest in a 21-day cycle. Schedule D: Starting at 20 mg QD (or BID) continuously in a 21-day cycle. Schedule E: Starting at 100 mg QD (or BID), on Day 1 and Day 2 every week in a 21-day cycle. Schedule F: Dose will be determined based on outcome of Schedule E. QD (or BID) on Day 1 every week and repeated in a 21-day cycle.	**Route of Administration:** TAK-931: oral

Duration of Treatment:	**Period of Evaluation:**
Patients will receive study drug until disease progression, unacceptable toxicity, withdrawal of consent, death, or termination of the study by the sponsor.	Patients will be followed for safety for approximately 30 days after their last dose of study drug. Patients will be followed for PFS for 6 months after the discontinuation of study treatment at maximum. It is anticipated that this study will last for approximately 3.5 years.

Main Criteria for Inclusion:

Adult male or female patients who are ≥20 years old with histologically confirmed, advanced nonhematologic tumors for which no effective standard treatment is available. Eligible patients must have adequate bone marrow reserve and renal and hepatic function based on minimum laboratory criteria, adequate cardiac function, Eastern Cooperative Oncology Group (ECOG) performance of 0 or 1, and a life expectancy of ≥3 months. In addition, patients must have recovered from all toxic effects of previous therapy, have suitable venous access for the collection of blood samples, and be willing to undergo serial skin punch biopsies.

Main Criteria for Exclusion:

Patients who have seizures requiring antiepileptic treatment, symptomatic and/or progressive central nervous system (CNS) metastases, ongoing medical conditions (such as acute exacerbations of chronic illnesses, serious infections, or major surgery within 4 weeks before receiving the first dose of study drug), uncontrolled comorbidities such as cardiac or blood pressure conditions that might compromise the patient's participation in the study will be excluded. In addition, patients who are treated with proton pump inhibitors (PPIs) or clinically significant enzyme inducers, and women who are either breastfeeding or pregnant will be excluded.

Main Criteria for Evaluation and Analyses:

The primary endpoints of the study are the number and percentage of patients with treatment-emergent adverse events (TEAEs) and first-cycle DLTs. The secondary endpoints are: PK parameters after the first dose of TAK-931 on C1D1, PK parameters after administration of multiple doses of TAK-931 on C1D7, C1D8 or C1D9, the change from baseline of pMCM2 (Ser40) levels in skin after administration of multiple doses of TAK-931, overall response rate (ORR), progression-free survival (PFS), and duration of response (DOR).

Statistical Considerations:

The primary endpoints of the study are the number and percentage of patients with TEAEs and first-cycle DLTs. An adaptive BLRM that implements escalation with overdose control will be used in this study for purposes of dose escalation recommendations and estimation of the MTD from the second dose cohort for Dosing Schedule A, B, C, E, and F. The 2-parameter model will be used and updated after each group of patients enrolled in the current dose level cohort. For each dose level, the posterior probability of having DLT rates that fall into the following intervals will be estimated:

- [0, 0.16): under-dosing.
- [0.16, 0.33): target toxicity.
- [0.33, 1.00]: excessive toxicity.

The selection of the next recommended dose will be determined from BLRM along with PK guidance and safety data evaluation.

The secondary endpoints include PK parameters after the first dose of TAK-931 on C1D1 and after multiple doses of TAK-931 on C1D7, C1D8 or C1D9, including C_{max}, time to first occurrence of maximum (peak) concentration (t_{max}), and the area under the plasma concentration-time curve (AUC) from time 0 to 24 hours (AUC_{24}) for QD dosing (or AUC_{12} for BID dosing), and AUC from time 0 to the time of the last quantifiable concentration (AUC_{last}). TAK-931 accumulation ratio ($R_{ac(AUC)}$) on C1D7, C1D8 or C1D9, apparent oral clearance (CL/F), and renal clearance (CLr) will be estimated for TAK-931. The change from baseline of phosphorylated MCM2 (Ser40) levels in skin will be summarized by dose levels. The efficacy parameters ORR, PFS, and DOR will also be summarized by dose levels.

Sample Size Justification:

It is anticipated that approximately 100 patients will be enrolled in this study including up to 6 dosing schedules and expansion cohort. For Dosing Schedules A, B, C, E, and F, a group of 3 patients will be enrolled in a TAK-931 dose cohort each time based on an adaptive design using BLRM with safety data evaluation and PK guidance. Each subject will participate in only 1 dose cohort. The total number of subjects to be enrolled is dependent upon the observed safety profile and PK guidance, which will determine the number of subjects per dose cohort, as well as the number of dose escalations required to achieve the MTD. From the simulation provided in Section 14.3, approximately 33 patients will be enrolled for up to 9 dose escalation cohorts in Dosing Schedule A. Based on the clinical safety, PK and pharmacodynamic information available as of 13 November 2016, the sample size for Dosing Schedule A is estimated to be approximately 25 patients including the 4 dose escalation cohorts and safety expansion cohort. During dose escalation phase, approximately 18 patients will be enrolled in up to 4 dose cohorts for Dosing Schedule B, approximately 15 patients will be enrolled in up to 3 dose cohorts for Dosing Schedule C, approximately 16 patients will be enrolled in up to 4 dose cohorts for Dosing Schedule E, and approximately 12 patients will be enrolled in up to 3 dose cohorts for Dosing Schedule F. The assumption may change based on the observed clinical safety profile. Once the MTD is determined, a safety expansion cohort of up to 16 patients (including patients treated at the same doses during dose escalation) may be initiated for all or some of the schedules. Additionally, approximately 25 patients will be enrolled in up to 3 dose cohorts for Dosing Schedule D. Dosing Schedule D is not guided by BLRM for dose escalation. It is anticipated that approximately 100 patients will be enrolled in this study.

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 in the template 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 and by doing so agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

5-HT_3	5-hydroxytryptamine (serotonin) type 3
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the plasma concentration-time curve
AUC_{12}	area under the plasma concentration-time curve from the time 0 to 12 hours
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
BCRP	breast cancer resistance protein
BID	twice daily
BLRM	Bayesian Logistic Regression Modeling
BNP	B-type natriuretic peptide
BUN	blood urea nitrogen
CDC7	cell division cycle 7
CIN	chromosome-instability
CL/F	apparent oral clearance
CLr	renal clearance
C_{max}	maximum observed plasma concentration
CNS	central nervous system
CR	complete response
eCRF	case report form (electronic or paper)
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
cci	cci
CXDX	Cycle X, Day X
CYP	cytochrome P-450
DDI	drug-drug interaction
DDR	DNA damage response
DI	dose intensity
DLBCL	diffuse large B cell lymphoma
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
ECHO	echocardiogram
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EF	ejection fraction

EOT	end of treatment
EWOC	escalation with overdose control
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
GCP	Good Clinical Practice
GGT	γ-glutamyl transferase
GI	gastrointestinal
GLP	Good Laboratory Practice
H_2	histamine-2 (receptor)
Hb	hemoglobin
HBV	hepatitis B virus
HBcAb	hepatitis B core antibody
HCV	hepatitis C virus
HCVAb	anti-hepatitis C antibody
HDPE	high-density polyethylene
HIV	human immunodeficiency virus
IB	investigator's brochure
IC_{50}	the concentration producing 50% inhibition
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IHC	immunohistochemistry
IP	intraperitoneal
IRB	institutional review board
JSH	Japan Society of Hepatology
CCI	CCI
LDH	lactate dehydrogenase
LVEF	left ventricular ejection fraction
MCM2	minichromosome maintenance complex-2
MedDRA	Medical Dictionary for Regulatory Activities
MIN	microsatellite-instability
MRI	magnetic resonance imaging
MSI	microsatellite instability
MSS	microsatellite stability
MTD	maximum tolerated dose
MUGA	multiple gated acquisition scan
NA	nucleoside antagonist
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSAIDs	nonsteroidal anti-inflammatory drugs
NT-proBNP	N-terminal pro-brain natriuretic peptide
ORR	overall response rate
PD	progressive disease (disease progression)
pMCM2	phosphorylation of minichromosome maintenance complex-2

PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetics
PO	*per os* (orally)
POTS	postural orthostatic tachycardia syndrome
PPI	proton pump inhibitor
PR	partial response
PTE	pretreatment event
QD	once daily
$R_{ac(AUC)}$	accumulation ratio based on AUC
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose(s)
SAE	serious adverse event
SAP	statistical analysis plan
SOP	standard operating procedures
STD_{10}	severely toxic dose in 10% of animals administered test article
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
TK	toxicokinetic
t_{max}	time to first occurrence of maximum (peak) concentration
ULN	upper limit of normal
UDPGA	uridine-5'-diphosphateglucuronic acid
V_{ss}	volume of distribution at steady state
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 deoxyribonucleic acid (DNA) replication by phosphorylating the minichromosome maintenance 2 (MCM2) complex [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) as well as 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 (DLBCL), oral squamous carcinoma, and breast, colon, colorectal, ovarian, and lung tumors [8-12]. However, it is not clear to what extent this increased expression reflects proliferative potential [13].

In vitro inhibition of the CDC7/DBF4 kinase complex arrests cell proliferation and induces apoptosis in cancer cell lines [14]. 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 [15,16]. Taken together, these data suggest that development of CDC7 kinase inhibitors present a novel class of molecular targets for cancer therapy [17].

Given that CDC7 is responsible for 2 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 single agents and in combination with other DNA damaging agents.

4.1.1 Nonclinical Experience

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 308 kinases. Of the 308 kinases, TAK-931 at 1 µM inhibited 10 kinases by 80% or more. The IC_{50} values for the 10 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 study demonstrating that TAK-931 is a highly potent and selective inhibitor of CDC7 kinase.

TAK-931 causes DNA replication stress by inhibition of 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}s ranging from 18 to 170 nM in these cell lines.

A comprehensive cell panel assay demonstrated that TAK-931 inhibits proliferation in a broad range of cancer cell lines across various organs (median EC_{50}=554.5 nM). CCI

CCI

The in vivo antitumor activity of TAK-931 administered orally (PO) as either a single agent CCI

CCI was evaluated in female BALB/c nude mice bearing COLO205 human colorectal adenocarcinoma xenografts CCI

Single treatments with TAK-931 using either continuous or intermittent dosing schedules demonstrate significant dose-dependent antitumor activity against COLO205 human colorectal adenocarcinoma xenograft tumors.

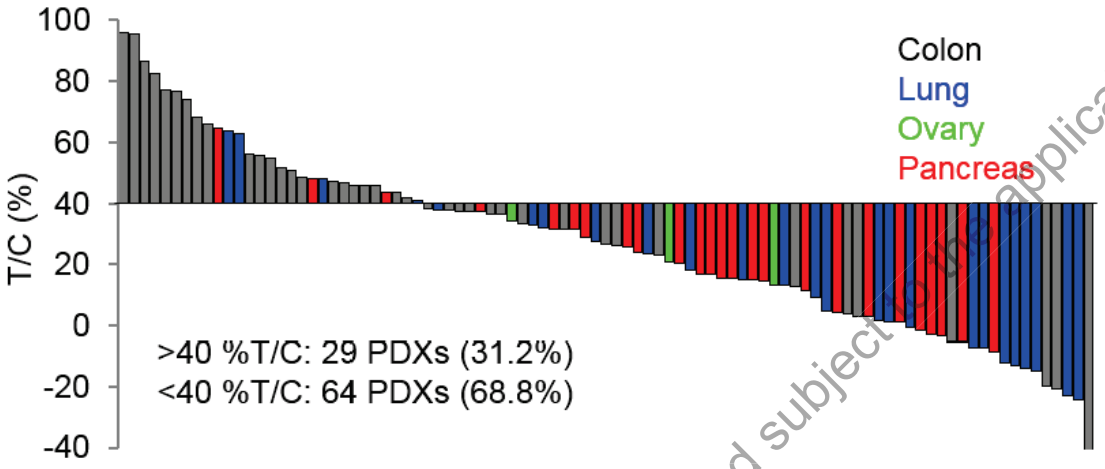
CCI

The in vivo antitumor activity of TAK-931 was further characterized utilizing up to 93 primary human xenograft tumors. In this preclinical "phase 2-like" study, mice with xenografted human primary tumors received TAK-931 60 mg/kg PO for 3 days on and 4 days off weekly for 21 days (a dose and schedule shown to be efficacious across multiple tumor models [Figure 4.a]). CCI

CCI

CCI

Figure 4.a Proof-of-Concept Studies Showing Antitumor Activity of TAK-931



Abbreviations: T/C=treatment-to-control; PDX=patient-derived xenograft.

The pharmacokinetic (PK) and pharmacodynamic response of TAK-931 was evaluated after a single PO 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. Phosphorylated MCM2 at Ser40, 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 a dose- and time-dependent manner in this xenograft model. Furthermore, antitumor activity and duration of saturated pMCM2 suppression in tumor was well-correlated in nude mouse 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 PO administration demonstrated 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) and dogs (2630 mL/hr/kg), and high volume of distribution at steady state (V_{ss}) in both species (rats: 2460 mL/kg; dogs: 3060 mL/kg). Both rats and dogs exhibited nonlinear oral PK.

Additionally, there were no pronounced sex-related differences in plasma concentrations or derived toxicokinetic (TK) parameters of TAK-931 (anhydrous) in Good Laboratory Practice (GLP)-compliant toxicity studies in Sprague-Dawley rats and beagle dogs; all GLP-compliant TK data were obtained with validated assays. TAK-931 exhibited nonlinear oral TK in rats and dogs

with single-dose maximum (peak) 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 with a higher dose. No accumulation of TAK-931 was observed in either species.

TAK-931 has high permeability and is a substrate for breast cancer resistance protein (BCRP), but is not likely a substrate for P-glycoprotein (P-gp) based on 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, the 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 (UDPGA) showed the compound is metabolized through glucuronidation by liver microsomes from all species except dogs.

Investigations into cytochrome P450 enzyme (CYP)-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, while involved in metabolism, is unlikely. TAK-931 is unlikely to cause DDIs as a perpetrator with concomitant medications metabolized via CYP isozymes at C_{max} values <800 ng/mL.

Details on these studies are provided in the TAK-931 investigator's brochure (IB).

4.1.2 Risks and Benefits

The TK profile and systemic toxic potential of TAK-931 have 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 cardiovascular changes observed. The effects on blood pressure and heart rate were dose-dependent and clearly related to compound concentration in plasma. The mechanism is likely related to the off-target pharmacological effects of TAK-931. The effects of TAK-931 on heart rate and blood pressure have been confirmed to be monitorable and reversible upon clearance of TAK-931. 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 monitored 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 generally consistent with inhibition of CDC7 activity, with test article-related findings in the hematopoietic and lymphoid systems, gastrointestinal mucosa, and reproductive organs. Decreased white blood cells or single cell necrosis in the gastrointestinal mucosa appeared from lower dose with minimal degree and its severity increased with increment of dose level. All target organ toxicities observed in the repeated-dose studies were generally monitorable and reversible, except for the effect on the germ cells.

On the basis of 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 reversible and monitorable. The primary toxicity (C_{max}-related) was cardiovascular effects (decreased blood pressure with reflex tachycardia). The DLTs with total exposure were effects on the gastrointestinal mucosa and lymphoid systems consistent with pharmacology-mediated CDC7 inhibition. The severely toxic dose in 10% of animals administered test article (STD_{10}) in rats was 180 mg/m^2 (15 mg/kg twice daily [BID]) and the highest nonseverely toxic dose (HNSTD) in dogs was 80 mg/m^2 (2 mg/kg BID). Dogs tolerated one-tenth of the rat STD_{10}. Therefore, the safe starting dose for the proposed open-label, dose escalation, in this study is 18 mg/m^2 daily, which is one-tenth of the STD_{10} in rodents. The proposed starting dose of TAK-931 is 30 mg daily, assuming a human body weight of 60 kg.

During this study, risk mitigation strategies include, but are not limited to, strict application of the study inclusion and exclusion criteria, frequent monitoring of clinical and laboratory results, guidelines for management and prophylaxis of potential toxicities, criteria for dose modification, and regular monitoring of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) by the sponsor.

Further details are presented in the TAK-931 IB.

4.2 Rationale for the Proposed Study

This is a first-in-human study designed to determine a safe and tolerated dose and schedule for TAK-931 in patients with nonhematologic tumors that can effectively inhibit the activity of CDC7 in tissue, as measured by inhibition of the phosphorylation of MCM2 (which is a target substrate of the CDC7/DBF4 complex) in skin biopsies [6].

5.0 STUDY OBJECTIVES

5.1 Primary Objectives

The primary objectives are:

- To evaluate the safety and tolerability of TAK-931.
- To identify the MTD or maximum tested dose of TAK-931 in adult patients with nonhematologic tumors.

5.2 Secondary Objectives

The secondary objectives are:

- To characterize the PK of TAK-931 in adult patients with nonhematologic tumors.
- To assess the pharmacodynamic effect of TAK-931 by measuring basal and postdose levels of phosphorylated MCM2 (Ser40), a CDC7 substrate, in skin.
- To assess preliminary clinical activity of TAK-931.

CCI [redacted]

CCI [redacted]

6.0 STUDY ENDPOINTS

6.1 Primary Endpoints

The primary endpoints are:

- The number and percentage of patients with first cycle DLTs.
- The number and percentage of patients with TEAEs.

6.2 Secondary Endpoints

The secondary endpoints 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_{24} (or AUC from time 0 to 12 hours [AUC_{12}] for BID dosing on C1D1), and AUC from time 0 to the time of the last quantifiable concentration (AUC_{last}).
- PK parameters after administration of multiple doses of TAK-931 (C1D7, C1D8, or C1D9): C_{max}, t_{max}, AUC_{24} (or AUC_{12} for BID dosing), and AUC_{last}.
- The change from baseline of phosphorylated MCM2 (Ser40) levels in skin after administration of multiple doses of TAK-931.
- Overall response rate (ORR) (complete response [CR] + partial response [PR]) as measured by Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1).
- Progression-free survival (PFS).
- Duration of response (DOR)

6.3 CCI Additional Endpoints

CCI [redacted]

The additional endpoint is:

- TAK-931 accumulation ratio ($R_{ac(AUC)}$) on C1D7, C1D8 or C1D9, apparent oral clearance (CL/F) and renal clearance (CLr) of TAK-931.

7.0 STUDY DESIGN

7.1 Overview of Study Design

This is a phase 1, open-label, dose-escalation study designed to evaluate the safety, tolerability, and PK and to determine the MTD or a maximum tested dose of TAK-931, a CDC7 inhibitor, in adult patients with histologically confirmed, nonhematologic (solid) tumors. Dose escalation of TAK-931 will be cohort based with an adaptive design using Bayesian Logistic Regression Modeling (BLRM) with PK guidance (except for Dosing Schedule D).

Eligibility will be determined during the screening period, which may last for up to 28 days before the C1D1 visit. Patients who meet all eligibility criteria and provide written informed consent will be enrolled in this study.

TAK-931 initially will be administered once daily (QD) for 14 days of each 21-day treatment cycle (Dosing Schedule A). The starting dose will be 30 mg. Subsequent cohorts may transition to a BID dosing schedule (by dividing the daily dose in 2) if C_{max}-related AEs are observed, or if it is recommended by potential pharmacodynamic effect in a cohort during escalation.

Up to 3 additional schedules will be tested after implementation of Amendment 03:

- Dosing Schedule B: TAK-931 will be administered QD or BID for 7 consecutive days followed by another 7 days of rest and repeated (ie, 7 days on and 7 days off treatment), for a cycle duration of 28 days. The starting dose of 60 mg QD was the maximum administered dose in Schedule A (2 out of 3 patients presented a DLT). Schedule B is less dose-intense than Schedule A: 14-day dosing over 28-day cycles versus 14-day dosing over 21-day cycles. Dose escalation will be governed using the same BLRM method with PK guidance as described in Section 9.3.
- Dosing Schedule C: Dosing Schedule C derives from Dosing Schedule B. TAK-931 will be administered QD or BID for 7 consecutive days followed by 14-day rest period in 21-day cycles. If, during the dose escalation of Schedule B, it is not possible to dose patients in the second half of Cycle 1 (Day 15 onwards) due to AEs not meeting DLT category, it may be decided to continue the escalation using Dosing Schedule C. The starting dose for this schedule will be the maximum administered dose in Schedule B. Dose escalation will be governed using the same BLRM method with PK guidance as described in Section 9.3.
- Dosing Schedule D: Schedule D will be implemented in parallel with Schedules A and B. Initially, TAK-931 will be administered at 20 mg QD continuously in cycles of 21 days. Further adjustment of the continuous TAK-931 dose may be possible in this schedule depending on the observed safety, PK, antitumor activity and pMCM2 inhibition.

Up to 2 additional schedules will be tested after implementation of Amendment 04:

- Dosing Schedule E: TAK-931 will be administered QD for 2 consecutive days followed by another 5 days of rest and repeated weekly (2 days on and 5 days off), for a cycle duration of 21 days. The starting dose will be 100 mg QD, the current maximum administered dose in

Schedule B. Schedule E is less dose-intense than Schedule B. Change from QD to BID (ie, splitting total daily dose) will be decided primarily if there are C_{max}-related TEAEs with QD administration during dose escalation. Changing from QD to BID is allowed for any given patient during treatment if clinically indicated. This decision can be extended to current or future patients receiving QD dosing. Dose escalation from dose level 2 onwards will be governed using the same BLRM method with PK guidance as described in Section 9.3.

- Dosing Schedule F: The decision to implement Schedule F will be determined based on the safety, tolerability, PK, and pharmacodynamics of Schedule E. TAK-931 will be administered QD or BID on Day 1 every week (1 day "on" and 6 days "off" treatment) in a 21-day treatment cycle. The starting dose will be determined based on data of Schedule E. The dose intensity (DI) of starting dose in Schedule F will not exceed that of the maximum administered dose in Schedule E. Dose escalation will be governed using the same BLRM method with PK guidance as described in Section 9.3. If Schedule E safety data suggest a once-weekly dosing schedule may allow higher dose escalation it may be decided to continue the escalation using Dosing Schedule F.

Patient assignment to a specific schedule will be decided jointly by the investigator and sponsor with the aim of maximizing enrollment efficiency in the study.

Approximately 100 patients will be enrolled into this study in up to 6 dosing schedules. A minimum of 3 patients will be enrolled in each cohort to support safety and PK-guided dose escalation. Once the MTD is determined, a safety expansion cohort of up to 16 patients may be initiated, including patients treated at the same doses during dose escalation, for all or some of the schedules, to better define the safety and tolerability of TAK-931 and to help in the selection of the schedule(s) for further development. The decision of whether to expand a specific schedule will be jointly considered by the investigators and the sponsor and based on the feasibility of the schedule to be further developed. Once MTD is determined, inpatient monitoring is not necessary and patients enrolled in the safety expansion cohort will be managed with modified Schedule of Events in Cycle 1 as specified in Appendix A.

Study drug may be discontinued early if a patient experiences study drug-related toxicities, if a patient requires prolonged treatment interruption to recover from toxicity, or if the toxicity recurs upon retreatment. Patients will attend the End-of-Treatment (EOT) visit 30 to 40 days after receiving their last dose of study drug or before initiating new anticancer therapy (whichever comes first). Patients who discontinue study drug treatment for reasons other than PD will undergo computed tomography (CT)/magnetic resonance imaging (MRI) scans every 12 weeks from EOT until the occurrence of PD, the start of subsequent antineoplastic therapy, or until 6 months after the discontinuation of study treatment, whichever occurs first.

To ensure patient safety and to minimize the number of patients exposed to nonefficacious doses, the dose escalation in Schedule A will consist of an initial accelerated escalation phase in which dose levels are increased by 100%. The accelerated escalation phase will transition to modified Fibonacci escalation steps after 1 patient experiences a DLT in Cycle 1 or when 2 patients experience Grade ≥2 hematologic or nonhematologic, related or possibly related, drug toxicity

(see Section 9.2) or when geometric mean plasma C_{max} for the cohort reaches or exceeds 800 ng/mL. For Schedules B, C, D, E, and F, accelerated escalation is not applicable. The dose escalation steps will be modified, as needed, based on clinical safety and PK results. The escalation steps for Schedules A, B, C, E, and F may also be modified based on accumulating PK data and BLRM that would provide narrower escalation steps and potentially decrease the number of patients exposed to doses above the MTD. In Schedule D, BLRM will not be applied. Clinical safety, PK, and pharmacodynamic information will be used to make escalation (or de-escalation) decisions.

There will be a minimum 1-week interval between C1D1 of the first patient dosed and C1D1 of the second patient dosed for each dose escalation cohort for Schedules A, B, and C. Subsequent patient dosing (third patient per cohort and beyond) may occur at a shorter interval (eg, <7 days from previous patient's C1D1 dosing) but no more than 1 patient will undergo C1D1 dosing within a 1-day period. These intervals are not applicable to patients enrolled in Schedule D, to cases of dose de-escalation and to patients enrolled in the safety expansion cohorts. For Schedules E and F, it is necessary to wait at least 24 hours from the last dose administered in the first week of treatment of the first patient to C1D1 of the second and third patients dosed in each escalation cohort.

Vital signs, physical examinations, adverse event (AE) assessments, laboratory values (chemistry, hematology, and urinalysis as specified in Section 10.4), and 12-lead electrocardiograms (ECGs) will be obtained to evaluate the safety and tolerability of TAK-931. There are specific Schedules of Events for each dosing schedule to be tested in this study. Patients will have their blood pressure and heart rhythm monitored starting on their first day of dosing (C1D1) and during dosing days in Cycle 1 inpatient observation (see Section 10.4.6 and Schedule of Events). Patients enrolled in Schedule D will not have intensive heart rate and blood pressure monitoring during Cycle 1 although they will be hospitalized for the duration of Cycle 1. Baseline blood pressure will be determined for each individual patient during the screening period, calculated as the median value of at least 3 separate measurements. Each patient's cardiac function will be assessed by either echocardiogram (ECHO) or multiple gated acquisition scan (MUGA) at the screening visit and on the first day of Cycle 2 (C2D1). Additional assessments during the study will include measurement of cardiac enzymes in serum that are predictive of acute injury (eg, troponin I or T) and chronic or progressive failure (eg, B-type natriuretic peptide [BNP] or N-terminal pro-brain natriuretic peptide [NT-proBNP]).

