Title: A Phase 1, Open-label Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of TAK-228 (a Catalytic TORC1/2 Inhibitor) as Single Agent in Adult East Asian Patients with Advanced Nonhematological Malignancies

NCT Number: NCT03370302

Protocol Approve Date: 8 February 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 Evaluate the Safety, Tolerability, and Pharmacokinetics of TAK-228 (a Catalytic TORC1/2 Inhibitor) as Single Agent in Adult East Asian Patients with Advanced Nonhematological Malignancies

A Phase 1 Study of TAK-228 in East Asian Patients with Advanced Nonhematological Malignancies

Sponsor:	Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited 40 Landsdowne Street Cambridge, MA USA 02139 Telephone: +1 (617) 679-7000 Please note: Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, may be referred to in this protocol as "Millennium," "Sponsor," or "Takeda".		
Study Number:	C31008		
IND Number:	Not Applicable	**EudraCT Number:**	Not Applicable
Compound:	TAK-228		
Date:	8 February 2018	Amendment Number:	02

Amendment History:

Date	Amendment Number	Region
2 August 2017	Initial Protocol	Global
25 October 2017	01	Global
8 February 2018	02	Global

1.0 ADMINISTRATIVE

1.1 Contacts

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

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

Takeda-sponsored investigators per individual country requirements will be provided with emergency medical contact information cards to be carried by each subject.

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

Contact Type/Role	Contact
Serious adverse event and pregnancy reporting	See Section 10.2.
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	PPD

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 trial disclosure laws, and regulations.

SIGNATURES

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

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

PPD

INVESTIGATOR AGREEMENT

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

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 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/Provence)

Location of Facility (Country)

1.3 Protocol Amendment 02 Summary of Changes

This document describes the changes in reference to the Protocol Incorporating Amendment No. 02.

The primary purpose of this amendment is to incorporate regulatory feedback from the Korean Ministry of Food and Drug Safety (MFDS).

Justification: The changes are being made to the protocol based upon feedback received from the MFDS. In addition, minor revisions (including grammatical and editorial changes) are included for clarification purposes. Full details on changes of text are given in Appendix I. The following is a summary of the changes made in the amendment:

1. Section 8.2: Removed the note for the relationship to be consistent with Section 10.2.
2. Section 9.4.2: Added smoking history.
3. Section 9.8: Added pregnancy to the discontinuation criteria for clarification.
4. Section 9.8: Revised the text for "replacement subject" for clarification.
5. Section 13.1.4: Added pharmacokinetic (PK) analysis plan for the samples obtained in Cycle 2 for QW arm.
6. Appendix A, Schedule of Events: Added additional ECG collection timepoints to collect additional data to verify and confirm that treatment with TAK-228 is not associated with an increased risk of cardiac events.
7. Appendix A: Revised Footnote a in Table A to clarify overnight fasting is not required for PK sampling on Cycle 1 Day 22.

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2.0 STUDY SUMMARY

Name of Sponsor(s): Millennium Pharmaceuticals, Inc.	**Compound:** TAK-228	
Title of Protocol: A Phase 1, Open-label Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of TAK-228 (a catalytic TORC1/2 inhibitor) as Single Agent in Adult East Asian Patients with Advanced Nonhematological Malignancies	**IND No.:** Not Applicable	**EudraCT No.:** Not Applicable
Study Number: C31008	**Phase:** 1	

Study Design:

This study is a multicenter, open-label, phase 1 trial of TAK-228 administered orally as a single agent in adult East Asian patients with advanced nonhematological malignancies for whom standard anticancer treatment is not available or is no longer effective.

The study will consist of 2 arms to evaluate the safety and tolerability, characterize the pharmacokinetics (PK), and determine the recommended phase 2 doses (RP2Ds) of single-agent TAK-228 to be used for 2 schedules (daily and weekly) in East Asian patients.

1. QD (daily dosing schedule) arm: milled TAK-228 will be administered on an empty stomach (nothing to eat or drink for at least 2 hours before and 1 hour after dosing), once daily, in repeated 28-day treatment cycles.
2. QW (weekly dosing schedule) arm: milled TAK-228 will be administered on an empty stomach in Cycle 1 and following a light meal in Cycle 2 and the subsequent cycles, weekly (ie, on Days 1, 8, 15, and 22), in repeated 28-day treatment cycles.

The 2 arms will enroll in parallel. Patient assignment to a specific schedule will be decided jointly by the investigator and sponsor with the aim of maximizing enrollment efficiency in the study.

During dose escalation, 2 planned dose levels of TAK-228 will be tested in each arm (2 mg and 4 mg in the QD arm; 20 mg and 30 mg in the QW arm) following standard 3+3 dose escalation rules. Dosing will increase to 4 mg in the QD arm or 30 mg in the QW arm, provided that the safety and tolerability of the starting dose have been demonstrated.

If a dose is deemed safe in any cohort based on 3+3 rules, then the cohort may be expanded to as many as 12 patients in total to further confirm safety, investigate the PK and determine the RP2D. At least 1 Japanese patient will be enrolled in each group of 3 patients during dose escalation. The total number of Japanese patients dosed at the RP2D level will be at least 6. On the basis of the geographic distribution of patients enrolled or any emerging safety or PK data, additional patients may be added, as needed, to further characterize the safety, tolerability, or PK in patients from a particular East Asian geographic region.

As Western population based RP2D have been defined as 4 mg for the QD schedule and 30 mg for the QW schedule, the dose escalation schemas in the current study are designed to confirm Cycle 1 based RP2D in East Asian patients or determine an alternative appropriate lower dose. Escalation beyond 4 mg QD or 30 mg QW is not expected to be necessary in this study. However, if TAK-228 exposures are unexpectedly lower than anticipated in the East Asian populations, and no dose limiting toxicity (DLT) have occurred in the dose escalation parts, the TAK-228 dose may be escalated further after discussion between the investigators and the sponsor based on the available PK and safety data.

If $\geq$2 of 6 patients experience a DLT at the starting dose level (ie, 2 mg in the QD arm or 20 mg in the QW arm), depending on the overall safety profile, the types of adverse events (AEs)/DLTs observed, and following the examination of the preliminary PK results in relation to the PK data in the Western population, a decision will be made either to evaluate a lower dose or to terminate the study, following discussion between the investigators and the sponsor.

For either treatment arm, more conservative dose escalation, evaluation of intermediate doses, and expansion of an existing or previously tested dose level are all permissible following discussions and agreement between the investigators and the sponsor, if such measures are needed for patient safety or for a better understanding of the

dose-toxicity and dose-exposure relationships of TAK-228.

Blood samples will be collected at prespecified time points in Cycle 1 Days 1, 2, 8, 15, 16, and 22 to characterize the PK of TAK-228 when given daily (QD) or weekly (QW). Blood samples will also be collected at prespecified time points during Cycle 2 Days 1 and 15 to characterize the PK of TAK-228 when given QW with light meals.

CCI [redacted]

Radiological tumor evaluations will be used to evaluate disease response according to Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (Version 1.1).

Toxicity will be evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.

Primary Objectives:

- To evaluate safety and tolerability and to determine RP2D of TAK-228 administered daily (QD arm) or weekly (QW arm) to East Asian patients with advanced nonhematological malignancies
- To characterize PK of TAK-228 in East Asian patients with advanced nonhematological malignancies

Secondary Objectives:

- To evaluate preliminary anti-tumor activity of TAK-228

Subject Population: Adult East Asian patients with advanced nonhematologic malignancies for whom standard treatment is not available or is no longer effective.

Planned Number of Subjects:	**Planned Number of Sites:**
Approximately 46 patients (23 patients each for QD and QW arms)	Approximately 4 sites in East Asian countries
Dose Level(s): QD arm: TAK-228 will be administered once daily, in repeated 28-day treatment cycles at 2 planned doses (2 mg, 4 mg). QW arm: TAK-228 will be administered weekly (on Days 1, 8, 15, and 22), in repeated 28-day treatment cycles at 2 planned dose (20 mg, 30 mg).	**Route of Administration:** Oral
Duration of Treatment: Patients will receive TAK-228 treatment until they experience disease progression, unacceptable toxicity, or withdraw consent.	**Period of Evaluation:** Patients will be followed for 30 days after the last dose of TAK-228.

Main Criteria for Inclusion:

1. Patients of the primary East Asian ethnicity (ie, Japanese, Korean, or Chinese) aged 18 years or older (if local regulation requires a minimum age for informed consent of more than 18 years, then patients must be the minimum age or older per the local regulation) when written study informed consent is obtained.
2. Patients with advanced nonhematologic malignancies, with the exception of primary brain tumor, and have failed or are not eligible for standard of care therapy. History of brain metastasis may be allowed if all of the following criteria are met:
   - Brain metastases have been treated.
   - There is no evidence of progression or hemorrhage after treatment.
   - Steroid has been discontinued for ≥4 weeks before the first dose of study drug.
   - There is no ongoing requirement for steroids or anti-epileptic drugs.

3. Received not more than 4 prior lines of systemic cytotoxic chemotherapy for advanced or metastatic disease.
4. Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1.
5. Screening clinical laboratory values as specified below:
   - Bone marrow reserve consistent with absolute neutrophil count (ANC) $\geq 2000/mm^3$, platelet count $\geq 125{,}000/mm^3$, and hemoglobin ≥ 10 g/dL without transfusion in the last 4 weeks.
     Note: Prophylactic transfusions of blood products or any prophylactic use of hematopoietic growth factors (such as erythropoietin, thrombopoietin, granulocyte colony stimulating factor [G-CSF], and granulocyte macrophage colony stimulating factor [GM-CSF]) is not permitted during the screening period.
   - Hepatic: Total bilirubin $\leq 1.5 \times$ upper limit of normal (ULN), alanine aminotransferase (ALT)/aspartate aminotransferase (AST) $\leq 2.5 \times$ ULN ($\leq 5 \times$ ULN if their elevation can be reasonably ascribed to the presence of hepatocellular carcinoma, biliary tract cancer, or metastatic disease in liver).
   - Adequate renal function, defined as meeting any 1 of the following criteria:
     - Serum creatinine $< 1.5 \times$ ULN.
     - Creatinine clearance based on the Cockcroft-Gault estimate ≥ 40 mL/min.
     - Creatinine clearance based on urine collection (12- or 24-hour) ≥ 40 mL/min.
   - Metabolic: Glycosylated hemoglobin (HbA1c) $\leq 7\%$, fasting serum glucose ≤ 130 mg/dL, and fasting triglycerides ≤ 300 mg/dL.
6. Female patients who:
   - Are postmenopausal (natural amenorrhea, not caused by other medical reasons) for at least 1 year before the screening visit, OR
   - Are surgically sterile, OR
   - If they are of childbearing potential, agree to practice 1 highly effective method of contraception and 1 additional effective (barrier) method at the same time, from the time of signing the informed consent through 90 days after the last dose of study drug, OR
   - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], condoms only, withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception.)

   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 subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods for the female partner], condoms only, withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception.)
7. Ability to swallow oral medications.
8. Voluntary written consent obtained 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.

Main Criteria for Exclusion:

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

1. Diagnosis of primary brain tumor.
2. Untreated brain metastasis or history of leptomeningeal disease or spinal cord compression.
3. Failed to recover from the reversible effects of prior anticancer therapies with the exception of alopecia, and after-effects associated with prior tyrosine kinase inhibitor therapy, such as hair depigmentation, hypothyroidism,

and/or splinter hemorrhage.

4. Received prior cancer therapy or other investigational therapy within 2 weeks before the first dose of study drug. For prior therapies with a half-life longer than 3 days, the interval must be at least 28 days before the first dose of study drug.
5. Initiation of hematopoietic growth factors within 1 week before the first dose of study drug.
6. Requirement of systemic corticosteroid treatment within 7 days before receiving the first dose of TAK-228. Inhalers and low-dose glucocorticoids for replacement therapy are allowed.
7. Manifestations of malabsorption caused by prior gastrointestinal surgery, gastrointestinal disease, or for some other reason that may alter the absorption of TAK-228. In addition, patients with enteric stomata are also excluded.
8. Poorly controlled diabetes mellitus defined as HbA1c >7%; patients with a history of transient glucose intolerance caused by corticosteroid administration are allowed if all other eligibility criteria are met.
9. Other clinically significant comorbidities, such as uncontrolled pulmonary disease (eg, severe chronic obstructive pulmonary disease with hypoxemia, interstitial lung disease, radiation induced lung injury), active central nervous system disease, active infection, or any other condition that could compromise the patient's safety and participation in the study per protocol.
10. Known human immunodeficiency virus infection.
11. Known hepatitis B surface antigen (HBsAg) positive, or known or suspected active hepatitis C virus (HCV) infection.
    Note: Patients who have isolated positive hepatitis B core antibody (HBcAb) and/or hepatitis B surface antibody (HBsAb) may be enrolled but must have an undetectable hepatitis B virus (HBV) viral load. Patients who have positive hepatitis C virus antibody (HCVAb) may be enrolled but must have an undetectable HCV viral load.
12. 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 Cycle 1 Day 1 before the first dose of the study drug.
    (Note: Female patients who are lactating will be excluded, even if they discontinue breastfeeding.)
13. History of any of the following within the last 6 months before the first dose of study drug:
    - Ischemic myocardial event, including angina requiring therapy and artery revascularization procedures.
    - Ischemic cerebrovascular event, including transient ischemic attack and artery revascularization procedures.
    - Requirement for inotropic support (excluding digoxin) or serious (uncontrolled) cardiac arrhythmia (including atrial flutter/fibrillation, ventricular fibrillation, or ventricular tachycardia).
    - Placement of a pacemaker for control of rhythm.
    - New York Heart Association Class III or IV heart failure.
    - Pulmonary embolism.
14. Significant active cardiovascular or pulmonary disease before the first dose of study drug, including:
    - Uncontrolled hypertension (ie, systolic blood pressure >180 mmHg; diastolic blood pressure >95 mmHg).
    - Pulmonary hypertension.
    - Uncontrolled asthma or oxygen saturation <90% by pulse oximetry on room air.
    - Significant valvular disease; severe regurgitation or stenosis by imaging independent of symptom control with medical intervention; or history of valve replacement.
    - Medically significant (symptomatic) bradycardia.
    - History of arrhythmia requiring an implantable cardiac defibrillator.
    - Baseline prolongation of the rate-corrected QT interval (QTc [eg, repeated demonstration of QTc interval >480 ms, or history of congenital long QT syndrome, or torsades de pointes]).
15. Diagnosed or treated for another malignancy within 2 years before the first dose or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.
16. Requirement of daily or chronic use of proton pump inhibitors (PPIs) and/or the use of a PPI within 7 days before

receiving the first dose of TAK-228. Use of PPIs is prohibited during the study.

Main Criteria for Evaluation and Analyses:

Primary:

- The number and percentage of patients with Treatment-emergent AEs (TEAEs).
- The number and percentage of patients with Grade 3 or higher TEAEs.
- The number and percentage of patients with serious TEAEs.
- Number of patients with DLTs during Cycle 1.
- The number and percentage of patients with TEAEs leading to study drug discontinuation.
- TAK-228 C_{max}, t_{max}, and AUC on Cycle 1 Days 1 and 15.

Secondary:

- Clinical benefit rate defined as the proportion of patients with a best overall response of complete response (CR), partial response (PR) or stable disease (SD) (SD of any duration).

Exploratory:

CCI [redacted]

Statistical Considerations:

Statistical analyses will be primarily descriptive in nature. Analyses for safety and binary response endpoints will be descriptive using percentages. No formal statistical hypothesis testing will be performed. A formal statistical analysis plan will be developed and finalized before database lock.

