Title: A Phase 1, Open-Label, Multicenter, Drug-Drug Interaction Study of TAK-788 and Midazolam, a Sensitive CYP3A Substrate, in Patients With Advanced Non–Small Cell Lung Cancer

NCT Number: NCT04051827

Protocol Approve Date: 03 September 2020

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, Multicenter, Drug-Drug Interaction Study of TAK-788 and Midazolam, a Sensitive CYP3A Substrate, in Patients With Advanced Non–Small Cell Lung Cancer

Drug-Drug Interaction Study of TAK-788 and Midazolam in Patients With Advanced Non–Small Cell Lung Cancer

Sponsor: Millennium Pharmaceuticals, Inc.*
40 Landsdowne Street
Cambridge, MA 02139
USA

*Please note: Millennium Pharmaceuticals is a wholly owned subsidiary of Takeda Pharmaceutical Company Limited and thereafter, any reference to the sponsor will use Takeda's name.

Study Number: TAK-788-1004

EudraCT Number: 2019-000725-44

Compound: TAK-788 (formerly AP32788)

Date: 03 September 2020 Amendment Number: 2

Amendment History:

Date	Amendment Number	Amendment Type (for use in Europe only)	Region
03 September 2020	2	Substantial	Global
03 April 2020	01	Substantial	Global
14 February 2019	Initial Protocol	Not applicable	Global

1.0 ADMINISTRATIVE INFORMATION

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 Development Center–sponsored investigators per individual country requirements will be provided with emergency medical contact information cards to be carried by each patient.

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.

The names and contact information for the medical monitor and responsible medical officer are in the study manual.

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 Council for Harmonisation E6 (R2) Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

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

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

PPD

1.3 Protocol Amendment 2 Summary of Changes

Protocol Amendment 2 Summary and Rationale:

This section describes the changes in reference to the protocol incorporating Amendment 2. The primary reasons for this amendment are to:

- Update cardiac monitoring based upon recent analysis of cardiac adverse events (AEs) reported across TAK-788 program.
- Incorporate changes due to coronavirus disease 2019 (COVID-19) public health emergency including direct-to-patient (DTP) dispensing as an alternative method of dispensing self-administered study drug, alternative methods for conducting patient visits, electronic informed consent (eConsent) language, accommodations to allow local disease assessments and remote source data verification as an alternative approach for monitoring visits.
- Revised management of drug-related diarrhea and inserted a table to improve readability.
- Update Appendix E Drugs That Interact With the CYP3A Family of Cytochromes-P450.
- Update Appendix F Drugs With a Risk of Torsades de Pointes.

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

Protocol Amendment 2		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 8.6.2 Diarrhea	Added Table 8.e Management of Drug-Related Diarrhea.	To update for consistency across the TAK-788 program.
Section 8.9 Preparation, Reconstitution, and Dispensation	Updated text to include DTP as an alternative method for dispensing self-administered study drug.	To ensure continuity of TAK-788 treatment due to coronavirus disease 2019 (COVID-19)-related quarantines, cancellations of on-site visits, or concerns about possible COVID-19 exposure.
Section 9.3 Study Procedures Section 9.3.1 Informed Consent Section 9.3.12.1 Hematology, Clinical Chemistry and Serology Section 9.3.16 Disease Assessment Section 9.3.19 Patient Dosing Diary Section 14.1 Study-Site Monitoring Visits	Updated text to include alternative methods for conducting patient visits and collecting data.	To ensure consistent patient monitoring and evaluation during the COVID-19 public health emergency.

Protocol Amendment 2		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 9.3.9 ECG Appendix A Schedule of Events	• Updated text to clarify repeat testing and additional echocardiograms (ECGs) may be performed at the investigator's discretion. • Updated ECG assessments for Part 2 to C2D1, C4D1, C7D1, every 4 cycles following C7, and end of treatment (EOT).	To update ECG assessments based upon recent analysis of cardiac AEs reported across TAK-788 program.
Section 9.3.11 Echocardiogram/MUGA Scan for Left Ventricular Ejection Fraction Appendix A Schedule of Events	• Added text to clarify additional cardiology consultation may be done during treatment according to medical judgment. • Updated echocardiogram (ECHO)/multigated acquisition (MUGA) scan for Part 2 to C2D1, C4D1, C7D1 and EOT.	To update ECHO/MUGA assessments based upon recent analysis of cardiac AEs reported across the TAK-788 program.
Appendix E Drugs That Interact With the CYP3A Family of Cytochrome P450	Updated Appendix E Drugs That Interact With the CYP3A Family of Cytochromes-P450.	To update for consistency with current references.
Appendix F Drugs With a Risk of Torsades de Pointes	Updated Appendix F Drugs With a Risk of Torsades de Pointes.	To update for consistency with current reference.

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, prescribing information, 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 Council for Harmonisation, E6 (R2) Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.0 of this protocol.
- Terms outlined in the clinical study site agreement.
- Responsibilities of the investigator (Appendix B).

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

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Province)

Location of Facility (Country)

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2.0 STUDY SUMMARY

Name of Sponsor: Millennium Pharmaceuticals, Inc *Please note: Millennium Pharmaceuticals is a wholly owned subsidiary of Takeda Pharmaceutical Company Limited and thereafter, any reference to the sponsor will use Takeda's name.	**Compound:** TAK-788
Title of Protocol: A Phase 1, Open-Label, Multicenter, Drug-Drug Interaction Study of TAK-788 and Midazolam, a Sensitive CYP3A Substrate, in Patients With Advanced Non–Small Cell Lung Cancer	**EudraCT No.:** 2019-000725-44
Study Number: TAK-788-1004	**Phase:** 1

Study Design:

This open-label, multicenter, drug-drug interaction study will consist of 2 parts: Part A (Cycle 1: PK Cycle) and Part B (Cycle 2 to Cycle 24: Treatment Cycles).

In Part A of the study, a fixed-sequence design over a single 30-day treatment cycle will be used (Cycle 1: PK Cycle and Cycle 2 Day1). After screening, eligible patients will be enrolled and will receive a single oral dose of midazolam 3 mg on Days 1 and 24 and a single IV dose of midazolam 1 mg as a 5-minute infusion on Days 2 and 25. Patients will also receive TAK-788 160 mg QD orally on Days 3 through 30. Serial PK blood samples will be collected to measure plasma concentrations of midazolam and its metabolite 1-hydroxymidazolam in the absence and presence of TAK-788 on study Days 1, 2, 24, and 25. TAK-788 PK blood samples to assess TAK-788 plasma concentrations and its active metabolites AP32960 and AP32914 will be collected predose on Days 24, 25, and 26 of cycle 1 as well as Day 1 of cycle 2 and postdose on Cycle 1 Day 24.

Further, biomarker blood samples will be collected on Days 1 and 24 predose to measure plasma concentrations of 4β-hydroxycholesterol and cholesterol, in addition to samples collected to assess for circulating tumor DNA as part of Cycle 1, 3, 5, and disease progression assessments.

After completion of Part A, patients may continue into Part B to continue treatment with TAK-788 (Cycle 2 to Cycle 24: Treatment Cycles). Any patients who are not PK-evaluable due to incomplete PK sample collections in Part A will be eligible to continue into Part B.

Part B of the study will consist of 28-day treatment cycles in which patients will continue to receive TAK-788 QD for up to 23 months (ie, Cycle 24) or until progressive disease, intolerable toxicity, or another discontinuation criterion is met, whichever is sooner.

TAK-788 dose may be reduced based on protocol-defined dose modification guidelines during the study. Safety and tolerability will be evaluated during the study by AE monitoring, clinical laboratory tests, vital signs, and physical examinations. The study will include a 30-day follow-up period after EOT for reporting of AEs.

CCI [redacted]

Primary Objectives:

The primary objective of this study is to characterize the effect of repeated oral administration of TAK-788 160 mg QD on the single oral- and IV-dose PK of midazolam.

Secondary Objectives:

The secondary objective of this study is to assess the safety and tolerability of TAK-788 in patients with advanced NSCLC.

Subject Population:

Approximately 26 patients ≥18 years with locally advanced or metastatic NSCLC who are refractory or who have relapsed to standard available therapies, will be enrolled in this study.

Number of Subjects: Approximately 26 patients to achieve approximately 12 PK-evaluable patients for assessment of the effect of repeated doses of TAK-788 on the PK of midazolam.	**Number of Sites**: 4 to 6 clinical sites; countries/regions are detailed in the study manual.
Dose Level(s): *Part A Cycle 1*: Day 1 and 24: oral midazolam 3 mg. Day 2 and 25: IV midazolam 1 mg. Days 3 to 30: oral TAK-788 160 mg QD. *Part B Cycle 2 to 24:* Oral TAK-788 160 mg (in cases of dose adjustments during Part A, the optimal tolerated dose from Part A (ie, 80 mg, 120 mg, or 160 mg OD).	**Route of Administration:** *Part A:* Midazolam, IV and oral. TAK-788, oral. *Part B:* TAK-788, oral.
Duration of Treatment: Cycle 1 to Cycle 24 (patients will be treated with TAK-788 until they experience progressive disease that requires an alternate therapy in the opinion of the investigator, intolerable toxicity, or another discontinuation criterion. Treatment with TAK-788 may be continued after progressive disease if, in the opinion of the investigator, the patient continues to experience clinical benefit).	**Period of Evaluation**: Screening (14 days prior to Cycle 1, Day 1) until 30 days after last day of study dosing.

Main Criteria for Inclusion:

1. Male or female patients aged ≥18 years.
2. Histologically or cytologically confirmed locally advanced NSCLC in which the patient is not a candidate for definitive therapy; **or**, the patient has recurrent or metastatic (Stage IV) disease.
3. Refractory or intolerant to standard available therapies.
4. Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1.
5. Minimum life expectancy of 3 months or more.
6. Adequate organ function as defined by the protocol criteria.
   a) Total serum bilirubin ≤1.5 × upper limit of normal (ULN) (≤3 × ULN for patients with Gilbert syndrome or if liver function abnormalities are due to underlying malignancy);
   b) Alanine aminotransferase and aspartate aminotransferase ≤2.5 × ULN (or ≤5 × ULN if liver function abnormalities are due to underlying malignancy);
   c) Estimated creatinine clearance ≥30 mL/min (calculated by using the Cockcroft-Gault equation);
   d) Serum albumin ≥2 g/dL;
   e) Serum lipase ≤1.5 × ULN; and
   f) Serum amylase ≤1.5 × ULN unless the increased serum amylase is due to salivary isoenzymes.
7. Adequate bone marrow function, as defined by the protocol criteria.
   a) Absolute neutrophil count ≥1.5 × 10^9/L;
   b) Platelet count ≥75 × 10^9/L; and
   c) Hemoglobin ≥9.0 g/dL.
8. Normal QT interval on screening ECG, defined as QTcF of ≤450 msec in males or ≤470 msec in females. (as

conducted and interpreted in accordance to local institutional practices and confirmed by PI).

9. All toxicities from prior anticancer therapy must have resolved to ≤Grade 1 according to the NCI CTCAE version 5.0 [1], or have resolved to baseline, at the time of first dose of TAK-788. Note: treatment-related Grade 2 or 3 alopecia and treatment-related Grade 2 peripheral neuropathy are allowed if deemed irreversible.
10. Female patients who are of childbearing potential, agree to comply with protocol-defined contraception criteria or practice true abstinence.
11. Male patients agree to practice effective barrier contraception during the entire study treatment period and through 30 days after the last dose of study drug, or agree to practice true abstinence.
12. If female, a negative serum or urine pregnancy test result during the screening period.
13. Suitable venous access for study-required blood sampling (ie, including for PK, pharmacodynamics, and clinical laboratory tests).
14. Willingness and ability to comply with scheduled visits and study procedures.
15. Signed and dated the informed consent indicating that the patient has been informed of all pertinent aspects of the study. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.

Main Criteria for Exclusion:

1. Previously received TAK-788.
2. Received a strong or moderate CYP3A inhibitor or strong or moderate CYP3A inducer within 2 weeks prior to the first dose of TAK-788.
3. Received small-molecule anticancer therapy (including but not limited to cytotoxic chemotherapy and investigational agents) within 2 weeks prior to the first dose of TAK-788.
4. Received antineoplastic monoclonal antibodies including check point inhibitors within 28 days of the first dose of TAK-788.
5. Received radiotherapy ≤14 days prior to the first dose of TAK-788. However, patients are allowed to receive any of the following treatments up to 7 days prior to the first dose: (a) Stereotactic radiosurgery (SRS), (b) stereotactic body radiation therapy (SBRT), or (c) palliative radiation outside the chest and brain.
6. Major surgery within 28 days prior to the first dose of TAK-788. Minor surgical procedures, such as catheter placement or minimally invasive biopsy, are allowed.
7. Diagnosed with another primary malignancy other than NSCLC except for adequately treated non-melanoma skin cancer or cervical cancer in situ; definitively treated non-metastatic prostate cancer; or another primary malignancy and is definitively relapse-free with at least 3 years elapsed since the diagnosis of the other primary malignancy.
8. Have known active brain metastases (have either previously untreated intracranial CNS metastases or previously treated intracranial CNS metastases with radiologically documented new or progressing CNS lesions). Brain metastases are allowed if they have been treated with surgery and/or radiation and have been stable without requiring corticosteroids to control symptoms within 7 days before the first dose of TAK-788, and have no evidence of new or enlarging brain metastases.
9. Current spinal cord compression (symptomatic or asymptomatic and detected by radiographic imaging) or leptomeningeal disease (symptomatic or asymptomatic).
10. Have uncontrolled hypertension. Patients with hypertension should be under treatment on study entry to control blood pressure.
11. Significant, uncontrolled, or active cardiovascular disease.
12. Treatment with medications known to be associated with the development of torsades de pointes (see Appendix F).
13. Current or history of interstitial lung disease, radiation pneumonitis that required steroid treatment, or drug-

related pneumonitis.

14. Ongoing or active infection including, but not limited to, the requirement for IV antibiotics, or a known history of human immunodeficiency virus infection. Testing is not required in the absence of history. Patients who are positive for hepatitis B surface antigen or anti-hepatitis C virus antibody may be eligible (see full protocol for further details).
15. Gastrointestinal illness or disorder that could affect oral absorption of TAK-788 or midazolam.
16. If female, the patient is lactating and breastfeeding. Female patients who are lactating will be eligible if they discontinue breastfeeding.
17. History of, or suspected, hypersensitivity or allergy to midazolam or its excipients or TAK-788.
18. Any condition or illness that, in the opinion of the investigator, might compromise patient safety or interfere with the evaluation of the safety of the study drug.
19. Admission or evidence of illicit drug use, drug abuse, or alcohol abuse.

Main Criteria for Evaluation and Analyses:

The primary endpoints of the study include, but are not limited to the following midazolam PK parameters after oral or IV administration in the presence and absence of TAK-788:

Primary Endpoints

- The geometric mean ratios and 90% CI of C_{max} and AUC_{∞} for midazolam administered orally with TAK-788 and when orally administered as midazolam alone.
- The geometric mean ratios and 90% CI of C_{max} and AUC_{∞} for midazolam administered intravenously with TAK-788 and when intravenously administered as midazolam alone.

Secondary Endpoints

The secondary endpoints of the study encompass the safety profile of TAK-788 and are as follows:

- AEs.
- Clinical laboratory tests (hematology and clinical chemistry).
- Vital signs.

Statistical Considerations:

For the estimation of the effect of TAK-788 on oral and IV midazolam PK, the ratios of geometric mean midazolam AUC_{∞} and C_{max} (to be measured both with vs without TAK-788 coadministration) and the associated 2-sided 90% CIs will be calculated on the basis of the within-patient variance using a mixed-effects analysis of variance (ANOVA) fitting terms for treatment (midazolam with or without TAK-788 coadministration). The patient will be treated as a random effect in the model. After log transformation, AUC_{∞} and C_{max} will be separately analyzed. Point estimates and adjusted 90% CIs for the difference in treatment will be calculated and then exponentially back-transformed to provide point and CI estimates for the ratios of interest.

