Title: A Phase 1/2 Study of the Oral EGFR/HER2 Inhibitor TAK-788 in Japanese Non-Small Cell Lung Cancer Patients

NCT Number: NCT03807778

Protocol Approve Date: 12-JAN-2022

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

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

- Named persons or organizations associated with the study.
- Patient identifiers within the text, tables, or figures or in by-patient data listings.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

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

PROTOCOL

A Phase 1/2 Study of the Oral EGFR/HER2 Inhibitor TAK-788 in Japanese Non-Small Cell Lung Cancer Patients

A Phase 1/2 Study of TAK-788 in Japanese Patients

Sponsor:	Takeda Pharmaceutical Company Limited. 1-1, Doshomachi 4-chome, Chuo-ku, Osaka-shi, Osaka, Japan
Study Number:	TAK-788-1003
EudraCT Number:	Not applicable
Compound:	TAK-788
Date:	12 January 2022 **Amendment Number:** 06

Amendment History:

Date	Amendment Number	Region
17 October 2018	Initial Protocol	All sites
22 November 2018	Amendment No. 01	All sites
20 December 2019	Amendment No. 02	All sites
27 January 2020	Amendment No. 03	All sites
25 June 2020	Amendment No. 04	All sites
27 July 2020	Amendment No. 05	All sites
12 January 2022	Amendment No. 06	All sites

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

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

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

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

The names and contact information for the medical monitor and responsible medical officer are in the protocol annex.

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

SIGNATURES

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

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

[redacted] Date

[redacted] Date

[redacted] Date

1.3 Protocol Amendment 06 Summary of Changes

This section describes the changes in reference from Amendment No. 05 to Amendment No. 06. Minor grammatical and editorial changes are included for clarification purposes only. Full details on changes of text are given in Appendix H.

The primary reasons for this amendment are to:

- Add management and dose modification guidelines for decreased ejection fraction, cardiac failure and QTc interval prolongation deemed TAK-788 related.
- Update the list of drugs known to be associated with the development of Torsades de Pointes.
- 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, and accommodations to allow local patient assessments.

Protocol Amendment 06		
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 8.1 Study Drug Administration Section 9.4 Study Procedures Section 9.4.18 Disease Assessment Section 14.1 Study-Site Monitoring Visits	Update text to include alternative methods for conducting patient visits and collecting data.	To ensure patient monitoring and evaluation during the coronavirus disease 2019 (COVID-19) public health emergency.
Section 8.4.1.1 Management of Selected Treatment-Related Adverse Events	Add dose modification table and supplemental description for loperamide dosing.	To align the current protocol with newly available safety information, and to ensure consistency in dose modifications guidelines across the TAK-788 program.
Section 8.7.3 Concomitant Medications with QTc Interval Prolongation Potential	Add additional guidance on the co-dosing of concomitant medications with QTc interval prolongation potential.	To provide additional precautionary guidance for investigators regarding the concomitant dosing of medications with QTc interval prolongation potential.
Section 8.13 Storage, Handling, and Accountability	Update text to include direct-to-patient as an alternative method for dispensing self-administered study drug.	To ensure continuity of TAK-788 treatment due to COVID-19 related quarantines, cancellations of on-site visits, or concerns about possible COVID-19 exposure.
Appendix F Drugs with a Risk of Torsades de Pointes	Replace the table with updated version.	For consistency across the TAK-788 program.

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2.0 STUDY SUMMARY

Name of Sponsor: Takeda Pharmaceutical Company Limited	**Compound:** TAK-788 (formerly AP32788)
Title of Protocol: A Phase 1/2 Study of the Oral EGFR/HER2 Inhibitor TAK-788 in Japanese Non-Small Cell Lung Cancer Patients	**EudraCT No.:** Not Applicable
Study Number: TAK-788-1003	**Phase:** 1/2

Study Design:

This is a Phase 1/2 study. Initially, the study started as a Phase 1 study to confirm the global recommended Phase 2 dose (RP2D) of 160 mg once daily (QD) in Japanese patients. After it was confirmed that the RP2D in Japanese patients was the same as the global RP2D, a Phase 2 part was added; the Phase 2 part is designed to evaluate the efficacy and safety of TAK-788 in treatment naive Japanese non-small cell lung cancer (NSCLC) patients with epidermal growth factor receptor (EGFR) exon 20 insertion mutation.

Phase 1 Part

The phase 1 part is an open-label, multicenter, dose-escalation part to evaluate the safety, tolerability and pharmacokinetics (PK) of TAK-788 in Japanese patients with locally advanced or metastatic NSCLC. The objectives of this part are to confirm 160 mg of TAK-788 orally administered QD, the maximum tolerated dose (MTD) for non-Japanese patients (hereinafter "global MTD") determined by the phase 1/2 study (Study AP32788-15-101) is tolerable in Japanese patients, identify dose-limiting toxicities (DLTs); and determine a RP2D based on the safety/PK profile and preliminary anti-tumor activity in Japanese patients.

The dose of TAK-788 will be started from 40 mg QD, followed by dose-escalation according to a Bayesian logistic regression model (BLRM) with overdose control escalation schema to confirm the tolerability of global MTD and determine RP2D in Japanese patients. BLRM in this study is based on the context of broader knowledge of safety, PK and anti-tumor activity of TAK-788 from the Study AP32788-15-101 and incorporates emerging information from this study. The study allows flexible cohort size, and approximately 3 DLT evaluable patients will be needed for each dose cohort. Safety data collected from patients enrolled at the starting dose will be added into BLRM, then the optimal route for escalation, ie, more patients should be enrolled at the starting dose or the dose should be escalated will be determined. Alternative regimens/schedule, more conservative dose escalation, evaluation of intermediate doses, flexible number of DLT evaluable patients for any dose cohort, evaluation of different doses in parallel cohorts and expansion of an existing dose level would be permitted by the discussions between the sponsor and the investigators, if such measures are needed for patient safety or for a better understanding of the dose-toxicity and dose-exposure relationship of TAK-788.

Before initiating the dosing of the next dose cohort, when Cycle 1 safety data are available for all patients in the current dose cohort (or dose cohorts if parallel dose cohorts are opened), an end of cohort meeting will be held. The study team consisting of sponsor representatives and investigators will review the safety of all treated patients and make decisions regarding dose escalation. In addition, the available PK and/or anti-tumor activity data will also be evaluated to support the dose escalation. Decisions from the end of cohort meeting for each dose will be documented in minutes and stored in the Trial Master File.

Dose escalation will be continued until an MTD for Japanese patients is determined, or the global MTD (160 mg QD) is confirmed to be safe and tolerable in Japanese patients. An RP2D less than the MTD may be chosen if aspects of tolerability or efficacy not encompassed by the MTD determination suggest utilizing a lower dose.

Further expansion of the cohort size may also occur at any dose to further confirm safety observations following identification of MTD/RP2D.

Phase 2 Part

The Phase 2 part is designed to evaluate the efficacy of TAK-788 at the RP2D (160 mg QD), which was determined in the Phase 1 part, in Japanese patients with locally advanced or metastatic NSCLC whose tumors

harbor EGFR exon 20 insertion mutations and who have not previously received systemic treatment for locally advanced or metastatic disease. All patients in the Phase 2 part will have a documented EGFR exon 20 insertion mutation by a local test prior to enrollment. The patients' tumor specimen will also be retrospectively confirmed for EGFR exon 20 insertion mutations by an analytically validated central test, and those patients with centrally confirmed mutation will be defined as centrally confirmed population.

The confirmed objective response rate (ORR), as assessed by Independent Review Committee (IRC) per RECIST v1.1, will be the primary endpoint in the Phase 2 part. The primary analysis will be conducted on centrally confirmed population. And, a secondary analysis will be performed on all enrolled patients who received at least one dose of TAK-788 (full analysis set [FAS]).

Study Objectives:

Phase 1 Part

Primary:

To confirm the tolerability of the global MTD (160 mg QD), identify DLTs, and determine RP2D of TAK-788 in Japanese NSCLC.

Secondary:

1. To determine the safety profile of orally administered TAK-788 in Japanese NSCLC patients.
2. To determine the PK of TAK-788 and its active metabolites (including, but not limited to, AP32960 and AP32914) in Japanese NSCLC patients.
3. To evaluate the anti-tumor activity of TAK-788 in Japanese NSCLC patients with EGFR or human epidermal growth factor 2 (HER2) mutations.

Phase 2 Part

Primary:

To determine the efficacy of TAK-788 as first-line treatment in patients with locally advanced or metastatic NSCLC harboring EGFR in-frame exon 20 insertion mutations, as evidenced by confirmed objective response rate (ORR), as assessed by the independent review committee (IRC).

Secondary:

1. To further characterize the efficacy of TAK-788 shown by confirmed ORR, as assessed by the investigator, duration of response, progression free survival (PFS), disease control rate (DCR), time to response by both investigator and IRC per RECIST v1.1 and overall survival (OS)
2. To assess the safety and tolerability of TAK-788
3. To collect sparse plasma concentration-time data of TAK788 and its active metabolites, (including, but not limited to, AP32960 and AP32914), to contribute to population PK and exposure-response analyses
4. To assess patient-reported symptoms (particular core symptoms of lung cancer), functioning, and health-related quality of life (HRQoL) with the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 and the EORTC lung cancer module QLQL-C13

Subject Population:

Japanese male or female patients with locally advanced (and not a candidate for definitive therapy) (Stage IIIB) or metastatic NSCLC (Stage IV).

Number of Subjects:	**Number of Sites:**
Approximately 58 to 63 patients total in the study. 1. Phase 1 Part Approximately 28 to 33 patients total 2. Phase 2 Part	Approximately 4 sites in Japan will participate in Phase 1 part. Approximately 25 sites in Japan will participate in Phase 2 part.

Approximately 30 patients	
Dose Levels: 1. Phase 1 Part Starting TAK-788 at a dose of 40 mg QD, and increasing until 160 mg QD. 2. Phase 2 Part 160 mg QD	**Route of Administration:** oral
Duration of Treatment: Patients will continue to be treated with TAK-788 until they experience progressive disease (PD) that requires an alternate therapy in the opinion of the investigator, intolerable toxicity, or another discontinuation criterion. Treatment may be continued after PD if, in the opinion of the investigator, the patient continues to experience clinical benefit.	**Period of Evaluation:** It is anticipated that total duration of an individual patient's study participation will be approximately 1.5 years in median duration, including a 2-3 week screening period, a treatment period with estimated average of 10-12 cycles (28 days each), and a follow-up period for approximately 30 days after the last dose of TAK-788. Only in the phase 2 part, the follow-up period for a patient begins after the last completed site visit and continues until patient contact ceases. The follow-up assessments (ie, contacting the patient for survival and subsequent anticancer therapy) must be performed every 12 weeks after the end of treatment (EOT). For patients who discontinue study treatment in the absence of PD, survival should be tracked and additional tumor assessment should be performed at the same time points as the study treatment (every 8 weeks until Week 56 [equivalent to Cycle 14 Day 28] and every 12 weeks thereafter) until PD or the start of another systemic anticancer therapy. After that, survival must be tracked every 12 weeks, and subsequent anticancer therapy should be recorded.
Approximate Duration of Study: For the Phase 1 part, the estimated time frame is approximately 3 years for completion, including 15 months to accrue patients and 1.5 years for the duration of the last patient's study participation. For the Phase 2 part, The total estimated duration is approximately 4 years, including approximately 1 year to accrue patients and 3 years for treatment and follow-up of the last patient.	
Inclusion Criteria: **<u>General Inclusion Criteria (Both in Phase 1 and Phase 2 Part)</u>** All patients must meet all of the following general inclusion criteria for study entry. 1. Male or female patients ≥20 years old. 2. Must have measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Previously irradiated lesions may not be used for target lesions, unless there is unambiguous radiological progression after radiotherapy. 3. Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1 (see Appendix D). 4. Minimum life expectancy of 3 months or more. 5. Adequate renal and hepatic function as defined by the following criteria: - Total serum bilirubin ≤1.5 × upper limit of normal (ULN) (≤3.0 × ULN for patients with Gilbert syndrome or if liver function abnormalities are due to underlying malignancy); - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 × ULN (or ≤5 × ULN if liver	

function abnormalities are due to underlying malignancy);
- Estimated creatinine clearance ≥30 mL/min (calculated by using the Cockcroft-Gault equation);
- Serum albumin ≥2 g/dL; and
- Serum lipase ≤1.5 × ULN; and
- Serum amylase ≤1.5 × ULN unless the increased serum amylase is due to salivary isozymes.

6. Adequate bone marrow function as defined by the following criteria:
   - Absolute neutrophil count ≥1.5 × 10^9/L;
   - Platelet count ≥75 × 10^9/L in Phase 1 Part and ≥100 × 10^9/L in Phase 2 Part; and
   - Hemoglobin ≥9.0 g/dL.
7. Normal QT interval on screening electrocardiogram (ECG), defined as QTcF of ≤450 ms in males or ≤470 ms in females.
8. Female patients who:
   - Are postmenopausal (natural amenorrhea and not due to other medical reasons) for at least 1 year before the screening visit, OR
   - Are surgically sterile, OR
   - If they are of childbearing potential, agree to practice 1 highly effective non-hormonal method of contraception and 1 additional effective (barrier) method (see Section 8.7.1) at the same time, from the time of signing the informed consent form (ICF) through 30 days after the last dose of study drug, OR
   - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject.

   Note: Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception.

   Male patients, even if surgically sterilized (ie, status postvasectomy), who:
   - Agree to practice effective barrier contraception (see Section 8.7.1) during the entire study treatment period and through 30 days after the last dose of study drug, OR
   - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject.

   Note: Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception.
9. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.
10. Willingness and ability to comply with scheduled visits and study procedures.

Phase-Specific Inclusion Criteria

In addition to the general inclusion criteria above, patients must also meet all criteria for the study phase in which their entry is proposed.

Phase 1 Part

1. Have histologically or cytologically confirmed locally advanced (and not a candidate for definitive therapy) (Stage IIIB) or metastatic NSCLC (Stage IV).
2. Refractory to standard available therapies.
3. All toxicities from prior therapy have resolved to ≤ grade 1 according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v5.0), or have resolved to baseline, at the time of first dose of TAK-788. Note: treatment-related grade >1 alopecia or treatment-related grade 2 peripheral neuropathy are allowed if deemed irreversible.

Phase 2 Part

1. Histologically or cytologically confirmed locally advanced not suitable for definitive therapy, recurrent, or metastatic (Stage IV) NSCLC.
2. Not received prior systemic treatment for locally advanced or metastatic disease (with the exception below):

   Neoadjuvant or adjuvant chemotherapy/immunotherapy for Stage I to III or combined modality chemotherapy/radiation for locally advanced disease is allowed if completed >6 months before the development of metastatic disease.
3. A documented EGFR in-frame exon 20 insertion (including A763_Y764insFQEA, V769_D770insASV, D770_N771insNPG, D770_N771insSVD, H773_V774insNPH, or any other in-frame exon 20 insertion mutation) by a local test that has been analytically validated per local authority guidelines. The EGFR exon 20 insertion mutation can be either alone or in combination with other EGFR or HER2 mutations except EGFR common mutations (exon 19 del or L858R).
4. Adequate tumor tissue available, either from primary or metastatic sites, for central laboratory confirmation of EGFR in-frame exon 20 insertion mutation (see laboratory manual). Note: confirmation of central test positivity is not required before the first dose of TAK-788.

Exclusion Criteria:

<u>General Exclusion Criteria (Both in Phase 1 and Phase 2 Part)</u>

Patients are not eligible for participation in the study if they meet any of the following exclusion criteria:

1. Have been 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 patients with another primary malignancy who are definitively relapse-free with at least 3 years elapsed since the diagnosis of the other primary malignancy.
2. Have undergone major surgery within 28 days prior to first dose of TAK-788. Minor surgical procedures, such as catheter placement or minimally invasive biopsy, are allowed.
3. Have current spinal cord compression (symptomatic or asymptomatic and detected by radiographic imaging) or leptomeningeal disease (symptomatic or asymptomatic).
4. Have significant, uncontrolled, or active cardiovascular disease, including, but not restricted to:
   - Myocardial infarction within 6 months prior to the first dose of study drug;
   - Unstable angina within 6 months prior to first dose;
   - Congestive heart failure within 6 months prior to first dose;
   - History of clinically significant (as determined by the treating physician) atrial arrhythmia;
   - Any history of ventricular arrhythmia; or
   - Cerebrovascular accident or transient ischemic attack within 6 months prior to first dose.
5. Have uncontrolled hypertension. Patients with hypertension should be under treatment on study entry to control blood pressure.
6. Currently being treated with medications known to be associated with the development of Torsades de Pointes (see Appendix F).
7. Have an ongoing or active infection, including, but not limited to, the requirement for intravenous antibiotics. Have a known history of HIV infection. Testing of HIV is not required in the absence of history.

   Hepatitis B surface antigen (HBsAg) positive patients are allowed to enroll if hepatitis B virus (HBV)-DNA is below 1000 copies/mL in the plasma.