Sample Size Justification:

For each arm, dose escalation will be conducted according to a standard 3+3 dose escalation schema. There are 2 planned dose cohorts in each of 2 arms (QD arm and QW arm) in this study. For each arm, 9 to 12 DLT-evaluable patients will be needed for the dose escalation portion. In addition, for each arm, additional 6 patients will be needed for safety expansion. Assuming a 20% dropout rate, approximately 23 patients will be needed for each arm to have 18 DLT-evaluable patients; the total sample size for this study will be 46.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

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

3.2 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

Abbreviation	Term
$5\text{-}HT_3$	5-hydroxytryptamine 3 serotonin receptor
ACVR1	activin A receptor, type 1
AE	adverse event
AKT	serine/threonine-specific protein kinase (also known as protein kinase B)
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BMPR1B	bone morphogenetic protein receptor type-1B
CK1	casein kinase 1
CL/F	apparent clearance after extravascular administration
C_{max}	maximum observed concentration
CR	complete response
CRO	contract research organization
CSF1R	colony stimulating factor 1 receptor
CSNK1D	casein kinase 1 isoform delta
CSNK1E	casein kinase 1 isoform epsilon
CSR	clinical study report
C_{trough}	observed concentration at the end of a dosing interval
CT	computed tomography
CYP	cytochrome P450
DDR1	discoidin domain receptor 1
DNA	deoxyribonucleic acid
DNA-PK	DNA-dependent protein kinase
DLT	dose limiting toxicity
DPP-4	dipeptidyl peptidase-4
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	End of Treatment
ER+	estrogen receptor positive
FLT3	FMS-like tyrosine kinase 3
FBG	fasting blood glucose
FDA	Food and Drug Administration
FIH	first-in-human
GCP	Good Clinical Practice

Abbreviation	Term
G-CSF	granulocyte colony stimulating factor
GLP	Good Laboratory Practice
GM-CSF	granulocyte macrophage colony stimulating factor
HbA1c	glycosylated hemoglobin
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCVAb	hepatitis C virus antibody
HDPE	high-density polyethylene
HER2-	human epidermal growth factor receptor-2 negative
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IRB	institutional review board
IV	intravenous(ly)
MedDRA	Medical Dictionary for Regulatory Activities
MEK1	mitogen-activated protein kinase 1
MEK2	mitogen-activated protein kinase 2
MFDS	Ministry of Food and Drug Safety
MRI	magnetic resonance imaging
mTOR	mammalian (or mechanistic) target of rapamycin
mTORC1	mTOR complex 1
mTORC2	mTOR complex 2
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
pAKT	phosphorylated protein kinase B
PD	progressive disease
PDGFRα	platelet-derived growth factor alpha receptor
PDGFRβ	platelet-derived growth factor beta receptor
PI3K	phosphoinositide 3-kinase
PI3KC2α	phosphoinositide 3-kinase-C2-alpha
PI3KC2β	phosphoinositide 3-kinase-C2-beta
PK	pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency
PO	orally
PPI	proton pump inhibitor

Abbreviation	Term
PR	partial response
PT/INR	prothrombin time/international normalized ratio
QD	once daily
QTc	corrected QT interval
QW	once weekly
RECIST	Response Evaluation Criteria in Solid Tumors
RIPK2	receptor-interacting protein kinase 2
RNA	ribonucleic acid
RP2D	recommended phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	terminal disposition phase half-life
TEAE	treatment-emergent adverse event
t_{max}	time of first occurrence of C_{max}
TORC1	mammalian (or mechanistic) target of rapamycin complex 1
TORC2	mammalian (or mechanistic) target of rapamycin complex 2
UGT	uridine diphosphate glucuronosyltransferase
ULN	upper limit of normal
Vz/F	apparent volume of distribution during the terminal disposition phase
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

The mammalian (or mechanistic) target of rapamycin (mTOR) is a central regulator of cell growth, metabolism, and angiogenesis that functions in 2 distinct multiprotein complexes: mTOR complex 1 (TORC1) and mTOR complex 2 (TORC2). mTOR kinase plays a key role in several pathways that are frequently dysregulated in human cancer [1]. Inhibiting mTOR may inhibit abnormal cell proliferation, tumor angiogenesis, and abnormal cellular metabolism, thus providing the rationale for mTOR inhibitors as potential agents in the treatment of a number of indications including solid tumor and hematological malignancies, either as monotherapy or in combination with other chemotherapeutic agents. Like rapamycin, several newly approved rapalogs (temsirolimus and everolimus) are specific and allosteric inhibitors of TORC1 but only partially inhibit TORC1 substrates. They do not directly inhibit TORC2, which has shown to be an emerging target in cancer research. TAK-228 (sapanisertib) is a novel, selective, orally bioavailable mTOR inhibitor that targets both TORC1 and TORC2, thus enabling more profound blockage of angiogenesis, growth, and survival signaling within the pathophysiologically relevant signaling pathway which may lead to increased antitumor activity.

TAK-228 is being investigated as a treatment for advanced solid tumors and hematologic malignancies, either as monotherapy or in combination with chemotherapy, other molecularly targeted therapies, or antihormonal agents. TAK-228 is also being developed in combination with TAK-117 (an oral phosphoinositide-3-kinase alpha inhibitor) as a treatment for advanced nonhematologic malignancies.

4.2 Nonclinical Experience

TAK-228 is an orally available, potent, and highly selective adenosine triphosphate competitive inhibitor of mTOR kinase that exhibits dual specificity against both the TORC1 and TORC2 complexes.

In vitro studies have demonstrated that TAK-228 selectively and potently inhibits mTOR kinase (1 nmol/L). Relative to mTOR inhibition, TAK-228 has >100-fold less potency on class I (PI3K isoforms α, β, γ, and δ), class II (PI3KC2α and PI3KC2β), and class III (VPS34) PI3K family members. TAK-228 inhibits (>80%) the biochemical activity of 5 kinases (mTOR, DNA-PK, PDGFRα, FLT3, and CK1 epsilon kinases) out of a panel of 222 protein kinases. Out of a panel of 402 distinct kinases, TAK-228 inhibits the ligand binding of only 10 receptor and intracellular protein kinases (ACVR1, BMPR1B, CSF1R, CSNK1D, CSNK1E, DDR1, MEK1, MEK2, PDGFRβ, and RIPK2). TAK-228 also displays potent cellular inhibition of both the TORC1 and TORC2 pathway with cellular pharmacodynamically active concentrations at 50% inhibition values of <10 nmol/L.

TAK-228, administered orally in multiple human tumor xenograft mouse models, can inhibit angiogenesis and tumor growth by inhibiting mTOR signaling at plasma concentrations associated with in vitro inhibition of mTOR in a dose- and time-dependent manner. These effects display a

clear pharmacokinetic (PK)-to-pharmacodynamic relationship [2]. TAK-228 inhibits the phosphorylation of ribosomal protein S6, eukaryotic translation initiation factor 4E binding protein 1, the downstream substrates of TORC1, and selectively inhibits serine/threonine-specific protein kinase (AKT) phosphorylation at Serine 473, as evidenced by decreased pAKT, the downstream substrate of TORC2 [2][3][4]. Dual TORC1/2 inhibition mitigates the feedback activation of AKT, which is known to cause resistance to TORC1-only inhibitors such as rapamycin [5]. TAK-228 inhibits mTOR signaling and has demonstrated anticancer activity against a number of human solid tumor cell-line xenograft mouse models, including phosphatase and tensin homolog mutant endometrial, breast, and renal cell carcinomas.

The toxicity profile of TAK-228 in rats and monkeys, as established in Good Laboratory Practice (GLP)-compliant repeat-dose studies, is consistent with pharmacologic inhibition of TORC1/2 activity. TAK-228 is not mutagenic or phototoxic, does not present a genotoxic risk, and has a low potential for adverse effects on the respiratory, cardiovascular, and central nervous systems.

Detailed information regarding the nonclinical pharmacology and toxicology of TAK-228 may be found in the Investigator's Brochure (IB).

4.3 Clinical Experience

As of the clinical data cutoff of 09 December 2016, TAK-228 is being investigated in 3 ongoing phase 2 studies: C31004, a study of TAK-228 as a single agent or in combination with paclitaxel or TAK-117 in patients with advanced, recurrent, or persistent endometrial cancer; C31005, a study of TAK-228 as a single agent or in combination with TAK-117 as compared with everolimus in patients with clear-cell renal cell carcinoma; C31006, a study of TAK-228 in combination with fulvestrant in women with estrogen receptor positive (ER+)/human epidermal growth factor receptor-2 negative (HER2-) advanced or metastatic breast cancer. In addition, C31001, a phase 1b/2 study is ongoing for TAK-228 in combination with exemestane or fulvestrant in women with ER+/HER2- advanced or metastatic breast cancer.

TAK-228 was investigated in 3 completed phase 1 studies in patients with advanced solid tumors or hematologic malignancies as a single agent (Studies INK128-001, INK128-002) or in combination with paclitaxel, with or without trastuzumab (Study INK128-003). Milled TAK-228 was investigated as either a single agent or in combination with paclitaxel in a completed phase 1 study in patients with advanced solid tumors (Study MLN0128-1004).

The effect of TAK-228 on the corrected QT interval (QTc) in patients with advanced solid tumors has been studied in the ongoing, single-arm, dedicated QTc study (Study C31002).

As of the clinical data cutoff (09 December 2016), a total of 538 patients across the studies had received at least 1 dose of study drug. A total of 25 deaths that occurred during treatment or within 30 days of the last study drug dose had been reported to the clinical database. Of these events, 1 case of ventricular fibrillation and cardiac arrest that occurred in Study INK128-001 was considered related to TAK-228. The most common treatment-emergent adverse events (TEAEs) observed with TAK-228 are consistent with the pharmacodynamic mechanism of mTOR inhibition that is also seen with rapalogs (TORC1 inhibition) or other dual TORC1/2 inhibitors.

The TEAEs observed across the TAK-228 single-agent studies include diarrhea, fatigue, vomiting, rash, mucosal inflammation, asthenia, dysgeusia, thrombocytopenia, stomatitis, blood creatinine increased, hyperglycemia, nausea, anorexia, and decreased appetite. In general, observed toxicities have been mostly Grade 1 or Grade 2 and have been manageable with supportive care and/or TAK-228 dose interruption or reduction.

Results from a dedicated QTc study, C31002 support the conclusion that 40 mg TAK-228 does not produce clinically relevant (ie, >20 msec) effects on QT interval in patients with cancer. Importantly, there was no concentration-dependent increase in the change from time-matched baseline individual QT interval correction in the PK/QTc analysis.

Further details on these studies are provided in the TAK-228 IB.

Clinical Pharmacokinetics of TAK-228

The PK parameters measured for TAK-228 in the phase 1 clinical studies have been generally consistent across a range of doses and schedules. TAK-228 has shown linear PK and fast oral absorption with single-dose median t_{max} occurring between 1 and 4 hours after dosing. The mean $t_{1/2}$ of TAK-228 is approximately 5 to 8 hours, and no accumulation has been observed in plasma after repeat daily dosing. Recently completed in-vitro metabolism experiments in human hepatocytes using ^{14}C labeled TAK-228 suggest that TAK-228 is metabolized primarily via cytochrome P-450 (CYP)1A2 (approximately 31% to 40%) with a minor contribution from CYP3A4 (approximately 11% to 22%). These data suggest that TAK-228 is also metabolized by direct glucuronidation (approximately 22%) as well as an unidentified non-uridine diphosphate glucuronosyltransferase (UGT) pathway (approximately 18%). The new data differ from the previous in-vitro CYP phenotyping data that was conducted using recombinant CYP enzymes, which suggested the involvement of CYP2C9 (approximately 35%), CYP2C19 (approximately 28%), and CYP3A4 (approximately 28%) in TAK-228 metabolism. Physiologically based pharmacokinetic modeling and simulation using the new metabolism data suggest that the risk for a metabolism based drug-drug interaction with TAK-228 appears to be low.

The PK properties of TAK-228 are further detailed in the IB.

4.4 Potential Risks and Benefits

The most common TEAEs observed with TAK-228 are consistent with the pharmacodynamic mechanism of mTOR inhibition and are also seen with other TORC1 or dual TORC1/2 inhibitors. The most common TEAEs observed across TAK-228 single-agent studies include diarrhea, fatigue, vomiting, rash, mucosal inflammation, asthenia, dysgeusia, thrombocytopenia, stomatitis, blood creatinine increased, hyperglycemia, nausea, anorexia, and decreased appetite.

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

Nonclinical data supporting the potential benefits of TAK-228 as anticancer therapy are summarized in Section 4.2. Preliminary signs of antitumor activity have been seen in patients treated with TAK-228, supporting further development of TAK-228 in clear-cell renal cell carcinoma, hormone-receptor positive breast cancer, and endometrial cancer. Further details are presented in the TAK-228 IB.

4.5 Rationale for the Proposed Study

To facilitate the global expansion of the TAK-228 program, this phase 1 study is to be conducted to evaluate the safety, tolerability, PK, and preliminary efficacy of single-agent TAK-228 in adult East Asian patients with advanced nonhematological malignancies.

To date TAK-228 clinical studies have only been conducted in Western regions. Based on the results of these studies, TAK-228 exhibits a manageable safety profile along with preliminary evidence of clinical activity in selected types of cancer including renal cell carcinoma, breast cancer, bladder cancer, and endometrial cancer. AEs reported in clinical studies to date are consistent with the mechanism of action of TAK-228 and are generally reversible and manageable. Results from the studies conducted in predominantly Western patients support the initiation of this phase 1 study in East Asian patients with advanced nonhematologic malignancies.

4.5.1 Rationale for Dose and Schedule Selection

In Study INK128-001 (FIH study) conducted in Western population, single-agent TAK-228 was administered with 4 dosing schedules (QD, QW, QD×3d QW [once daily for 3 consecutive days followed by a 4-day dosing holiday every week] and QD×5d QW [once daily for 5 consecutive days followed by a 2-day dosing holiday every week]) in a 28-day cycle in patients with advanced nonhematological malignancies. QD and QW schedules were selected for further development in combination with either exemestane or fulvestrant in women with ER+/HER2- breast cancer, and QW dosing schedule was selected for further development in patients with clear-cell renal cell carcinoma and endometrial cancer. To support future clinical development in those indications in East Asian patients, single-agent TAK-228 given with QD or QW schedule will be evaluated in this study. This study will consist of 2 arms: the QD arm and the QW arm.

The selected doses for QD and QW schedules to be tested in this study are based on the findings from 3 studies conducted in Western patients: INK128-001, MLN0128-1004, and C31001.

4.5.1.1 QW Dosing

In Study INK128-001, 116 patients with advanced solid tumors received single-agent TAK-228 (2 to 40 mg with 4 dosing schedules in 28 day cycles) in the dose escalation phase. Doses of 40 mg QW, 30 mg QW, and 5 mg QD were further evaluated in an additional 82 patients in the expansion part, where 30 mg QW and 5 mg QD were selected as the recommended phase 2 doses (RP2Ds) and schedules for further development of TAK-228.

Scale-up manufacturing of TAK-228 required the introduction of a physical milling step to control particle size distribution of TAK-228 drug substance. With the introduction of milled TAK-228,

the recommended dose to be used for QW schedule was further confirmed in Study MLN0128-1004. A total of 14 patients were enrolled and assigned, sequentially, to 2 QW dosing cohorts (20 mg QW and 30 mg QW). PK, safety, and tolerability were evaluated (Table 4.a).