No interim analysis is planned.

PK-Evaluable Population

Patients will be considered PK-evaluable if they meet **all** of the following criteria during study Part A, Cycle 1:

1. Received the protocol-specified dosing regimen without dose reductions prior to Day 26.
2. Experienced no dose interruptions within 1 week prior to Day 24.
3. Experienced no more than 1 day of dose interruption within the first 14 days of TAK-788 treatment.
4. Did not receive any excluded concomitant medications through the completion of PK sampling (Day 26).
5. There is sufficient midazolam concentration-time data to permit the reliable estimation of PK parameters by noncompartmental analysis methods.

Assessment of the PK-evaluable population will be conducted when dosing and safety (ie, vomiting) data become

available and prior to study closure.

PK and Pharmacodynamics Analyses

In Part A (Cycle 1: PK Cycle), oral and IV PK parameters (including but not limited to AUC_{∞}, $C_{max,}$ and t_{max}) of midazolam and 1 hydroxymidazolam in the presence and absence of TAK-788 will be summarized using descriptive statistics.

The oral bioavailability of midazolam and the 1-hydroxymidazolam to midazolam AUC ratios following IV and oral midazolam dosing will be descriptively summarized, in the absence and presence of TAK-788.

Plasma concentrations and PK parameters of TAK-788 and its active metabolites AP32960 and AP32914 will be listed by patient and summarized using descriptive statistics.

Safety Analyses

Safety will be evaluated by the incidence of AEs, severity and type of AEs, and by changes from baseline in the patient's clinical laboratory results, weight, and vital signs. Exposure to study drug and reasons for discontinuation will be tabulated. TEAEs that occur after administration of the first dose of any study drug and through 30 days after the last dose of TAK-788 will be tabulated.

Additional safety analyses may be performed to most clearly enumerate rates of toxicities and to further define the safety profile of TAK-788.

Sample Size Justification:

It is anticipated that approximately 26 patients will be enrolled in this study to obtain approximately 12 PK-evaluable patients. The sample size calculation was based on the expected 2-sided 90% CI for the difference in the paired, log-transformed AUC_{∞} mean values for midazolam in the absence and presence of TAK-788. CC [redacted]

Assuming that the AUC_{∞} ratio for midazolam in the presence versus absence of TAK-788 is 1, with a sample size of 12, the 90% CI for the AUC_{∞} ratio is expected to be 0.82 to 1.23 on the basis of the variance assumptions. Assuming that the AUC_{∞} ratio for midazolam in the presence versus absence of TAK-788 is X, with a sample size of 12, the 90% CI for the AUC_{∞} ratio is expected to be 0.82X to 1.23X on the basis of the variance assumptions.

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 supplier list in the study manual. The identified vendors will perform specific study-related activities either 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 drug, their expertise in the therapeutic area and the conduct of clinical research, and study participation. The signatory coordinating investigator will be required to review and sign the clinical study report (CSR) and by doing so agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

AE	adverse event
AUC	area under the plasma concentration-time curve
AUC_{∞}	area under the plasma concentration-time curve from time 0 to infinity
AUC_t	area under the plasma concentration-time curve from time 0 to time
C_{max}	maximum observed plasma concentration
CNS	central nervous system
COVID-19	coronavirus disease 2019
eCRF	electronic case report form
CR	complete response
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
CYP	cytochrome P450
DCR	disease control rate
DLT	dose-limiting toxicity
DOR	duration of response
DTP	direct-to-patient
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eConsent	electronic informed consent
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EOT	end of treatment
FDA	[United States] Food and Drug Administration
GCP	Good Clinical Practice
HER2	human epidermal growth factor 2
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IRB	institutional review board
IV	intravenous
L858R	Leu858Arg
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	magnetic resonance imaging
MUGA	multigated acquisition scan

NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	non–small cell lung cancer
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency of Japan
PO	oral administration
PR	partial response
QD	once daily
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended phase 2 dose
SAE	serious adverse event
SBRT	stereotactic body radiation therapy
SD	stable disease
SRS	stereotactic radiosurgery
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse events
TKI	tyrosine kinase inhibitors
t_{max}	time of first occurrence of maximum observed concentration
ULN	upper limit of the normal range
UK	United Kingdom
US	United States
WHO	World Health Organization
WT	wild-type

3.4 Corporate Identification

Millennium	Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited

4.0 INTRODUCTION

4.1 Disease Background

Specific genetic alterations that drive the proliferation of cancer cells, such as those resulting in activation of certain tyrosine kinases, render many cancers highly sensitive to therapeutic agents that inhibit the affected kinase (ie, tyrosine kinase inhibitors [TKIs]). These include activating mutations in the epidermal growth factor receptor (EGFR), which have been identified in 21% to 40% of patients with non–small cell lung cancer (NSCLC) [7,8]. There are multiple classes of activating mutations in EGFR that vary widely in their degree of sensitivity to available TKIs. Since inhibition of wild-type (WT) EGFR in normal tissues is associated with dose-limiting toxicities (DLTs), substantial clinical benefit has generally been associated with TKIs that inhibit specific, activated variants of EGFR more potently than they inhibit WT EGFR.

The most common activating mutations in EGFR are in-frame deletions in exon 19 and a Leu858Arg (L858R) substitution in exon 21, together accounting for about 90% of all EGFR-activating mutations [9]. Erlotinib and gefitinib ("first generation" EGFR TKIs), as well as afatinib (a "second generation" EGFR TKI), potently inhibit these mutants in vitro and induce high response rates of about 60% to 70% in patients with these mutations [10]. Although these TKIs are approved for use in patients with these specific mutations, their clinical efficacy is ultimately limited by the development of resistance, such as by mutation of the EGFR kinase domain gatekeeper residue (T790M), which occurs in 50% of patients [11,12]. Osimertinib has recently been approved in patients with common mutations as the firstline treatment option, following the first approval in patients with metastatic EGFR T790M mutation–positive NSCLC and who have progressed on or after EGFR TKI therapy [5,6].

For erlotinib and gefitinib, high response rates have largely been restricted to patients with the most common activating mutants; however, preliminary results with afatinib suggest that relatively high response rates are also achieved in patients with a second class of activating mutants, so-called "uncommon" mutants, such as those occurring at other amino acids in exons 19 and 21 (eg, G719 and L861) [13]. Afatinib was recently approved by the Food and Drug Administration (FDA) for a broadened indication in first-line treatment of patients with metastatic NSCLC whose tumors have nonresistant EGFR mutations to include patients whose tumors harbor uncommon mutations, such as L861Q, G719X, and S768I [14].

The final class of EGFR-activating mutations, known as exon 20 insertions, account for approximately 9% of EGFR-mutant NSCLC [15]. Unlike mutations in exons 19 or 21, almost all EGFR exon 20 insertions confer in vitro and primary clinical resistance to the 4 approved EGFR TKIs erlotinib, gefitinib, afatinib and osimertinib [13,16,17]. Patients with NSCLC containing EGFR exon 20 insertions exhibit clinical characteristics similar to those carrying common EGFR mutations (eg, young, nonsmoker, with adenocarcinoma subtype) [18], consistent with potential roles as driver mutations that could confer benefit to targeted therapy. In summary, while erlotinib, gefitinib, afatinib, dacomitinib, and osimertinib are approved by the FDA for use in patients with NSCLC containing common activating mutations in EGFR (ie, exon 19 deletions and L858R substitutions) and afatinib was recently approved by the FDA for a broadened

indication that includes the uncommon EGFR mutations, such as L861Q, G719X, and S768I, no targeted therapies are approved for patients with EGFR exon 20 insertions.

Human epidermal growth factor 2 (HER2) mutations, typically consisting of in-frame insertions in exon 20, have also been identified as potential oncogenic drivers in 2% to 4% of patients with NSCLC. These patients exhibit clinical characteristics similar to patients with EGFR mutations [19-21]. Currently, no therapies are approved for use in patients with NSCLC who have HER2-activating mutations.

To address limitations of existing therapies targeting EGFR and HER2, the sponsor is developing TAK-788 (formerly AP32788), a novel, synthetic, orally-administered TKI.

4.2 TAK-788 Nonclinical Experience

In nonclinical studies, TAK-788 potently inhibits all activated forms of EGFR tested, including those containing exon 20 activating insertions, other uncommon activating mutations, and the common activating mutations (exon 19 deletions and L858R) with or without the T790M resistance mutation. TAK-788 also potently inhibits HER2 activated by exon 20 insertions and point mutations, as well as by amplification. TAK-788 inhibits all of these variants more potently than it inhibits WT EGFR, suggesting it may have the selectivity necessary to achieve levels of exposure required to inhibit all activated forms of these kinases.

Further information on the nonclinical properties of TAK-788 can be found in the current Investigator's Brochure.

4.3 TAK-788 Clinical Experience

Study AP32788-15-101 is an ongoing first-in-human, open-label, multicenter study to determine the recommended phase 2 dose (RP2D) of TAK-788, in addition to the clinical safety, tolerability, and antitumor activity of TAK-788. The trial is being conducted in 3 parts: a dose-escalation phase (3+3 design) (Part 1), followed by an expansion phase with the RP2D (Part 2) and a pivotal extension phase after early proof-of-concept and confirmation of the RP2D (Part 3).

As of the 21 March 2018 data cut-off, a total of 57 patients have been treated with 8 different once-daily (QD) doses and 2 different twice daily doses evaluated. Median age of enrolled patients was 61 years, with 97% having received 2 or more prior anticancer therapies. The majority of patients (68%) had an EGFR exon 20 insertion mutation. All 6 patients (100%) in the 160 mg QD cohort had EGFR exon 20 insertion mutations.

Treatment-emergent adverse events (TEAEs) occurred in 96.5% of patients in the full analysis set and 97.0% of patients in the dose cohorts that received 80, 120, or 160 mg TDD. The TEAEs by System Organ Class that occurred in ≥50% of patients in the dose cohorts that received 80, 120, or 160 mg TDD were gastrointestinal disorders (84.8%) and skin and subcutaneous tissue disorders (63.6%) (data on file). A total of 5 DLTs were observed in Part 1 of the study. The DLTs included 2 events of pneumonitits (one event was Grade 3, the other Grade 5); 1 event of Grade 3 diarrhoea, and 1 event whereby 25% of planned dosing was missed due to TEAEs

(Grade 2 diarrhea, fatigue, and dehydration). Nine patients (15.8%) in the full analysis set died due to a TEAE, with 8 of the deaths occurring in patients receiving 40 mg QD or less of TAK-788, and were due to lung cancer related reasons. Within the 80 mg, 120 mg and 160 mg TDD group, 40% of patients (6 of 15) with EGFR exon 20 insertion mutations had an objective response; 93% (14 of 15 patients) within this group experienced disease control. In the 160 mg QD cohort, 2 of 3 patients (67%) with EGFR exon 20 insertion mutations had an objective response, with 100% experiencing disease control.

In summary, in Study AP32788-15-101, TAK-788 was generally well tolerated, and preliminary anticancer activity was observed in patients with EGFR exon 20 insertion-positive NSCLC who had been previously treated.

4.4 Rationale for the Proposed Study

Data from in vitro induction studies have indicated concentration-dependent cytochrome P450 (CYP) 3A4 induction by TAK-788 and its 2 active metabolites, AP32960 and AP32914. In addition, TAK-788 clinical pharmacokinetic (PK) data from the 160 mg QD regimen in the AP32788-15-101 study indicated autoinduction of the apparent oral clearance of TAK-788 following multiple-dose administration, likely via induction of CYP3A. It is well known that CYP3A subfamily enzymes are a major determinant of first-pass and systemic drug clearance in humans for drugs that are mainly cleared via hepatic metabolism. Therefore, this study is designed to evaluate the effect of repeat-dose administration of TAK-788 on the single oral- and intravenous (IV)-dose PK of midazolam, a sensitive CYP3A probe substrate, to determine whether TAK-788, 160 mg QD, produces clinically meaningful CYP3A induction in humans, and, if so, to inform strategies to manage potential drug-drug interactions between TAK-788 and coadministered CYP3A substrates.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

The primary objective of this study is to characterize the effect of repeated oral administration of TAK-788 160 mg QD on the single oral- and IV-dose PK of midazolam.

5.1.2 Secondary Objective

The secondary objective of this study is to assess the safety and tolerability of TAK-788 in patients with advanced NSCLC.

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5.2 Endpoints

5.2.1 Primary Endpoints

The primary endpoints of this study are midazolam PK parameters in the presence and absence of TAK-788, to include the following:

- The geometric mean ratios and 90% CI of C_{max} and AUC_{∞} for midazolam administered orally with TAK-788 and when orally administered as midazolam alone.
- The geometric mean ratios and 90% CI of C_{max} and AUC_{∞} for midazolam administered intravenously with TAK-788 and when intravenously administered as midazolam alone.

5.2.2 Secondary Endpoints

The secondary endpoints of the study to assess the safety and tolerability TAK-788, are as follows:

- Adverse events (AEs).
- Clinical laboratory tests (hematology, and clinical chemistry).
- Vital signs.

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6.0 STUDY DESIGN

6.1 Overview of Study Design

This phase 1, open-label, multicenter, drug-drug interaction study will consist of 2 parts: Part A (Cycle 1: PK cycle) and Part B (Cycle 2 to Cycle 24: Treatment Cycles). The patient population will consist of adult patients with locally advanced or metastatic NSCLC that is refractory to standard available therapies. It is expected that approximately 26 patients will be enrolled in the study.

In Part A of the study, a fixed-sequence design over a single 30-day duration including 28 days of treatment with TAK-788 will be used (Cycle 1: PK Cycle and Cycle 2 Day 1) (Table 6.a). After screening, eligible patients will be enrolled and will receive a single oral dose of midazolam 3 mg on Day 1 **and** Day 24 and a single IV dose of midazolam 1 mg as a 5-minute infusion on Day 2 **and** Day 25. Patients also will receive TAK-788 160 mg QD orally on Days 3 **through** Day 30 (see Table 8.a for standard dosing, and Table 8.b and Table 8.c for dose adjustments). Serial PK blood samples will be collected to measure plasma concentrations of midazolam and its metabolite 1-hydroxymidazolam in the absence and presence of TAK-788. In addition, TAK-788 PK blood sample will be collected prior dosing on Cycle 1 Day 24, 25, 26 and Cycle 2 Day 1 and post dosing on Day 24 to assess TAK-788 plasma concentrations and its active metabolites AP32960 and AP32914 Table 6.a. Further, biomarker blood samples will be collected on Days 1 and 24 prior to dosing, to measure plasma concentrations of 4β-hydroxycholesterol and cholesterol, in addition circulating tumor DNA sampling which will be collected as part of assessments during Cycles 1, 3, and 5, and at the time of progressive disease assessments. (see Table 6.a).

PK-Evaluable Population

Patients will be considered PK-evaluable if they meet **all** of the following criteria during study Part A, Cycle 1:

1. Received the protocol-specified dosing regimen without dose reductions prior to Day 26.
2. Experienced no dose interruptions within one week prior to Day 24.
3. Experienced no more than 1 day of dose interruption within the first 14 days of TAK-788 treatment.

4. Did not receive any excluded concomitant medications through the completion of PK sampling (Day 26).

Assessment of the PK-evaluable population will be conducted when dosing and safety (ie, vomiting) data become available and prior to study closure.

Table 6.a Study Design for Part A (Cycle 1: PK Cycle and Cycle 2 Day 1)

Study Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	C2 D1
Midazolam 3 mg PO [a]	X																							X							
Midazolam 1 mg IV		X																							X						
TAK-788 160 mg dosing			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PK Blood Samples [b]	X	X	X																					X	X	X					X
CCI																															
Cholesterol Blood Samples [d]	X																							X							

C: cycle; D: day; IV: intravenous; PK: pharmacokinetic; PO: oral.

Pre- and postflushing information is provided in the pharmacy manual.

[a] A detailed PK blood sampling schedule for midazolam is provided in Appendix A Table A-2.

