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

NCT Number: NCT03708211

Protocol Approve Date: 21 June 2018

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

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

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

PROTOCOL

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

Sponsor:	Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited 40 Landsdowne Street Cambridge, MA 02139 USA Telephone: +1 (617) 679-7000 Please note: Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, may be referred to in this protocol as "Millennium," "Sponsor," or "Takeda".
Study Number:	TAK-931-1003
IND Number:	127,176
EudraCT Number:	2017-004629-34
Compound:	TAK-931
Date:	21 June 2018
Version/Amendment Number:	Original

1.0 ADMINISTRATIVE

1.1 Contacts

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

Serious adverse event (SAE) and pregnancy reporting information is presented in Section 10.2, 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 Sections 10.2 and 10.4

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 (ICH) E6 Good Clinical Practice (GCP): Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical study disclosure laws, and regulations.

SIGNATURES

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

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

PPD

INVESTIGATOR AGREEMENT

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

- The ethical principles that have their origin in the Declaration of Helsinki.
- ICH, E6 GCP: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2 of this protocol.
- Terms outlined in the clinical study site agreement.
- Responsibilities of the investigator (Appendix B).

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

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Province)

Location of Facility (Country)

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2.0 STUDY SUMMARY

Name of Sponsor: Millennium Pharmaceuticals, Inc.	**Compound:** TAK-931	
Title of Protocol: A Phase 1, Open-Label Study to Assess the Relative Bioavailability, Effect of Food, and Gastric pH Modification on the Pharmacokinetics of TAK-931 in Patients With Advanced Solid Tumors	**IND No.:** 127,176	**EudraCT No.:** 2017-004629-34
Study Number: TAK-931-1003	**Phase:** 1	

Study Design:

Part 1: Assessment of Relative Bioavailability of TAK-931 Tablets in Reference to Powder-in-Capsule

Approximately 20 patients (to ensure 14-16 patients evaluable for pharmacokinetics [PK]) will be randomized in a crossover fashion to receive in Cycle 0 a single dose of TAK-931 80 mg powder-in-capsule (PIC) or tablet on Day 1 and a single dose of TAK-931 80 mg with the alternate formulation on Day 3 (PIC to tablet, or tablet to PIC; n of ~10/sequence). Blood samples will be collected predose and up to 48 hours postdose at predetermined time points to measure plasma drug concentrations to evaluate the relative bioavailability of TAK-931 tablets in reference to the PIC formulation. There will be no TAK-931 dosing on Day 2 or Day 4. Starting on Day 5, patients will continue to receive TAK-931 50 mg PIC once daily (QD) for 12 days followed by a 7-day rest period.

Starting at Cycle 1, patients will 50 mg PIC QD for 14 days, followed by 7-day rest period, in 21-day treatment cycles until one of the discontinuation criteria is met.

Part 2: Assessment of the Effect of Food and Esomeprazole, a Proton Pump Inhibitor, on the PK of TAK-931 as a Tablet

After the preliminary PK data from part 1 have been analyzed to estimate the relative bioavailability of the tablet formulation in reference to PIC, the dose of TAK-931 tablet will be calculated to provide total exposure (area under the concentration-time curve [AUC]) comparable to the 80-mg dose of PIC. In part 2, approximately 24 patients (to ensure 14-16 patients evaluable for PK) will be randomized in a crossover fashion to receive in Cycle 0 a single dose of the TAK-931 tablet formulation with or without a standard high-fat breakfast on Day 1, with the alternate food intake condition and dosing on Day 3 (fasted to fed or fed to fasted; n of ~12/sequence). Blood samples will be collected predose and for up to 48 hours postdose at predetermined time points to measure plasma drug concentrations to characterize the effect of food on the PK profile of TAK-931 tablet. Starting from Day 5, patients will receive esomeprazole 40 mg QD through Day 13. On Day 12, each patient will receive a single dose of the TAK-931 tablet formulation, and PK samples will be collected up to 48 hours postdose (Day 14 predose). Starting on Day 14, patients will continue to receive TAK-931 tablets at a dose expected to achieve exposures comparable to 50 mg PIC QD for 11 days, followed by a 7-day rest period, until a discontinuation criterion is met.

Starting at Cycle 1, patients will receive the TAK-931 tablet formulation at a dose expected to achieve exposures comparable to 50 mg PIC QD for 14 days, followed by 7-day rest period, in 21-day treatment cycles.

Primary Objectives:

Part 1

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

Part 2

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

Secondary Objectives:

Part 1

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

Part 2

- Further characterize the PK of TAK-931 administered as the tablet formulation under fasted and fed conditions.
- Further characterize the PK of TAK-931 administered as the tablet formulation in the presence or absence of esomeprazole, a PPI.
- Assess the safety and tolerability of TAK-931 administered as the tablet formulation under fed and fasted conditions.
- Assess the antitumor activity of TAK-931 in patients with locally advanced or metastatic solid tumors.

Subject Population: Adult patients with histologically or cytologically confirmed metastatic or locally advanced or metastatic solid tumors for whom there is no available standard treatment with proven survival benefit, this therapy is not indicated, or it is refused by the patient.

Number of Patients:	**Number of Sites:**
A total of approximately 44 patients: 20 patients to obtain 14 to 16 evaluable patients in part 1 and 24 patients to obtain 14 to 16 evaluable patients in part 2.	Estimated total: 3 to 4 sites in The Netherlands
Doses: Part 1: 80 mg single dose on Day1 and Day 3 respectively followed by 50 mg QD thereafter. Part 2: Tablet single dose providing an AUC comparable to the 80-mg single dose of PIC on Day 1, Day 3, and Day 12 followed by a tablet QD dose providing an AUC comparable to 50-mg dose of PIC.	**Route of Administration:** Oral
Duration of Treatment: Patients may receive TAK-931 until they experience progressive disease or unacceptable toxicity or until any other discontinuation criterion is met. The maximum scheduled duration of treatment will be 1 year; however, patients receiving clinical benefit (per the investigator and as agreed by the sponsor's medical monitor) can continue on treatment beyond 1 year with the explicit approval of the sponsor's medical monitor.	**Period of Evaluation:** Patients will be followed for safety for approximately 30 days after their last dose of study drug or until the start of subsequent anticancer therapy, whichever occurs first. All patients will be followed for progression-free survival (PFS). It is anticipated that this study will last for approximately 24 months.

Main Criteria for Inclusion:

- Adult patients with histologically or cytologically confirmed metastatic or locally advanced or metastatic solid tumors for whom there is no available standard treatment with proven survival benefit, this therapy is not indicated, or it is refused by the patient.
- Eastern Cooperative Oncology Group performance status of 0 to 1.
- Adequate bone marrow reserve and renal and hepatic function based on the following laboratory parameters:
  - Absolute neutrophil count $\geq 1.5 \times 10^9$/L, platelet count $\geq 75.0 \times 10^9$/L, and hemoglobin ≥ 85 g/L.

- Total bilirubin ≤1.5 times the institutional upper limit of the normal range (ULN) or total bilirubin <3.0 times ULN in patients with well documented Gilbert´s Syndrome.
- Serum alanine aminotransferase or aspartate aminotransferase ≤3.0 times the ULN (<5 times ULN if liver enzyme elevations are due to hepatocellular cancer, biliary tract cancer, or metastatic disease in the liver).
- Creatinine <1.5 times the institutional ULN or estimated creatinine clearance using the Cockcroft-Gault formula ≥30 mL/min for patients with serum creatinine concentrations above institutional limits.

- Left ventricular ejection fraction ≥50% as measured by echocardiogram or multiple gated acquisition scan within 4 weeks before receiving the first dose of study drug.
- Recovered to Grade 1 or baseline from all toxic effects of previous therapy (except alopecia or neuropathy).

Main Criteria for Exclusion:

- Patients who require continuous use of PPIs or histamine-2 receptor antagonists and patients who are taking PPIs within 5 days before the first dose of study drug.
- Treatment with clinically significant enzyme inducers, such as phenytoin, carbamazepine, enzalutamide, mitotane, ritonavir, rifampin, or St John's wort within 14 days before the first dose of study drug.
- Treatment with systemic anticancer treatments or any investigational products within 28 days before the first dose of study drug or 5 half-lives, whichever is shorter.
- Patients with hypertension that is unstable or not controlled despite appropriate medical therapy.
- Patients with treated brain metastases are eligible if there is no evidence of progression for at least 4 weeks after central nervous system-directed treatment, as ascertained by clinical examination and brain imaging (magnetic resonance imaging or computed tomography) during the screening period.
- Known history of HIV infection.
- Known hepatitis B (HBV) surface antigen seropositive or detectable hepatitis C infection viral load. Note: Patients who have positive hepatitis B core antibody or hepatitis B surface antigen antibody can be enrolled but must have an undetectable hepatitis B viral load.
- Known gastrointestinal (GI) disease or GI procedure that could interfere with the GI absorption of study drug, such as total gastrectomy or GI conditions that could substantially modify gastric pH or GI transit.

Main Criteria for Evaluation and Analyses:

Primary:

Part 1

- Ratio of geometric mean of the following PK parameters for TAK-931 tablets in reference to PIC and associated 90% CIs:
  - Maximum observed concentration (C_{max}).
  - AUC from time 0 to time of the last quantifiable concentration (AUC_{last}).
  - AUC from time 0 to infinity (AUC_{∞}).

Part 2

- Ratio of geometric mean of the following PK parameters for TAK-931 tablets under fed and fasted conditions and associated 90% CIs:
  - C_{max}.
  - AUC_{last}.
  - AUC_{∞}.
- Ratio of geometric mean of the following PK parameters for TAK-931 tablets in the presence and absence of esomeprazole and associated 90% CIs:

- C_{max}.
- AUC_{last}.
- AUC_{∞}.

- Summary statistics of the following PK parameters for TAK-931:
  - C_{max}.
  - AUC_{last}.
  - AUC_{∞}.

Secondary:

Part 1

- PK parameters of TAK-931 following single-dose administrations as PIC and tablets at 80 mg:
  - Time of first occurrence of C_{max} (t_{max}).
  - Apparent clearance after extravascular administration (CL/F).
  - Terminal disposition phase half-life ($t_{1/2z}$).
- Antitumor activity:
  - Overall response rate (ORR).
  - PFS.
  - Disease control rate (DCR).
  - Duration of response (DOR).
- Safety:
  - Percentage of serious adverse events (SAEs), treatment-emergent adverse events (TEAEs), Grade ≥3 TEAEs, TEAEs leading to discontinuation or dose modification, and percentage of laboratory abnormalities.

Part 2

- PK parameters:
  - t_{max}, CL/F, and $t_{1/2z}$ of TAK-931 tablets following single-dose administration under fasting and fed conditions.
  - t_{max}, CL/F, and $t_{1/2z}$ of TAK-931 tablets following single-dose administration in the absence and in the presence of esomeprazole.
- Antitumor activity:
  - ORR.
  - PFS.
  - DCR.
  - DOR.
- Safety:
  - Percentage of serious adverse events (SAEs), treatment-emergent adverse events (TEAEs), Grade ≥3 TEAEs, TEAEs leading to discontinuation or dose modification, and percentage of laboratory abnormalities.

Statistical Considerations:

A total of approximately 44 patients: (20 patients to obtain 14-16 evaluable patients in part 1 and 24 patients to obtain 14-16 evaluable patients in part 2) will be enrolled in study. Results will be summarized using descriptive statistics.