   Patients who have positive hepatitis C virus (HCV) antibody can be enrolled but must have HCV-RNA undetectable in the plasma.
8. Currently have or have a history of interstitial lung disease (ILD), radiation pneumonitis that required steroid treatment, drug-related pneumonitis, or other clinically significant pneumonitis.

9. Female patients who are lactating and breastfeeding or have a positive serum pregnancy test during the screening period.

   Note: Female patients who are lactating will be eligible if they discontinue breastfeeding.
10. Have gastrointestinal illness or disorder that could affect oral absorption of TAK-788.
11. Have 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 drug.

Phase-Specific Exclusion Criteria

In addition to the general exclusion criteria above, patients are not eligible for participation in the study phase if they meet any of the following exclusion criteria for the study phase in which their entry is proposed.

Phase 1 Part

1. Previously received TAK-788.
2. Received small-molecule anticancer therapy (including cytotoxic chemotherapy and investigational agents) within 14 days prior to the first dose of TAK-788 (except for reversible EGFR tyrosine kinase inhibitors [TKIs; ie, erlotinib or gefitinib] up to 7 days prior to the first dose of TAK-788).
3. Received antineoplastic monoclonal antibodies including immunotherapy within 28 days prior to the first dose of TAK-788.
4. Received radiotherapy within 14 days prior to the first dose of TAK-788. Stereotactic radiosurgery (SRS) and stereotactic body radiosurgery are allowed up to 7 days prior to the first dose.
5. Have symptomatic CNS metastases (parenchymal or leptomeningeal) at screening or asymptomatic disease requiring corticosteroids to control symptoms within 7 days prior to the first dose of TAK-788.

   Note: If a patient has worsening neurological symptoms or signs due to CNS metastases, the patient needs to complete local therapy and be neurologically stable (with no requirement for corticosteroids or use of anticonvulsants) for 7 days prior to the first dose of TAK-788. Patients with no prior history of signs or symptoms of CNS metastases but who receive prophylactic steroids or anticonvulsants are allowed.
6. Received a strong cytochrome P450 (CYP)3A inhibitor or strong CYP3A inducer within 2 weeks prior to first dose of TAK-788.

Phase 2 Part

1. Received radiotherapy within 14 days before the first dose of TAK-788 or has not recovered from radiotherapy-related toxicities. Stereotactic radiosurgery, stereotactic body radiotherapy, or palliative radiation outside the chest and brain is allowed up to 7 days before the first dose of TAK-788.
2. 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.
3. Received a moderate or strong CYP3A inhibitor or moderate or strong CYP3A inducer within 10 days prior to first dose of TAK-788.
4. Have cardiac ejection fraction <50% by echocardiogram or multigated acquisition (MUGA) scan at screening.

Main Criteria for Evaluation and Analyses:

Phase 1 Part

Primary Endpoint:

RP2D of orally administered TAK-788 in Japanese NSCLC patients.

Secondary Endpoints:

1. Safety profile of orally administered TAK-788:
   - The number and percentage of patients with treatment-emergent adverse events (TEAEs).
   - The number and percentage of patients with first cycle DLTs.
2. DLTs of orally administered TAK-788.
3. MTD of orally administered TAK-788.
4. Plasma PK parameters of TAK-788 and its active metabolites (including, but not limited to, AP32960 and AP32914) after a single oral dose: Maximum plasma concentration (C_{max}), time to C_{max} (t_{max}), area under the plasma concentration-time curve from time 0 to 24 hours (AUC_{24}) and from time 0 to the time of the last quantifiable concentration (AUC_{last}), and dose proportionality for C_{max} and AUC (if data allows).
5. Plasma PK parameters of TAK-788 and its active metabolites (including, but not limited to, AP32960 and AP32914) at steady state after multiple oral doses: Maximum plasma concentration at steady state ($C_{max,ss}$), time to $C_{max,ss}$ ($t_{max,ss}$), AUC_{24} at steady state ($AUC_{24,ss}$), extent of accumulation ratio on multiple dosing (R_{ac}), and dose proportionality for C_{max} and AUC (if data allows).
6. Investigator assessed objective response rate (ORR) using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 in patients with EGFR or HER2 mutations.

Safety Endpoints:

The safety endpoints are:

1. Adverse events (AEs).
2. Laboratory values.
3. Vital signs.
4. Electrocardiograms (ECGs).

Phase 2 Part

Primary Endpoint:

Confirmed ORR, as assessed by the IRC, per RECIST v1.1.

Secondary Endpoints:

1. Confirmed ORR, as assessed by the investigator, per RECIST v1.1.
2. Duration of response, as assessed by the IRC and the investigator.
3. Time to response, as assessed by the IRC and the investigator.
4. DCR (the percentage of patients with best response of complete response [CR], partial response [PR], or SD), as assessed by the IRC and the investigator, per RECIST v1.1, for 42 days or more after initiation of study drug.
5. PFS, as assessed by the IRC and the investigator.
6. Overall survival (OS).
7. Patient-reported symptoms (particular core symptoms of lung cancer), functioning, and health-related quality of life (HRQoL) with the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 and the EORTC lung cancer module QLQ-LC13.

Safety Endpoints:

1. AEs.
2. Laboratory values.
3. Vital signs.
4. Physical examination findings.

Statistical Considerations:

Phase 1 Part

Descriptive statistics and analyses will be provided for each dose level, and for patients combined across dose levels where applicable. All patients who receive at least 1 dose of TAK-788 will be included in the safety analysis.

The MTD will be determined based on the DLT within the first 28 days of treatment (end of Cycle 1). Evaluable patients must complete at least 75% of their planned doses, unless missed doses are due to AEs. An adaptive BLRM that implements escalation with overdose control will be used in this study for purposes of dose escalation recommendations and estimation of the MTD. Data from the Study AP32788-15-101 will be used as prior information in the BLRM. For each dose level, the posterior probability of having DLT rates that fall into the following intervals will be estimated:

- [0, 0.21): under-dosing.
- [0.21, 0.33): target toxicity.
- [0.33, 1.00]: excessive toxicity.

BLRM will recommend a dose which follows the Escalation With Overdose Control (EWOC) principle and has the highest posterior probability of having a DLT rate that falls into the interval [0.21, 0.33) as the target toxicity rate at MTD. Following the EWOC principle, the posterior probability of the recommended dose having a DLT rate above 0.33 must not exceed 30%. The selection of the next recommended dose will be determined along with other available information, such as safety, PK and efficacy.

The MTD may be declared as the current dose if the following stopping rules is met:

- At least 9 patients are evaluable in the study and at least 6 patients are evaluable at the current dose, and the current dose is the recommended dose for the next cohort.

Alternative stopping rules may also be considered following discussions between the sponsor and the investigators.

Phase 2 Part

For the primary endpoint, confirmed ORR as assessed by an IRC and its 2-sided 90% CI will be provided using centrally confirmed population, defined as patients who have confirmed harboring EGFR exon 20 insertion mutation by central test, and have received at least 1 dose of study drug. The secondary analysis will be performed on FAS population, defined as enrolled patients who received at least one dose of study drug.

For the primary analysis in the phase 2 part, a 2-stage design [20] will be used. The first 14 "centrally confirmed" patients in the phase 2 part are included in Stage 1, and further patients will be continuously enrolled into Stage 2. An interim analysis for both futility and efficacy will be conducted in Stage 1. The proportion of patients achieving a confirmed objective response, per IRC, will be used as the endpoint for the interim analysis. The interim analysis will be performed when the first 14 "centrally confirmed" patients in the phase 2 part have had the opportunity to complete the Cycle 7 Day 1 disease assessment (i.e. 3rd disease assessment after initiation of the study treatment). Enrollment will not be suspended during evaluation of these 14 "centrally confirmed" patients; however, patients enrolled after the 14th patient in the phase 2 part will NOT be included in the interim analysis, even if their objective response results were available on the cutoff date.

If the number of patients with confirmed objective response is 5 or fewer of the 14 "centrally confirmed" patients, enrollment will be stopped entirely for futility. Additionally, if the number of patients with confirmed objective response is 9 or more of the 14"centrally confirmed" patients, it will be decided that TAK-788 is efficacious in this population.

In other cases (i.e. number of patients with confirmed objective response is between 6 to 8), the study will continue until the 26"centrally confirmed" patients have had the opportunity to complete the Cycle 7 Day 1 disease assessment. If the number of patients with confirmed objective response in these 26 patients is 14 or more, it will be decided that TAK-788 has demonstrated sufficient efficacy to reject the null hypothesis.

For the secondary endpoints except for quality of life (QOL), all variables will be summarized descriptively

using both the centrally confirmed population and FAS. QOL will be summarized descriptively using FAS. Continuous variables will be summarized using the number of patients, mean, standard deviation, median, minimum, and maximum, and categorical variables will be summarized using the number and percentage per category. Time-to-event variables will be summarized using Kaplan-Meier methodology, and Kaplan-Meier plots will be provided. Kaplan-Meier estimates and 95% CI will be calculated for quantiles and some specified time points.

Pharmacokinetic Analysis

The PK parameters for TAK-788 and its active metabolites, including, but not limited to, AP32960 and AP32914, will include (but are not limited to) the following.

Following a Single Oral Dose in the Phase 1 Part:

Maximum plasma concentration (C_{max}), time to C_{max} (t_{max}), and area under the plasma concentration-time curve from time 0 to 24 hours (AUC_{24}) and from time 0 to the time of the last quantifiable concentration (AUC_{last}). Dose proportionality for C_{max} and AUC may be assessed if data allows.

Following Multiple Oral Doses (Steady State) in the Phase 1 Part:

Maximum plasma concentration at steady state ($C_{max,ss}$), time to $C_{max,ss}$ ($t_{max,ss}$), AUC_{24} at steady state ($AUC_{24,ss}$), and extent of accumulation ratio on multiple dosing (R_{ac}). Dose proportionality for C_{max} and AUC may be assessed if data allows.

PK Analysis in the Phase 2 Part:

The plasma concentration-time data of TAK-788 and its active metabolites, including, but not limited to, AP32960 and AP32914 will be pooled with data from other TAK 788 clinical studies in patients with cancer to contribute to population PK analyses. Results of the population PK analyses of data from this study will also contribute to exposure-response analyses of safety and efficacy. The analysis plans for the population PK and exposure-response analyses will be separately defined, and the results of these analyses will be reported separately.

Sample Size Justification:

Phase 1 Part

The Phase 1 part will adopt an adaptive design using BLRM with safety data evaluation and other available information, such as PK and efficacy. The design allows flexible cohort size. The total number of subjects in this study is dependent on the observed safety profile and other available information, which will determine the number of patients per dose cohort, as well as the number of dose escalations required to achieve the MTD. It is anticipated that approximately 21 patients will be required to determine MTD. Assuming a 15% dropout rate and potentially up to 5 patients will be enrolled for any cohort to further confirm the safety, the total sample size for this study will be approximately 28-33.

Phase 2 Part

The purpose of the phase 2 part of this study is to determine the confirmed ORR of orally administered TAK-788 as the first line treatment at RP2D determined in the Phase 1 part in patients with NSCLC with EGFR exon 20 insertion mutations. The sample size was determined so that it would allow us to state that the true ORR is greater than threshold response rate of 35%. The expected true ORR of TAK-788 is 60% in treatment naive population. Twenty-six (26) patients with NSCLC with tumors harboring EGFR exon 20 insertion mutations with confirmation of central test will allow the study to have over 80% power to rule out an uninteresting rate of 35% in this population with a 1-sided alpha of 0.05 according to the two-stage design (Mander and Thompson, 2010) with futility and efficacy interim analysis described in the above “Statistical Consideration”.

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 protocol annex. The vendors identified in the protocol annex 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 medication, 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

Abbreviation	Term
AE	adverse event
AFIB	atrial fibrillation
AFL	atrial flutter
ALT	alanine aminotransferase
APL	acute promyelocytic leukemia
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{24}	area under the concentration-time curve from time 0 to 24 hours
$AUC_{24,ss}$	area under the concentration-time curve from time 0 to 24 hours, at steady state
AUC_{last}	area under the concentration-time curve from time 0 to time of the last quantifiable concentration
β-hCG	beta-human chorionic gonadotropin
BLRM	Bayesian logistic regression model
CI	confidence interval
CL/F_{ss}	apparent clearance at steady state
C_{max}	maximum observed concentration
$C_{max,ss}$	maximum observed concentration during a dosing interval, at steady state
CNS	central nervous system
COVID-19	coronavirus disease 2019
CR	complete response
CRO	contract research organization
CSF	cerebrospinal fluid
CSR	clinical study report
CT	computed tomography
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CxDx	Cycle x Day x
CYP	cytochrome P450
DCR	disease control rate
DDI	drug-drug interaction
DLT	dose-limiting toxicity
DTP	direct-to-patient
ECG	electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EES	erythromycin ethylsuccinate
EGFR	epidermal growth factor receptor
EORTC	European Organisation for Research and Treatment of Cancer

Abbreviation	Term
EOT	end of treatment
EWOC	Escalation With Overdose Control
FAS	full analysis set
FDA	Food and Drug Administration (United States)
FFPE	formalin fixed paraffin embedded
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
GERD	gastroesophageal reflux disease
GI	gastrointestinal
GM-CSF	granulocyte macrophage-colony stimulating factor
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HER2	human epidermal growth factor 2
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
IBS	irritable bowel syndrome
IC_{50}	50% inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
ILD	interstitial lung disease
IRB	Institutional Review Board
IRC	independent review committee
KL-6	Krebs von den Lungen-6
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MI	myocardial infarction
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multigated acquisition
N/A	not applicable
NCI	National Cancer Institute (of the United States)
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression free survival
PJP	pneumocystis jiroveci pneumonia

Abbreviation	Term
PK	pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency
PONV	post-operative nausea and vomiting
PR	partial response
PSVT	paroxysmal supraventricular tachycardia
QD	once daily
QLQ	Quality of Life Questionnaire
QLQ-LC13	Quality of Life Questionnaire, lung cancer module
QOL	quality of life
QT	QT interval; a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle
QTc	heart rate-corrected QT interval (calculated)
QTcF	QT interval corrected (Fridericia)
R_{ac}	accumulation ratio
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended phase 2 dose
SAE	serious adverse event
SD	stable disease
SP-D	surfactant protein-D
SRS	stereotactic radiosurgery
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
t_{max}	time of first occurrence of maximum observed concentration
$t_{max,ss}$	time of first occurrence of maximum observed concentration during a dosing interval, at steady state
UK	United Kingdom
US	United States
ULN	upper limit of normal
VF	ventricular fibrillation
VT	ventricular tachycardia
WBRT	whole brain radiation therapy
WHO	World Health Organization

3.4 Corporate Identification

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

4.0 INTRODUCTION

4.1 Background

Specific genetic lesions 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%-40% of patients with non-small cell lung cancer (NSCLC) [1][2]. 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 EGFR in normal tissues is associated with dose limiting toxicities, substantial clinical benefit has generally been associated with TKIs that inhibit specific, activated variants of EGFR more potently than they inhibit wild-type 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 [3]. The remaining 10% to 15% of de novo EGFR mutations comprise a cluster of in-frame insertions in exon 20 that account for ~2% of all NSCLC [4][5][6] and the rarer EGFR 'uncommon' point mutations that account for the remainder (~1%).

Unlike mutations in exons 19 or 21, almost all EGFR exon 20 insertions confer in vitro and primary clinical resistance to erlotinib, gefitinib, and afatinib [7][8][9]. Patients with NSCLC containing EGFR exon 20 insertions exhibit clinical characteristics similar to those carrying common EGFR mutations [4] (eg, young, nonsmoker, with adenocarcinoma subtype), consistent with potential roles as driver mutations that could confer benefit to targeted therapy. In summary, while erlotinib, gefitinib, and afatinib are approved for use in NSCLC patients with common activating mutations in EGFR (ie, exon 19 deletions and L858R substitutions), no targeted therapies are approved for patients with EGFR exon 20 insertions or other uncommon EGFR mutations in Japan.

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 NSCLC patients. These patients exhibit clinical characteristics similar to EGFR-mutated patients [10][11][12]. Currently, no targeted therapies are approved for use in NSCLC patients with HER2 activating mutations.

To address limitations of existing therapies targeting EGFR and HER2, TAK-788 (formerly AP32788), a novel, synthetic, orally-administered TKI has been developed. 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 wild-type EGFR, suggesting it may have the selectivity necessary to achieve levels of exposure required to inhibit all activated forms of these kinases.

4.2 Rationale for the Proposed Study

Based on the promising activity profile of TAK-788 in vitro and in vivo, as well as its toxicological profile, a phase 1/2 study of TAK-788 (Study AP32788-15-101) had been initiated in the United States, and maximum tolerated dose (MTD) was confirmed as 160 mg once daily (QD) (hereinafter "global MTD").

In order to confirm the global MTD is tolerable in Japanese patients and determine the recommended phase 2 dose (RP2D) in Japanese, a phase 1 study in Japanese NSCLC patients is proposed.

Also, after the confirmation of RP2D in Japanese, phase 2 part to evaluate efficacy and safety of TAK-788 in treatment naive Japanese patients of NSCLC harboring EGFR exon 20 insertion mutations was added.