[b] To measure plasma concentrations of midazolam and its metabolite 1-hydroxymidazolam, blood samples will be collected predose and over 24 hours after the oral dose on Days 1 and 24 and predose and over 24 hours after the IV dose on Days 2 and 25. To measure trough plasma concentrations of TAK-788 and its active metabolites AP32960 and TAK-914, PK blood samples will be collected predose on Days 24, 25, and 26 of Cycle 1 as well as Cycle 2 Day 1. In addition, serial PK blood samples will be collected over 24 hours postdose on Day 24 to measure plasma concentrations of TAK-788, AP32960, and AP32914.

[c] ACCI

[d] A cholesterol blood sample will be collected predose on Days 1 and 24 to measure plasma concentrations of 4β-hydroxycholesterol and cholesterol.

After completion of Part A, patients may continue into Part B to continue treatment with TAK-788 (Cycle 2 to Cycle 24: Treatment Cycles). Any patients who are not PK-evaluable in Part A may be eligible to continue into Part B.

Part B of the study will consist of 28-day treatment cycles in which patients will continue to receive TAK-788 until completion of Cycle 24, or until progressive disease (PD), intolerable toxicity, or another discontinuation criterion is met, whichever is sooner.

During each treatment cycle, the TAK-788 dose may be reduced based on dose modification guidelines to 120, or 80 mg QD in patients who do not tolerate the 160 mg dose (see Section 8.2). However, any patient who experiences dose reduction prior to Day 26 in Part A Cycle 1 will not be considered as a PK-evaluable patient. The study will include a 30-day follow-up period after EOT. Safety and tolerability will be evaluated during the study by AE monitoring, clinical laboratory tests, vital signs, and physical examinations until 30 days after EOT. Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0 [1].

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Additional details regarding the timing of study procedures are provided in the Schedule of Study Events (Appendix A Table A-1 for Part A and Table A-3 for Part B).

6.2 Number of Patients

Approximately 26 patients with locally advanced or metastatic NSCLC will be enrolled in this study from 4 to 6 clinical sites to achieve approximately 12 PK-evaluable patients for assessment of the effect of repeated doses of TAK-788 on the PK of midazolam. Study regions will be provided in the study manual.

6.3 Duration of Study

6.3.1 Duration of an Individual Patient's Study Participation

The PK cycle in Part A will be completed after patients finish a single 30-day cycle. Following PK cycle in Part A, patients may enter Part B and continue daily treatment with TAK-788 in 28-day repeated treatment cycles until completion of Cycle 24, or until PD, intolerable toxicity, or another discontinuation criterion is met. Treatment with TAK-788 may be continued after PD if, in the opinion of the investigator, the patient continues to experience clinical benefit. Patients will have an assessment at 30 days after treatment discontinuation.

The maximum duration of study participation for an individual patient will be approximately 26 months (which includes the screening period, the Part A PK cycle, a maximum of 23 cycles in Part B, and the 30-day follow-up period after EOT).

6.3.2 End of Study/Study Completion Definition and Planned Reporting

6.3.2.1 Study Duration

6.3.2.1.1 Primary Study Duration

The estimated time frame for primary completion of the study is 13 to 15 months, which includes an estimated 12- to 14-month enrollment period and the PK Cycle in Part A of the study. Analyses for the primary and exploratory endpoints, except antitumor activity, will be conducted after 12 PK-evaluable patients complete Part A of the study, at which time, the CSR will be developed and include an analyses of PK and safety. Assessment of the PK-evaluable population will be conducted when dosing and safety (ie, vomiting) data become available and prior to study closure.

Other Planned Analyses

A CSR addendum for exploratory efficacy and additional safety is planned when all enrolled patients have completed Part B of the study (approximately 2 years after enrollment of the last patient).

The total duration of the study is anticipated to be up to approximately 3 years, including the enrollment period, Part A PK cycle, Part B treatment cycles, and follow-up period.

6.3.3 Timeframes for Primary and Secondary Endpoints to Support Disclosures

Please refer to Table 6.b for disclosure information for the primary and secondary endpoints.

Table 6.b Primary and Secondary Endpoints for Disclosures

	Definition	Maximum Time Frame (For an Individual Patient)
Primary Endpoints		
Midazolam AUC_{∞}.	Area under the concentration-time curve from time 0 to infinity.	From predose up to 24 hours after the oral dose on Days 1 and 24 and from predose up to 24 hours after the IV dose on Days 2 and 25, for a total time frame of 26 days.
Midazolam C_{max}.	Maximum observed concentration.	
Midazolam t_{max}.	Time of first occurrence of C_{max}.	
Secondary Endpoints		
AEs.	See Section 10.1.2 and 10.1.3.	From the first dose of study drug through the 30-day follow-up period, for a total time frame of up to approximately 25 months.
Clinical laboratory tests (hematology, and clinical chemistry).	See Table 9.a.	From the first dose of study drug through the 30-day follow-up period, for a total time frame of up to approximately 25 months.
Vital signs.	DBP, SBP, heart rate, respiratory rate, and body temperature.	From the first dose of study drug through the 30-day follow-up period, for a total time frame of up to approximately 25 months.

AE: adverse event; DBP: diastolic blood pressure; IV: intravenous; SBP: systolic blood pressure.

6.3.4 Total Study Duration

Part A will consist of a single 30-day PK cycle. Part B will consist of repeated 28-day treatment cycles for up to 23 cycles of treatment (24 cycles in total, including Part A), or until PD, intolerable toxicity, or another discontinuation criterion. Treatment with TAK-788 may be continued after PD if, in the opinion of the investigator, the patient continues to experience clinical benefit. The total duration of the study is anticipated to be up to approximately 3 years, including the enrollment period, Part A PK cycle, Part B treatment cycles, and follow-up period.

6.3.5 Post-Trial Access

The clinical study database will be closed approximately 2 years after the last patient has been enrolled in the study. Patients will be allowed to continue treatment if, in the opinion of the investigator and confirmed by the sponsor, the patient has experienced a clinically important benefit from TAK-788, has no alternative therapeutic option, and would be harmed without continued access.

Continued access to TAK-788 for patients will be terminated for those individuals who no longer benefit from TAK-788, the benefit-risk no longer favors the individual, if TAK-788 becomes available either commercially or via another access mechanism, or when an alternative appropriate therapy becomes available. Post-trial access may be terminated in a country or

geographical region where marketing authorization has been rejected, the development of TAK-788 has been suspended or stopped by the sponsor, or TAK-788 can no longer be supplied.

7.0 STUDY POPULATION

Approximately 26 patients with locally advanced or metastatic NSCLC who are refractory or who have relapsed to standard therapies and meet all protocol-defined eligibility criteria, will be enrolled in this study.

7.1 Inclusion Criteria

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

1. Male or female patients aged ≥18 years.
2. Histologically or cytologically confirmed locally advanced NSCLC in which the patient is not a candidate for definitive therapy; **or,** the patient has recurrent, or metastatic (Stage IV) disease.
3. Refractory or intolerant to standard available therapies.
4. Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1.
5. Minimum life expectancy of 3 months or more.
6. Adequate organ function as defined by the following criteria:
   a) Total serum bilirubin ≤1.5 × upper limit of normal (ULN) (≤3 × ULN for patients with Gilbert syndrome or if liver function abnormalities are due to underlying malignancy);
   b) Alanine aminotransferase and aspartate aminotransferase ≤2.5 × ULN (or ≤5 × ULN if liver function abnormalities are due to underlying malignancy);
   c) Estimated creatinine clearance ≥30 mL/min (calculated by using the Cockcroft-Gault equation);
   d) Serum albumin ≥2 g/dL; and
   e) Serum lipase ≤1.5 × ULN; and
   f) Serum amylase ≤1.5 × ULN unless the increased serum amylase is due to salivary isoenzymes.
7. Adequate bone marrow function as defined by the following criteria:
   a) Absolute neutrophil count ≥1.5 × 10^9/L;
   b) Platelet count ≥75 × 10^9/L; and
   c) Hemoglobin ≥9.0 g/dL.
8. Normal QT interval on screening ECG, defined as QTcF of ≤450 msec in males or ≤470 msec in females. (as conducted and interpreted in accordance to local institutional practices and confirmed by PI).

9. All toxicities from prior anticancer therapy must have resolved to ≤Grade 1 according to the NCI CTCAE version 5.0 [1], or have resolved to baseline, at the time of first dose of TAK-788. Note: treatment-related Grade 2 or 3 alopecia and treatment-related Grade 2 peripheral neuropathy are allowed if deemed irreversible.
10. Female patients who:
    a) Are postmenopausal for at least 1 year before the screening visit, or
    b) Are surgically sterile, or
    c) If they are of childbearing potential, agree to practice 1 highly effective, nonhormonal method of contraception and 1 additional effective (barrier) method at the same time, from the time of signing the informed consent through 30 days after the last dose of study drug (see Table 8.d), or
    d) Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together).
11. Male patients, even if surgically sterilized (ie, status postvasectomy), who:
    a) Agree to practice effective barrier contraception during the entire study treatment period and through 30 days after the last dose of study drug (Table 8.d), or
    b) Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together).
12. If female, a negative serum or urine pregnancy test result during the screening period.
13. Suitable venous access for study-required blood sampling (ie, including for PK, pharmacodynamics, and clinical laboratory tests).
14. Willingness and ability to comply with scheduled visits and study procedures.
15. Signed and dated the informed consent indicating that the patient has been informed of all pertinent aspects of the study. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.

7.2 Exclusion Criteria

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

1. Previously received TAK-788.
2. Received a strong or moderate CYP3A inhibitor or strong or moderate CYP3A inducer within 2 weeks prior to the first dose of TAK-788.
3. Received small-molecule anticancer therapy (including but not limited to cytotoxic chemotherapy and investigational agents) within 2 weeks prior to the first dose of TAK-788.
4. Received antineoplastic monoclonal antibodies including check point inhibitors within 28 days of the first dose of TAK-788.
5. Received radiotherapy ≤14 days prior to the first dose of TAK-788. However, patients are allowed to receive any of the following treatments up to 7 days prior to the first dose: (a) Stereotactic radiosurgery (SRS), (b) stereotactic body radiation therapy (SBRT), or (c) palliative radiation outside the chest and brain.
6. Major surgery within 28 days prior to the first dose of TAK-788. Minor surgical procedures, such as catheter placement or minimally invasive biopsy, are allowed.
7. Diagnosed with another primary malignancy other than NSCLC except for adequately treated non-melanoma skin cancer or cervical cancer in situ; definitively treated non-metastatic prostate cancer; or another primary malignancy and is definitively relapse-free with at least 3 years elapsed since the diagnosis of the other primary malignancy.
8. Have known active brain metastases (have either previously untreated intracranial CNS metastases or previously treated intracranial CNS metastases with radiologically documented new or progressing CNS lesions). Brain metastases are allowed if they have been treated with surgery and/or radiation and have been stable without requiring corticosteroids to control symptoms within 7 days before the first dose of TAK-788, and have no evidence of new or enlarging brain metastases.
9. Current spinal cord compression (symptomatic or asymptomatic and detected by radiographic imaging) or leptomeningeal disease (symptomatic or asymptomatic).
10. Have uncontrolled hypertension. Patients with hypertension should be under treatment on study entry to control blood pressure.
11. Significant, uncontrolled, or active cardiovascular disease, including, but not limited to the following:
    a) Myocardial infarction within 6 months prior to the first dose of study drug;
    b) Unstable angina within 6 months prior to the first dose of study drug;
    c) Congestive heart failure within 6 months prior to the first dose of study drug. Cardiac ejection fraction <50% by echocardiogram (ECHO) or multigated acquisition (MUGA) scan;

d) History of clinically significant (as determined by the treating physician) atrial arrhythmia;

e) Any history of ventricular arrhythmia; or

f) Cerebrovascular accident or transient ischemic attack within 6 months prior to the first dose of study drug.

12. Treatment with medications known to be associated with the development of torsades de pointes (see Appendix F).
13. Current or history of interstitial lung disease, radiation pneumonitis that required steroid treatment, or drug-related pneumonitis.
14. Ongoing or active infection including, but not limited to, the requirement for IV antibiotics, or a known history of human immunodeficiency virus infection. Testing is not required in the absence of history.

    Patients who are positive for hepatitis B surface antigen can be enrolled if hepatitis B virus DNA is below 1000 copies/mL in the plasma. Patients who are positive for anti-hepatitis C virus antibody can be enrolled but must not have detectable hepatitis C virus RNA in the plasma.
15. Gastrointestinal illness or disorder that could affect oral absorption of TAK-788 or midazolam.
16. If female, the patient is lactating and breastfeeding. Female patients who are lactating will be eligible if they discontinue breastfeeding.
17. History of, or suspected, hypersensitivity or allergy to midazolam or its excipients or TAK-788.
18. Any condition or illness that, in the opinion of the investigator, might compromise patient safety or interfere with the evaluation of the safety of the study drug.
19. Admission or evidence of illicit drug use, drug abuse, or alcohol abuse.

    NOTE: In accordance with local institutional practice, patients will be monitored for any signs or symptoms associated with alcohol or illicit drug abuse. PIs should advise subject to avoid excessive alcohol consumption while enrolled in this study. Medical use of cannabis is allowed, if it is legal where the patient resides and no alternative treatment is available, on the basis of case by-case review and agreement by the medical monitor.

8.0 STUDY DRUG

8.1 Study Drug Administration

All protocol-specified criteria for administration of study drug must be met and documented before drug administration. Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified subinvestigators. A summary of assessments and procedures are provided in Table A-1 (for Part A), and Table A-3 (for Part B),

with dose adjustments guidelines outlined in Table 8.b and Table 8.c; in addition, PK and biomarker assessments for Part A are provided in Table A-2. A summary of study drug administration is provided in this section, additional details on dosing administration and procedures are provided in study manual.

On Day 1 of Part A (Cycle 1: PK Cycle), all eligible enrolled patients will report to the clinic and receive an oral dose of midazolam 3 mg in accordance with dose administration guidance outlined in Table 8.a.

Table 8.a Summary of Dose Administration

Part A Midazolam Administration [a, b]	
Day 1 and 24	**Dose:** 3 mg PO with approximately 8 ounces (240 mL) of water on an empty stomach (defined as fasting for 2 hours prior to dosing and 2 hours after dosing; subjects may not consume water during the fasting period except during dose administration). NOTE: On Day 24, TAK-788 should be administered immediately after oral midazolam administration. Total water intake for both midazolam and TAK-788 dosing should be approximately 8 ounces (240 mL) of water on an empty stomach.
Day 2 and 25	**Dose:** 1 mg IV (with or without food). NOTE: Refer to Part A TAK-788 administration for further guidance on co-administration.
Part A TAK-788 Administration [a]	
Day 3 to 30 Except Day 24	**Dose:** 160 mg daily. Administer with approximately 8 ounces (240 mL) of water with or without a low-fat meal (ie, ≤350 calories and ≤15% of calories from fat).
Days 24, 25	**Dose:** 160 mg daily. TAK-788 is to be taken immediately after midazolam administration (on Day 24, immediately after oral administration of midazolam with total 240 mL water on an empty stomach; and Day 25, immediately after IV administration of midazolam with 240 mL water with or without a low-fat meal). NOTE: Refer to Midazolam text for co-administration.
Part B TAK-788 Administration [c]	
Day 1 to 28	**Dose:** 160 mg daily. Administer with approximately 8 ounces (240 mL) of water with or without a low-fat meal (ie, ≤350 calories and ≤15% of calories from fat).

IV: intravenous; PO: oral.
[a] Refer to the study manuals for complete Part A dosing details.
[b] Refer to current Midazolam package insert for further details on the safety and clinical oversight associated with midazolam administration
[c] Refer to the study manuals for complete Part B dosing details.

8.1.1 Part A Study Dosing

Midazolam will be administered at clinic on study Day 1, Day 2, Day 24, and Day 25 during Part A (Cycle 1: PK Cycle), as outlined in Table 8.a.

On study Days 3 through 30, TAK-788 capsules will be self-administered orally at home at 160 mg QD, except on Days 3, 24, 25, and 26, on which the TAK-788 160 mg dose will be administered in the clinic. Patients will be instructed to take each TAK-788 dose at approximately the same time each day, approximately 24 hours apart (ie, in the morning).