Sample Size Justification:

The sample size calculation is based on the expected 2-sided 90% CI for the difference in the paired, log transformed AUC (or C_{max}) means of TAK-931 administered as tablet and PIC formulations. On the basis of preliminary data obtained from Study TAK-931-1002, the within-subject coefficient of variation was estimated to be 35.0% for AUC and 36.9% for C_{max}. Assuming the true/assumed AUC (or C_{max}) ratio is 1.0, with a sample size of 14 evaluable patients, the 90% CI of the ratio of geometric means is expected to be (0.795-1.257) for AUC and (0.786-1.272) for C_{max} on the basis of the previously discussed variance assumptions. If the ratio is X, the 90% CI of the ratio of geometric means is expected to be within (0.795X-1.257X) for AUC and (0.786X-1.272X) for C_{max}. Patients who are not PK-evaluable may be replaced to ensure the availability of 14 to 16 PK-evaluable patients for the final analysis of part 1 and part 2, respectively.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities except for 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

%CV	coefficient of variation
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the plasma concentration-time curve
AUC_{∞}	area under the concentration-time curve from time 0 to infinity
AUC_{24}	area under the plasma concentration-time curve from time 0 to 24 hours
AUC_{last}	area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration
BP	blood pressure
CDC7	cell division cycle 7
CL/F	Apparent clearance after extravascular administration
C_{max}	maximum observed plasma concentration
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CCI	[redacted]
CYP	cytochrome P-450
DCR	disease control rate
DDI	drug-drug interaction
DDR	DNA damage response
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOT	end-of-treatment
FDA	Food and Drug Administration
FIH	first-in-human
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GI	gastrointestinal
H_2	histamine-2
HBV	hepatitis B virus

HCV	hepatitis C virus
HR	heart rate
IB	investigator's brochure
IC_{50}	concentration producing 50% inhibition
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IHC	immunohistochemistry
IRB	institutional review board
MCM2	minichromosome maintenance complex 2
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	magnetic resonance imaging
MSI	microsatellite instability
MSI-H	microsatellite instability-high
MSS	microsatellite stability
MTD	maximum tolerated dose
MUGA	multiple-gated acquisition
NCI	National Cancer Institute
CCI	[redacted]
ORR	overall response rate
OTC	over-the-counter
PD	progressive disease/disease progression
PDX	primary tumor xenograft
PFS	progression-free survival
P-gp	P-glycoprotein
PIC	powder-in-capsule (formulation)
PK	pharmacokinetic(s)
pMCM2	phosphorylation of MCM2 at serine-40
PMDA	Pharmaceuticals and Medical Devices Agency of Japan
PPI	proton pump inhibitor
PR	partial response
PTE	pretreatment event
QD	once daily
QTc	QT interval corrected for heart rate
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SD	stable disease
SOE	schedule of events
SUSAR	suspected unexpected serious adverse reaction

$t_{1/2z}$	terminal disposition phase half-life
TEAE	treatment-emergent adverse event
TGI	tumor growth inhibition
t_{max}	time of first occurrence of maximum observed plasma concentration
ULN	upper limit of the normal range
WBC	white blood cell
WHO	World Health Organization

3.4 Corporate Identification

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

4.0 INTRODUCTION

4.1 Background

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

Furthermore, elevated CDC7 expression has been reported in various cancers and correlates with poor prognosis, such as in diffuse large B-cell lymphoma, oral squamous carcinoma, and breast, colon, colorectal, ovarian, and lung tumors [8-12]. 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 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. Given the dual mechanism of action of CDC7, inhibitors of CDC7 may also produce clinical activity both as single agents and in combination with other DNA-damaging drugs.

4.1.1 Nonclinical Experience

4.1.1.1 Nonclinical Pharmacology

CCI

[redacted]

CCI

[redacted]

4.1.1.2 Nonclinical Pharmacokinetics and Pharmacodynamics

CCI

[redacted]

CCI

TAK-931 exhibited nonlinear PK following oral dosing in rats and dogs with single-dose maximum observed concentration (C_{max}) and ea under the plasma concentration-time curve (AUC) from time 0 to 24 hours (AUC_{24}) increasing in a greater-than-dose-proportional manner at higher doses. No accumulation of TAK-931 was observed in either species.

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

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

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

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

Investigations into cytochrome P450 (CYP) enzyme-mediated metabolism showed that CYP2D6 and CYP3A are the main CYPs involved in the metabolism of TAK-931. There is a DDI potential with uridine 5'-diphospho-glucuronosyltransferase inducers; however, the DDI potential with CYP inhibitors, though they are involved in metabolism, is unlikely. TAK-931 is unlikely to cause DDIs with concomitant medications metabolized via CYP isozymes at C_{max} values <800 ng/mL.

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

4.1.1.3 Nonclinical Toxicology

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

The primary dose-limiting toxicities (DLTs), particularly in the dog, appear to be associated with C_{max} and are closely associated with the observed cardiovascular changes. The effects on blood pressure (BP) and heart rate (HR) 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. It has been confirmed that the effects of TAK-931 on HR and BP are 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 monitorable with clinical chemistry, and renal tubular damage is considered to be reversible.

The target organ toxicities after repeated dosing of TAK-931 were largely similar in rats and dogs and were generally consistent with inhibition of CDC7 activity. Test article-related findings included the hematopoietic and lymphoid systems, gastrointestinal (GI) mucosa, and reproductive organs. Decreased white blood cell (WBC) count or single cell necrosis in the GI mucosa appeared with minimal degree at lower doses and severity increased with dose level. All target organ toxicities observed in the repeat-dose studies were generally monitorable and reversible, except for the effect on 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 considered to be monitorable and reversible. The primary C_{max}-related toxicity was cardiovascular effects (decreased BP with reflecting tachycardia). The DLTs related to total exposure were effects on the GI mucosa and lymphoid systems consistent with pharmacology-mediated CDC7 inhibition.

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

4.1.2 Clinical Experience

TAK-931 is being evaluated in 2 ongoing studies: TAK-931-1002, a phase 1 first-in-human (FIH) study in adult Japanese patients with histologically confirmed solid tumors; and TAK-931-2001, a phase 2 study in patients with metastatic pancreatic cancer or metastatic colon cancer. After TAK-931 50 mg once daily (QD) was established as the maximum tolerated dose (MTD) under Schedule A (14 days of treatment followed by 7 days of rest in a 21-day cycle) in study TAK-931-1002, an expansion cohort was added at that dose and 16 additional patients were enrolled. As of 04 January 2018, a total of 49 patients had received at least 1 dose of TAK-931, administered as a single agent in Schedule A (n = 25), Schedule B (n=12, QD for 7 consecutive days followed by another 7 days of rest and repeated in a 28-day cycle), and Schedule D (n = 12, QD continuously in a 21-day cycle).

4.1.2.1 Safety

DLTs occurred in 5 patients in Study TAK-931-1002. Two DLTs were Grade 4 neutropenia at 60 mg QD for 14 days in a 21-day cycle. Three DLTs were febrile neutropenia events (all Grade 3): 1 occurred at 50 mg under dosing Schedule A and the other 2 at 80 mg under dosing Schedule B. Four of these 5 DLTs were serious, and all 5 resolved.

A total of 20 serious treatment-emergent adverse events (TEAEs), regardless of causality, were reported in 12 patients treated in Study TAK-931-1002, as of the 04 January 2018 cutoff date. Of these, 3 SAEs were reported in 2 patients in the 60 mg cohort (neutropenia, nausea, decreased appetite), and 1 SAE was reported in the 40 mg cohort (pleural effusion).

Grade ≥3 TEAEs reported in 2 or more patients in Study TAK-931-1002 as of 04 January 2018 included neutropenia (37%), leukopenia (12%), WBC count decreased (10%), febrile neutropenia (6%), anemia (4%), and decreased appetite (4%). Seven of the 23 total patients treated developed at least 1 Grade ≥3 TEAE. There were no deaths.

The most common TEAEs regardless of causality reported in at least 2 patients in Study TAK-931-1002 as of the 04 January 2018 cutoff date included nausea (49%), neutropenia (43%), WBC count decreased (29%), decreased appetite (27%), alopecia (22%), vomiting (20%), diarrhoea (18%), anaemia (16%), leukopenia (16%), uncoded (16%), malaise (14%), pyrexia (14%), oedema peripheral (12%), constipation (10%), fatigue (10%), and hypoalbuminaemia (10%). Forty-eight of the 49 total patients treated developed at least 1 TEAE.

Refer to the IB for additional information.

4.1.2.2 PK

Absorption of TAK-931 was fast following single or multiple oral dose administrations, with a median time of first occurrence of C_{max} (t_{max}) of 1 to 4 hours. Systemic exposures (AUC) of TAK-931 increased in approximately a dose-proportional manner over the range of 20 to 80 mg QD. The interpatient variability (coefficient of variation [%CV]) in TAK-931 C_{max} was <50% and AUC ≤30%. TAK-931 showed minimal accumulation following multiple-dose administration, consistent with a mean terminal disposition phase half-life ($t_{1/2z}$) of 4.3 to 6.2 hours.

4.1.3 Benefits and Risks

The current study is an open-label clinical pharmacology study to assess the relative bioavailability, effect of food, and gastric pH modification on the PK of TAK-931 in patients with advanced solid tumors. Some tumor indications are suggested as preferred based on the information in Section 4.1.1.1. Regardless, patients should have exhausted available standard therapeutic options with a proven survival benefit. Because Studies TAK-931-1002 and TAK-931-2001 are in progress and only a limited number of patients have been treated with TAK-931, there are no established benefits of this drug and the available safety information for the proposed dose is described in Section 4.1.2.1.

Based on the available clinical and preclinical data, it is reasonable to consider this trial for patients with advanced solid tumors for whom there is no available standard treatment with proven survival

benefit. Based on the nonclinical data in Section 4.1.1.1, some indications may have a higher probability of clinical benefit: high-grade serous ovarian cancer, uterine carcinosarcoma, squamous esophageal cancer, squamous NSCLC, squamous head and neck cancers, rectal adenocarcinoma, and in general tumors with known *TP53* gene mutations. For any of these preferred indications, patients should have exhausted standard therapeutic options with a proven survival benefit.

4.2 Rationale for the Proposed Study

This study will enroll approximately 44 patients. In part 1, approximately 20 patients will be enrolled to obtain 14 to 16 evaluable patients to assess the relative bioavailability of the TAK-931 tablet formulation in reference to the powder-in-capsule (PIC) formulation. In part 2, approximately 24 patients will be enrolled to obtain 14 to 16 evaluable patients to assess the effects of food and esomeprazole on the PK of TAK-931 tablets.

4.2.1 Part 1: Assessment of Relative Bioavailability of TAK-931 Tablets in Reference to PIC

In addition to the PIC formulation, a tablet formulation of TAK-931 has been developed for clinical use. The rationale for conducting this study is to characterize the relative bioavailability of TAK-931 administered as a tablet in reference to the PIC formulation. A tablet of 80 mg is the highest dose strength being evaluated in clinical studies. The prototype tablet was designed as an immediate-release formulation and possesses a similar rapid dissolution profile to the PIC formulation under acidic conditions. In vitro dissolution profiles for 10, 25, and 80 mg tablets and capsules are considered similar at low pH. Part 1 of this study will estimate the relative bioavailability of the tablet in reference to the PIC formulation to enable the transition from PIC to tablet in clinical development.

4.2.2 Part 2: Assessment of the Effect of Food and Esomeprazole on PK of TAK-931 as Tablet

Food can alter the rate or extent of absorption or both of orally administered antineoplastic agents, which can have clinical implications in the treatment of patients with cancer. Ingestion of food has several physiologic GI effects including delayed gastric emptying, stimulated bile flow, changed GI pH, and increased splanchnic blood flow. Food may also alter the bioavailability of a drug by physically or chemically interacting with a dosage form or a drug substance. Because food may change the bioavailability of a drug, a food effect study is being conducted to assess the effects of food on the rate and extent of drug absorption when the drug is administered after a high-calorie and high-fat meal has been ingested. This part of the study will therefore evaluate the effect of a high-fat meal on the PK of TAK-931 administered as the tablet formulation.

TAK-931 (basic pKa of 6.23 and an acidic pKa of 11.1) exhibits pH-dependent solubility with low aqueous solubility at basic pH. Therefore, it is possible that concomitant administration of gastric acid-reducing agents, such as proton pump inhibitors (PPIs) and histamine-2 (H_2) receptor antagonists, could decrease TAK-931 systemic exposures. This part of the study is therefore

designed to additionally evaluate the effect of multiple-dose administrations of esomeprazole, a PPI, on the PK of TAK-931 administered as a tablet formulation.