Serial blood samples for determination of the plasma concentration of TAK-931 [redacted] will be obtained during Cycle 1 at prespecified time points as described in the respective Schedule of Events.

pMCM2 (Ser40) will be detected semiquantitatively by immunohistochemistry of histologic sections of formalin-fixed, paraffin-embedded (FFPE) skin [redacted] biopsies. The finding of inhibition of pMCM2 (Ser40) in the on-treatment specimen compared with the pretreatment specimen will demonstrate that TAK-931 is reaching and affecting the target in surrogate tissue [redacted] at the tested dose. This information may be used to refine the dose escalation steps and to define a future recommended Phase 2 dose(s) (RP2D). [redacted]

CCI [redacted]

Skin punch biopsies will be obtained for all patients either during screening or predose on C1D1, and for patients in Schedules A to D postdose on any dosing day after the completion of 3 consecutive dosing days (eg, Day 4 or after) in Cycle 1. Postdose skin biopsy will be obtained on Day 9 in Schedule E, and on Day 8 in Schedule F. Other time points for biopsy collection (for example in Cycle 1 week 3 or outside Cycle 1) can be agreed with the sponsor. CCI [redacted]

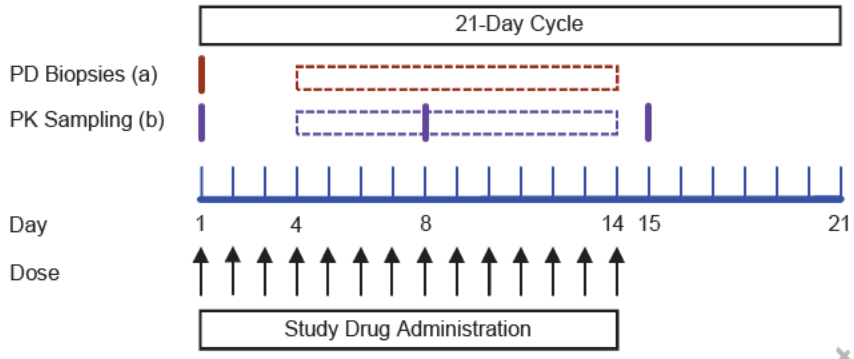
CCI [redacted] It is strongly recommended that postdose skin biopsies CCI [redacted] are collected between 4 and 9 hours after study drug administration (simultaneously if possible).

If skin biopsy CCI [redacted] is taken on a non-PK sampling day, sparse PK plasma sample should be collected at predose, 1 to 3 hours postdose, and 4 to 9 hours postdose on the day of biopsy. The exact dosing, biopsy, and PK sampling date and times will be recorded.

See Figure 7.a for an overview of the study design (Cycle 1).

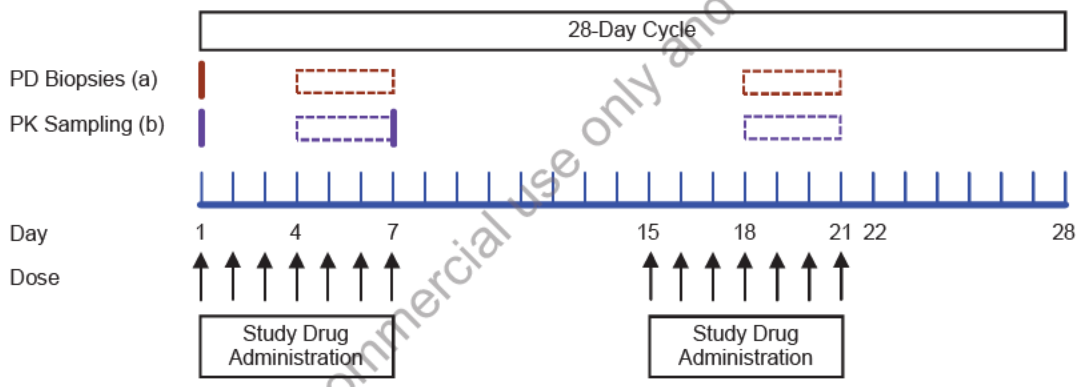
Figure 7.a Overview of Study Design (Cycle 1)

Dosing Schedule A (14 days on, 7 days off; 21-day cycle)



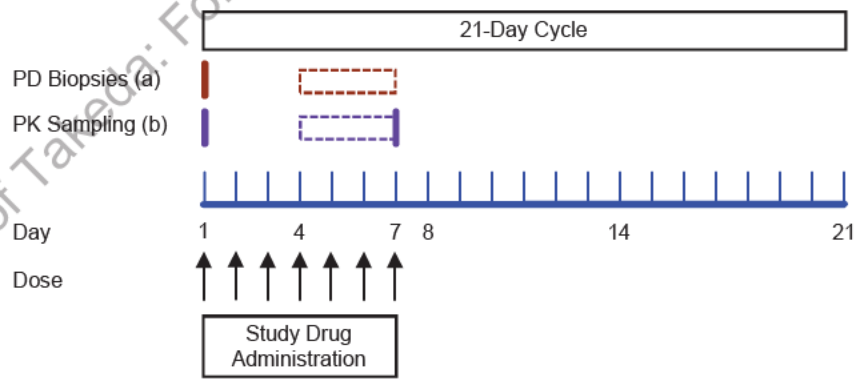
Abbreviation: PD, pharmacodynamic.

Dosing Schedule B (7 days on, 7 days off; 28-day cycle)



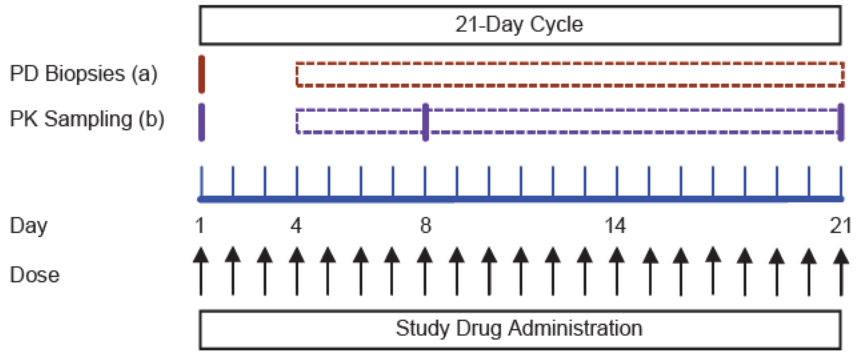
Abbreviation: PD, pharmacodynamic.

Dosing Schedule C (7 days on, 14 days off; 21-day cycle)



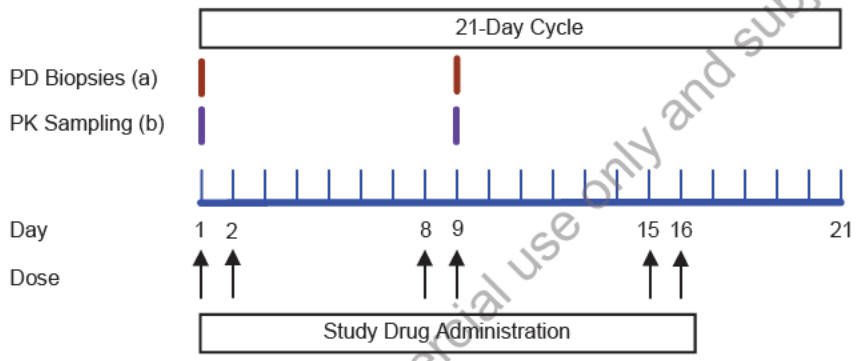
Abbreviation: PD, pharmacodynamic.

Dosing Schedule D (continuous dosing; 21-day cycle)



Abbreviation: PD, pharmacodynamic.

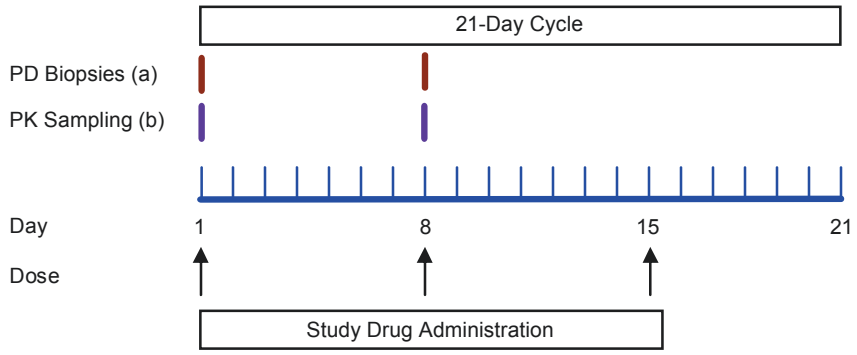
Dosing Schedule E (2 days on, 5 days off; 21-day cycle)



Other time points for biopsy collection (for example in Cycle 1 Week 3 or outside Cycle 1) can be agreed with the sponsor.

Abbreviation: PD, pharmacodynamic.

Dosing Schedule F (once weekly; 21-day cycle)



Other time points for biopsy collection (for example in Cycle 1 Week 3 or outside Cycle 1) can be agreed with the sponsor.

Abbreviation: PD, pharmacodynamic.

(a) A bar shows the predose sampling point for biopsies. A dotted box shows the postdose sampling point for biopsies with sampling window (after completion of 3 consecutive dosing days).

(b) A bar shows the series PK sampling (see Table Ga to Table Ge,f). If skin [redacted] biopsy is taken on a non-series PK sampling day, sparse PK plasma sample should be collected at predose, at 1 to 3 hours postdose, and at 4 to 9 hours postdose on the day of biopsy (dotted box).

Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03, effective date 14 June 2010 [20]. DLTs are defined in Section 9.2.

7.2 Number of Patients

Approximately 100 patients will be enrolled in this study from approximately 2 to 4 study centers in Japan. Enrollment is defined as when the written informed consent has been obtained and the subject's eligibility has been confirmed per the inclusion and exclusion criteria.

7.3 Duration of Study

Patients will receive TAK-931 until they experience disease progression, unacceptable toxicity, withdrawal of consent, death, or termination of the study by the sponsor (Section 10.7). Patients will be followed for 30 days after the last dose of study drug or until the start of subsequent alternative anticancer therapy to permit the detection of any delayed AEs. Patients who discontinue study treatment for reasons other than PD will continue PFS follow-up every 12 weeks from EOT until the occurrence of PD, the start of subsequent antineoplastic therapy, or until 6 months after the discontinuation of study treatment, whichever occurs first.

It is anticipated that this study will last for approximately 3.5 months per cohort and 3.5 months for the safety expansion cohort or 42 months for dose escalation and the safety expansion cohorts (approximately 3.5 years).

8.0 STUDY POPULATION

8.1 Inclusion Criteria

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

1. Male or female patients 20 years or older.
2. Histologically confirmed diagnosis of an advanced, nonhematologic/solid tumor (with the exception of primary brain tumor).
3. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (refer to Appendix D).
4. Patients for whom no effective standard therapy is available.
5. Life expectancy of ≥3 months.
6. Female patients who:
   - Are postmenopausal (natural amenorrhea and not due to other medical reasons) for at least 1 year before the screening visit, OR
   - Are surgically sterile, OR
   - If they are of childbearing potential, agree to practice 2 effective methods of contraception, 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 subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception.)

   Male patients, even if surgically sterilized (eg, 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 subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods for the female partner] and withdrawal are not acceptable methods of contraception.)
   - Agree not to donate sperm during this study and for 120 days after receiving their last dose of study drug.
7. 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.
8. Ability to swallow oral medications, willingness to undergo serial skin punch biopsies, and suitable venous access for the study-required PK and pharmacodynamic sampling.

9. Clinical laboratory values as specified below within 28 days before the first dose of study drug:
    - Bone marrow reserve consistent with absolute neutrophil count (ANC) ≥1500/mm^3, platelet count ≥100,000/mm^3, and hemoglobin ≥9 g/dL.
    - Total bilirubin must be <1.5 times the upper limit of normal (ULN).
    - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) must be ≤3×ULN. AST and ALT may be elevated up to 5 times the ULN if their elevation can be reasonably ascribed to the presence of hepatocellular carcinoma, biliary tract cancer, or metastatic disease in liver.
    - Serum albumin ≥3.0 g/dL.
    - Serum creatinine <1.5 times the institutional ULN or creatinine clearance based on the Cockcroft-Gault estimate ≥50 mL/minute for patients with serum creatinine concentrations above institutional limits (refer to Appendix E).
10. Left ventricular ejection fraction (LVEF) >50% as measured by ECHO or MUGA within 4 weeks before receiving the first dose of study drug.
11. Recovered (Grade ≤1 toxicity) from the reversible effects of prior anticancer therapy. Patients with ongoing toxicities at baseline may be eligible; however, any Grade 2 baseline toxicity (except for alopecia) should be discussed with the medical monitor.

8.2 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 (see Appendix G) within 14 days before the first dose of study drug.
3. Treatment with any investigational products within 30 days before the first dose of study drug.
4. Female patients who are lactating and breastfeeding or 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.
5. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.
6. 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.
- Thromboembolic events (eg, deep vein thrombosis, pulmonary embolism, or symptomatic cerebrovascular events).
- Significant, uncontrolled cardiac arrhythmia (including atrial flutter/fibrillation, ventricular fibrillation, or ventricular tachycardia).
- Use of rate control drugs for arrhythmias (including beta blockers [such as metoprolol], acetylcholine, digoxin, and non-dihydropyridine calcium channel blockers diltiazem and verapamil).
- Placement of a pacemaker for control of cardiac rhythm.
- Requirement for inotropic support (including digoxin).
- New York Heart Association Class II to IV heart failure (Appendix F).
- Any other cardiac condition that in the opinion of the investigator could pose an additional risk for the participation in the study (eg, pericardial effusion or restrictive cardiomyopathy).
- Baseline prolongation of the rate-corrected QT interval (QTc; eg, repeated demonstration of QTc interval >480 msec, or history of congenital, long QT syndrome, or torsades de pointes).

7. Patients with any of the following blood pressure conditions:
   - History of orthostatic hypotension or syncope that required medical intervention. Orthostatic hypotension is defined as a 20 mmHg fall in systolic blood pressure and/or a 10 mmHg fall in diastolic blood pressure within 2 to 5 minutes of quiet standing immediately after a 5-minute period of supine rest.
   - Postural orthostatic tachycardia syndrome (POTS) or postural tachycardia syndrome (defined as an increase in heart rate of >30 beats per minute over baseline after 10 minutes of quiet standing).
   - Hypertension that is unstable or not controlled by medication.
8. Seizures requiring antiepileptic treatment.
9. History of uncontrolled brain metastasis unless:
   - Previously treated with surgery, whole-brain radiation, or stereotactic radiosurgery.
   - Stable disease for ≥60 days, without steroid use (or stable steroid dose established for ≥28 days before the first dose of TAK-931).
10. Symptomatic and/or progressive central nervous system (CNS) metastases.

11. Ongoing medical conditions, such as acute exacerbations of chronic illnesses, serious infections, or major surgery within 4 weeks before receiving the first dose of study drug.
12. Known history of human immunodeficiency virus (HIV) infection.
13. Known hepatitis B (HBV) surface antigen seropositive or detectable hepatitis C (HCV) infection viral load. Note: Patients who have positive hepatitis B core antibody or hepatitis B surface antibody can be enrolled but must have an undetectable hepatitis B viral load. Patients who have positive hepatitis C antibody must have an undetectable hepatitis C viral load.
14. 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.

9.0 STUDY DRUG

9.1 Study Drug Administration

All protocol-specific criteria for administration of study drug must be met and documented prior to 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 according to the assigned dosing schedule (Figure 7.a). TAK-931 will be administered to patients on an empty stomach. Patients should not eat for 2 hours before taking the capsules with 8 ounces of water. Patients should be instructed to eat a meal or snack >1 hour after taking study drug. In case of postdose biopsy, patients may drink water only after taking the study drug as indicated by the local surgical procedures.

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 for QD, ±6 hours for BID), 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, a patient should never repeat a dose or double-up on doses.

TAK-931 will be administered only during the stipulated days for each schedule. TAK-931 doses missed due to any reason, including treatment interruption due to toxicity, will not be made up by extending the cycle length (either 21 or 28 days).

9.2 Definitions of Dose-Limiting Toxicity

Toxicity will be evaluated according to the NCI CTCAE, version 4.03, effective 14 June 2010 [20]. These criteria are provided in the Study Manual. 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 as 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 lasting more than 7 consecutive days. A platelet count <10,000/mm^3 at any time is a DLT.
- 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 (7 days for Schedules D, E, and F) due to a lack of adequate recovery of treatment-related hematological or nonhematologic toxicities.
- Grade 2 ejection fraction (EF) decreased by ECHO or MUGA.
- Other Grade 2 nonhematologic toxicities that are considered by the investigator to be related to study drug and dose-limiting.
- Patients who receive <50% of doses of the planned TAK 931 dosing in Cycle 1 for related AEs: <7 QD doses or <14 BID doses for Schedules A and B; <4 QD doses or <7 BID doses for Schedule C and; <11 QD doses or <21 BID doses for Schedule D, <3 QD doses or <6 BID doses for Schedule E, <2 QD doses or <3 BID doses for Schedule F.
- Grade 3 or greater nonhematologic toxicity with the following exceptions:
  - Grade 3 arthralgia/myalgia that responds to nonsteroidal anti-inflammatory drugs (NSAIDs).
  - Grade 3 fatigue that lasts less than 1 week.
  - Isolated Grade ≥3 laboratory abnormalities if it is asymptomatic and resolves to Grade ≤1 or baseline levels in ≤7 days.
  - 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 (serotonin) type 3 [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.

9.3 Dose Escalation Rules

The safe starting dose of TAK-931 in humans is 30 mg/day based on one-tenth of the STD$_{10}$ in rodents. Possible toxicities in clinical studies are hematologic and gastrointestinal effects based on the mechanism of action. Transient hypotension with reflex tachycardia was seen in dogs with approximately C_{max}>1000 ng/mL due to vasodilatation and decreased peripheral resistance. This would translate to C_{max} of 1584 ng/mL in humans by correcting the difference in TAK-931 plasma protein binding for humans and dogs.

To ensure patient safety and minimize the number of patients exposed to nonefficacious doses, dose escalation in Schedule A will consist of an initial accelerated escalation phase in which dose levels are increased by 100%. This accelerated escalation is not applicable to Schedules B, C, D, E, and F. The accelerated escalation phase will transition to modified Fibonacci escalation steps after 1 patient experiences a DLT in Cycle 1 or when 2 patients experience Grade ≥2 hematologic or nonhematologic related or possibly related drug toxicity or when geometric mean plasma C_{max} for the cohort reaches or exceeds 800 ng/mL. Hematologic, cardiovascular, gastrointestinal, and other nonhematologic AEs that will be considered DLTs are summarized in Section 9.2. An expansion cohort of up to 15 patients (including patients treated at the same dose during doses escalation) may be treated with all or some schedules to better define the safety and tolerability of TAK-931.

For Schedules A, B, C, E, and F, the dose escalation steps will be modified as needed, based on accumulating PK data and clinical safety (utilizing BLRM) that would provide narrower escalation steps and potentially decrease the number of patients exposed to doses above the MTD (see details in Section 14.3). In addition, there will be a minimum of a 1-week interval between C1D1 of the first patient dosed and C1D1 of the second patient dosed for each dose escalation cohort for Schedules A, B, and C. Subsequent patient dosing (third patient per cohort and beyond) may occur at a shorter interval (eg, <7 days from previous patient's C1D1 dosing), but no more than 1 patient will undergo C1D1 dosing within a 1-day period. These intervals are not applicable to patients enrolled in Schedule D, to cases of dose de-escalation and to patients enrolled in the safety expansion cohorts. For Schedules E and F, it is necessary to wait at least 24 hours from the last dose administered in the first week of treatment of the first patient to C1D1 of the second and third patients dosed in each escalation cohort.

The Schedule D starting dose level is 20 mg QD, to be administered continuously in 21-day cycles. As with the other schedules, the DLT-observation period will be in Cycle 1. However, with this schedule, there is a higher risk of delayed or cumulative toxicity after Cycle 1. For this reason, patients in this schedule will be evaluated every week at least during Cycles 2 and 3. After Cycle 1, AEs meeting DLT definitions will be managed according to Section 9.4.3 guidelines. In case of non-dose-limiting drug-related AEs that preclude a safe TAK-931 administration, the preference will be to interrupt treatment for 1 week to allow for recovery and then re-start treatment at the same dose (See Section 9.4.3). This strategy will help define the period during which TAK-931 can be dosed continuously at low doses and to determine, if necessary, standardized dosing breaks. For Schedule D, BLRM will not be used to guide escalation decisions. Other dose levels (including de-escalation to 10 mg, escalation to 30 mg QD or BID administration) may be possible depending on the observed safety, treatment interruptions, PK, antitumor activity, and pMCM2 pharmacodynamics.

Dose Escalation With PK Guidance

The 2-parameter BLRM implementing the escalation with overdose control (EWOC) principle [21,22] will be used to inform dose escalation decisions and MTD estimation from the second dose cohort in Dosing Schedule A, B, C, E, and F. The starting dose level is 30 mg QD for Schedule A, 60 mg QD for Schedule B, the maximum administered dose in Schedule B will be used for Schedule C, 20 mg QD for Schedule D, 100 mg QD for Schedule E. The starting dosing for

Schedule F will be determined based on clinical data of Schedule E. The DI of the starting dose in Schedule F will not exceed that of the maximum administered dose in Schedule E. If transition to BID administration is decided during dose escalation, the next dose level will have the same total daily dose used in the previous level divided in 2 equal doses administered every 12 hours. An individual patient can be changed from QD to BID based on clinical safety only if allowed by the sponsor. Initially, 3 patients will be enrolled at starting dose level. The following rules will be used only for this initial dose level for Schedules A, B, and C:

- If no DLTs are observed in Cycle 1, 3 patients will be enrolled at the next dose level.
- If 2 or more of the first 3 patients experience a DLT in Cycle 1, then the starting dose level will be considered not tolerated.
- If 1 patient experiences a DLT in Cycle 1, 3 more patients will be enrolled at the starting dose.
  - If no more than 1 patient out of the 6 total patients has a Cycle 1 DLT, 3 patients will be enrolled at the next dose level.
  - If 3 or more of the 6 patients experience a Cycle 1 DLT, the starting dose level will be considered not tolerated.
  - If 2 of the 6 patients have a Cycle 1 DLT, 3 additional patients will be enrolled. If any of those 3 additional patients have a Cycle 1 DLT, the starting dose will be considered not tolerated. If none of the 3 additional patients have a Cycle 1 DLT, the starting dose will be considered the MTD.

Once the dose is escalated above the starting dose level, the BLRM (with PK guidance) will be used for all subsequent dose recommendations. The recommended dose will be that which has the highest posterior probability of having a DLT rate that falls into the interval [0.16, 0.33). Following the EWOC principle, the posterior probability of the recommended dose having a DLT rate above 0.33 must not exceed 35%. In addition, the PK profile will also be evaluated to support the dose escalation. Escalation will continue until one of the following stopping rules is met:

- At least 6 patients are enrolled at the current dose and the current dose is the recommended dose for the next group of patients, or
- At least 9 patients are enrolled at the next recommended dose and the posterior probability of the next recommended dose having a DLT rate that falls into the interval [0.16, 0.33) exceeds 50%.

Once either of the above rules has been met, MTD may be declared. Alternative stopping rules may also be considered following discussions between the sponsor and the investigators.

For Schedule D, initially 3 patients will be dosed with 20 mg QD, if 0 or 1 DLT is observed in Cycle 1, 3 more patients will be enrolled in this cohort. If 0 or 1 DLT is observed out of 6 patients in total, the 20-mg dose level will be considered tolerated and escalation up to 30 mg will be considered. If 3 or more out of these 6 patients has a DLT (or ≥2 patients out the first 3), the 20-mg dose level will be considered not tolerated, and de-escalation to 10 mg QD or stopping Schedule D

will be considered. If 2 of the 6 patients have a DLT, 3 additional patients will be enrolled. If any of those 3 additional patients have a DLT, the 20-mg dose level will be considered not tolerated. If none of the 3 additional patients have a DLT, the 20-mg dose level will be considered the MTD. For Schedule D escalation decisions, all the available safety and dose modification information after Cycle 1 will be considered.

More conservative dose escalation, evaluation of intermediate doses, and expansion of an existing dose level are all permissible following discussions between the sponsor and the investigators, if such measures are needed for patient safety or for a better understanding of the dose-related toxicity, exposure, or pharmacodynamics of TAK-931.

9.4 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).

9.4.1 Intrapatient Dose Escalation

Intrapatient dose escalation is not allowed; however, it would be possible to change from QD to BID administration based on individual patient clinical safety if allowed by the sponsor (eg, if C_{max}-related toxicity is observed).

9.4.2 Criteria for Beginning or Delaying a Subsequent Treatment Cycle

Before starting a new treatment cycle, TAK-931–related AEs or laboratory abnormalities that require dose modification must have returned to Grade ≤1 or baseline levels. For Schedule B these criteria also apply to Day 15 dosing. For Schedules E and F, in general these criteria also apply to Day 8 and Day 15 dosing; however, for patients with Grade 2 neutropenia on Day 8 or Day 15, treatment can be administered at the investigator's discretion. For Schedule D, this requirement is applicable also for restarting treatment after an interruption due to toxicity.

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 the previously established safe dose level or below.