After Day 24 predose PK samples for midazolam and TAK-788, patients will take 3 mg oral dose of midazolam first, immediately followed by administration of the 160 mg dose of TAK-788 with total approximately 8 ounces (240 mL) of water (used for both midazolam and TAK-788). No food should be allowed for at least 2 hours prior to and 2 hours postdose of midazolam and TAK-788 on Day 24.

On the morning of Day 25 of Part A, patients will return to the clinic. After collection of the pre-dose PK blood samples, patients will be administered an IV dose of midazolam 1 mg as a 5-minute infusion first, immediately followed by administration of the 160 mg dose of TAK-788 with approximately 8 ounces (240 mL) of water, with or without a low-fat meal.

On the morning of Day 26, patients will return to the clinic for collection of the predose PK blood sample and then will be administered the TAK-788 160 mg dose with approximately 8 ounces (240 ml) of water with or without a low-fat meal. Patients will continue to self-administer TAK-788 QD with approximately 8 ounces (240 ml) of water on Days 27 through 30 of Part A with or without a low-fat meal.

8.1.2 Part B Study Dosing

During Part B of the study, patients continuing in the study will return to the clinic for visits on Day 1 of Cycle 2 and each treatment cycle thereafter. In Part B Cycle 2, patients will receive TAK-788 at the dose that they were receiving (and tolerating) at the end of Part A and will continue treatment until Cycle 24, or until the first incidence of PD, unacceptable toxicity, or another discontinuation criterion is met. On Day 1 of each treatment cycle, TAK-788 capsules will be dispensed to patients for oral QD administration on Days 1 through 28. The Day 1 TAK-788 dose will be administered in the clinic (refer to the study manual for details regarding TAK-788 administration and dosing). During Part B of the study, patients will take the TAK-788 dose with approximately 8 ounces (240 mL) of water with or without a low-fat meal.

8.1.3 Additional Study Dosing Guidance

During study Part A and B, the date and time of TAK-788 administration should be recorded in the patient's dosing diary. Patients who forget to take their scheduled dose of study drug should be instructed not to make up the missed dose (if >6 hours after scheduled time of administration). The patient should record any missed doses in the dosing diary. If emesis occurs after study drug administration, the patient should simply adhere to the dosing schedule and resume dosing at the next scheduled dosing time with the prescribed dosage. The timing of emesis relative to study drug administration should be recorded. Patients should not repeat a dose, nor attempt to make up missed doses by doubling a given dose.

8.2 Dose Modification Guidelines

8.2.1 Dose Modifications of TAK-788

The allowable daily modified doses of TAK-788 in this study are 120 mg and 80 mg. Doses may be reduced, in accordance with the dose-reduction scheme shown in Table 8.b, if the patient is intolerant to their current dose.

Table 8.b Recommended TAK-788 Dose Reduction Levels

Starting Dose (Part A)	First Dose Adjustment	Second Dose Adjustment
160 mg QD	120 mg QD	80 mg QD

QD: once daily.

TAK-788 dose interruption or reductions will be implemented for patients who experience treatment-related AEs as indicated in the following section and in Table 8.c. After dose reduction, patients should continue therapy at the reduced dose. Dose reductions may be implemented a second time if additional toxicity ensues. If study drug is held for more than 2 weeks, resumption of therapy must be discussed with the sponsor. In general, re-escalation of doses will occur only in consultation with the sponsor, as stipulated in Section 8.2.3 below. If toxicity requiring dose reduction occurs at the 80 mg dose, therapy should be discontinued. Toxicity grades will be defined by NCI CTCAE v5.0. Please note that patients who experience dose reduction during cycle 1 in part A of the study may be considered as PK-unevaluable (Section 13.1.1.1).

Table 8.c TAK-788 Dose Modification Recommendations for Treatment-Related AEs

Toxicity Grade	Action
Non-hematologic toxicity	
Grade 1	Continue therapy at same dose level.
Grade 2	Continue therapy at same dose level. If symptoms are intolerable, recurrent, or not controlled by supportive care, withhold therapy until symptoms remit and reduce to next lower dose level. [a]
Grade 3	Withhold therapy until toxicity is ≤Grade 1 or has returned to baseline, then resume therapy. Therapy may be resumed at the same dose or at the next lower dose level, based on the investigator's judgment. [a]
Grade 4	Withhold therapy until toxicity is ≤Grade 1 or has returned to baseline, then resume therapy at the next lower dose level. Therapy may also be discontinued based on the investigator's judgment.
Hematologic toxicity	
Grade 1	Continue therapy at same dose level.
Grade 2	Continue therapy at same dose level.
Grade 3	Withhold therapy until toxicity is ≤Grade 2 or has returned to baseline, then resume therapy. Therapy may be resumed at the same dose or at the next lower dose level, based on the investigator's judgment.
Grade 4	Withhold therapy until toxicity is ≤Grade 2 or has returned to baseline, then resume therapy at the next lower dose level. Therapy may also be discontinued based on the investigator's judgment.

[a] For cases of pneumonitis, investigators should follow guidance in Section 8.6.4.

Further instructions for dose modification/management of nausea and emesis, diarrhea, asymptomatic lipase/amylase elevation, and pneumonitis can be found in Section 8.6.

8.2.2 Dose Modifications of Midazolam

Midazolam dose modification is not allowed.

8.2.3 Re-escalation of TAK-788 Dose After Dose Reduction

After dose reduction for toxicity, the dose may be re-escalated to the original dose level only after discussion with the sponsor. For dose re-escalation, the escalation dose must not exceed 160 mg QD, and the patient must have recovered from the AE.

8.3 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study:

- Any other systemic anticancer therapy including, but not limited to, chemotherapeutic agents, immunotherapy, biological response modifiers (excluding growth factors), radiotherapy, and/or systemic hormonal therapy (with the exception of local therapies, including SRS, used

for palliative or symptomatic control of existing lesions, with appropriate treatment interruption at the discretion of the investigator).

- Any other investigational agent or device.
- Medications that are known to be associated with the development of torsades de pointes (see Appendix F). Medications that prolong the QT interval, but are not known to be associated with torsades de pointes, should be avoided but are not prohibited.
- Grapefruit or grapefruit-containing products, pomegranate-, pomelo-, or star fruit juice-containing products, and Seville oranges.
- Medications that are moderate or strong inducers or inhibitors of the CYP3A subfamily of CYP enzymes in Part A Cycle 1 (see Appendix E). In Part B, only strong inducers or inhibitors of the CYP3A enzymes are excluded as concomitant medications.
- Extensive surgery requiring in-patient care (patients may have an interruption in therapy for 2 weeks should emergency surgery be required).
- Any illicit substance. Note: Medical use of cannabis is allowed, if it is legal where the patient resides and no alternative treatment is available, on the basis of case-by-case review and agreement by the medical monitor.

8.4 Permitted Concomitant Medications and Procedures

During the study, palliative therapy and supportive care are permitted for management of symptoms and underlying medical conditions that may develop during the study (to include steriodal dosing for palliative care). Once a patient has begun treatment, a condition may arise that requires the initiation of a new concomitant treatment. Patients with CNS lesions requiring local radiotherapy such as SRS are allowed to continue study drug after appropriate interruption, as determined by the investigator with sponsor agreement.

Concomitant medications for all ongoing medical history conditions or AEs, as well as prophylactic treatments and supplements, must be reported from the date the informed consent is signed through the 30-day follow-up period after EOT. All concomitant medications related to serious or study-drug–related toxicities must be reported until the medication is no longer taken or until patient contact ceases.

8.5 Precautions and Restrictions

8.5.1 TAK-788

8.5.1.1 CYP3A Substrates (Including Hormonal Contraceptives)

TAK-788 potently induces CYP3A in vitro and may decrease concentrations of concomitantly administered CYP3A substrates. Based on emerging clinical PK data (Study AP32788-15-101), autoinduction of the apparent oral clearance of TAK-788 has been observed following multiple-dose administration at 160 mg QD, likely explained by induction of CYP3A including

hormonal contraceptives, can result in decreased concentrations and loss of efficacy of these coadministered drugs.

Medications that are CYP3A substrates and which have narrow therapeutic index, including alfentanil, cyclosporine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus, and all statins may be concurrently administered with TAK-788 with caution. Patients should be closely monitored for signs of changed tolerability or effectiveness as a result of increased or decreased exposure of the concomitant medication while receiving TAK-788.

If a patient's clinical condition requires treatment with this class of medications specified above, the clinical details of the situation should be discussed with the medical monitor at the earliest possible time to determine whether it is safe for the patient to continue treatment with TAK-788.

8.5.1.2 Pregnancy and Breastfeeding

TAK-788 demonstrated embryofetal toxicity in rats and, similar to other EGFR inhibitors, has the potential to cause embryofetal harm; therefore, female patients participating in this study should avoid becoming pregnant, breastfeeding a baby, or donating eggs, and male patients should avoid impregnating a female partner and donating sperm for 30 days after the last dose of TAK-788.

As specified in Section 7.1, female patients of childbearing potential must agree to use 1 highly effective (ie, results in a low failure rate when used consistently and correctly) nonhormonal method and 1 additional effective (barrier) method of contraception (see Table 8.d) from the time of signing of the informed consent and through 30 days after the last dose of study drug or must agree to practice true abstinence. Male patients must agree to practice effective barrier contraception during the entire study treatment period and through 30 days after the last dose of study drug, or must agree to practice true abstinence.

In Parts A and B of the study, a pregnancy test will be performed for each female patient of childbearing potential at the time points specified in Section 9.3.13. A negative pregnancy test must be documented prior to administration of study drug. Please refer to Section 10.4 for pregnancy reporting requirements.

Table 8.d Highly Effective Methods of Contraception and Additional Effective Barrier Methods

Highly Effective Nonhormonal Methods	Additional Effective Barrier Methods
• Nonhormonal intrauterine device (IUD) • Bilateral tubal occlusion • Vasectomized sole sexual partner • Sexual abstinence (no sexual intercourse)	• Male or female condom with or without spermicide (female and male condoms should not be used together) • Cap, diaphragm, or sponge with spermicide

Note that hormonal contraceptives are permitted to be used for purposes other than pregnancy prevention during the study if clinically indicated but may not be considered as a highly effective method of contraception.

It is not known whether TAK-788 passes into the breast milk. Mothers should not breastfeed during study drug administration.

8.5.2 Midazolam

Midazolam is a short-acting benzodiazepine that depresses activity of the CNS and has been associated with respiratory depression, most often when used concomitantly with other CNS depressants (eg, opioids and other benzodiazepines). Therefore, all patients will be closely monitored for respiratory and cardiac function (ie, pulse oximetry) after administration of midazolam on Days 1, 2, 24, and 25 of Part A of the study. Immediate availability of reversal agents (eg, flumazenil), resuscitative drugs, equipment for ventilation and intubation, and personnel trained in their use and skilled in airway management should be assured. Please refer to the midazolam prescribing information for full details regarding the use of midazolam.

Midazolam causes sedation. Patients should not drive, operate dangerous tools or machinery, or engage in any other potentially hazardous activity that requires full alertness and coordination after receiving midazolam on Days 1, 2, 24, and 25 of Part A of the study.

8.6 Management of Selected Treatment-Related Clinical Events

8.6.1 Nausea and Emesis

Standard antiemetics, such as prochlorperazine, may be used for the treatment of vomiting. Taking the study drug with food may reduce nausea. Prophylactic antiemetics may be used.

8.6.2 Diarrhea

On the basis of clinical findings and known class effect, patients should be monitored for the onset of diarrhea. Symptomatic care, such as site-provided loperamide where available (refer to the pharmacy manual for details), may be needed to manage diarrhea. Sites should follow their local standard of care. Table 8.e provides guidance to manage drug-related diarrhea.

Table 8.e Management of Drug-Related Diarrhea

	Guidance	Action with TAK-788
No diarrhea or Cycle 1, Day 1	• Primary prophylactic antidiarrheal medications may be used after discussion with the sponsor. Maintain fluid intake to prevent dehydration; monitor and replace electrolytes as appropriate, and adjust diet as per standard medical practice.	Continue TAK-788.
First evidence of loose stool, increased frequency of bowel movements (<4 stools per day over baseline) Grade 1	• Patient should be instructed to contact the study doctor/team as soon as convenient. • Symptomatic care, such as loperamide, may be given according to the investigator's clinical judgment. • Patient should be instructed to drink fluids and adjust their diet to avoid fried, greasy, high-fiber, or spicy foods. • Other medications (such as diphenoxylate hydrochloride with atropine sulfate) and supportive care may be added according to the institution's standard of care. • Secondary prophylaxis in patients who have experienced diarrhea with TAK-788 is allowed.	Continue TAK-788. No dose modification unless intolerant to TAK-788. Refer to Table 8.c and Table 8.b if TAK-788 not tolerated.
For increase of 4-6 stools per day over baseline; Grade 2	• Patient should be instructed to contact study doctor/team immediately. • Should prescribe loperamide at 4 mg, then 2 mg every 2 to 4 hours until the patient is symptom free for 12 hours. • Patient should be instructed to drink fluids and adjust their diet to avoid fried, greasy, high-fiber, or spicy foods. • Symptom directed assessment for clinical sequela is encouraged per standard medical practice. • Other medications (such as diphenoxylate hydrochloride with atropine sulfate) and supportive care may be added according to the institution's standard of care. • Secondary prophylaxis in patients who have experienced diarrhea with TAK-788 is allowed.	Continue TAK-788. No dose modification is necessary unless the patient does not tolerate TAK-788 or the symptom recurs. Refer to Table 8.c and Table 8.b if TAK-788 not tolerated.

Table 8.e Management of Drug-Related Diarrhea

	Guidance	Action with TAK-788
For increase of >7 stools per day over baseline; Grade 3 or Grade 4 diarrhea	• Patient should be instructed to contact study doctor/team immediately. • Evaluate patient for clinical sequela is recommended. Evaluate need for additional or alternative supportive care and provide any based on clinical judgement • Administer loperamide: initial dose of 4 mg (2 tablets/capsules) with the first bout of diarrhea followed by 2 mg (1 tablet/capsule) every 4 hours or after every unformed stool (maximum 16 mg daily) and continue loperamide at this frequency until diarrhea free for 12 hours. Then titrate the amount of loperamide used to keep diarrhea controlled (<4 stools/day). • Other medications (such as diphenoxylate hydrochloride with atropine sulfate, octreotide, IV fluids) and other supportive care may be added according to the institution's standard of care. • Patient should be instructed to drink fluids and adjust their diet to avoid fried, greasy, high-fiber, or spicy foods; additional dietary adjustment may be needed based on clinical judgment. • Secondary prophylaxis in patients who have experienced diarrhea with TAK-788 is allowed.	Stop TAK-788 until recovery to Grade ≤1. Refer to Table 8.c and Table 8.b if TAK-788 not tolerated.

8.6.3 Asymptomatic Lipase/Amylase Elevation

In the event of Grade 3 asymptomatic lipase/amylase elevation (>5.0 x ULN), withhold therapy until toxicity is ≤Grade 2. Therapy may be resumed at the same dose or at the next lower dose level, based on the investigator's judgment. In the event of Grade 2 asymptomatic lipase/amylase elevation (>2-≤5 × ULN), continue therapy at the same dose level or at the next lower dose level, based on the investigator's judgment. In either case, close monitoring of patients with respect to lipase/amylase levels and clinical symptoms are highly recommended.

8.6.4 Pneumonitis

Withhold TAK-788 for acute onset of unexplained new or progressive pulmonary symptoms, such as dyspnea, cough, and fever and during diagnostic workup for pneumonitis/interstitial lung disease. For suspected cases of pneumonitis of any grade, investigators should rule out infection, PD, and pulmonary embolism as other etiologies for the pulmonary symptoms and should closely monitor the patient. If pneumonitis of any grade is confirmed, TAK-788 should be permanently discontinued. Treatment with corticosteroids should be considered as appropriate.