Part 2 of this study will be initiated only after the preliminary data from part 1 are available to estimate the relative bioavailability of the tablet formulation in reference to PIC. Based on this estimate, the dose of TAK-931 tablets will be calculated to provide total exposure (AUC) comparable to that achieved at the 80 mg dose of PIC. Part 2 will evaluate the effect of food and esomeprazole, a PPI, on the PK of the tablet formulation at the above calculated dose level to ensure that assessment of food effect and the effect of esomeprazole are being performed at a clinically relevant dose of TAK-931 as tablet formulation.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objectives

The primary objectives are:

Part 1

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

Part 2

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

5.1.2 Secondary Objectives

The secondary objectives are:

Part 1

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

Part 2

- Further characterize the PK of TAK-931 administered as the tablet formulation under fasted and fed conditions.
- Further characterize the PK of TAK-931 administered as the tablet formulation in the presence or absence of esomeprazole, a PPI.
- Assess the safety and tolerability of TAK-931 administered as the tablet formulations under fed and fasted conditions.
- Assess the antitumor activity of TAK-931 in patients with locally advanced or metastatic solid tumors.

5.1.3 Exploratory Objectives

CCI

[redacted]

5.2 Endpoints

5.2.1 Primary Endpoints

The primary endpoints are:

Part 1

- Ratio of geometric mean of the following PK parameters for TAK-931 tablets in reference to PIC and associated 90% CIs:
  - C_{max}.
  - AUC from time 0 to time of the last quantifiable concentration (AUC_{last}).
  - AUC from time 0 to infinity (AUC_{∞}).

Part 2

- Ratio of geometric mean of the following PK parameters for TAK-931 tablets under fed and fasted conditions and associated 90% CIs:
  - C_{max}.
  - AUC_{last}.
  - AUC_{∞}.
- Ratio of geometric mean of the following PK parameters for TAK-931 tablets in the presence and absence of esomeprazole and associated 90% CIs:
  - C_{max}.
  - AUC_{last}.
  - AUC_{∞}.
- Summary statistics of the following PK parameters for TAK-931:
  - C_{max}.
  - AUC_{last}.
  - AUC_{∞}.

5.2.2 Secondary Endpoints

The secondary endpoints are:

Part 1

- PK parameters of TAK-931 following single-dose administrations as PIC and tablets at 80 mg:
  - t_{max}.
  - Apparent clearance after extravascular administration (CL/F).
  - $t_{1/2z}$.
- Antitumor activity:
  - Overall response rate (ORR).
  - Progression-free survival (PFS).
  - Disease control rate (DCR).
  - Duration of response (DOR).
- Safety:
  - Percentage of SAEs, TEAEs, Grade ≥3 TEAEs, TEAEs leading to discontinuation or dose modification, and percentage of laboratory abnormalities.

Part 2

- PK parameters:
  - t_{max}, CL/F, and $t_{1/2z}$ of TAK-931 tablets following single-dose administration under fasted and fed conditions.
  - t_{max}, CL/F, and $t_{1/2z}$ of TAK-931 tablets following single-dose administration in the absence and presence of esomeprazole.
- Antitumor activity:
  - ORR.
  - PFS.
  - DCR.
  - DOR.

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

5.2.3 Exploratory Endpoints

CCI

[redacted]

6.0 STUDY DESIGN

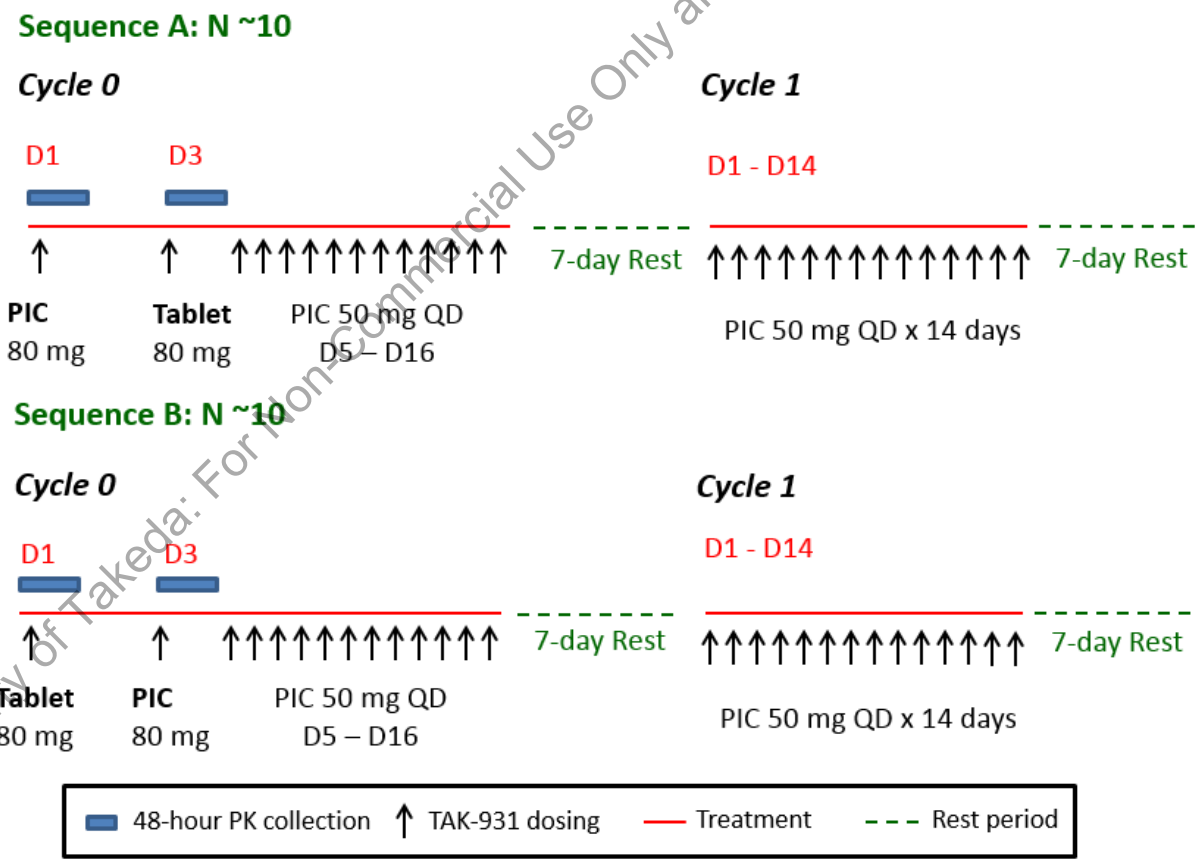
6.1 Overview of Study Design

6.1.1 Part 1: Assessment of Relative Bioavailability of TAK-931 Tablet in Reference to PIC

Approximately 20 patients (to ensure 14-16 patients evaluable for PK) will be randomized in a crossover fashion to receive a single dose of TAK-931 80 mg PIC or tablet on Cycle 0 Day 1 and a single dose of TAK-931 80 mg with the alternate formulation on Day 3 (PIC to tablet, or tablet to PIC; n of ~10/sequence). Blood samples will be collected predose and up to 48 hours postdose at predetermined time points to measure plasma drug concentrations to evaluate the relative bioavailability of TAK-931 tablets in reference to the PIC formulation. There will be no TAK-931 dosing on Day 2 or Day 4. Starting on Day 5, patients will continue to receive TAK-931 50 mg PIC QD for 12 days followed by a 7-day rest period.

Starting at Cycle 1, patients will receive 50 mg PIC QD for 14 days followed by 7-day rest period in 21-day treatment cycles until one of the discontinuation criteria is met.

Figure 6.a Part 1: Relative Bioavailability of TAK-931 Tablets in Reference to PIC



Abbreviations: D, Day; PIC, powder-in-capsule; PK, pharmacokinetics; QD, once daily.

6.1.2 Part 2: Assessment of the Effect of Food and Esomeprazole, a PPI, on the PK of TAK-931 as a Tablet

After the preliminary PK data from part 1 have been analyzed to estimate the relative bioavailability of the tablet formulation in reference to PIC, the single dose of TAK-931 tablet to be used on Cycle 0 Day 1, Day 3, and Day 12 will be calculated to provide total exposure (AUC) comparable to the 80-mg dose of PIC. In part 2, approximately 24 patients (to ensure 14-16 patients evaluable for PK) will be randomized in a crossover fashion to receive a single dose of the TAK-931 tablet formulation with or without a standard high-fat breakfast on Cycle 0 Day 1, with the alternate food intake condition and dosing on Day 3 (fasted to fed or fed to fasted; n of ~12/sequence). Blood samples will be collected predose and for up to 48 hours postdose at predetermined time points to measure plasma drug concentrations to characterize the effect of food on the PK of TAK-931 tablet. Starting from Day 5, patients will receive esomeprazole 40 mg QD through Day 13. On Day 12, each patient will receive a single dose of the TAK-931 tablet formulation, and PK samples will be collected up to 48 hours postdose (Day 14 predose). Starting on Day 14, patients will continue to receive TAK-931 tablets at a dose expected to achieve exposures comparable to 50 mg PIC QD for 9 days followed by a 7-day rest period until a discontinuation criterion is met.

Starting at Cycle 1, patients will receive the TAK-931 tablet formulation at a dose expected to achieve exposures comparable to 50 mg PIC QD for 14 days followed by 7-day rest period in 21-day treatment cycles.

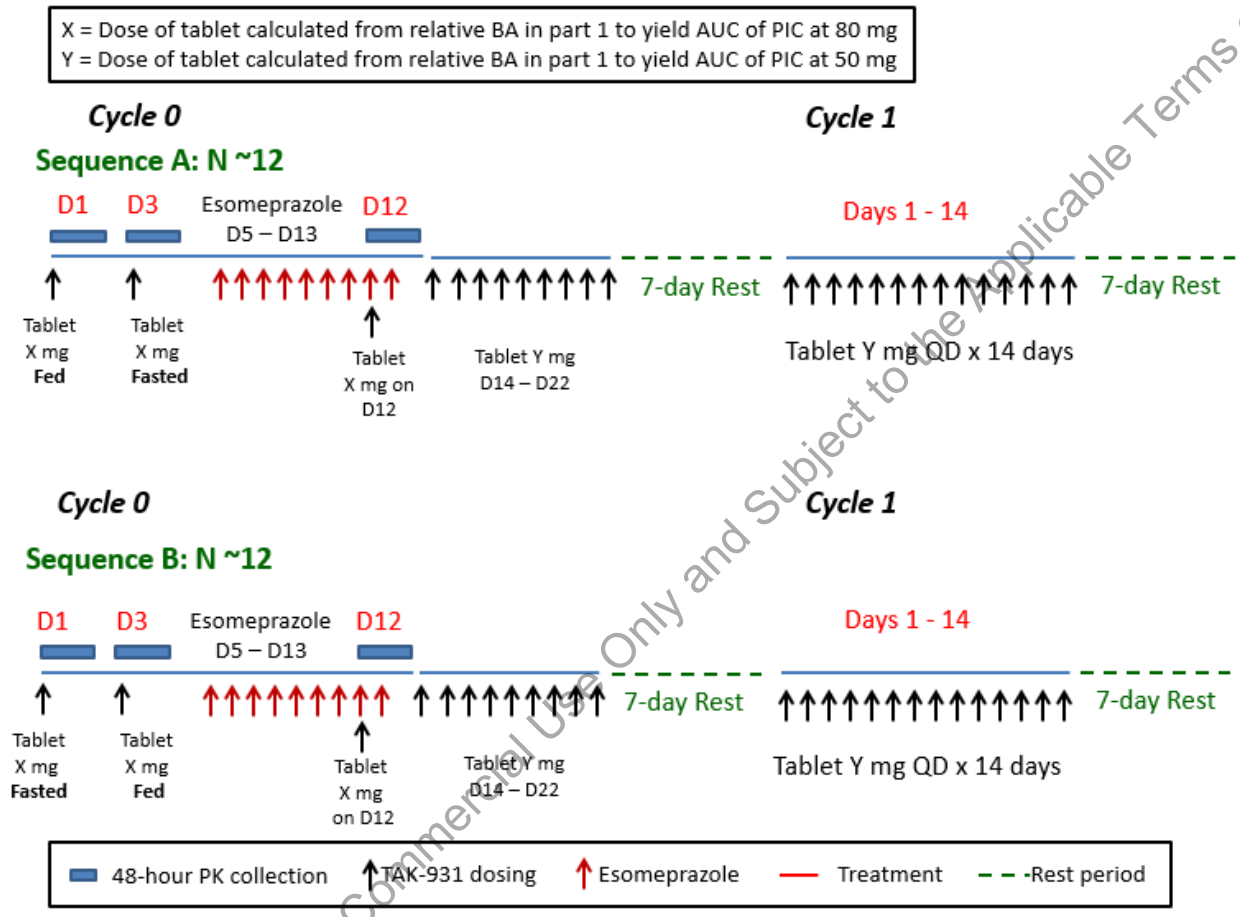
This study is an open-label, multicenter, phase 1 study of TAK-931 in adult patients with locally advanced or metastatic solid tumors. The patient population will consist of adults previously diagnosed with any form of locally advanced or metastatic solid tumor for whom there is no available standard treatment with proven survival benefit. Based on the nonclinical data in Section 4.1.1.1, some indications may have a higher probability of clinical benefit with TAK-931: high-grade serous ovarian cancer, uterine carcinosarcoma, squamous esophageal cancer, squamous NSCLC, squamous head and neck cancers, rectal adenocarcinoma, and in general tumors with known *TP53* gene mutations. For any of these preferred indications, patients should have exhausted standard therapeutic options with a proven survival benefit.