9.4.3 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 9.a 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. In events where there are 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 9.5.

Table 9.a 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 to 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 the previous safe dose level or below.
Grade 3 AEs	Hold TAK-931 until resolution to Grade ≤1 or baseline, and 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.

Abbreviations: AE, adverse event.

When a dose reduction occurs, the TAK-931 dose will be reduced to the next lower dose that has been established as a safe dose during dose escalation. If initial dose adjustment does not provide sufficient relief, the dose of TAK-931 can be further reduced 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. Dose reductions due to AEs of 1 or 2 dose levels are generally recommended.

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 remaining dosing period scheduled. In this case, the patient can complete Cycle 1 at a reduced dose level.

9.4.4 Criteria for Discontinuation of TAK-931

TAK-931 should be discontinued in patients experiencing an AE in Cycle 1 meeting criteria for a DLT 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, 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 the previously safe dose level or below 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, then the patient should have study treatment discontinued unless the investigator considers that the patient will receive benefit continuing in the study. If treatment discontinuation is determined, the EOT visit should be completed within 30 to 40 days of the last administration of TAK-931.

9.5 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, G-CSF, blood products (RBC and platelet transfusions), and pain medications are permitted as needed per American Society of Hematology (ASH)/ASCO guidelines or local institutional practice. However, 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.

9.5.1 Hematologic Toxicities

Please refer to Table 9.b for dose delay and reduction recommendations for hematologic toxicities. TAK-931 should be held if a 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 (red blood cell [RBC] or platelet) 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, GM- CSF) are not allowed in Cycle 1 before confirmation of DLT. In case of a first event, a dose reduction is preferred over the usage of myeloid growth factors.

Table 9.b TAK-931 Dose Adjustments for Hematologic Toxicities

Criteria	Action
Neutropenia (ANC)	
Grade 1 (ANC <LLN-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 >7 days, 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) without fever	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-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.

9.5.2 Gastrointestinal Adverse Events

Nausea and/or Vomiting

This study will not initially use prophylactic antiemetics. However, a patient who develops nausea and/or vomiting will be actively managed by using optimal antiemetic treatment based on local standard practice. Additionally, antiemetics could be used prophylactically as clinically indicated following the occurrence of first event of TAK-931–related or possibly related nausea and/or vomiting. An optimal antiemetic regimen is defined as one that uses both a 5-HT_3 antagonist and a corticosteroid given in standard doses and according to standard schedules. PPIs and anti-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.

9.5.3 Hepatobiliary Disorders

Liver function tests should be monitored throughout participation in the study (AST, ALT, ALP, and bilirubin). If abnormalities are observed, the subject 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 subjects who develop elevated transaminases.

Dose interruption should be considered in any subject who develops Grade 2 elevated transaminases lasting longer than 2 weeks or at any time if subject develops a Grade ≥3 elevation. If transaminase levels resolve to Grade ≤1 or baseline within 14 days of dose interruption, treatment should be restarted at a reduced dose level.

Subjects who develop elevation of transaminase AST or ALT >3 times upper limit of normal (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. Strict monitoring (daily or every other day) of liver function tests should be established.

9.5.4 Cardiac Toxicities

A MUGA scan or echocardiogram (ECHO) will be performed at screening, predose on C2D1, and at end-of-treatment follow-up. ECHO or MUGA will also be performed if symptoms of heart failure are noted. Patients with significant abnormalities should be treated as per standard of care at their institution documenting the treatment in the electronic case report forms (eCRFs). In case of Grade ≥2 decrease in cardiac ejection fraction, treatment should be discontinued until resolution to Grade ≤1, then the study drug will be resumed at a reduced dose level.

The routine 12-lead ECG will be performed predose in Cycle 1 at the specified time points including 2, 4, and 8 hours postdose as described in Schedule of Events. Single safety ECGs will be collected before administration of TAK-931 on Day 1 of Cycle 2 and at the EOT visit. In case of Grade 3 QTc prolongation or arrhythmia, 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 deemed necessary) should be put in place immediately after observation of the QTc prolongation or arrhythmia. Review of concomitant medications 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 QTc 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 the approval from the sponsor (see Section 9.4.4).

9.5.5 Hypotension

Transient hypotension with reflex tachycardia was observed in toxicology studies with dogs at C_{max}. For this reason, close blood pressure (BP) and heart rhythm monitoring is indicated during

Cycle 1, and after Cycle 1 if clinically indicated. This monitoring takes advantage of the hospitalization requirement for the first cycle in phase 1 studies performed in Japan.

In Cycle 1, heart rhythm will be continuously monitored with electronic equipment at a minimum on Days 1 through 3 in all patients except those enrolled in Schedule D and in the safety expansion cohorts. For Schedules E and F, continuous heart rhythm monitoring will be performed on all dosing days in Cycle 1, starting before dosing and up to 12 hours after the intake of the dose. Continuous monitoring should not interfere with in-hospital normal patient activities including eating, sleeping, walking, or personal care. Blood pressure will also be measured (as described in Section 10.4.6) before dosing and 2, 4, and 8 hours after dosing on Days 1 through 3 in Cycle 1 and if the patient presents with symptoms. For Schedules E and F, blood pressure will be measured before dosing and 2, 4, and 8 hours after dosing on all dosing days in Cycle 1. Outside this window in Cycle 1 and for patients enrolled in Schedule D and the safety expansion cohorts, resting heart rate and BP will be assessed and recorded once at the estimated C_{max} time (approximately 2 hours after dosing) together with orthostatic changes in both. Orthostatic heart rate and BP are required for patients enrolled in Schedules E and F but not for those enrolled in Schedule D.

- 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. Individual patient's baseline normal BP is defined as the median of at least 3 BP measurements taken during the screening period (the median value of systolic BP and diastolic BP will be evaluated separately). No treatment modification or monitoring is indicated.
- Grade 2 hypotension: hypotension with compatible symptoms and reflex tachycardia (or Grade 2 presyncope). BP, heart rate, and ECG will be performed on the spot. Repeated assessments should be performed as clinically indicated. Treat according to local practice. After recovery and normalization to baseline, the patient can continue receiving treatment with the same dose if it is the first occurrence or with a reduced dose if it is a reoccurrence.
- Grade ≥3 hypotension: Stop treatment. Treat the event according local practice. Consider continuous electronic monitoring of heart rhythm, BP, and ECG until complete normalization of vital signs. Depending on the seriousness of the event, associated pathologies, and recovery consider either discontinuing the patient's treatment or continue treatment at a reduced dose level.

For patients experiencing Grade ≥2 hypotension at any time during Cycle 1, careful BP monitoring as described for Cycle 1 Days 1 through 3 should be performed in the following 3 administration days of TAK-931.

For any patient experiencing Grade ≥2 hypotension on non-PK sampling days during Cycle 1, an additional PK plasma specimen should be collected (if feasible) at the time of the event.

The patient 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 heart rate and BP. The patient also should be advised not to perform dangerous activities or to drive during the C_{max} time.

If the hypotensive event recurs, the patient should be advised to contact the site for instructions. BP and heart rate monitoring should be instituted at home and values recorded in the patient's diary.

9.6 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 30 days from the last dose or before initiation of new anticancer therapy (whichever comes first) will be recorded on the designated electronic case report form (eCRF). Subjects 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:

- Use of myeloid growth factors (eg, G-CSF, GM-CSF) are not allowed in the first cycle before confirmation of DLT, but may be administered to manage patients who experience severe and/or febrile neutropenia if clinically indicated in accordance with American Society of Clinical Oncology (ASCO) guidelines and/or institutional practices. For the first episode of neutropenia, dose reduction is preferred. Use of myeloid growth factors with Grade 4 neutropenia in Cycle 1 is considered a DLT.
- Any investigational agent other than TAK-931
- Medications used for rate control of arrhythmias and cardiac frequency (including beta blockers [such as metoprolol], acetylcholine, digoxin, and non-dihydropyridine calcium channel blockers diltiazem and verapamil).
- Clinically significant cytochrome P450 enzyme inducers (see Appendix G) within 14 days prior to 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 before enrollment 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 dose and 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 (Day -1) through the last day of active TAK-931 dosing in the treatment cycle. Intermittent use may be considered especially during the resting 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 dose and schedule and suitability of the patient for continued study participation.
- Over-the-counter (OTC) 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.

Patients currently on chronic erythropoietin support for anemia may continue to receive erythropoietin; however, initiation of new erythropoietin therapy is not allowed during the first cycle. Initiation of prophylactic growth factors will be allowed after the first cycle. Note: Erythropoietin has not been approved for the treatment of anemia associated with cancer chemotherapy in Japan.

9.7 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 on the eCRF.

9.8 Precautions and Restrictions

9.8.1 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 group and male patients should use effective methods of contraception through 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 2 effective methods of contraception from the time of signing of the informed consent form 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 subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception.)

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

- 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 subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods for the female partner] and withdrawal are not acceptable methods of contraception.) AND
- Agree not to donate sperm during this study and for 120 days after receiving their last dose of study drug.

Contraception methods meeting criteria defined above are provided below. If male condoms were used as a barrier method by male subjects, his partner must use intrauterine devices (Copper T, or Progesteron T) or hormonal contraceptives (combined pills) instead of spermicide.

Table 9.c Contraceptive Methods

Barrier Methods (Each Time the Subject has Intercourse):	Intrauterine Devices:	Hormonal Contraceptives
• Male condom PLUS spermicide* • Cap* (plus spermicidal cream* or jelly*) PLUS male condom and spermicide* • Diaphragm (plus spermicidal cream* or jelly*) PLUS male condom and spermicide*	• Copper T PLUS condom or spermicide* • Progesterone T PLUS condom or spermicide*	• Implants* • Hormone injections* • Combined pills • Minipills* • Patches* • Vaginal ring* PLUS male condom and spermicide*

* Spermicide, cap, spermicidal cream, jelly, implant, hormone injections, minipills, patches, and vaginal ring are not used in Japan.

9.8.2 Females Who are Lactating or Breastfeeding

Female patients who are lactating must refrain from breastfeeding from the start of study participation (Section 8.2, exclusion criterion #4) through 30 days after the last dose of study drug.

9.8.3 Patients with Prior Exposure to Hepatitis B or Hepatitis C

Patients who have detectable hepatitis B or C viral loads are excluded from study participation (see Section 8.2, exclusion criterion #13). 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 re-activation every 2 months. Patients who develop detectable HBV or HCV in their blood 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. Refer to the Japan Society of Hepatology (JSH) Guidelines for the management of Hepatitis B Virus infection [23].

9.8.4 Photosensitivity

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. 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).

9.9 Blinding and Unblinding

Not applicable. This is an open-label study.

9.10 Description of Investigational Agents

TAK-931 will be supplied as capsules for oral administration. TAK-931 is available in 3 dose strengths of 10, 25, and 80 mg—each containing 10, 25, and 80 mg of TAK-931, respectively. CC CCI [redacted]

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 color, size 4 capsule.
- 80-mg TAK-931 capsules: white, opaque color, size 3 capsule.

Refer to the TAK-931 IB for full details.

9.11 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.

9.12 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 (HDPE) bottles with polypropylene, child-resistant caps, and an induction seal.

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

9.13 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. All temperature excursions 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 pick-up 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.

9.14 Other Protocol-Specified Materials

Not applicable.

10.0 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.

10.1 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.

10.2 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).

10.3 Treatment Group Assignments

Patient assignment to a specific schedule will be decided jointly by the investigator and sponsor with the aim of maximizing enrollment efficiency in the study. The dose escalation scheme is outlined in Section 9.3.

10.4 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 Table Ga through Table Ge,f (Appendix A). All EOT evaluations should occur 30 to 40 days after the last dose of study drug. Patients enrolled in the safety expansion cohorts will be managed with modified Schedule of Events in Cycle 1 as specified in Appendix A; hospitalization is not required for these cohorts.

10.4.1 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.

10.4.2 Patient Demographics

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

10.4.3 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 for it. In addition, concomitant medications will be recorded as specified in Section 10.4.8.

10.4.4 Physical Examination

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

10.4.5 Patient Height and Weight

Height will be measured only 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.

10.4.6 Vital Signs

Standard vital signs should be obtained at least once during a visit specified in the Schedule of Events and will include temperature (may be oral or body temperature), blood pressure, and heart rate/pulse. Orthostatic vital sign measurements will include blood pressure and heart rate/pulse while supine (after 5 minutes in this position) and standing (after 2 minutes in this position) measurements at the visits specified in the Schedule of Events.

10.4.7 Pregnancy Test

A serum pregnancy test will be performed for women of childbearing potential at screening and within 4 days prior to 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, FSH >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 C1D1 serum pregnancy results will not be available before dosing, a urine pregnancy test may be performed.

10.4.8 Concomitant Medications and Procedures

Medications used by the patient and therapeutic procedures completed by the patient will be recorded in the eCRF from the first dose of study drug through 30 days after the last dose of study drug or before initiation of new anticancer therapy (whichever comes first). See Section 9.6 and

Section 9.7 for a list of medications and therapies that are prohibited and/or allowed during the study.

10.4.9 Adverse Events

Monitoring of TEAEs, serious and nonserious, will be conducted throughout the study as specified in the Schedule of Events. Refer to Section 11.0 for details regarding definitions, documentation, and reporting of pretreatment events (PTEs), TEAEs, and SAEs.

10.4.10 Enrollment

Enrollment is defined as when the written informed consent has been obtained and the subject's eligibility has been confirmed per the inclusion and exclusion criteria. Procedures for completion of the enrollment information are described in the Study Manual.

10.4.11 Electrocardiogram

Continuous cardiac rhythm monitoring and standard 12-lead ECGs will be administered at the time points specified in the Schedule of Events. Patients will be in the supine position for at least 5 minutes before the ECG is to be performed. Additional ECGs may be obtained as clinically indicated.

10.4.12 Eastern Cooperative Oncology Group Performance Status

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

10.4.13 Echocardiogram or Multiple Gated Acquisition Scan

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

10.4.14 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 10.a and urine samples for analysis of the parameters shown in Table 10.b will be obtained as specified in the Schedule of Events.

Table 10.a Clinical Chemistry and Hematology Tests

Hematology	Serum Chemistry	
Hematocrit	Albumin	Chloride
Hemoglobin	Alkaline phosphatase	γ-Glutamyl transferase
Leukocytes with differential	Alanine aminotransferase	Glucose
Absolute neutrophil count	Aspartate aminotransferase	Lactate dehydrogenase
Platelet (count)	Bilirubin (total)	Magnesium
	Blood urea nitrogen	Phosphate
	Calcium	Potassium
	Bicarbonate (HCO_3^-)	Sodium
	Creatinine	Urate

Table 10.b Clinical Urinalysis Tests

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

Fecal immunochemical testing for detecting blood in the stool will be obtained at screening and prior to C2D1 and C3D1. If a patient has a positive FIT test at screening, further collection is not required. If a patient has a negative FIT test at screening but a positive FIT test during study treatment, a consultation is recommended with a gastroenterologist to evaluate the patient for subacute gastro-intestinal injury as the source of the detected occult blood.

Blood samples for analysis of cardiac enzymes (ie, troponin I or T, BNP, or NT-proBNP) will be obtained as specified in the Schedule of Events.

HBV and HCV screening should be conducted during the screening period if valid results from prior testing that have been confirmed by the investigator are not available. HBV screening will include testing for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb) and hepatitis B core antibody (HBcAb). For patients who test positive for HBsAg, HBsAb or HBcAb, HBV DNA will also be assessed at screening. HCV screening will include testing for the anti-HCV antibody (HCVAb). Patients who test positive for HCVAb will also be tested for HCV RNA at screening.

Note that patients who have positive HBcAb or HBsAb can be enrolled but must have undetectable hepatitis B viral load. Patients who have a positive HCVAb can be enrolled but must have undetectable hepatitis C viral load.

Patients who are HBcAb positive or HCVAb positive with a negative viral load at screening who are enrolled in this study will be monitored by assessment of viral load (DNA titers for HBV, RNA titers for HCV) every 2 months.

HIV screening should be conducted during the screening period if valid results from prior testing that have been confirmed by the investigator are not available.

10.4.15 Skin Punch Biopsies

pMCM2 will be detected semiquantitatively by IHC of histologic sections of formalin-fixed, paraffin-embedded skin biopsies. Skin punch biopsies (2-4 mm) will be obtained for all patients either during screening or predose on C1D1, and for patients in Schedule A to D postdose on any drug dosing day after 3 consecutive dosing days (eg, Day 4 or after) in Cycle 1. A postdose skin biopsy will be obtained on Day 9 in Schedule E and on Day 8 in Schedule F. Other time points for biopsy collection outside Cycle 1 can be performed if explicitly approved by the sponsor. It is strongly recommended that postdose skin biopsies are collected 4-9 hours after study drug administration [redacted] Refer to Section 10.4.21 for sample retention.

[redacted]

[redacted]

[redacted]

[redacted]

10.4.18 Disease Assessment

Patients will undergo a CT scan (with contrast) or MRI, as appropriate, to monitor and assess disease status. Investigators will assess patients' disease status using RECIST guidelines (version 1.1), where measurable disease is defined as ≥1 extraosseous lesion that can be accurately measured in at least 1 dimension [24]. Specific disease sites that cannot be adequately imaged by CT may be documented by MRI. Anatomical measurements will be collected at baseline and at each subsequent evaluation for each target lesion using an imaging modality consistent with that used at screening. The same method (CT with contrast, MRI, or bone scan) must be consistently used on a patient throughout the study. Bone scans may be performed on patients with bone metastases rather than CT or MRI.

Objective assessments will be performed at each time point as described in the Schedule of Events. When possible, the same qualified physician will interpret results to reduce variability.

Radiographic images will be maintained at the site, and test results and physicians' findings will be filed in patient source documents. The sponsor may request electronic images for those patients who demonstrate a response.

10.4.19 Pharmacokinetic Measurements

Serial blood and urine specimens for PK analysis of TAK-931 will be collected at the time points specified in Table Ga through Table Ge,f (Appendix A). 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 on the eCRF.

If a skin biopsy [CCI redacted] is taken on a non-PK sampling day, sparse PK plasma samples should be collected at predose, at 1 to 3 hours postdose, and at 4 to 9 hours postdose on the day of biopsy. The exact dosing, biopsy, and PK sampling date and time will be recorded. It is preferable but not necessary to synchronize [CCI redacted], skin biopsy, and PK sampling.

For the timed 12-hour urine collection on C1D1, 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. After the administration of the first dose of TAK-931, all subsequent voided urine through the point of collection of the 12-hour PK sample on Day 1 will be collected and will constitute the 0- to 12-hour postdose urine specimen collection. At the end of the 12-hour period, when the 12-hour PK plasma specimen is obtained, the patient must void completely so that all the urine during the timed period is collected. The volume of the urine collected during the 12-hour period on C1D1 will be recorded, and a 50-mL aliquot of collected urine will be shipped for bioanalysis. 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 metabolites.

[CCI redacted]

[CCI redacted]

CCI [redacted]

10.4.21 Sample Retention

CCI [redacted] skin tissues CCI [redacted] for DNA measurements will be stored at BioStorage Technologies (Indiana USA) up to 15 years after the date of study completion as identified in the clinical study report (CSR) and will be destroyed by a third-party vendor identified by BioStorage Technologies per company standard operating procedures (SOP). CCI [redacted] skin tissues will be stored at ambient temperature CCI [redacted]. If patients withdraw consent, the samples will be discarded following the local procedure (ie, where the sample resides at the time of withdrawal and the investigator needs to inform the sponsor patient's intent to withdraw immediately). 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.

10.5 Completion of Treatment

Patients will be considered to have completed study treatment if they discontinue study drug for any of the reasons outlined in Section 10.7.

10.6 Completion of Study

Patients will be considered to have completed the study if they withdraw from the study for any of the reasons outlined in Section 10.8.

10.7 Discontinuation of Treatment With Study Drug and Patient Replacement

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

- Adverse event.
- Protocol deviation.
- Complete response.
- Progressive disease.
- Withdrawal by subject.
- Lost to follow-up.
- Initiation of another systemic anticancer treatment.
- Study terminated by sponsor.
- Other.

Once study drug has been discontinued, all study procedures outlined for the EOT visit will be completed as specified in the Schedule of Events. The primary reason for study drug discontinuation will be recorded on the eCRF.

Patients who receive <75% of their assigned TAK-931 doses (ie, <11 QD doses or <21 BID doses for Schedules A and B; <6 QD doses or <11 BID doses for Schedule C; and <16 QD doses or <32 BID doses for Schedule D; <5 QD doses or <9 BID doses for Schedule E; <2 QD doses or <5 BID doses for Schedule F) in Cycle 1 for reasons other than study drug-related AEs will be replaced.

10.8 Withdrawal of Patients From Study

A patient may be withdrawn from the study for any of the following reasons:

- Lost to follow-up.
- Complete response.
- Progressive disease.
- Withdrawal by subject.
- Death.
- Initiation of another systemic anticancer treatment.
- Study terminated by sponsor.
- Other.

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.

10.9 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.

During the Cycle 1 inpatient dosing period, study drug will be administered under supervision of site personnel. From Cycle 2 onwards, patients will receive a sufficient quantity of study drug. Patients will be given a diary to record study drug dosing. The study center staff will check the patient's drug diary versus the patient's supply of TAK-931 capsules to assess compliance.

Tests and procedures should be performed on schedule; however, unless otherwise specified, occasional changes are allowable within a 3-day window for holidays, vacations, and other administrative reasons. If extenuating circumstances prevent a patient from beginning treatment or completing a planned procedure or assessment within 3 days of the scheduled time, the patient may continue the study only with the written permission of the medical monitor.

10.10 Post-treatment Follow-up Assessments (Progression-Free Survival)

Patients who stop treatment for any reason other than PD will continue to have PFS follow-up visits. The PFS follow-up visit should be conducted at the site every 12 weeks from the EOT visit until the occurrence of PD, the start of subsequent antineoplastic therapy, or until 6 months after the patient discontinued treatment, whichever occurs first.

NOTE: During PFS follow-up, study drug-related SAEs must be reported to the sponsor's Department of Pharmacovigilance or designee. This includes deaths that the investigator considers related to study drug and that occur during the post-treatment follow-up period. Refer to Section 11.0 for details regarding definitions, documentation, and reporting of SAEs.

11.0 ADVERSE EVENTS

11.1 Definitions

11.1.1 Pretreatment Event Definition

A pretreatment event is any untoward medical occurrence in a patient or subject who has signed informed consent to participate in a study but before administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

11.1.2 Adverse Event Definition

AE means any untoward medical occurrence in a patient or subject 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.

11.1.3 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 11.2 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 white blood cell 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.

11.2 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 11.3 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 and serious pretreatment events (as defined in Section 11.1) must be reported (see Section 11.3 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 or serious pretreatment event may be requested by Takeda. SAE report information must be consistent with the data provided on the eCRF.

SAE Reporting Contact Information

Bell Medical Solutions, Inc

PPD

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 intensity of the event and the relationship of the event to study drug administration. For serious pretreatment events, the investigator must determine both the intensity of the event and the relationship of the event to study procedures.

Intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, Version 4.03, effective date 14 June 2010 [20]. The criteria are provided in the Study Manual.

Relationship to study drug administration will be determined by the investigator responding "yes" or "no" to this question: Is there a reasonable possibility that the AE is associated with the study drug?

11.3 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 first dose of study drug 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.
- Serious pretreatment events will be reported to the Takeda Global Pharmacovigilance department or designee from the time of the signing of the informed consent form (ICF) up to first dose of study drug, but will not be recorded in the eCRF.
- Related and unrelated SAEs will be reported to the Takeda Global Pharmacovigilance department or designee from the first dose of study drug 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)

11.4 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 the European Medicines Agency (EMA), investigators and IRBs or the head of the study site, as applicable. 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 report 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 where these 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.

11.5 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 faxing a completed Pregnancy Form to the Takeda Global Pharmacovigilance department or designee (see Section 11.2). 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 faxing a completed Pregnancy Form to the Takeda Global Pharmacovigilance department or designee (see Section 11.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

11.6 Procedures for Reporting Product Complaints

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 email addresses below:

Call Center	Phone Number	E-mail	Fax	Hours
Dohmen Life Science Services	PPD PPD	PPD	PPD	Mon-Fri 9 AM to 7 PM ET

Abbreviation: ET, Eastern standard time.

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and sent to Bell Medical Solutions, Inc (refer to Section 11.2).

12.0 STUDY-SPECIFIC COMMITTEES

No steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study.

13.0 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, PTEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization (WHO) Drug Dictionary.

13.1 Electronic Case Report Forms

Completed eCRFs are required for each subject who was administered study drug.

The sponsor or its designee will supply investigative sites with access to eCRFs and will make arrangements to 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 subject'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.

13.2 Record Retention

The investigator and the head of the institution agree to keep the records stipulated in Section 13.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), 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 subject's chart to ensure long term

legibility. Furthermore, International Conference on Harmonisation (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 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/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.

14.0 STATISTICAL METHODS

14.1 Statistical and Analytical Plans

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

14.1.1 Populations for Analysis

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 pharmacokinetic population is defined as all patients for whom there are sufficient dosing and TAK-931 concentration-time data to reliably estimate the PK parameter(s). This population will be used for analyses of PK parameters.
- Pharmacodynamics population: The pharmacodynamics population is defined as all patients who receive at least the first dose of TAK-931, have a baseline skin punch [CCI] biopsy sample, and have at least 1 additional postbaseline skin punch [CCI] biopsy sample. The skin [CCI] biopsies must contain detectable basal pMCM2 signals to permit an estimate of pMCM2 (Ser40) levels.
- DLT-evaluable population: The DLT-evaluable population is defined as all patients who receive at least 75% of their planned TAK-931 doses for their first cycle of treatment (unless interrupted by study drug-related AEs) and who have sufficient follow-up data to allow the investigators and sponsor to determine whether DLT occurred. Patients who receive <75% of doses of TAK-931 in Cycle 1 for reasons other than study drug-related AEs are not evaluable for DLT and will be replaced. Patients will be analyzed by the dose level to which they were originally assigned, including those who receive subsequent treatment at a lower or higher dose level.
- Response-evaluable population: The response-evaluable population is defined as patients who receive at least 1 dose of study drug, have measurable disease at baseline, and at least 1 post-baseline response assessment. The response-evaluable population will be used for the analysis of ORR and DOR.