8.7 Blinding and Unblinding

Because this is an open-label study, there will be no study drug blinding.

8.8 Description of Investigational Agents

TAK-788 drug product will be supplied as 40 mg capsules for oral dosing. TAK-788 is manufactured under current Good Manufacturing Practice in accordance with approved procedures.

Midazolam is a short-acting benzodiazepine that is a probe substrate of CYP3A. Midazolam hydrochloride for oral and IV administration will be obtained from commercial sources. The precautions, warnings, contraindications, and AEs associated with midazolam therapy are included in the midazolam prescribing information.

Additional details regarding the description of TAK-788 and midazolam are provided in the pharmacy manual.

8.9 Preparation, Reconstitution, and Dispensation

Disruption to site visits due to the COVID-19 pandemic may require the site to use an alternative method for dispensing TAK-788 to ensure continuity of treatment. If allowed by country regulation/ethics committees, TAK-788 can be shipped DTP from the investigation site to the patient's home address via courier if needed. Additional details regarding study drug preparation and dispensation are provided in the pharmacy manual.

8.10 Packaging and Labeling

TAK-788 capsules will be supplied in white HDPE (high-density polyethylene) bottles with child-resistant caps with liner. Bottle labels will bear the appropriate label text as required by governing regulatory agencies. At a minimum, such text will include product name, product strength, number of capsules, and lot number.

8.11 Storage, Handling, and Accountability

The recommended storage condition for TAK-788 is controlled room temperature. Midazolam hydrochloride should be stored in accordance with the product's prescribing information. Storage area temperature conditions must be monitored and recorded daily. All temperature excursions must be reported to the sponsor for assessment and determination for continued use.

The study pharmacist or designee at the site will be responsible for handling and dispensing study drug, and completing associated documentary paperwork. Supplies will be shipped to the investigative site at appropriate intervals, depending on patient accrual. The site must use an appropriate dispensing log/accountability form provided by the sponsor, or an acceptable substitute approved by the sponsor. Each time study drug is dispensed to a patient, the following information must be recorded: the patient's initials, the patient's study number, drug product strength, quantity dispensed with the corresponding lot number, and the initials of the person dispensing the drug. These logs are to be maintained by the study pharmacist in the pharmacy

throughout the duration of the study and will be periodically verified by a representative of the sponsor.

The investigator is responsible for ensuring that the study drug provided to the patient and returned from the patient are accounted for and noted in source documentation.

All used bottles of study drug must be destroyed in an appropriate manner according to the standard practice at each study center. Destruction of such supplies will be documented, and a representative of the sponsor will verify disposition records. During the trial and at termination, patients must return all unused study drug supplies, and the return of these unused study drug supplies must be recorded. Returned supplies must not be redispensed. No other utilization of TAK-788 intended for use in this study is authorized by the sponsor. The principal investigator or his/her designee will be responsible for the appropriate handling and disposition of residual study drug. Each site is responsible for proper and careful destruction of study drug returned by patients.

Periodically, throughout and at the conclusion of the study, a representative of the sponsor will conduct an inventory of unused study drug. At the completion of the trial, a final study drug accountability review will be conducted. Any discrepancies must be investigated and all unused study drug must be destroyed on site per the standard operating procedures of the investigative site.

9.0 STUDY CONDUCT

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

9.1 Study Personnel and Organizations

Contact information for the project clinician, the central laboratory conducting the analysis of PK samples, coordinating investigator, interactive response technology provider, and contract research organization (CRO) team may be found in the study manual. The list of investigators is available in the sponsor's investigator database.

9.2 Arrangements for Recruitment of Patients

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

9.3 Study Procedures

Timing of assessments and procedures are outlined in the Schedule of Events (SOE) (Appendix A Table A-1 for Part A; and, Table A-3 for Part B). Timing of PK and pharmacodynamic assessments in Part A is specified in Appendix A Table A-2. The EOT visit is to be completed only when study dosing is permanently withdrawn (ie, either Part A or Part B of

the study). Safety procedures (ie, ECG, clinical laboratory tests, and vital signs) must be completed prior to dose administration, as applicable; all other procedures can be performed after study dosing. Unless otherwise noted, tests and procedures should be performed as scheduled in the SOEs.

During Part A of the study (Cycle 1: PK Cycle), study clinic visits will take place on Days 1, 2, 3, 24, 25, and 26. Blood samples for midazolam PK characterization will be collected over the 24-hour postdose period on Days 1, 2, 24, and 25. Blood samples for TAK-788 PK characterization will be collected on Days 24, 25, and 26. Patients will be closely monitored for respiratory and cardiac function (ie, pulse oximetry) after administration of midazolam on these days. Predose PK blood sample will be collected on Cycle 2 Day 1.

During Part B, study clinic visits will take place on Day 1 of each cycle for assessment of ECOG performance status, weight, and vital signs, and 12-lead ECGs (Cycle 2 only), physical examinations (PE) (symptom-directed on Day 1 of each cycle, with a full PE at EOT visit), and clinical laboratory tests. Predose PK blood sample will be collected on Cycle 2 Day 1. Imaging assessments will be conducted every 8 weeks (ie, on Day 28 [± 3 days] of every even-numbered cycle) up to Cycle 14, and every 12 weeks (ie, on Day 28 [± 3 days] every 3 cycles) thereafter. Part B, Day 1 assessments must be completed prior to study dosing, with the exception of AE assessments, which will be conducted both prior to and after study dosing. Treatment delays should not impact imaging schedule. Please refer to Appendix A Table A-1 for Part A and Table A-3 for Part B for timing of assessments. The timing of PK and pharmacodynamic assessments in Part A is specified in Appendix A Table A-2. Additional details are provided as necessary in the sections that follow.

Sites will make every effort to see patients in the clinic for assessments. In unavoidable circumstances, such as the COVID-19 public health emergency, exceptions can be made for alternative methods for conducting patient visits/assessments and ideally should be approved by the sponsor or designee. These methods may include remote visits being conducted by phone (eg, collection of AEs and monitoring) or video conferencing (Telehealth or Telemedicine, physician/patient preferred methodology), or alternative site/location (eg, collection of safety assessments). Remote visits and telemedicine must comply with national and local laws and regulations. Remote visits and telemedicine are not permitted during the first cycle. Such instances will be documented in the study records.

9.3.1 Informed Consent

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

Patients will be given an informed consent for review and signature; patients consenting via the eConsent, where this is available, will electronically sign consent forms (paper consents will be used if required by local regulations). eConsent provides the same information as that provided in written consent, but the electronic format may include multimedia components. It is important to note that eConsent is not meant to replace the important discussion between the participant

and site staff. As with traditional consenting, the site will continue to own the consenting process. The requirements of informed consent are described in Section 15.2

9.3.2 Enrollment

Patients will be considered enrolled after initial study dose has been administered; and, considered registered, prior to enrollment, after successful entry into the study interactive response technology (IRT) system. All screening procedures, as outlined in Table A-1 must be completed, and eligibility confirmed by the PI, prior to enrollment. Those patients not meeting eligibility criteria, are deemed screen-failures and noted as such (with reason for screen-failure) in source documentation.

9.3.3 Screening

Informed consent may be signed anytime prior to performance of any study-related procedure not part of standard medical care. However, the procedure performed under standard of care must meet the protocol requirements if used for screening. Screening assessments must be performed no more than 14 days before randomization. The allowable window for the disease assessment is 21 days before randomization. However, whenever feasible, baseline imaging should be performed as close as possible to randomization.

Patients who have signed informed consent and subsequently fail to meet the inclusion and/or exclusion criteria are defined as screen failures. Patients who screen fail may later be re-screened with prior sponsor approval. Any patient who is re-screened after screen failure must, in addition to the failed test, repeat only those screening tests that have fallen outside the specified screening period, as outlined in the SOE. Once the investigator determines that screening will not continue for a patient and the patient will not be enrolled in the study, the screen failure should be documented on the Eligibility Criteria eCRF.

All AEs and SAEs must be reported during the screening period until the patient has been determined to be a screen failure.

9.3.4 Patient Demographics

Patient demographic characteristics will be collected at screening and will include, age, sex, race, and ethnicity (optional depending on country).

9.3.5 Medical/Surgical History

A complete medical history will be taken at screening. Information to be documented includes relevant past illnesses, smoking history, ongoing medical conditions, and surgical procedures (not related to the primary diagnosis).

9.3.5.1 Diagnosis and Disease History

The initial cancer diagnosis and the current cancer stage at the time of screening, along with tumor histology, mutation status and all sites of disease, should be recorded.

9.3.5.2 Prior Cancer Therapy

Information regarding prior cancer therapy will be taken at screening, and includes cancer-related surgical procedures, radiation, and systemic therapies. Surgical procedures include curative and palliative, as well as diagnostic procedures (eg, biopsy). Radiation will include both definitive and palliative treatment. Systemic therapy includes all regimens given, type of regimen (eg, neoadjuvant, adjuvant, for advanced/metastatic disease), each drug name in a regimen, the start and stop dates of each drug, the best response to the regimen, and the reason for discontinuation. Experimental or investigational therapy history must also be recorded.

9.3.6 Patient Height and Weight

The patient's height will be measured during screening (within 14 days before the first dose of study drug).

The patient's weight will be measured on Day 1 of each cycle and at EOT (Parts A and B).

9.3.7 Vital Signs

Vital signs will be measured at each visit before dose administration of study drug(s) in Parts A and B, after 3 to 5 minutes in the supine position, and will include measurements of diastolic and systolic blood pressure, respiratory rate, heart rate, pulse oximetry, and body temperature. Any change in a vital sign measurement that is judged by the investigator as clinically significant will be recorded on both the source documentation and in the eCRF as an AE, and monitored as described in Section 10.3.

9.3.8 ECOG Performance Status

ECOG performance status will be assessed and recorded at screening on Day 1 of each cycle, and at EOT. Please refer to Appendix D for the ECOG scale.

9.3.9 ECG

A 12-lead ECG will be performed prior to dosing at timepoints specified in the SOE (Appendix A). Repeat testing during screening and throughout the study is permitted. In addition to the prespecified time points, additional ECGs may be performed at the investigator's discretion to ensure patient safety. ECG is also considered at any time the study patients complain of a lightheadedness, near syncope, or syncope with or without palpitations. The ECGs will be performed at the study sites, to be conducted and interpreted in accordance to local institutional practices and confirmed by the PI. Any change in ECG measurement that is judged by the investigator as clinically significant will be recorded on both the source documentation and in the eCRF as an AE, and monitored as described in Section 10.3.

9.3.10 Physical Examination

A physical examination will be completed in accordance with the study site's standard of care at the times specified in Appendix A Table A-1 for Part A; and, Table A-3 for Part B. Additional symptom-directed evaluations may be performed.

A complete physical examination must be performed at screening, the extent of which should be consistent with the patient's medical history and underlying disease. Subsequent physical examinations may be directed to relevant findings.

The EOT physical examination should be a complete physical examination. The physical examination at the end of the 30-day follow-up period may be directed to any relevant findings.

9.3.11 Echocardiogram/MUGA Scan for Left Ventricular Ejection Fraction

Conduct cardiac monitoring, including assessment of left ventricular ejection fraction (LVEF) at specified timepoints in the SOE (Appendix A). Cardiac monitoring and cardiology consultation may be done during treatment at other times according to medical judgment. Assess LVEF in patients who develop relevant cardiac signs or symptoms during treatment.[22] Any change in cardiac monitoring that is judged by the investigator as clinically significant will be recorded on both the source documentation and in the eCRF as an AE, and monitored as described in Section 10.2.

9.3.12 Clinical Laboratory Evaluations

Hematology, serum chemistry, and serology assessments will be performed locally, with reference ranges provided in the electronic data capture (EDC) system. Clinical laboratory evaluations will be performed according to the SOE throughout the study.

Instructions for handling and shipping clinical laboratory samples are provided in the study laboratory manual.

9.3.12.1 Hematology, Clinical Chemistry and Serology

Clinical laboratory tests that will be performed are listed in Table 9.a. Blood samples for hematology and clinical chemistry tests will be collected as specified in Appendix A Table A-1 for Part A and Table A-3 for Part B. In extenuating circumstances, such as the COVID-19 public health emergency, patients may use alternative site/location for the collection of clinical laboratory test if approved by the sponsor or designee. Such instances will be documented in the study records.

HBV and HCV testing will be performed at screening. As appropriate and according to local guidelines for the management of HBV infection, HBV screening may include the following: HBsAg, hepatitis B surface antibody, and hepatitis B core antibody. Patients who are HBsAg positive will also be tested for HBV DNA. HBsAg-positive patients are allowed to enroll if HBV DNA is below 1000 copies/mL in the plasma with HBV DNA monitoring every 12 weeks. Initiation of antiviral treatment should follow local practice if HBV DNA >1000 copies is detected in the plasma during the study. HCV screening will include HCVAb. Patients who test positive for HCVAb will also be tested for HCV RNA at screening.

Table 9.a Clinical Laboratory Tests

Hematology	Serum Chemistry
• Hemoglobin. • WBC count with 5-part differential (lymphocytes, monocytes, neutrophils, eosinophils, basophils). • Platelet count.	• Albumin. • Total protein. • Alkaline phosphatase (ALP). • Alanine transaminase (ALT/serum glutamic pyruvic transaminase [SGPT]). • Aspartate transaminase (AST/serum glutamic oxaloacetic transaminase [SGOT]). • Amylase. • Bilirubin (total and direct/indirect). • Blood urea nitrogen (BUN). • Calcium. • Creatinine. • Chloride. • Glucose. • Lipase. • Phosphorous. • Magnesium. • Potassium. • Sodium. • Bicarbonate or total carbon dioxide.

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; LDH: lactate dehydrogenase; SGOT: serum glutamic oxaloacetic transaminase; SGPT: serum glutamic pyruvic transaminase; WBC: white blood cell.

Any change in clinical laboratory values that is judged by the investigator as clinically significant will be recorded on both the source documentation and in the eCRF as an AE, and monitored as described in Section 10.3.

9.3.13 Pregnancy Test

A serum or urine pregnancy test will be performed for women of childbearing potential during screening and within 1 day before the first dose of study drug on Cycle 1 Day 1.

The test results must be negative and available before the first dose of study drug is administered. Pregnancy testing must be conducted every 4 weeks thereafter and at EOT Additional pregnancy testing may be required or recommended according to local guidelines and regulations.

Pregnancy tests will not be performed for women who are not of childbearing potential (status posthysterectomy, postbilateral oophorectomy, or postmenopausal [defined as amenorrhea for at least 12 months]).

9.3.14 AEs

Monitoring of AEs, serious and nonserious, will be conducted throughout the study as specified in Appendix A Table A-1 for Part A; and Table A-3 for Part B.

Please refer to Section 10.0 for details regarding definitions, documentation, and reporting of AEs and serious adverse events (SAEs).

9.3.15 Concomitant Medications and Procedures

Concomitant medications and procedures will be recorded in the electronic case report form (eCRF) from the date the informed consent is signed through the 30-day follow-up period following EOT. Please refer to Section 8.3 for a description of excluded concomitant medications and procedures, and Section 8.4 for a description of permitted concomitant medications and procedures during the study.

9.3.16 Disease Assessment

Patients will undergo CT and MRI scanning with contrast, (unless contrast media is contraindicated) to monitor and assess disease progression using RECIST version 1.1 (see Appendix G).

At screening, disease assessment must include imaging of the chest, abdomen, pelvis, and brain using appropriate radiological procedures (computed tomography [CT] scans or MRI with contrast, unless contrast media is contraindicated). Imaging of the brain (contrast-enhanced MRI is preferred) is required at screening for all patients, and will be repeated post-baseline for patients with CNS metastases at baseline.

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.

Disease assessment by CT or MRI scan will be performed at screening (ie, as close as possible to Day 1 of Cycle 1, but no more than 21 days before the first dose of TAK-788 on Day 1 of Cycle 1), and at 8-week intervals thereafter (ie, on Day 28 [±3 days] of every even-numbered cycle) through 14 cycles after the initial dose of TAK-788, and every 3 cycles thereafter until PD (Appendix A Table A-1 for Part A; and, Table A-3 for Part B). Treatment delays should not impact imaging schedule.