In the phase 1 part, the patient population of the trial will include Japanese patients with locally advanced or metastatic NSCLC. The objectives of the phase 1 part are to confirm global MTD is tolerable in Japanese patients and to determine a RP2D based on the safety/pharmacokinetic (PK) profile and evaluate preliminary anti-tumor activity in Japanese patients.

In the phase 2 part, treatment naive Japanese NSCLC patients with EGFR exon 20 insertion mutations will be included. The objectives of the phase 2 part are to confirm efficacy and safety of TAK-788 in Japanese patients and primary endpoint is the confirmed objective response rate (ORR) by RECIST v1.1 assessed by independent review committee (IRC).

4.2.1 Rationale for Dose

In Study AP32788-15-101, a total 38 dose-limiting toxicity (DLT) evaluable patients were enrolled to 5 to 180 mg dose cohort. No DLT were observed in the 5, 10, 20 and 40 mg dose cohort (3, 3, 5 and 6 evaluable subjects, respectively), but 1 DLT was observed in 1 of 6 evaluable patients at each 80, 120, 160 mg dose cohort, and 2 DLTs were observed among 3 evaluable patients at 180 mg dose cohort. While DLTs were observed at 80 mg or more, overall TAK-788 was well tolerable and class AE such as diarrhea is considered manageable. However, considering TAK-788 has never been administered in Japanese patients, 40 mg QD, which is the half of 80 mg QD and no DLT was observed, is considered to be an appropriate starting dose in the phase 1 part.

In the phase 2 part, 160 mg QD, which is confirmed as the RP2D in Japanese patients in prior phase 1 part will be used.

4.2.2 Benefit-Risk

Clinical investigation of the potential benefit of TAK-788 is ongoing through a comprehensive and global development plan that involves Study AP32788-15-101 and TAK-788-3001. The current Investigator's Brochure describes the known safety profile of TAK-788. The known safety profile indicates that the types of AEs reported with TAK-788 are generally manageable

and reversible. While some of these potential toxicities may be serious, they can be managed by clinical monitoring and standard medical intervention or dose modifications.

Overall, the benefit-risk assessment for TAK-788 based on the available experience is expected to be favorable.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Phase 1 Part

5.1.1.1 Primary Objective

The primary objective is:

- To confirm the tolerability of the global MTD (160 mg QD), identify dose-limiting toxicities (DLTs), and determine RP2D of TAK-788 in Japanese NSCLC patients.

5.1.1.2 Secondary Objectives

The secondary objectives are:

1. To determine the safety profile of orally administered TAK-788 in Japanese NSCLC patients.
2. To determine the PK of TAK-788 and its active metabolites (including, but not limited to, AP32960 and AP32914) in Japanese NSCLC patients.
3. To evaluate the anti-tumor activity of TAK-788 in Japanese NSCLC patients with EGFR or HER2 mutations.

5.1.2 Phase 2 Part

5.1.2.1 Primary Objectives

To determine the efficacy of TAK-788 as first-line treatment in patients with locally advanced or metastatic NSCLC harboring EGFR in-frame exon 20 insertion mutations, as evidenced by confirmed objective response rate (ORR), as assessed by the independent review committee (IRC) per RECIST v1.1.

5.1.2.2 Secondary Objectives

1. To further characterize the efficacy of TAK-788 shown by confirmed ORR, as assessed by the investigator, duration of response, progression free survival (PFS), disease control rate (DCR), time to response by both investigator and IRC per RECIST v1.1 and overall survival (OS).
2. To assess the safety and tolerability of TAK-788.
3. To collect sparse plasma concentration-time data of TAK788 and its active metabolites, (including, but not limited to, AP32960 and AP32914), to contribute to population PK and exposure-response analyses.

4. To assess patient-reported symptoms (particular core symptoms of lung cancer), functioning, and health-related quality of life (HRQoL) with the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 and the EORTC lung cancer module QLQ-LC13.

5.2 Endpoints

5.2.1 Phase 1 Part

5.2.1.1 Primary Endpoint

The primary endpoint is:

- RP2D of orally administered TAK-788 in Japanese NSCLC patients.

5.2.1.2 Secondary Endpoints

The secondary endpoints are:

1. Safety profile of orally administered TAK-788:
   - The number and percentage of patients with treatment-emergent adverse events (TEAEs).
   - The number and percentage of patients with first cycle DLTs.
2. DLTs of orally administered TAK-788.
3. MTD of orally administered TAK-788.
4. Plasma PK parameters of TAK-788 and its active metabolites after a single oral dose: Maximum plasma concentration (C_{max}), time to C_{max} (t_{max}), area under the plasma concentration-time curve from time 0 to 24 hours (AUC_{24}) and from time 0 to the time of the last quantifiable concentration (AUC_{last}), and dose proportionality for C_{max} and AUC (if data allows).
5. Plasma PK parameters of TAK-788 and its active metabolites at steady state after multiple oral doses: Maximum plasma concentration at steady state ($C_{max,ss}$), time to $C_{max,ss}$ ($t_{max,ss}$), AUC_{24} at steady state ($AUC_{24,ss}$), extent of accumulation ratio on multiple dosing (R_{ac}), and dose proportionality for C_{max} and AUC (if data allows).
6. Investigator assessed objective response rate (ORR) using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 in patients with EGFR or HER2 mutations.

5.2.1.3 Safety Endpoints

The safety endpoints are:

1. Adverse events (AEs).
2. Laboratory values.

3. Vital signs.
4. Electrocardiograms (ECGs).

5.2.2 Phase 2 Part

5.2.2.1 Primary Endpoint:

Confirmed ORR, as assessed by the IRC, per RECIST v1.1.

5.2.2.2 Secondary Endpoints:

1. Confirmed ORR, as assessed by the investigator, per RECIST v1.1.
2. Duration of response, as assessed by the IRC and the investigator.
3. Time to response, as assessed by the IRC and the investigator.
4. DCR (the percentage of patients with best response of complete response [CR], partial response [PR], or SD of 42 days or longer), as assessed by the IRC and the investigator, per RECIST v1.1.
5. PFS, as assessed by the IRC and the investigator.
6. OS.
7. Patient-reported symptoms (particular core symptoms of lung cancer), functioning, and health-related quality of life (HRQoL) with the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 and the EORTC lung cancer module QLQ-LC13.

5.2.2.3 Safety Endpoints:

1. AEs.
2. Laboratory values.
3. Vital signs.
4. Physical examination findings.

6.0 STUDY DESIGN

6.1 Overview of Study Design

This is a Phase 1/2 study. Initially, the study started as a Phase 1 study to confirm the global RP2D of 160 mg QD in Japanese patients. After it was confirmed that the RP2D in Japanese patients was the same as the global RP2D, a Phase 2 part was added; the Phase 2 part is designed to evaluate the efficacy and safety of TAK-788 in treatment naive Japanese NSCLC patients with EGFR exon 20 insertion mutation.

Phase 1 Part

An open-label, multicenter, dose-escalation part to evaluate the safety, tolerability and pharmacokinetics (PK) of TAK-788 in Japanese patients with locally advanced or metastatic NSCLC. The objectives of Phase 1 part are to confirm 160 mg QD of TAK-788 orally administered, the MTD for non-Japanese patients (hereinafter "global MTD") determined by the phase 1/2 study (Study AP32788-15-101) is tolerable in Japanese patients, identify DLTs; and determine a RP2D based on the safety/PK and preliminary anti-tumor activity in Japanese patients.

Phase 1 part consists of screening period, treatment period, and follow-up period. The screening period begins when the informed consent form is signed, and continues until the first dose of study drug is administered at the Cycle 1, Day 1 (C1D1) visit. The follow-up period begins at the last dose of TAK-788 and continues until the 30 days after the last dose assessments.

Subject eligibility will be determined during the screening period, which must be no more than 14 days prior to the C1D1 visit. The allowable window for the tumor imaging screening assessment is 21 days prior to the C1D1 visit. Patients who meet all eligibility criteria and provide written informed consent will be enrolled in this study.

All the enrolled subjects will receive TAK-788 orally once daily. Each 28-day dosing period is referred to as 1 cycle. The expected total duration of patient participation is approximately 1.5 years, including a 2-3 week screening period, a treatment period with estimated average of 10-12 cycles in responding patients (participation for patients who do not respond will likely be of shorter duration), and a follow-up period for approximately 30 days after the last dose of TAK-788.

The dose of TAK-788 will be started 40 mg QD, followed by dose-escalation according to a Bayesian logistic regression model (BLRM) with overdose control escalation schema to confirm the tolerability of global MTD and determine RP2D in Japanese patients. BLRM in this study is based on the context of broader knowledge of safety, PK and anti-tumor activity of TAK-788 from the Study AP32788-15-101 and incorporates emerging information from this study. The study allows flexible cohort size, and approximately 3 DLT-evaluable patients will be needed for each dose cohort. Safety data collected from patients enrolled at the starting dose will be added into BLRM, then the optimal route for escalation, ie, more patients should be enrolled at the starting dose or the dose should be escalated, will be determined. Alternative regimens/schedule,

more conservative dose escalation, evaluation of intermediate doses, flexible number of DLT evaluable patients for any dose cohort, evaluation of different doses in parallel cohorts and expansion of an existing dose level would be permitted by the discussions between the sponsor and the investigators, if such measures are needed for patient safety or for a better understanding of the dose-toxicity and dose-exposure relationship of TAK-788.

Before initiating the dosing of the next dose cohort, when Cycle 1 safety data are available for all patients in the current dose cohort (or dose cohorts if parallel dose cohorts are opened), an end of cohort meeting will be held. The study team consisting of sponsor representatives and investigators will review the safety of all treated patients and make decisions regarding dose escalation. In addition, the available PK and/or anti-tumor activity data will also be evaluated to support the dose escalation. Decisions from the end of cohort meeting for each dose will be documented in minutes and stored in the Trial Master File.

Dose escalation will be continued until an MTD for Japanese patients is determined or the global MTD (160 mg QD) is confirmed to be safe and tolerable in Japanese patients. The RP2D is the MTD or less. An RP2D less than the MTD may be chosen if aspects of tolerability or efficacy not encompassed by the MTD determination suggest utilizing a lower dose.

Further expansion of the cohort size may also occur at any dose to further confirm safety observations following identification of MTD/RP2D.

Phase 2 Part

The Phase 2 part is designed to evaluate the efficacy of TAK-788 at the RP2D (160 mg QD), which was determined in the Phase 1 part, in Japanese patients with locally advanced or metastatic NSCLC whose tumors harbor EGFR exon 20 insertion mutations and who have not previously received systemic treatment for locally advanced or metastatic disease. All patients in the Phase 2 part will have a documented EGFR exon 20 insertion mutation by a local test prior to enrollment. Also, the patient's tumor specimen will be retrospectively confirmed for EGFR exon 20 insertion mutations by an analytically validated central test, and those patients with centrally confirmed mutation will be defined as centrally confirmed population.

The confirmed ORR, as assessed by IRC per RECIST v1.1, will be the primary endpoint in the Phase 2 part. The primary analysis will be conducted on patients with centrally confirmed population. And, a secondary analysis will be performed on all enrolled patients who received at least one dose of TAK-788 (full analysis set [FAS]).

6.2 Number of Patients

Approximately 58 to 63 patients in total in the study.

Phase 1 Part

It is anticipated that approximately 21 patients will be required for MTD determination in Phase 1 Part. Assuming a 15% dropout rate and potentially up to 5 patients will be enrolled for any cohort to further confirm the safety, approximately 28-33 patients will be enrolled in Phase 1 Part.

Phase 2 Part

Approximately 30 patients will be enrolled in Phase 2 Part.

6.3 Duration of Study

6.3.1 Duration of an Individual Patient's Study Participation

Patients will continue to be treated with TAK-788 until they experience progressive disease (PD) that requires an alternate therapy in the opinion of the investigator, intolerable toxicity, or another discontinuation criterion. Treatment may be continued after PD if, in the opinion of the investigator, the patient continues to experience clinical benefit.

It is anticipated that total duration of an individual patient's study participation will be approximately 1.5 years in median duration, including a 2-3 week screening period, a treatment period with estimated average of 10-12 cycles (28 days each) and a follow-up period for approximately 30 days after the last dose of TAK-788.

Only in the phase 2 part, the follow-up period for a patient begins after the last completed site visit and continues until patient contact ceases. The follow-up assessments (ie, contacting the patient for survival and subsequent anticancer therapy) must be performed every 12 weeks after the end of treatment (EOT). For patients who discontinue study treatment in the absence of PD, survival should be tracked and additional tumor assessment should be performed at the same time points as the study treatment (every 8 weeks until Week 56 [equivalent to Cycle 14 Day 28] and every 12 weeks thereafter) until PD or the start of another systemic anticancer therapy. After that, survival must be tracked every 12 weeks, and subsequent anticancer therapy should be recorded.

6.3.2 Total Study Duration

End of study (completion) date is defined as all patients have completed all study visits or have otherwise discontinued from the study.

For the Phase 1 part, the estimated time frame is approximately 3 years for completion, including 15 months to accrue patients and 1.5 years for the duration of the last patient's study participation.

For the Phase 2 part, the estimated duration is approximately 4 years, including approximately 1 year to accrue patients and 3 years for treatment and follow-up of the last patient.

6.3.3 Timeframes for Primary and Secondary Endpoints to Support Disclosures

All primary and secondary endpoints for disclosure is summarized in Table 6.a.

Table 6.a Primary and Secondary Endpoints for Disclosures

Endpoint	Definition	Maximum Time Frame
Phase 1 Part		
Primary: RP2D of orally administered TAK-788 in Japanese NSCLC patients.	The RP2D is the MTD or less. An RP2D less than the MTD may be chosen if aspects of tolerability or efficacy not encompassed by the MTD determination suggest utilizing a lower dose.	Up to approximately 28 days (End of Cycle 1).
Secondary: The number and percentage of patients with TEAEs and with first cycle DLTs	See details in Section 13.1.	Up to approximately 1.5 years.
Secondary: DLTs and MTD of orally administered TAK-788	See details in Section 8.2.	Up to approximately 28 days (End of Cycle 1).
Secondary: Plasma PK parameters of TAK-788 and its active metabolites (AP32960 and AP32914) after a single oral dose and at steady state after multiple oral doses	See details in Section 13.1.	Predose and multiple time points up to approximately 57 days (C3D1).
Phase 2 Part		
Primary: Confirmed ORR, as assessed by the IRC, per RECIST v1.1	The proportion of patients who are confirmed to have achieved CR or PR. Confirmed responses are responses that persist on repeat imaging ≥4 weeks after initial response.	At the time of the primary endpoint analysis in Phase 2 part.
Secondary: Confirmed ORR, as assessed by the investigator per RECIST v1.1	The proportion of patients who are confirmed to have achieved CR or PR. Confirmed responses are responses that persist on repeat imaging ≥4 weeks after initial response.	At the time of the primary endpoint analysis in Phase 2 part.
Secondary: Duration of response, Time to response, DCR and PFS, as assessed by the IRC and the investigator	DCR: The percentage of patients with best response of CR, PR or SD. PFS: The time interval from the date of treatment until the first date at which the criteria for PD.	At the time of the primary endpoint analysis in Phase 2 part.
Secondary: OS	The interval from the date of randomization until death.	At the time of the primary endpoint analysis in Phase 2 part.
Secondary: Patient-reported symptoms (particular core symptoms of lung cancer), functioning, and health-related quality of life (HRQoL) with the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 and the EORTC lung cancer module QLQ-LC13	Quality of life scale/item scores as defined in the EORTC QLQ-C30 and QLQ-LC13 scoring manual.	At the time of the primary endpoint analysis in Phase 2 part.

CxDx, Cycle x Day x; CR, complete response; DCR, disease control rate; DLT, dose-limiting toxicity; EORTC, European Organisation for Research and Treatment of Cancer; IRC, independent review committee; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival;

PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetic; PR, partial response; QLQ, Quality of Life Questionnaire; QLQ-LC13, Quality of Life Questionnaire, lung cancer module; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended phase 2 dose; SD, stable disease; TEAE, treatment-emergent adverse event.

6.3.4 Post-trial Access

Patients will be allowed to continue treatment with TAK-788 after the clinical study database is closed 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.

Duration of Posttrial Access

Continued access to TAK-788 for participants 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. Posttrial access may be terminated in Japan where marketing authorization has been rejected.