14.1.2 Procedures for Handling Missing, Unused, and Spurious Data

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.

14.1.3 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 dose cohort.

14.1.4 Pharmacokinetic Analysis

PK parameters will be estimated using non-compartmental methods with WinNonlin® Phoenix™ Version 6.2 or higher (Pharsight Corp., Mountain View, CA). The plasma PK parameters will be estimated from the concentration-time profiles for all PK population patients.

The plasma and urine PK of TAK-931 after the first dose on C1D1 and after multiple doses on C1D7 (Schedules B and C), C1D8 (Schedules A and D), or C1D7, C1D8 or C1D9 (Schedules E and F) will be determined based on the PK parameters below, as permitted by data.

- C_{max}.
- t_{max}.
- AUC_{24} (or AUC_{12} for BID dosing) and AUC_{last} after the first dose on C1D1 and after administration of multiple doses on C1D7, C1D8, or C1D9.
- CL/F, $R_{ac(AUC)}$ (for C1D7, C1D8 or C1D9 only).
- Amount of TAK-931 excreted over 12 hours Ae_{12} (C1D1 only), CLr (C1D1 only).

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 also tabulated using summary statistics by dose cohort. Individual and mean plasma concentration-time profiles will be plotted by dose cohort.

14.1.5 Safety Analysis

The incidence of DLT will be tabulated for each dose cohort. 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 for each dose cohort. 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 and up through approximately 30 days after the last dose of study drug, and severity, as well as by changes from baseline in the patient's vital signs, weight, ECG, and clinical laboratory results using the Safety population. Exposure to study drug will be summarized and reasons for discontinuation will be tabulated. ECHO, MUGA, and additional assessments such as measurement of cardiac enzymes in serum that are predictive of acute injury (eg, troponin I or T) and chronic or progressive failure (eg, B-type natriuretic peptide [BNP] or N-terminal pro-brain natriuretic peptide [NT-proBNP]) may also be summarized. Safety will be summarized by dose level within each dose cohort.

TEAEs will be tabulated according to the MedDRA by system organ class, high level terms, and preferred terms and will include the following categories:

- TEAEs.
- Drug-related TEAEs.
- Grade ≥3 TEAEs.
- Grade ≥3 drug-related TEAEs.
- The most commonly reported 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) and other safety parameters as deemed appropriate will be presented for all scheduled measurements over time. Mean laboratory values over time will be plotted for key laboratory parameters.

Shift tables for laboratory parameters and other safety parameters as deemed appropriate will be generated based on changes in NCI CTCAE grade from baseline to the worst post-baseline value. Graphical displays of key safety parameters, such as scatter plots of baseline versus worst post-baseline 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 QTc with Fridericia correction, and PR), 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.

14.1.6 Efficacy Analysis

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

The estimate of the ORR will be presented with 2-sided 95% exact binomial confidence intervals for each dose cohort. ORR will be analyzed using the response-evaluable population.

PFS is defined as the time from the date of first dose to the date of first documentation of progressive disease or death due to any cause, whichever occurs first. The Kaplan-Meier survival curves, 25th, 50th (median), and 75th percentiles (if estimable), along with their 2-sided 95%

confidence intervals will be provided for each dose cohort. PFS will be analyzed using safety population.

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

14.1.7 Pharmacodynamic Analysis

The change from baseline of pMCM2 (Ser40) levels in skin will be descriptively summarized by dose cohort. CCI

CCI

CCI

14.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

14.3 Determination of Sample Size

It is anticipated that approximately 100 patients will be enrolled in this study including up to 6 dosing schedules and expansion cohort. Once the MTD is determined, a safety expansion cohort of up to 16 patients (including patients treated at the same dose during dose escalation) may be initiated for all or some of the schedules.

An adaptive approach with BLRM will be used for dose escalation in Dosing Schedules A, B, and C. BLRM implements dose escalation with overdose control principle [21,22] that informs dose escalation decisions and MTD estimation, along with clinical safety data evaluation and PK guidance.

The 2-parameter model used is as follows:

$$\ln\left(\frac{\pi_i}{1-\pi_i}\right) = \ln(\alpha) + \beta \ln\left(\frac{\text{dose}_i}{\text{dose}_{ref}}\right), \alpha > 0, \beta > 0$$

where π_i is the DLT rate for $dose_i$ and $dose_{ref}$ is a reference dose. A quantile-based, non-informative, bivariate normal prior will be used for ln(α) and ln(β). This prior will be assigned based on prestudy estimates of the DLT rate at each dose level, as described in Neuenschwander, et al [21].

The model will be updated after each group of 3 patients enrolled in the current dose level. For each dose level, the posterior probability of having DLT rates that fall into the following intervals will be estimated:

- [0, 0.16): under-dosing.
- [0.16, 0.33): target toxicity.
- [0.33, 1.00]: excessive toxicity.

The next recommended dose will be selected as described in Section 9.3.

Dosing Schedule A:

A group of 3 patients will be enrolled in a TAK-931 dose cohort each time based on BLRM, with safety data evaluation and PK guidance. Each subject will participate in only 1 dose cohort. An example of possible dose escalation with accelerated escalation and modified Fibonacci escalation steps is shown in Table 14.a. The actual dose levels may be adjusted based on the observed safety profile. The simulation to evaluate the sample size is performed based on possible dose level range (30, 50, 60, 80, 100, 120, 150, 200, 240, 300, 400, 480, 500, 600, 800, 1000, 1200, 1600, and 2000 mg) from Table 14.a. The simulation considers the escalation transition to modified Fibonacci escalation steps. The simulation is performed based on 6 scenarios of the assumed true DLT rates at dose levels (30, 50, 60, 80, 100, 120, 150, 200, 240, 300, 400, 480, 500, 600, 800, 1000, 1200, 1600, and 2000 mg), representing various distributions of toxicity across dose levels, detailed as shown in Table 14.b. The curve of the dose-DLT relationship becomes steeper and MTD is reached earlier from Scenario 1 to Scenario 6. It is assumed that the probability of having accelerated escalation phase transition to modified Fibonacci escalation steps is 20% more than the probability of having 1 DLT event. The quantile-based, noninformative, bivariate normal prior of ln(α) and ln(β) is determined based on prestudy estimates of DLT rate (0.01, 0.02, 0.03, 0.04, 0.05, 0.08, 0.11, 0.14, 0.19, 0.21, 0.25, 0.29, 0.33, 0.40, 0.50, 0.60, 0.70, 0.80, and 0.90) at various dose levels (30, 50, 60, 80, 100, 120, 150, 200, 240, 300, 400, 480, 500, 600, 800, 1000, 1200, 1600, and 2000 mg). Table 14.c shows the operating characteristic results.

In Scenario 1, the probability of recommending a target dose is above 70% when the true DLT rate increases slowly with dose, and the target true DLT occurs at the highest dose level (2000 mg). In Scenario 1, the average number of patients required is approximately 30 with fewer than 2 DLTs expected on average. The true DLT rates in Scenarios 2 and 3 increase faster than Scenario 1, and both have less chance of successfully recommending target dose levels, since the dose level just below the lowest target dose level (1200 and 300 mg, respectively) has a DLT rate very close to 16%. The chance of recommending a toxic dose is very low in both scenarios (2.7% and 0.9%, respectively). The average number of patients required is approximately 28 and 22, respectively, with fewer than 3 DLTs expected on average. In Scenario 4, with further faster increase of DLT

rate over doses, there is a 79% probability of recommending target dose levels, whereas the probability of recommending toxic doses is low (4.7%). The average number of patients required is approximately 20 with fewer than 4 DLTs expected on average. In Scenario 5, when the starting dose is the only target dose, and the second dose level has a DLT rate close to 33%, there is 29% chance of claiming the starting dose is MTD, and approximately 45% chance of claiming all doses are toxic. Most of the patients (around 70%) do not receive doses above the MTD dose. The average number of patients required is approximately 11 with fewer than 4 DLTs expected on average. In Scenario 6 when all doses are toxic, there is a 96.5% chance of successfully claiming all doses are toxic. The average number of patients required is approximately 5 and fewer than 3 DLTs are expected on average.

The accuracy of the BLRM recommendation relies on the true DLT rate, thus the clinical PK guidance and safety evaluation are combined to support the dose escalation.

From a simulation analysis, approximately 33 patients may be needed for up to 9 dose escalation cohorts in Dosing Schedule A. The candidate dose levels may be adjusted according to accumulating knowledge of observed safety profile in the study. The simulation provides the maximum sample size evaluated using different dosing scenarios. As an example, a hypothetical dose escalation step based on Scenario 4 of true DLT rate is shown in Table 14.d to illustrate how BLRM guides dose escalation.

Table 14.a An Example of Possible Dose Escalation With Accelerated and Modified Fibonacci Escalation

	Dose Level	Daily Dose (BID Dose), mg	Alternative Modified Fibonacci Escalation [a]			
Accelerated Escalation	1	30	50	80 (40) [c]	100 (50)	120 (60)
	2	60	100 (50) [b]	150 (75)	*200 (100)*	*240 (120)*
	3	120 (60) [b]	*200 (100)*	*300 (150)*	*400 (200)*	*500 (250)*
	4	*240 (120)*	*400 (200)*	*600 (300)*	*800 (400)*	*1000 (500)*
Modified Fibonacci Escalation	5	*480 (240)*	—	—	—	—
	6	*800 (400)*	—	—	—	—
	7	*1200 (600)*	—	—	—	—
	8	*1600 (800)*	—	—	—	—
	9	*2000 (1000)* [c]	—	—	—	—

Abbreviation: BID, twice daily.
Assumes an initial C_{max} of 40 ng/mL after a single 30 mg dose and linear increase in C_{max} with rising doses.
Accelerated escalation: 100%, Modified Fibonacci escalation: ~67%, ~50%, ~33%, and ~20% to 25%.
Italics indicates that the predicted C_{max} for a single dose at the dose level will likely be >IC_{90} for pMCM2 inhibition.
[a] Alternative standard escalation is the transition to standard escalation during the accelerated escalation phase before Cohort 5 has been enrolled.
[b] A BID schedule will be instituted in Cohort 3 if the pharmacokinetic profile supports this schedule.
[c] Not applicable if the mean C_{max} in the prior dose cohort is >800 ng/mL.

Table 14.b Dose Escalation Simulation Study of the Probability of Dose-Limiting Toxicity

	True P(DLT) at each scenario					
Dose Level	**1**	**2**	**3**	**4**	**5**	**6**
30 mg [a]	0.000	0.001	0.029	0.046	0.275	0.586
50 mg	0.000	0.001	0.048	0.086	0.363	0.621
60 mg	0.000	0.003	0.058	0.106	0.407	0.638
80 mg	0.000	0.004	0.071	0.134	0.448	0.656
100 mg	0.001	0.006	0.083	0.162	0.490	0.674
120 mg	0.001	0.007	0.096	0.189	0.532	0.692
150 mg	0.001	0.010	0.108	0.215	0.562	0.707
200 mg	0.002	0.014	0.129	0.259	0.613	0.731
240 mg	0.003	0.017	0.145	0.294	0.653	0.750
300 mg	0.004	0.021	0.159	0.322	0.679	0.764
400 mg	0.005	0.029	0.184	0.349	0.723	0.788
480 mg	0.007	0.034	0.203	0.404	0.759	0.807
500 mg	0.008	0.036	0.207	0.411	0.764	0.810
600 mg	0.011	0.045	0.228	0.443	0.792	0.826
800 mg	0.017	0.064	0.270	0.507	0.846	0.860
1000 mg	0.028	0.093	0.314	0.556	0.885	0.887
1200 mg	0.039	0.123	0.359	0.605	0.924	0.915
1600 mg	0.092	0.251	0.478	0.671	0.979	0.967
2000 mg	0.219	0.651	0.638	0.690	1.000	1.000

Abbreviation: P(DLT), probability of a DLT at each dose level.
[a] Starting dose.

Table 14.c Operating Characteristics for Bayesian Logistic Regression Modeling Dose Escalation Rule

	Probability of recommending a:			Average proportion of patients receiving a:			Average number of patients	
Scenario	Low Dose	Target Dose	High Dose	Low Dose	Target Dose	High Dose	Per Study	Experiencing DLT per Study
1	29.3%	70.7%	NA	84.6%	15.4%	NA	30.3	1.64
2	63.5%	33.7%	2.72%	86.0%	10.2%	3.80%	27.8	2.55
3 [a]	65.7%	33.2%	0.90%	85.0%	14.5%	0.51%	21.7	2.42
4 [b]	15.2%	79.0%	4.74%	45.2%	52.0%	2.83%	19.5	3.27
5 [c]	NA	29.2%	26.1%	NA	69.5%	30.5%	10.9	3.66
6 [d]	NA	NA	3.52%	NA	NA	100%	4.95	2.92

Abbreviations: DLT, dose-limiting toxicity; NA, not available.
Low Dose, true DLT rate is [0, 0.16); Target Dose, true DLT rate is [0.16, 0.33); High Dose, true DLT rate is [0.33, 1.00].
[a] Probability of 0.24% to claim all doses are toxic.
[b] Probability of 1.00% to claim all doses are toxic.
[c] Probability of 44.6% to claim all doses are toxic.
[d] Probability of 96.5% to claim all doses are toxic.

Table 14.d Hypothetical Dose Escalation Step

Step	Dose (mg)	No. of Patients	No. of DLTs	Next Recommended Dose (mg)
1	30	3	0	60
2	30	3	0	
	60	3	1	100
3	30	3	0	
	60	3	1	
	100	3	0	150
4	30	3	0	
	60	3	1	
	100	3	0	
	150	3	2	100
5	30	3	0	
	60	3	1	
	100	6	2	
	150	3	2	60
6	30	3	0	
	60	6	1	
	100	6	2	
	150	3	2	60 mg is claimed as the MTD

Abbreviation: MTD, maximum tolerated dose.

Based on the clinical safety, PK and pharmacodynamic information available as of 13 November 2016, the sample size for Dosing Schedule A is estimated to be approximately 25 patients including the 4 dose escalation cohorts and safety expansion cohort.

Dosing Schedules B and C:

Similarly, in Dosing Schedules B and C, the sample size is evaluated in the simulation using BLRM for up to 4 dose cohorts in Schedule B (60, 80, 100, and 120 mg) and up to 3 dose cohorts in Schedule C (100, 120, and 150 mg). The candidate dose levels may be adjusted according to accumulating knowledge of observed safety profile in the study. It is anticipated that approximately 18 patients will be enrolled in Dosing Schedule B and approximately 15 patients will be enrolled in Dosing Schedule C for dose escalation cohorts.

Dosing Schedule D:

Approximately 25 patients will be enrolled for Dosing Schedule D to test lower TAK-931 doses. The starting dose is 20 mg. Depending on clinical, PK, and pharmacodynamic information, it may be possible to explore a 10-mg dose even if the 20-mg dose is found to be safe. Also, if the 20-mg initial dose level is tolerable, it may be possible to escalate to 30 mg.

Dosing Schedules E and F:

In Dosing Schedules E and F, the sample size is evaluated in the simulation using BLRM for up to 4 dose cohorts in Schedule E (100, 120, 150, and 200 mg) and up to 3 dose cohorts in Schedule F (200, 240, and 300 mg). The candidate dose levels may be adjusted according to accumulating knowledge of the observed safety profile in the study. It is anticipated that approximately 16 patients will be enrolled in Dosing Schedule E and approximately 12 patients will be enrolled in Dosing Schedule F for dose escalation cohorts.

15.0 QUALITY CONTROL AND QUALITY ASSURANCE

15.1 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 (if blinding is not jeopardized), including but not limited to the investigator's binder, study medication, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the informed consent forms), 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.

15.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. 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 subject'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 subject, 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 investigator can deviate and change from the protocol for any medically unavoidable reason, for example, to eliminate an immediate hazard to study subjects, 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 appropriate) 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.

15.3 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 United States Food and Drug Administration [FDA], the United Kingdom [UK] Medicines and Healthcare Products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). 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 15.1.

16.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) 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.

16.1 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, subject 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 subject informed consent 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, informed consent form) reviewed; and state the approval date. The sponsor will notify the 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 informed consent form, recruitment materials intended for viewing by subjects, 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.

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

16.2 Subject Information, Informed Consent, and Subject 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 informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form and the subject 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 informed consent form 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 informed consent form and if applicable, the subject authorization form. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor prior to use.

The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. 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 subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject'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 subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the informed consent form and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and prior to the subject entering into the study. The subject or the subject'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 informed consent form and subject authorization (if applicable) at the time of consent and prior to subject entering 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 informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects or the relevant subject'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 subject's medical record, and the subject should receive a copy of the revised informed consent form.

16.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject'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, FDA, Medicines and Healthcare Products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject'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 subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 16.2).

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

16.4 Publication, Disclosure, and Clinical Trial Registration Policy

16.4.1 Publication and Disclosure

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.

16.4.2 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 before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (as applicable), country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating trial sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once subjects 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 subject 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.

16.4.3 Clinical Trial Results Disclosure

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

16.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject 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 subjects. Refer to the Clinical Study Site Agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

17.0 REFERENCES

1. Labib K. How do Cdc7 and cyclin-dependent kinases trigger the initiation of chromosome replication in eukaryotic cells? Genes & Development 2010;24(12):1208-19.
2. Masai H, Matsui E, You Z, Ishimi Y, Tamai K, Arai K. Human Cdc7-related kinase complex. In vitro phosphorylation of MCM by concerted actions of Cdks and Cdc7 and that of a criticial threonine residue of Cdc7 bY Cdks. Journal of Biological Chemistry 2000;275(37):29042-52.
3. Bousset K, Diffley JF. The Cdc7 protein kinase is required for origin firing during S phase. Genes Dev 1998;12(4):480-90.
4. Furuya K, Miyabe I, Tsutsui Y, Paderi F, Kakusho N, Masai H, et al. DDK phosphorylates checkpoint clamp component Rad9 and promotes its release from damaged chromatin. Molecular Cell 2010;40(4):606-18.
5. Swords R, Mahalingam D, O'Dwyer M, Santocanale C, Kelly K, Carew J, et al. Cdc7 kinase - a new target for drug development. European Journal of Cancer 2010;46(1):33-40.
6. Montagnoli A, Moll J, Colotta F. Targeting cell division cycle 7 kinase: a new approach for cancer therapy. Clinical Cancer Research 2010;16(18):4503-8.
7. Yamada M, Watanabe K, Mistrik M, Vesela E, Protivankova I, Mailand N, et al. ATR-Chk1-APC/CCdh1-dependent stabilization of Cdc7-ASK (Dbf4) kinase is required for DNA lesion bypass under replication stress. Genes & Development 2013;27(22):2459-72.
8. Hou Y, Wang HQ, Ba Y. Effects of CDC7 gene silencing and Rituximab on apoptosis in diffuse large B cell lymphoma cells. Journal of Cancer Research & Clinical Oncology 2012;138(12):2027-34.
9. Cheng AN, Jiang SS, Fan CC, Lo YK, Kuo CY, Chen CH, et al. Increased Cdc7 expression is a marker of oral squamous cell carcinoma and overexpression of Cdc7 contributes to the resistance to DNA-damaging agents. Cancer Letters 2013;337(2):218-25.
10. Bonte D, Lindvall C, Liu H, Dykema K, Furge K, Weinreich M. Cdc7-Dbf4 kinase overexpression in multiple cancers and tumor cell lines is correlated with p53 inactivation. Neoplasia (New York) 2008;10(9):920-31.
11. Kulkarni AA, Kingsbury SR, Tudzarova S, Hong HK, Loddo M, Rashid M, et al. Cdc7 kinase is a predictor of survival and a novel therapeutic target in epithelial ovarian carcinoma. Clinical Cancer Research 2009;15(7):2417-25.
12. Chen HJ, Zhu Z, Wang XL, Feng QL, Wu Q, Xu ZP, et al. Expression of huCdc7 in colorectal cancer. World Journal of Gastroenterology 2013;19(20):3130-3.
13. Malumbres M. Physiological relevance of cell cycle kinases. Physiological Reviews 2011;91(3):973-1007.

14. Sasi NK, Tiwari K, Soon FF, Bonte D, Wang T, Melcher K, et al. The potent Cdc7-Dbf4 (DDK) kinase inhibitor XL413 has limited activity in many cancer cell lines and discovery of potential new DDK inhibitor scaffolds. PLoS One 2014;9(11):e113300.
15. Yamada M, Masai H, Bartek J. Regulation and roles of Cdc7 kinase under replication stress. Cell Cycle 2014;13(12):1859-66.
16. Kastan MB, Bartek J. Cell-cycle checkpoints and cancer. Nature 2004;432(7015):316-23.
17. Sawa M, Masai H. Drug design with Cdc7 kinase: a potential novel cancer therapy target. Drug Design, Development and Therapy 2008;2:255–64.
18. Simons CC, Hughes LA, Smits KM, Khalid-de Bakker CA, de Bruine AP, Carvalho B, et al. A novel classification of colorectal tumors based on microsatellite instability, the CpG island methylator phenotype and chromosomal instability: implications for prognosis. Ann Oncol 2013;24(8):2048-56.
19. Vilar E, Gruber SB. Microsatellite instability in colorectal cancer-the stable evidence. Nat Rev Clin Oncol 2010;7(3):153-62.
20. Common Terminology Criteria for Adverse Events (CTCAE). National Cancer Institute, National Institutes of Health, U.S. Department of Health and Human Services Series v4.03. June 14, 2010. Publication No. 09-5410.
21. Neuenschwander B, Branson M, Gsponer T. Critical aspects of the Bayesian approach to phase I cancer trials. Statistics in Medicine 2008;27(13):2420-39.
22. Babb J, Rogatko A, Zacks S. Cancer phase I clinical trials: efficient dose escalation with overdose control. Statistics in Medicine 1998;17(10):1103-20.
23. JSH. JSH Guidelines for the Management of Hepatitis B Virus Infection. Hepatology Research 44(Suppl. 1):1-58. doi:10.1111/hepr.12269.
24. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47.
25. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. American Journal of Clinical Oncology 1982;5(6):649-55.
26. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41.
27. The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9 ed. Boston, MA: Little, Brown & Co; 1994.

Appendix A Schedule of Events

Table Aa Schedule of Events for Treatment Cycle 1 (Dosing Schedule A) (14 days on, 7 days off; 21-Day Cycle)

		Day																				
	Screening [a]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Informed consent	X																					
Inclusion/exclusion criteria	X																					
HBV, HCV, and HIV testing	X																					
Demographics	X																					
Medical history [b]	X	X																				
Physical examination [b,s]	X	X							X							X						
Height	X																					
Weight		X																				
Vital signs [c,s]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)
ECOG performance status	X																					
12-Lead ECG [d,e,s]	X	X [e]							X [e]						X [e]							
Continuous heart rhythm monitor [f,s]		X	X	X																		
ECHO/MUGA	X																					
Disease assessment [g]	X																					
Monitoring of concomitant medications and procedures		Recorded from first dose of study drug through up to 30 days after the last dose of study drug or before initiation of new anticancer therapy (whichever comes first).																				
Adverse event reporting		Recorded from first dose of study drug through up to 30 days after the last dose of study drug or before initiation of new anticancer therapy (whichever comes first).																				
	Serious adverse events [h] 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 anticancer therapy (whichever comes first).																					
TAK-931 administration [i]		X	X	X	X	X	X	X	X	X	X	X	X	X	X							

Footnotes are on last table page.

Table Aa Schedule of Events for Treatment Cycle 1 (Dosing Schedule A) (14 days on, 7 days off; 21-Day Cycle) (continued)

	Screening [a]	Day																				
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Samples/Laboratory Assessments																						
Pregnancy test [j]	X	X																				
Hematology/chemistry [k,s]	X	X				X			X				X			X			X			
Urinalysis [l]	X	X																				
Fecal immunochemical testing	X																					
Blood sample for cardiac enzymes [m]	X	X							X							X						
[redacted]																						
Skin punch [o,q]	X (or C1D1)	(X)			◄- -►																	
[redacted]					To be obtained postdose on any drug dosing day after 3 consecutive dosing days.																	
[redacted]																						
Urine and blood sample for PK	Urine and blood samples for PK analysis will be collected on the days and time points specified in Table Ga.																					

Abbreviations: BP, blood pressure; C_{max}, maximum observed plasma concentration; CT, computed tomography; CxDx, Cycle x, Day x; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ICF, informed consent form; IEC, independent ethics committee; IRB, institutional review board; MRI, magnetic resonance imaging; MUGA, multiple gated acquisition (scan); PK, pharmacokinetic(s); POTS, postural orthostatic tachycardia syndrome; QD, once daily.

[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 physical examination and medical history are not required if the screening physical examination was conducted and medical history obtained within 4 days before administration of the first dose of study drug (C1D1).

[c] Perform vital sign measurements including orthostatic measurements before dosing. Also, perform vital sign measurements on C1D1, C1D2, C1D3, and C1D8 at 2, 4, and 8 hours postdose (just before PK sampling). On C1D4 to C1D14 (except C1D8), resting and orthostatic heart rate and BP will be assessed and recorded at the estimated C_{max} time (approximately 2 hours postdose). If the investigator considers that it is otherwise safe, the patient can be discharged after Day 15 assessments making sure that the patient returns for C1D18 evaluation. If the investigator considers that it is in the patient's best interest to remain hospitalized during the third week, then scheduled assessments in parentheses (X) will be performed and recorded. Orthostatic measurements of BP and pulse/heart rate should be conducted with the patient in a supine position after the patient has been resting quietly for 5 minutes followed by a second measurement after the patient has been standing for 2 minutes. At screening, also measure heart rate after 10 minutes of quiet standing to confirm POTS. At least 3 separate resting (after 4 to 5 minutes' rest in sitting position). BP measurements should be taken during the screening and the median of those measurements will be utilized as baseline BP reference of individual patient (median of systolic BP and diastolic BP will be evaluated separately).