More frequent imaging is recommended at any time, if clinically indicated; confirmation of complete response (CR) or partial response (PR) may be performed at least 4 weeks after the initial response. In extenuating circumstances during the COVID-19 public health emergency, patients may use alternative site for imaging if approved by the sponsor or designee.

In the event of antitumor response, the sponsor may request electronic images for those patients who demonstrate tumor reduction.

9.3.17 PK Measurements

Serial blood samples for the determination of plasma concentrations of midazolam and its metabolite 1-hydroxymidazolam will be collected during Part A (Cycle 1: PK Cycle), on Days 1, 2, 3 (ie, Day 2: 24 hours), 24, 25, and 26 (ie, Day 25: 24 hours), as described in Appendix A Table A-2. Additional blood samples for the determination of plasma concentrations of TAK-788 and its active metabolites AP32960 and AP32914 will be collected on Days 24, 25, and 26 of Cycle 1 as well as Day 1 of Cycle 2 (predose), with additional serial blood samples to be collected on Day 24 (postdose), as described in Appendix A Table A-2. The exact date and time of each PK sample collection should be recorded.

Plasma concentrations of midazolam, 1-hydroxymidazolam and, TAK-788, AP32960, and AP32914 will be measured using validated liquid chromatography-tandem mass spectrometry assays. Details regarding the preparation, handling, and shipping of the PK samples are provided in the study manual.

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9.3.19 Patient Dosing Diary

A patient dosing diary will be completed during Part A and Part B of the study. Patients are to bring unused TAK-788 and the dosing diary with them to each clinic visit. The study center staff will check the diary and the patient's supply of TAK-788 to assess adherence to the treatment regimen. In case of extenuating circumstances that prevent a patient from attending the study site (eg, the COVID-19 pandemic), TAK-788 drug packs and dosing diaries should be returned at the next available on-site clinic visit.

Please refer to the study manual for complete instructions.

9.3.20 End-of-Treatment Assessments

End-of-Treatment assessments must be performed within 14 days of the patient's last dose of study drug or the patient/investigator decision to discontinue study treatment, whichever occurs

later. Physical examinations, laboratory tests (hematology, chemistry), and ECG can be omitted if they had been previously performed within 14 days since the last assessments and if, in the investigator's judgment, significant change is unlikely. Disease assessment does not need to be repeated if obtained within 28 days of last dose.

9.3.21 30 Days After Last Dose

The 30 Days After Last Dose assessments must be performed within 30 days (±7 days) after the last dose of study treatment. Physical examinations, laboratory tests (hematology, chemistry), and ECG can be omitted if the visit occurs within 10 days of the End-of-Treatment assessment and there have been no clinically significant findings. Any new systemic anticancer therapies that the patient has begun to receive since the end of treatment should be reported at this visit. For both the End-of-Treatment and 30 Days After Last Dose assessments, information may be collected from tests performed for the study or as part of the patient's routine medical care.

9.4 Completion of Study Treatment (for Individual Patients)

Patients will be considered to have completed study treatment at the last dose of TAK-788 or when the investigator and patient decide that the patient will receive no further TAK-788, whichever occurs later.

9.5 Completion of Study (for Individual Patients)

A patient will be considered to have completed the study at the completion of 30 days after last day follow-up visit or at completion of a total of 24 cycles of treatment. Subjects not continuing on study beyond Part A, must complete End of Treatment visit and 30 days after last dose visit.

9.6 Discontinuation of Treatment With Study Drug

Study drug must be permanently discontinued for patients meeting any of the following criteria:

- Patient meets the discontinuation rules for pneumonitis.
- Pregnancy.
- Entry into another therapeutic clinical study or start of new anticancer therapy.

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

- AE.
- Protocol deviation.
- Clinical progressive disease.
- Documented Progression of disease based on RECIST v1.1.
- Note: Treatment of patients with TAK-788 may be continued, despite progression by RECIST v1.1 (see Appendix G), at the discretion of the investigator, if there is still evidence of clinical benefit. Takeda should be informed if this decision is made.

- Study terminated by sponsor.
- Withdrawal by subject.
- Lost to follow-up.
- Other.

The primary reason for study drug discontinuation will be recorded in the eCRF.

Treatment with study drug may also be discontinued due to AE or as a result of patient decision and/or PI judgement (noting AE, or other as causality for discontinuation in study CRF, as applicable).

Once study drug has been discontinued, all study procedures outlined for the EOT visit will be completed as specified in Appendix A Table A-1 for Part A; and Table A-3 for Part B. The patient will be followed for 30 days after the EOT visit for drug safety.

In the case of study termination by the sponsor, eligible patients may continue TAK-788 as described in Section 6.3.5.

9.7 Withdrawal of Patients From Study

A patient may choose to be withdrawn from the study at any time.

Patients will be considered a study withdrawal for any of the following reasons:

- Lost to follow-up.
- Study terminated by sponsor.
- Withdrawal by subject.
- Death.
- PD.
- Initiation of new anticancer therapies.
- Other (outcomes of study withdrawal, not defined by categories provided).

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

9.8 Study or Site Termination

If the sponsor, investigator, medical monitor, or regulatory agencies discover conditions during the study that indicate that the study or site should be terminated, this action may be taken after appropriate consultation between the sponsor and the investigator (in the case of site termination). Conditions that may warrant termination of the study include, but are not limited to:

- The discovery of a serious, unexpected, or unacceptable risk to subjects enrolled in the study.

- The decision on the part of the sponsor to suspend or discontinue testing, evaluation, or development of the study drug.
- Submission of knowingly false information from the research facility to the sponsor, medical monitor, or regulatory authorities.
- Insufficient adherence to protocol requirements.

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 AE Definition

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

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

10.1.3 SAE Definition

SAE means any untoward medical occurrence that at any dose:

- Results in **death.**
- Is **life-threatening** (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient **hospitalization or prolongation of an existing hospitalization** (see clarification in the paragraph in Section 10.2 on planned hospitalizations).
- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**.

- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life-threatening, or require hospitalization, but may be considered serious when, on the basis of appropriate medical judgment, it may jeopardize the patient, require medical or surgical intervention to prevent one 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 laboratory abnormality, will be determined using the NCI CTCAE, version 5.0, dated 27 November 2017 [1]. Clarification should be made between an SAE and an AE that is considered severe in intensity (Grade 3 or 4) because the terms *serious* and *severe* are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000/mm^3 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

10.2 Procedures for Recording and Reporting AEs and SAEs

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

Regardless of causality, SAEs must be reported (see Section 10.3 for the period of observation) by the investigator to the Takeda Global Pharmacovigilance department or designee within 24 hours of becoming aware of the event. This will be done by transmitting an EDC SAE report. If transmission of an EDC SAE report is not feasible, then a facsimile of the completed Takeda paper-based SAE form will be sent. In case of fax, site personnel need to confirm successful transmission of all pages and include an e-mail address on the fax cover sheet so that an acknowledgment of receipt can be returned via e-mail within 1 business day. A sample of the paper-based SAE form and processing directions are in the study manual. Information in the SAE report or form must be consistent with the data provided on the eCRF.

If information not available at the time of the first report becomes available at a later date, then the investigator will transmit a follow-up EDC SAE report (or a paper-based SAE form if an

EDC SAE report is not feasible) or provide other documentation immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

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

Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the 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.

Severity (toxicity grade) for each AE, including any laboratory abnormality, will be determined using the NCI CTCAE, version 5.0, dated 27 November 2017 [1]. The criteria are provided in the study manual. Selected asymptomatic laboratory values may also constitute AEs as defined by the NCI CTCAE.

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

10.3 Monitoring of AEs and Period of Observation

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

- AEs 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 will be reported to the Takeda Global Pharmacovigilance department or designee from the signing of informed consent 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 sending a completed pregnancy form to the Takeda Global Pharmacovigilance department or designee. The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor must also be contacted immediately by sending a completed pregnancy form to the Takeda Global Pharmacovigilance department or designee. 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 email addresses provided below.

A medication error is a preventable event that involves an identifiable patient and 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 email addresses provided below.

Product	Call Center	Phone Number	Email	Fax
TAK-788	PPD			

Product complaints and medication errors in and of themselves are not AEs. If a product complaint or a medication error results in an SAE, the SAE should be reported.

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

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

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

After completion of the entry process, computer logic checks will be run to identify items such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designee) 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 the 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 designee) will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal-sensitive paper, source worksheets, all original signed and dated ICFs, subject authorization forms regarding the use of personal health information (if separate from the ICFs), electronic copies of eCRFs including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities and the sponsor (or 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 (R2) Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (R2) (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 (R2)

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.

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

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

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

A data review will be conducted before database lock. This review will assess the accuracy and completeness of the study database, patient evaluability, and appropriateness of the planned statistical methods.

PK and safety analyses will be conducted after all patients complete Cycle 1 (Part A) of the study.

13.1.1 Analysis Sets

13.1.1.1 PK-Evaluable Population

PK-Evaluable Population

Patients will be considered PK-evaluable if they meet **all** of the following criteria during study Part A, Cycle 1:

1. Received the protocol-specified dosing regimen without dose reductions prior to Day 26.
2. Experienced no dose interruptions within 1 week prior to Day 24.
3. Experienced no more than 1 day of dose interruption within the first 14 days of TAK-788 treatment.
4. Did not receive any excluded concomitant medications through the completion of PK sampling (Day 26).

The PK-evaluable population will be used for all PK analyses. Assessment of the PK-evaluable population will be conducted when dosing and safety (ie, vomiting) data become available and prior to study closure.

13.1.1.2 Safety Population

The safety population is defined as all patients who received at least 1 dose of any study drug (TAK-788 or midazolam). The safety population will be used for all safety analyses.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized, including sex, age, race, weight, height, and other variables as appropriate.

13.1.3 PK Analysis

In Part A (Cycle 1: PK Cycle), individual and mean plasma concentration data for midazolam and its metabolite 1-hydroxymidazolam after oral dosing of midazolam on Days 1 and 24 and IV dosing of midazolam on Days 2 and 25 will be plotted over time and listed by patient in the absence and presence of TAK-788. Plasma PK parameters of midazolam and 1-hydroxymidazolam for individual patients after oral and IV dosing of midazolam in the absence and presence of TAK-788 will be derived using noncompartmental analysis methods. Plasma concentrations and PK parameters (including but not limited to AUC_{∞}, C_{max}, and t_{max}) of midazolam and 1-hydroxymidazolam in the presence and absence of TAK-788 will be summarized using descriptive statistics.

For the estimation of the effect of TAK-788 on the PK of oral- and IV-dose midazolam, the ratios of geometric mean midazolam AUC_{∞} (or area under the plasma concentration-time curve from time 0 to time [AUC_t]) and C_{max} (in the absence and presence of TAK-788) and the associated 2-sided 90% CIs will be calculated on the basis of the within-patient variance using a mixed-effects analysis of variance (ANOVA) model fitting terms for treatment (midazolam in the absence and presence of TAK-788). The patient will be treated as a random effect in the model. After log transformation, AUC_{∞} and C_{max} will be separately analyzed. Point estimates and adjusted 90% CIs for the difference in treatment will be calculated and then exponentially back transformed to provide point and CI estimates for the ratios of interest.

The oral bioavailability of midazolam and the 1-hydroxymidazolam to midazolam AUC ratios following IV and oral midazolam dosing will be descriptively summarized, in the absence and presence of TAK-788.

Plasma concentrations of TAK-788 and its active metabolites AP32960 and AP32914 will be listed by patient and summarized using descriptive statistics. Individual and mean plasma concentrations of TAK-788, AP32960, and AP32914 will be plotted over time. Plasma PK parameters for TAK-788, AP32960, and AP32914 for individual patients will be derived using noncompartmental analysis methods and listed by patient and summarized using descriptive statistics.

13.1.4 Safety Analysis

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

TEAEs that occur after administration of the first dose of any study drug and through 30 days after the last dose of TAK-788 will be tabulated.

AEs will be tabulated using the MedDRA and will include, but are not limited to, the following subsets:

- TEAEs.
- Drug-related TEAEs.
- Grade 3 or higher TEAEs.
- Grade 3 or higher drug-related TEAEs.
- Most commonly reported TEAEs (ie, those events occurring in ≥10% of all patients).
- TEAEs resulting in study drug dose reduction.
- TEAEs resulting in study drug dose modification (as defined as dose interruption, dose reduction, or permanent discontinuation).
- SAEs.

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

Actual values (and/or change from baseline) in clinical laboratory variables, weight, and vital signs will be summarized by scheduled time point using descriptive statistics. Mean or median key laboratory variables over time will be plotted. Shift tables for clinical laboratory variables will be generated to show changes in NCI CTCAE, version 5.0 grade from the baseline value to the worst postbaseline value.

All concomitant medications collected from screening through the study period will be classified to generic terms according to the WHO Drug Dictionary.

Additional safety analyses may be performed to most clearly enumerate rates of toxicities and to further define the safety profile of TAK-788.

CCI

[redacted]

CCI [redacted]

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned for this study.

13.3 Determination of Sample Size

It is anticipated that approximately 26 patients will be enrolled in this study to obtain approximately 12 PK-evaluable patients. The sample size calculation was based on the expected 2-sided 90% CI for the difference in the paired, log-transformed AUC_∞ mean values for midazolam in the absence and presence of TAK-788. CCI [redacted]

Assuming that the AUC_∞ ratio for midazolam in the presence versus absence of TAK-788 is 1, with a sample size of 12, the 90% CI for the AUC_∞ ratio is expected to be 0.82 to 1.23 on the basis of the variance assumptions. Assuming that the AUC_∞ ratio for midazolam in the presence versus absence of TAK-788 is X, with a sample size of 12, the 90% CI for the AUC_∞ ratio is expected to be 0.82X to 1.23X on the basis of the variance assumptions.

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.

In the event a monitor cannot visit the site in a timely manner due to the COVID-19 pandemic, alternative monitoring approaches, such as remote source data verification or telephone contact, may be used to ensure data quality and integrity and maintain patient safety. Alternative monitoring approaches should be used only where allowed by applicable local regulations and permitted by the IRB/IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or designee (as long as blinding is not jeopardized) including, but not limited to, the investigator's binder, study medication, subject medical records, informed consent documentation,

documentation of subject authorization to use personal health information (if separate from the ICFs), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the subject's source documents. 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 the primary study assessment.

The sponsor will assess any protocol deviation; if it is likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated, it may be reported to regulatory authorities as a serious breach of GCP and the protocol.

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 United States [US] FDA, the United Kingdom [UK] Medicines and Healthcare products Regulatory Agency [MHRA], the Pharmaceuticals and Medical Devices Agency of Japan [PMDA]). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, 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 state and federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those American sites unwilling to provide names and titles of all members because of privacy and conflict of interest concerns should instead provide a Federalwide Assurance number or comparable number assigned by the US Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the investigator's brochure, a copy of the ICF, and, if applicable, subject recruitment materials and 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 its exact protocol title, number, and version date; identify versions of other documents (eg, ICF) reviewed; and state the approval date. If required by country or regional regulations or procedures, approval from the competent regulatory authority will be obtained before commencement of the study or implementation of a substantial amendment. 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 the 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 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, and 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. If 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 to participate in the study. If the subject, or the subject's legally acceptable representative, determines that he or she will participate in the study, then the ICF and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and before the subject enters into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using a ballpoint pen with either blue or black ink. The investigator must also sign and date the ICF and subject authorization (if applicable) at the time of consent and before the subject enters into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original ICF, 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 be linked to the sponsor's clinical study database or documentation only via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

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

Copies of any subject source documents that are provided to the sponsor must have certain identifying personal information removed, eg, 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 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 by Takeda policy/standards. Takeda contact information, along with investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

As needed, Takeda and investigator/site contact information may be made public to support participant access to trials via registries. In certain situations/registries, Takeda may assist participants or potential participants in finding 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 preferred by 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 (clinicaltrialsregister.eu, if applicable), and other publicly accessible websites (including the Takeda corporate site) and registries, as required by Takeda policy/standards, applicable laws, and/or regulations.