7.0 STUDY POPULATION

7.1 Inclusion Criteria

General Inclusion Criteria (Both in Phase 1 and Phase 2 Part)

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

1. Male or female patients ≥20 years old.
2. Must have measurable disease by RECIST v1.1. Previously irradiated lesions may not be used for target lesions, unless there is unambiguous radiological progression after radiotherapy (see Appendix C).
3. Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1 (see Appendix D).
4. Minimum life expectancy of 3 months or more.
5. Adequate renal and hepatic function as defined by the following criteria:
   - Total serum bilirubin ≤1.5 × upper limit of normal (ULN) (≤3.0 × ULN for patients with Gilbert syndrome or if liver function abnormalities are due to underlying malignancy);
   - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 × ULN (or ≤5 × ULN if liver function abnormalities are due to underlying malignancy);
   - Estimated creatinine clearance ≥30 mL/min (calculated by using the Cockcroft-Gault equation);
   - Serum albumin ≥2 g/dL; and
   - Serum lipase ≤1.5 × ULN; and
   - Serum amylase ≤1.5 × ULN unless the increased serum amylase is due to salivary isoenzymes.
6. Adequate bone marrow function as defined by the following criteria:
   - Absolute neutrophil count ≥1.5 × 10^9/L;
   - Platelet count ≥75 × 10^9/L in Phase 1 Part and ≥100 × 10^9/L in Phase 2 Part; and
   - Hemoglobin ≥9.0 g/dL.
7. Normal QT interval on screening ECG, defined as QTcF of ≤450 ms in males or ≤470 ms in females.
8. Female patients who:
   - Are postmenopausal (natural amenorrhea and not due to other medical reasons) for at least 1 year before the screening visit, OR
   - Are surgically sterile, OR

- If they are of childbearing potential, agree to practice 1 highly effective non-hormonal method of contraception and 1 additional effective (barrier) method (see Section 8.7.1) at the same time, from the time of signing the informed consent form (ICF) through 30 days after the last dose of study drug, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject.

  Note: Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception.

Male patients, even if surgically sterilized (ie, status postvasectomy), who:

- Agree to practice effective barrier contraception (see Section 8.7.1) during the entire study treatment period and through 30 days after the last dose of study drug, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject.

  Note: Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception.

9. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.
10. Willingness and ability to comply with scheduled visits and study procedures.

Phase-Specific Inclusion Criteria

In addition to the general inclusion criteria above, patients must also meet all criteria for the study phase in which their entry is proposed.

Phase 1 Part

1. Have histologically or cytologically confirmed locally advanced (and not a candidate for definitive therapy) (Stage IIIB) or metastatic NSCLC (Stage IV).
2. Refractory to standard available therapies.
3. All toxicities from prior therapy have resolved to ≤ grade 1 according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v5.0), or have resolved to baseline, at the time of first dose of TAK-788. Note: treatment-related grade >1 alopecia or treatment-related grade 2 peripheral neuropathy are allowed if deemed irreversible.

Phase 2 Part

1. Histologically or cytologically confirmed locally advanced not suitable for definitive therapy, recurrent, or metastatic (Stage IV) NSCLC.
2. Not received prior systemic treatment for locally advanced or metastatic disease (with the exception below): Neoadjuvant or adjuvant chemotherapy/immunotherapy for Stage I to III or combined modality chemotherapy/radiation for locally advanced disease is allowed if completed >6 months before the development of metastatic disease.
3. A documented EGFR in-frame exon 20 insertion (including A763_Y764insFQEA, V769_D770insASV, D770_N771insNPG, D770_N771insSVD, H773_V774insNPH, or any other in-frame exon 20 insertion mutation) by a local test that has been analytically validated per local authority guidelines. The EGFR exon 20 insertion mutation can be either alone or in combination with other EGFR or HER2 mutations except EGFR common mutations (exon 19 del or L858R).
4. Adequate tumor tissue available, either from primary or metastatic sites, for central laboratory confirmation of EGFR in-frame exon 20 insertion mutation (see laboratory manual). Note: confirmation of central test positivity is not required before the first dose of TAK-788.

7.2 Exclusion Criteria

General Exclusion Criteria (Both in Phase 1 and Phase 2 Part)

Patients are not eligible for participation in the study if they meet any of the following exclusion criteria.

1. Have been 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 patients with another primary malignancy who are definitively relapse-free with at least 3 years elapsed since the diagnosis of the other primary malignancy.
2. Have undergone major surgery within 28 days prior to first dose of TAK-788. Minor surgical procedures, such as catheter placement or minimally invasive biopsy, are allowed.
3. Have current spinal cord compression (symptomatic or asymptomatic and detected by radiographic imaging) or leptomeningeal disease (symptomatic or asymptomatic).
4. Have significant, uncontrolled, or active cardiovascular disease, including, but not restricted to:
    - Myocardial infarction within 6 months prior to the first dose of study drug;
    - Unstable angina within 6 months prior to first dose;
    - Congestive heart failure within 6 months prior to first dose;
    - History of clinically significant (as determined by the treating physician) atrial arrhythmia;

- Any history of ventricular arrhythmia; or
- Cerebrovascular accident or transient ischemic attack within 6 months prior to first dose.

5. Have uncontrolled hypertension. Patients with hypertension should be under treatment on study entry to control blood pressure.
6. Currently being treated with medications known to be associated with the development of Torsades de Pointes (see Appendix F).
7. Have an ongoing or active infection, including, but not limited to, the requirement for intravenous antibiotics. Have a known history of HIV infection. Testing of HIV is not required in the absence of history.

   Hepatitis B surface antigen (HBsAg) positive patients are allowed to enroll if hepatitis B virus (HBV)-DNA is below 1000 copies/mL in the plasma.

   Patients who have positive hepatitis C virus (HCV) antibody can be enrolled but must have HCV-RNA undetectable in the plasma.
8. Currently have or have a history of interstitial lung disease (ILD), radiation pneumonitis that required steroid treatment, or drug-related pneumonitis.
9. Female patients who are lactating and breastfeeding or have a positive serum pregnancy test during the screening period.

   Note: Female patients who are lactating will be eligible if they discontinue breastfeeding.
10. Have gastrointestinal illness or disorder that could affect oral absorption of TAK-788.
11. Have 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 drug.

Phase-Specific Exclusion Criteria

In addition to the general exclusion criteria above, patients are not eligible for participation in the study phase if they meet any of the following exclusion criteria for the study phase in which their entry is proposed.

Phase 1 Part

1. Previously received TAK-788.
2. Received small-molecule anticancer therapy (including cytotoxic chemotherapy and investigational agents) within 14 days prior to the first dose of TAK-788 (except for reversible EGFR TKIs [ie, erlotinib or gefitinib] up to 7 days prior to the first dose of TAK-788).
3. Received antineoplastic monoclonal antibodies including immunotherapy within 28 days prior to the first dose of TAK-788.

4. Received radiotherapy within 14 days prior to the first dose of TAK-788, Stereotactic radiosurgery (SRS) and stereotactic body radiosurgery are allowed up to 7 days prior to the first dose.
5. Have symptomatic CNS metastases (parenchymal or leptomeningeal) at screening or asymptomatic disease requiring corticosteroids to control symptoms within 7 days prior to the first dose of TAK-788.

   Note: If a patient has worsening neurological symptoms or signs due to CNS metastases, the patient needs to complete local therapy and be neurologically stable (with no requirement for corticosteroids or use of anticonvulsants) for 7 days prior to the first dose of TAK-788. Patients with no prior history of signs or symptoms of CNS metastases but who receive prophylactic steroids or anticonvulsants are allowed.
6. Received a strong cytochrome P450 (CYP)3A inhibitor or strong CYP3A inducer within 2 weeks prior to first dose of TAK-788 (see Appendix E).

Phase 2 Part

1. Received radiotherapy within 14 days before the first dose of TAK-788 or has not recovered from radiotherapy-related toxicities. Stereotactic radiosurgery, stereotactic body radiotherapy, or palliative radiation outside the chest and brain is allowed up to 7 days before the first dose of TAK-788.
2. 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.
3. Received a moderate or strong CYP3A inhibitor or moderate or strong CYP3A inducer within 10 days prior to first dose of TAK-788 (see Appendix E).
4. Have cardiac ejection fraction <50% by echocardiogram or multigated acquisition (MUGA) scan at screening.

8.0 STUDY DRUG

8.1 Study Drug Administration

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

If emesis occurs after study drug ingestion, the dose will not be re-administered, and patients should resume dosing at the next scheduled time with the prescribed dosage. Patients should record the occurrence of the emesis in their patient diary. Under no circumstance should a patient repeat a dose or double-up doses.

Phase 1 Part

TAK-788 drug product will be administered orally. TAK-788 will be self-administered by the patient. The starting dose will be 40 mg orally administered once daily, and increasing up to 160 mg which is MTD identified in non-Japanese patients. Each 28-day dosing period is referred to as 1 cycle. Patients will take the prescribed dose with water with or without a low-fat meal (ie, ≤350 kcal and ≤15% of calories from fat). 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). Missed doses should be recorded in an appropriate source record (eg, clinic chart), patient diary, and study drug administration electronic case report form (eCRF).

Phase 2 Part

TAK-788 drug product will be administered orally. TAK-788 will be self-administered by the patient. The dose will be 160 mg orally administered once daily. Each 28-day dosing period is referred to as 1 cycle. Patients will take the prescribed dose with water with or without a low-fat meal (ie, ≤350 kcal and ≤15% of calories from fat). 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). Missed doses should be recorded in an appropriate source record (eg, clinic chart), patient diary, and study drug administration eCRF.

In case of extenuating circumstances that prevent a patient from attending the study site (eg, the COVID-19 pandemic), drug packs and patient diaries should be returned at the next available on-site clinic visit.

8.2 Definitions of DLT (Phase 1 Part only)

A DLT is a drug-related toxicity that is observed to occur within the first 28 days of treatment (end of Cycle 1) as defined below. Toxicity grades will be defined by the NCI CTCAE v5.0. DLTs are defined by the following:

- Non-hematologic toxicities
  - Any ≥ grade 3 non-hematologic toxicity, with the exception of self-limiting or medically controllable toxicities (eg, nausea, vomiting, fatigue, electrolyte disturbances, hypersensitivity reactions) lasting <3 days, and excluding alopecia.
- Hematologic toxicities
  - Febrile neutropenia not related to underlying disease (fever, >101°F [>38.3°C]; absolute neutrophil count $<0.5 \times 10^9$/L);
  - Prolonged grade 4 neutropenia (≥7 days) (if granulocyte-colony stimulating factor [G-CSF] is required, the event will be considered as DLT irrespective of the duration);
  - Neutropenic infection: ≥ grade 3 neutropenia with ≥ grade 3 infection;
  - Thrombocytopenia ≥ grade 3 with bleeding, ≥ grade 3 requiring platelet transfusion or grade 4 without bleeding lasting ≥7 days.

    Note: Prophylactic platelet transfusions or prophylactic use of hematopoietic growth factors (such as thrombopoietin, G-CSF, and granulocyte macrophage-colony stimulating factor [GM-CSF]*) is not permitted during the DLT evaluation period.
    *thrombopoietin and GM-CSF have not been approved for the treatment of anemia associated with cancer chemotherapy in Japan.
- Missed ≥25% of planned doses of TAK-788 over 28 days due to treatment-related AEs in the first cycle.

8.3 Dose Escalation Rules (Phase 1 Part Only)

The starting dose in the study will be 40 mg, followed by dose escalation up to 160 mg which is MTD identified in non-Japanese patients. The dose escalation steps after the starting dose will be modified as needed, using BLRM based on accumulating broader knowledge of safety, PK and anti-tumor activity of TAK-788 obtained from this study and the Study AP32788-15-101, which could potentially reduce the escalation steps and potentially decrease the number of patients exposed to subtherapeutic doses.

The MTD will be determined based on the DLT within the first 28 days of treatment (end of Cycle 1). Evaluable patients must complete at least 75% of their planned doses, unless missed doses are due to AEs. An adaptive BLRM that implements escalation with overdose control will be used in this study for purposes of dose escalation recommendations and estimation of the MTD. Data from the Study AP32788-15-101 will be used as prior information in the BLRM. For each dose level, the posterior probability of having DLT rates that fall into the following intervals will be estimated:

- [0, 0.21): under-dosing.
- [0.21, 0.33): target toxicity.

- [0.33, 1.00]: excessive toxicity.

BLRM will recommend a dose which follows the Escalation With Overdose Control (EWOC) principle and has the highest posterior probability of having a DLT rate that falls into the interval [0.21, 0.33) as the target toxicity rate at MTD. Following the EWOC principle, the posterior probability of the recommended dose having a DLT rate above 0.33 must not exceed 30%. The selection of the next recommended dose will be determined along with other available information, such as safety, PK and efficacy. Regarding the safety, all AEs observed in all of the enrolled patients, including those observed in DLT non-evaluable patients, will be evaluated in concert with DLTs when making the decision on selecting next dose level.

More conservative dose escalation, evaluation of intermediate doses, and expansion of an existing dose level are all permissible following discussions between the sponsor and the investigators if such measures are needed for patient safety or for a better understanding of the dose-toxicity and dose-exposure relationship of TAK-788.

The MTD may be declared as the current dose if the following stopping rules is met:

- At least 9 patients are evaluable in the study and at least 6 patients are evaluable at the current dose, and the current dose is the recommended dose for the next cohort.

Alternative stopping rules may also be considered following discussions between the sponsor and the investigators.

8.3.1 Intra-patient Dose Escalation (Phase 1 Part only)

Intra-patient dose escalation will be allowed in each patient while on the study if all of the following conditions are met:

1) The patient tolerated his/her starting dose without a DLT.
2) Cycle 2 PK samples have been drawn per protocol.
3) The dose to be escalated had been evaluated to be safe, and the decision for intra-patient dose escalation will be made together with the sponsor and the investigators in end of cohort meeting.

8.4 Dose Modification Guidelines

8.4.1 Dose Delays or Reductions

Dose delays or reductions will be implemented for patients who experience TEAEs as indicated in the following section and in Table 8.a. Proposed dose-reduction levels for the Phase 2 part are summarized in Table 8.b.

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 8.4.2. If toxicity requiring dose reduction occurs in the first dose cohort (in phase 1 part), discontinue therapy.

Table 8.a Dose Modifications

Toxicity Grade	Action
Non-Hematologic Toxicity	
Grade 1	Continue therapy at the same dose level.
Grade 2	Continue therapy at the 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.
Grade 3	Withhold therapy until toxicity is ≤ grade 1 or has returned to baseline, then resume therapy. Therapy may be resumed at the most recent dose or at the next lower dose level, based on the investigator's judgment.
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 the same dose level.
Grade 2	Continue therapy at the 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 most recent 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.

Table 8.b Proposed Dose Reduction Level of Phase 2 Part

Dosing	Dose Level
Starting dose	160 mg QD
First dose reduction	120 mg QD
Second dose reduction	80 mg QD

Abbreviations: QD, once daily.

8.4.1.1 Management of Selected Treatment-Related Adverse Events

If selected treatment-related adverse events are occurred, they should be managed as below,

Nausea and Emesis

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

Diarrhea

Based on pre-clinical findings and known class effect, patients should be monitored for the onset of diarrhea. Symptomatic care, such as loperamide, may be given at first evidence of loose stool, increased frequency of bowel movement, or at grade 1 diarrhea, according to the investigator's clinical judgment (not to exceed total dose of 16 mg over 24 hours). For grade 2 diarrhea, administer loperamide at 4 mg, then 2 mg every 2 to 4 hours until the patient is symptom-free for 12 hours (not to exceed total dose of 16 mg over 24 hours). No dose modification is necessary unless the patient does not tolerate TAK-788 or the symptom recurs. For grade ≥3 diarrhea despite loperamide, treatment will be withheld until recovery to grade ≤1 diarrhea. Secondary prophylaxis in patients who have experienced diarrhea with TAK-788 treatment is allowed. Other medications (such as diphenoxylate hydrochloride with atropine sulfate) and supportive care may be added according to the institution's standard of care. Primary prophylactic antidiarrheal medications may be used after discussion with the sponsor.

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.

Asymptomatic Lipase/Amylase Elevation

In the event of grade 3 asymptomatic lipase/amylase elevation (>5.0 × 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 to ≤5.0 × ULN), continue therapy at 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 of lipase/amylase levels and clinical symptoms are highly recommended.

Cardiac Events: QTc Interval Prolongation and Heart Failure

TAK-788 dose modification guidelines, outlined in Table 8.c, should be closely followed for patients who experience QTc interval prolongation or heart failure deemed related to TAK-788 dosing. TAK-788 dose reduction levels should follow the schedule outlined in Table 8.b.

Table 8.c TAK-788 Dose Modification for TEAEs of QTc Interval Prolongation and

Heart Failure

Toxicity Grade	Parameters	TAK-788 Dose Modification
QTc Interval Prolongation		
Grade 2	QTc Interval of 481 to 500 msec.	**First Occurrence:** • Withhold TAK-788 dosing until QTc interval recovers to a ≤Grade 1 or baseline. • Once recovered, resume TAK-788 at the most recent dose. **Recurrence:** • Withhold TAK-788 until ≤ Grade 1 or baseline. • Once recovered, resume TAK-788 dosing at the next lower dose level or permanently discontinue dosing, based on clinical judgement.
Grade 3	≥501 msec *or* Increases of >60 msec from baseline.	**First Occurrence:** • Withhold TAK-788 until ≤ Grade 1 or baseline. • Once recovered, resume TAK-788 dosing at the next lower dose level, or permanently discontinue TAK-788 dosing, based on clinical judgement. **Recurrence:** • Permanently discontinue TAK-788 dosing.
Grade 4	Torsades de Pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmias.	Permanently discontinue TAK-788 dosing.
Decreased Ejection Fraction		
Grade 2: Ejection fraction - asymptomatic.	Resting ejection fraction 50% to 40% *or* Decrease from baseline 10% to 19%.	• Withhold TAK-788 until recovered to baseline. • If the patient recovers to baseline within 2 weeks of dose interruption, resume TAK-788 at the most recent dose level or the next lower dose level, in accordance with clinical judgement. • If the patient does not resume to baseline within 2 weeks of dose interruption, permanently discontinue TAK-788 dosing.
≥Grade 3: Ejection fraction - asymptomatic.	Resting ejection fraction ≤39% *or* ≥ 20% decrease from baseline.	Permanently discontinue TAK-788 dosing.