[d] The schedule for ECG sampling may be modified based on data from previous cohorts.
[e] All 12-lead ECG recordings should be made with the patient in a supine position. On C1D1, C1D8, and C1D14, a 12-lead ECG should be recorded before vital sign measurements and before administration of TAK-931; recordings should also be made at 2, 4, and 8 hours postdose on these days. As noted in footnote f, spot 12-lead ECG recordings may be done to assess an abnormal rhythm that is detected during monitoring and may require medical intervention. ECG should also be performed for patients experiencing Grade ≥2 hypotension during Cycle 1(See footnote f).
[f] Continuous patient heart rhythm monitoring while the patient is undergoing inpatient observation will start before the administration of the first dose of TAK-931 on C1D1 to C1D3 inclusive. For patients experiencing Grade ≥2 hypotension at any time during Cycle 1, continuous heart rhythm monitoring, and BP and ECG assessment at 2, 4, and 8 hours postdose should be performed in the following 3 administration days even if they are at a reduced dose level. Spot 12-lead ECG assessments may be done to assess an abnormal rhythm that is detected during monitoring and may require medical intervention. Continuous monitoring should not interfere with in-hospital normal patient activities including eating, sleeping, walking, or personal care.
[g] 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 on patients with bone metastases rather than CT or MRI. See Section 10.4.18 for more details.
[h] Including serious pretreatment events; see Section 11.2.
[i] Initially, TAK-931 will be administered orally QD for 14 days of a 21-day cycle followed by 7 days off. The starting dose will be 30 mg. Study drug will be administered to patients on an empty stomach. Patients should not eat for 2 hours before taking the capsules with 8 ounces of water. Patients should be instructed to eat a meal or snack >1 hour after taking the study drug. See Section 9.1.
[j] A serum beta-human chorionic gonadotropin (β-hCG) 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 (ie, 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.
[k] 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 10.4.14. New clinically significant Grade ≥2 results should be repeated within 3 days and followed until recovery.
[l] Complete urinalysis with qualitative analysis for protein at screening and C1D1. Positive results may require quantitative analysis (assessment of urine protein to creatinine ratio).Refer to Section 10.4.14 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.
[m] A blood sample will be obtained at the screening visit and predose on C1D1, C1D8, and C1D15 for measurement of cardiac enzymes in serum that monitor for acute injury (ie, troponin I or T) or chronic or progressive failure (ie, B-type natriuretic peptide [BNP] or N-terminal pro-brain natriuretic peptide [NT-proBNP]). If screening cardiac enzymes measurement was performed within 4 days before the C1D1 dose, it does not need to be repeated on C1D1.
[n] A blood sample will be obtained before administration of TAK-931 and will be processed for plasma.
[o] Skin punch biopsies (2-4 mm) will be obtained for all patients either during screening or predose on C1D1 and postdose on any drug dosing day after 3 consecutive dosing days (eg, Days 4-14) in Cycle 1.
CCI [redacted]
[q] It is strongly recommended that postdose skin biopsies CCI [redacted] are collected between 4 to 9 hours after study drug administration (simultaneously if possible). CCI [redacted]. It is acceptable to use an archival predose biopsy collected before study enrollment if no other anticancer systemic treatment was administered between the biopsy collection and the enrollment in the study.
CCI [redacted]
[s] **Patients enrolled in the safety expansion cohorts** are not required to be hospitalized for Cycle 1. Physical examination and 12-lead ECG measurements will be performed at

screening and on C1D1. Vital sign measurement as well as hematology and chemistry test will be performed at screening and on Days 1, 8, and 15. Continuous heart rhythm monitoring is not required. The other tests or examinations will be the same as dose escalation cohorts.
Note: Tests and procedures should be performed on schedule, but occasional changes are allowable (±3 days) with permission of the medical monitor for holidays, vacations, and other administrative reasons. **If extenuating circumstances prevent a patient from beginning treatment or completing a scheduled procedure or assessment within this time, the patient may continue the study only with the written permission of the medical monitor.**

Table Ab Schedule of Events for Treatment Cycle 2 Through PFS Follow-up (Dosing Schedule A) (14 days on, 7 days off; 21-Day Cycle)

	Cycle 2 and Subsequent Cycles						EOT [a]	PFSFU
	Day 1	**Day 5**	**Day 8**	**Day 12**	**Day 15**	**Day 18**		
Symptom-directed physical examination [b]	X						X	
Weight	X [c]						X	
Vital signs [d,s]	X				X		X	
ECOG performance status [e]	X						X	
12-Lead ECG [f]	X						X	
ECHO/MUGA [g]	X						X	
Disease assessment [h]					X (starting at C3 and performed between D15 and D1 of the next cycle, then Q3C thereafter)		X [i]	X [j] (Q 12 weeks)
Monitoring of concomitant medications and procedures	Recorded from first dose of study drug through up to 30 days after the last dose of study drug or before initiation of new anticancer therapy (whichever comes first).							
Adverse event reporting	Recorded from first dose of study drug through up to 30 days after the last dose of study drug or before initiation of new anticancer therapy (whichever comes first).							
	Serious adverse events [k] 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 anticancer therapy (whichever comes first).							X [t]
TAK-931 administration [l]	Days 1 through 14 of each treatment cycle							
Samples/Laboratory Assessments								
Pregnancy Test [m]							X	
Hematology/Chemistry [n,s]	X	X [o]	X [o]	X [o]	X	X [o]	X	
Urinalysis [p]	X [p]							
Fecal immunochemical testing [q]	X							
Blood sample for cardiac enzymes [r]	X							

Abbreviations: BP, blood pressure; C, cycle; CxDx, Cycle x, Day x; CT, computed tomography; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; EOT, End of Treatment; FIT, fusion-inferred threshold; IEC, independent ethics committee; IRB, institutional review board; MRI, magnetic resonance imaging;

MUGA, multiple gated acquisition (scan); PFSFU, progression-free survival follow-up; Q, every; QD, once daily.
[a] Patients who discontinue TAK-931 treatment early should complete the EOT visit approximately 30-40 days after the last dose of TAK-931 or before the start of subsequent anticancer therapy if that occurs sooner.
[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.
[d] Perform vital sign measurements including orthostatic measurements prior to dosing. Orthostatic measurements of BP and pulse should be conducted with the patient in a supine position after the patient has been resting quietly for 5 minutes, followed by a second measurement after the patient has been standing for 2 minutes.
[e] ECOG performance status will be performed within 3 days before the beginning (Day 1) of each treatment cycle and at the EOT visit.
[f] 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.
[g] ECHO and/or MUGA should be performed predose on C2D1 and at the EOT visit. The same modality should be used as on the screening visit.
[h] Baseline CT (with contrast) or MRI scan of the chest, abdomen, and pelvis must be at screening, after which CT (with contrast) or MRI may be performed at the end of every third cycle (ie, on or before the start of Cycle 4, Day 1; Cycle 7, Day 1; Cycle 10, Day 1, etc), as clinically indicated, according to standard of care. The same imaging modality (CT [with contrast] MRI, or bone scan) should be used on a patient as at the screening visit and throughout the study. Bone scans may be performed on patients with bone metastases rather than CT or MRI. See Section 10.4.18 for more details.
[i] 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.
[j] Patients who discontinue study treatment for reasons other than PD will undergo CT/MRI scans every 12 weeks (±1 week) from EOT until the occurrence of PD, the start of subsequent antineoplastic therapy, or until 6 months after discontinuation of study treatment, whichever occurs first.
[k] Including serious pretreatment events; see Section 11.2.
[l] Initially, TAK-931 will be administered orally QD for 14 days of a 21-day cycle followed by 7 days off. The starting dose will be 30 mg. Study drug will be administered to patients on an empty stomach. Patients should not eat for 2 hours before taking the capsules with 8 ounces of water. Patients should be instructed to eat a meal or snack >1 hour after taking study drug. See Section 9.1.
[m] 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.
[n] See Section 9.4. New Grade ≥3 results should be repeated a minimum of every 3 days until recovered to Grade ≤2.
[o] The hematology and chemistry blood samples on Days 5, 12, and 18 of each cycle starting with Cycle 2 may be waived if there is no evidence of Grade ≥3 analytical toxicity in the previous cycle. After Cycle 3, the Day 8 blood samples can also be waived in patients without evidence of Grade ≥3 analytical toxicity in the previous cycle.
[p] 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 10.4.14 for required clinical urinalysis tests.
[q] A stool sample for fecal immunochemical testing may be collected within 4 days before dosing on C2D1 and C3D1. If a patient has a positive FIT at screening, no further collection is required.
[r] A blood sample will be obtained predose on C2D1 for measurement of cardiac enzymes in serum that monitor for acute injury (ie, troponin I or T) or chronic or progressive failure (ie, B-type natriuretic peptide [BNP] or N-terminal pro-brain natriuretic peptide [NT-proBNP]).
[s] From Cycle 7 and beyond the hematology and chemistry tests and vital sign measurements will only be conducted on Day 1 of each cycle if in the opinion of the investigators is safe.
[t] After EOT, only related SAEs must be reported to the sponsor's Department of Pharmacovigilance or designee.
Note: Tests and procedures should be performed on schedule, but occasional changes are allowable (±3 days) with permission of the medical monitor for holidays, vacations, and other administrative reasons. **If extenuating circumstances prevent a patient from beginning treatment or completing a scheduled procedure or assessment within this time, the patient may continue the study only with the written permission of the medical monitor.**

Table Ba Schedule of Events for Treatment Cycle 1 (Dosing Schedule B) (7 days on, 7 days off; 28-Day Cycle)

	Screening [a]	Day 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Informed consent	X																												
Inclusion/exclusion criteria	X																												
HBV, HCV, and HIV testing	X																												
Demographics	X																												
Medical history [b]	X	X																											
Physical examination [b,t]	X	X							X							X							X						
Height	X																												
Weight		X																											
Vital signs [c,t]	X	X	X	X	X	X	X	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	X	X	X	X	X	X	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
ECOG performance status	X																												
12-Lead ECG [d,e,t]	X	X [e]						X [e]														X [e]							
Continuous heart rhythm monitor [f,t]		X	X	X																									
ECHO/MUGA	X																												
Disease assessment [g]	X																												
Monitoring of concomitant medications and procedures		Recorded from first dose of study drug through up to 30 days after the last dose of study drug or before initiation of new anticancer therapy (whichever comes first).																											
Adverse event reporting		Recorded from first dose of study drug through up to 30 days after the last dose of study drug or before initiation of new anticancer therapy (whichever comes first).																											
	Serious adverse events [h] 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 anticancer therapy (whichever comes first).																												
TAK-931 administration [i]		X	X	X	X	X	X	X								X	X	X	X	X	X	X							

Footnotes are on last table page.

Table Ba Schedule of Events for Treatment Cycle 1 (Dosing Schedule B) (7 days on 7 days off; 28-Day Cycle) (continued)

		Day																										
	Screening [a]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Samples/Laboratory Assessments																													
Pregnancy test [j]	X	X																											
Hematology/chemistry [k,t]	X	X				X			X				X [l]			X			X				X			X [l]			
Urinalysis [m]	X	X																											
Fecal immunochemical testing	X																												
Blood sample for cardiac enzymes [n,t]	X	X							X							X							X						
CCI																													
Skin punch [p,r]	X (or C1D1)	(X)			◄- - - - - - - - - - ►														◄- - - - - - - - - - ►										
CCI					To be obtained postdose on any drug dosing day after 3 consecutive dosing days														To be obtained postdose on any drug dosing day after 3 consecutive dosing days										
CCI																													
Urine and blood sample for PK	Urine and blood samples for PK analysis will be collected on the days and time points specified in Table Gb.																												

Abbreviations: BID, twice daily; BP, blood pressure; CxDx, Cycle x, Day x; C_{max}, maximum observed plasma concentration; CT, computed tomography; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ICF, informed consent form; IEC, independent ethics committee; IRB, institutional review board; MRI, magnetic resonance imaging; MUGA, multiple gated acquisition (scan); PK, pharmacokinetic(s); POTS, postural orthostatic tachycardia syndrome; QD, once daily.

[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 physical examination and medical history are not required if the screening physical examination was conducted and medical history obtained within 4 days before administration of the first dose of study drug (C1D1).

[c] Perform vital sign measurements including orthostatic measurements before dosing. Also, perform vital sign measurements on C1D1, C1D2, C1D3, and C1D7 at 2, 4, and 8 hours postdose (just before PK sampling). On C1D4 to C1D6 and C1D15 to C1D21, resting and orthostatic heart rate and BP will be assessed and recorded at the estimated C_{max} time (approximately 2 hours postdose). If the investigator considers that it is otherwise safe, the patient can be discharged during dose holidays (ie, between Days 8-14 as well as after Day 22 assessments). If the investigator considers that it is in the patient's best interest to remain hospitalized during the second and/or fourth week, then scheduled assessments in parentheses (X) will be performed and recorded. Orthostatic measurements of BP and pulse/heart rate should be conducted with the patient in a supine position after the patient has been resting quietly for 5 minutes, followed by a second measurement after the patient has been standing for 2 minutes. At screening, also measure heart rate after 10 minutes of quiet standing to confirm POTS. At least 3 separate resting (after 4 to 5 minutes' rest in sitting position) BP measurements should be taken during the screening and the median of those measurements will be utilized as baseline BP reference of individual patient (median of systolic BP and diastolic BP will be evaluated separately).

[d] The schedule for ECG sampling may be modified based on data from previous cohorts.

[e] All 12-lead ECG recordings should be made with the patient in a supine position. On C1D1, C1D7, and C1D21, a 12-lead ECG should be recorded before vital sign measurements and before administration of TAK-931; recordings should also be made at 2, 4, and 8 hours postdose on these days. As noted in footnote f, spot 12-lead ECG recordings may be done to assess an abnormal rhythm that is detected during monitoring and may require medical intervention. ECG should also be performed for patients experiencing Grade ≥2 hypotension during Cycle 1(See footnote f).

[f] Continuous patient heart rhythm monitoring while the patient is undergoing inpatient observation will start before the administration of the first dose of TAK-931 on C1D1 to C1D3 inclusive. For patients experiencing Grade ≥2 hypotension at any time during Cycle 1, continuous heart rhythm monitoring, and BP and ECG assessment at 2, 4, and 8 hours postdose should be performed in the following 3

administration days even if they are at a reduced dose level. Spot 12-lead ECG assessments may be done to assess an abnormal rhythm that is detected during monitoring and may require medical intervention. Continuous monitoring should not interfere with in-hospital normal patient activities including eating, sleeping, walking, or personal care.

[g] 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 on patients with bone metastases rather than CT or MRI. See Section 10.4.18 for more details.

[h] Including serious pretreatment events; see Section 11.2.

[i] TAK-931 will be administered orally QD (or BID) for 7 days followed by another 7 days of rest and repeated for a cycle duration of 28 days. The starting dose will be 60 mg. Study drug will be administered to patients on an empty stomach. Patients should not eat for 2 hours before taking the capsules with 8 ounces of water. Patients should be instructed to eat a meal or snack >1 hour after taking the study drug. See Section 9.1.

[j] A serum beta-human chorionic gonadotropin (β-hCG) 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 (ie, 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.

[k] 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 10.4.14. New clinically significant Grade ≥2 results should be repeated within 3 days and followed until recovery.

[l] If a patient is discharged from hospital during drug holidays, the hematology and chemistry tests on Days 12 and 25 can be waived at investigator discretion.

[m] Complete urinalysis with qualitative analysis for protein at screening and C1D1. Positive results may require quantitative analysis (assessment of urine protein to creatinine ratio).Refer to Section 10.4.14 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 at the screening visit and predose on C1D1, C1D8, and C1D22 for measurement of cardiac enzymes in serum that monitor for acute injury (ie, troponin I or T) or chronic or progressive failure (ie, B-type natriuretic peptide [BNP] or N-terminal pro-brain natriuretic peptide [NT-proBNP]). For dose escalation cohorts, the test on C1D15 is not necessary. If screening cardiac enzymes measurement was performed within 4 days before the C1D1 dose, it does not need to be repeated on C1D1.

CCI [redacted]

Skin punch biopsies (2-4 mm) will be obtained for all patients either during screening or predose on C1D1 and postdose on any drug dosing day after 3 consecutive dosing days (eg, Days 4-7 or Days 18-21) in Cycle 1.

CCI [redacted]

[r] It is strongly recommended that postdose skin biopsies CCI [redacted] are collected between 4 to 9 hours after study drug administration (simultaneously if possible). CCI [redacted] It is acceptable to use an archival predose biopsy collected before study enrollment if no other anticancer systemic treatment was administered between the biopsy collection and the enrollment in the study.

CCI [redacted]

[t] **Patients enrolled in the safety expansion cohorts** are not required to be hospitalized for Cycle 1. Physical examination, vital sign measurement as well as hematology, chemistry, and cardiac enzyme tests will be performed at screening and on Days 1 and 15. Continuous heart rhythm monitoring is not required. Twelve-lead ECG measurements are required at screening and on C1D1. The other tests or examinations will be the same as dose escalation cohorts.

Note: Tests and procedures should be performed on schedule, but occasional changes are allowable (±3 days) with permission of the medical monitor for holidays, vacations, and other administrative reasons. **If extenuating circumstances prevent a patient from beginning treatment or completing a scheduled procedure or assessment within this time, the patient may continue the study only with the written permission of the medical monitor.**

Table Bb Schedule of Events for Treatment Cycle 2 Through PFS Follow-up (Dosing Schedule B) (7 days on, 7 days off; 28-Day Cycle)

	Cycle 2 and Subsequent Cycles						EOT [a]	PFSFU
	Day 1	**Day 5**	**Day 8**	**Day 15**	**Day 18**	**Day 22**		
Symptom-directed physical examination [b]	X						X	
Weight	X [c]						X	
Vital signs [d,s]	X			X			X	
ECOG performance status [e]	X						X	
12-Lead ECG [f]	X						X	
ECHO/MUGA [g]	X						X	
Disease assessment [h]						X (starting at C3 and performed between D22 and D1 of the next cycle, then Q3C thereafter)	X [i]	X [j] (Q 12 weeks)
Monitoring of concomitant medications and procedures	Recorded from first dose of study drug through up to 30 days after the last dose of study drug or before initiation of new anticancer therapy (whichever comes first).							
Adverse event reporting	Recorded from first dose of study drug through up to 30 days after the last dose of study drug or before initiation of new anticancer therapy (whichever comes first).							
	Serious adverse events [k] 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 anticancer therapy (whichever comes first).							X [t]
TAK-931 administration [l]	Days 1 through 7 of each treatment cycle			Days 15 through 21 of each treatment cycle				
Samples/Laboratory Assessments								
Pregnancy Test [m]							X	
Hematology/Chemistry [n,s]	X	X [o]	X [o]	X	X [o]	X [o]	X	
Urinalysis [p]	X [p]							
Fecal immunochemical testing [q]	X							
Blood sample for cardiac enzymes [r]	X							

Abbreviations: BID, twice daily; BP, blood pressure; C, cycle; CxDx, Cycle x, Day x; CT, computed tomography; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; EOT, End of Treatment; FIT, fusion-inferred threshold; IEC, independent ethics committee; IRB, institutional review board; MRI, magnetic resonance

imaging; MUGA, multiple gated acquisition (scan); PFSFU, progression-free survival follow-up; Q, every; QD, once daily.
[a] Patients who discontinue TAK-931 treatment early should complete the EOT visit approximately 30-40 days after the last dose of TAK-931 or before the start of subsequent anticancer therapy if that occurs sooner.
[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.
[d] Perform vital sign measurements including orthostatic measurements prior to dosing. Orthostatic measurements of BP and pulse should be conducted with the patient in a supine position after the patient has been resting quietly for 5 minutes followed by a second measurement after the patient has been standing for 2 minutes.
[e] ECOG performance status will be performed within 3 days before the beginning (Day 1) of each treatment cycle and at the EOT visit.
[f] 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.
[g] ECHO and/or MUGA should be performed predose on C2D1 and at the EOT visit. The same modality should be used as on the screening visit.
[h] Baseline CT (with contrast) or MRI scan of the chest, abdomen, and pelvis must be at screening, after which CT (with contrast) or MRI may be performed at the end of every third cycle (ie, on or before the start of Cycle 4, Day 1; Cycle 7, Day 1; Cycle 10, Day 1, etc), as clinically indicated, according to standard of care. The same imaging modality (CT [with contrast] MRI, or bone scan) should be used on a patient as at the screening visit and throughout the study. Bone scans may be performed on patients with bone metastases rather than CT or MRI. See Section 10.4.18 for more details.
[i] 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.
[j] Patients who discontinue study treatment for reasons other than PD will undergo CT/MRI scans every 12 weeks (±1 week) from EOT until the occurrence of PD, the start of subsequent antineoplastic therapy, or until 6 months after discontinuation of study treatment, whichever occurs first.
[k] Including serious pretreatment events; see Section 11.2.
[l] TAK-931 will be administered orally QD (or BID) for 7 days followed by another 7 days of rest and repeated for a cycle duration of 28 days. The starting dose will be 60 mg. Study drug will be administered to patients on an empty stomach. Patients should not eat for 2 hours before taking the capsules with 8 ounces of water. Patients should be instructed to eat a meal or snack >1 hour after taking study drug. See Section 9.1.
[m] 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.
[n] See Section 9.4. New Grade ≥3 results should be repeated a minimum of every 3 days until recovered to Grade ≤2.
[o] The hematology and chemistry blood samples on Days 5, 8, 18 and 22 of each cycle starting with Cycle 2 may be waived if there is no evidence of Grade ≥3 analytical toxicity in the previous cycle.
[p] 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 10.4.14 for required clinical urinalysis tests.
[q] A stool sample for fecal immunochemical testing may be collected within 4 days before dosing on C2D1 and C3D1. If a patient has a positive FIT at screening, no further collection is required.
[r] A blood sample will be obtained predose on C2D1 for measurement of cardiac enzymes in serum that monitor for acute injury (ie, troponin I or T) or chronic or progressive failure (ie, B-type natriuretic peptide [BNP] or N-terminal pro-brain natriuretic peptide [NT-proBNP]).
[s] From Cycle 7 and beyond the hematology and chemistry tests and vital sign measurements will only be conducted on Day 1 of each cycle if in the opinion of the investigators is safe.
[t] After EOT, only related SAEs must be reported to the sponsor's Department of Pharmacovigilance or designee.
Note: Tests and procedures should be performed on schedule, but occasional changes are allowable (±3 days) with permission of the medical monitor for holidays, vacations, and other administrative reasons. **If extenuating circumstances prevent a patient from beginning treatment or completing a scheduled procedure or assessment within this time, the patient may continue the study only with the written permission of the medical monitor.**

Table Ca Schedule of Events for Treatment Cycle 1 (Dosing Schedule C) (7 days on, 14 days off; 21-day Cycle)

		Day																			
	Screening [a]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**
Informed consent	X																					
Inclusion/exclusion criteria	X																					
HBV, HCV, and HIV testing	X																					
Demographics	X																					
Medical history [b]	X	X																				
Physical examination [b,t]	X	X							X													
Height	X																					
Weight		X																				
Vital signs [c,t]	X	X	X	X	X	X	X	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
ECOG performance status	X																					
12-Lead ECG [d,e,t]	X	X [e]						X [e]														
Continuous heart rhythm monitor [f,t]		X	X	X																		
ECHO/MUGA	X																					
Disease assessment [g]	X																					
Monitoring of concomitant medications and procedures		Recorded from first dose of study drug through up to 30 days after the last dose of study drug or before initiation of new anticancer therapy (whichever comes first).																				
Adverse event reporting		Recorded from first dose of study drug through up to 30 days after the last dose of study drug or before initiation of new anticancer therapy (whichever comes first).																				
	Serious adverse events [h] 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 anticancer therapy (whichever comes first).																					
TAK-931 administration [i]		X	X	X	X	X	X	X														

Footnotes are on last table page.

Table Ca Schedule of Events for Treatment Cycle 1 (Dosing Schedule C) (7 days on 14 days off; 21-day Cycle) (continued)

	Screening (a)	Day 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Samples/Laboratory Assessments																						
Pregnancy test j	X	X																				
Hematology/chemistry k,t	X	X				X			X				X [l]			X			X [l]			
Urinalysis [m]	X	X																				
Fecal immunochemical testing	X																					
Blood sample for cardiac enzymes [n,t]	X	X							X							X						
CCI																						
Skin punch [p,r]	X (or C1D1)	(X)			◄- - - - - - - - - - ►																	
CCI					To be obtained postdose on any drug dosing day after 3 consecutive dosing days.																	
CCI																						
Urine and blood sample for PK	Urine and blood samples for PK analysis will be collected on the days and time points specified in Table Gc.																					

Abbreviations: BID, twice daily; BP, blood pressure; CxDx, Cycle x, Day x; C_{max}, maximum observed plasma concentration; CT, computed tomography; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ICF, informed consent form; IEC, independent ethics committee; IRB, institutional review board; MRI, magnetic resonance imaging; MUGA, multiple gated acquisition (scan); PK, pharmacokinetic(s); POTS, postural orthostatic tachycardia syndrome; QD, once daily.

[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 physical examination and medical history are not required if the screening physical examination was conducted and medical history obtained within 4 days before administration of the first dose of study drug (C1D1).