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

15.5 Insurance and Compensation for Injury

Each 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. Please refer to the clinical study site agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

16.0 REFERENCES

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Appendix A Schedule of Events

Table A-1 Schedule of Events for Part A (Cycle 1, 30-Day PK Cycle)

Subjects not continuing on study beyond Part A, must complete an EOT visit and 30 day follow up visit as described in Table A-3.

Assessment	Screening [a] ≤14 days to Day 1	Cycle 1					
		Day 1	Day 2	Day 3	Day 24	Day 25	Day 26
Informed consent [a]	X						
Inclusion/exclusion criteria	X						
Demographics	X						
Medical history	X						
Prior anticancer therapy	X						
Height	X						
Weight	X	X					
Vital signs [b]	X	X	X	X	X	X	X
ECOG performance status	X	X					
12-lead ECG [c]	X	X	X	X	X	X	
Echocardiogram/MUGA for LVEF [d]	X						
Physical examination [e]	X	X					X
Clinical laboratory tests [f]	X	X					
Serology [g]	X						
Pregnancy test [h]	X	X					
Adverse events (including SAEs)	Recorded from the signing of the informed consent form through 30 days after the last dose of study drug.						
Concomitant medications and procedures	Recorded from the signing of the informed consent form through 30 days after the last dose of study drug.						
Imaging assessments [i]	X						
Blood samples for PK		X	X	X	X	X	X
Blood samples for pharmacodynamics and other biomarkers [j]		X			X		
Midazolam 3 mg single PO dose		X			X		
Midazolam 1 mg single IV dose			X			X	

Assessment	Screening [a] ≤14 days to Day 1	Cycle 1					
		Day 1	Day 2	Day 3	Day 24	Day 25	Day 26
TAK-788 QD administration [k]				X (Days 3-30)			
Dispensation of TAK-788 and patient diary			X				
Assessment of patient dosing diary					X	X	X

CT: computed tomography; β-hCG: β-human chorionic gonadotropin; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOT: end of treatment; IV: intravenous; LVEF: left ventricular ejection fraction; MUGA: multigated acquisition; PK: pharmacokinetics.

NOTE: Variations of visit schedule during cycle 1 for PK evaluation will be evaluated and approved by the sponsor on a case by case basis.

[a] Informed consent may be signed anytime prior to randomization and must be signed before performance of any study-related procedure not part of standard medical care. Screening assessments must be performed no more than 14 days before C1D1. The allowable window for the disease assessment is 21 days before C1D1. However, whenever feasible, baseline imaging should be performed as close as possible to C1D1.

[b] Vital signs will be measured at each visit before dose administration of TAK-788 study drug(s) in Parts A and B, after 3 to 5 minutes in the supine position, and will include measurements of diastolic and systolic blood pressure, respiratory rate, heart rate, pulse oximetry, and body temperature.

[c] Procedures to be performed before dosing.

[d] Echocardiogram/MUGA scan must be performed at screening for LVEF and may be performed at other times according to medical judgement.

[e] A complete physical examination is to be performed during screening. Symptom-directed physical examinations are to be performed afterwards.

[f] Clinical laboratory tests (hematology, and clinical chemistry) to be performed on Day 1 (with -2 day window for C1D1) of each cycle before dosing. See Table 9.a for the list of tests to be performed.

[g] HBV screening may include the following: HBsAg, hepatitis B surface antibody, and hepatitis B core antibody, in accordance with local institutional practices. Patients who test positive for HBsAg will also be tested for HBV DNA at screening. HCV screening will include HCVAb. Patients who test positive for HCVAb will also be tested for HCV RNA at screening (see Section 9.3.12.1).

[h] For all women of childbearing potential, urine or serum β-hCG test is to be performed within 1 day before first dose of study drug. Refer to Section 9.3.13 for additional information.

[i] Imaging baseline disease assessments during screening should be conducted ≤21 Days prior to Cycle 1 Day 1, yet as close to as possible to Day 1. Assessments will consist of CT/MRI scans of the chest, abdomen, brain, and pelvis for all patients. Imaging of the brain (contrast-enhanced MRI is preferred) is required at screening for all patients, and will be repeated postbaseline for patients with CNS metastases at baseline. (see Section 9.3.16).

[j] Biomarker blood samples are to be collected at predose on Days 1 and 24 to measure plasma concentrations of 4β-hydroxycholesterol and cholesterol; Day 1 predose sample will include assessment for expression of circulating tumor DNA.

[k] TAK-788 160 mg QD is to be administered from Day 3 through Day30 in Part A and continues to subsequent cylces. TAK-788 dose may be reduced based on dose modification guidelines to 120 or 80 mg in patients who do not tolerate the 160 mg dose.

Table A-2 PK and Pharmacodynamic Blood Sampling Schedule

	Cycle 1								Cycle 2
	Day 1		Day 2	Day 24			Day 25		Day 1
Blood Sampling Time	**Oral Midazolam PK [a]**	**PD [b]**	**IV Midazolam PK [a]**	**Oral Midazolam PK [a]**	**TAK-788 PK [c]**	**PD [g]**	**IV Midazolam PK [a]**	**TAK-788 PK [c]**	**TAK-788 PK [c]**
Predose (within 1 hour before dosing) [f]	X	X	X	X	X	X		X	X
0.25 hours postdose (±3 minutes)	X			X					
0.5 hours postdose (±5 minutes)	X			X					
0.75 hour postdose (±10 minutes)	X			X					
1 hour postdose (±15 minutes)	X			X	X				
1.5 hours postdose (±15 minutes)	X			X					
2 hours postdose (±15 minutes)	X			X	X				
4 hours postdose (±30 minutes)	X			X	X				
6 hours postdose (±1 hour)	X			X	X				
8 hours postdose (±1 hour)	X			X	X				
Predose (within 1 hour before dosing) [d]			X				X		
Immediately EOI (+3 minutes) [e]			X				X		
10 minutes EOI (±3 minutes)			X				X		
20 minutes EOI (±3 minutes)			X				X		
30 minutes EOI (±5 minutes)			X				X		
1 hour EOI (±15 minutes)			X				X		
2 hours EOI (±15 minutes)			X				X		
4 hours EOI (±30 minutes)			X				X		
6 hours EOI (±1 hour)			X				X		
8 hours EOI (±1 hour)			X				X		
24 hours EOI (±1 hours) [f]			X [f]				X [f]	X	

EOI: end of infusion; IV: intravenous; PD: pharmacodynamics; PK: pharmacokinetics.

[a] Blood samples for the measurement of concentrations of midazolam and its metabolite 1-hydroxymidazolam in plasma.

[b] Blood samples for the measurement of concentrations of 4β-hydroxycholesterol and cholesterol in plasma and other biomarkers.

[c] Blood samples for the measurement of concentrations of TAK-788 and its metabolites AP32960 and AP32914 in plasma.

Table A-2 PK and Pharmacodynamic Blood Sampling Schedule

	Cycle 1								Cycle 2
	Day 1		Day 2	Day 24			Day 25		Day 1
Blood Sampling Time	**Oral Midazolam PK [a]**	**PD [b]**	**IV Midazolam PK [a]**	**Oral Midazolam PK [a]**	**TAK-788 PK [c]**	**PD [g]**	**IV Midazolam PK [a]**	**TAK-788 PK [c]**	**TAK-788 PK [c]**

[d] Blood samples also serve as the 24-hour postdose blood samples for oral midazolam.

[e] It is critical that this blood sample is drawn immediately at the end of infusion with as little delay as possible.

[f] Blood sample to be collected before TAK-788 dosing. Days 2 and 25 24-hour PK samples will be collected predose on Days 3 and 26, respectively.

[g] Blood samples for the measurement of concentrations of 4b-hydroxycholesterol and cholesterol in plasma only.

Table A-3 Schedule of Events for Part B (Repeat 28-Day Treatment Cycles)

Assessment	Treatment Cycles [a]					EOT	30 Days After EOT Follow-up
	Cycle 2 (±3 days)	Cycle 3 (±3 days)	Every 4 Weeks	Every 8 Weeks	Every 12 Weeks, After 14 Cycles		
	Day 1 (±3 days) [b]	Day 1 (±3 days) [b]	Day 1 (±3 days) [b]	Day 1 (±3 days) [b]	Day 1 (±3 days) [b]		
Weight	X		X			X	
Vital signs [c]	X		X			X	X
ECOG performance status	X		X			X	
12-lead ECG [d]	X		C4D1, C7D1, and every 4 cycles following C7			X	
Echocardiogram/MUGA for LVEF [e]	X		C4D1 and C7D1 only			X	
Physical examination [f]	X		X			X	X
Clinical laboratory tests [g]	X		X			X	X
Serology [h]					X		
Pregnancy test [i]	X		X			X	
Adverse events (including SAEs)	Recorded from the signing of the informed consent form through 30 days after the last dose of study drug.						
Concomitant medications and procedures	Recorded from the signing of the informed consent form through 30 days after the last dose of study drug.						
Imaging assessments [j]	X [k]			X [k]	X [k]	X [k]	
TAK-788 QD administration [l]	X (Day 1-28 every treatment cycle)						
Assessment of patient dosing diary	X		X	X	X		
PK	X (predose)						

Table A-3 Schedule of Events for Part B (Repeat 28-Day Treatment Cycles)

Assessment	Treatment Cycles [a]					EOT	30 Days After EOT Follow-up
	Cycle 2 (±3 days)	Cycle 3 (±3 days)	Every 4 Weeks	Every 8 Weeks	Every 12 Weeks, After 14 Cycles		
	Day 1 (±3 days) [b]	Day 1 (±3 days) [b]	Day 1 (±3 days) [b]	Day 1 (±3 days) [b]	Day 1 (±3 days) [b]		
Biomarker [m]			X (C3 and C5 only)			X (at disease progression)	

AE: adverse event; CT: computed tomography; C: Cycle; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOT: end of treatment; β-hCG: β-human chorionic gonadotropin; LVEF: left ventricular ejection fraction; MRI: magnetic resonance imaging; MUGA: multigated acquisition; QD, once daily; SAE: serious adverse event.

[a] Treatment cycles are 28 days in duration and are to continue until disease progression, intolerable toxicity, or another discontinuation criterion is met.

[b] Assessments outlined for Day 1 must be performed prior to study dosing, with the exception of adverse event assessments which must be performed both prior to and after study dosing.

[c] Vital signs are to be measured just before dosing on Day 1 of each cycle; as needed throughout the study; and at EOT.

[d] ECGs will occur at C2D1, C4D1, C7D1, and every 4 cycles following C7 and continue throughout the treatment period and EOT.

[e] Echocardiogram/MUGA scan must be performed on C2D1, C4D1, C7D1, and EOT for LVEF and may be performed at other times according to medical judgment.

[f] Symptom-directed physical examinations will be performed on Day 1 of each cycle and at the 30-day follow-up visit. A complete physical examination is to be conducted at screening and EOT.

[g] Clinical laboratory tests (hematology, and clinical chemistry) are to be performed on Day 1 of each cycle before dosing and at EOT. See Table 9.a for the list of tests to be performed.

[h] HBV screening may include the following: HBsAg, hepatitis B surface antibody, and hepatitis B core antibody, in accordance with local institutional practices. Patients who test positive for HBsAg will also be tested for HBV DNA at screening. HCV screening will include HCVAb. Patients who test positive for HCVAb will also be tested for HCV RNA at screening (see Section 9.3.12.1).

[i] For all women of childbearing potential, a urine or serum β-hCG pregnancy test is to be performed within 1 day before first dose of study drug (Cycle 1 Day 1, Part A). The test results must be negative and available before the first dose of study drug is administered. Pregnancy testing must be conducted every 4 weeks (±3 days) thereafter and at EOT. Refer to Section 9.3.13 for additional information.

[j] CT/MRI is to be performed every 8 weeks, at the end of every even-numbered cycle (ie, 2, 4, 6, etc) up to Cycle 14, and every 12 weeks (ie, every 3 cycles) thereafter and at EOT. Imaging assessments will consist of CT scans of the chest, abdomen, and pelvis for all patients. Imaging of the brain (contrast-enhanced MRI is preferred) is required at screening for all patients, and will be repeated postbaseline for patients with CNS metastases at baseline (see Section 9.3.16).

[k] Imaging is to be performed at 8-week intervals in part B (ie, on Day 28 [±3 days] of every even-numbered cycle) through 14 cycles after the initial dose of TAK-788, and every 3 cycles thereafter until PD and at EOT. If there is PD during study treatment, imaging assessment need not be repeated at EOT. Imaging assessments will consist of CT scans of the chest, abdomen, and pelvis for all patients. Imaging of the brain (contrast-enhanced MRI is preferred) is required at screening for all patients, and will be repeated postbaseline for

Table A-3 Schedule of Events for Part B (Repeat 28-Day Treatment Cycles)

Assessment	Treatment Cycles [a]					EOT	30 Days After EOT Follow-up
	Cycle 2 (±3 days)	Cycle 3 (±3 days)	Every 4 Weeks	Every 8 Weeks	Every 12 Weeks, After 14 Cycles		
	Day 1 (±3 days) [b]	Day 1 (±3 days) [b]	Day 1 (±3 days) [b]	Day 1 (±3 days) [b]	Day 1 (±3 days) [b]		

patients with CNS metastases at baseline (see Section 9.3.16). Disease assessment at EOT does not need to be repeated if obtained within 28 days of last dose

[l] TAK-788 160 mg QD is to be administered once per day from Day 1 through Day 28 of each treatment cycle. TAK-788 dose may be reduced based on dose modification guidelines to 120 or 80 mg in patients who do not tolerate the 160 mg dose.

[m] Biomarker assessment will include circulating DNA to be evaluated at Cycle 3, and Cycle 5, as well as at the time of disease progression.

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 responsibilities imposed on investigators by the FDA are summarized in the Statement of Investigator (Form FDA 1572), which must be completed and signed before the investigator may participate in this study.

The investigator agrees to assume the following responsibilities by signing a Form FDA 1572:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.
4. 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.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56, ICH, and local regulatory requirements.
7. 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.
8. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH, and local regulations, are met.
9. 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.
10. 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.

11. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
12. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
13. 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 the investigator, including his or her name, address, and other identifying personal information. In addition, the investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the UK, US, and Japan), including the following:

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

The 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 the 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.

The 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 the investigator's own country.

The 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, 1982 [23].

Appendix E Drugs That Interact With the CYP3A Family of Cytochrome P450

Drugs listed in Table A-4 below are moderate inducers or inhibitors or strong inducers or inhibitors of the CYP3A family and are prohibited as concomitant medications with TAK-788, with the exception of nonsystemic use.

Table A-4 Schedule of Events for Drugs Inducing or Inhibiting CYP3A Metabolism That Prohibited Concomitant Medications With TAK-788

Moderate CYP3A Inducers [a]
bosentan efavirenz etravirine phenobarbital primidone
Strong CYP3A Inducers [a]
apalutamide carbamazepine enzalutamide mitotane phenytoin rifampin St John's wort
Moderate CYP3A Inhibitors [b]
aprepitant ciprofloxacin conivaptan crizotinib cyclosporine diltiazem dronedarone erythromycin fluconazole fluvoxamine imatinib tofisopam verapamil
Strong CYP3A Inhibitors [b]
boceprevir clarithromycin cobicistat danoprevir and ritonavir elvitegravir and ritonavir grapefruit juice idelalisib indinavir and ritonavir itraconazole ketoconazole lopinavir and ritonavir

nefazodone
nelfinavir
paritaprevir and ritonavir and (ombitasvir and/or dasabuvir)
posaconazole
ritonavir
saquinavir and ritonavir
telaprevir
telithromycin
tipranavir and ritonavir
troleandomycin
voriconazole

CYP: cytochrome P450.

This list is not intended to be exhaustive, and a similar restriction will apply to other agents that are known to strongly or moderately modulate CYP3A activity. Appropriate medical judgment is required. Please contact the sponsor with any queries.