Toxicity will be evaluated according to NCI CTCAE, version 5.0, effective date 27 November 2017 [18].

Adverse events (AEs) will be assessed and laboratory values, vital signs, and electrocardiograms (ECGs) will be obtained to evaluate the safety and tolerability of TAK-931.

Serial blood samples for determination of the plasma concentration of TAK-931 and corresponding triplicate ECGs (part 1 only) will be obtained during Cycle 0 at prespecified time points as described in the schedule of events (SOE) (Appendix A) and in Section 9.4.

Figure 6.b Part 2: Assessment of Effects of High-Fat Meal and Esomeprazole on TAK-931 Tablet PK Profile



Abbreviations: AUC, area under the plasma concentration-time curve; BA, bioavailability; D, Day; PIC, powder-in-capsule; PK, pharmacokinetics; QD, once daily.

6.2 Number of Patients

A total of approximately 44 patients will be enrolled in this study (approximately 20 patients to obtain 14 to 16 evaluable patients in part 1 and approximately 24 patients to obtain 14 to 16 evaluable patients in part 2 [see Section 13.1.1 for definition of evaluable]). These patients will be enrolled at approximately 3-4 study centers in the Netherlands. Enrollment is defined as signing of the informed consent form (ICF).

Patients are considered PK evaluable if they complete the protocol-specified dosing and PK assessments in Cycle 0 (see Section 13.1.1). Patients may be replaced if they are not evaluable for PK. Specifically, patients will not be considered evaluable if 1 of the following occurs during Cycle 0:

- Vomit within 2 hours of taking the Day 1 or Day 3 dose of TAK-931 in Cycle 0 (part 1 and part 2).
- Vomit within 2 hours of taking the Day 12 dose of TAK-931 in Cycle 0 (part 2).
- Fail to consume at least 75% of the meal (part 2 food effect assessment).
- Miss 1 or more doses of esomeprazole (part 2 esomeprazole DDI assessment).
- Take any excluded medication that, in the assessment of the Takeda clinical pharmacologist, may compromise PK evaluability for the assessment of relative bioavailability and effects of food or PPIs on TAK-931 PK.

6.3 Duration of Study

6.3.1 Duration of an Individual Patient's Study Participation

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

All patients will attend an end-of-treatment (EOT) visit 30 days (+10 days) after receiving their last dose of study drug or before the start of subsequent systemic anticancer therapy, whichever occurs first, to permit detection of any delayed TEAEs and resolution of ongoing events. Patients with unresolved TEAEs will continue the periodic safety follow-up until complete resolution or stabilization (established as squealae) occurs. Patients who discontinue study treatment for reasons other than PD will continue PFS follow-up every 12±1 weeks from the EOT visit until the occurrence of PD, loss to follow-up, consent withdrawal, death, the start of subsequent systemic antineoplastic therapy, or study termination (Section 9.7).

6.3.2 End of Study/Study Completion Definition and Planned Reporting

Patients will be followed for safety for approximately 30 days after their last dose of study drug or until the start of subsequent anticancer therapy, whichever occurs first. All patients will be followed for PFS. It is anticipated that this study will last for approximately 24 months.

6.3.3 Time Frames for Primary and Secondary Endpoints to Support Disclosures

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

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

Table 6.a Primary and Secondary Endpoints for Disclosures

Endpoint	Definition	Maximum Time Frame
Primary:		
Part 1: • Ratio of geometric mean of the following PK parameters for TAK-931 tablets in reference to PIC and associated 90% CIs: – C_{max}. – AUC_{last}. – AUC_{∞}.	See Section 5.2.1	30 days
Part 2: • Ratio of geometric mean of the following PK parameters for TAK-931 tablets under fed and fasted conditions and associated 90% CIs: – C_{max}. – AUC_{last}. – AUC_{∞}. • Ratio of geometric mean of the following PK parameters for TAK-931 tablets in the presence and absence of esomeprazole and associated 90% CIs: – C_{max}. – AUC_{last}. – AUC_{∞}. • Summary statistics of the following PK parameters for TAK-931: – C_{max}. – AUC_{last}. – AUC_{∞}.	See Section 5.2.1	30 days
Secondary:		
Part 1: • PK parameters of TAK-931 following single-dose administrations as PIC and tablets at 80 mg: – t_{max}. – CL/F. – $t_{1/2z}$.	See Section 5.2.2	30 days

Table 6.a Primary and Secondary Endpoints for Disclosures (continued)

Endpoint	Definition	Maximum Time Frame
• Antitumor activity: – ORR. – PFS. – DCR. – DOR.	See Section 5.2.2	1 year
• Safety: percentage of SAEs, TEAEs, Grade ≥3 TEAEs, TEAEs leading to discontinuation or dose modification, and percentage of laboratory abnormalities using NCI CTCAE version 5.0.	See Section 5.2.2	1 year
Part 2:	See Section 5.2.2	30 days
• PK parameters following single-dose TAK-931 administration under fasted and fed conditions: – t_{max}. – CL/F. – $t_{1/2z}$.		
• PK parameters following single-dose TAK-931 administration in the presence and absence of esomeprazole: – t_{max}. – CL/F. – $t_{1/2z}$.	See Section 5.2.2	30 days
• Antitumor activity – ORR. – PFS. – DCR. – DOR.	See Section 5.2.2	1 year
• Safety: percentage of SAEs, TEAEs, Grade ≥3 TEAEs, TEAEs leading to discontinuation or dose modification, and percentage of laboratory abnormalities using NCI CTCAE version 5.0.	See Section 5.2.2	1 year

Abbreviations: AUC_{∞}, area under the concentration-time curve from time 0 to infinity; AUC_{last}, area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration; CL/F, apparent clearance after extravascular administration; C_{max}, maximum observed plasma concentration; DCR, disease control rate; DOR, duration of response; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; ORR, overall response rate; PIC, powder-in-capsule; PFS, progression-free survival; PK, pharmacokinetic(s); SAE, serious adverse event; $t_{1/2z}$, terminal disposition phase half-life; TEAE, treatment-emergent adverse event; t_{max}, time of first occurrence of maximum observed plasma concentration.

6.3.4 Total Study Duration

Patients will be followed for safety for approximately 30 days after their last dose of study drug or until the start of subsequent anticancer therapy, whichever occurs first. All patients will be followed for PFS. It is anticipated that this study will last for approximately 24 months.

7.0 STUDY POPULATION

This study will include adult patients with histologically or cytologically confirmed metastatic or locally advanced solid tumors for whom there is no available standard treatment with proven survival benefit, this therapy is not indicated, or it is refused by the patient.

7.1 Inclusion Criteria

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

1. Male or female patients aged 18 years or older.
2. Adult patients with histologically or cytologically confirmed metastatic or locally advanced solid tumors for whom there is no available standard treatment with proven survival benefit, this therapy is not indicated, or it is refused by the patient. Based on the nonclinical data in Section 4.1.1.1, the following indications may have a higher probability of clinical benefit: high-grade serous ovarian cancer, uterine carcinosarcoma, squamous esophageal cancer, squamous NSCLC, squamous head and neck cancers, rectal adenocarcinoma, and in general tumors with known *TP53* gene mutations. For any of these preferred indications, patients should have exhausted standard therapeutic options with a proven survival benefit.
3. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1.
4. Adequate bone marrow reserve and renal and hepatic function based on the following laboratory parameters:
   - Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L, platelet count $\geq 75 \times 10^9$/L, and hemoglobin ≥85 g/L.
   - Total bilirubin ≤1.5 times the institutional upper limit of the normal range (ULN) or total bilirubin <3.0 times the ULN in patients with well-documented Gilbert syndrome.
   - Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≤3.0 times the ULN (<5 times the ULN if liver enzyme elevations are due to hepatocellular cancer, biliary tract cancer, or metastatic disease in the liver).
   - Creatinine ≤1.5 times the institutional ULN or estimated creatinine clearance using the Cockcroft-Gault formula ≥30 mL/min for patients with serum creatinine concentrations above institutional limits.
5. Left ventricular ejection fraction ≥50% as measured by echocardiogram (ECHO) or multiple gated acquisition (MUGA) scan within 4 weeks before receiving the first dose of study drug.
6. Recovered to Grade 1 or baseline from all toxic effects of previous therapy (except alopecia or neuropathy).
7. Female patients who:
   - Are postmenopausal for at least 1 year before the screening visit, OR
   - Are surgically sterile, OR

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

8. Male patients, even if surgically sterilized (ie, status postvasectomy), who:
   - Agree to practice effective barrier contraception during the entire study treatment period and through 120 days after the last dose of study drug, OR
   - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.) AND
   - Agree not to donate sperm during this study and for 120 days after receiving their last dose of study drug.
9. 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.
10. Suitable venous access for the study-required blood sampling including PK and pharmacodynamic sampling.
11. Patients must have a radiographically or clinically evaluable tumor, but measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) (version 1.1) [19] is not required for participation in this study.

7.2 Exclusion Criteria

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

1. 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.
2. Treatment with systemic anticancer treatments or investigational products within 28 days before the first dose of study drug or 5 half-lives, whichever is shorter.
3. Patients who require continuous use of PPIs or H_2 receptor antagonists and patients who are taking PPIs within 5 days before the first dose of study drug.
4. Treatment with clinically significant enzyme inducers, such as phenytoin, carbamazepine, enzalutamide, mitotane, ritonavir, rifampin, or St John's wort within 14 days before the first dose of study drug.

5. Patients with hypertension that is unstable or not controlled despite appropriate medical therapy.
6. Patients with treated brain metastases are eligible if there is no evidence of progression for at least 4 weeks after central nervous system-directed treatment, as ascertained by clinical examination and brain imaging (magnetic resonance imaging [MRI] or computed tomography [CT]) during the screening period.
7. Known history of HIV virus infection.
8. Known hepatitis B virus (HBV) surface antigen seropositive or detectable hepatitis C virus (HCV) infection viral load. Note: Patients who have positive hepatitis B core antibody or hepatitis B surface antigen antibody can be enrolled but must have an undetectable HBV viral load.
9. Known GI disease or GI procedure that could interfere with the GI absorption of study drug, such as total gastrectomy or GI conditions that could substantially modify gastric pH or GI transit.
10. Part 2 only: known hypersensitivity to PPIs (eg, angioedema or anaphylaxis have occurred).
11. Part 2 only: not being able or willing to take one high fat breakfast as indicated in the protocol.
12. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.