[c] Perform vital sign measurements including orthostatic measurements before dosing. Also, perform vital sign measurements on C1D1, C1D2, C1D3, and C1D7 at 2, 4, and 8 hours postdose (just before PK sampling). On C1D4 to C1D6, resting and orthostatic heart rate and BP will be assessed and recorded at the estimated C_{max} time (approximately 2 hours postdose). If the investigator considers that it is otherwise safe, the patient can be discharged after D8 assessments. If the investigator considers that it is in the patient's best interest to remain hospitalized during the second and third weeks, then scheduled assessments in parentheses (X) will be performed and recorded. Orthostatic measurements of BP and pulse/heart rate should be conducted with the patient in a supine position after the patient has been resting quietly for 5 minutes followed by a second measurement after the patient has been standing for 2 minutes. At screening, also measure heart rate after 10 minutes of quiet standing to confirm POTS. At least 3 separate resting (after 4 to 5 minutes' rest in sitting

position) BP measurements should be taken during the screening and the median of those measurements will be utilized as baseline BP reference of individual patient (median of systolic BP and diastolic BP will be evaluated separately).

[d] The schedule for ECG sampling may be modified based on data from previous cohorts.

[e] All 12-lead ECG recordings should be made with the patient in a supine position. On C1D1 and C1D7, a 12-lead ECG should be recorded before vital sign measurements and before administration of TAK-931; recordings should also be made at 2, 4, and 8 hours postdose on these days. As noted in footnote f, spot 12-lead ECG recordings may be done to assess an abnormal rhythm that is detected during monitoring and may require medical intervention. ECG should also be performed for patients experiencing Grade ≥2 hypotension during Cycle 1(See footnote f).

[f] Continuous patient heart rhythm monitoring while the patient is undergoing inpatient observation will start before the administration of the first dose of TAK-931 on C1D1 to C1D3 inclusive. For patients experiencing Grade ≥2 hypotension at any time during Cycle 1, continuous heart rhythm monitoring, and BP and ECG assessment at 2, 4, and 8 hours postdose should be performed in the following 3 administration days even if they are at a reduced dose level. Spot 12-lead ECG assessments may be done to assess an abnormal rhythm that is detected during monitoring and may require medical intervention. Continuous monitoring should not interfere with in-hospital normal patient activities including eating, sleeping, walking, or personal care.

[g] 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 on patients with bone metastases rather than CT or MRI. See Section 10.4.18 for more details.

[h] Including serious pretreatment events; see Section 11.2.

[i] TAK-931 will be administered orally QD (or BID) for 7 days of a 21-day cycle followed by 14 days off. The starting dose will be maximum administered dose in Schedule B. Study drug will be administered to patients on an empty stomach. Patients should not eat for 2 hours before taking the capsules with 8 ounces of water. Patients should be instructed to eat a meal or snack >1 hour after taking the study drug. See Section 9.1.

[j] A serum beta-human chorionic gonadotropin (β-hCG) 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 (ie, 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.

[k] 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 10.4.14. New clinically significant Grade ≥2 results should be repeated within 3 days and followed until recovery.

[l] If a patient is discharged from hospital during drug holidays, the hematology and chemistry tests on Days 12 and 18 can be waived at investigator discretion.

[m] Complete urinalysis with qualitative analysis for protein at screening and C1D1. Positive results may require quantitative analysis (assessment of urine protein to creatinine ratio).Refer to Section 10.4.14 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 at the screening visit and predose on C1D1 and C1D8 for measurement of cardiac enzymes in serum that monitor for acute injury (ie, troponin I or T) or chronic or progressive failure (ie, B-type natriuretic peptide [BNP] or N-terminal pro-brain natriuretic peptide [NT-proBNP]). For dose escalation cohorts, the test on C1D15 is not necessary. If screening cardiac enzymes measurement was performed within 4 days before the C1D1 dose, it does not need to be repeated on C1D1.

CCI [redacted]

[p] Skin punch biopsies (2-4 mm) will be obtained for all patients either during screening or before study drug administration on C1D1 and postdose on any drug dosing day after 3 consecutive dosing days (eg, Days 4-7) in Cycle 1.

CCI [redacted]

It is strongly recommended that postdose skin biopsies CCI [redacted] are collected between 4 to 9 hours after study drug administration (simultaneously if possible). CCI [redacted] It is acceptable to use an archival predose biopsy collected before study enrollment if no other anticancer

systemic treatment was administered between the biopsy collection and the enrollment in the study.

CCI [redacted]

Patients enrolled in the safety expansion cohorts are not required to be hospitalized for Cycle 1. Physical examination and 12-lead ECG measurements will be performed at screening and on Day 1. Vital sign measurement as well as hematology, chemistry, and cardiac enzyme tests will be performed at screening and on Days 1 and 15. Continuous heart rhythm monitoring is not required. The other tests or examinations will be the same as dose escalation cohorts.

Note: Tests and procedures should be performed on schedule, but occasional changes are allowable (±3 days) with permission of the medical monitor for holidays, vacations, and other administrative reasons. **If extenuating circumstances prevent a patient from beginning treatment or completing a scheduled procedure or assessment within this time, the patient may continue the study only with the written permission of the medical monitor.**

C [redacted]
C

C

Table Cb Schedule of Events for Treatment Cycle 2 Through PFS Follow-up (Dosing Schedule C) (7 days on, 14 days off; 21-Day Cycle)

	Cycle 2 and Subsequent Cycles						EOT [a]	PFSFU
	Day 1	**Day 5**	**Day 8**	**Day 12**	**Day 15**	**Day 18**		
Symptom-directed physical examination [b]	X						X	
Weight	X [c]						X	
Vital signs [d]	X						X	
ECOG performance status [e]	X						X	
12-Lead ECG [f]	X						X	
ECHO/MUGA [g]	X						X	
Disease assessment [h]					X (starting at C3 and performed between D15 and D1 of the next cycle, then Q3C thereafter).		X [i]	X [j] (Q 12 weeks)
Monitoring of concomitant medications and procedures	Recorded from first dose of study drug through up to 30 days after the last dose of study drug or before initiation of new anticancer therapy (whichever comes first).							
Adverse event reporting	Recorded from first dose of study drug through up to 30 days after the last dose of study drug or before initiation of new anticancer therapy (whichever comes first).							
	Serious adverse events [k] 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 anticancer therapy (whichever comes first).							**X** [s]
TAK-931 administration [l]	Days 1 through 7 of each treatment cycle							
Samples/Laboratory Assessments								
Pregnancy Test [m]							X	
Hematology/Chemistry [n]	X	X [o]	X [o]	X [o]	X	X [o]	X	
Urinalysis [p]	X [p]							
Fecal immunochemical testing [q]	X							
Blood sample for cardiac enzymes [r]	X							

Abbreviations: BID, twice daily; BP, blood pressure; C, cycle; CxDx, Cycle x, Day x; CT, computed tomography; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; EOT, End of Treatment; FIT, fusion-inferred threshold; IEC, independent ethics committee; IRB, institutional review board; MRI, magnetic resonance

imaging; MUGA, multiple gated acquisition (scan); PFSFU, progression-free survival follow-up; Q, every; QD, once daily.

[a] Patients who discontinue TAK-931 treatment early should complete the EOT visit approximately 30-40 days after the last dose of TAK-931 or before the start of subsequent anticancer therapy if that occurs sooner.

[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.

[d] Perform vital sign measurements including orthostatic measurements prior to dosing. Orthostatic measurements of BP and pulse should be conducted with the patient in a supine position after the patient has been resting quietly for 5 minutes followed by a second measurement after the patient has been standing for 2 minutes.

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

[f] 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.

[g] ECHO and/or MUGA should be performed predose on C2D1 and at the EOT visit. The same modality should be used as on the screening visit.

[h] Baseline CT (with contrast) or MRI scan of the chest, abdomen, and pelvis must be at screening, after which CT (with contrast) or MRI may be performed at the end of every third cycle (ie, on or before the start of Cycle 4, Day 1; Cycle 7, Day 1; Cycle 10, Day 1, etc), as clinically indicated, according to standard of care. The same imaging modality (CT [with contrast] MRI, or bone scan) should be used on a patient as at the screening visit and throughout the study. Bone scans may be performed on patients with bone metastases rather than CT or MRI. See Section 10.4.18 for more details.

[i] 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.

[j] Patients who discontinue study treatment for reasons other than PD will undergo CT/MRI scans every 12 weeks (±1 week) from EOT until the occurrence of PD, the start of subsequent antineoplastic therapy, or until 6 months after discontinuation of study treatment, whichever occurs first.

[k] Including serious pretreatment events; see Section 11.2.

[l] TAK-931 will be administered orally QD (or BID) for 7 days of a 21-day cycle followed by 14 days off. The starting dose will be maximum administered dose in Schedule B. Study drug will be administered to patients on an empty stomach. Patients should not eat for 2 hours before taking the capsules with 8 ounces of water. Patients should be instructed to eat a meal or snack >1 hour after taking study drug. See Section 9.1.

[m] 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.

[n] See Section 9.4. New Grade ≥3 results should be repeated a minimum of every 3 days until recovered to Grade ≤2.

[o] The hematology and chemistry blood samples on Days 5, 8, 12, and 18 of each cycle starting with Cycle 2 may be waived if there is no evidence of Grade ≥3 analytical toxicity in the previous cycle. From Cycle 7 and beyond the hematology and chemistry tests will only be conducted on Day 1 of each cycle if in the opinion of the investigators is safe.

[p] 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 10.4.14 for required clinical urinalysis tests.

[q] A stool sample for fecal immunochemical testing may be collected within 4 days before dosing on C2D1 and C3D1. If a patient has a positive FIT at screening, no further collection is required.

[r] A blood sample will be obtained predose on C2D1 for measurement of cardiac enzymes in serum that monitor for acute injury (ie, troponin I or T) or chronic or progressive failure (ie, B-type natriuretic peptide [BNP] or N-terminal pro-brain natriuretic peptide [NT-proBNP]).

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

Note: Tests and procedures should be performed on schedule, but occasional changes are allowable (±3 days) with permission of the medical monitor for holidays, vacations, and other administrative reasons. **If extenuating circumstances prevent a patient from beginning treatment or completing a scheduled procedure or assessment within this time, the patient may continue the study only with the written permission of the medical monitor.**

Table Da Schedule of Events for Treatment Cycle 1 (Dosing Schedule D) (Continuous Schedule; 21-Day Cycle)

	Screening [a]	Day 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Informed consent	X																					
Inclusion/exclusion criteria	X																					
HBV, HCV, and HIV testing	X																					
Demographics	X																					
Medical history [b]	X	X																				
Physical examination [b,q]	X	X																				
Height	X																					
Weight		X																				
Vital signs [c,q]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG performance status	X																					
12-Lead ECG [d,q]	X	X [d]																				
ECHO/MUGA	X																					
Disease assessment [e]	X																					
Monitoring of concomitant medications and procedures		Recorded from first dose of study drug through up to 30 days after the last dose of study drug or before initiation of new anticancer therapy (whichever comes first).																				
Adverse event reporting		Recorded from first dose of study drug through up to 30 days after the last dose of study drug or before initiation of new anticancer therapy (whichever comes first).																				
	Serious adverse events [f] 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 anticancer therapy (whichever comes first).																					
TAK-931 administration [g]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Footnotes are on last table page.

Table Da Schedule of Events for Treatment Cycle 1 (continued) (Dosing Schedule D) (Continuous Schedule; 21-day Cycle)

	Screening [a]	Day																				
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Samples/Laboratory Assessments																						
Pregnancy test [h]	X	X																				
Hematology/chemistry [i,q]	X	X				X			X				X			X			X			
Urinalysis [j]	X	X																				
Fecal immunochemical testing	X																					
Blood sample for cardiac enzymes [k]	X	X																				
[redacted]																						
Skin punch [m,o]	X (or C1D1)	(X)			←--→																	
[redacted]					To be obtained postdose on any drug dosing day after 3 consecutive dosing days.																	
[redacted]																						
Urine and blood sample for PK	Urine and blood samples for PK analysis will be collected on the days and time points specified in Table Gd.																					

Abbreviations: BID, twice daily; BP, blood pressure; CxDx, Cycle x, Day x; C_{max}, maximum observed plasma concentration; CT, computed tomography; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ICF, informed consent form; IEC, independent ethics committee; IRB, institutional review board; MRI, magnetic resonance imaging; MUGA, multiple gated acquisition (scan); PK, pharmacokinetic(s); POTS, postural orthostatic tachycardia syndrome; QD, once daily.

[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 physical examination and medical history are not required if the screening physical examination was conducted and medical history obtained within 4 days before administration of the first dose of study drug (C1D1).

[c] Perform vital sign measurements including orthostatic and resting measurements at screening. On C1D1 resting heart rate and BP will be measured at predose. On C1D1 through C1D21, resting heart rate and BP will be assessed and recorded at the estimated C_{max} time (approximately 2 hours postdose). Orthostatic measurements of BP and pulse/heart rate should be conducted with the patient in a supine position after the patient has been resting quietly for 5 minutes followed by a second measurement after the patient has been standing for 2 minutes. At screening, also measure heart rate after 10 minutes of quiet standing to confirm POTS. At least 3 separate resting (after 4 to 5 minutes' rest in sitting position) BP measurements should be taken during the screening and the median of those measurements will be utilized as baseline BP reference of individual patient (median of systolic BP and diastolic BP will be evaluated separately).

[d] All 12-lead ECG recordings should be made with the patient in a supine position. On C1D1, a 12-lead ECG should be recorded before administration of TAK-931 and before vital

sign measurements at approximately 2 hours postdose. ECG should also be performed for patients experiencing Grade ≥2 hypotension during Cycle 1.

[e] 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 on patients with bone metastases rather than CT or MRI. See Section 10.4.18 for more details.

[f] Including serious pretreatment events; see Section 11.2.

[g] TAK-931 will be administered orally QD (or BID) continuously in a 21-day cycle. The starting dose will be 20 mg. Study drug will be administered to patients on an empty stomach. Patients should not eat for 2 hours before taking the capsules with 8 ounces of water. Patients should be instructed to eat a meal or snack >1 hour after taking the study drug. See Section 9.1.

[h] A serum beta-human chorionic gonadotropin (β-hCG) 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 (ie, 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.

[i] 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 10.4.14. New clinically significant Grade ≥2 results should be repeated within 3 days and followed until recovery.

[j] Complete urinalysis with qualitative analysis for protein at screening and C1D1. Positive results may require quantitative analysis (assessment of urine protein to creatinine ratio).Refer to Section 10.4.14 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.

[k] A blood sample will be obtained at the screening visit and predose on C1D1 for measurement of cardiac enzymes in serum that monitor for acute injury (ie, troponin I or T) or chronic or progressive failure (ie, B-type natriuretic peptide [BNP] or N-terminal pro-brain natriuretic peptide [NT-proBNP]). If screening cardiac enzymes measurement was performed within 4 days before the C1D1 dose, it does not need to be repeated on C1D1.

CCI [redacted]

[m] Skin punch biopsies (2-4 mm) will be obtained for all patients either during screening or predose on C1D1 and postdose on any drug dosing day after 3 consecutive dosing days (eg, Days 4-21) in Cycle 1.

CCI [redacted]

[o] It is strongly recommended that postdose skin biopsies CCI [redacted] are collected between 4 to 9 hours after study drug administration (simultaneously if possible). CCI [redacted] It is acceptable to use an archival predose biopsy collected before study enrollment if no other anticancer systemic treatment was administered between the biopsy collection and the enrollment in the study.

CCI [redacted]

[q] **Patients enrolled in the safety expansion cohorts** are not required to be hospitalized for Cycle 1. Physical examination, vital sign measurement, and 12-ECG measurements will be performed at screening and on Day 1. Hematology and chemistry tests will be performed at screening and on Days 1, 8, and 15. Continuous heart rhythm monitoring is not required. The other tests or examinations will be the same as dose escalation cohorts.

Note: Tests and procedures should be performed on schedule, but occasional changes are allowable (±3 days) with permission of the medical monitor for holidays, vacations, and other administrative reasons. **If extenuating circumstances prevent a patient from beginning treatment or completing a scheduled procedure or assessment within this time, the patient may continue the study only with the written permission of the medical monitor.**

Table Db Schedule of Events for Treatment Cycle 2 Through PFS Follow-up (Dosing Schedule D) (Continuous Schedule; 21-day Cycle)

	Cycle 2 and Subsequent Cycles						EOT [a]	PFSFU
	Day 1	**Day 5**	**Day 8**	**Day 12**	**Day 15**	**Day 18**		
Symptom-directed physical examination [b]	X						X	
Weight	X [c]						X	
Vital signs [d]	X						X	
ECOG performance status [e]	X						X	
12-Lead ECG [f]	X						X	
ECHO/MUGA [g]	X						X	
Disease assessment [h]					X (starting at C3 and performed between D15 and D1 of the next cycle, then Q3C thereafter)		X [i]	X [j] (Q 12 weeks)
Monitoring of concomitant medications and procedures	Recorded from first dose of study drug through up to 30 days after the last dose of study drug or before initiation of new anticancer therapy (whichever comes first).							
Adverse event reporting	Recorded from first dose of study drug through up to 30 days after the last dose of study drug or before initiation of new anticancer therapy (whichever comes first).							
	Serious adverse events [k] 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 anticancer therapy (whichever comes first).							X [s]
TAK-931 administration [l]	Days 1 through 21 of each treatment cycle							
Samples/Laboratory Assessments								
Pregnancy Test [m]							X	
Hematology/Chemistry [n]	X	X [o]	X	X [o]	X	X [o]	X	
Urinalysis [p]	X [p]							
Fecal immunochemical testing [q]	X							
Blood sample for cardiac enzymes [r]	X							

Abbreviations: BID, twice daily; BP, blood pressure; C, cycle; CxDx, Cycle x, Day x; CT, computed tomography; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; EOT, End of Treatment; FIT, fusion-inferred threshold; IEC, independent ethics committee; IRB, institutional review board; MRI, magnetic resonance

imaging; MUGA, multiple gated acquisition (scan); PFSFU, progression-free survival follow-up; Q, every; QD, once daily.
[a] Patients who discontinue TAK-931 treatment early should complete the EOT visit approximately 30-40 days after the last dose of TAK-931 or before the start of subsequent anticancer therapy if that occurs sooner.
[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.
[d] Perform resting vital sign measurement (after 4 to 5 minutes' rest in sitting position) prior to dosing.
[e] ECOG performance status will be performed within 3 days before the beginning (Day 1) of each treatment cycle and at the EOT visit.
[f] 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.
[g] ECHO and/or MUGA should be performed predose on C2D1 and at the EOT visit. The same modality should be used as on the screening visit.
[h] Baseline CT (with contrast) or MRI scan of the chest, abdomen, and pelvis must be at screening, after which CT (with contrast) or MRI may be performed at the end of every third cycle (ie, on or before the start of Cycle 4, Day 1; Cycle 7, Day 1; Cycle 10, Day 1, etc), as clinically indicated, according to standard of care. The same imaging modality (CT [with contrast] MRI, or bone scan) should be used on a patient as at the screening visit and throughout the study. Bone scans may be performed on patients with bone metastases rather than CT or MRI. See Section 10.4.18 for more details.
[i] 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.
[j] Patients who discontinue study treatment for reasons other than PD will undergo CT/MRI scans every 12 weeks (±1 week) from EOT until the occurrence of PD, the start of subsequent antineoplastic therapy, or until 6 months after discontinuation of study treatment, whichever occurs first.
[k] Including serious pretreatment events; see Section 11.2.
[l] TAK-931 will be administered orally QD (or BID) continuously in a 21-day cycle. The starting dose will be 20 mg. Study drug will be administered to patients on an empty stomach. Patients should not eat for 2 hours before taking the capsules with 8 ounces of water. Patients should be instructed to eat a meal or snack >1 hour after taking study drug. See Section 9.1.
[m] 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.
[n] See Section 9.4. New Grade ≥3 results should be repeated a minimum of every 3 days until recovered to Grade ≤2.
[o] The hematology and chemistry blood samples on Days 5, 12, and 18 of each cycle starting with Cycle 2 may be waived if there is no evidence of Grade ≥3 analytical toxicity in the previous cycle. From Cycle 7 and beyond the hematology and chemistry tests will only be conducted on Day 1 of each cycle if in the opinion of the investigators is safe.
[p] 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 10.4.14 for required clinical urinalysis tests.
[q] A stool sample for fecal immunochemical testing may be collected within 4 days before dosing on C2D1 and C3D1. If a patient has a positive FIT at screening, no further collection is required.
[r] A blood sample will be obtained predose on C2D1 for measurement of cardiac enzymes in serum that monitor for acute injury (ie, troponin I or T) or chronic or progressive failure (ie, B-type natriuretic peptide [BNP] or N-terminal pro-brain natriuretic peptide [NT-proBNP]).
[s] After EOT, only related SAEs must be reported to the sponsor's Department of Pharmacovigilance or designee.
Note: Tests and procedures should be performed on schedule, but occasional changes are allowable (±3 days) with permission of the medical monitor for holidays, vacations, and other administrative reasons. **If extenuating circumstances prevent a patient from beginning treatment or completing a scheduled procedure or assessment within this time, the patient may continue the study only with the written permission of the medical monitor.**

Table Ea Schedule of Events for Treatment Cycle 1 (Dosing Schedule E) (Daily for 2 Days Followed by 5 Days of Rest per Week in a 21-Day Cycle)

		Day																				
	Screening [a]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**
Informed consent	X																					
Inclusion/exclusion criteria	X																					
HBV, HCV, and HIV testing	X																					
Demographics	X																					
Medical history [b]	X	X																				
Physical examination [b,q]	X	X							X							X						
Height	X																					
Weight		X																				
Vital signs [c,q]	X	X	X	(X)	(X)	(X)	(X)	(X)	X	X	(X)	(X)	(X)	(X)	(X)	X	X	(X)	(X)	(X)	(X)	(X)
ECOG performance status	X																					
12-Lead ECG [d,q]	X	X [d]							X							X						
ECHO/MUGA	X																					
Disease assessment [e]	X																					
Monitoring of concomitant medications and procedures		Recorded from first dose of study drug through up to 30 days after the last dose of study drug or before initiation of new anticancer therapy (whichever comes first).																				
Adverse event reporting		Recorded from first dose of study drug through up to 30 days after the last dose of study drug or before initiation of new anticancer therapy (whichever comes first).																				
	Serious adverse events [f] 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 anticancer therapy (whichever comes first).																					
Continuous heart rhythm monitor [r,q]		X	X						X	X						X	X					
TAK-931 administration [g]		X	X						X	X						X	X					

Footnotes are on last table page.

Table Ea Schedule of Events for Treatment Cycle 1 (continued) (Dosing Schedule E) (Daily for 2 Days Followed by 5 Days of Rest per Week in a 21-Day Cycle)

		Day																			
	Screening [a]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Samples/Laboratory Assessments																						
Pregnancy test [h]	X	X																				
Hematology/chemistry [i,q]	X	X				X			X				X			X			X			
Urinalysis [j]	X	X																				
Fecal immunochemical testing	X																					
Blood sample for cardiac enzymes [k]	X	X							X							X						
CCI																						
CCI																						
Skin punch [m,o]	X (or C1D1)	(X)								X												
CCI																						
Urine and blood sample for PK	Urine and blood samples for PK analysis will be collected on the days and time points specified in Table Ge,f.																					

Abbreviations: BID, twice daily; BP, blood pressure; CxDx, Cycle x, Day x; C_{max}, maximum observed plasma concentration; CT, computed tomography; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ICF, informed consent form; IEC, independent ethics committee; IRB, institutional review board; MRI, magnetic resonance imaging; MUGA, multiple gated acquisition (scan); PK, pharmacokinetic(s); POTS, postural orthostatic tachycardia syndrome; QD, once daily.
Note: Parentheses indicate the test or procedure is to be performed under certain conditions.
[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 physical examination and medical history are not required if the screening physical examination was conducted and medical history obtained within 4 days before administration of the first dose of study drug (C1D1).
[c] Perform vital sign measurements including orthostatic measurements before dosing. Also, perform vital sign measurements on C1D1, C1D2, C1D8, C1D9, C1D15, and C1D16 at 2, 4, and 8 hours postdose (just before PK sampling if on PK sampling day). If the investigator considers that it is otherwise safe, the patient can be discharged during dose holidays. If the investigator considers that it is in the patient's best interest to remain hospitalized, then scheduled assessments in parentheses (X) will be performed and recorded. Orthostatic measurements of BP and pulse/heart rate should be conducted with the patient in a supine position after the patient has been resting quietly for 5 minutes followed by a second measurement after the patient has been standing for 2 minutes. At screening, also measure heart rate after 10 minutes of quiet standing to confirm POTS. At least 3 separate resting

(after 4 to 5 minutes' rest in sitting position) BP measurements should be taken during the screening and the median of those measurements will be utilized as baseline BP reference of individual patient (median of systolic BP and diastolic BP will be evaluated separately).

[d] All 12-lead ECG recordings should be made with the patient in a supine position. On C1D1, C1D8, and C1D15, a 12-lead ECG should be recorded before administration of TAK-931 and before vital sign measurements at approximately 2, 4, 8 hours postdose. ECG should also be performed for patients experiencing Grade ≥2 hypotension during Cycle 1.

[e] 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 on patients with bone metastases rather than CT or MRI. See Section 10.4.18 for more details.

[f] Including serious pretreatment events; see Section 11.2.

[g] TAK-931 will be administered orally QD (or BID by dividing in 2 the total daily dose only if allowed by the sponsor) on Day 1 and 2 of every week in a 21-day cycle. The starting dose will be 100 mg. Study drug will be administered to patients on an empty stomach. Patients should not eat for 2 hours before taking the capsules with 8 ounces of water. Patients should be instructed to eat a meal or snack >1 hour after taking the study drug. See Section 9.1.