Toxicity Grade	Parameters	TAK-788 Dose Modification
Heart Failure		
Any Grade		Permanently discontinue TAK-788 dosing.
Heart failure - symptomatic		

QTc: corrected QT interval; TEAE: treatment-emergent adverse event.

8.4.2 Dose Re-escalation

Dosing reduced for toxicity may be re-escalated to the original dose only after discussion with the sponsor. For dose re-escalation, the following conditions have to be met.

1) The original dose does not exceed the MTD (160 mg QD).
2) The patient recovered from the AE.
3) The reduced dose is considered subtherapeutic in the opinion of the investigator.
4) The AE is not considered clinically significant in the judgment of the investigator, with exceptions such as ILD/pneumonitis, hepatic injury, acute pancreatitis.

For patients who continue the treatment despite radiologic PD (as described in Section 8.4.3), the dose may be escalated to a higher dose that is determined not to exceed the MTD, following discussion with the sponsor.

8.4.3 Criteria for Discontinuation of Study Drug

Patients will be discontinued from further study drug administration in the event of any of the following:

- Intolerable toxicity as determined by the investigator.
- PD requiring an alternate therapy, in the opinion of the investigator.

  Note: Treatment of patients with TAK-788 may be continued, despite progression by RECIST v1.1, at the discretion of the investigator, if there is still evidence of clinical benefit.
- Patient meets the discontinuation rules for pneumonitis (Section 8.4.1.1).
- Entry into another therapeutic clinical study or start of new anticancer therapy.
- Significant deviation from the protocol or eligibility criteria, in the opinion of the sponsor's medical monitor or investigator.
- Noncompliance with study or follow-up procedures.
- Pregnancy.
- Patient withdrawal of consent or decision to discontinue participation.
- Termination of the study by the sponsor.

- Any other reason that, in the opinion of the investigator, would justify removal of the patient from the study.

8.5 Excluded Concomitant Medications and Procedures

The medications and procedures which a patient is not allowed to use at the time of screening and prior to the first dose of TAK-788 are described in inclusion and exclusion criteria.

The following concurrent medications and procedures are prohibited **until the study drug discontinuation described in Section 9.9**. If a patient's clinical condition requires treatment with one of the prohibited classes of medications specified below, 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.

- Any other 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);
- Use of any other investigational drug or device;
- Medications that are known to be associated with the development of Torsades de Pointes. Medications that prolong the QT interval, but are not known to be associated with Torsades de Pointes, should be avoided but are not prohibited (see Appendix F);
- Herbal preparations or related over-the-counter preparations containing herbal ingredients, or other folk remedies;
- Grapefruit or grapefruit-containing products, pomegranate, pomelo, or star fruit juice containing products, and Seville oranges;
- Extensive surgery requiring in-patient care (patients may have an interruption in therapy for 2 weeks should emergency surgery be required);
- Medications that are moderate or strong inducers, or moderate or strong inhibitors of the CYP3A family of Cytochromes P450 (see Appendix E), with the exception of nonsystemic use (eg, topical);
- Any illicit substance.

The following concurrent medications, exposure to which may be affected by TAK-788, may be allowed with caution, and 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:

- Medications that are CYP3A substrates and which have narrow therapeutic index including alfentanil, cyclosporine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus, and all statins;

- CYP2C8 sensitive substrates, including repaglinide, dasabuvir and amodiaquine;
- Warfarin, a CYP2C9 sensitive substrate;
- S-mephenytoin, a CYP2C19 sensitive substrate.

8.6 Permitted Concomitant Medications and Procedures

Palliative therapy and supportive care are permitted during the course of the trial for management of symptoms and underlying medical conditions that may develop during the study.

8.7 Precautions and Restrictions

8.7.1 Pregnancy and Contraception

TAK-788 demonstrated embryo-fetal toxicity in rats and, similar to other EGFR inhibitors, has the potential to cause embryo-fetal 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. Female patients of childbearing potential and male patients will be informed as to the potential risk of conception while participating in this study and will be advised that they must use effective contraception (ie, results in a low failure rate when used consistently and correctly), as specified below. A pregnancy test will be performed on each pre-menopausal female patient of childbearing potential at screening, immediately prior to the first dose of study drug, once every 4 weeks while on treatment, and again at treatment discontinuation during the End-of-Treatment visit. A negative pregnancy test must be documented prior to administration of study drug.

Female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit, OR
- Surgically sterile, OR
- If they are of childbearing potential, agree to practice the following 1 highly effective non-hormonal method and 1 additional effective (barrier) method of contraception at the same time, from the time of signing ICF through 30 days after the last dose of study drug, OR

  <u>Highly effective non-hormonal methods:</u>

  – Intrauterine device (IUD).
  – Bilateral tubal occlusion.
  – Vasectomised sole sexual partner.

  <u>Additional effective (barrier) methods:</u>

  – Male condom with or without spermicide.

- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject.

  Note: Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception.

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

- Agree to practice effective barrier contraception (eg, latex condom with a spermicidal agent) during the entire study treatment period and through 30 days after the last dose of study drug, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject.

  Note: Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception.

If a patient is confirmed pregnant during the study, study drug administration must be discontinued immediately. The investigator must immediately notify the sponsor's medical monitor of this event and record the pregnancy on the paper Pregnancy Form. Initial information regarding a pregnancy must be immediately sent to the Takeda Global Pharmacovigilance department or designee.

The investigator must immediately report follow-up information to the sponsor regarding the course of the pregnancy, including perinatal and neonatal outcome. If the pregnancy results in the birth of a child, additional follow-up information may be requested. If the pregnancy results in spontaneous abortion or stillbirth, the event should be reported as an SAE.

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.

Pregnancy outcomes also must be collected for the female partners of any male patients who took study drug in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the female partner.

It is not known whether TAK-788 passes into the breast milk. Mothers should not breastfeed during the entire study treatment period and through 30 days after the last dose of study drug.

8.7.2 Potential Drug Interactions

In vitro reaction phenotyping studies with human liver microsomes and selective CYP inhibitors, and recombinant human CYPs, indicate that TAK-788 is mostly metabolized by CYP3A4/5. Therefore, it is likely that orally administered CYP3A4/5 inhibitors and/or inducers may affect plasma drug levels of TAK-788 and its active metabolites (including, but not limited to,

AP32960 and AP32914) and cause potential clinical drug-drug interactions (DDIs). Medications, and dietary (grapefruit-containing products) or herbal products that are moderate or strong inhibitors, or moderate or strong inducers of CYP3A4/5 should be avoided (see Appendix E).

Based on nonclinical in vitro data, TAK-788, AP32914, and AP32960 are not anticipated to inhibit CYP1A2-, CYP2C9-, CYP2C19-, or CYP2D6-mediated metabolism of co-administered drugs. Given the inhibition constant (Ki) values ($IC_{50}/2$) and the expected plasma exposures of TAK-788, AP32914, and AP32960 in humans, TAK-788, AP32914, and AP32960 are not likely to exhibit DDIs due to inhibition of CYP2B6, CYP2C8, or CYP3A4/5. TAK-788 showed time-dependent inhibition of CYP3A4/5 in vitro, with a 10-fold IC_{50} shift (22.3 to 2.51 µM [testosterone 6β-hydroxylation] and 19.7 to 1.98 µM [midazolam 1'-hydroxylation]). TAK-788 and its active metabolites, AP32960 and AP32914, were potent inducers of CYP3A4 in vitro at concentrations ≥1 µM; however, the induction effect was much lower at concentrations ≤0.1 µM with little-to-no induction observed at 0.01 µM. Given that activation of the pregnane X receptor results in co-induction of CYP3A and CYP2C isozymes, it was considered likely that TAK-788 and its metabolites could induce CYP2C isozymes. Testing of the potential of TAK-788 to induce CYP2C isozymes in vitro revealed weak induction of CYP2C isozymes at up to 5 µM TAK-788; however, TAK-788 metabolites have not been tested. Based on in vitro results, there is a potential DDI of TAK-788 and its active metabolites, AP32960 and AP32914, with CYP3A substrates as a perpetrator.

TAK-788 induces CYP3A, 2C8, and 2C9 in vitro and may decrease concentrations of concomitantly administered CYP3A, 2C8, and 2C9 substrates. Based on emerging clinical PK data from this study, 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 by TAK-788. Coadministration of TAK-788 with substrates of CYP3A, including hormonal contraceptives, and other pregnane X receptor–inducible enzymes (eg, CYP2C9, CYP2C19) and transporters (eg, P-glycoprotein), may result in decreased concentrations and loss of efficacy of these coadministered drugs.

8.7.3 Concomitant Medications with QTc Interval Prolongation Potential

Investigators should provide close oversight of patients when co-dosing TAK-788 with concomitant medications with known QTc interval prolongation. Additional ECGs, as clinically indicated should be conducted in accordance with the investigator's judgement. Dose modification for patients exhibiting QTc interval prolongation is outlined in Section 8.4.1.1. Restricted concomitant medications with a known risk of Torsades de Pointes are provided in Appendix F.

8.8 Management of Clinical Events

8.8.1 Management of Adverse Drug Reactions

Comprehensive assessments of any study drug-related AEs (adverse drug reactions) experienced by the patient will be performed throughout the course of the study. Anticipated adverse drug

reactions that may be experienced are described in the Investigator's Brochure. The severity of the event, as well as clinical judgment, will be utilized to determine appropriate management of the patient for any AE experienced while participating in this study.

8.8.2 Management of Selected Treatment-Related Adverse Events

Management of selected treatment-related AEs are provided in Section 8.4.1.1.

8.9 Blinding and Unblinding

This is an open-label study.

8.10 Description of Investigational Agents

TAK-788 drug product is a nonsterile, oral, capsule dosage form, supplied in a white, opaque, hard gelatin capsule shell containing 40 mg (as free base) of TAK-788 succinate salt as 100% active pharmaceutical ingredient (API). No other ingredients are included in the drug product.

For additional details, refer to the Investigator's Brochure and Pharmacy Manual.

8.11 Preparation, Reconstitution, and Dispensation

TAK-788 dosage forms will be provided in labeled bottles in accordance with all applicable regulations. Materials provided by the sponsor should be dispensed to patients with clear administration instructions from the investigator.

Detailed instructions for dispensing TAK-788 dosage forms are provided in the Pharmacy Manual.

TAK-788 is an anticancer drug, and as with other potentially toxic compounds, caution should be exercised when handling TAK-788.

8.12 Packaging and Labeling

TAK-788 drug product will be provided by the sponsor. TAK-788 drug product will be supplied in white 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.

8.13 Storage, Handling, and Accountability

The recommended storage condition for TAK-788 drug product is at a temperature thermostatically maintained at the usual customary working environment of 1°C to 30°C, as experienced in pharmacies, hospitals, and warehouses.

The study pharmacist or designee at the site will be responsible for handling and dispensing study drug and completing associated documentary paperwork. Supplies are 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 medication is dispensed to a patient, the following information must be recorded: the patient identification number, drug product strength, quantity dispensed with the corresponding lot number, and the signs 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.

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/IRB, TAK-788 can be shipped DTP from the investigation site to the patient's home address via courier if needed.

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.

8.13.1 Disposition of Used Supplies

All used bottles of study drug can 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.

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 of residual study drug.

8.13.2 Inventory of Unused Supplies

During the study 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.

The sponsor will confirm an inventory of unused study drug periodically during the study, and at the completion of the study, a final study drug accountability review will be conducted. Any discrepancies must be investigated.

The on-site pharmacist will immediately return unused study drugs to the sponsor after the study is closed at the study site.

Please refer to the Pharmacy Manual for additional instructions.

8.14 Other Protocol-Specified Materials

Not applicable.

9.0 STUDY CONDUCT

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

9.1 Study Personnel and Organizations

The contact information for the Takeda clinician, other third-party vendors participating in the study as well as the list of investigators can be found in the protocol annex or Study Manual.

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).

9.3 Treatment Group Assignments

After written informed consent has been obtained, the patient will be assigned a patient identification number.

Patients who meet all eligibility criteria and provide written informed consent will be enrolled in this study, and the treatment of TAK-788 will be started. In Phase 1 part, the dose level to be administered will be determined according to the dose escalation scheme outlined in Section 8.3. In Phase 2 part, the dose will be 160 mg orally administered once daily.

Patients who screen fail may later be re-screened with prior sponsor approval.

9.4 Study Procedures

The study procedures to be performed at screening and throughout the entire study are listed in the schedule of events (Appendix A), which is meant to provide a convenient display of the timing and scope of required assessments expected at each visit, but does not provide a comprehensive description of each assessment. Additional details are provided as necessary in the sections that follow.

The ICF may be signed more than 21 days before C1D1. Screening assessments must be performed within 14 days before C1D1, with the exception of tumor imaging assessment, for which the allowable window is 21 days before C1D1.

Investigators must be familiar with the details of this section and use it in conjunction with the table to adequately carry out the required study assessments. All study assessments should occur within ±3 days of the scheduled study day unless otherwise noted in the schedule of events descriptions or table. A cycle is defined as 28 days.

In Phase 1, patients will be hospitalized during DLT evaluation in Cycle 1. If a patient needs to be discharged temporarily during the period, the investigator must obtain an approval from the sponsor. The investigator must document the confirmation record for stabilization of the

patient's symptoms per the available data in an appropriate source record (eg, medical records) before the patient's temporary discharge.

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. Such instances will be documented in the study records.

9.4.1 Informed Consent

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

9.4.2 Patient Demographics

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

9.4.3 Medical/Surgical History

During the screening period, a complete medical history will be compiled for each patient. Information to be recorded includes relevant past illnesses, smoking classification, ongoing medical conditions, and surgical procedures (not related to the primary diagnosis).

9.4.4 Diagnosis and Cancer History

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

9.4.5 Mutation Status

Mutation status at baseline (eg, activating mutations in EGFR or HER2, as well as other previously identified abnormalities in other genes) should be recorded if available. Information on the specific point mutations, deletions, insertions, or gene rearrangements observed should be recorded, if available.

Phase 2 Part

All patients in the Phase 2 part will have a documented EGFR exon 20 insertion mutation by a local test prior to enrollment, and the patient's tumor specimen will be retrospectively confirmed for EGFR exon 20 insertion mutations by an analytically validated central test. Local testing can be technology agnostic (polymerase chain reaction, digital polymerase chain reaction, Sanger sequencing, or next-generation sequencing) as long as it is analytically validated and performed by an accredited local laboratory. Local mutation testing can be conducted from either tumor specimen or liquid biopsy.

9.4.6 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, neo adjuvant, adjuvant, for advanced/metastatic disease), number of cycles administered for each regimen, 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.

9.4.7 Physical Examination

A complete physical examination must be performed at screening, the extent of which should be consistent with medical history and the patient's underlying disease. Subsequent physical examinations as described in the schedule of events (Appendix A) may be directed to relevant findings. The End-of-Treatment physical examination should be a complete physical examination. The physical examination 30 days after last dose may be directed to any relevant findings.

9.4.8 Height and Weight

Height and weight will be measured during screening. Weight should be repeated on C1D1 prior to first dose, regardless of the time from screening, and it will also be assessed per the schedule of events (Appendix A) throughout the study.

9.4.9 Vital Signs and Auscultation

Vital signs include temperature, pulse, respiratory rate, blood pressure (when patient is seated), and percutaneous oxygen saturation. Vital signs and auscultation should be repeated on C1D1 prior to first dose, regardless of the time from screening. Vital signs and auscultation will also be assessed per the schedule of events (Appendix A) throughout the study.

9.4.10 ECOG Performance Status

The patient's performance status must be assessed using the ECOG performance scale during screening. ECOG performance status will also be assessed per the schedule of events (Appendix A) throughout the study. The ECOG performance scale is provided in Appendix D.

9.4.11 Cardiac monitoring

Phase 1 Part

Cardiac monitoring may be done according to medical judgement and as clinically indicated.

Phase 2 Part

Conduct cardiac monitoring, including assessment of LVEF by ECHO/MUGA at baseline (screening), Cycle 2 Day 1, Cycle 4 Day 1, Cycle 7 Day 1 and the end of treatment (Appendix A). In addition, cardiac monitoring may be done at other times according to medical judgement and as clinically indicated.

Both Phase 1 and Phase 2 Part

Assess LVEF in patients who develop relevant cardiac signs or symptoms [13]. 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 10.3.