Table 4.a Dose Limiting Toxicities Observed with Weekly TAK-228 in Study MLN0128-1004

Dose of Milled TAK-228	Number of Evaluable Patients	DLTs Observed in Cycle 1
20 mg QW	6	None
30 mg QW	6	None

Abbreviations: DLTs=dose limiting toxicity, QW=once weekly

As none of the patients in either dose cohort experienced dose limiting toxicity (DLT) in Cycle 1, a dose of 30 mg TAK-228 QW was selected for further development. No clinically meaningful differences in PK of TAK-228 were noted between the unmilled TAK-228 (Study INK128-001) and milled TAK-228 (Study MLN0128-1004) when given QW.

The starting dose for QW arm in this study will be 20 mg. This dose is lower than the current RP2D (30 mg) for milled TAK-228 determined in Western population when administered on a QW schedule in a 28-day cycle and is considered a safe starting dose to evaluate the PK characteristics and safety and tolerability of single agent QW schedule in East Asian patients. TAK-228 doses for subsequent cohorts may be escalated to 30 mg depending upon tolerability observed in the prior cohort.

During Phase 1 and Phase 2 development of TAK-228 QW doses have been administered under either fed or fasted conditions. Fed administration is expected to improve the tolerability of TAK-228. The effects of food on a 4 mg dose of TAK-228 PK were evaluated in Study MLN0128-1004. Administration of a 4 mg dose of TAK-228 following a standard high-fat breakfast was associated with a 40% reduction in C_{max} and a delay in t_{max} (median t_{max} 6 hours [fed] vs. 2 hours [fasted]), without any meaningful change in AUC.

The apparent lack of food effect on systemic exposure (AUC) and improved long term tolerability following a light meal support oral dosing of TAK-228 in the fed state after Cycle 2. In Study C31008, patients in the QW arm will receive TAK-228 in the fasted state during Cycle 1 and after a light meal during Cycle 2 and beyond. Serial PK samples to characterize the PK of TAK-228 will be collected during Cycle 1 (fasted dosing) and sparse PK samples will be collected during Cycle 2 (fed dosing), which will enable the comparison of the PK of TAK-228 between Asian patients and Western patients in the both dosing conditions.

4.5.1.2 QD Dosing

The RP2D of 4 mg milled TAK-228 QD in combination with either exemestane or fulvestrant was determined in the phase 1b dose finding portion of Study C31001. In the phase 1b portion of the study, 12 patients were initially dosed in a safety lead-in with 5 mg QD of the unmilled TAK-228 material in combination with either fulvestrant or exemestane (6 patients each). No DLTs were observed during Cycle 1; however, 6 of the 12 patients did require dose reductions in Cycles 2 and

3 (2 patients each), and 1 patient each in Cycles 4 and 7. In order to evaluate the safety of milled TAK-228 material, escalation cohorts of 3 mg and 4 mg QD of the milled material were studied in combination: 6 patients at the 3 mg dose (3 in combination with exemestane and 3 with fulvestrant) and 6 patients at the 4 mg dose (all with exemestane). Of the 6 patients treated with 4 mg TAK-228 in combination with exemestane, 1 experienced a DLT of nausea and diarrhea. After review of the data with the investigators, including events occurring outside of the DLT evaluation period, it was agreed to stop escalation and move forward with 4 mg QD in the phase 2 portion of the study (in combination with either exemestane or fulvestrant), as well as in Study C31006 (in combination with fulvestrant). As of data cut of February 2016, 79 patients have been treated in the phase 2 portion of Study C31001 with 4 mg QD TAK-228 in combination with fulvestrant or exemestane.

Study MLN0128-1004 demonstrated that there were no meaningful differences in the PK of TAK-228 administered as 4 mg unmilled versus milled active pharmaceutical ingredient capsules under fasting conditions. In study C31008, TAK-228 4 mg QD will be administered under fasting conditions to avoid possible reductions in C_{max} of TAK-228 at the lower dose of 4 mg.

The starting dose for the QD arm in this study will be 2 mg, which is 50% below the current RP2D (4 mg) for milled TAK-228 determined in Western population when administered on a QD schedule, in a 28-day cycle. This dose is considered a safe starting dose to evaluate the PK characteristics and the safety and tolerability of the single-agent QD schedule in East Asian patients. During the treatment period, the QD dose of TAK-228 may be escalated to 4 mg, depending upon tolerability observed in the prior cohort.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objectives

The primary objectives are:

- To evaluate safety and tolerability and to determine RP2D of TAK-228 administered daily (QD arm) or weekly (QW arm) to East Asian patients with advanced nonhematological malignancies.
- To characterize PK of TAK-228 in East Asian patients with advanced nonhematological malignancies.

5.1.2 Secondary Objectives

The secondary objective is:

- To evaluate preliminary anti-tumor activity of TAK-228.

5.1.3 Exploratory Objectives

CCI

[redacted]

5.2 Endpoints

5.2.1 Primary Endpoints

The primary endpoints are:

- The number and percentage of patients with TEAEs.
- The number and percentage of patients with Grade 3 or higher TEAEs.
- The number and percentage of patients with serious TEAEs.
- Number of patients with DLTs during Cycle 1.
- The number and percentage of patients discontinuing study drug due to TEAEs.
- TAK-228 C_{max}, T_{max}, and AUC on Cycle 1 Days 1 and 15.

5.2.2 Secondary Endpoints

The secondary endpoint is:

- Clinical benefit rate defined as the proportion of patients with a best overall response of complete response (CR), partial response (PR) or stable disease (SD) (SD of any duration).

5.2.3 Exploratory Endpoints

CCI

[redacted]

6.0 STUDY DESIGN

6.1 Overview of Study Design

This study is a multicenter, open-label, phase 1 study of TAK-228 administered orally as a single agent in adult East Asian patients with advanced nonhematological malignancies for whom effective standard anticancer treatment is not available or is no longer effective.

The study will consist of 2 arms to evaluate the safety and tolerability, characterize the PK, and determine the RP2Ds of single-agent TAK-228 to be used for 2 schedules (daily and weekly) in East Asian patients.

1. QD (daily dosing schedule) arm: milled TAK-228 will be administered on an empty stomach, once daily, in repeated 28-day treatment cycles.
2. QW (weekly dosing schedule) arm: milled TAK-228 will be administered on an empty stomach in Cycle 1 and following a light meal in Cycle 2 and the subsequent cycles, weekly (ie, on Days 1, 8, 15, and 22), in repeated 28-day treatment cycles.

The 2 arms will enroll in parallel. Patient assignment to a specific schedule will be decided jointly by the investigator and sponsor with the aim of maximizing enrollment efficiency in the study.

During dose escalation, 2 planned dose levels of TAK-228 will be tested in each arm (2 mg and 4 mg in the QD arm; 20 mg and 30 mg in the QW arm) following standard 3+3 dose escalation rules. Dosing will increase to 4 mg in QD arm or 30 mg in QW arm, provided that the safety and tolerability of the starting dose has been demonstrated (Figure 6.a).

If a dose is deemed safe in any cohort based on 3+3 rules, then the cohort may be expanded to as many as 12 patients in total to further confirm safety, investigate PK and determine RP2D. At least 1 Japanese patient will be enrolled in each group of 3 patients during dose escalation. The total number of Japanese patients dosed at the RP2D level will be at least 6. On the basis of the geographic distribution of patients enrolled or any emerging safety data or PK, additional patients may be added, as needed, to further characterize the safety, tolerability, or PK in patients from a particular East Asian geographic region.

As Western population based RP2D have been defined as 4 mg for the QD schedule and the 30 mg QW schedule, the dose escalation schemas in the current study are designed to confirm Cycle 1 based RP2D in East Asian patients or determine an alternative appropriate lower dose. Escalation beyond 4 mg QD or 30 mg QW is not expected to be necessary in this study. However, if TAK-228 exposures are unexpectedly lower than anticipated in the East Asian populations, and no DLTs have occurred in the dose escalation parts, the TAK-228 dose may be escalated further after discussion between the investigators and the sponsor based on the available PK and safety data.

If ≥2 of 6 patients experience a DLT at the starting dose level (ie, 2 mg in QD arm or 20 mg in QW arm), depending on the overall safety profile, the types of AEs/DLTs observed, and following the examination of the preliminary PK results in relation to the PK data in the Western population, a decision will be made either to evaluate a lower dose or to terminate the study, following discussion between the investigators and the sponsor.

For either treatment arm, more conservative dose escalation, evaluation of intermediate doses, and expansion of an existing or previously tested dose level are all permissible following discussions and agreement between the investigators and the sponsor, if such measures are needed for patient safety or for a better understanding of the dose-toxicity and dose-exposure relationships of TAK-228.

Blood samples will be collected at prespecified time points in Cycle 1 Days 1, 2, 8, 15, 16, and 22 to characterize the PK of TAK-228 when given daily (QD) or weekly (QW). Blood samples will also be collected at prespecified time points during Cycle 2 Days 1 and 15 to characterize the PK of TAK-228 when given QW with light meals. Details of the PK measurements are described in Section 9.4.20.

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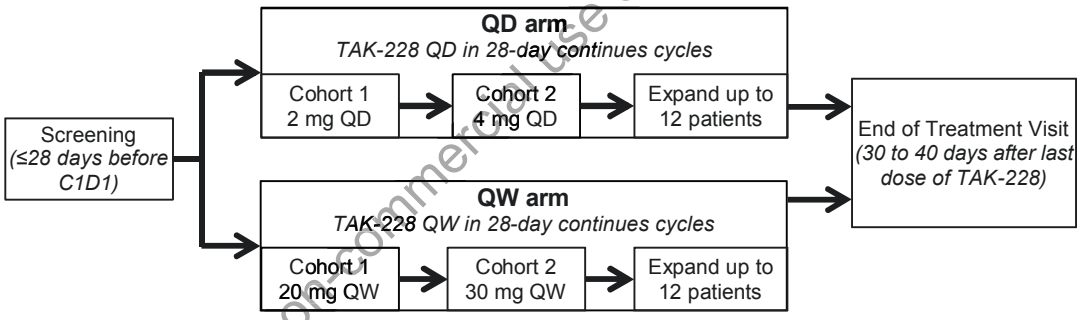
Radiological tumor evaluations will be used to evaluate disease response according to Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (Version 1.1) [6].

Toxicity will be evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03, effective date 14 June 2010 [7]. Dose-limiting toxicities (DLTs) are defined in Section 8.2.

Figure 6.a Study Overview Diagram



Abbreviations: C1D1=Cycle 1 Day 1, QD=once daily, QW=once weekly

6.2 Number of Patients

Approximately 36 DLT-evaluable patients (approximately 18 patients in each arm) will be enrolled from approximately 4 study sites in East Asia. Enrollment is defined as the time of the first dose of TAK-228. Assuming a 20% dropout rate, approximately 23 patients will be needed for each arm to have approximately 18 DLT-evaluable patients; the total sample size for this study will be approximately 46.

6.3 Duration of Study

6.3.1 Duration of an Individual Patient's Study Participation

Patients may receive study drug until they experience disease progression, unacceptable toxicity, withdrawal of consent, or for any of the other reasons outlined in Section 9.8 and the maximum duration of treatment for patients will be 12 months except as set forth in Section 9.6.

Patients will be followed for 30 days after the last dose of TAK-228 to permit further detection of any treatment-related AEs.

6.3.2 End of Study/Study Completion Definition and Planned Reporting

Primary Completion/Study Completion

The final analyses for the safety, PK, and efficacy endpoints and authoring of a clinical study report (CSR) will be conducted after all patients enrolled in the study have completed the study treatment and a 30-day safety follow-up. The estimated time frame for study completion is approximately 23 months. The study is considered completed after the last patient completes study treatment and a 30-day safety follow-up.

6.3.3 Timeframes for Primary and Secondary Endpoints to Support Disclosures

Please 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 (a)
Primary:		
• The number and percentage of patients with TEAEs (b).	The number and percentage of patients with TEAEs.	Approximately 23 months.
• The number and percentage of patients with Grade 3 or higher TEAEs.	The number and percentage of patients with Grade 3 or higher TEAEs.	Approximately 23 months.
• The number and percentage of patients with serious TEAEs.	The number and percentage of patients with serious TEAEs.	Approximately 23 months.
• Number of patients with DLTs during Cycle 1.	Number of patients with DLTs during Cycle 1.	Up to dosing on Cycle 2 Day 1.
• The number and percentage of patients with TEAEs leading study drug discontinuation.	The number and percentage of patients with TEAEs leading study drug discontinuation.	Approximately 22 months.
• TAK-228 C_{max} on Cycle 1 Days 1 and 15 by dose.	Geometric mean and CV for C_{max} on Cycle 1 Days 1 and 15 by dose in the PK-evaluable population.	Up to Cycle 1 Day 15.
• TAK-228 t_{max} on Cycle 1 Days 1 and 15 by dose.	Median (range) for t_{max} on Cycle 1 Days 1 and 15 by dose in the PK-evaluable population.	Up to Cycle 1 Day 15.
• TAK-228 AUC on Cycle 1 Days 1 and 15 by dose.	Geometric mean and CV for AUC on Cycle 1 Days 1 and 15 by dose in the PK-evaluable population.	Up to Cycle 1 Day 15.
Secondary		
Clinical benefit rate	Proportion of patients with a best overall response of CR + PR + SD (SD of any duration).	Approximately 23 months.

Abbreviations: AUC=area under the plasma concentration-time curve, C_{max}=maximum observed concentration, CR=complete response, CV=coefficient of variation, DLT=dose-limiting toxicity, PK=pharmacokinetic(s), PR=partial response, SD=stable disease, TEAE=treatment-emergent adverse event, t_{max}=time of first occurrence of C_{max}
(a) Time to last assessment for that endpoint for an individual patient.
(b) TEAEs are defined as AEs that occur after the first dose of study drug until 30 days after the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first.

6.3.4 Total Study Duration

It is anticipated that this study will last for approximately 23 months.

7.0 STUDY POPULATION

7.1 Inclusion Criteria

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

1. Patients of the primary East Asian ethnicity (ie, Japanese, Korean, or Chinese) aged 18 years or older (if local regulation requires a minimum age for informed consent of more than 18 years, then patients must be the minimum age or older per the local regulation) when written study informed consent is obtained.
2. Patients with advanced nonhematologic malignancies, with the exception of primary brain tumor, and have failed or are not eligible for standard of care therapy. History of brain metastasis may be allowed if all of the following criteria are met:
   - Brain metastases have been treated.
   - There is no evidence of progression or hemorrhage after treatment.
   - Steroid has been discontinued for ≥4 weeks before the first dose of study drug.
   - There is no ongoing requirement for steroids or anti-epileptic drugs.
3. Received not more than 4 prior lines of systemic cytotoxic chemotherapy for advanced or metastatic disease.
4. Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1.
5. Screening clinical laboratory values as specified below:
   - Bone marrow reserve consistent with absolute neutrophil count (ANC) ≥2000/mm^3, platelet count ≥125,000/mm^3, and hemoglobin ≥10 g/dL without transfusion in the last 4 weeks.
     Note: Prophylactic transfusions of blood products or any prophylactic use of hematopoietic growth factors (such as erythropoietin, thrombopoietin, granulocyte colony stimulating factor [G-CSF], and granulocyte macrophage colony stimulating factor [GM-CSF]) is not permitted during the screening period.
   - Hepatic: Total bilirubin ≤1.5 × upper limit of normal (ULN), alanine aminotransferase (ALT)/aspartate aminotransferase (AST) ≤2.5 × ULN (≤5 × ULN if their elevation can be reasonably ascribed to the presence of hepatocellular carcinoma, biliary tract cancer, or metastatic disease in liver).
   - Adequate renal function, defined as meeting any 1 of the following criteria:
     – Serum creatinine <1.5 × ULN.
     – Creatinine clearance based on the Cockcroft-Gault estimate ≥40 mL/min.
     – Creatinine clearance based on urine collection (12- or 24-hour) ≥40 mL/min.