8.0 STUDY DRUG

8.1 Study Drug Administration

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

8.1.1 Day 1 and Day 3 of Cycle 0, Part 1 Relative Bioavailability Assessment

TAK-931 will be administered to patients on an empty stomach except water from 2 hours before taking the study drug until completion of collection of the 4-hour ECG/PK samples on Day 1 and Day 3 of Cycle 0. Each dose of the study drug will be given orally with at least 8 ounces (230 mL) of water. Accordingly, patients will be instructed to eat a meal or snack at least 2 hours before dosing, and to eat a meal or snack after the 4-hour triplicate ECG and blood sample for PK analysis are collected.

8.1.2 Day 1 and Day 3 of Cycle 0, Part 2 Food Effect Assessment

For the fasted treatment, the Day 1 or Day 3 dose of TAK-931 will be administered with 240 mL (8 fluid ounces) of water following an overnight fast, including no medications, of approximately 10 hours. In addition, no food will be allowed for 2 hours after the Day 1 or Day 3 dose. Water is allowed as desired except for 1 hour before and after TAK-931 administration. For the fed treatment, following an overnight fast (including no medications) of approximately 10 hours, patients will start the recommended meal 30 minutes before administration of the Day 1 or Day 3 dose. Table 8.a shows the approximate composition of a high-fat breakfast. Patients should finish the entire meal in 30 minutes or less; TAK-931 will be administered 30 minutes after start of the meal with 240 mL (8 fluid ounces) of water. No food will be allowed for at least 2 hours postdose. Water is allowed as desired except for 1 hour before and 1 hour after TAK-931 administration. Patients will be randomized to receive a standard high-fat meal before dosing on Day 1 or Day 3 of Cycle 0.

Table 8.a Approximate Composition of High-Fat Breakfast

	Kcal	Protein (g)	Fat (g)	Carbohydrate (g)
2 slices whole-wheat bread (approx 70 g)	154	6.2	1.8	28.4
15 g halvarine [a]	112	0.1	12.3	0.2
2 fried eggs in 15 g halvarine [a]	220	14.4	17.6	0.9
40 g bacon [b]	151	7.2	13.6	0.0
115 g fried potatoes	130	2.5	5.2	18.3
240 mL whole milk	151	8.4	8.2	10.8
TOTAL	918	38.8	58.7	58.6

[a] Reduced-fat margarine.
[b] Vegetarians may substitute 50 g of brie cheese for bacon.

8.1.3 Day 12 of Cycle 0, Part 2 Esomeprazole DDI Assessment

TAK-931 will be administered to patients with esomeprazole on an empty stomach except water from 2 hours before and 2 hours after taking the study drug. Each dose of the study drug will be given orally with at least 8 ounces (230 mL) of water.

8.1.4 TAK-931 Multiple-Dose Administration in Cycle 0 and Beyond

Patients should be instructed to take their study medication at approximately the same time each day and not to take more than the prescribed dose at any time. Patients should swallow the study medication whole and not chew it, open it, or manipulate it in any way before swallowing. If a patient fails to take the TAK-931 dose within the time frame specified (±12 hours), that dose should be skipped. Patients should record any skipped doses in their dosing diary (see the 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) or tablets are visible in the vomitus, replacement capsule(s) or tablets should be taken; otherwise the dose will not be readministered, and patients should simply adhere to the dosing schedule and resume dosing at the next scheduled time with the prescribed dosage. Patients should record the time of the emesis in their dosing diary (see Study Manual). Except for the case of emesis with visible capsules in the vomitus as described above, patients should never repeat a dose or double-up on doses.

Beginning with Cycle 1 and after, TAK-931 will be administered only during Days 1 to 14 of each 21-day cycle of study participation. TAK-931 doses missed due to any reason, including treatment interruption due to toxicity, will not be made up by extending the 14-day treatment period during the 21-day cycle. Patients in part 1 will receive 50 mg PIC. Patients in part 2 will receive the tablet formulation at a dose that produces comparable exposure to 50 mg PIC as determined in part 1.

8.2 Reference/Control Therapy

No reference or control therapy will be used. Esomeprazole will be used in Cycle 0 of part 2 to assess the effects of modifying gastric pH on the PK of TAK-931.

8.3 Dose Modification Guidelines

Dose modification guidelines for toxicities, based on the type and severity of AEs and causality determination by investigators, are described below for TAK-931. Further clarification can be obtained in consultation with the sponsor clinician (or designee). In general it is recommended to reduce the dose of TAK-931 in 10-mg increments (for example from 50 mg to 40 mg). Reductions below 30 mg (PIC or tablets) are not recommended unless the investigator believes that the patient is deriving benefit from treatment.

8.3.1 Criteria for Beginning or Delaying a Subsequent Treatment Cycle

Before starting a new treatment cycle, TAK-931–related AEs or laboratory abnormalities must have returned to Grade ≤1 or baseline levels or to a level considered acceptable by the physician (eg, hypophosphatemia that can be managed by oral replacement).

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 the patient is receiving clinical benefit as assessed by the investigator, with agreement by the sponsor's medical monitor. TAK-931 dosing may be continued at a reduced dose level.

For Cycle 1 onward, treatment with TAK-931 will use a cycle length of 21 days. For a new cycle of treatment to begin, the patient must meet the following criteria:

- ANC must be $\geq 1.5 \times 10^9$/L.
- Platelet count must be $\geq 75.0 \times 10^9$/L.

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

8.3.2 Criteria for Dose Interruption During a Cycle

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 or a subsequent occurrence.

Refer to Table 8.b for general dose modification recommendations. When the dose of TAK-931 is withheld according to these criteria, clinical and laboratory reevaluation should be repeated at least weekly or more frequently, depending on the nature of the toxicity observed until the toxicity resolves to Grade ≤1 or baseline. For transient laboratory abnormalities that, per investigator assessment, are not clinically significant or drug-related, continuation of therapy without dose modification is permissible upon discussion with the sponsor. See details for the management of specific TEAEs in Section 8.7.

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

Criteria	Action
Grade 1 AEs	No dose reductions or interruptions
Grade 2 AEs	Treat according to local practice. Whether to hold treatment or to continue treatment at the same or at a reduced dose is at the discretion of the investigator. Patients experiencing Grade 2 AEs considered related to study treatment that are not easily managed or corrected and are not tolerable to the patient, or AEs that are not acceptable in the investigator's judgment, should have study treatment interrupted until the AE resolves to Grade ≤1 or baseline and then restarted at the same dose or, depending on the toxicity, at a reduced dose level.
Grade 3 and Grade 4 non–life-threatening AEs	Hold TAK-931 until resolution to Grade ≤1 or baseline, then resume treatment at either the same dose or a reduced dose level at the discretion of the investigator and after discussion with the sponsor.
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 the patient is receiving 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.

Abbreviation: AE, adverse event.

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

8.3.3 Criteria for Discontinuation of TAK-931

TAK-931 should be discontinued for patients experiencing an AE 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 a reduced dose level when toxicity recovers to Grade ≤1 or baseline.

If more than 2 dose reductions are required, or if the next cycle of TAK-931 is delayed for >14 days because of TAK-931–related toxicities, study treatment should be discontinued unless the investigator believes that the patient will benefit from continuing in the study. Further dose reduction must be discussed with and approved by the sponsor's medical monitor. If treatment

discontinuation is determined, the EOT visit should be completed within 30 to 40 days after the last administration of TAK-931 or before initiation of new anti-cancer therapy (whichever occurs first).

8.4 Excluded Concomitant Medications and Procedures

All prescription and over-the-counter (OTC) medications, including influenza vaccines, taken by a patient since signing the ICF through the EOT visit or before initiation of new anti-cancer therapy (whichever occurs first) will be recorded in the designated electronic case report forms (eCRFs). Patients must be instructed not to take any medications, including OTC medications and herbal supplements, without first consulting with the investigator.

The following medications and procedures are prohibited during the study:

- Patients currently on chronic erythropoietin support for anemia may continue to receive erythropoietin, but initiation of new erythropoietin therapy is not allowed during Cycle 0 [20].
- Any investigational agent other than TAK-931.
- Any concurrent antineoplastic therapy (eg, chemotherapy, hormonal therapy, immunotherapy, radiation therapy except for palliative radiation therapy and once PD is ruled out), or standard or investigational agents for treatment of cancer.
- Clinically significant CYP enzyme inducers, such as phenytoin, carbamazepine, enzalutamide, mitotane, ritonavir, rifampin, or St John's wort, within 14 days before the first dose of TAK-931 and during the study.
- Chronic concomitant administration of any PPI is not allowed during the study except for the esomeprazole indicated in Cycle 0 of part 2. Patients receiving PPI therapy must stop using the PPI for 5 days before their first dose of TAK-931. Examples of PPIs include omeprazole, esomeprazole, pantoprazole, lansoprazole, vonoprazan, and rabeprazole. During study participation, patients who develop new clinical symptoms that require treatment with PPIs should be discussed with the sponsor to determine the dose, schedule, and suitability of the patient for continued study participation.
- H_2 receptor antagonists (eg, cimetidine, nizatidine, and ranitidine) are not permitted from the day before the first dose (Day -1) through the last day of TAK-931 dosing in the treatment cycle. Intermittent use may be considered especially during the 1-week rest period if needed. Patients who require additional therapy with H_2 receptor antagonists during the active treatment period with TAK-931 should be discussed with the sponsor to determine the dose, schedule, and suitability of the patient for continued study participation. During Cycle 0 in part 2, OTC antacid preparations such as calcium carbonate are not allowed.

8.5 Permitted Concomitant Medications and Procedures

Other medications considered necessary for the safety and wellbeing of the patient may be administered at the discretion of the investigator. Any concomitant medications added or discontinued during the study should be recorded in the eCRF. Use of myeloid growth factors (eg,

granulocyte colony-stimulating factor [G-CSF], granulocyte-macrophage colony-stimulating factor) may be administered to manage patients who experience severe and/or febrile neutropenia if clinically indicated in accordance with the American Society of Clinical Oncology (ASCO) guidelines and/or institutional practices. For the first episode of neutropenia, dose reduction is preferred [21].

During Cycle 0 in part 1 and from Cycle 1 and after in both parts, OTC antacid preparations are allowed but should not be taken from 2 hours before and until 2 hours after administration of TAK-931. They are allowed as needed on non-dosing days.

8.6 Precautions and Restrictions

Patients must be educated about adequate and safe storage of TAK-931 at home. They must be informed about safe self-administration of the drug following the directions given in Section 8.1. and Section 8.12.

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

8.6.1 Pregnancy and Contraception

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

Female patients must meet 1 of the following:

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

Male patients, even if surgically sterilized (eg, status postvasectomy) must agree to 1 of the following:

- Agree to practice effective barrier contraception during the entire study treatment period and through 120 days after the last dose of study drug, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation

methods for the female partner], withdrawal spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.) AND

- Agree not to donate sperm during the study and for 120 days after receiving their last dose of study drug.

8.6.2 Females Who are Lactating or Breastfeeding

Female patients who are lactating must refrain from breastfeeding from the start of study participation (Section 7.2, exclusion criterion #1) through 30 days after the last dose of study drug.

8.6.3 Patients With Prior Exposure to Hepatitis B or Hepatitis C

Patients who have detectable HBV or HCV viral loads are excluded from study participation (see Section 7.2, exclusion criterion #8). Patients with prior exposure to HBV or HCV who have subsequently cleared the infection (based on a negative viral load) are allowed on study, but should be monitored for 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 per institutional guidelines, and 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 nucleoside antagonist prophylaxis and after a discussion with the Takeda medical monitor to review the potential benefit versus risk to the patient in the setting of a controlled HBV or HCV infection.