9.4.12 Clinical Laboratory Evaluations

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

9.4.12.1 Clinical Chemistry, Hematology, and Urinalysis

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

Table 9.a Clinical Chemistry and Hematology Tests

Hematology	Serum Chemistry	
Hematocrit	Albumin	Chloride
Hemoglobin	Alkaline phosphatase (ALP)	Creatinine
Leukocytes with differential	Alanine aminotransferase (ALT)	C-reactive protein (CRP)
- absolute neutrophil count	Amylase	Glucose
- basophils count	Aspartate aminotransferase (AST)	Lipase
- eosinophils count	Bicarbonate (or carbon dioxide) (*Option*)	Magnesium
- lymphocytes count	Bilirubin (at least total and direct, or total and indirect)	Phosphate
- monocytes count	Blood urea nitrogen (BUN)	Protein (total protein)
Platelet count	Calcium	Potassium
		Sodium

Table 9.b Clinical Urinalysis Tests

Urinalysis	
Glucose	pH
Ketones	Protein
Occult blood	Specific gravity
	Urobilinogen

9.4.12.2 Serology

Serological assessments including HIV, HBsAg, HBV-DNA, HCV antibody, and HCV-RNA will be performed at screening. For patients who are positive for HBsAg or HCV antibody, the on-study testing should be performed according to the schedule of events (Appendix A). HIV test will not be required in the absence of HIV infection history.

9.4.12.3 KL-6 and SP-D

Krebs von den Lungen-6 (KL-6) and surfactant protein-D (SP-D) are used for evaluation of ILD/pneumonitis. Serum levels of KL-6 and SP-D will be assessed at screening, at 8-week intervals thereafter (on Day 1 [±3 days] of every even-numbered cycle), and at the time of diagnosis of ILD or pneumonitis (unscheduled collection).

9.4.13 Chest X-ray

Chest X-ray will be performed according to the schedule of events (Appendix A).

9.4.14 Pregnancy Test

The pregnancy test must be a beta-human chorionic gonadotropin (β-hCG) test, and either urine or serum can be used. Women who are not of childbearing potential (status post-hysterectomy, status post-bilateral oophorectomy, or post-menopausal [defined as amenorrhea for at least 12 months]) and men do not need to have the test performed.

Women of childbearing potential must be known to be negative pregnancy test at screening (serum test only) and within 7 days prior to the first dose of study drug (either urine or serum test). And the pregnancy test (either urine or serum test) must also be completed once every 4 weeks thereafter and at the End-of-Treatment assessment.

9.4.15 Electrocardiogram

All ECGs must be 12-lead ECGs. An ECG is required at screening to determine eligibility; this may be a single ECG. Single ECGs will also be assessed per the schedule of events (Appendix A) throughout the study. In addition to the pre-specified time points, additional ECGs may be performed at the investigator's discretion to ensure patient safety. In particular, ECG monitoring should be performed during the study if a patient has, during the study, been prescribed medication that can prolong the QT interval or medication that can potentially alter the QT interval (other than medications explicitly prohibited). ECGs will be recorded electronically and will be evaluated locally. For consistency, the Fridericia correction – QTcF – method must be used for all calculations of QTc intervals.

9.4.16 Adverse Events

Monitoring of AEs, serious and nonserious, will be conducted from the date the informed consent is signed until 30 days after the last dose of study drug or before initiation of new

anticancer therapy (whichever comes first). Refer to Section 10.0 for details regarding definitions, documentation, and reporting of AEs and SAEs.

9.4.17 Concomitant Medications and Procedures

Concomitant treatments 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 until 30 days after the last dose of study drug or before initiation of new systemic anticancer therapy (whichever comes first).

9.4.18 Disease Assessment

At screening, disease assessment must include imaging of the chest, abdomen, pelvis, and brain using appropriate radiological procedures (computed tomography [CT] scans or magnetic resonance imaging [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.

Patients must have at least 1 measurable lesion per RECIST v1.1 (see Appendix C). Previously irradiated lesions may not be used for target lesions, unless there is unambiguous radiological progression after radiotherapy. For Phase 1 part, brain lesions may be used as target lesions provided they are ≥10 mm and have not been: 1) previously treated with whole brain radiation therapy (WBRT) within 3 months, or 2) previously treated by SRS or surgical resection.

Local site investigator/radiology assessment based on RECIST version 1.1 will be used to determine subject eligibility. In extenuating circumstances during the COVID-19 public health emergency, patients may use alternative site for imaging during the study period if approved by the sponsor or designee.

Target and non-target lesions must be selected at study start and assessed throughout the course of treatment according to RECIST v1.1 guidelines. Disease assessment by CT and MRI scans will be performed at screening and at 8-week intervals thereafter (on Day 28 [±3 days in Phase 1 part and ±7 days in Phase 2 part] of every even-numbered cycle) through cycle 14 after the initial dose of study drug, and every 3 cycles thereafter until PD. More frequent imaging is recommended at any time if clinically indicated. Imaging assessment will also be performed at End-of-Treatment if more than 4 weeks have passed since the last imaging assessment. The same imaging modality should be used at each assessment, if possible.

PR and CR should be confirmed by a repeat tumor imaging assessment not less than 4 weeks from the date the response was first documented. The tumor imaging for confirmation of response may be performed at the earliest 4 weeks after the first indication of response, or at the next scheduled scan (ie, 8 or 12 weeks later), whichever is clinically indicated. Patients will then return to regular scheduled imaging, starting with the next scheduled imaging time point. Patients who obtain a confirmation scan or unscheduled scan do not need to undergo the next scheduled tumor imaging if it is <4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point. Imaging assessment will also be performed at end of treatment if

more than 4 weeks have passed since the last imaging assessment. The same imaging modality at the same institution should be used at each assessment, if possible, irrespective of study drug interruption or actual dosing. All radiographic images (eg, CT scan, MRI) performed during the study will be submitted to IRC for central review. The investigator assessment of the images will also be collected.

9.4.19 Samples for Pharmacokinetic and Biomarker Analyses

Primary Specimen Collection

#	Specimen Name in Schedule of Procedures	Primary Specimen	Primary Specimen Derivative 1	Primary Specimen Derivative 2	Description of Intended Use	Sample Collection
1	Archival (Banked) Tumor Tissue Sample (surgical resection)	FFPE block FFPE slides	DNA RNA		Biomarker measurements	Mandatory
2	Fresh Tumor Tissue Biopsy Sample	Fresh tumor tissue	FFPE block FFPE slides	DNA RNA	Biomarker measurements	Mandatory if archival (banked) tumor tissue is not available
3	Fresh Tumor Tissue Biopsy Sample at disease progression	Fresh tumor tissue	FFPE block FFPE slides		Biomarker measurements	Optional
4	Plasma Sample for Cell Free DNA	Plasma	DNA		Biomarker measurements	Mandatory
5	Plasma Sample for Cholesterol	Plasma			Biomarker measurements	Mandatory
6	Plasma Samples for TAK-788 PK	Plasma			PK measurements	Mandatory
7	CSF sample for TAK-788 PK	Cerebrospinal fluid			PK measurements	Optional
8	Matched Plasma Samples for TAK-788 PK	Plasma			PK measurements	Mandatory if cerebrospinal fluid is collected

Abbreviations: CSF, cerebrospinal fluid; FFPE, formalin fixed paraffin embedded; PK, pharmacokinetic(s).

9.4.19.1 PK sample

Phase 1 Part

Blood samples will be collected at pre-specified time points (pre- and post-dosing) (see PK Sampling Time Points in Appendix A) to assess the plasma concentrations of TAK-788 and active metabolites (including, but not limited to, AP32960 and AP32914) and PK parameters following a single dose and multiple doses (steady state).

Phase 2 Part

The plasma concentrations of TAK-788 and active metabolites (including, but not limited to, AP32960 and AP32914) will be measured centrally.

Both Phase 1 Part and Phase 2 Part

If lumbar puncture is performed as part of the standard of care, remaining CSF samples should be analyzed to determine the concentration of TAK-788 and its active metabolites, including, but not limited to, AP32914 and AP32960 (≥500 µL is sufficient), and these samples should have matched blood samples (for PK analyses) when possible (Section 9.4.21).

9.4.19.2 Biomarker sample (Phase 2 Part Only)

1) Plasma Samples for Cell Free DNA

Plasma samples will be collected for evaluating circulating cell-free DNA at the time points specified in the schedule of events (Appendix A). Only mutations associated with tumor DNA will be sequenced. Details regarding the preparation, handling, and shipping of the blood samples are provided in the laboratory manual.

2) Plasma Samples for Cholesterol

Plasma samples will be collected for evaluating 4-beta-OH-cholesterol/cholesterol at the time points specified in the schedule of events (Appendix A). Details regarding the preparation, handling, and shipping of the blood samples are provided in the laboratory manual.

9.4.20 Tumor Tissue Sample (Phase2 Part Only)

All patients in the Phase 2 part must submit an available formalin fixed paraffin embedded (FFPE) tumor tissue sample during screening for confirmation of mutation status by central testing. The tumor tissue will also be used for exploratory biomarker studies, including but not limited to molecular genetic analysis of EGFR, HER2, and other genes implicated in tumor biology. An immunoprofiling study may be conducted if enough tissue is available. The tumor tissue may be archived tissue or fresh tissue if archived tumor tissue is not available.

Patients who are not centrally confirmed to have EGFR exon 20 insertion mutations may continue to receive study drug if they are receiving clinical benefit at the discretion of the investigator and with the sponsor's approval; these patients will continue in the study and have data collected per the schedule of events.

9.4.21 Cerebrospinal Fluid (CSF) Collection

If lumbar puncture is performed as part of the standard of care, remaining CSF samples should be analyzed to determine the concentration of TAK-788 and its active metabolites, including, but not limited to, AP32914 and AP32960 (≥500 µL is sufficient), and these samples should have matched blood samples (for PK analyses) when possible (Section 9.4.19.1).

9.4.22 Patient-Reported Outcome Assessments (Phase 2 Part Only)

Patient-reported outcomes will be collected by administering the following paper questionnaires: the EORTC QLQ-C30 (v3.0) and the lung cancer-specific module (the EORTC QLQ-LC13, v3.0) as described in the schedule of events (Appendix A). These assessments have been studied

extensively, have evidence of reliability and validity in the current patient population, and are suitable for use in global clinical studies. The questionnaires will be administered to patients in their local language, if available.

On the study days they are administered, the questionnaires should be completed by patients prior to any testing or discussion with the physician. The patient should be given sufficient space and time to complete the questionnaires. The patient should complete the questionnaires on their own without any assistance from site staff or a caregiver. If the patients arrive for their scheduled visits, the questionnaires are intended to be self-reported and should not be interviewer-administered.

The EORTC QLQ-C30 is a cancer-specific questionnaire initially tested in lung cancer patients [14]. The EORTC QLQ-C30 will be scored for 5 functional scales (physical, role, cognitive, emotional, and social functioning); 3 symptom scales (fatigue, pain, and nausea/vomiting); and a global health status/QoL scale. Six single-item scales also are included (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties).

The LC13 module was constructed in parallel with the core QLQ-C30. It comprises 13 questions assessing lung cancer-associated symptoms (cough, hemoptysis, dyspnea, and site-specific pain), treatment-related side effects (sore mouth, dysphagia, peripheral neuropathy, and alopecia), and use of pain medication [15][16]. The LC13 module incorporates 1 multi-item scale to assess dyspnea, and a series of single items assessing pain, coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia, and haemoptysis.

For both the QLQ-C30 and QLQ-LC13, raw scores are converted into scale scores ranging from 0 to 100. For the functional scales and the global health status scale, higher scores represent better HRQoL, whereas for the symptom scales lower scores represent better HRQoL. All items in this questionnaire relate to a recall period of 1 week.

Note: Signs and symptoms assessed with the patient-reported outcome questionnaires will not be considered AEs unless entered as such into the eCRF.

9.5 Documentation of Subject Failure

Investigators must account for all subjects who sign informed consent.

If the subject is found to be not eligible before the first dose, the investigator should complete the applicable eCRF.

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

- Death.
- AE.
- Screen failure (failed inclusion criteria or did meet exclusion criteria).
- Protocol deviation.
- Lost to follow-up.

- Withdrawal by subject.
- Study terminated by sponsor.

Patient identification codes assigned to subjects who fail screening should not be reused.

9.6 Completion of Study Treatment (for Individual Patients)

Patients will be considered to have completed study treatment if they receive the study treatment until PD that requires an alternate therapy in the opinion of the investigator, intolerable toxicity, or until they discontinue treatment for other reasons.

End-of-Treatment assessments (see Appendix A) 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, urinalysis), 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. For the End-of-Treatment assessments, information may be collected from tests performed for the study or as part of the patient's routine medical care.

9.7 Follow-Up After Last Dose

The 30 Days After Last Dose assessments (see Appendix A) must be performed within 30 days (±7 days) after the last dose of study treatment. Physical examinations, laboratory tests (hematology, chemistry, urinalysis), 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 the 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.

Follow-up assessments for PFS and OS are performed in the Phase 2 Part. Detailed information is provided in Section 9.12.

9.8 Completion of Study (for Individual Patients)

Phase 1 Part

Patients will be considered to have completed the study if they complete the 30 Days After Last Dose assessments.

Phase 2 Part

Patients will be considered to have completed the study if they are followed until death or until the sponsor terminates the study.

9.9 Discontinuation of Treatment With Study Drug

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

- AE.
- Protocol deviation.
- PD.
- Symptomatic deterioration.
- Lack of efficacy.
- Pregnancy (patient must be discontinued).
- Study terminated by sponsor.
- Withdrawal by subject.
- Lost to follow-up.
- Other.

Once study drug has been discontinued, all study procedures outlined for the end-of-treatment visit will be completed as specified in the schedule of events. The primary reason for study drug discontinuation will be recorded on the eCRF.

In the case of study termination by the sponsor, eligible patients may have continued access to TAK-788 as described in Section 6.3.4.

9.10 Withdrawal of Patients From Study

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

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

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

9.11 Study Compliance

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

Patients will be provided a patient diary in which the date and time of study drug administration will be recorded. Patients who forget to take or miss their dose should not make up the missed dose. Any missing doses must be recorded in an appropriate source record (eg, clinic chart),

patient diary card, and study drug administration eCRF. In addition, patients will be instructed to use the diary card to record whether the dose was taken with or without a low-fat meal. Training of patients should be documented in the appropriate source record (eg, clinic chart). When possible, patients should take the study drug under observation during scheduled study visits to the clinic where a predose blood sample is collected. The investigator is responsible for ensuring that the patient diary card(s) are accounted for and noted in source documentation.

9.12 Post-Treatment Follow-up Assessments (PFS and OS, Phase 2 Part Only)

Only in the phase 2 part, patients who stop treatment for any reason other than PD will continue to have PFS follow-up visits and OS follow-up visits.
The PFS follow-up visit should be performed every 8 weeks until Week 56 (equivalent to Cycle 14 Day 28), and every 12 weeks (±14 days) thereafter, from the EOT visit to the occurrence of documented PD or the start of subsequent anticancer therapy.

After the occurrence of documented PD or the start of subsequent anticancer therapy, patients will continue to have OS follow-up visits. The OS follow-up visits should be performed every 12 weeks (±14 days) until death, loss to follow-up, consent withdrawal, study termination, or any of the circumstances described in Section 9.10 occur.

The duration of OS follow-up will be 3 years after enrollment of the last patient, or until all patients have discontinued study treatment, whichever occurs later.

Survival information and death details may be collected by methods that include, but are not limited to, telephone, email, and mail.
NOTE: Related SAEs must be reported to the Takeda Global Pharmacovigilance department or designee. This includes deaths that the investigator considers related to study drug that occur during the post-treatment follow-up. Details about definition, documentation, and reporting of SAEs are provided in Section 10.1.2 and Section 10.2.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 AE Definition

An AE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study; it does not necessarily have to have a causal relationship with this treatment or study participation.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the study participation whether or not it is considered related to the drug.

This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the study participation.

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

10.1.2 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 lab abnormality, will be determined using the NCI CTCAE, version 5.0, effective 27 November 2017 [17]. 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 (as defined in Section 10.1.2) must be reported (see Section 10.3 for the period of observation) by the investigator to the Takeda Global Pharmacovigilance department or designee (contact information provided below). This should be done by faxing the SAE Form within 24 hours after becoming aware of the event. The SAE Form, created specifically by Takeda, will be provided to each clinical study site. A sample of the SAE Form may be found in the Study Manual. Follow-up information on the SAE may be requested by Takeda. Information in the SAE report must be consistent with the data provided on the eCRF.

SAE Reporting Contact Information

BELLSYSTEM24, Inc.

Toll-free fax: [redacted]

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

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 lab abnormality, will be determined using the NCI CTCAE, version 5.0, effective 27 November 2017 [17].

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

10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

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

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

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

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

A medication error is a preventable event that involves an identifiable patient and 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.

Call Center	Phone Number	Email	Fax
Dohmen Life Science Services (DLSS)	[redacted] Non-toll-free number: [redacted]	[redacted]	[redacted]

Product complaints and medication errors in and of themselves are not AEs. If a product complaint or a medication error results in an SAE, an SAE Form should be completed and sent to BI Medical, Inc (refer to Section 10.2).

10.6 Safety Reporting to Investigators, IRBs, 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, investigators, and IRBs and/or the head of each study site, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as 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.

11.0 STUDY-SPECIFIC COMMITTEES

For the Phase 1 part, no steering committee, data safety monitoring committee, or clinical endpoint committee will be used.

For the Phase 2 part, an IRC and a steering committee will be formed.