- Metabolic: Glycosylated hemoglobin (HbA1c) ≤7%, fasting serum glucose ≤130 mg/dL, and fasting triglycerides ≤300 mg/dL.

6. Female patients who:
   - Are postmenopausal (natural amenorrhea, not caused by other medical reasons) for at least 1 year before the screening visit, OR
   - Are surgically sterile, OR
   - If they are of childbearing potential, agree to practice 1 highly effective method of contraception and 1 additional effective (barrier) method (see Appendix G) at the same time, from the time of signing the informed consent through 90 days after the last dose of study drug, OR
   - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], condoms only, withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception.)

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 subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods for the female partner], condoms only, withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception.)

7. Ability to swallow oral medications.
8. Voluntary written consent obtained 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.

7.2 Exclusion Criteria

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

1. Diagnosis of primary brain tumor.
2. Untreated brain metastasis or history of leptomeningeal disease or spinal cord compression.
3. Failed to recover from the reversible effects of prior anticancer therapies with the exception of alopecia, and after-effects associated with prior tyrosine kinase inhibitor therapy, such as hair depigmentation, hypothyroidism, and/or splinter hemorrhage.
4. Received prior cancer therapy or other investigational therapy within 2 weeks before the first dose of study drug. For prior therapies with a half-life longer than 3 days, the interval must be at least 28 days before the first dose of study drug.

5. Initiation of hematopoietic growth factors within 1 week before the first dose of study drug.
6. Requirement of systemic corticosteroid treatment within 7 days before receiving the first dose of TAK-228. Inhalers and low-dose glucocorticoids for replacement therapy are allowed.
7. Manifestations of malabsorption caused by prior gastrointestinal surgery, gastrointestinal disease, or for some other reason that may alter the absorption of TAK-228. In addition, patients with enteric stomata are also excluded.
8. Poorly controlled diabetes mellitus defined as HbA1c >7%; patients with a history of transient glucose intolerance caused by corticosteroid administration are allowed if all other eligibility criteria are met.
9. Other clinically significant comorbidities, such as uncontrolled pulmonary disease (eg, severe chronic obstructive pulmonary disease with hypoxemia, interstitial lung disease, radiation induced lung injury), active central nervous system disease, active infection, or any other condition that could compromise the patient's safety and participation in the study per protocol.
10. Known human immunodeficiency virus infection.
11. Known hepatitis B surface antigen (HBsAg) positive, or known or suspected active hepatitis C virus (HCV) infection.
    Note: Patients who have isolated positive hepatitis B core antibody (HBcAb) and/or hepatitis B surface antibody (HBsAb) (ie, in the setting of negative HBsAg) may be enrolled but must have an undetectable hepatitis B virus (HBV) viral load. Patients who have positive hepatitis C virus antibody (HCVAb) may be enrolled but must have an undetectable HCV viral load.
12. 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 Cycle 1 Day 1 before the first dose of the study drug.
    (Note: Female patients who are lactating will be excluded, even if they discontinue breastfeeding.)
13. History of any of the following within the last 6 months before the first dose of study drug:
    - Ischemic myocardial event, including angina requiring therapy and artery revascularization procedures.
    - Ischemic cerebrovascular event, including transient ischemic attack and artery revascularization procedures.
    - Requirement for inotropic support (excluding digoxin) or serious (uncontrolled) cardiac arrhythmia (including atrial flutter/fibrillation, ventricular fibrillation, or ventricular tachycardia).
    - Placement of a pacemaker for control of rhythm.
    - New York Heart Association Class III or IV heart failure.

- Pulmonary embolism.

14. Significant active cardiovascular or pulmonary disease before the first dose of study drug, including:
    - Uncontrolled hypertension (ie, systolic blood pressure >180 mmHg; diastolic blood pressure >95 mmHg).
    - Pulmonary hypertension.
    - Uncontrolled asthma or oxygen saturation <90% by pulse oximetry on room air.
    - Significant valvular disease; severe regurgitation or stenosis by imaging independent of symptom control with medical intervention; or history of valve replacement.
    - Medically significant (symptomatic) bradycardia.
    - History of arrhythmia requiring an implantable cardiac defibrillator.
    - Baseline prolongation of the rate QTc (eg, repeated demonstration of QTc interval >480 ms, or history of congenital long QT syndrome, or torsades de pointes).
15. Diagnosed or treated for another malignancy within 2 years before the first dose or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.
16. Requirement of daily or chronic use of proton pump inhibitors (PPIs) and/or the use of a PPI within 7 days before receiving the first dose of TAK-228. Use of PPIs is prohibited during the study.

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). If required by local regulations or local clinical guidelines or preferred by the investigator, study drugs and protocol assessments may be administered in an in-patient setting during Cycle 1 (eg. patients enrolled in Japan in dose escalation cohorts will be hospitalized during Cycle 1 DLT evaluation period).

TAK-228 will be administered according to the assigned dosing schedule (ie, QD or QW schedule). For the QD arm, TAK-228 will be dosed daily in 28-day cycles. For the QW arm, TAK-228 will be dosed weekly in 28-day cycles (ie, on Days 1, 8, 15 and 22). TAK-228 will be administered at approximately the same time on each dosing day. On dosing days when the patient does not have a clinic visit, patients will take their assigned TAK-228 dose at home. TAK-228 will be taken on an empty stomach in all cycles in the QD arm and Cycle 1 in the QW arm. Patients should be instructed to refrain from eating and drinking (except water and prescribed medications) for 2 hours before and 1 hour after each dose. In Cycle 2 and subsequent cycles in the QW arm, TAK-228 will be administered following a light meal. It is recommended that each dose of TAK-228 be taken with 240 mL of water.

Table 8.a Nutritional Information for a Light Meal

	Low-Fat Breakfast	Light Snack
Nutritional information	Approximately 330 kilo calories, with 9 g of fat	Approximately 100 to 300 kilo calories, with 1.5 g of fat

During the study treatment period, patients will be instructed to record in their dosing diary (see the Pharmacy Manual) each TAK-228 dose they take. If severe emesis or mucositis prevents the patient from taking a TAK-228 dose, that dose will be skipped. If emesis occurs after TAK-228 ingestion, the dose should be counted as missed and will not be re-administered, and patients should simply adhere to the dosing schedule and resume dosing at the next scheduled time with the prescribed dosage. Patients should record the time of the emesis in their dosing diary (see the Study Manual). Under no circumstance should a patient repeat a dose or double-up doses. A forgotten or missed dose of TAK-228 should be taken if it is possible to do so within 12 hours of the scheduled dosing time for the QD arm and within 24 hours of the scheduled dosing time for the QW arm; otherwise, that dose should be skipped, and the next dose should be taken as scheduled. Any skipped dose should be considered a missed dose.

8.2 Definitions of Dose Limiting Toxicity

Toxicity will be evaluated according to NCI CTCAE (Version 4.03, effective 14 June 2010) [7]. DLT is defined as any of the following events that occur within the first 28 days of the

administration of TAK-228 and are considered by the investigator to be at least possibly related to therapy with TAK-228.

- Grade 3 or higher nonhematologic toxicity, except for the following:
  - Inadequately treated Grade 3 nausea and/or vomiting and Grade 3 diarrhea (all subjects should receive optimal antiemetic and/or antidiarrheal prophylaxis and/or treatment. Optimal antiemetic prophylaxis is defined as an antiemetic regimen that includes 5-hydroxytryptamine 3 serotonin receptor (5-HT_3) antagonists and a corticosteroid given in standard doses and according to standard schedules).
  - Grade 3 hyperglycemia lasting ≤14 days (all patients should receive optimal antiglycemic treatment, including insulin).
  - Grade 3 rash lasting ≤3 days (all patients should receive topical steroid treatment, oral antihistamines, and oral steroids, if necessary).
- Grade 3 thrombocytopenia with hemorrhage or requiring platelet transfusion.
- Grade 3 anemia requiring blood transfusion.
- Grade 4 neutropenia lasting >7 days.
- Grade 3 or higher neutropenia of any duration accompanied by fever ≥38.5°C and/or systemic infection.
- Any other ≥Grade 4 hematologic toxicity.
- Inability to administer at least 75% of planned doses of TAK-228 within Cycle 1 due to treatment-related toxicity.
- Any clinically significant occurrence that the investigator and sponsor agree would place patients at an undue safety risk.

Note: Prophylactic transfusions of blood products or any prophylactic use of hematopoietic growth factors (such as erythropoietin, thrombopoietin, G-CSF, and GM-CSF) is not permitted during the DLT evaluation period.

Patients who experience an AE that meets the definition of a DLT during or after completing Cycle 1 should have their study drug treatment interrupted. If the event resolves to Grade 1 or baseline values within 2 weeks of interrupting planned therapy, and in the opinion of the investigator and the sponsor's project clinician the benefits of continuing treatment outweigh the risks posed by the toxicity, patients may continue study treatment with TAK-228 dose reduction with approval of the sponsor's project clinician.

Although DLTs may occur at any point during treatment, only DLTs occurring during Cycle 1 of treatment will necessarily influence decisions regarding dose escalation, expansion of a dose level, or evaluation of intermediate dose levels. Patients will be monitored through all cycles of therapy for treatment-related toxicities.

8.3 Dose Escalation Rules

This study will use 3+3 dose escalation rules. The starting dose will be 2 mg in the QD arm and 20 mg in the QW arm. Provided the safety and tolerability of the starting dose has been demonstrated, the dose will be escalated to 4 mg in Cohort 2 QD arm and 30 mg in Cohort 2 QW arm (Table 8.b).

Table 8.b Planned Dose Levels

Dose Level	Dose (unit)	
	QD arm	QW arm
1	2 mg QD	20 mg QW
2	4 mg QD	30 mg QW

More conservative dose escalation, evaluation of intermediate doses, and expansion of an existing or previously tested dose level are all permissible following discussions and agreement between the investigators and the sponsor, if such measures are needed for patient safety or for a better understanding of the dose-toxicity and dose-exposure relationship of TAK-228.
Abbreviations: QD=once daily, QW=once weekly.

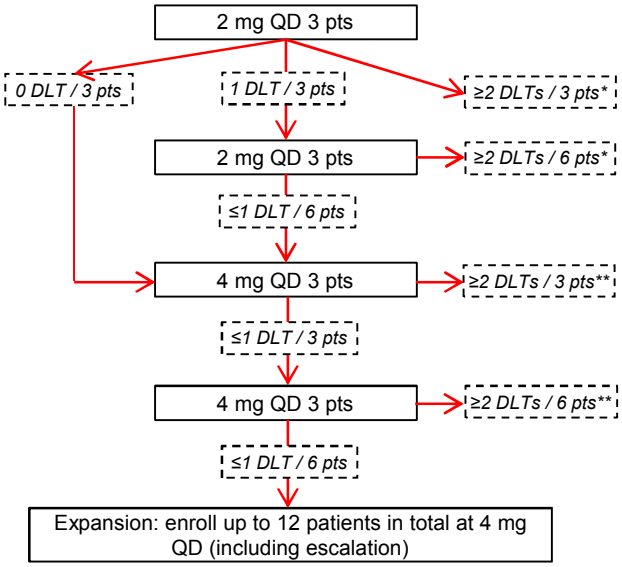
Specific rules for the 3+3 algorithm are as follows:

1. If 0 of 3 patients experiences a DLT, dose escalation will proceed to the next higher dose level, at which 3 patients will be enrolled.
2. If 1 of 3 patients experiences a DLT, 3 more patients will be enrolled at the same dose level. Escalation will continue if 1 of 6 patients experiences a DLT.
3. If 2 or more patients at any dose level experience a DLT, dosing will stop, and 1 of the following options may be chosen by the sponsor:
   a) Three additional patients will be treated at the previous dose level if fewer than 6 patients have been studied at that dose level, or the lower dose level may be declared as tolerable if 6 patients have already been dosed.
   b) An intermediate dose may be tested.
4. If 0 of 3 patients experiences DLT at the highest dose level, 3 additional patients will be enrolled at that dose level, making a total of 6 patients in the dose escalation phase at the highest dose level.

Escalation beyond 4 mg QD or 30 mg QW is not anticipated in this study. However, if TAK-228 exposures are unexpectedly lower than anticipated in the East Asian populations, and no DLTs have occurred during dose escalation, the TAK-228 dose may be escalated further after discussion between the investigator and the sponsor, based on available PK and safety data.

Dose escalation algorithms are outlined in Figure 8.a for the QD arm and Figure 8.b for the QW arm.

Figure 8.a QD Arm Dose Escalation Algorithm



Abbreviations: DLT=dose limiting toxicity, QD=once daily.

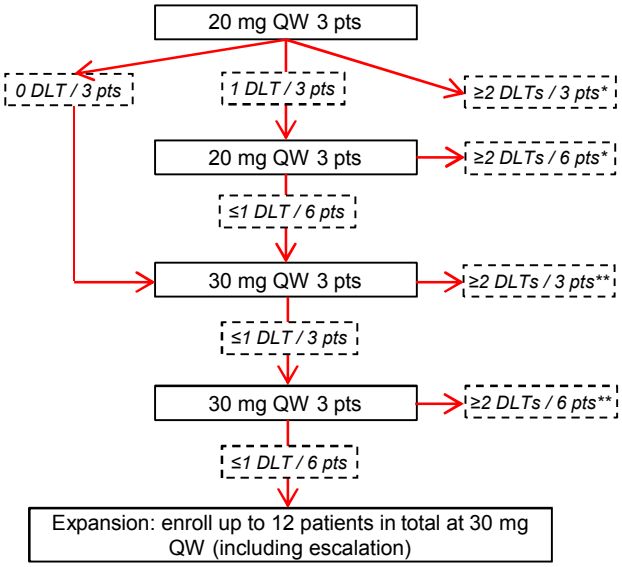
* Stop the study or evaluate a lower dose following discussion between investigators and the sponsor.

** Stop enrollment and 1 of the following options will be chosen following discussion between the sponsor and investigators:

(a) Three additional patients will be treated at the previous dose level if fewer than 6 patients have been studied at that dose level, or declare the lower dose level as tolerable dose if 6 patients have already been dosed.

(b) An intermediate dose between 2 mg and 4 mg may be tested.

Figure 8.b QW Arm Dose Escalation Algorithm



Abbreviations: DLT=dose limiting toxicity, QW=once weekly.
* Stop the study or evaluate a lower dose following discussion between investigators and the sponsor.
** Stop enrollment and following discussion between the sponsor and investigators, either 3 additional patients will be treated to the previous dose level if fewer than 6 patients have been studied at that dose level, or declare the lower dose level as tolerable dose if 6 patients have already been dosed.

While the primary escalation schema is designed to determine a classic Cycle 1-based maximum tolerated dose (MTD), dose escalation may be halted at any time after consultation between the sponsor and investigators if cumulative toxicity beyond Cycle 1 indicates that a given dose exceeds a tolerable RP2D. The MTD and/or RP2D should be evaluated with a total of ≥6 DLT-evaluable patients. The RP2D will be determined on the basis of the safety, tolerability, and preliminary PK and efficacy data (if available) observed in Cycle 1 and beyond. Intrapatient dose escalation is not allowed in this protocol.

DLT-evaluable patient is defined as patients who have received at least 75% of planned doses of TAK-228 in Cycle 1 (21 doses for the QD arm and 3 doses for QW arm) unless interrupted by study drug-related AEs and have sufficient follow-up data to allow the sponsor and investigator to determine whether DLT occurred.