[h] A serum beta-human chorionic gonadotropin (β-hCG) 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 (ie, 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.

[i] 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 10.4.14. New clinically significant Grade ≥2 results should be repeated within 3 days and followed until recovery.

[j] Complete urinalysis with qualitative analysis for protein at screening and C1D1. Positive results may require quantitative analysis (assessment of urine protein to creatinine ratio). Refer to Section 10.4.14 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.

[k] A blood sample will be obtained at the screening visit and predose on C1D1, C1D8 and C1D15 for measurement of cardiac enzymes in serum that monitor for acute injury (eg, troponin I or T) or chronic or progressive failure (eg, B-type natriuretic peptide [BNP] or N-terminal pro-brain natriuretic peptide [NT-proBNP]). If screening cardiac enzymes measurement was performed within 4 days before the C1D1 dose, it does not need to be repeated on C1D1.

CCI [redacted]

[m] Skin punch biopsies (2-4 mm) will be obtained for all patients either during screening or predose on C1D1 and postdose on C1D9 or C1D16.

CCI [redacted]

[o] It is strongly recommended that postdose skin biopsies CCI [redacted] are collected between 4 to 9 hours after study drug administration (simultaneously if possible). CCI [redacted] It is acceptable to use an archival predose biopsy collected before study enrollment if no other anticancer systemic treatment was administered between the biopsy collection and the enrollment in the study.

CCI [redacted]

Patients enrolled in the safety expansion cohorts are not required to be hospitalized for Cycle 1. Physical examination, vital sign measurement, and 12-lead ECG measurements will be performed at screening and on Day 1. Hematology and chemistry tests will be performed at screening and on Days 1, 8, and 15. Continuous heart rhythm monitoring is not required. The other tests or examinations will be the same as dose escalation cohorts.

[r] Continuous patient heart rhythm monitoring while the patient is undergoing inpatient observation will start before the administration of TAK-931 on each dosing day for up to 12 hours after intake of the dose. For patients experiencing Grade ≥2 hypotension at any time during Cycle 1, continuous heart rhythm monitoring, and BP and ECG assessment at 2, 4, and 8 hours postdose if it is on a dosing day should be performed in the following 3 administration days even if they are at a reduced dose level. Spot 12-lead ECG assessments may be done to assess an abnormal rhythm that is detected during monitoring and may require medical intervention. Continuous monitoring should not interfere with in-hospital normal patient activities including eating, sleeping, walking, or personal care.

Note: Tests and procedures should be performed on schedule, but occasional changes are allowable (±3 days) with permission of the medical monitor for holidays, vacations, and other administrative reasons. **If extenuating circumstances prevent a patient from beginning treatment or completing a scheduled procedure or assessment within this time, the patient may continue the study only with the written permission of the medical monitor.**

Table Eb Schedule of Events for Treatment Cycle 2 Through PFS Follow-up (Dosing Schedule E) (Daily for 2 Days Followed by 5 Days of Rest per Week in a 21-Day Cycle)

	Cycle 2 and Subsequent Cycles							
	Day 1	**Day 5**	**Day 8**	**Day 12**	**Day 15**	**Day 18**	**EOT [a]**	**PFSFU**
Symptom-directed physical examination [b]	X						X	
Weight	X [c]						X	
Vital signs [d]	X						X	
ECOG performance status [e]	X						X	
12-Lead ECG [f]	X						X	
ECHO/MUGA [g]	X						X	
Disease assessment [h]					X (starting at C3 and performed between D15 and D1 of the next cycle, then Q3C thereafter)		X [i]	X [j] (Q 12 weeks)
Monitoring of concomitant medications and procedures	Recorded from first dose of study drug through up to 30 days after the last dose of study drug or before initiation of new anticancer therapy (whichever comes first).							
Adverse event reporting	Recorded from first dose of study drug through up to 30 days after the last dose of study drug or before initiation of new anticancer therapy (whichever comes first).							
	Serious adverse events [k] 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 anticancer therapy (whichever comes first).							X [s]
TAK-931 administration [l]	Days 1, 2, 8, 9, 15, and 16 of each treatment cycle							
Samples/Laboratory Assessments								
Pregnancy Test [m]							X	
Hematology/Chemistry [n]	X	X [o]	X	X [o]	X	X [o]	X	
Urinalysis [p]	X [p]							
Fecal immunochemical testing [q]	X							
Blood sample for cardiac enzymes [r]	X							

Abbreviations: BID, twice daily; BP, blood pressure; C, cycle; CxDx, Cycle x, Day x; CT, computed tomography; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; EOT, End of Treatment; FIT, fusion-inferred threshold; IEC, independent ethics committee; IRB, institutional review board; MRI, magnetic resonance

imaging; MUGA, multiple gated acquisition (scan); PFSFU, progression-free survival follow-up; Q, every; QD, once daily.
[a] Patients who discontinue TAK-931 treatment early should complete the EOT visit approximately 30-40 days after the last dose of TAK-931 or before the start of subsequent anticancer therapy if that occurs sooner.
[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.
[d] Perform resting vital sign measurement (after 4 to 5 minutes' rest in sitting position) prior to dosing.
[e] ECOG performance status will be performed within 3 days before the beginning (Day 1) of each treatment cycle and at the EOT visit.
[f] 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.
[g] ECHO and/or MUGA should be performed predose on C2D1 and at the EOT visit. The same modality should be used as on the screening visit.
[h] Baseline CT (with contrast) or MRI scan of the chest, abdomen, and pelvis must be at screening, after which CT (with contrast) or MRI may be performed at the end of every third cycle (ie, on or before the start of Cycle 4, Day 1; Cycle 7, Day 1; Cycle 10, Day 1, etc), as clinically indicated, according to standard of care. The same imaging modality (CT [with contrast] MRI, or bone scan) should be used on a patient as at the screening visit and throughout the study. Bone scans may be performed on patients with bone metastases rather than CT or MRI. See Section 10.4.18 for more details.
[i] 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.
[j] Patients who discontinue study treatment for reasons other than PD will undergo CT/MRI scans every 12 weeks (±1 week) from EOT until the occurrence of PD, the start of subsequent antineoplastic therapy, or until 6 months after discontinuation of study treatment, whichever occurs first.
[k] Including serious pretreatment events; see Section 11.2.
[l] TAK-931 will be administered orally QD (or BID only if indicated by the sponsor) on Days 1 and 2 of each week in a 21-day cycle. The starting dose will be 100 mg. Study drug will be administered to patients on an empty stomach. Patients should not eat for 2 hours before taking the capsules with 8 ounces of water. Patients should be instructed to eat a meal or snack >1 hour after taking study drug. See Section 9.1.
[m] 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.
[n] See Section 9.4. New Grade ≥3 results should be repeated a minimum of every 3 days until recovered to Grade ≤2.
[o] The hematology and chemistry blood samples on Days 5, 12, and 18 of each cycle starting with Cycle 2 may be waived if there is no evidence of Grade ≥3 analytical toxicity in the previous cycle. From Cycle 7 and beyond the hematology and chemistry tests will only be conducted on Day 1 of each cycle if in the opinion of the investigators is safe.
[p] 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 10.4.14 for required clinical urinalysis tests.
[q] A stool sample for fecal immunochemical testing may be collected within 4 days before dosing on C2D1 and C3D1. If a patient has a positive FIT at screening, no further collection is required.
[r] A blood sample will be obtained predose on C2D1 for measurement of cardiac enzymes in serum that monitor for acute injury (ie, troponin I or T) or chronic or progressive failure (ie, B-type natriuretic peptide [BNP] or N-terminal pro-brain natriuretic peptide [NT-proBNP]).
[s] After EOT, only related SAEs must be reported to the sponsor's Department of Pharmacovigilance or designee.
Note: Tests and procedures should be performed on schedule, but occasional changes are allowable (±3 days) with permission of the medical monitor for holidays, vacations, and other administrative reasons. **If extenuating circumstances prevent a patient from beginning treatment or completing a scheduled procedure or assessment within this time, the patient may continue the study only with the written permission of the medical monitor.**

Table Fa Schedule of Events for Treatment Cycle 1 (Dosing Schedule F) (Once Weekly in a 21-Day Cycle)

		Day																			
	Screening [a]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**
Informed consent	X																					
Inclusion/exclusion criteria	X																					
HBV, HCV, and HIV testing	X																					
Demographics	X																					
Medical history [b]	X	X																				
Physical examination [b,q]	X	X							X							X						
Height	X																					
Weight		X																				
Vital signs [c,q]	X	X	(X)	(X)	(X)	(X)	(X)	(X)	X	(X)	(X)	(X)	(X)	(X)	(X)	X	(X)	(X)	(X)	(X)	(X)	(X)
ECOG performance status	X																					
12-Lead ECG [d,q]	X	X [d]							X							X						
ECHO/MUGA	X																					
Disease assessment [e]	X																					
Monitoring of concomitant medications and procedures		Recorded from first dose of study drug through up to 30 days after the last dose of study drug or before initiation of new anticancer therapy (whichever comes first).																				
Adverse event reporting		Recorded from first dose of study drug through up to 30 days after the last dose of study drug or before initiation of new anticancer therapy (whichever comes first).																				
	Serious adverse events [f] 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 anticancer therapy (whichever comes first).																					
Continuous heart rhythm monitoring [r,q]		X							X							X						
TAK-931 administration [g]		X							X							X						

Footnotes are on last table page.

Table Fa Schedule of Events for Treatment Cycle 1 (continued) (Dosing Schedule F) (Once Weekly in a 21-Day Cycle)

	Screening [a]	Day 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Samples/Laboratory Assessments																						
Pregnancy test [h]	X	X																				
Hematology/chemistry [t,q]	X	X				X			X				X			X			X			
Urinalysis [J]	X	X																				
Fecal immunochemical testing	X																					
Blood sample for cardiac enzymes [k]	X	X							X							X						
CCI																						
CCI																						
Skin punch [m,o]	X (or C1D1)	(X)							X													
CCI																						
Urine and blood sample for PK	Urine and blood samples for PK analysis will be collected on the days and time points specified in Table Ge,f.																					

Abbreviations: BID, twice daily; BP, blood pressure; CxDx, Cycle x, Day x; C_{max}, maximum observed plasma concentration; CT, computed tomography; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ICF, informed consent form; IEC, independent ethics committee; IRB, institutional review board; MRI, magnetic resonance imaging; MUGA, multiple gated acquisition (scan); PK, pharmacokinetic(s); POTS, postural orthostatic tachycardia syndrome; QD, once daily.
Note: Parentheses indicate the test or procedure is to be performed under certain conditions.
[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 physical examination and medical history are not required if the screening physical examination was conducted and medical history obtained within 4 days before administration of the first dose of study drug (C1D1).
[c] Perform vital sign measurements including orthostatic measurements before dosing. Also, perform vital sign measurements on C1D1, C1D8, and C1D15 at 2, 4, and 8 hours postdose (just before PK sampling if on PK sampling day). If the investigator considers that it is otherwise safe, the patient can be discharged during dose holidays. If the investigator considers that it is in the patient's best interest to remain hospitalized, then scheduled assessments in parentheses (X) will be performed and recorded. Orthostatic measurements of BP and pulse/heart rate should be conducted with the patient in a supine position after the patient has been resting quietly for 5 minutes followed by a second measurement after the patient has been standing for 2 minutes. At screening, also measure heart rate after 10 minutes of quiet standing to confirm POTS. At least 3 separate resting (after 4 to 5 minutes' rest in sitting position) BP measurements should be taken during the screening and the median of those measurements will be utilized as baseline BP reference of individual patient

(median of systolic BP and diastolic BP will be evaluated separately).
[d] All 12-lead ECG recordings should be made with the patient in a supine position. On C1D1, C1D8, and C1D15, a 12-lead ECG should be recorded before administration of TAK-931 and before vital sign measurements at approximately 2, 4 and 8 hours postdose. ECG should also be performed for patients experiencing Grade ≥2 hypotension during Cycle 1.
[e] 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 on patients with bone metastases rather than CT or MRI. See Section 10.4.18 for more details.
[f] Including serious pretreatment events; see Section 11.2.
[g] TAK-931 will be administered orally QD (or BID by dividing the QD dose in 2 and only if approved by the sponsor) on Day 1 every week in a 21-day cycle. The starting dose will be determined after Schedule E dose escalation is completed. Study drug will be administered to patients on an empty stomach. Patients should not eat for 2 hours before taking the capsules with 8 ounces of water. Patients should be instructed to eat a meal or snack >1 hour after taking the study drug. See Section 9.1.
[h] A serum beta-human chorionic gonadotropin (β-hCG) 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 (ie, 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.
[i] 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 10.4.14. New clinically significant Grade ≥2 results should be repeated within 3 days and followed until recovery.
[j] Complete urinalysis with qualitative analysis for protein at screening and C1D1. Positive results may require quantitative analysis (assessment of urine protein to creatinine ratio).Refer to Section 10.4.14 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.
[k] A blood sample will be obtained at the screening visit and predose on C1D1, C1D8, and C1D15 for measurement of cardiac enzymes in serum that monitor for acute injury (ie, troponin I or T) or chronic or progressive failure (ie, B-type natriuretic peptide [BNP] or N-terminal pro-brain natriuretic peptide [NT-proBNP]). If screening cardiac enzymes measurement was performed within 4 days before the C1D1 dose, it does not need to be repeated on C1D1.
CCI [redacted]
[m] Skin punch biopsies (2-4 mm) will be obtained for all patients either during screening or predose on C1D1 and postdose on C1D8 or C1D15.
CCI [redacted]
[o] It is strongly recommended that postdose skin biopsies CCI [redacted] are collected between 4 to 9 hours after study drug administration (simultaneously if possible). CCI [redacted] It is acceptable to use an archival predose biopsy collected before study enrollment if no other anticancer systemic treatment was administered between the biopsy collection and the enrollment in the study.
CCI [redacted]
[q] Patients enrolled in the safety expansion cohorts are not required to be hospitalized for Cycle 1. Physical examination, vital sign measurement, and 12-lead ECG measurements will be performed at screening and on Day 1. Hematology and chemistry tests will be performed at screening and on Days 1, 8, and 15. Continuous heart rhythm monitoring is not required. The other tests or examinations will be the same as dose escalation cohorts.
[r] Continuous patient heart rhythm monitoring while the patient is undergoing inpatient observation will start before the administration of TAK-931 for up to 12 hours after intake of the dose on each dosing day. For patients experiencing Grade ≥2 hypotension at any time during Cycle 1, continuous heart rhythm monitoring, and BP and ECG assessment at 2, 4, and 8 hours postdose should be performed in the following 3 administration days even if they are at a reduced dose level. Spot 12-lead ECG assessments may be done to assess an abnormal rhythm that is detected during monitoring and may require medical intervention. Continuous monitoring should not interfere with in-hospital normal patient activities including eating, sleeping, walking, or personal care.
[s] Or C1D15.

Note: Tests and procedures should be performed on schedule, but occasional changes are allowable (±3 days) with permission of the medical monitor for holidays, vacations, and other administrative reasons. If extenuating circumstances prevent a patient from beginning treatment or completing a scheduled procedure or assessment within this time, the patient may continue the study only with the written permission of the medical monitor.

Table Fb Schedule of Events for Treatment Cycle 2 Through PFS Follow-up (Dosing Schedule F) (Continuous Schedule; Once Weekly in a 21-Day Cycle)

	Cycle 2 and Subsequent Cycles						EOT [a]	PFSFU
	Day 1	**Day 5**	**Day 8**	**Day 12**	**Day 15**	**Day 18**		
Symptom-directed physical examination [b]	X						X	
Weight	X [c]						X	
Vital signs [d]	X						X	
ECOG performance status [e]	X						X	
12-Lead ECG [f]	X						X	
ECHO/MUGA [g]	X						X	
Disease assessment [h]					X (starting at C3 and performed between D15 and D1 of the next cycle, then Q3C thereafter)		X [i]	X [j] (Q 12 weeks)
Monitoring of concomitant medications and procedures	Recorded from first dose of study drug through up to 30 days after the last dose of study drug or before initiation of new anticancer therapy (whichever comes first).							
Adverse event reporting	Recorded from first dose of study drug through up to 30 days after the last dose of study drug or before initiation of new anticancer therapy (whichever comes first).							
	Serious adverse events [k] 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 anticancer therapy (whichever comes first).							X [s]
TAK-931 administration [l]	Days 1, 8, and 15 of each treatment cycle							
Samples/Laboratory Assessments								
Pregnancy Test [m]							X	
Hematology/Chemistry [n]	X	X [o]	X	X [o]	X	X [o]	X	
Urinalysis [p]	X [p]							
Fecal immunochemical testing [q]	X							
Blood sample for cardiac enzymes [r]	X							

Abbreviations: BID, twice daily; BP, blood pressure; C, cycle; CxDx, Cycle x, Day x; CT, computed tomography; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; EOT, End of Treatment; FIT, fusion-inferred threshold; IEC, independent ethics committee; IRB, institutional review board; MRI, magnetic resonance

imaging; MUGA, multiple gated acquisition (scan); PFSFU, progression-free survival follow-up; Q, every; QD, once daily.
[a] Patients who discontinue TAK-931 treatment early should complete the EOT visit approximately 30-40 days after the last dose of TAK-931 or before the start of subsequent anticancer therapy if that occurs sooner.
[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.
[d] Perform resting vital sign measurement (after 4 to 5 minutes' rest in sitting position) prior to dosing.
[e] ECOG performance status will be performed within 3 days before the beginning (Day 1) of each treatment cycle and at the EOT visit.
[f] 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.
[g] ECHO and/or MUGA should be performed predose on C2D1 and at the EOT visit. The same modality should be used as on the screening visit.
[h] Baseline CT (with contrast) or MRI scan of the chest, abdomen, and pelvis must be at screening, after which CT (with contrast) or MRI may be performed at the end of every third cycle (ie, on or before the start of Cycle 4, Day 1; Cycle 7, Day 1; Cycle 10, Day 1, etc), as clinically indicated, according to standard of care. The same imaging modality (CT [with contrast] MRI, or bone scan) should be used on a patient as at the screening visit and throughout the study. Bone scans may be performed on patients with bone metastases rather than CT or MRI. See Section 10.4.18 for more details.
[i] 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.
[j] Patients who discontinue study treatment for reasons other than PD will undergo CT/MRI scans every 12 weeks (±1 week) from EOT until the occurrence of PD, the start of subsequent antineoplastic therapy, or until 6 months after discontinuation of study treatment, whichever occurs first.
[k] Including serious pretreatment events; see Section 11.2.
[l] TAK-931 will be administered orally QD (or BID only if indicated by the sponsor) on Days 1 and 2 of each week) in a 21-day cycle. The starting dose will be determined after Schedule E dose escalation is completed. Study drug will be administered to patients on an empty stomach. Patients should not eat for 2 hours before taking the capsules with 8 ounces of water. Patients should be instructed to eat a meal or snack >1 hour after taking study drug. See Section 9.1.
[m] 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.
[n] See Section 9.4. New Grade ≥3 results should be repeated a minimum of every 3 days until recovered to Grade ≤2.
[o] The hematology and chemistry blood samples on Days 5, 12, and 18 of each cycle starting with Cycle 2 may be waived if there is no evidence of Grade ≥3 analytical toxicity in the previous cycle. From Cycle 7 and beyond the hematology and chemistry tests will only be conducted on Day 1 of each cycle if in the opinion of the investigators is safe.
[p] 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 10.4.14 for required clinical urinalysis tests.
[q] A stool sample for fecal immunochemical testing may be collected within 4 days before dosing on C2D1 and C3D1. If a patient has a positive FIT at screening, no further collection is required.
[r] A blood sample will be obtained predose on C2D1 for measurement of cardiac enzymes in serum that monitor for acute injury (ie, troponin I or T) or chronic or progressive failure (ie, B-type natriuretic peptide [BNP] or N-terminal pro-brain natriuretic peptide [NT-proBNP]).
[s] After EOT, only related SAEs must be reported to the sponsor's Department of Pharmacovigilance or designee.
Note: Tests and procedures should be performed on schedule, but occasional changes are allowable (±3 days) with permission of the medical monitor for holidays, vacations, and other administrative reasons. **If extenuating circumstances prevent a patient from beginning treatment or completing a scheduled procedure or assessment within this time, the patient may continue the study only with the written permission of the medical monitor.**

Table Ga Pharmacokinetic Sample Breakdown (Dosing Schedule A)

	Cycle 1						
	Day 1			Day 8		Day 15	Day X[b]
	Orthostatics (BP and HR) [a]	Plasma	Urine	Orthostatics (BP and HR) [a]	Plasma	Plasma	Plasma
Predose	X	X	X [c,d]	X	X	X [e]	X
30 min postdose (±5 min)		X			X		
1 hour postdose (±10 min) [f]		X			X		
2 hours postdose (±20 min)	X	X		X	X		
4 hours postdose (±30 min)	X	X		X	X		
6 hours postdose (±60 min)		X			X		
8 hours postdose (±60 min)	X	X		X	X		
12 hours postdose (±60 min) [g]		X			X		
24 hours postdose (±3 hours) [h]	X	X		X	X		
1-3 hours postdose							X
4-9 hours postdose							X

Abbreviations: AE, adverse event; BP, blood pressure; BID, twice daily; CxDx, Cycle x, Day x; ECG, electrocardiogram; HR, heart rate; QD, once daily; PK, pharmacokinetic(s).
[a] Orthostatic measurements should be completed immediately after recording a 12-lead ECG and before collection of the corresponding PK sample.
[b] If skin biopsy CCI is taken on a non-PK sampling day, sparse PK plasma samples should be collected on that day (Day X). The exact PK sampling date and time will be recorded.
[c] Predose spot urine collection: The patient should be asked to void completely approximately 30 minutes before the administration of the first dose of TAK-931.
[d] Timed urine collection: The 12-hour urine collection begins on Day 1 at the time of TAK-931 administration and ends 12 hours later when the 12-hour PK plasma specimen is collected. See Section 10.4.19.
[e] After the patient has completed 14 days of continuous dosing, a PK sample should be collected either approximately 12 hours after administration of the last dose of study drug on Cycle 1 Day 14 in the BID dosing schedule or approximately 24 hours after administration of the last dose of study drug on Cycle 1 Day 14 in the QD dosing schedule.
[f] Patients should be provided food/allowed to eat immediately after the 1-hour PK sample has been obtained.
[g] The 12-hour PK plasma specimen should be collected before the administration of the evening dose of TAK-931 in the BID dosing schedule.
[h] For QD dosing only: The 24-hour assessments of orthostatics should be performed and the PK plasma specimen collected before administration of the morning dose of TAK-931.
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.

Table Gb Pharmacokinetic Sample Breakdown (Dosing Schedule B)

	Cycle 1					
	Day 1			Day 7		Day X [b]
	Orthostatics (BP and HR) [a]	Plasma	Urine	Orthostatics (BP and HR) [a]	Plasma	Plasma
Predose	X	X	X [c,d]	X	X	X
30 min postdose (±5 min)		X			X	
1 hour postdose (±10 min) [e]		X			X	
2 hours postdose (±20 min)	X	X		X	X	
4 hours postdose (±30 min)	X	X		X	X	
6 hours postdose (±60 min)		X			X	
8 hours postdose (±60 min)	X	X		X	X	
12 hours postdose (±60 min) [f]		X			X	
24 hours postdose (±3 hours) [g]	X	X		X	X	
1-3 hours postdose						X
4-9 hours postdose						X

Abbreviations: AE, adverse event; BP, blood pressure; BID, twice daily; CxDx, Cycle x, Day x; ECG, electrocardiogram; HR, heart rate; QD, once daily; PK=pharmacokinetic(s).
[a] Orthostatic measurements should be completed immediately after recording a 12-lead ECG and before collection of the corresponding PK sample.
[b] If skin biopsy [redacted] is taken on a non-PK sampling day, sparse PK plasma samples should be collected on the same day (Day X). The exact PK sampling date and time will be recorded.
[c] Predose spot urine collection: The patient should be asked to void completely approximately 30 minutes before the administration of the first dose of TAK-931.
[d] Timed urine collection: The 12-hour urine collection begins on Day 1 at the time of TAK-931 administration and ends 12 hours later when the 12-hour PK plasma specimen is collected. See Section 10.4.19.
[e] Patients should be provided food/allowed to eat immediately after the 1-hour PK sample has been obtained.
[f] The 12-hour PK plasma specimen should be collected before the administration of the evening dose of TAK-931 in the BID dosing schedule.
[g] For QD dosing only: The 24-hour assessments of orthostatics should be performed and the PK plasma specimen collected before administration of the morning dose of TAK-931.
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.

Table Gc Pharmacokinetic Sample Breakdown (Dosing Schedule C)

	Cycle 1					
	Day 1			Day 7		Day X [b]
	Orthostatics (BP and HR) [a]	Plasma	Urine	Orthostatics (BP and HR) [a]	Plasma	Plasma
Predose	X	X	X [c,d]	X	X	X
30 min postdose (±5 min)		X			X	
1 hour postdose (±10 min) [e]		X			X	
2 hours postdose (±20 min)	X	X		X	X	
4 hours postdose (±30 min)	X	X		X	X	
6 hours postdose (±60 min)		X			X	
8 hours postdose (±60 min)	X	X		X	X	
12 hours postdose (±60 min) [f]		X			X	
24 hours postdose (±3 hours) [g]	X	X		X	X	
1-3 hours postdose						X
4-9 hours postdose						X

Abbreviations: AE, adverse event; BP, blood pressure; BID, twice daily; CxDx, Cycle x, Day x; ECG, electrocardiogram; HR, heart rate; QD, once daily; PK, pharmacokinetic(s).
[a] Orthostatic measurements should be completed immediately after recording a 12-lead ECG and before collection of the corresponding PK sample.
[b] If skin biopsy CCI is taken on a non-PK sampling day, sparse PK plasma samples should be collected on the same day (Day X). The exact PK sampling date and time will be recorded.
[c] Predose spot urine collection: The patient should be asked to void completely approximately 30 minutes before the administration of the first dose of TAK-931.
[d] Timed urine collection: The 12-hour urine collection begins on Day 1 at the time of TAK-931 administration and ends 12 hours later when the 12-hour PK plasma specimen is collected. See Section 10.4.19.
[e] Patients should be provided food/allowed to eat immediately after the 1-hour PK sample has been obtained.
[f] The 12-hour PK plasma specimen should be collected before the administration of the evening dose of TAK-931 in the BID dosing schedule.
[g] For QD dosing only: The 24-hour assessments of orthostatics should be performed and the PK plasma specimen collected before administration of the morning dose of TAK-931.
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.