8.6.4 Photosafety

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

8.7 Management of Specific AE

Therapies that are required to manage AEs and control cancer symptoms are allowed per standard clinical practice, unless specifically excluded. Supportive care agents, such as erythropoietin and G-CSF are permitted as needed per the ASCO [20,21] guidelines. Blood products (red blood cell [RBC] and platelet transfusions), and pain medications are permitted per local institutional practice. Each treatment intervention should be clearly documented.

8.7.1 Hematologic Toxicities

Refer to Table 8.c for dose delay and reduction recommendations for hematologic toxicities. Dosing with TAK-931 should be held if significant treatment-emergent cytopenia or bleeding is suspected to be related to, or can be worsened by, study treatment. Precautionary measures should be taken to prevent bleeding and overwhelming infections. Blood transfusions (RBC or platelet) and hematopoietic or thrombopoietic stimulating factors may be used to treat cytopenia/

thrombocytopenia at the discretion of the investigator per standard clinical practice. For a first event, a dose reduction is preferred over the use of myeloid growth factors [20].

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

Criteria	Action
Neutropenia (ANC)	
Grade 1 (ANC <LLN to 1.5 × 10^9 cells/L)	Continue TAK-931 at the same dose level.
Grade 2 (ANC 1.0 to <1.5 × 10^9 cells/L)	Continue TAK-931 at the same dose level.
Grade 3 (ANC 0.5 to <1 × 10^9cells/L) 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 <0.5 × 10^9 cells/L) without fever.	Withhold dose until resolved to Grade ≤1 or baseline, then resume treatment at a reduced dose level.
Febrile neutropenia (ANC <1.0 × 10^9 cells/L, with a single temperature of >38.3°C or sustained temperature of ≥38°C for more than 1 h)	Withhold dose until fever/infection have recovered and ANC is Grade ≤1 or baseline, then resume treatment at a reduced dose level.
Thrombocytopenia (PLT)	
Grade 1 (PLT <LLN to 75.0 × 10^9 cells/L)	Continue TAK-931 at the same dose level.
Grade 2 (PLT <75.0 to 50.0 × 10^9 cells/L)	Continue TAK-931 at the same dose level.
Grade 3 (PLT <50.0 to 25.0 × 10^9 cells/L) 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 <25.0 × 10^9cells/L) without bleeding	Withhold dose until resolved to Grade ≤1 or baseline, then resume treatment at a reduced dose level.
Platelets <10,000 cells/mm^3, thrombocytopenia Grade ≥3 associated clinically significant bleeding	Consider permanently withdrawing the patient from the study, except when the investigator determines that the patient is obtaining clinical benefit and has discussed this with the sponsor.

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

8.7.2 GI AEs

Nausea and/or Vomiting

This study will not initially employ prophylactic antiemetics; however, a patient who develops nausea and/or vomiting will be actively managed by employing optimal antiemetic treatment per local standard practice. Additionally, antiemetics could be used prophylactically as clinically indicated following the occurrence of the first event of TAK-931–related or possibly related nausea and/or vomiting. An optimal antiemetic regimen is defined as one that employs both a 5-hydroxytryptamine 3 serotonin antagonist and a corticosteroid given in standard doses and according to standard schedules. PPIs and H_2 receptor antagonists are not allowed during treatment.

Diarrhea

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

8.7.3 Hepatobiliary Disorders

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

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

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

8.7.4 Cardiac Toxicities

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

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

8.7.5 Hypotension

Transient hypotension with reflex tachycardia was observed in toxicology studies with dogs at t_{max}. This risk has not been substantiated in Japanese patients dosed up to 80 mg in the FIH study.

If a hypotensive event occurs, the patient should be advised to contact the site for instructions. BP and HR monitoring should be performed at home, if indicated by the investigator, and values recorded in the patient's diary.

If a hypotensive event occurs at the site, the patient can be discharged only if no clinically relevant BP or HR changes occurred during the observation period. If the investigator notes changes in BP/HR and/or symptoms of concern, subsequent doses of TAK-931 should be administered at the site with the same monitoring as for Days 1 and 3 of Cycle 0 until the risk is confirmed or discharged.

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

8.8 Blinding and Unblinding

This is an open-label study.

8.9 Description of Investigational Agents

TAK-931 will be supplied as PIC for oral administration in part 1 as indicated. TAK-931 PIC is available in 3 dose strengths, 10, 25, and 80 mg of TAK-931 in addition to the following inactive ingredients: mannitol (filler), colloidal silicon dioxide (flow aid), and hard gelatin capsule.

The dose strength of each capsule is differentiated by size and color:

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

TAK-931 will be supplied as tablets for oral administration in parts 1 and 2 as indicated. TAK-931 tablets are available in 3 dose strengths, 10, 25, and 80 mg of TAK-931 in addition to the following inactive ingredients: mannitol (filler), microcrystalline cellulose (filler), and croscarmellose sodium (disintegrant)

The dose strength of each tablet is differentiated by size:

- 10 mg TAK-931 tablets: white, round, approximately 5.5 mm in diameter.
- 25 mg TAK-931 tablets: white, round, approximately 6.4 mm in diameter.
- 80 mg TAK-931 tablets: white, round, approximately 9.5 mm in diameter.

Refer to the TAK-931 IB for full details.

8.10 Preparation, Reconstitution, and Dispensation

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

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

8.11 Packaging and Labeling

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

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

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

The clinical sites will obtain esomeprazole and will apply study labels provided by the sponsor. The precautions, warnings, contraindications, and adverse events associated with esomeprazole are included in the prescribing information [22].

8.12 Storage, Handling, and Accountability

8.12.1 TAK-931

Upon receipt at the investigative site, TAK-931 should be stored in the original bottles until use. Capsules should be stored at 2°C to 8°C (refrigerated) and tablets should be stored at 15°C to 25°C (room temperature). All temperature excursions at the site pharmacy will be reported to the sponsor for assessment and authorization for continued use. All investigational supplies must be stored in a secure area with controlled access and will be stored in original packaging. All TAK-931 should be used before the retest expiry date.

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

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

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

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

Please refer to the study manual for additional instructions.

8.12.2 Esomeprazole

The container should be stored at the investigative site at controlled room temperature (25°C; excursions permitted from 15°C to 30°C) and used before the expiration date indicated on the label or accompanying documentation. Tablets are not intended to be broken or manipulated in any way. Dispense in a tight container if the product package is subdivided. For complete storage and handling information, refer to documentation provided with the commercial product [22].

8.13 Other Protocol-Specified Materials

Not applicable.

9.0 STUDY CONDUCT

This study will be conducted in compliance with the protocol, GCP, applicable regulatory requirements, and ICH guidelines.

9.1 Study Personnel and Organizations

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

9.2 Arrangements for Recruitment of Patients

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

9.3 Treatment Group Assignments

Central randomization (non–center-specific) will be used. Additional instructions are available in the study manual.

9.3.1 Part 1

Patients will be randomly assigned in a 1:1 ratio with a block size of 2 to receive a single dose of TAK-931 either as PIC or tablet on Day 1 of Cycle 0. These patients will then be administered in the alternate formulation on Day 3 of Cycle 0. Details of treatments are in Section 6.1.1.

9.3.2 Part 2

Patients will be randomly assigned in a 1:1 ratio with a block size of 2 to receive a single dose of TAK-931 with or without a standard high-fat breakfast (see Section 8.1.2) on Day 1 of Cycle 0. These patients will then be administered in the alternate food intake condition on Day 3 of Cycle 0. Details of treatments are in Section 6.1.2.

9.4 Study Procedures

Refer to the SOE (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 procedures should be performed on schedule for all visits. The timing of PK assessments is specified in Appendix A, Tables 1, 2, and 4. All EOT evaluations should occur 30 to 40 days after the last dose of study drug.

Refer to the SOE (Appendix A) for timing of assessments. Additional details are provided as necessary in the sections that follow.

9.4.1 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.

9.4.2 Patient Demographics

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

9.4.3 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, with a breakdown by treatment intention (neoadjuvant, adjuvant, or metastatic); line of therapy for metastatic disease, regimen, and drug(s); treatment start and stop dates (including at least month and year); best response; and PD date. Known genetic and serum tumor biomarkers previously analyzed at the site should be recorded. In addition, concomitant medications will be recorded as specified in Section 9.4.8.

9.4.4 Physical Examination

A physical examination will be completed per standard of care at the times specified in the SOE (Appendix A). Any clinically relevant findings are to be documented.

9.4.5 Patient Height and Weight

Height and weight will be measured only once during screening (within 28 days before the first dose of TAK-931).

9.4.6 Vital Signs

Standard vital signs should be obtained at least once during each visit specified in the SOE (Appendix A) and will include temperature (may be oral or axillary temperature), BP, and HR.

9.4.7 Pregnancy Test

A serum pregnancy test will be performed for women of childbearing potential at screening and again at Cycle 0 Day 1 if the screening test was performed more than 4 days before the first dose of study drug.

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

- Those who have not undergone hysterectomy or bilateral oophorectomy, AND

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

The results from these tests must be available and negative before the first dose of study drug is administered. If Cycle 0, Day 1 serum pregnancy results will not be available before dosing, a urine pregnancy test may be performed.

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

9.4.8 Concomitant Medications and Procedures

Medications used by the patient and therapeutic procedures completed by the patient will be recorded in the eCRF from the ICF signature through the EOT visit or before initiation of new anti-cancer therapy, whichever occurs first. See Sections 8.4 and 8.5 for a list of medications and therapies that are prohibited or allowed during the study.

9.4.9 AEs

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

9.4.10 Enrollment

Enrollment is defined as the randomization date. Procedures for completing the enrollment information are described in the study manual. Information regarding patients who do not meet the study entry criteria will be collected in a separate log.

9.4.11 ECG

9.4.11.1 Safety ECGs

Standard 12-lead ECGs will be performed at the time points specified in the SOE (Appendix A). All machine-generated tracings should be acquired in the supine position after patients have been resting for 5 minutes. A qualified person will interpret the ECGs locally. Additional ECGs may be obtained as clinically indicated at the discretion of the investigator (see Section 8.7.5).

9.4.11.2 Triplicate ECGs

Time-matched triplicate ECGs and PK samples will be collected during Cycle 0 on Days 1 and 3 of part 1 (Appendix A, Table 4). Triplicate ECGs will be recorded electronically and transmitted to a central vendor for storage.

Before each nominal triplicate ECG sampling time point, patients must maintain a supine position for 15 minutes. Each ECG recording of the triplicate ECGs should occur within 3 minutes of the previous recording and over a 10-minute window.

For these matched PK/triplicate ECG collections, the PK blood sample should be collected only after completion of the triplicate ECG collection. It is recommended that patients refrain from eating or limit themselves to bland food for 2 hours before and until completion of the 4-hour triplicate ECG measurements. The PK blood draws will occur immediately following the completion of the triplicate ECG extractions on Days 1 and 3 of Cycle 0.

9.4.12 ECHO or MUGA Scan

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

9.4.13 ECOG Performance Status

ECOG performance status (Appendix D) will be assessed at the times specified in the SOE.

9.4.14 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 9.a will be obtained as specified in the SOE.

Table 9.a Clinical Chemistry and Hematology Tests

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

Creatinine clearance will be estimated using the Cockroft-Gault formula as follows:

$$Estimated\ creatinine\ clearance = [(140 - Age) * Mass(kg)\ ] / [72 * serum\ creatinine(mg/dL)]$$

For female patients, the result of the formula above should be multiplied by 0.85.

9.4.15 Disease Assessment

Patients will undergo CT scan, with contrast as appropriate (areas of known or clinically suspected disease), or MRI scan to monitor and assess PD, using RECIST, version 1.1 [19] as outlined in the SOE (Appendix A). Brain CT scan evaluation at screening is not required in the absence of symptoms.