Patients who are not considered DLT-evaluable for the given dose cohort will be replaced within the same cohort. However, all AEs observed in each dose cohort, including those observed in DLT non-evaluable patients, will be considered together with DLTs when making dose escalation decisions.

8.4 Dose Modification Guidelines

8.4.1 Intrapatient Dose Escalation

Intrapatient dose escalation is not allowed.

8.4.2 Criteria for Beginning or Delaying a Subsequent Treatment Cycle

TAK-228 will be administered in continuous cycles. For a new cycle of treatment to begin, subjects must be free of Grade 3 or greater TAK-228-related AEs or laboratory abnormalities. Guidelines for TAK-228 interruption are provided in Section 8.4.3 and for dose reduction in Section 8.4.4. If there is a delay of a subsequent cycle longer than 2 weeks because of incomplete recovery from treatment-related toxicity, the patient will be withdrawn from treatment unless there is clinical benefit as assessed by the investigator, with agreement by the sponsor's project clinician.

8.4.3 Criteria for Dose Interruption During a Cycle

Subjects who experience an AE that meets the definition of a DLT during or after completing Cycle 1 should have their study drug treatment interrupted as described in Section 8.2.

TAK-228 administration must be interrupted for treatment-related AEs that are Grade 3 or higher despite supportive treatment per standard clinical practice.

The following nonhematologic AEs would not require study drug interruption:

- Grade 3 or higher nausea and/or emesis in the absence of optimal antiemetic prophylaxis. (Optimal antiemetic prophylaxis is defined as an antiemetic regimen that employs both a 5-HT_3 antagonist and a corticosteroid given in standard doses and according to standard schedules.)
- Grade 3 or higher diarrhea that occurs in the absence of optimal supportive therapy.
- Grade 3 fatigue.

Patients who have study drug interrupted because of treatment-related AEs may resume study drug treatment only upon resolution of the AE to ≤Grade 1 (Grade 2 for hyperglycemia or rash) or to baseline within 2 weeks.

8.4.4 Criteria for Dose Reduction

TAK-228 administration must be interrupted for treatment-related AEs that are Grade 3 or higher despite supportive treatment per standard clinical practice. If the event resolves to Grade 1 (or Grade 2 for hyperglycemia or rash, as detailed in Section 8.8.1 and 8.8.4, respectively) or to baseline values within 2 weeks of interrupting treatment, the patient may resume study treatment at reduced dose by 1 dose level. If a subject does not tolerate the starting dose, then the investigator and the sponsor's project clinician should discuss whether the subject would benefit from a further dose reduction.

All patients who continue to experience any toxicity (hematologic or nonhematologic) of a severity that requires more than 2 dose reductions of TAK-228, given administration of appropriate supportive care, should discontinue study treatment. However, if the patient has evidence of clinical benefit and is considered to possibly benefit from continued study treatment, the patient may continue study treatment with further dose reductions, upon review and written approval by the sponsor's project clinician. These circumstances should be discussed on a case-by-case basis. As a general rule, if a patient requires dose reduction because of a study drug-related toxicity, the drug dose may not be re-escalated.

8.4.5 Criteria for Discontinuation

If TAK-228 dosing is delayed because of TAK-228-related toxicities for longer than 14 consecutive days despite supportive treatment per standard clinical practice or if more than 2 TAK-228 dose reductions are required, then study drug treatment should be stopped. However, if the patient has evidence of clinical benefit and is considered to possibly benefit from continued protocol treatment, the patient may continue protocol treatment with further dose reductions, upon review and approval by the sponsor's project clinician.

For all patients, the End of Treatment (EOT) visit should be completed within 30 to 40 days after the last dose of study drug, or before the start of subsequent antineoplastic therapy, whichever occurs first.

8.5 Excluded Concomitant Medications and Procedures

The following medications, therapies, and foods are prohibited during the study, except as indicated below:

- Other investigational agents or mTOR inhibitors.
- Other anticancer therapies, including chemotherapy, immunotherapy, radioimmunotherapy, targeted agents, radiation, or surgery (patients can have palliative radiation or surgery during the study for preexisting lesions).
- Systemic corticosteroids (either intravenously [IV] or oral steroids), unless necessary for treatment of a TAK-228-related AE (eg, rash). Inhalers and low-dose glucocorticoids for replacement therapy are allowed.
- Anti-epileptic drugs for patients with a history of treated brain metastasis.
- Strong CYP1A2 inhibitors and clinically significant enzyme inducers may not be used within 7 days before the first dose of TAK-228 or at any time during Cycle 1 (see the nonexhaustive list provided in Appendix H). After Cycle 1, strong CYP1A2 inhibitors and CYP inducers should be administered with caution and at the discretion of the investigator. Alternative treatments, if available, should be considered.
- Concomitant administration of any PPI is not permitted during the study. All patients are required to stop taking PPIs at least 7 days before receiving the first dose of study drug.

Examples of PPIs include omeprazole, esomeprazole, pantoprazole, lansoprazole, and rabeprazole.

- Histamine H_2 receptor antagonists may be allowed if needed, provided that the histamine H_2 receptor antagonist is not taken within 12 hours before or within 6 hours after study drug administration. Patients receiving histamine H_2 receptor antagonists must stop using these medications for at least 24 hours before their first dose of study drug. Examples of histamine H_2 receptor antagonists include ranitidine, famotidine, nizatidine, and cimetidine.
- Administration of neutralizing antacids and calcium preparations is permitted except from 4 hours before until 2 hours after study drug administration. Some antigas preparations may also have antacid properties and should also not be permitted from 4 hours before until 2 hours after study drug administration

8.6 Permitted Concomitant Medications and Procedures

Prophylactic use of anti-emetic (including ondansetron and granisetron), antinausea, and antidiarrheal medications is encouraged, and these may be administered before the first dose of study drug, as needed throughout the study before each dosing, and as clinically indicated per standard practice.

Concomitant treatment with bisphosphonates is permitted for treatment of osteoporosis or management of existing bone metastasis if initiated at least 4 weeks before the first dose of study drug. Bisphosphonates should be given after Cycle 1 to minimize confounding factors that may contribute to potential drug-related toxicities.

Other medications considered necessary for the safety and wellbeing of the patient may be administered at the discretion of the investigator. Any concomitant medications added or discontinued during the study should be recorded on the electronic case report form (eCRF).

8.7 Precautions and Restrictions

The only dietary restrictions imposed on study patients include avoidance of foods listed in Section 8.5 and Appendix H starting 1 week before the first dose of study drug and throughout the study, consumption of a light meal prior to weekly TAK-228 administration (QW Arm, from Cycle 2 onward) and fasting for glucose sampling and monitoring (as outlined in Appendix A and Section 9.4.15). Patients who show evidence of hyperglycemia during the study should be encouraged to follow a low carbohydrate diet.

8.7.1 Pregnancy and Contraception

It is not known what effects TAK-228 has on human pregnancy or development of the embryo or fetus. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of reproductive age group and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.

1. Some examples of effective contraceptive methods include intrauterine devices and hormonal contraceptives (Appendix G).
2. Use only contraceptive methods that are locally approved and available in each country.
3. 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 and 1 additional effective (barrier) method of contraception from the time of signing of the informed consent form (ICF) through 90 days after the last dose of study drug, or
   - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)
4. Male patients, even if surgically sterilized (ie, 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 subject. (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.)

8.7.2 Patients With Prior Exposure to HBV or HCV

Patients who have detectable HBV or HCV viral loads are excluded from study participation (see Section 7.2, Exclusion Criterion #11). Patients with prior exposure to HBV or HCV who have subsequently cleared the infection (determined by a negative viral load) are allowed in the study, but should be monitored for reactivation every 2 months. Patients who develop detectable HBV or HCV in their blood during the study will have TAK-228 treatment interrupted and will be treated with antivirals medication per local institutional standard practice; a consultation with a hepatologist should be considered. For such patients enrolled in Japan, HBV infection will be treated as per the Japan Society of Hepatology Guidelines for the Treatment of Immunosuppression- or Chemotherapy-Induced Reactivation of Hepatitis B Virus Infection.

Resuming TAK-228 after HBV or HCV is no longer detected may be considered in the setting of continued prophylaxis and after a discussion with the sponsor's project clinician to review the potential benefit versus risk to the patient in the setting of a controlled HBV or HCV infection.

8.7.3 Overdose

There is no specific antidote for overdose with TAK-228. Patients who experience overdose should be closely monitored and general supportive care should be instituted.

8.8 Management of Clinical Events

Detailed TAK-228 dose modification and prevention/prophylaxis guidelines for specific clinical events are provided in the following sections. General guidelines for TAK-228 interruption and dose reduction are provided in Section 8.4.3 and Section 8.4.4.

8.8.1 Management of Hyperglycemia

On the basis of the clinical experience in TAK-228 trials, most episodes of hyperglycemia observed occurred within the first 60 days after initiation of treatment with TAK-228 and have been either Grade 1 or Grade 2, and have responded quickly to oral metformin. Hyperglycemia has not been dose-limiting since the institution of a standard regimen for early treatment of hyperglycemia.

All patients developing hyperglycemia during the study should have their glucose closely monitored by study staff. The investigator may choose to continue close monitoring of patients who develop Grade 1 hyperglycemia (fasting glucose >ULN ≤160 mg/dL) or, alternatively, consider initiating treatment with an oral hypoglycemic agent, such as metformin. All patients with ≥Grade 2 hyperglycemia (fasting glucose >160 mg/dL) must be treated aggressively with oral hypoglycemic agents and/or insulin as clinically indicated. The investigator should consult an endocrinologist, if needed, to aid in optimizing the patient's hyperglycemia treatment plan.

It is recommended that patients be initially treated with a fast acting insulin sensitizer such as metformin at 500 mg orally (PO) QD, and titrate up to a maximum of 1000 mg PO twice daily as needed. Concurrent addition to metformin of dipeptidyl peptidase-4 (DPP-4) inhibitors (eg, sitagliptin or vildagliptin) and/or insulin should also be considered. Oral sulfonylureas (eg, glipizide or glyburide) should be used with caution, due to the higher risk of inducing hypoglycemia in patients. The dose of oral hypoglycemic agents should be adjusted in patients with renal insufficiency. In addition, patients should be encouraged to follow a low carbohydrate diet once hyperglycemia is first observed.

If any fasting serum glucose reading performed at the site indicates hyperglycemia (>ULN or ≥110 mg/dL), the study staff should first confirm that the patient was fasting at the time of blood specimen collection (ie, nothing by mouth for at least 8 hours before collection). To aggressively manage the hyperglycemia per standard clinical practice, the following guidelines (Table 8.c) are provided to aid the investigator in initiating antiglycemic therapies.

Table 8.c Management of Hyperglycemia

Grade	Description	Treatment	Dose Modification
1	FBG >ULN-160 mg/dL	Continue close monitoring of blood glucose. Initiate oral hypoglycemic agent.	None
2	FBG >160-250 mg/dL	Initiate oral hypoglycemic agent and/or insulin if not well controlled on oral agent.	None
≥3	FBG >250 mg/dL	Initiate oral hypoglycemic agent and/or insulin.	Interrupt TAK-228 until ≤ Grade 2. Resume TAK-228 based on timing of recovery: • ≤1 week: resume at same dose and schedule. • >1 but ≤2 weeks: reduce to the next lower dose. • >2 weeks: discontinue TAK-228 treatment permanently.

Prevention/Prophylaxis

- Follow fasting serum glucose levels during clinic visits.
- Monitor home glucometer test results.
- Check HbA1c levels every 3 months during therapy.
- Recommend lifestyle modifications, as appropriate (balanced diet, limited alcohol consumption, increased physical activity).
- Most episodes of Grade 1 and 2 hyperglycemia respond quickly to oral metformin. Early initiation of therapy is recommended to prevent higher grade hyperglycemia.
- FBG levels ≥150 mg/dL by glucometer should be followed by closer monitoring of serum glucose and possible intervention.

Abbreviations: FBG=fasting blood glucose; HbA1c=glycosylated hemoglobin; ULN=upper limit of normal.

8.8.2 Management of Hyperlipidemia

Guidance on study drug dose modification for patients with hyperlipidemia is provided in Table 8.d.

Table 8.d Management of Hyperlipidemia

Grade	Description	Treatment	Dose Modification
1	Cholesterol: >ULN-300 mg/dL Triglycerides: >150-300 mg/dL	None	None
2	Cholesterol: >300-400 mg/dL Triglycerides: >300-500 mg/dL	Treat hyperlipidemia according to standard guidelines. Triglycerides ≥500 mg/dL should be treated urgently because of the risk of pancreatitis.	Maintain dose if tolerable. If toxicity becomes intolerable, interrupt TAK-228 dosing until recovery to ≤ Grade 1. Resume TAK-228 at same dose.
3	Cholesterol: >400-500 mg/dL Triglycerides: >500-1000 mg/dL	Same as for Grade 2	Interrupt TAK-228 until recovery to ≤ Grade 1 or baseline, then resume TAK-228 with the next lower dose.
4	Cholesterol: >500 mg/dL Triglycerides: >1000 mg/dL	Same as for Grade 2	Discontinue TAK-228 treatment permanently.

Prevention/Prophylaxis

- Lifestyle modifications, as appropriate (balanced diet, limited consumption of alcoholic beverages, increased physical activity).

Abbreviation: ULN=upper limit of normal.

8.8.3 Management of Oral Mucositis

Guidance on study drug dose modification for patients with oral mucositis is provided in Table 8.e.

Table 8.e Management of Oral Mucositis

Grade	Description	Treatment	Dose Modification
1	Asymptomatic or mild symptoms	Nonalcoholic mouthwash or 0.9% saltwater rinse; consider topical corticosteroids at earliest signs of mucositis.	None
2	Moderate pain not interfering with oral intake; modified diet indicated	Topical analgesic mouth treatments; topical corticosteroids; initiate antiviral or antifungal therapy, if indicated.	Maintain dose if tolerable. If toxicity becomes intolerable, interrupt TAK-228 dosing until recovery to ≤ Grade 1. Resume TAK-228 at same dose.
3	Severe pain interfering with oral intake	Same as for Grade 2; consider intralesional corticosteroids.	Interrupt TAK-228 until recovery to ≤ Grade 1, then resume TAK-228 with the next lower dose.
4	Life-threatening consequences	Same as for Grade 2; consider intralesional corticosteroids.	Discontinue TAK-228 treatment permanently.

Prevention/Prophylaxis

- Consider initiation of a nonalcoholic mouthwash or 0.9% saltwater rinses 4 to 6 times daily with start of therapy before signs of mucositis develop.
- Avoid using agents containing hydrogen peroxide, iodine, and thyme derivatives in management of stomatitis as they may worsen mouth ulcers.

8.8.4 Management of Rash

Patients who develop Grade 4 rash should permanently discontinue study treatment, unless they derive clinical benefit, in which case they may be retreated at a reduced dose level after recovery to ≤Grade 1 severity. Grade 4 rash is defined as rash acneiform/papulopustular with papules and/or pustules covering any percentage of body surface area, which may or may not be associated with symptoms of pruritus or tenderness, and are associated with extensive superinfection, with intravenous antibiotics indicated; life-threatening consequences (NCI CTCAE version 4.03, effective date 14 June 2010 [7]).

Guidance on study drug dose modification for patients with rash is provided in Table 8.f.