Table Gd Pharmacokinetic Sample Breakdown (Dosing Schedule D)

	Cycle 1					
	Day 1			Day 8	Day X [b]	Day 21
	BP and HR [a]	Plasma	Urine	Plasma	Plasma	Plasma
Predose	X	X	X [c,d]	X	X	
30 min postdose (±5 min)		X		X		
1 hour postdose (±10 min) [e]		X		X		
2 hours postdose (±20 min)	X	X		X		
4 hours postdose (±30 min)		X		X		
6 hours postdose (±60 min)		X		X		
8 hours postdose (±60 min)		X		X		
12 hours postdose (±60 min) [f]		X		X		
24 hours postdose (±3 hours) [g]		X		X		X (h)
1-3 hours postdose					X	
4-9 hours postdose					X	

Abbreviations: AE, adverse event; BP, blood pressure; BID, twice daily; CxDx, Cycle x, Day x; ECG, electrocardiogram; HR, heart rate; QD, once daily; PK, pharmacokinetic(s).
[a] Resting BP and HR will be measured.
[b] If skin biopsy [redacted] is taken on a non-PK sampling day, sparse PK plasma samples should be collected on the same day (Day X). The exact PK sampling date and time will be recorded.
[c] Predose spot urine collection: The patient should be asked to void completely approximately 30 minutes before the administration of the first dose of TAK-931.
[d] Timed urine collection: The 12-hour urine collection begins on Day 1 at the time of TAK-931 administration and ends 12 hours later when the 12-hour PK plasma specimen is collected. See Section 10.4.19.
[e] Patients should be provided food/allowed to eat immediately after the 1-hour PK sample has been obtained.
[f] The 12-hour PK plasma specimen should be collected before the administration of the evening dose of TAK-931 in the BID dosing schedule.
[g] For QD dosing only: The PK plasma specimen collected before administration of the morning dose of TAK-931.
[h] For BID dosing, the PK plasma specimen should be collected 12 hours (±60 min) after the evening dose on Day 21 and before the administration of the morning dose of TAK-931 on Day 22.
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.

Table Ge,f Pharmacokinetic Sample Breakdown (Dosing Schedules E and F)

	Cycle 1					
	Day 1			Day 9 for Schedule E, Day 8 for Schedule F		Day X [b]
	Orthostatic BP and HR [a]	Plasma	Urine	Orthostatic BP and HR [a]	Plasma	Plasma
Predose	X	X	X [c,d]	X	X	X
30 min postdose (±5 min)		X			X	
1 hour postdose (±10 min) [e]		X			X	
2 hours postdose (±20 min)	X	X		X	X	
4 hours postdose (±30 min)	X	X			X	
6 hours postdose (±60 min)		X			X	
8 hours postdose (±60 min)	X	X		X	X	
12 hours postdose (±60 min) [f]		X			X	
24 hours postdose (±3 hours) [g]	X	X		X	X	
1-3 hours postdose						X
4-9 hours postdose						X

Abbreviations: AE, adverse event; BP, blood pressure; BID, twice daily; CxDx, Cycle x, Day x; ECG, electrocardiogram; HR, heart rate; QD, once daily; PK, pharmacokinetic(s).
[a] Orthostatic measurements should be completed immediately after recording a 12-lead ECG and before collection of the corresponding PK sample.
[b] If skin biopsy [redacted] is taken on a non-PK sampling day, sparse PK plasma samples should be collected on the same day (Day X). The exact PK sampling date and time will be recorded.
[c] Predose spot urine collection: The patient should be asked to void completely approximately 30 minutes before the administration of the first dose of TAK-931.
[d] Timed urine collection: The 12-hour urine collection begins on Day 1 at the time of TAK-931 administration and ends 12 hours later when the 12-hour PK plasma specimen is collected. See Section 10.4.19.
[e] Patients should be provided food/allowed to eat immediately after the 1-hour PK sample has been obtained.
[f] The 12-hour PK plasma specimen should be collected before the administration of the evening dose of TAK-931 in the BID dosing schedule.
[g] For QD dosing only: the 24-hour orthostatic assessments should be performed before PK plasma specimen collection in the morning on the following day.
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.

Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject 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 subjects, prior to 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 subjects. 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 subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an informed consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject'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: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. American Journal of Clinical Oncology 1982;5(6):649-55 [25].

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 [26].

Appendix F New York Heart Association Classification of Cardiac Disease

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, MA: Little, Brown & Co; 1994:253-256.[27]

Appendix G Clinically Significant Strong Metabolic Enzyme Inducers

Inducers[a]
Carbamazepine
Enzalutamide
Mitotane
Phenytoin
Rifampin
St. John's wort

[a] This is not an exhaustive list; refer to the following source: fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664 htm#table3-3 (accessed 15 February 2018).

Appendix H Detailed Description of Amendments to Text

This document describes changes in reference to Protocol Incorporating Amendment 04. Original text that was deleted or revised in Amendment 04 is indicated using strikethrough font. New or revised text adopted in Amendment 03 is shown in bold red font.

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: Added Dosing Schedules E and F.

The primary change occurs in Section 7.1 Overview of Study Design:

Initial wording:

…

TAK-931 initially will be administered once daily (QD) for 14 days of each 21-day treatment cycle (Dosing Schedule A). The starting dose will be 30 mg. If the preliminary PK data from the first 2 dose escalation cohorts in any schedule support BID dosing, subsequent cohorts may transition to a BID dosing schedule (by dividing the daily dose in 2) either before or when a geometric mean C_{max} of 800 ng/mL is predicted after a single dose of TAK-931 on C1D1 in a cohort or if C_{max}-related AEs are observed, or if it is recommended by potential pharmacodynamic effect.

…

To ensure patient safety and to minimize the number of patients exposed to non-efficacious doses, the dose escalation in Schedule A will consist of an initial accelerated escalation phase in which dose levels are increased by 100%. The accelerated escalation phase will transition to modified Fibonacci escalation steps after 1 patient experiences a DLT in Cycle 1 or when 2 patients experience ≥Grade 2 hematologic or non-hematologic related or possibly related drug toxicity (see Section 9.2) or when geometric mean plasma C_{max} for the cohort reaches or exceeds 800 ng/mL. For Schedules B, C and D accelerated escalation is not applicable. The dose escalation steps will be modified, as needed, based on clinical safety and PK results. The escalation steps for Schedules A, B and C may also be modified based on accumulating PK data and BLRM that would provide narrower escalation steps and potentially decrease the number of patients exposed to doses above the MTD. In Schedule D, BLRM will not be applied. Clinical safety, PK and pharmacodynamic information will drive escalation (or de-escalation) decisions.

There will be a minimum 1-week interval between C1D1 of the first patient dosed and C1D1 of the second patient dosed for each dose escalation cohort. Subsequent patient dosing (third patient per cohort and beyond) may occur at a shorter interval (eg, <7 days from previous patient's C1D1 dosing) but no more than 1 patient will undergo C1D1 dosing within a 1-day period. These intervals are not applicable to patients enrolled in Schedule D, to cases of dose de-escalation and to patients enrolled in the

safety expansion cohorts.

…

Skin punch biopsies will be obtained for all patients either during screening or predose on C1D1 and postdose on any dosing day after the completion of 3 consecutive dosing days (eg, Day 4 or after) in Cycle 1. CCI [redacted] It is acceptable to use an archival predose biopsy collected before study enrollment if no other anticancer systemic treatment was administered between the biopsy collection and the enrollment into this study. It is strongly recommended that postdose skin biopsies CCI [redacted] are collected between 4 to 9 hours after study drug administration (simultaneously if possible).

Amended or new wording:

TAK-931 initially will be administered once daily (QD) for 14 days of each 21-day treatment cycle (Dosing Schedule A). The starting dose will be 30 mg. ~~If the preliminary PK data from the first 2 dose escalation cohorts in any schedule support BID dosing, s~~Subsequent cohorts may transition to a BID dosing schedule (by dividing the daily dose in 2) ~~either before or when the geometric mean C_{max} of 800 ng/mL is predicted after a single dose of TAK-931 on C1D1 in a cohort or~~ if C_{max}-related AEs are observed, or if it is recommended by potential pharmacodynamic effect **in a cohort during escalation**.

…

Up to 2 additional schedules will be tested after implementation of Amendment 04:

- **Dosing Schedule E: TAK-931 will be administered QD for 2 consecutive days followed by another 5 days of rest and repeated weekly (2 days on and 5 days off), for a cycle duration of 21 days. The starting dose will be 100 mg QD, the current maximum administered dose in Schedule B. Schedule E is less dose-intense than Schedule B. Change from QD to BID (ie, splitting total daily dose) will be decided primarily if there are C_{max}-related TEAEs with QD administration during dose escalation. Changing from QD to BID is allowed for any given patient during treatment if clinically indicated. This decision can be extended to current or future patients receiving QD dosing. Dose escalation from dose level 2 onwards will be governed using the same BLRM method with PK guidance as described in Section 9.3.**
- **Dosing Schedule F: The decision to implement Schedule F will be determined based on the safety, tolerability, PK, and pharmacodynamics of Schedule E. TAK-931 will be administered QD or BID on Day 1 every week (1 day on and 6 days off treatment) in a 21-day treatment cycle. The starting dose will be**

determined based on data of Schedule E. The dose intensity (DI) of starting dose in Schedule F will not exceed that of the maximum administered dose in Schedule E. Dose escalation will be governed using the same BLRM method with PK guidance as described in Section 9.3. If Schedule E safety data suggest a once-weekly dosing schedule may allow higher dose escalation it may be decided to continue the escalation using Dosing Schedule F.

…

To ensure patient safety and to minimize the number of patients exposed to non-efficacious doses, the dose escalation in Schedule A will consist of an initial accelerated escalation phase in which dose levels are increased by 100%. The accelerated escalation phase will transition to modified Fibonacci escalation steps after 1 patient experiences a DLT in Cycle 1 or when 2 patients experience Grade ≥2 hematologic or nonhematologic related or possibly related drug toxicity (see Section 9.2) or when geometric mean plasma C_{max} for the cohort reaches or exceeds 800 ng/mL. For Schedules B, C, ~~and~~ D**, E, and F**, accelerated escalation is not applicable. The dose escalation steps will be modified, as needed, based on clinical safety and PK results. The escalation steps for Schedules A, B, ~~and~~ C**, E, and F** may also be modified based on accumulating PK data and BLRM that would provide narrower escalation steps and potentially decrease the number of patients exposed to doses above the MTD. In Schedule D, BLRM will not be applied. Clinical safety, PK, and pharmacodynamic information will be used to make escalation (or de-escalation) decisions.

There will be a minimum 1-week interval between C1D1 of the first patient dosed and C1D1 of the second patient dosed for each dose escalation cohort **for Schedules A, B, and C**. Subsequent patient dosing (third patient per cohort and beyond) may occur at a shorter interval (eg, <7 days from previous patient's C1D1 dosing) but no more than 1 patient will undergo C1D1 dosing within a 1-day period. These intervals are not applicable to patients enrolled in Schedule D, to cases of dose de-escalation and to patients enrolled in the safety expansion cohorts. **For Schedules E and F, it is necessary to wait at least 24 hours from the last dose administered in the first week of treatment of the first patient to C1D1 of the second and third patients dosed in each escalation cohort.**

…

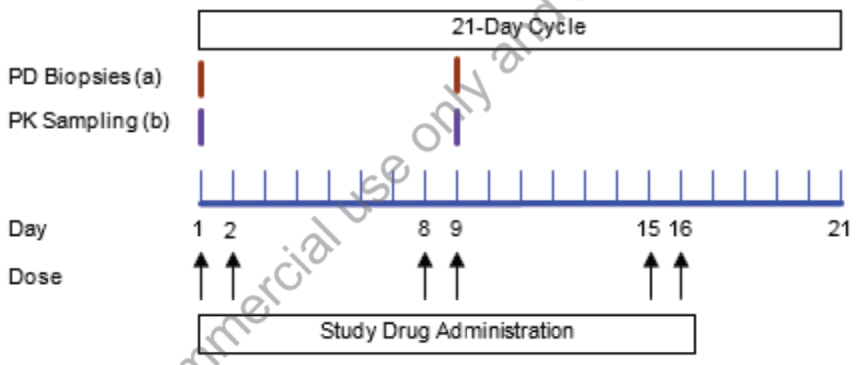
Skin punch biopsies will be obtained for all patients either during screening or predose on C1D1**, and for patients in Schedules A to D postdose on any dosing day after the completion of 3 consecutive dosing days (eg, Day 4 or after) in Cycle 1. Postdose skin biopsy will be obtained on Day 9 in Schedule E, and on Day 8 in Schedule F. Other time points for biopsy collection (for example in Cycle 1 week 3 or outside Cycle 1) can be agreed with the sponsor.** CCI [redacted]

CCI [redacted]

CCI [redacted] It is acceptable to use an archival predose biopsy collected before study enrollment if no other anticancer systemic treatment was administered between the biopsy collection and the enrollment into this study. It is strongly recommended that postdose skin biopsies CCI [redacted] are collected between 4 and 9 hours after study drug administration (simultaneously if possible).

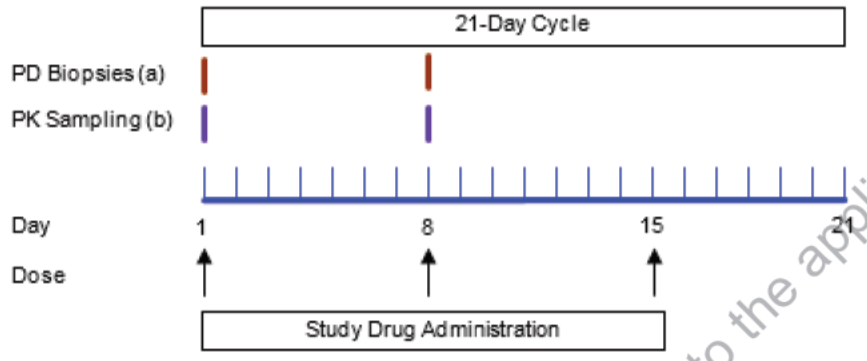
…

Dosing Schedule E (2 days on, 5 days off; 21-day cycle)



Other timepoints for biopsy collection (for example in Cycle 1 Week 3 or outside Cycle 1) can be agreed with the Sponsor.

Dosing Schedule F (once weekly; 21-day cycle)



Other timepoints for biopsy collection (for example in Cycle 1 Week 3 or outside Cycle 1) can be agreed with the Sponsor.

Rationale for Change:

To explore once and twice weekly dosing regimens.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY.
- Section 9.2 Definitions of Dose-Limiting Toxicity.
- Section 9.3 Dose Escalation Rules.
- Section 9.5.5 Hypotension.
- Section 10.4 Study Procedures.
- Section 10.4.15 Skin Punch Biopsies [redacted]
- Section 10.7 Discontinuation of Treatment With Study Drug and Patient Replacement.
- Section 14.3 Determination of Sample Size.
- Appendix A, Schedule of Events, Table Ea, Table Eb, Table Fa, Table Fb, and Table Ge,f.

Change 2: Modified schedule for skin punch [redacted]

The primary changes occur in Section 10.4.15 Skin Punch Biopsies [redacted]

Initial wording:	Section 10.4.15: pMCM2 will be detected semiquantitatively by IHC of histologic sections of formalin-fixed, paraffin-embedded skin biopsies. Skin punch biopsies (2-4 mm) will be obtained for all patients either during screening or predose on C1D1 and postdose on any drug dosing day after 3 consecutive dosing days (eg, Day 4 or after) in Cycle 1. It is strongly recommended that postdose skin biopsies are collected between 4 to 9 hours after study drug administration [redacted]. Refer to Section 10.4.21 for sample retention. [redacted] [redacted]

Amended or new wording:

Section 10.4.15:

pMCM2 will be detected semiquantitatively by IHC of histologic sections of formalin-fixed, paraffin-embedded skin biopsies. Skin punch biopsies (2-4 mm) will be obtained for all patients either during screening or predose on C1D1, and **for patients in Schedule A to D** postdose on any drug dosing day after 3 consecutive dosing days (eg, Day 4 or after) in Cycle 1. **A postdose skin biopsy will be obtained on Day 9 in Schedule E and on Day 8 in Schedule F. Other time points for biopsy collection outside Cycle 1 can be performed if explicitly approved by the sponsor.** It is strongly recommended that postdose skin biopsies are collected between 4 to 9 hours after study drug administration CCI [redacted]. Refer to Section 10.4.21 for sample retention.

CCI [redacted]

CCI [redacted]

Rationale for Change:

Added biopsy schedule for Dosing Schedules E and F.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY.
- Section 7.1 Overview of Study Design.

Change 3: Clarified method of calculation for the TAK-931 accumulation ratio.

The primary change occurs in Section 14.1.4 Pharmacokinetic Analysis:

Initial wording:	Rac
Amended or new wording:	~~Rac~~ $R_{ac(AUC)}$

Rationale for Change:

Clarified the method used to calculate the accumulation ratio.

Various other sections also contain this change.

Change 4: Updated nonclinical data.

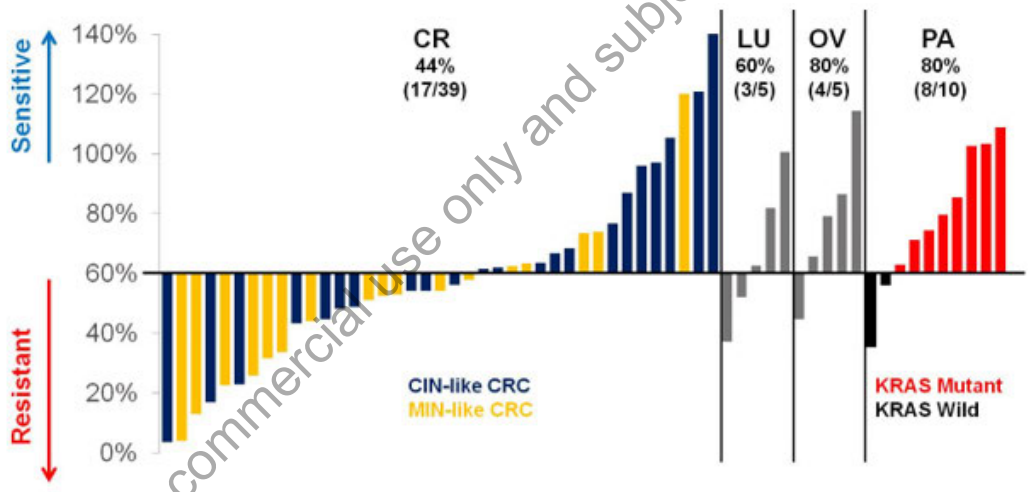
The primary change occurs in Section 4.1.1 Nonclinical Experience:

Initial wording:

…

The in vivo antitumor activity of TAK-931 was further characterized utilizing up to 59 primary human xenograft tumors. In this preclinical "phase 2-like" study, mice with xenografted human primary tumors received TAK-931 60 mg/kg PO for 3 days on and 4 days off weekly for 21 days (a dose and schedule shown to be efficacious across multiple tumor models [Figure 4.a]). Response characterized by tumor growth inhibition and survival was then analyzed relative to the underlying mutation status of the primary human tumors as well as gene expression profile to identify potential genetic biomarkers associated with resistance and sensitivity to TAK-931.

…



CR=colorectal, CRC=colorectal cancer, LU=lung, OV=ovarian, PA=pancreatic.

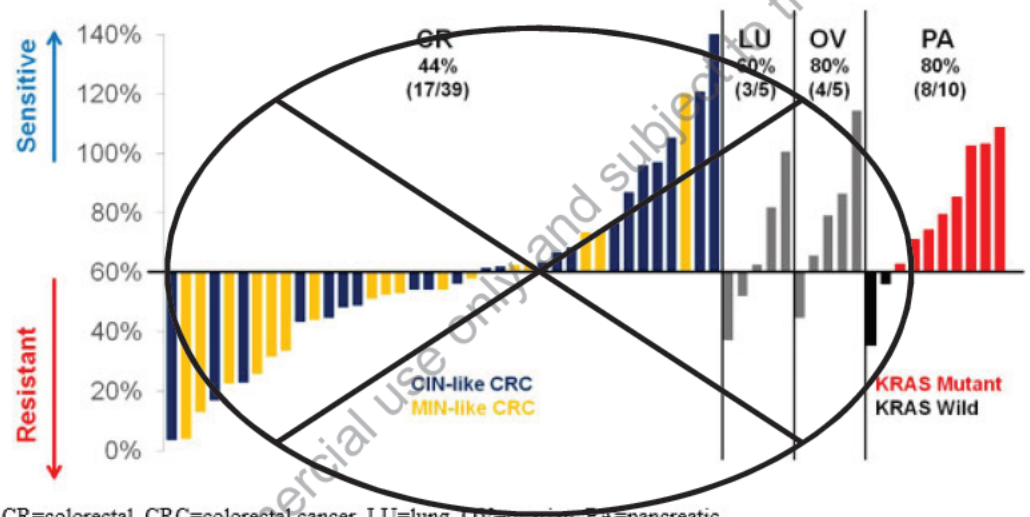
…

Amended or new wording:

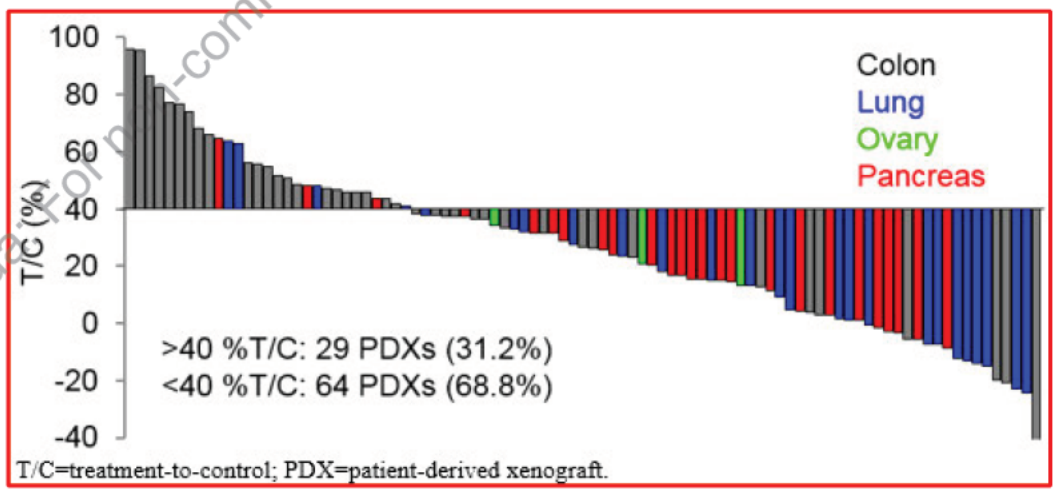
…

The in vivo antitumor activity of TAK-931 was further characterized utilizing up to ~~59~~93 primary human xenograft tumors. In this preclinical "phase 2-like" study, mice with xenografted human primary tumors received TAK-931 60 mg/kg PO for 3 days on and 4 days off weekly for 21 days (a dose and schedule shown to be efficacious across multiple tumor models [Figure 4.a]). Response characterized by tumor growth inhibition and survival was then analyzed relative to the underlying mutation status of the primary human tumors as well as gene expression profile to identify potential genetic biomarkers associated with resistance and sensitivity to TAK-931.

…



CR=colorectal, CRC=colorectal cancer, LU=lung, OV=ovarian, PA=pancreatic.



T/C=treatment-to-control; PDX=patient-derived xenograft.

…

Rationale for Change:

- This data was updated to provide more recent information.

Change 5: Added appendix of clinically significant strong metabolic enzyme inducers.

The primary change occurs in Appendix G, Clinically Significant Strong Metabolic Enzyme Inducers:

New wording:

Appendix G Clinically Significant Strong Metabolic Enzyme Inducers

Inducers[a]
Carbamazepine
Enzalutamide
Mitotane
Phenytoin
Rifampin
St. John's wort

[a] This is not an exhaustive list; refer to the following source: fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table3-3 (accessed 15 February 2018).

Rationale for Change:

Clarified which compounds are strong metabolic enzyme inducers.

The following sections also contain this change:

- Section 8.2 Exclusion Criteria.
- Section 9.6 Excluded Concomitant Medications and Procedures.

Change 6: Revised criteria for beginning or delaying a subsequent treatment cycle.

The primary changes occur in Section 9.4.2 Criteria for Beginning or Delaying a Subsequent Treatment Cycle:

Amended or new wording:	Before starting a new treatment cycle, TAK-931–related AEs or laboratory abnormalities that require dose modification must have returned to Grade ≤1 or baseline levels. For Schedule B these criteria also apply to Day 15 dosing. For Schedules E and F, **in general** these criteria also apply to Day 8 and Day 15 dosing; **however, for patients with Grade 2 neutropenia on Day 8 or Day 15, treatment can be administered at the investigator's discretion**. For Schedule D, this requirement is applicable also for restarting treatment after an interruption due to toxicity. …

Rationale for Change:

Added greater latitude for investigator to treat patients with Grade 2 neutropenia on Day 8 or Day 15.