11.1 Steering Committee

A steering committee will be established for the Phase 2 part. Its purpose is to function in an advisory capacity to 1) provide input on study conduct and progress; 2) ensure scientific and ethical integrity of the study; and 3) provide ongoing oversight of safety and efficacy in this open-label study. The steering committee will include clinicians who are experts in the clinical care and investigation of the targeted patient population and will also include sponsor representatives. In addition to general study oversight, the committee will be responsible for periodic review of study data to evaluate the safety profile of TAK-788, assess accumulating signals of efficacy, evaluate data quality, and provide input on operational aspects of the study. The committee may make recommendations for the sponsor's consideration based on periodic review. The steering committee charter will define the responsibilities of the committee.

11.2 IRC

A central blinded IRC with no knowledge of the patients' status on treatment will evaluate all images collected during the study for all IRC-assessed endpoints. An IRC charter defines the procedures used by the committee.

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 ICF.

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

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

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

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

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

12.2 Record Retention

The investigator and the head of the institution agree to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated ICFs, electronic copies of eCRFs, including the audit trails, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long term legibility. Furthermore, ICH

E6 Section 4.9.5 requires the investigator and the head of the institution to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the clinical study site agreement between the investigator and/or the head of the institution and sponsor.

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

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

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

13.1.1 Analysis Sets

Phase 1 Part

- Safety population:

  The safety population is defined as all patients who receive at least 1 dose of TAK-788.

- Pharmacokinetic population:

  The pharmacokinetic population is defined as all patients for whom there are sufficient dosing and TAK-788 concentration-time data to reliably estimate the PK parameter(s). This population will be used for analyses of PK parameters.

- DLT-evaluable population:

  The DLT-evaluable population is defined as all patients who receive at least 75% of their planned TAK-788 doses for their first cycle of treatment (unless interrupted by study drug-related AEs). Patients who receive <75% of doses of TAK-788 in Cycle 1 for reasons other than study drug-related AEs are not evaluable for DLT. Patients will be analyzed by the dose level to which they were originally assigned, including those who receive subsequent treatment at a lower or higher dose level.

- Response-evaluable population:

  The response-evaluable population is defined as patients who receive at least 1 dose of TAK-788, have measurable disease at baseline, and at least 1 post-baseline response assessment. The response-evaluable population will be used for the analysis of ORR.

Phase 2 Part

- Safety population:

  The safety population is defined as all patients who receive at least 1 dose of TAK-788.

- Pharmacokinetic population:

  The pharmacokinetic population is defined as patients who receive at least 1 dose of TAK-788 and have at least 1 plasma concentration data after administration of TAK-788. This population will be used for population PK analyses.

- Centrally confirmed population:

The centrally confirmed population is defined as the first 26 patients who have confirmed harboring EGFR exon 20 insertion mutation by central test and have received at least 1 dose of TAK-788.

- FAS:

  FAS is defined as all patients who received at least one dose of TAK-788.

13.1.2 Procedures for Handling Missing, Unused, and Spurious Data

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

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

13.1.3 Analysis of Demographics and Other Baseline Characteristics

Demographic (age, sex, and other parameters as appropriate) and baseline disease characteristics (weight, height, and other parameters as appropriate) will be summarized for the Phase 1 part and Phase 2 part separately. For continuous variables, descriptive statistics (number, mean, standard deviation, median, minimum, and maximum) will be provided. For categorical variables, patient counts and percentages will be provided. Categories for missing data will be presented as needed.

13.1.4 Pharmacokinetic Analysis

Where possible, the following PK parameters (as appropriate) will be determined for TAK-788 and its active metabolites, including, but not limited to, AP32960 and AP32914, respectively.

Phase 1 Part

Following a single oral dose in the Phase 1 part:

- C_{max}
- t_{max}
- AUC_{24}
- AUC_{last}
- Dose proportionality for C_{max} and AUC may be assessed if data allows.

Following multiple oral doses (steady state) in the Phase 1 part:

- $C_{max,ss}$
- $t_{max,ss}$
- $AUC_{24,ss}$

- R_{ac}
- Dose proportionality for C_{max} and AUC may be assessed if data allows.

PK parameters will be summarized using descriptive statistics. Individual TAK-788 concentration-versus-time data and individual PK parameters will be presented in listings and also tabulated using summary statistics by dose cohort. Individual and mean plasma concentration-time profiles will be plotted by dose cohort.

Phase 2 Part

The plasma concentration-time data of TAK-788 and its active metabolites, including AP32960 and AP32914, will be pooled with data from other TAK-788 clinical studies to contribute to population PK analyses. Results of the population PK analyses of data from this study will also contribute to exposure-response analyses of safety and efficacy. The analysis plans for the population PK and exposure-response analyses will be separately defined, and the results of these analyses will be reported separately.

13.1.5 Efficacy Evaluation

13.1.5.1 Primary Endpoint and Analytical Methods (Phase 2 Part Only)

The primary endpoint is confirmed ORR, as assessed by IRC per RECIST v1.1.

Primary Analysis

The primary analysis will be conducted using centrally confirmed population. The point estimate and 90% 2-sided CI for the confirmed ORR as assessed by an IRC will be provided based on stage-wise ordering [18].

Secondary Analysis

Confirmed ORR as assessed by an IRC and its 2-sided 95% exact binominal CI will be provided using FAS.

13.1.5.2 Secondary Endpoints and Analytical Methods

Phase 1 Part

Investigator assessed ORR using RECIST v1.1 will be evaluated. The estimate of the ORR will be presented with 2-sided 95% exact binomial confidence intervals for each cohort and each mutation type.

Phase 2 Part

Confirmed ORR assessed by the investigator in the centrally confirmed population and the FAS, and the 2-sided 95% CIs will be calculated.

DCR assessed by the investigator and the IRC in the centrally confirmed population and the FAS, and the 2-sided 95% CIs will be calculated.

For time-to-event efficacy endpoints including PFS, OS, and duration of response, survival curves and median values (if estimable), along with their 2-sided 95% CIs will be computed using Kaplan-Meier method in the centrally confirmed population and the FAS. The PFS rates, OS rates, and duration of response rates at 12 and 24 months and the associated 2-sided 95% CIs will be computed using the Kaplan-Meier method. Time to response will be summarized only for responders using descriptive statistics.

13.1.6 Safety Analysis

Phase 1 Part

Safety will be evaluated by the incidence of TEAEs, defined as any AEs that occur after administration of the first dose of study drug and up through approximately 30 days after the last dose of study drug, and severity, as well as by changes from baseline in the patient's vital signs, weight, ECG, and clinical laboratory results using the Safety population. Safety will be summarized by dose level within each dose cohort.

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

- TEAEs.
- Drug-related TEAEs.
- Grade ≥3 TEAEs.
- Grade ≥3 drug-related TEAEs.
- The most commonly reported TEAEs (≥10% of all patients).
- SAEs.

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

And the incidence of DLT (as defined in Section 8.2) will be tabulated for each dose cohort. In addition, to assess the relationship between toxicities and TAK-788 dose, the preferred term of individual toxicities will be summarized by their frequency and intensity for each dose cohort. The DLT-evaluable population will be used for the analysis of DLT.

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

ECG intervals (QT and QTcF, and PR), QRS duration, and ventricular rate will be summarized at each scheduled time point, along with mean change from baseline to each posttreatment time point. The number and percentage of patients with ECG abnormalities will be summarized at each time point.

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

Phase 2 Part

Safety will be evaluated by the incidence of TEAEs, defined as any AEs that occur after administration of the first dose of study drug and up through approximately 30 days after the last dose of study drug, and severity, as well as by changes from baseline in the patient's vital signs, weight, ECG, and clinical laboratory results using the Safety population.

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

- TEAEs.
- Drug-related TEAEs.
- Grade ≥3 TEAEs.
- Grade ≥3 drug-related TEAEs.
- The most commonly reported TEAEs (≥10% of all patients).
- SAEs.

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

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

ECG intervals (QT and QTcF and PR), QRS duration, and ventricular rate will be summarized at each scheduled time point, along with mean change from baseline to each posttreatment time point. The number and percentage of patients with ECG abnormalities will be summarized at each time point.

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

13.1.7 Patient-Reported Outcome Data Analysis (Phase 2 Part Only)

The main patient-reported outcomes endpoints of interest for the Phase 2 Part will be the core symptoms of lung cancer (eg, dyspnea, cough, and chest pain) as measured by EORTC QLQ-C30 and QLQ LC13. The QLQ-C30 will be scored according to the EORTC QLQ-C30 (v3.0) Scoring Manual [19] including transformation of responses into scores for analysis and the handling of missing data. The EORTC QLQ-C30 (v3.0) Scoring Manual also includes instructions for scoring the QLQ-LC13.

The actual value and change from baseline of the subscale scores for EORTC QLQ-C30 and QLQ LC13 will be summarized using descriptive statistics over time.

More details will be provided in the statistical analysis plan.

13.2 Interim Analysis and Criteria for Early Termination

Phase 1 Part

No interim analysis is planned.

Phase 2 Part

For the primary analysis in the Phase 2 part, 2-stage design [20] will be used. The first 14 "centrally confirmed" patients in the Phase 2 part are to be included in Stage 1, and further patients will be continuously enrolled into Stage 2. An interim analysis for both futility and efficacy will be conducted in Stage 1. The proportion of patients achieving an objective response, per IRC, will be used as the endpoint for the interim analysis. The interim analysis will be performed when the first 14 "centrally confirmed" patients in the Phase 2 part have had the opportunity to complete the Cycle 7 Day 1 disease assessment (i.e. third disease assessment after initiation of the study treatment). Enrollment will not be suspended during evaluation of these 14 "centrally confirmed" patients; however, patients enrolled after the 14th patient in the Phase 2 part will NOT be included in the interim analysis, even if their objective response were available on the cutoff date.

If the number of patients with confirmed objective response is 5 or fewer in the 14 "centrally confirmed" patients, enrollment will be stopped entirely for futility. Additionally, if the number of patients with confirmed objective response is 9 or more in the 14"centrally confirmed" patients, it will be decided that TAK-788 is efficacious in this population.

In other cases (i.e. number of patients with confirmed objective response is between 6 to 8 in the 14), the study will continue until 26 "centrally confirmed" patients have had the opportunity to complete the Cycle 7 Day 1 disease assessment. If the number of patients with confirmed objective response in these 26 patients is 14 or more, it will be decided that TAK-788 has demonstrated sufficient efficacy to reject the null hypothesis. For this analysis, the best overall response for the first 14 "centrally confirmed" patients at the interim analysis will be used without any update.

To maintain confidentiality of interim result and to preserve trial integrity, the interim analysis will be conducted by an independent statistical center. Until the analysis for the 26 "centrally confirmed" patients (Stage 1 + Stage 2; conducted when all 26 patients had an opportunity to complete the Cycle 7 Day 1 disease assessment), the sponsor and its designee will not have any access to the efficacy data based on IRC assessment, except for the written notification from the independent statistical center that tells whether the results of the interim analysis met predefined criteria of futility, efficacy, or not met both. However, if the futility or efficacy is confirmed at the interim analysis, the IRC-assessed efficacy data will be fully disclosed to the sponsor immediately after the written notification is provided.

13.3 Determination of Sample Size

Phase 1 Part

Phase 1 part will adopt an adaptive design using BLRM with safety data evaluation and other available information, such as PK and efficacy. The design allows flexible cohort size. The total number of subjects in Phase 1 part is dependent on the observed safety profile and other available information, which will determine the number of patients per dose cohort, as well as the number of dose escalations required to achieve the MTD. It is anticipated that approximately 21 patients will be required to determine MTD. Assuming a 15% dropout rate and potentially up to 5 patients will be enrolled for any cohort to further confirm the safety, the total sample size for Phase 1 part will be approximately 28-33.

The description, prior calibration and operating characteristics of the BLRM are included in Appendix G.

Phase 2 Part

The purpose of the Phase 2 part of this study is to determine the confirmed ORR of orally administered TAK-788 as the first line treatment at RP2D determined in the Phase 1 part in patients with NSCLC with EGFR exon 20 insertion mutations. The sample size was determined so that it would allow us to state that the true ORR is greater than threshold response rate of 35%. The expected true ORR of TAK-788 is 60% in treatment naive population. Twenty-six (26) patients with NSCLC with tumors harboring EGFR exon 20 insertion mutations with confirmation of central test will allow the study to have over 80% power to rule out an uninteresting rate of 35% in this population with a 1-sided alpha of 0.05 according to the two-stage design with futility and efficacy interim analysis described in Section 13.2.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

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

All aspects of the study and its documentation will be subject to review by the sponsor or designee including, but not limited to, the investigator's binder, study medication, subject medical records, informed consent documentation, 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.

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.

14.2 Protocol Deviations

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

The investigator should document all protocol deviations.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the United States [US] Food and Drug Administration [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 Approval

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

The sponsor or designee will supply relevant documents for submission to the respective IRB 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 for approval. The IRB'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 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. This may include notification to the IRB 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, and submission of the investigator's final status report to IRB. All IRB 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 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 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 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 approval of the ICF. The ICF must be approved by both the IRB and the sponsor before use.

The ICF 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 to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB.

The subject 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 determines that he or she will participate in the study, then the ICF must be signed and dated by the subject at the time of consent and before the subject enters into the study. The subject 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 at the time of consent and before the subject enters into the study.

Once signed, the original ICF 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 shall be given to the subject.

All revised ICFs must be reviewed and signed by relevant subjects 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 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 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

In order 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 facility name, investigator's city, country, and recruiting status will be registered and available for public viewing.

15.4.3 Clinical Trial Results Disclosure

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

Data Sharing

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

15.5 Insurance and Compensation for Injury

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

16.0 REFERENCES

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Appendix A Schedule of Events

Phase 1 Part

		Treatment period											Follow-up period
		Cycle 1					Cycle 2		Cycle 3 and Subsequent Cycles				
Day (D) (a)	Screening (b)	D1 (c)	D2	D8	D15	D22	D1 (c)	D2	Every 4 wks (d)	Every 8 wks (e)	Every 12 wks (f)	End of Treatment (g)	30 Days After Last Dose (h)
Informed consent	X												
Demographics	X												
Medical/surgical history	X												
Diagnosis and cancer history	X												
Mutation status (i)	X												
Prior cancer therapy	X												
Physical examination	X	X					X		X			(X)	(X)
Height	X												
Weight, Vital signs and auscultation	X	X			X		X		X			X	X
ECOG Performance Status	X	X					X		X			X	X
Cardiac monitoring (including LVEF by ECHO/MUGA)		Cardiac monitoring may be done during treatment according to medical judgement and as clinically indicated											
Hematology/chemistry/urinalysis	X	X			X		X		X			(X)	(X)
Serology	X										X (j)		
KL-6, SP-D	X						X			X (k)			
Chest X-ray	X			X		X	X						
Pregnancy test (l)	X (m)	X (n)					X		X			X	
ECG	X						X		X			(X)	(X)
TAK-788 administration		X (once daily)											
Adverse events/Concomitant medications		Throughout study (o)											
PK sampling (Plasma samples for TAK-788 PK) (p)		X	X (q)	X	X	X	X	X (q)	X (C3D1 only)				
Disease assessment	X									X (r)	X (r)	X	
CSF collection (CSF sample for TAK-788 PK) (s)		As determined by the investigator (as part of standard of care)											

Abbreviations: AE, adverse event; CSF, cerebrospinal fluid; CT, computed tomography; CxDx, Cycle x Day x; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; ICF, informed consent form; ILD, interstitial lung disease; KL-6, Krebs von den Lungen-6; MRI, magnetic resonance imaging; MTD, maximum tolerated dose; MUGA, multigated acquisition; PD, progressive disease; PK, pharmacokinetic(s); SP-D, surfactant protein-D.