Table 8.f Management of Rash

Grade	Description	Treatment	Dose Modification
≤2	Macules/papules covering ≤30% body surface area with or without symptoms.	Consider treatment with topical steroid cream/ointment and/or oral antihistamines.	None
3	Macules/papules covering >30% body surface area with or without symptoms.	Consider treatment with topical steroid cream/ointment, oral antihistamines, and/or pulsed steroids.	Interrupt TAK-228 until ≤ Grade 2; resume TAK-228 based on timing of recovery: • ≤2 weeks: resume TAK-228 with the next lower dose. • >2 weeks: discontinue TAK-228 treatment.
4	Rash acneiform/ papulopustular with papules and/or pustules covering any percentage of body surface area, which may or may not be associated with symptoms of pruritus or tenderness, and are associated with extensive superinfection with intravenous antibiotics indicated; life threatening consequences.	Same as for Grade 3.	Permanently discontinue TAK-228, unless patient is deriving clinical benefit, in which case resume at a reduced dose level after recovery to ≤Grade 1 severity.

Prevention/Prophylaxis:

- Rash should be managed aggressively. The investigator should consider consulting a dermatologist or other specialist, if needed.
- A skin biopsy at the site of rash should be considered as soon as possible after the initial episode.

8.8.5 Management of Nausea/Vomiting

Guidance on study drug dose modification for patients with nausea and/or vomiting is provided in Table 8.g.

Table 8.g Management of Nausea/Vomiting

Grade	Description	Treatment	Dose Modification
≤2	Loss of appetite with or without decreased oral intake; 1 to 5 episodes of vomiting within 24 hours	Maximize antiemetic therapy. Consider IV fluid hydration.	None
≥3	Inadequate oral intake; ≥6 episodes of vomiting within 24 hours	Maximize antiemetic therapy. Initiate tube feeding, IVF or TPN.	If experienced for ≤72 hours, interrupt TAK-228 until ≤ Grade 1, then resume TAK-228 without dose modification. If experienced for >72 hours despite optimal therapy, interrupt TAK-228 until ≤ Grade 1, then resume TAK-228 with the next lower dose.
Prevention/Prophylaxis			
Prophylactic use of anti-emetic, antinausea, and antidiarrheal medications is encouraged, and these may be administered before each dose of TAK-228 as needed throughout the study.			

Abbreviations: IV=intravenous(ly); IVF=intravenous fluids; TPN=total parenteral nutrition.

8.8.6 Management of AST/ALT Elevations

Patients who develop Grade 3 or Grade 4 AST/ALT elevation in combination with Grade 2 total bilirubin elevation when alternative causes cannot be identified (ie, Hy's Law) should permanently discontinue study treatment.

Guidance on dose adjustment for patients with AST/ALT elevations is provided in Table 8.h.

Table 8.h Management of AST/ALT Elevations

Grade	Description	Treatment	Dose Modification
1	>ULN to 3×ULN	None	None
2	Asymptomatic with levels 3 to 5×ULN; >3×ULN with the appearance of worsening fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia.	• Closely monitor LFTs at least weekly or more frequently as indicated. • Assess patient for other causes of transaminitis (eg, past medical history, concomitant medications).	None
3	>5 to 20×ULN; >5×ULN for >2 weeks	Same as for Grade 2.	Interrupt TAK-228 until ≤ Grade 1 or baseline; Resume TAK-228 with the reduced doses. Permanently discontinue TAK-228 if in combination with Grade 2 total bilirubin elevation when alternative causes cannot be identified.
4	>20×ULN	Same as for Grade 2.	Discontinue TAK-228 treatment permanently.
Prevention/Prophylaxis: Ensure proper screening of patients for study participation.			

Abbreviation: ALT=alanine aminotransferase, AST=aspartate aminotransferase, LFTs=liver function tests, ULN=upper limit of normal.

8.8.7 Management of Non-Infectious Pneumonitis

Guidance for the management of pneumonitis is provided in Table 8.i.

Table 8.i Management of Non-Infectious Pneumonitis

Grade	Description	Treatment	Dose Modification
1	Asymptomatic: Radiographic findings only.	Rule out infection and closely monitor.	None
2	Symptomatic: Not interfering with activities of daily living.	Rule out infection and consider treatment with corticosteroids until symptoms improve to ≤ Grade 1.	Interrupt TAK-228 • When symptoms ≤ Grade 1, resume TAK-228 with the dose reduced by 1 level. • If no recovery within 2 weeks, then discontinue TAK-228.
3	Symptomatic: Interfering with activities of daily living; Requires administration of oxygen.	Rule out infection and consider treatment with corticosteroids until symptoms improve to ≤ Grade 1.	Interrupt TAK-228 until symptoms resolve to ≤ Grade 1. • Consider resuming TAK-228 with the reduced dose. • If toxicity recurs at Grade 3, discontinue TAK-228 treatment permanently.
4	Life-threatening: Ventilatory support indicated.	Rule out infection and consider treatment with corticosteroids.	Discontinue TAK-228 treatment permanently.

8.8.8 Management of Other Nonhematologic Toxicities

Guidance on dose adjustment for patients with other nonhematologic toxicities is provided in Table 8.j.

Patients who develop Grade 4 nonhematological toxicities (with the exception of isolated asymptomatic laboratory values) should permanently discontinue study treatment, unless they derive clinical benefit, in which case they may be retreated at a reduced dose level after recovery to ≤Grade 1 severity.

Table 8.j Management of Other Nonhematologic Toxicities (Including Asthenia, Weakness, and Fatigue)

Grade	Description	Treatment	Dose Modification
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.	Initiate appropriate medical therapy and monitor.	If tolerable, then no adjustment is required.
2	Moderate; minimal, local or noninvasive intervention indicated.	Initiate appropriate medical therapy and monitor.	• If tolerable, no adjustment required. • If toxicity becomes intolerable, interrupt TAK-228 until recovery to ≤ Grade 1, then resume TAK-228 at same dose.
≥3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated		Interrupt TAK-228 until recovery to ≤ Grade 1 or baseline. Resume TAK-228 with the dose of TAK-228 reduced by 1 level. Patients who develop Grade 4 nonhematological toxicities (with the exception of isolated asymptomatic laboratory values) should permanently discontinue study treatment, unless they derive clinical benefit, in which case they may be retreated at a reduced dose level after recovery to ≤ Grade 1 severity.

8.9 Blinding and Unblinding

This is an open-label study; no blinding methods will be used.

8.10 Description of Investigational Agents

Upon receipt of drug supply, contents must be verified promptly and the proper contacts notified of any discrepancies or damages as described in the Study/Pharmacy Manual.

TAK-228 will be supplied as capsules for oral administration. TAK-228 is available in 3 dose strengths—1 mg, 3 mg, and 5 mg—each containing 1 mg, 3 mg, and 5 mg of TAK-228, respectively, in addition to the following inactive ingredients: microcrystalline cellulose (solid filler/diluents), magnesium stearate (lubricant), and hard gelatin capsule.

All 3 dose strengths are formulated into size 2 capsules, and each dose strength is differentiated by color, as listed below:

- 1 mg TAK-228 capsules: white opaque color.

- 3 mg TAK-228 capsules: Swedish orange opaque color.
- 5 mg TAK-228 capsules: gray opaque color.

8.11 Preparation, Reconstitution, and Dispensation

TAK-228 study drug will be provided in labeled bottles in accordance with all applicable regulations. TAK-228 will be dispensed with dosing instructions for home use, including the requirement that capsules are stored in their original containers and that capsules be swallowed whole and not opened, chewed, or manipulated in any way. Materials provided by the sponsor should be dispensed to patients with clear administration instructions from the investigator.

TAK-228 is an anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling TAK-228 capsules.

8.12 Packaging and Labeling

TAK-228 will be provided by Millennium and will be handled at the investigative site as open-label material. TAK-228 will be provided in 30-ct, 60-cc high-density polyethylene (HDPE) bottles with polypropylene, child-resistant caps and induction seal.

TAK-228 will be packaged and labeled in accordance with all applicable regulations.

8.13 Storage, Handling, and Accountability

Upon receipt at the investigative site, TAK-228 study drug should be stored in the original bottles until use and stored at room temperature from 15°C to 30°C. All temperature excursions will be reported to the sponsor for assessment and authorization for continued use. All investigational supplies must be stored in a secure area with controlled access and will be stored in original packaging. All study drugs should be used before the retest expiry date. Storage area temperature conditions must be monitored and recorded daily. A daily temperature log will also be kept at the study site.

A drug dispensing log, including records of drug received from the sponsor and TAK-228 drug dispensed to the patients, will be provided and kept at the study site.

Because TAK-228 is an investigational agent, it should be handled with due care. In case of contact with broken capsules, raising dust should be avoided during the clean-up operation. The product may be harmful if inhaled, ingested, or absorbed through the skin. Gloves and protective clothing should be worn during the clean-up operation. The area should be ventilated and the spill site washed after material pick-up is complete. The spilled material should be disposed of as hazardous medical waste in compliance with federal, state, and local regulations. In case of contact with the powder (eg, from a broken capsule), skin should be washed immediately with soap and copious amounts of water for at least 15 minutes. In case of contact with the eyes, copious amounts of water should be used to flush the eyes for at least 15 minutes. Medical personnel should be notified.

Patients will be given clear dosing instructions from the investigator for home storage and administration of TAK-228 capsules, including the requirement that the capsules must be stored in their original containers and that the capsules are to be swallowed whole and not chewed or manipulated in any way. Patients will also receive diary cards to record dosing compliance with their TAK-228 treatment assignment, with instructions for their completion. Patients will be instructed to return any unused TAK-228 study drug in the original packaging along with their completed diary cards at the appropriate visits.

Please refer to the Study Manual and the Pharmacy Manual for additional instructions.

8.14 Other Protocol-Specified Materials

Not applicable.

9.0 STUDY CONDUCT

This trial 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 sponsor's project clinician for this study, the central laboratory and any additional clinical laboratories, and other third-party vendors 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

This is a phase 1 study to study 2 dosing schedules (QD schedule and QW schedule). Patients will be assigned to a dose cohort using the dose escalation rules as described in Section 8.3. The 2 arms will enroll in parallel. Patient assignment to a specific schedule will be decided jointly by the investigator and sponsor with the aim of maximizing enrollment efficiency in the study. At least 1 Japanese patient will be enrolled in each group of 3 patients during dose escalation. The total number of Japanese patients dosed at the RP2D level will be at least 6.

9.4 Study Procedures

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

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, smoking history, 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 for it. In addition, concomitant medications will be recorded as specified in Section 9.4.10.

9.4.4 Physical Examination

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

9.4.5 Patient Height and Weight

Height will be measured only during Screening. Weight will be measured at the time points specified in the Schedule of Events (Appendix A).

9.4.6 Vital Signs

Vital sign measurements include blood pressure (diastolic and systolic), pulse, temperature, and oxygen saturation. Vital signs will be assessed at the time points specified in the Schedule of Events (Appendix A) except oxygen saturation, which will be measured by pulse oximetry at Screening and on Day 15 of Cycles 1 and 2.

9.4.7 Pregnancy Test

A serum pregnancy test will be performed for women of childbearing potential at Screening and again at Cycle 1 Day 1. A urine pregnancy test will be performed predose on Day 1 of all cycles, and negative results must be obtained before the first dose of TAK-228 may be administered. If the serum pregnancy test is performed within 3 days before the first dose and the result is negative, the urine pregnancy test on Cycle 1 Day 1 may be waived.

Women of childbearing potential are defined as any sexually active female patients who meet both of 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; loss of menopausal periods following chemotherapy may not rule out childbearing potential).

9.4.8 Eastern Cooperative Oncology Group Performance Status

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

9.4.9 Electrocardiogram

A single, 12-lead electrocardiogram (ECG) will be performed at the time points specified in the Schedule of Events (Appendix A). Additional ECGs may be obtained as clinically indicated.

9.4.10 Concomitant Medications and Procedures

Medications used by the patient and therapeutic procedures completed by the patient will be recorded in the eCRF according to the Schedule of events (Appendix A). See Section 8.5 and Section 8.6 for medications and therapies that are prohibited or allowed during the study.

9.4.11 Adverse Events

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

9.4.12 Enrollment

A subject is considered to be enrolled in the study when the first dose of study drug is administered. Procedures for completing the enrollment information are described in the Study Manual.

9.4.13 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed locally. Clinical laboratory evaluations will be performed as outlined below.

9.4.13.1 Hematology, Chemistry, Coagulation and Urinalysis

Blood samples for analysis of the hematology, chemistry, and coagulation parameters shown in Table 9.a, as well as urine samples for analysis of the urinalysis parameters shown in Table 9.b will be obtained at the time points specified in the Schedule of Events (Appendix A). Results of hematology and chemistry labs must be available and reviewed by the investigator before enrollment and initial administration of study drug.

Table 9.a Hematology, Chemistry, and Coagulation Tests

Hematology and Coagulation	Serum Chemistry	
Hematocrit	Albumin	Gamma glutamyl transferase
Hemoglobin	Alkaline phosphatase	Glucose
Leukocytes with differential	ALT	HbA1c
Neutrophils (ANC)	Amylase	Lactate dehydrogenase
Platelet (count)	AST	Magnesium
	Bilirubin (total and direct)(a)	Phosphate
Activated partial thromboplastin time (aPTT)	Blood urea nitrogen or urea	Potassium
	Calcium (total)	Sodium
Prothrombin time/international normalized ratio (PT/INR)	Carbon dioxide or bicarbonate (if available as part of blood chemistry panel of local lab)	Protein (total)
		Urate
	Chloride	
	Creatinine	

Abbreviations: ALT=alanine aminotransferase, ANC=absolute neutrophil count, aPTT=activated partial thromboplastin time, AST=aspartate aminotransferase, HbA1c=glycosylated hemoglobin, PT/INR=prothrombin time/international normalized ratio.
(a) Direct bilirubin will be measured only if total bilirubin is altered.

Table 9.b Urinalysis Tests

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

9.4.14 Fasting Lipid Profile

Prospective monitoring for hyperlipidemia will be managed through fasting lipid testing at the time points specified in the Schedule of Events (Appendix A). Patients are required to fast overnight (nothing except water and prescribed medications after midnight or for a minimum of 8 hours) for each of these measurements. The fasting lipid profile is shown in Table 9.c.

Table 9.c Fasting Lipid Profile

Fasting Lipid Profile	
Cholesterol (total)	High-density lipoprotein cholesterol
Triglycerides	Low-density lipoprotein cholesterol

9.4.15 Fasting Serum Glucose

Fasting serum glucose will be measured in the study site at the time points specified in the Schedule of Events (Appendix A) before administration of TAK-228, and at other times at the discretion of the investigator. Patients are required to fast overnight (nothing except water and prescribed medications after midnight or for a minimum of 8 hours) for each of these measurements. In Cycle 2 and subsequent cycles in the QW arm, the sample should be taken predose; after predose blood draws are complete, patients receiving TAK-228 QW should consume a light meal before dosing (Section 8.1). In-home glucose monitoring is not required on days when fasting glucose is measured in the study site.

9.4.16 Hepatitis Testing

HBV and HCV testing will be performed at Screening. As appropriate and according to local guidelines for the management of hepatitis B virus infection, HBV screening may include the following: HBsAg, HBsAb, HBcAb, and HBV DNA. HCV screening will include the anti-HCV antibody (HCVAb). Patients who test positive for HCVAb will also be tested for HCV RNA at Screening.

Note that patients who have negative HBsAg but positive HBcAb and/or HBsAb may be enrolled but must have undetectable HBV viral load. Patients who have a positive HCVAb can be enrolled but must have undetectable HCV viral load.

Patients who are HBsAg negative but HBsAb and/or HBcAb positive, and/or HCVAb positive with negative viral load at Screening, enrolled in this study will be monitored by assessment of viral load (eg. HBV-DNA titer; HCV-RNA titer) every 2 month during the study treatment.