Primary determination of disease status will be based on local investigator assessment. The collection and central storage of scans are planned in case more detailed analysis of imaging data, as determined by the sponsor, is needed.

Tests will be repeated at the frequency specified in the SOE.

9.4.16 Biomarker, Pharmacodynamic, and PK Samples

9.4.16.1 Primary Specimen Collection for PK CCI

Blood samples will be collected at the time points detailed in the SOE (Appendix A) for plasma concentration measurements of TAK-931 CCI. The primary specimen collection is presented in Table 9.b.

Details on sample handling, storage, shipment, and analysis are provided in the laboratory manual.

Table 9.b Primary Specimen Collection

Specimen Name in Schedule of Events	Primary Specimen	Intended Use	Sample Collection
CCI			
Plasma sample for TAK-931 PK	Plasma	PK measurements	Mandatory

Abbreviations: CCI circulating tumor DNA; PK, pharmacokinetic.

9.4.16.2 CCI

CCI

9.4.17 PK Measurements

Serial blood specimens for PK analysis of TAK-931 will be collected at the time points specified in the SOE (Appendix A, Table 4). The dates and exact times of administration of TAK-931 before collection of the blood sample for PK analysis and the dates and exact times of the postdose PK sample collection will be recorded in the eCRF.

Plasma samples may be stored for possible future analysis of TAK-931 metabolites and to test for inversion of the single chiral center within TAK-931.

PK parameters to be assessed are described in Section 5.2.2 and samples will be collected according to the SOE (Appendix A, Table 4).

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

9.4.18 CCI

CCI [redacted]

9.5 Completion of Study Treatment (for Individual Patients)

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

9.6 Completion of Study (for Individual Patients)

Patients will be considered to have completed the study if they are discontinued from study drug and 1 or more of the following situations occurs:

- Death.
- PD.
- Start of new systemic treatment.
- Consent withdrawal.
- Study terminated by the sponsor.
- Lost to follow-up
- Transfer of patient to a long-term safety study, named patient program, compassionate use program, or similar.

Once a patient completes the study, all study procedures outlined for the EOT visit will be completed as specified in the SOE (Appendix A).

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 after the EOT visit 30 days after last dose is completed.

9.7 Discontinuation of Treatment With Study Drug and Patient Replacement

Patients will be informed that they have the right to discontinue study treatment at any time for any reason, without prejudice to their medical care.

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

- AE.
- Major protocol deviation.

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

Once study drug has been discontinued, all study procedures outlined for the EOT and PFS visits will be completed as specified in the SOE (Appendix A). The primary reason for study drug discontinuation will be recorded on the eCRF.

Note that some patients may discontinue study drug for reasons other than PD before completing the full treatment course; these patients will remain in the study for posttreatment assessments as outlined in the SOE until PD occurs. See Section 13.1.1 for patient replacement in the PK-evaluable population.

9.8 Withdrawal of Patients From Study

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

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

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

9.9 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.

Patients are responsible for taking and storing TAK-931 at home as instructed by site personnel and will receive a sufficient quantity of study drug for 1 cycle of treatment. Patients will be given a diary to record study drug dosing and associated events (time of intake, doses missed, vomiting,

symptoms, etc). The study center staff will check the patient's drug diary versus the patient's supply of TAK-931 to assess compliance.

Tests and procedures should be performed on schedule; however, unless otherwise specified, occasional changes are allowable within a 2-day window for holidays, vacations, and other administrative reasons.

9.10 Posttreatment Follow-up Assessments (PFS)

The EOT visit for all patients will take place 30 to 40 days after the last dose.

Patients who stop treatment for any reason other than progressive disease (or clinical deterioration) will continue to have PFS follow-up visits. PFS follow-up visits should be conducted at the site every 12 weeks from the EOT visit until the occurrence of death, PD, start of a new systemic anticancer treatment, consent withdraw, or loss to follow up, whichever occurs first.

The end-of-study visit is to be completed when the patient discontinues from the follow-up period. See the SOE for appropriate assessments during follow-up.

NOTE: Related SAEs must be reported to the Takeda Global Pharmacovigilance department or designee. This includes deaths that the investigator considers related to study drug that occur during posttreatment follow-up. Refer to Section 10.0 for details regarding definitions, documentation, and reporting of SAEs.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 PTE Definition

A PTE 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.

10.1.2 AE 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.

10.1.3 SAE Definition

SAE means any untoward medical occurrence that at any dose:

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

development of drug dependency or drug abuse; any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

In this study, intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, version 5.0, effective date 27 November 2017 [18]. Clarification should be made between an SAE and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are not synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is not the same as *serious*, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a WBC count of 1000/mm^3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

10.2 Procedures for Recording and Reporting AEs and SAEs

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

Regardless of causality, SAEs must be reported (see Section 10.3 for the period of observation) by the investigator to the Takeda Global Pharmacovigilance department or designee within 24 hours of becoming aware of the event. This will be done by transmitting an electronic data capture (EDC) SAE report. If transmission of an EDC SAE report is not feasible, then a facsimile of the completed Takeda paper-based SAE form will be sent. A sample of the paper-based SAE form and processing directions are in the study manual. Information in the SAE report or form must be consistent with the data provided on the eCRF.

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

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

Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the study are not to be considered AEs unless the condition deteriorated in an unexpected manner during the study; eg, surgery was performed earlier or later than planned.

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

Severity (toxicity grade) for each AE, including any laboratory abnormality, will be determined using the NCI CTCAE, version 5.0, effective 27 November 2017 [18]. The criteria are provided in the study manual.

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

10.3 Monitoring of AEs and Period of Observation

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

- AEs
  - AEs will be reported from the signing of informed consent through 30 days after administration of the last dose of study drug and recorded in the eCRFs.
- SAEs
  - Serious PTEs will be reported to the Takeda Global Pharmacovigilance department or designee from the time of the signing of the ICF up to first dose of study drug, and will also be recorded in the eCRF.
  - Related and unrelated treatment-emergent 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 and recorded in the eCRF. After this period, only related SAEs must be reported to the Takeda Global Pharmacovigilance department or designee. SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

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

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

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

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately report this via the phone numbers or e-mail addresses provided below.

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

Call center	Phone number	E-mail	Fax
PPD			

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 Cognizant (refer to Section 10.2).

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

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, including the European Medicines Agency, investigators and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as an 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 product's administration or in the overall conduct of the study. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

11.0 STUDY-SPECIFIC COMMITTEES

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

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the data management plan. If selected for coding, AEs, 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.

12.1 eCRFs

Completed eCRFs are required for each subject who signs an ICF.

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.

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated ICFs, subject authorization forms regarding the use of personal health information (if separate from the ICFs), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal-sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long-term legibility. Furthermore, ICH E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years

after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the clinical study site agreement between the investigator and sponsor.

Refer to the clinical study site agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

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

13.1.1 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.
- PK population: The PK population is defined as all patients for whom there are sufficient dosing and TAK-931 concentration-time data to reliably estimate the PK parameters. This population will be used for analyses of PK parameters. Patients who have any of the occurrences listed in Section 6.2 during Cycle 0 will not be considered PK-evaluable and may be replaced.
- Response-evaluable population: The response-evaluable population is defined as patients who receive at least 1 dose of study drug, have measurable disease at baseline, and have at least 1 postbaseline response assessment.

13.1.2 Procedures for Handling Missing, Unused, and Spurious Data

All available safety, tolerability, antitumor activity, 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.

13.1.3 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.

13.1.4 Antitumor Activity Analysis

Secondary antitumor activity parameters are ORR, PFS, DCR, and DOR. DCR will be assessed per RECIST version 1.1 (CR + PR + SD; SD must be ≥1 post baseline CT scan evaluation from treatment initiation to qualify for DCR).

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

PFS is defined as the time from the date of randomization to the date of first documentation of PD or death due to any cause, whichever occurs first. The Kaplan-Meier survival curves, 25th, 50th

(median), and 75th percentiles (if estimable), along with their 2-sided 95% CIs and percentage of censored observations will be provided. PFS will be analyzed using the safety population.

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

13.1.5 PK Analysis

13.1.5.1 Part 1

For the relative bioavailability assessment, the ratio (tablet to PIC) of geometric mean AUC_{last}, AUC_{∞} and C_{max} and associated 2-sided 90% CIs will be calculated, based on the within-patient variance estimated by analysis of variance. The PK population will be used for the analysis.

13.1.5.2 Part 2

For the food effect assessment, the ratio (fed to fasted) of geometric mean AUC_{last}, AUC_{∞} and C_{max} and associated 2-sided 90% CIs will be calculated, based on the within-patient variance estimated by analysis of variance. For evaluating the effect of esomeprazole on TAK-931 PK, the ratio (presence of esomeprazole to absence of esomeprazole) of geometric mean AUC_{last}, AUC_{∞}, and C_{max} and associated 2-sided 90% CIs will be calculated based on the within-patient variance estimated by analysis of variance. The PK population will be used for these analyses.

TAK-931 PK parameters will be estimated using noncompartmental methods with WinNonlin Phoenix version 6.2 or higher (Pharsight Corp, Mountain View, California). Descriptive statistics for TAK-931 plasma concentrations and the following PK parameters will be tabulated by formulation (part 1), food intake state (fed or fasted, part 2) and the use of esomeprazole (in the presence or absence of esomeprazole, part 2):

- C_{max}.
- CL/F.
- t_{max}.
- AUC_{last}.
- AUC_{∞}.
- $t_{1/2z}$.

Individual TAK-931 concentration-time data and individual PK parameters will be presented in listings and tabulated using summary statistics. Individual and mean plasma concentration-time profiles will be plotted.

13.1.6 CCI

CCI

[redacted]

13.1.7 Safety Analysis

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

TEAEs will be tabulated according to the MedDRA by System Organ Class, High Level Term, and Preferred Term and will include the following categories:

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

Listings of TEAEs resulting in study drug discontinuation and dose modification will be provided.

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

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

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

Concomitant medications collected from ICF signature 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.

ECG Analysis

ECG intervals (QT, QTc, 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. Patients will undergo ECGs as specified in the Schedule of Events (Appendix A, Tables 1, 2, and 4).

13.2 Determination of Sample Size

The sample size calculation is based on the expected 2-sided 90% CI for the difference in the paired, log transformed AUC (or C_{max}) means of TAK-931 administered as tablet and PIC formulations. On the basis of the preliminary data obtained from Study TAK-931-1002, the within-subject %CV was estimated to be 35.0% for AUC and 36.9% for C_{max}. Assuming the true/assumed AUC (or C_{max}) ratio is 1.0, with a sample size of 14 evaluable patients, the 90% CI of the ratio of geometric means is expected to be (0.795-1.257) for AUC and (0.786-1.272) for C_{max} on the basis of the previously discussed variance assumptions. If the ratio is X, the 90% CI of the ratio of geometric means is expected to be within (0.795X-1.257X) for AUC and (0.786X-1.272X) for C_{max}. Patients who are not PK-evaluable may be replaced to ensure the availability of 14 to 16 PK-evaluable patients for the final analysis of part 1 and part 2.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

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

All aspects of the study and its documentation will be subject to review by the sponsor or designee (as long as 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 ICFs), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The 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. If a significant deviation occurs, 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.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

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

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, 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" listed in Appendix B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable local 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 US 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 IB, a copy of the ICF, 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, ICF) reviewed; and state the approval date. The sponsor will ship drug the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the study. Until the site receives notification, no protocol activities, including screening may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the ICF, recruitment materials intended for viewing by 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.

15.2 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 ICF, 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 ICF 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 ICF will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

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

The ICF, 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 ICF, 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 ICF 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 before the subject enters 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 ICF and subject authorization (if applicable) at the time of consent and before 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 ICFs 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 ICF.

15.3 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, US FDA, MHRA, and PMDA), 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 15.2).