[a] fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-3 (accessed 25 August 2020).

[b] fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-2 (accessed 25 August 2020).

Appendix F Drugs With a Risk of Torsades de Pointes

The website crediblemeds.org/everyone/composite-list-all-qtdrugs/ lists 4 categories of QT-prolonging drugs and may be used as a guide for this protocol. Categories include "Drugs with Known TdP Risk," "Drugs with Possible TdP Risk," "Drugs with Conditional TdP Risk," and "Drugs to be Avoided by Congenital Long QT Patients." The investigative site should register (under the "For Healthcare Providers" tab) to access these categories. If the investigative site does not wish to register, a composite list, including all categories, is available.

Drugs with a known risk of torsades de pointes are listed in Table A-5 below and are the only category of QT-prolonging drugs that are prohibited in this study.

Note: The website and table are only to be used as a guideline and are not comprehensive. It is the investigator's responsibility to ensure that any drugs under consideration have not been newly identified as causing torsades de pointes.

Table A-5 Drugs With a Known Risk of Causing Torsades de Pointes (Prohibited in This Study)

Generic Name	Brand Name	Class/Clinical Use
Aclarubicin	Aclacin, Aclacinomycine, Aclacinon, Aclaplastin, Jaclacin	Anticancer
Amiodarone	Cordarone, Pacerone, Nexterone	Antiarrhythmic / abnormal heart rhythm
Anagrelide	Agrylin, Xagrid	Phosphodiesterase 3 inhibitor / thrombocythemia
Arsenic trioxide	Trisenox	Anticancer / leukemia
Astemizole	Hismanal	Antihistamine / allergic rhinitis
Azithromycin	Zithromax, Zmax	Antibiotic / bacterial infection
Bepridil	Vascor	Antianginal / angina pectoris (heart pain)
Cesium chloride	Energy Catalyst	Toxin/ alternative therapy cancer
Chloroquine	Aralen	Antimalarial / malaria
Chlorpromazine	Thorazine, Largactil, Megaphen	Antipsychotic, antiemetic / schizophrenia, nausea, many others
Chlorprothixene	Truxal	Antipsychotic / schizophrenia
Cilostazol	Pletal	Phosphodiesterase 3 inhibitor/ intermittent claudication
Ciprofloxacin	Cipro, Cipro-XR, Neofloxin	Antibiotic / bacterial infection
Cisapride	Propulsid	GI stimulant / increase GI motility
Citalopram	Celexa, Cipramil	Antidepressant, SSRI / depression
Clarithromycin	Biaxin, Prevpac	Antibiotic / bacterial infection
Cocaine	Cocaine	Local anesthetic / anesthesia (topical)
Disopyramide	Norpace	Antiarrhythmic / abnormal heart rhythm
Dofetilide	Tikosyn	Antiarrhythmic / abnormal heart rhythm

Generic Name	Brand Name	Class/Clinical Use
Domperidone	Motilium, Motillium, Motinorm Costi, Nomit	Antinausea / nausea, vomiting
Donepezil	Aricept	Cholinesterase inhibitor / dementia (Alzheimer's disease)
Dronedarone	Multaq	Antiarrhythmic / abnormal heart rhythm
Droperidol	Inapsine, Droleptan, Dridol, Xomolix	Antipsychotic, antiemetic / anesthesia (adjunct), nausea
Erythromycin	E.E.S., Robimycin, EMycin, Erymax, Ery-Tab, Eryc Ranbaxy, Erypar, Eryped, Erythrocin Stearate Filmtab, Erythrocot, E-Base, Erythroped, Ilosone, MY-E, Pediamycin, Abboticin, Abboticin-ES, Erycin, PCE Dispertab, Stiemycine, Acnasol, Tiloryth	Antibiotic / bacterial infection, increase GI motility
Escitalopram	Cipralex, Lexapro, Nexito, Anxiset-E, Exodus, Esto, Seroplex, Elicea, Lexamil, Lexam, Entact, Losita, Reposil, Animaxen, Esitalo, Lexamil	Antidepressant, SSRI / depression (major), anxiety disorder
Flecainide	Tambocor, Almarytm, Apocard, Ecrinal, Flécaine	Antiarrhythmic / abnormal heart rhythm
Fluconazole	Diflucan, Trican	Antifungal / fungal infection
Gatifloxacin	Tequin	Antibiotic / bacterial infection
Grepafloxacin	Raxar	Antibiotic / bacterial infection
Halofantrine	Halfan	Antimalarial / malaria
Haloperidol	Haldol, Aloperidin, Bioperidolo, Brotopon, Dozic, Duraperidol, Einalon S, Eukystol, Halosten, Keselan, Linton, Peluces, Serenace, Serenase, Sigaperidol	Antipsychotic / schizophrenia, agitation
Hydroquinidine, dihydroquinidine	Serecor	Antiarrhythmic / arrhythmia
Hydroxychloroquine	Plaquenil, Quineprox	Antimalarial, anti-inflammatory / malaria, SLE, rheumatoid arthritis
Ibogaine	None	Psychedelic / narcotic addiction, unproven
Ibutilide	Corvert	Antiarrhythmic / abnormal heart rhythm
Levofloxacin	Levaquin, Tavanic	Antibiotic / bacterial infection
Levomepromazine (methotrimeprazine)	Nosinan, Nozinan, Levoprome	Antipsychotic / schizophrenia
Levomethadyl acetate	Orlaam	Opiate agonist / narcotic dependence
Levosulpiride	Lesuride, Levazeo, Enliva	Antipsychotic / schizophrenia
Mesoridazine	Serentil	Antipsychotic / schizophrenia
Methadone	Dolophine, Symoron, Amidone, Methadose, Physeptone, Heptadon	Opiate agonist / pain, narcotic dependence
Moxifloxacin	Avelox, Avalox, Avelon	Antibiotic / bacterial infection
Nifekalant	Shinbit	Antiarrhythmic / arrhythmia

Generic Name	Brand Name	Class/Clinical Use
Ondansetron	Zofran, Anset, Ondemet, Zuplenz, Emetron, Ondavell, Emeset, Ondisolv, Setronax	Antiemetic / nausea, vomiting
Oxaliplatin	Eloxatin	Antineoplastic agent / cancer
Papaverine HCl (Intra-coronary)	None	Vasodilator, coronary / diagnostic adjunct
Pentamidine	Pentam	Antifungal / fungal infection (pneumocystis pneumonia)
Pimozide	Orap	Antipsychotic / Tourette's disorder
Probucol	Lorelco	Antilipemic / hypercholesterolemia
Procainamide	Pronestyl, Procan	Antiarrhythmic / abnormal heart rhythm
Propofol	Diprivan, Propoven	Anesthetic, general / anesthesia
Quinidine	Quinaglute, Duraquin, Quinact, Quinidex, Cin-Quin, Quinora	Antiarrhythmic / abnormal heart rhythm
Roxithromycin	Rulide, Xthrocin, Roxl-150, Roxo, Surlid, Rulide, Biaxsig, Roxar, Roximycinv, Roxomycin, Rulid, Tirabicin, Coroxin	Antibiotic / bacterial infection
Sevoflurane	Ultane, Sojourn	Anesthetic, general / anesthesia
Sotalol	Betapace, Sotalex, Sotacor	Antiarrhythmic / abnormal heart rhythm
Sparfloxacin	Zagam	Antibiotic / bacterial infection
Sulpiride	Dogmatil, Dolmatil, Eglonyl, Espiride, Modal, Sulpor	Antipsychotic, atypical / schizophrenia
Sultopride	Barnetil, Barnotil, Topral	Antipsychotic, atypical / schizophrenia
Terfenadine	Seldane	Antihistamine / allergic rhinitis
Terlipressin	Teripress, Glypressin, Terlipin, Remestyp, Tresil, Teriss	Vasoconstrictor / septic shock
Terodiline	Micturin, Mictrol	Muscle relaxant / bladder spasm
Thioridazine	Mellaril, Novoridazine, Thioril	Antipsychotic / schizophrenia
Vandetanib	Caprelsa	Anticancer / cancer (thyroid)

Source: crediblemeds.org/everyone/composite-list-all-qtdrugs/ [Accessed 25 August 2020].
GI: gastrointestinal; SLE: systemic lupus erythematosus; SSRI: selective serotonin reuptake inhibitor.
Drugs generally accepted by the CredibleMeds QTDrug List Advisory Board to have a known risk of causing torsades de pointes.

Appendix G Response Evaluation Criteria in Solid Tumors (RECIST Version 1.1)

Note: These criteria are adapted from Eisenhauer et al [24].

Choosing Target Lesions

- Select up to 5 lesions (up to 2 per organ).
- Select largest reproducibly measurable lesions.
- If the largest lesion cannot be measured reproducibly, select the next largest lesion which can be.
- Add up LD (longest diameters) of non-nodal lesions (axial plane).
- Add short axis diameters of nodes.
- This is the SLD (sum of the longest diameters).

Non-Target Lesions

- All other sites of disease present at baseline and not classified as target lesions will be classified as non-target lesions, including any measurable lesions that were not chosen as target lesions.
- It is possible to record multiple non-target lesions involving the same organ as a single item on the eCRF (eg, "multiple enlarged pelvic lymph nodes").

Determining Response

- Assess at baseline and on study with consistent modalities (CT, MRI, PET/CT):
  - Measure target lesions and calculate SLD.
  - Visually assess non-target lesions.
  - Search for new lesions.
  - Combine these assessments into the overall response.

Target Lesion Response

Complete Response (CR)	• Disappearance of all extranodal target lesions. • All pathological lymph nodes must have decreased to <10 mm in short axis.
Partial Response (PR)	• At least a 30% decrease in the SLD of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD)	• SLD increased by at least 20% from the smallest value on study (including baseline, if that is the smallest) • The SLD must also demonstrate an absolute increase of at least 5 mm. (2 lesions increasing from 2 mm to 3 mm, for example, does not qualify).
Stable Disease (SD)	• Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
Non-evaluable (NE)	• One or more lesions cannot be evaluated due to missing data or poor image quality unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response (eg, PD based on other findings).

SLD: sum of the longest diameters.

Non-Target Lesion Response

Complete Response (CR)	• Disappearance of all extranodal non-target lesions • All lymph nodes must be non-pathological in size (<10 mm short axis) • Normalization of tumor marker level
Non-CR/Non-PD	• Persistence of one or more non-target lesions(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD)	• Unequivocal progression of existing non-target lesions. (Subjective judgment by experienced reader)
Unable to Evaluate (UE)	• One or more lesions cannot be evaluated due to missing data or poor image quality unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response (eg, PD based on other findings)

New Lesions

- Should be unequivocal and not attributable to differences in scanning technique or findings that may not be a tumor (does not have to meet criteria to be "measurable").
- If a new lesion is equivocal, continue to next time point. If confirmed at that time, PD is assessed at the date when the lesion was first seen.
- Lesions identified in anatomic locations not scanned at baseline are considered new.
- New lesions on ultrasound should be confirmed on CT or MRI.

Evaluation of Overall Time Point Response for Patients with Measurable Disease at Baseline

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	NE	No	PR
PR	Non-PD or NE	No	PR
SD	Non-PD or NE	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

NE: Not Evaluable.

Appendix H Protocol History

Date	Amendment Number	Amendment Type (for use in Europe only)	Region
03 September 2020	2	Substantial	Global
03 April 2020	01	Substantial	Global
14 February 2019	Initial Protocol	Not applicable	Global

Protocol Amendment 01 Summary and Rationale:

This document describes the changes in reference to the protocol incorporating Amendment 01. The primary reasons for this amendment are to:

- Provide clarification for some of the protocol language.
- Increase the number of planned patients to 26.
- Provide clarification of screening windows and rescreening.
- Provide clarification of inclusion and exclusion requirements.
- Provide updated information for potential effect of TAK-788 to cause embryofetal harm and relevant restrictions for patient reproductive behavior.
- Provide clarification for management of diarrhea and pneumonitis.
- Provide safety monitoring of left ventricular ejection fraction (LVEF).
- Provide instructions for Acknowledgement of Receipt when a serious adverse event (SAE) is submitted to Takeda or designee by facsimile (fax).

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

Protocol Amendment		
Summary of Changes Since the Last Version of the Approved Protocol		
Amendment Number 01	**Amendment Date 03 April 2020**	**Global**
Description of Each Change and Rationale		**Sections Affected by Change**
Description	***Rationale***	***Location***
1. Added separate inclusion criterion (No 6.f) for serum amylase (≤1.5 × upper limit of normal [ULN] unless the increased serum amylase is due to salivary isoenzymes).	Clarification	Section 2.0 Study Summary Section 7.1 Inclusion Criteria

Protocol Amendment		
Summary of Changes Since the Last Version of the Approved Protocol		
Amendment Number 01	**Amendment Date 03 April 2020**	**Global**
2. Added clarification of exclusion criterion for central nervous system (CNS) metastases (No 8) for previously treated, untreated, or progressing CNS lesions.	Clarification	Section 2.0 Study Summary Section 7.2 Exclusion Criteria
3. Added clarification of exclusion criterion for congestive heart failure (No 11.c) to include cardiac ejection fraction <50% by echocardiogram (ECHO) or multiple gated acquisition scan (MUGA).	Clarification	Section 7.2 Exclusion Criteria
4. Increased the number of planned patients to 26 and added that assessment of the PK-evaluable population will be conducted when dosing and safety (ie, vomiting) data become available and prior to study closure.	To adjust for non-evaluable subjects that may result from dosing and safety (ie, vomiting) issues.	Section 2.0 Study Summary Section 6.1 Overview of Study Design Section 6.2 Number of Patients Section 6.3.2.1 Study Duration Section 7.0 Study Population Section 13.1.1.1 PK-Evaluable Population Section 13.3 Determination of Sample Size
5. Added clarification that fasting for 2 hours prior to and 2 hours after oral midazolam dosing included consumption of water except during dose administration.	Clarification	Section 8.1 Study Drug Administration (Table 8.a)
6. Added potential effect of TAK-788 to cause embryofetal harm (based on embryofetal toxicity study in rats).	To provide updated safety information	Section 8.5.1.2 Pregnancy and Breastfeeding
7. Added clarification for management of diarrhea.	Clarification	Section 8.6.2 Diarrhea
8. Added clarification for management of pneumonitis.	Clarification	Section 8.6.4 Pneumonitis
9. Added new section for screening that describes the time windows relative to randomization, rescreening, and collection of AEs during screening.	Clarification	Section 9.3.3 Screening Schedule of Events Table Part A, footnote "a"
10. Added instructions for investigators to record clinically significant changes in vital sign measurements in the electronic case report form (eCRF) as an AE.	Clarification	Section 9.3.7 Vital Signs

Protocol Amendment		
Summary of Changes Since the Last Version of the Approved Protocol		
Amendment Number 01	**Amendment Date 03 April 2020**	**Global**
11. Added instructions for investigators to record clinically significant changes in electrocardiogram (ECG) measurements in the eCRF as an AE.	Clarification	Section 9.3.9 ECG
12. Added cardiac monitoring of left ventricular ejection fraction (LVEF) by echocardiogram/Multigated Acquisition (MUGA) Scan.	To provide monitoring of LVEF	Section 9.3.11 Echocardiogram/ MUGA Scan for Left Ventricular Ejection Fraction. Appendix A Schedule of Events Tables Part A and Part B, including footnote "d"
13. Added instructions for investigators to record clinically significant changes in clinical laboratory evaluations in the eCRF as an AE.	Clarification	Section 9.3.12.1 Hematology, Clinical Chemistry and Serology
14. Added language for acknowledgement of receipt when a serious adverse event (SAE) is submitted to Takeda or designee by facsimile.	Clarification	Section 10.2 Procedures for Reporting AEs and SAEs
15. Minor editorial revisions were made for clarification throughout the document.	Administrative	Throughout the protocol

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Approval	04-Sep-2020 12:31 UTC
	Biostatistics Approval	04-Sep-2020 12:58 UTC
	Clinical Pharmacology Approval	04-Sep-2020 13:10 UTC