9.4.17 In-Home Daily Fasting Glucose Monitoring

In addition to obtaining fasting glucose levels at the site visits as outlined in the Schedule of Events (Appendix A), all patients enrolled in the study will be given a glucometer to monitor their daily fasting blood glucose (FBG) levels at home. The level should be collected daily, predose on dosing days, and at approximately the same time each day. Before checking their blood glucose levels, patients should fast overnight (nothing except water and/or medications after midnight or for a minimum of 8 hours before the assessment). After fasted testing is complete, patients in the QW arm (Cycle 2 and subsequent cycles) should consume a light meal before TAK-228 dosing (Section 8.1).

On Cycle 1 Day 1, the patient will be provided an in-home glucometer. Patients will be trained on proper use of the glucometer and instructed to collect a daily FBG level every morning (predose on dosing days), starting on Cycle 1 Day 2. Patients will be instructed to bring the glucometer with them to each study visit so that the data collected can be reviewed and recorded in the source documents. Investigators will be responsible for reviewing the home glucose monitoring logs for hyperglycemia.

The patient will be instructed to contact the site immediately if the value is abnormal (ie, ≥150 mg/dL) for further instructions on the management of their hyperglycemia. Hyperglycemia observed during home glucose monitoring should be confirmed in the study site.

If no irregularities in the FBG level are observed during a minimum of 2 consecutive months, then the frequency of in-home FBG testing can be reduced to a minimum frequency of once weekly, depending on the investigator's judgment. Patients will continue to notify the investigator of FBG levels that exceed 150 mg/dL and, if blood glucose levels are not well controlled, or if the patient requires either oral hypoglycemic agents or insulin to control blood glucose levels, then the frequency of in-home testing of FBG levels will be reinstated to daily. See also Section 8.8.1.

9.4.18 DNA Measurements

CCI

[redacted]

9.4.19 Disease Assessment

Patients will undergo a computed tomography (CT) scan (with contrast) as appropriate to monitor and assess disease progression, using RECIST guidelines (Version 1.1), where measurable disease is defined as ≥1 extraosseous lesion that can be accurately measured in at least 1 dimension[6]. Specific disease sites that cannot be adequately imaged by CT may be documented by magnetic resonance imaging (MRI). Anatomical measurements will be collected at baseline and at each subsequent evaluation for each target lesion using an imaging modality consistent with that used at

Screening. The same method (CT with contrast, MRI, or bone scan) must be consistently used on a patient throughout the study. Bone scans may be performed on patients with bone metastases rather than CT or MRI.

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

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

9.4.20 Pharmacokinetic Measurements

Serial blood samples for PK analysis of TAK-228 will be collected at the time points specified in the Pharmacokinetic Sample Breakdown table (Table A in Appendix A). The dates and exact times of administration of TAK-228 before collection of the blood sample for PK analysis and the dates and exact times of the postdose PK sample collection will be recorded on the eCRF.

9.5 Documentation of Subjects Failure

Investigators must account for all subjects who sign informed consent.

If the subject is found to be not eligible before the first dose, the investigator should complete the eCRF. Interactive response technology should be used to provide notification of subject failure.

The primary reason for subject failure is recorded in the eCRF using the following categories:

- Death.
- Adverse Event.
- Screen Failure (failed inclusion criteria or did meet exclusion criteria).
- Protocol deviation.
- Lost to follow-up.
- Withdrawal by subject.
- Study terminated by sponsor.
- Pregnancy.

Subject numbers assigned to subjects who fail screening should not be reused.

9.6 Completion of Study Treatment (for Individual Patients)

Patients will be considered to have completed treatment if they discontinue treatment with study drug for any of the reasons outlined in Section 9.8 and the maximum duration of treatment for patients will be 12 months.

If, after discussion between the investigator and the sponsor, it is determined that a patient would derive benefit from treatment beyond 12 months, then sponsor will make TAK-228 available for such patient, except in the event of any of the following:

- Progression of disease.
- Unacceptable toxicity.
- Pregnancy.
- Termination of the sponsor's development of the TAK-228 or sponsor otherwise decides not to seek registration of TAK-228 in the country in which the patient seeks access; or
- TAK-228 becomes commercially available.

9.7 Completion of Study (for Individual Patients)

Patients will be considered to have completed the study if they discontinue treatment and complete EOT visit.

9.8 Discontinuation of Treatment With Study Drug and Patient Replacement

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

- Adverse Event.
- Protocol deviation.
- Progressive disease (PD).
- Study terminated by sponsor.
- Withdrawal by subject.
- Lost to follow-up.
- Death.
- Pregnancy.
- Other.

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

Patients who receive <75% of planned doses of TAK-228 in Cycle 1 for reasons other than related AEs during dose escalation are not considered DLT-evaluable and additional patients will be enrolled for DLT evaluation.

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 will receive a sufficient quantity of TAK-228 for each treatment cycle and a diary in which to record their dosing. The study site staff will check the patient's diary versus the patient's supply of remaining TAK-228 at each study visit to ensure proper compliance with dosing. Patients who are not compliant with the dosing schedule may be withdrawn from the study.

Tests and procedures should be performed on schedule, but unless otherwise specified, occasional changes are allowable within a 2-day window for holidays, vacations, and other administrative reasons. If extenuating circumstances prevent a patient from beginning treatment or completing a planned procedure or assessment within 2 days of the scheduled time, the patient may continue the study at the discretion of the investigator and after consultation with the sponsor's project clinician or designee. However, the timing of PK assessment as specified in the Schedule of Events (Table A in Appendix A) is not flexible.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 Pretreatment Event Definition

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

10.1.2 Adverse Event Definition

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

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

10.1.3 Serious Adverse Event Definition

SAE means any untoward medical occurrence that at any dose:

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

blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

In this study, intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, Version 4.03, effective date 14 June 2010 [7]. Clarification should be made between an SAE and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

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

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

Regardless of causality, SAEs and serious pretreatment events (as defined in Section 10.1) must be reported (see Section 10.3 for the period of observation) by the investigator to the Takeda Global Pharmacovigilance department or designee (contact information provided below). This should be done by faxing the SAE Form within 24 hours after becoming aware of the event. The SAE Form, created specifically by Takeda, will be provided to each clinical study site. A sample of the SAE Form may be found in the Study Manual. Follow-up information on the SAE or serious pretreatment event may be requested by Takeda. SAE report information must be consistent with the data provided on the eCRF.

SAE Reporting Contact Information

PPD

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

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. For serious pretreatment events, the investigator must determine both the severity (toxicity grade) of the event and the causality of the event in relation to study procedures.

Severity (toxicity grade) for each AE, including any lab abnormality, will be determined using the NCI CTCAE, Version 4.03, effective date 14 June 2010 [7]. 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 Adverse Events and Period of Observation

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

- AEs will be reported from the signing of informed consent through 30 days after administration of the last dose of study drug and recorded in the eCRFs.
- SAEs
  - Serious pretreatment events 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 [redacted] (refer to Section 10.2)

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

The sponsor or its designee will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators and IRBs or IECs or the head of the study site, 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 or its designee 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 trial. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

11.0 STUDY-SPECIFIC COMMITTEES

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, pretreatment events, 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, contract research organization (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 following procedure is applied for the countries except for Japan.

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

The following procedure is applied for Japanese sites only.

The investigator and the head of the institution agree to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating 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), and query responses/ 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 and the head of the institution 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/or the head of the institution and the sponsor.

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

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) 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.

Statistical analyses will be primarily descriptive and graphical in nature. No formal statistical hypothesis testing will be performed.

13.1.1 Analysis Sets

Analysis sets will include the following:

- Safety analysis set: patients who receive at least 1 dose of study drug. The safety analysis set will be used for all safety analyses (except for DLT analysis) and efficacy analyses.
- PK analysis set: patients with sufficient dosing and PK data to reliably estimate 1 or more PK parameters will be included in the PK analyses.
- DLT-evaluable set: patients who have received at least 75% of planned doses of TAK-228 in Cycle 1 (21 doses for the QD arm and 3 doses for QW arm) unless interrupted by study drug-related AEs and have sufficient follow-up data considered by sponsor and investigator to determine whether DLT occurred.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized, including sex, age, race, weight, height, and other parameters as appropriate. No inferential statistics will be carried out.

13.1.3 Efficacy Analysis

All efficacy analyses will be performed using the safety analysis set.

Data listings will present the tumor measurements from CT or MRI (including changes from baseline), disease response category (ie, CR, PR, SD, and PD), best overall response, duration of response, and duration of SD or other appropriate measures of efficacy.

The clinical benefit rate, defined as the proportion of patients with a best overall response of CR, PR, or SD will be summarized.

13.1.4 Pharmacokinetic Analysis

All PK analyses will be performed using the PK analysis set.

Plasma TAK-228 concentrations obtained from Cycle 1 will be summarized by descriptive statistics according to nominal (scheduled) time postdose and day for each arm. Mean and individual plasma TAK-228 concentration data from Cycle 1 will be plotted over time for each day (Days 1 and 15) for each arm. All plasma concentration data will be listed by arm.

PK parameters will be calculated on Cycle 1 Days 1 and 15 for TAK-228 by noncompartmental analysis as permitted by the data. These parameters will include, but will not be limited to, C_{max}, t_{max}, and AUC. PK parameters will be summarized using descriptive statistics for each arm and day. Individual PK parameters will be listed by arm.

Plasma TAK-228 concentrations obtained from Cycle 2 will be summarized by descriptive statistics according to nominal (scheduled) time postdose and day for the QW arm only.

13.1.5 Safety Analysis

All safety analyses will be performed using the safety analysis set. The DLT-evaluable analysis set will be used for the analysis of DLTs.

Safety will be evaluated by the incidence of AEs, severity and type of AEs, and by changes from baseline in the patient's vital signs, weight, and clinical laboratory results using the safety analysis set. Exposure to study drug and reasons for discontinuation will be tabulated.

TEAEs that occur after administration of the first dose of study drug and through 30 days after the last dose of study drug will be tabulated.

Adverse events will be tabulated according to MedDRA and will include the following categories:

- DLTs.
- TEAEs.
- Drug-related TEAEs.
- Grade 3 or higher TEAEs.
- Grade 3 or higher drug-related TEAEs.
- The most commonly reported TEAEs.
- Serious TEAEs.

The most commonly reported TEAEs will be tabulated by MedDRA preferred term.

A listing of deaths within 30 days of the last dose of study drug and TEAEs resulting in study drug discontinuation will be provided.

Shift tables based on changes in NCI CTCAE grade from baseline to the worst postbaseline value for laboratory parameters will be generated.

Concomitant medications will be summarized according to WHO Drug Dictionary preferred term.

Additional safety analyses may be performed to more clearly enumerate rates of toxicities and to further define the safety profile of TAK-228 QD and TAK-228 QW.

13.2 Interim Analysis and Criteria for Early Termination

No formal interim analysis is planned for this study.

13.3 Determination of Sample Size

For each arm, dose escalation will be conducted according to a standard 3+3 dose escalation schema. There are 2 planned dose cohorts in each of 2 arms (QD arm and QW arm) in this study. For each arm, 9 to 12 DLT-evaluable patients will be needed for the dose escalation portion. In addition, for each arm, another 6 patients will be needed for safety expansion. Assuming a 20% dropout rate, approximately 23 patients will be needed for each arm to have 18 DLT-evaluable patients; the total sample size for this study will be 46.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

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

All aspects of the study and its documentation will be subject to review by the sponsor or designee, including but not limited to the Investigator's Binder, study medication, 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. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or IEC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment. A Protocol Deviation Form should be completed by the site and signed by the sponsor or designee for any significant deviation from the protocol.

The procedure below applies to Japanese sites only.

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

The investigator should document all protocol deviations.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

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

15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the 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 notify site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the trial. Until the site receives notification, no protocol activities, including screening may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the ICF, recruitment materials intended for viewing by 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 entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the 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 ICF, 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 ICF, 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 may be used to verify the subject and accuracy of the subject's unique identification number.

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

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication

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

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

15.4.2 Clinical Trial Registration

To ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites on or before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, country, and recruiting status will be registered and available for public viewing.

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

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

15.4.3 Clinical Trial Results Disclosure

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

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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4. Hassan B, Akcakanat A, Takafumi S, Evans K, Adkins F, Meric-Bernstam F. MTOR Inhibitor MLN0128 has Antitumor Efficacy in Cell Lines With Intrinsic and Acquired Rapamycin-Resistance. Academic Surgical Congress 2013(Abstract ASC20130420).
5. De P, Sun Y, Wu H, Rommel C, Yi L, Dey N, et al. Pre-clinical potency of INK128, a highly potent TORC1/2 kinase inhibitor in the HER2 amplified breast cancer model. Cancer Research 2012;72(Abstract 2240).
6. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47.
7. U.S. Department of Health and Human Services, National Institutes of Health National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE). Version 4.03. 14 June 2010.

Appendix A Schedule of Events

	Screening (a) (within 28 Days before C1D1)	Cycles 1 and 2			Cycles 3, 4, 5, and 6			Cycle ≥7	EOT Visit (b)
		Day 1	Day 8 (±2 Days)	Day 15 (±2 Days)	Day 1	Day 8 (±2 Days)	Day 15 (±2 Days)	Day 1	
Study Procedures									
Informed consent (c)	X								
Eligibility criteria	X								
Demographics	X								
Medical history	X								
Physical examination	X	X		X	X		X	X	X
Height	X								
Weight	X	X		X	X		X	X	X
Vital signs (d)	X	X	X	X	X	X	X	X	X
ECOG performance status	X	X		X	X		X	X	X
Single, 12-lead ECG (e)	X1	X2 (e)	X1 (e)	X1 (e)	X1 (e)				X1
Concomitant medications and procedures reporting	X	Recorded from first dose of study drug through 30 days after the last dose of study drug.							
SAE reporting (f)	SAEs (f) recorded from signing of the ICF through 30 days after the last dose of study drug.								
Adverse event reporting (f)	Recorded from signing of the ICF through 30 days after the last dose of study drug.								
TAK-228 Dosing									
Single agent QD arm (g)		QD continuously							
Single agent QW arm (g)		Days 1, 8, 15, and 22 of each 28-day cycle							
Samples and Laboratory Assessments									
Hematology	X1	X1 (h)	X1	X1	X1 (h)	X1	X1	X1 (h)	X1
Chemistry	X1	X1 (h)	X1	X1	X1 (h)	X1	X1	X1 (h)	X1
Urinalysis	X1 (i)	X1 (h)			X1 (h)			X1 (h)	X1
Coagulation (PT/INR, aPTT)	X1	X1			X1			X1	X1

	Screening (a) (within 28 Days before C1D1)	Cycles 1 and 2			Cycles 3, 4, 5, and 6			Cycle ≥7	EOT Visit (b)
		Day 1	Day 8 (±2 Days)	Day 15 (±2 Days)	Day 1	Day 8 (±2 Days)	Day 15 (±2 Days)	Day 1	
HbA1c	X1	X (j)			X(j)			Q3C(j)	
Fasting lipid profile	X1 (k)	X1			X1			X1	X1
Fasting serum glucose (l)	X1	X1	X1	X1	X1			X1	X1
In-home fasting glucose monitoring (m)		Measured daily (predose)							
Pregnancy test (n)	X1	X1(n)			X1			X1	
HBV and HCV screening (o)	X								
CCI									
Disease assessment (q)	X				Q2C (q)			Q2C(q)	X(q)
Plasma sample for TAK-228 PK	Plasma sample for TAK-228 PK analysis will be collected on the days and time points specified in the separate table.								

aPTT=activated partial thromboplastin time; C=cycle; CT=computed tomography; DNA=deoxyribonucleic acid; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=End of Treatment; ET=early termination; HbA1c=glycosylated hemoglobin; HBV=hepatitis B virus; HCV=hepatitis C virus; ICF=informed consent form; INR=international normalized ratio; MRI=magnetic resonance imaging; PK=pharmacokinetic; PT=prothrombin time; Q=every; QD=once daily; QW=once weekly; SAE=serious adverse event; X#=number of samples required (eg, 2 samples=X2).