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

15.4 Publication, Disclosure, and Clinical Study Registration Policy

15.4.1 Publication

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

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

15.4.2 Clinical Study Registration

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

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

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

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

15.4.3 Clinical Study Results Disclosure

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

15.5 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.

16.0 REFERENCES

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Appendix A Schedule of Events

Table 1: Schedule of Events for Treatment Part 1, Cycle 0 (16 Days)

	Screening [a]	Day 1	Day 3	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 16
Informed consent [a]	X											
Inclusion/exclusion criteria	X											
Demographics	X											
Medical history	X											
Symptom-directed physical examination [b]	X	X										X
Height	X											
Weight	X											
Vital signs [c]	X	X [c]										X
ECOG performance status	X	X										
Safety ECG [d]	X											
12-Lead ECG (triplicate)		X [e]	X [e]									
ECHO/MUGA scan (LVEF) [f]	X											
Disease assessment [g]	X											
HBV/HCV testing	X											
Monitoring of concomitant medications and procedures	Recorded from the signing of ICF through 30 days after the last dose of study drug (EOT visit)											
Adverse event reporting	Recorded from the signing of ICF through 30 days after the last dose of study drug (EOT visit)											
	SAEs [h] will be reported from signing of the ICF through 30 days after the last dose of study drug (EOT visit). Only drug-related SAEs should be reported >30 days from last dose.											
TAK-931 administration [i]		X	X	Day 5 through Day 16								
Samples/Laboratory Assessments												
Pregnancy test [j]	X	X										
Hematology/chemistry [k]	X	X										X [n]
CCI	[redacted]											
Plasma sample for TAK-931 PK [l]		Refer to Table 4, below.										

Footnotes are on last page of schedule of assessments tables.

Table 2: Schedule of Events for Treatment Part 2, Cycle 0 (22 Days)

	Scr [a]	D1	D3	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15	D16	D17	D18	D19	D20	D21	D22
Informed consent	X																				
Inclusion/exclusion criteria	X																				
Demographics	X																				
Medical history	X																				
Symptom-directed physical examination [b]	X	X																			X
Height	X																				
Weight	X																				
Vital signs [d]	X	X [d]									X										X
ECOG performance status	X	X																			
Safety ECG [d]	X																				
ECHO/MUGA scan (LVEF) [f]	X																				
Disease assessment [g]	X																				
HBV/HCV testing	X																				
Monitoring of concomitant medications and procedures	Recorded from the signing of ICF through 30 days after the last dose of study drug (EOT visit)																				
Adverse event reporting	Recorded from the signing of ICF through 30 days after the last dose of study drug (EOT visit)																				
	SAEs [h] will be reported from signing of the ICF through 30 days after the last dose of study drug (EOT visit). Only drug-related SAEs should be reported >30 days from last dose.																				
TAK-931 administration [i]		X	X								X		X	X	X	X	X	X	X	X	X
Esomeprazole administration				X	X	X	X	X	X	X	X	X									
Samples/Laboratory Assessments																					
Pregnancy test [j]	X	X																			
Hematology/ chemistry [k]	X	X									X [o]										X [n]
CCI																					
Plasma sample for TAK-931 PK [l]	Refer to Table 4, below.																				

Footnotes are on last page of schedule of assessments tables.

Table 3: Schedule of Events for Treatment Cycle 1 (21 Days) Through End of Treatment (Parts 1 and 2)

	Day 1	Day 14	Day 15	EOT	Follow-up PFS
Symptom-directed physical examination [b]	X			X	
Vital signs [c]	X			X	
ECOG performance status	X			X	
SafetyECG [d]				X	
ECHO/MUGA scan (LVEF) [f]				X	
Disease assessment [f]	Every third cycle starting at the end of Cycle 3			X	X (Q12wk)
Monitoring of concomitant medications and procedures	Recorded from the signing of ICF through 30 days after the last dose of study drug (EOT visit)				
AE reporting	Recorded from the signing of ICF through 30 days after the last dose of study drug (EOT visit)				
	SAEs [m] will be reported from signing of the ICF through 30 days after the last dose of study drug (EOT visit). Only drug-related SAEs should be reported >30 days from last dose.				
TAK-931 administration [i]	Days 1 to 14 of each 21-day cycle				
CCI					
Hematology/chemistry [o]	X		X	X	

Abbreviations: C, cycle; CCI circulating tumor DNA; D, Day; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; EOT, end of treatment; HBV, hepatitis B virus; HCV hepatitis C virus; ICF, informed consent form; LVEF, left ventricular ejection fraction; MUGA, multiple-gated acquisition; PFS, progression-free survival; PK, pharmacokinetic(s); Q, every; QD, once daily; SAE, serious adverse event; Scr, screening.

Note: Tests and procedures should be performed on schedule, but occasional changes are allowable (±2 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.

[a] Unless otherwise noted, the screening visit must occur within 28 days before the day of the first dose of study drug (C0D1). The ICF may be signed more than 28 days before C0D1.

[b] The symptom-directed physical examination will be conducted at the screening visit, within 3 days before dosing on Day 1 of each treatment cycle, on Day 16 (part 1) or Day 22 (part 2) of Cycle 0, and at the EOT/early termination visit. The symptom-directed physical examination may be performed at other visits during the treatment cycle at the discretion of the investigator.

[c] Perform vital signs measurement before dosing. On C0D1 only, perform vital signs measurements at 1, 3, and 8 hours (±10 minutes) postdose. Vital signs outside of C0D1 will be collected before dosing of TAK-931 as a single determination. Blood pressure should be determined with the patient in a supine position after the patient has been quietly for 5 minutes.

[d] Safety ECG should be acquired predosing and in the supine position after patients have been resting for 5 minutes.

[e] Triplicate 12-lead ECGs will be performed as detailed in Table 4 below. The schedule for ECG sampling may be modified on the basis of data from previous cohorts.

[f] ECHO estimate of the LVEF can be measured as an alternative to MUGA scan.

[g] Radiological evaluations (computed tomography [CT] scan or magnetic resonance imaging as clinically indicated in areas of known or clinically suspected disease) will be employed to assess the status of the patient's underlying disease. Brain CT scan evaluation at screening is not required in the absence of symptoms. An evaluation of lesions will be performed during screening (within 28 days before the first dose of study drug) and every 3rd cycle beginning with Cycle 3. Refer to Section 9.4.15 for details.

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

[i] For part 1, Cycle 0 patients will be randomized to Sequence A (1 dose of 80 mg powder-in-capsule [PIC] on Day 1 followed by 1 dose of 80 mg tablet on Day 3) or Sequence B (1 dose of 80 mg tablet on Day 1 followed by 1 dose of 80 mg PIC on Day 3). From Day 5 through Day 16 inclusive, all patients regardless of the sequence will receive 1 daily dose of TAK-931 50 mg PIC followed by 7 days of rest. For part 2, Cycle 0 patients will be randomized to receive a tablet of TAK-931 on Days 1 either of a fed or a fasted state followed by another tablet of TAK-931 on Day 3 in the alternate fasted or fed state. In both sequences, patients will receive 1 dose of TAK-931 on Day 12, followed by 1 tablet QD from Days 14 through 22 inclusive. After Day 22 administration, there is a 1-week rest period before Cycle 1 Day 1. In parts 1 and 2 Cycle 1 and after, TAK-931 will be administered on Days 1 to 14 inclusive of 21-day cycles. In part 1, the dose for Cycle 1 and after is 50 mg PIC QD. In part 2 TAK-931 will be administered QD in tablets at the dose that produces comparable exposure to 50 mg PIC as determined in part 1. The study center staff will cross-check the patient's diary against the patient's supply of oral TAK-931 on Days 1 and 14 of each cycle to assess compliance.

[j] A serum human chorio gonadotropin beta pregnancy test will be performed only for patients of childbearing potential during screening and again at C0D1 (baseline) if the screening test was performed more than 4 days before the first dose of any 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 C0D1), or as otherwise required by local regulations. If Cycle 0 Day 1 serum pregnancy results are not 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 independent ethics committee/institutional review board, or if required by local regulations.

[k] The hematology and chemistry blood samples for C0D1 may be collected within 4 days before dosing to ensure patient eligibility on Day 1. If screening clinical laboratory testing was performed within 4 days before the C0D1 dose, it need not be repeated on C0D1. For hematology and chemistry panels, refer to Table 9.a.

[l] Time points for blood samples for PK analysis will be collected as specified in Table 4 below.

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

[n] Safety laboratory samples can be collected up to 2 days before the actual visit date. In Cycle 4 and beyond, the hematology and chemistry tests will be conducted on Day 1 of each cycle only if, in the opinion of the investigator, it is safe to do so. For hematology and chemistry panels, refer to Table 9.a.

Table 4: PK and Triplicate ECG Sampling Schedule

	Part 1, Cycle 0							Part 2, Cycle 0							
	D1		D2 [b]	D3 [b]		D4 [b]	D5 [b]	D1 [b]	D2 [b]	D3 [b]	D4 [b]	D5 [b]	D12 [b]	D13 [b]	D14 [b]
	Triplicate ECG [a]	PK	PK	Triplicate ECG [a]	PK	PK	PK	PK	PK	PK	PK	PK	PK	PK	PK
Predose (within 1 h before dosing)	X	X	X [c]		X [d]	X [e]	X [f]	X	X [c]	X [d]	X [e]	X [f]	X	X [g]	X [h]
30 min postdose (±5 min)		X			X			X		X			X		
1 h postdose (±20 min)	X	X		X	X			X		X			X		
2 h postdose (±30 min)	X	X		X	X			X		X			X		
4 h postdose (±30 min)	X	X		X	X			X		X			X		
6 h postdose (±30 min)		X			X			X		X			X		
8 h postdose (±30 min)	X	X		X	X			X		X			X		
24 h postdose (±1 h)		X [c]			X [e]			X [c]		X [e]			X [g]		
48 h postdose (±1 h)		X [d]			X [f]			X [d]		X [f]			X [h]		

Abbreviations: Cx, Cycle; Dx, Day; ECG, electrocardiogram; PK, pharmacokinetic(s).

Note: When the timing of a PK or safety laboratory blood sample coincides with the timing of ECG measurements, the ECG will be completed before the collection of the blood sample. The triplicate ECG measurements should be completed immediately before the corresponding PK blood draw.

Note: All PK analyses will be performed using plasma samples.

[a] Triplicate 12-lead ECG measurements are to be performed with the patient supine, completed after a 15-minute rest period, and will be recorded within 3 minutes of the previous recording over a 10-minute window.

[b] Patients should be instructed to come to the clinic in the morning without taking their morning doses of study drug(s). The timing of the morning visits should occur at approximately the same time as the morning dosing times on previous days of the cycle.

[c] 24 hours after Day 1 dose.

[d] 48 hours after Day 1 dose. The sample should be collected prior to the Day 3 dosing of TAK-931.

[e] 24 hours after Day 3 dose.

[f] 48 hours after Day 3 dose. The sample should be collected prior to the Day 5 dosing of TAK-931 (part 1).

[g] 24 hours after Day 12 dose.

[h] 48 hours after Day 12 dose. The sample should be collected prior to the Day 14 dosing of TAK-931 (part 2).

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 by signing a Form FDA 1572:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol. If the investigator/institution retains the services of any individual or party to perform study related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those study related duties and functions and should implement procedures to ensure the integrity of the study related duties and functions performed and any data generated.
3. Ensure that study related procedures, including study specific (non routine/non standard panel) screening assessments are NOT performed on potential subjects, before the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56, ICH, and local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to 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 ICF 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 ICF 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.
12. Report adverse reactions to the sponsor promptly. In an SAE occurs, 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, US, 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 study 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 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 [23].

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 [24].

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Approval	26-Jun-2018 10:59 UTC
	Clinical Pharmacology Approval	26-Jun-2018 12:30 UTC
	Clinical Approval	27-Jun-2018 08:46 UTC
	Statistical Approval	27-Jun-2018 13:54 UTC