Tests and procedures should be performed on schedule, but occasional changes are allowable (±2 days) with permission from the sponsor's project clinician for holidays, vacations, and other administrative reasons.

(a) Screening assessments are performed within 28 days before Cycle 1 Day 1, unless otherwise specified. Screening assessments performed not more than 3 days before the Cycle 1 Day 1 need not be repeated, unless otherwise specified.

(b) End of treatment will occur 30 days (+10 days) after the last dose of study drug, or at the start of subsequent antineoplastic therapy, whichever occurs first.

(c) The ICF may be signed more than 28 days before Cycle 1 Day 1 dosing.

(d) Vital sign measurements include blood pressure (diastolic and systolic), pulse, temperature, and oxygen saturation. Oxygen saturation will be measured by pulse oximetry at Screening and on Day 15 of Cycles 1 and 2.

(e) When the timing of an ECG coincides with blood samples for PK, the ECG should be completed first. On Cycle 1 Day 1 and Cycle 2 Day 1, an ECG should be completed predose in addition to 2 hours (±30 min) postdose. For Days 8 and 15 in Cycles 1 and 2 as well as Day 1 in Cycle 3 through 6, an ECG should be completed predose.

(f) Including serious and non-serious events before the first dose (ie. pretreatment events).

(g) For QD arm, TAK-228 will be administered on an empty stomach throughout the study. For QW arm, TAK-228 will be administered on an empty stomach in Cycle 1 and following a light meal in Cycle 2 and the subsequent cycles.

(h) May be assessed up to 24 hours before the study visit.

(i) For screening, creatinine clearance must be ≥40 mL/min based either on Cockcroft-Gault estimate or based on a 12- or 24-hour urine collection.

(j) During the Study Treatment period, HbA1c will be tested on Day 1 of Cycles 2 through 5, and on Day 1 of every third cycle thereafter (ie, Cycle 8, 11, 14, etc.).

(k) To be completed within 14 days before Cycle 1 Day 1.

(l) Fasting serum glucose will be measured in the study sites. Patients are required to fast overnight (nothing except water and prescribed medications after midnight or for ≥8 hours before the assessment) for each measurement.

(m) Patients will be given a glucometer on Cycle 1 Day 1 to monitor daily fasting glucose levels at home throughout the study starting on Cycle 1 Day 2, and will be instructed to notify the investigators when the fasting glucose is abnormal (ie, ≥150 mg/dL). In-home glucose monitoring is not required on days when fasting glucose is measured in the study sites.

(n) A serum pregnancy test will be performed for women of childbearing potential at Screening and again at Cycle 1 Day 1. A urine pregnancy test must be performed predose on Day 1 of all cycles, with negative results available before the first dose of TAK-228 may be administered in that cycle. If a serum pregnancy test is performed within 3 days before the first dosing and the result is negative, the urine pregnant test may be waived on Cycle 1 Day 1.

(o) Patients with prior exposure to HBV or HCV who have subsequently cleared the infection (determined by a negative viral load) are allowed in the study, but should be monitored for reactivation every 2 months. Patients who develop detectable HBV or HCV in their blood during the study will have TAK-228 treatment interrupted and will be treated with antivirals medication per local institutional standard practice; a consultation with a hepatologist should be considered.

(p) To be collected predose on Cycle 1 Day 1.

(q) Baseline CT (with contrast) or MRI scan of the chest, abdomen, and pelvis must be obtained within 4 weeks before the first dose of TAK-228 and at Cycle 3 Day 1, after which CT (with contrast) or MRI may be performed every 2 cycles (ie, Cycle 5 Day 1, Cycle 7 Day 1, Cycle 9 Day 1 etc.), as clinically indicated, according to standard of care. The same imaging modality (CT [with contrast], MRI, or bone scan) should be used on a patient throughout the study. Bone scans may be performed on patients with bone metastases rather than CT or MRI. Scans are permitted up to 7 days in advance of the scheduled visit. At EOT, tumor assessments will be done only on patients who have not previously demonstrated disease progression in the study unless completed within the previous 4 weeks.

Table A Pharmacokinetic Sampling Time Points

PK Sampling Time Point for QD and QW Arms	**Cycle 1 Day 1** (Study drug taken on an empty stomach [a])	**Cycle 1 Day 2**	**Cycle 1 Day 8** (Study drug taken on an empty stomach [a])	**Cycle 1 Day 15** (Study drug taken on an empty stomach [a])	**Cycle 1 Day 16**	**Cycle 1 Day 22** (Study drug taken on an empty stomach [a])
Predose (within 0.5 hours)	X1		X1	X1		X1
0.5 hours postdose (± 10 min)	X1			X1		
1 hour postdose (± 10 min)	X1			X1		
2 hours postdose (± 30 min)	X1			X1		
3 hours postdose (± 30 min)	X1			X1		
4 hours postdose (± 30 min)	X1			X1		
6 hours postdose (± 30 min)	X1			X1		
8 hours postdose (± 45 min)	X1			X1		
24 hours postdose (± 1 hour)		X1 (Predose on Day 2 for QD arm)			X1 (Predose on Day 16 for QD arm)	

PK Sampling Time Point for QW Arm only	**Cycle 2 Day 1 (c)** (Study drug taken after light meal)	**Cycle 2 Day 15 (c)** (Study drug taken after light meal)
At time of clinic visit (anytime postdose)		X1
Approximately 1 hour after previous PK sample collection		X1
1-2 hours postdose (±15 min)	X1	
3-6 hours postdose (±30 min)	X1(b)	

min=minutes; PK=pharmacokinetic; QD=daily; QW=weekly; X#=number of samples required (eg, 1 sample=X1).
(a) Patients will be instructed to fast overnight (nothing except water and prescribed medications after midnight or for a minimum of 8 hours) for Cycle 1 Days 1, 8, and 15 visits only. For Cycle 1 Day 22, patients need not be fasted overnight but are to be instructed to refrain from eating and drinking (except water and prescribed medications) for 2 hours before and 1 hour after the dose. Patients will receive study drug with a full glass of water (240 mL).
(b) Two samples will be taken no less than 1 hour apart within the specified window.
(c) Patients may bring a light meal with them to this visit. After completion of fasting serum glucose sampling, patients will begin consuming the meal within 30 min before dosing, after which they will take their regularly scheduled doses of TAK-228. The exact date/time of meal consumption, TAK-228 dosing, and PK sampling must be recorded in the eCRF. Over the course of the study, a distribution of sampling times within this time range is encouraged.

Appendix B Responsibilities of the Investigator

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

The investigator agrees to assume the following responsibilities:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study related procedures, including study specific (nonroutine/nonstandard panel) screening assessments are NOT performed on potential subjects, 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 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 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. This responsibility lies on the appropriate individual, designated by the site in Japan.
12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix C Investigator Consent to Use of Personal Information

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

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

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

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

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

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

Appendix D ECOG Scale for Performance Status

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

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. American Journal of Clinical Oncology 1982;5(6):649-55.

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

$$\frac{(140 - \text{age [years]}) \times \text{weight [kg]}}{0.81 \times (\text{serum creatinine [}\mu\text{mol/L]})}$$

For women:

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

OR

$$\frac{0.85\ (140 - \text{age [years]}) \times \text{weight [kg]}}{0.81 \times (\text{serum creatinine [}\mu\text{mol/L]})}$$

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

Appendix F New York Heart Association Classification of Cardiac Disease

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

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

Appendix G Methods of Contraception Considered to be Effective

Acceptable Methods Considered Highly Effective

Birth control methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective. Such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (a):
  - Oral.
  - Intravaginal.
  - Transdermal.
- Progestogen-only hormonal contraception associated with inhibition of ovulation (a):
  - Oral.
  - Injectable.
  - Implantable (b).
- Intrauterine device (b).
- Intrauterine hormone-releasing system (b).
- Bilateral tubal occlusion (b).
- Vasectomized partner (b) (c).
- Sexual abstinence (d).

Methods that are Considered Less Highly Effective

Acceptable birth control methods that result in a failure rate of more than 1% per year include:

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action.
- Male or female condom with or without spermicide (e).
- Cap, diaphragm, or sponge with spermicide (e).

Source: European Heads of Medicines Agencies (HMA) Clinical Trial Facilitation Group (CTFG); see hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_ CTFG_Contraception.pdf

(a) Hormonal contraception may be susceptible to interaction with the investigational medicinal product, which may reduce the efficacy of the contraception method.

(b) Contraception methods that in the context of this guidance are considered to have low user dependency.

(c) Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the woman of childbearing potential participant of the study and that the vasectomized partner has received medical assessment of the surgical success.

(d) In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

(e) A combination of male condom with either cap, diaphragm or sponge with spermicide (double-barrier methods) are also considered acceptable, but not highly effective, birth control methods.

Appendix H List of Relevant Cytochrome P450 Inhibitors and Inducers

Moderate CYP1A2 Inhibitors		
cimetidine	methoxsalen	
Strong CYP1A2 Inhibitors		
fluvoxamine	ciprofloxacin	
Clinically Significant Enzyme Inducers		
carbamazepine	rifabutin	St. Johns Wort
phenobarbital	rifampin	phenytoin
rifapentine		

Source: fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm.
Note that these lists are not exhaustive.

Appendix I Detailed Description of Amendments to Text

This document describes changes in reference to Protocol Incorporating Amendment No. 02.

Original text that was deleted or revised in Amendment No. 02 is indicated using italics and underline font. New or revised text adopted in Amendment No. 02 is shown in bold font.

Page 18, Section 3.3, List of Abbreviations

Added Text

MFDS: Ministry of Food and Drug Safety

Rationale for Amendment

To update the list of abbreviations with additional terms.

Page 37, Section 8.2, Definitions of Dose Limiting Toxicity

Existing Text

Toxicity will be evaluated according to NCI CTCAE (Version 4.03, effective 14 June 2010) [7]. DLT is defined as any of the following events that occur within the first 28 days of the administration of TAK-228 and are considered by the investigator to be at least possibly related to therapy with TAK-228 *(note that AEs for which the relationship to study drug cannot be ruled out should be considered possibly related to study drug)*.

Revised Text

Toxicity will be evaluated according to NCI CTCAE (Version 4.03, effective 14 June 2010) [7]. DLT is defined as any of the following events that occur within the first 28 days of the administration of TAK-228 and are considered by the investigator to be at least possibly related to therapy with TAK-228.

Rationale for Amendment

Removed the note for the relationship to be consistent with Section 10.2.

Page 56, Section 9.4.2, Patient Demographics

Existing Text

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

Revised Text

The date of birth, race, ethnicity, **smoking history,** and sex of the patient are to be recorded during Screening.

Rationale for Amendment

Added smoking history to be recorded during Screening.

Page 63, Section 9.8, Discontinuation of Treatment With Study Drug and Patient Replacement

Added Text

Pregnancy.

Rationale for Amendment

Added pregnancy to the discontinuation criteria for clarification. (To incorporate feedback from the MFDS.)

Page 63, Section 9.8, Discontinuation of Treatment With Study Drug and Patient Replacement

Existing Text

Patients who receive <75% of planned doses of TAK-228 in Cycle 1 for reasons other than related AEs during dose escalation are not considered DLT-evaluable and *will be replaced.*

Revised Text

Patients who receive <75% of planned doses of TAK-228 in Cycle 1 for reasons other than related AEs during dose escalation are not considered DLT-evaluable and **additional patients will be enrolled for DLT evaluation.**

Rationale for Amendment

Revised the text for clarification. (To incorporate feedback from the MFDS.)

Page 73, Section 13.1.4, Pharmacokinetic Analysis

Added Text

Plasma TAK-228 concentrations obtained from Cycle 2 will be summarized by descriptive statistics according to nominal (scheduled) time postdose and day for the QW arm only.

Rationale for Amendment

Added PK analysis plan for the samples obtained in Cycle 2 for QW arm. (To incorporate feedback from the MFDS.)

Page 82, Appendix A, Schedule of Events

Existing Text

	Screening (a) (within 28 Days before C1D1)	Cycles 1 and 2			Cycles 3, 4, 5, and 6			Cycle ≥7	EOT Visit (b)
		Day 1	Day 8 (±2 Days)	Day 15 (±2 Days)	Day 1	Day 8 (±2 Days)	Day 15 (±2 Days)	Day 1	
Study Procedures									
Single, 12-lead ECG (e)	X1	X2 (e)							X1
TAK-228 Dosing									
Single agent QD arm (g)		QD continuously							
Single agent QW arm (g)		Days 1, 8, 15, and 22 of each 28-day cycle							

(e) When the timing of an ECG coincides with blood samples for PK, the ECG should be completed first. On Cycle 1 Day 1 and Cycle 2 Day 1, an ECG should be completed predose in addition to 2 hours (±30 min) postdose.

Revised Text

	Screening (a) (within 28 Days before C1D1)	Cycles 1 and 2			Cycles 3, 4, 5, and 6			Cycle ≥7	EOT Visit (b)
		Day 1	Day 8 (±2 Days)	Day 15 (±2 Days)	Day 1	Day 8 (±2 Days)	Day 15 (±2 Days)	Day 1	
Study Procedures									
Single, 12-lead ECG (e)	X1	X2 (e)	**X1 (e)**	**X1 (e)**	**X1 (e)**				X1
TAK-228 Dosing									
Single agent QD arm (g)		QD continuously							
Single agent QW arm (g)		Days 1, 8, 15, and 22 of each 28-day cycle							

(e) When the timing of an ECG coincides with blood samples for PK, the ECG should be completed first. On Cycle 1 Day 1 and Cycle 2 Day 1, an ECG should be completed predose in addition to 2 hours (±30 min) postdose. **For Days 8 and 15 in Cycles 1 and 2 as well as Day 1 in Cycle 3 through 6, an ECG should be completed predose.**

Rationale for Amendment

Added additional ECG collection timepoints to collect additional data to verify and confirm that treatment with TAK-228 is not associated with an increased risk of cardiac events. (To incorporate feedback from the MFDS.)

Page 85, Appendix A, Footnote a in Table A

Existing Text

(a) Patients will be instructed to fast overnight (nothing except water and prescribed medications after midnight or for a minimum of 8 hours). Patients *then* will receive study drug with a full glass of water (240 mL).

Revised Text

(a) Patients will be instructed to fast overnight (nothing except water and prescribed medications after midnight or for a minimum of 8 hours) **for Cycle 1 Days 1, 8, and 15 visits only**. **For Cycle 1 Day 22, patients need not be fasted overnight but are to be instructed to refrain from eating and drinking (except water and prescribed medications) for 2 hours before and 1 hour after the dose.** Patients will receive study drug with a full glass of water (240 mL).

Rationale for Amendment

Revised Footnote a in Table A to clarify overnight fasting is not required for PK sampling on Cycle 1 Day 22.

Overall

Correct typographical errors, punctuation, grammar, and formatting.

These changes are not listed individually.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Approval	27-Feb-2018 09:24 UTC
	Biostatistics Approval	27-Feb-2018 14:12 UTC
	Clinical Pharmacology Approval	27-Feb-2018 14:13 UTC
	Clinical Approval	27-Feb-2018 21:56 UTC