(a) All study assessments should occur within ±3 days of the scheduled study day unless otherwise noted. A cycle is defined as 28 days.
(b) Unless otherwise noted, the screening visit must occur within 14 days before the day of the first dose of study drug (C1D1). The ICF may be signed more than 21 days before C1D1.
(c) Unless otherwise noted, it must occur before TAK-788 administration.
(d) Unless otherwise noted, it must occur on Day 1 (±3 days) of every cycles
(e) Unless otherwise noted, it must occur on Day 1 (±3 days) of every even-numbered cycles (ie, Cycles 4, 6, 8 and thereafter every 2 cycles)
(f) Unless otherwise noted, it must occur on Day 1 (±3 days) of every 3 cycles (ie, Cycles 3, 6, 9 and thereafter every 3 cycles).
(g) 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, urinalysis), 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. For the End-of-Treatment assessments, information may be collected from tests performed for the study or as part of the patient's routine medical care.
(h) 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, urinalysis), 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 the 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.
(i) Only for patients who have information of mutation status
(j) For patients who are positive for HBsAg or HCV antibody at screening, the on-study testing should be performed in cycles 3, 6, 9 and thereafter every 3 cycles.
(k) Serum levels of KL-6 and SP-D will be assessed on Day 1 (±3 days) of every even-numbered cycles. And unscheduled collection may be allowed in case of occurrence of ILD or pneumonitis occurs.
(l) Only for females of childbearing potential. Unless otherwise noted, either urine or serum can be used.
(m) Females of childbearing potential must be negative pregnancy test using serum.
(n) Females of childbearing potential must be negative pregnancy test (using either urine or serum test) within 7 days prior to the first dose of study drug.
(o) AEs and concomitant treatments will be recorded in the eCRF from the date the informed consent is signed until 30 days after the last dose of study drug or before initiation of new anticancer therapy (whichever comes first).
(p) Blood samples will be collected immediately prior to the first dose (time 0; pre-dose), and at 0.5, 1 hour (±5 minutes), 2, 4, 6, 8 hours (±10 minutes), and 24 hours (±60 minutes) after the first dose on C1D1. The 24 hour sample will be collected prior to drug administration on C1D2. Blood samples will be collected prior to dosing on C1D8, C1D15, and C1D22. Blood samples will also be collected pre-dose and at 0.5, 1 hour (±5 minutes), 2, 4, 6, 8 hours (±10 minutes), and 24 hours (±60 minutes) after administration of TAK-788 on C2D1. The 24-hour sample will be collected prior to drug administration on C2D2. A PK sample will also be collected pre-dose on C3D1. The sampling time point is summarized in the table on the next page.
(q) Blood samples will be collected 24 hours (±60 minutes) after the dose on C1D1 or C2D1.
(r) Disease assessment by CT and MRI scans will be performed at screening and at 8-week intervals thereafter (on Day 28 [±3 days] of every even-numbered cycle) through cycle 14 after the initial dose of study drug, and every 3 cycles thereafter until PD.
(s) If lumbar puncture is performed as part of the standard of care, remaining CSF samples should be analyzed to determine the concentration of TAK-788 and its active metabolites, including, but not limited to, AP32914 and AP32960 (≥500 μL is sufficient), and these samples should have matched blood samples (for PK analyses) when possible.

Phase 2 Part

	Screening (a)	Treatment period							Follow-up period		
		Cycle 1		Cycle 2	Cycle 3 and Subsequent Cycles			End of Treatment (b)	30 Days After Last Dose (c)	PFS (d)	Overall Survival (e)
					Every 4 wks	Every 8 wks	Every 12 wks				
Day (D) (f)		D1 (g)	D15	D1	D1	D1	D1			D1	
Visit Window			±3 days	±3 days	±3 days	±3 days	±3 days	+14 days	±7 days	±14 days	±14 days
Informed consent (a)	X										
Demographics	X										
Medical/surgical history	X										
Diagnosis and cancer history	X										
Mutation status (based on local test)	X										
Prior cancer therapy	X										
Patient reported outcome (h)	X	X (i)		X	X (up to C14)		X (Starting C15)	X	X		
Physical examination	X	X (i)		X	X			(X)	(X)		
Height	X										
Weight, Vital signs and auscultation	X	X	X	X	X			X	X		
ECOG Performance Status	X	X (i)		X	X			X	X		
Cardiac monitoring (including LVEF by ECHO/MUGA) (j)	X			X			X (C4D1, C7D1 only)	X			
Hematology/chemistry/urinalysis	X	X (i)	X	X	X			(X)	(X)		
Serology	X						X (k)				
KL-6, SP-D	X			X		X (l)					
Chest X-ray	X			X							
Pregnancy test (m)	X (n)	X (o)		X	X			X			
ECG	X			X	X			(X)	(X)		
TAK-788 administration	X (once daily)										
Adverse events/Concomitant medications	Throughout study (p)										

Phase 2 Part (Cont.)

	Screening (a)	Treatment period							Follow-up period		
		Cycle 1		Cycle 2	Cycle 3 and Subsequent Cycles			End of Treatment (b)	30 Days After Last Dose (c)	PFS (d)	Overall Survival (e)
					Every 4 wks	Every 8 wks	Every 12 wks				
Day (D) (f)		D1 (g)	D15	D1	D1	D1	D1			D1	
Visit Window			±3 days	±3 days	±3 days	±3 days	±3 days	+14 days	±7 days	±14 days	±14 days
PK sampling (Plasma sample for TAK-788 PK) (q)		X	X	X	X (C3D1, C4D1, C5D1 only)						
Biomarker (r)											
Plasma sample for Cholesterol		X		X							
Plasma sample for Cell Free DNA		X		X	X (C5D1 only)			X			
Archival banked tumor tissue sample (s)	X										
Fresh tumor tissue biopsy sample at disease progression (t)								X (at PD)			
Disease assessment	X					X (u)	X (u)	X (v)		X	
CSF collection (CSF sample for TAK-788 PK and matched plasma sample for TAK-788 PK) (w)		As determined by the investigator (as part of standard of care)									
Subsequent anticancer therapy/survival											X

Abbreviations: AE, adverse event; CSF, cerebrospinal fluid; CT, computed tomography; CxDx, Cycle x Day x; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; EORCT, European Organisation for Research and Treatment of Cancer; EOT, End of Treatment; FFPE, formalin fixed paraffin embedded; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; ICF, informed consent form; ILD, interstitial lung disease; KL-6, Krebs von den Lungen-6; MRI, magnetic resonance imaging; MTD, maximum tolerated dose; MUGA, multigated acquisition; PD, progressive disease; PFS, progression free survival; PK, pharmacokinetic(s); QLQ, Quality of Life Questionnaire; QLQ-LC30, Quality of Life Questionnaire, lung cancer module; SP-D, surfactant protein-D.

(a) Screening assessments must be performed within 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. Informed consent may be signed more than 21 days before C1D1 and must be signed before performance of any study-related procedure not part of standard medical care.

(b) 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, urinalysis), 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. For the End-of-Treatment assessments, information may be collected from tests performed for the study or as part of the patient's routine medical care.

(c) The 30 Days after last dose assessments must be performed within 30 days (±7 days) after the last dose of study treatment or until the start of new systemic anticancer treatment, whichever occurs first. Physical examinations, laboratory tests (hematology, chemistry, urinalysis), 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. For the 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.
(d) Every 8 weeks until Week 56 (equivalent to Cycle 14 Day 28), and every 12 weeks (±14 days) thereafter, from the EOT visit to the occurrence of PD or the start of subsequent anticancer therapy.
(e) Every 12 weeks (±14 days) until death, loss to follow-up, consent withdrawal, study termination, or any of the circumstances described in Section 9.10 occur, after the occurrence of documented PD or the start of subsequent anticancer therapy.
(f) A cycle is defined as 28 days. A day is defined as a calendar day. Visit windows are as specified in the table, unless noted otherwise. Disease assessments have a ±7-day visit window.
(g) Unless otherwise noted, it must occur before TAK-788 administration.
(h) EORTC QLQ-C30 and EORTC QLQ-LC13 should be administered to patients when they arrive for their scheduled visits, before any clinical measurements, assessments, evaluations, or procedures being performed.
(i) Does not need to be performed on C1D1 if performed for screening within 7 days before C1D1, and, in the opinion of the investigator, there is no reason to believe the assessment has substantially changed.
(j) Cardiac monitoring must be performed on baseline (screening), C2D1, C4D1, C7D1 and EOT. In addition to these timepoints, Cardiac monitoring may be done at additional timepoints according to medical judgement and as clinically indicated.
(k) For patients who are positive for HBsAg or HCV antibody at screening, the on-study testing should be performed in cycles 3, 6, 9 and thereafter every 3 cycles.
(l) Serum levels of KL-6 and SP-D will be assessed on Day 1 of every even-numbered cycles. And unscheduled collection may be allowed in case of occurrence of ILD or pneumonitis occurs.
(m) Only for females of childbearing potential. Unless otherwise noted, either urine or serum can be used.
(n) Females of childbearing potential must be negative pregnancy test using serum.
(o) Females of childbearing potential must be negative pregnancy test (using either urine or serum test) within 7 days prior to the first dose of study drug.
(p) AEs and concomitant treatments will be recorded in the eCRF from the date the informed consent is signed until 30 days after the last dose of study drug or before initiation of new anticancer therapy (whichever comes first).
(q) The sampling time point is summarized in the table on PK Sampling Time Points.
(r) Plasma samples will be collected for evaluating circulating biomarkers including 4-beta-OH-cholesterol/cholesterol and cell free DNA. Collection at C1D1 should be collected prior dosing; plasma for cell free DNA should be double spun.
(s) Remaining tissue at initial diagnosis or archival tissue can be used. If it is not available, fresh tumor tissue sample correction (FFPE slides or FFPE block) is needed.
(t) An optional tumor tissue biopsy (FFPE) will be obtained at the time of disease progression.
(u) Disease assessment by CT and MRI scans will be performed at screening and at 8-week intervals thereafter (on Day 28 [±7 days] of every even-numbered cycle) through cycle 14 after the initial dose of study drug, and every 3 cycles thereafter until PD.
(v) It will also be performed at EOT if more than 4 weeks have passed since the last imaging assessment.
(w) If lumbar puncture is performed as part of the standard of care, remaining CSF samples should be analyzed to determine the concentration of TAK-788 and its active metabolites, including, but not limited to, AP32914 and AP32960 (≥500 μL is sufficient), and these samples should have matched blood samples (for PK analyses) when possible.

PK Sampling Time Points

Phase 1 Part

PK Sampling Time Points	Cycle 1					Cycle 2		Cycle 3
	Day 1	Day 2	Day 8	Day 15	Day 22	Day 1	Day 2	Day 1
Predose	X	(X) (a)	X	X	X	X	(X) (b)	X
0.5 hours postdose (±5 min)	X					X		
1 hour postdose (±5 min)	X					X		
2 hours postdose (±10 min)	X					X		
4 hours postdose (±10 min)	X					X		
6 hours postdose (±10 min)	X					X		
8 hours postdose (±10 min)	X					X		
24 hours postdose (±60 min)	X (predose on C1D2)					X (predose on C2D2)		

Abbreviations: CxDx, Cycle x Day x; PK, pharmacokinetic.
(a) This is the same sample as the one to be collected 24 hours after the dose on C1D1.
(b) This is the same sample as the one to be collected 24 hours after the dose on C2D1.

Phase 2 Part

PK Sampling Time Points	Cycle 1		Cycle 2	Cycle 3	Cycle 4	Cycle 5
	Day 1	Day 15	Day 1	Day 1	Day 1	Day 1
Predose (as close as possible to 24 hours after previous dose)		X	X	X	X	X
1 to 2 hours postdose (±10 min)	X			X		
2 to 4 hours postdose (±20 min)		X			X	
4 to 6 hours postdose (±30 min)			X			X

Abbreviations: CxDx, Cycle x Day x; eCRF, electronic case report form; PK, pharmacokinetic.
The pre-dose samples should be collected as close as possible to 24 hours after the prior dose of TAK-788. The exact dates and times of each PK sample collection should be recorded on the electronic case report form (eCRF). On the PK sampling days and clinic visit days, patients should take the study drug at the clinic. The exact dates and times of the 2 prior doses of TAK-788 taken at home and 1 prior dose taken in the clinic on each PK sampling day (except C1D1) should be recorded on the eCRF. The exact dates and times of all doses taken at home should be recorded on the patient diary card.

Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations. The investigator agrees to assume the following responsibilities:

1. Conduct the appropriate study in accordance with the protocol and GCP considering the rights, safety and wellbeing of human subjects.
2. When a part of the important activities related to the study are delegated to the sub-investigator or the study collaborator, prepare the lists of activities to be delegated and responsible personnel, submit the lists to the head of the study in advance to get them accepted.
3. Prepare a written informed consent form and other written information, and update as appropriate.
4. Confirm the contents of the clinical study agreement.
5. Provide necessary information on the protocol, medications and responsibilities of individual personnel to the investigator and study collaborator, and provide guidance and supervision.
6. Screen subjects who meet the requirements of the protocol, provide the explanation of the study in writing and obtain the written consent.
7. Assume responsibility for all the medical judgement related to the study.
8. Ensure in collaboration with the head of the study that sufficient medical care on all clinically significant adverse events related to the study are provided to subjects throughout and beyond the period when subjects participate in the study.
9. If a subject consults other medical institution or other department, notify the physician of the medical institution or department of the subject's participation in the study upon obtaining the consent of the subject, as well as the end and termination of the study in writing, and document such records.
10. In case of urgent report of a SAE, immediately notify the head of the study and the sponsor in writing.
11. Prepare correct and complete (e)CRFs, and submit them to the sponsor with electronic signature.
12. Check and confirm the contents of (e)CRFs prepared by the sub-investigator or transcribed from the source data by the study collaborator, and submit them to the sponsor with electronic signature.
13. Discuss any proposal from the sponsor including update of the protocol.
14. Notify the director of the site of the end of the study in writing.

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

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 longest diameters (LD) of non-nodal lesions (axial plane)
- Add short axis diameters of nodes
- This is the "sum of the longest diameters" (SLD)

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. (Two 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)

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
Source: Eisenhauer EA, 2009 [21].

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 [22].

Appendix E Drugs That Interact with the CYP3A Family of Cytochromes P450

Drugs listed below that are moderate or strong inducers, or moderate or strong inhibitors of the CYP3A family of Cytochromes P450 are prohibited as concomitant medications with TAK-788, with the exception of nonsystemic use.

Drugs Inducing or Inhibiting CYP3A Metabolism That Are Prohibited as Concomitant Medications with TAK-788, with the Exception of Nonsystemic Use

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
cobicistat
danoprevir and ritonavir
elvitegravir and ritonavir
grapefruit juice
indinavir and ritonavir
itraconazole
ketoconazole
lopinavir and ritonavir

Strong CYP3A Inhibitors (b)
paritaprevir and ritonavir and (ombitasvir and/or dasabuvir)
posaconazole
ritonavir
saquinavir and ritonavir
telaprevir
telithromycin
tipranavir and ritonavir
troleandomycin
voriconazole

Note: 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's medical monitor with any queries.

(a) fda.gov/Drugs/ drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-3 (accessed 05 December 2019).

(b) fda.gov/Drugs/ drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-2 (accessed 05 December 2019)

Appendix F Drugs with a Risk of Torsades de Pointes

The website crediblemeds.org/everyone [Accessed: 19 November 2021] 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.

Drugs with a known risk of Torsades de Pointes are listed in the table 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.

Drugs Generally Accepted by the CredibleMeds QTDrug List Advisory Board to have a Known Risk of Causing Torsades de Pointes; Prohibited in this Study

Generic Name	Brand Name	General Indication [a]	Source [a]
Analgesics/Anethesic			
Cocaine	Numbrino	Local anesthestic for mucus membranes of the nasal cavity (for diagnostic or surgical procedures).	Numbrino (cocaine hydrochloride) PI
Propofol	Diprivan, Propoven	Initiation and maintenance of general anesthesia or sedation in accordance with the approved label.	Diprrivan (propofol) PI
Sevoflurane	Ultane, Sojourn	Induction and maintenance of general anesthesia.	Ultane (sevoflurane) PI
Anti-allergy Agents			
Astemizole	Hismanal	Treatment of allergic rhinitis, allergic conjunctivitis, and chronic urticaria.	Hismanal (astemizole) US PI
Terfenadine	Seldane	Antihistamine/allergic rhinitis	Not available
Anticancer Treatments			
Aclarubicin	Aclacin, Aclacinomycine, Aclacinon, Aclaplastin, Jaclacin	Treatment of malignant blood disorders.	Aclarubicin (aclarubicin hydrochloride) SmPC
Arsenic trioxide	Trisenox	Treatment of APL.	Trisenox (arsenic trioxide for injection) PI
Oxaliplatin	Eloxatin	Treatment of advanced colorectal rectal cancer.	Eloxatin (Oxaloplatin for Injection) PI
Vandetanib	Caprelsa	Treatment of medullary thyroid cancer.	Capresla (vandetanib) PI

Generic Name	Brand Name	General Indication [a]	Source [a]
Anti-infectives			
Azithromycin	Zithromax, Zmax	Treatment of bacterial infections as outlined in the approved label.	Zithromax (azithromycin) PI
Chloroquine	Aralen	Antimalarial /Treatment of malaria .	Aralen (chloroquine phosphate) PI
Ciprofloxacin	Cipro, Cipro-XR, Neofloxin	Treatment of bacterial infections as designated by the label.	Cipro (ciprofloxacin hydrochloride) PI
Clarithromycin	Biaxin, Prevpac	Treatment of bacterial infections as designated by the label.	Biaxin (clarithromycin) PI
Erythromycin	Abboticin, Abboticin-ES, Acnasol, E Base, EES, EMycin, Erycin, Eryc Ranbaxy, Erymax, Erypar, Eryped, Ery-Tab, Erythrocin Stearate Filmtab, Erythrocot, Erythroped, Ilosone, MY-E, Pediamycin, PCE Dispertab, Robimycin, Stiemycine, Tiloryth, Zineryt	Treatment (and for some agents, the prevention) of bacterial infections as outlined in the approved label.	Erycin (erythromycin) PI
Fluconazole	Diflucan, Trican	Treatment for fungal infections as outlined in the approved label.	Diflucan (Fluconazole Tablets) (Fluconazole for Oral Suspension) PI
Gatifloxacin	Tequin	Treatment and prevention of bacterial infections as outlined in the approved package insert.	Tequin (gatifloxcacin) PI
Grepafloxacin	Raxar	Treatment of infections caused by strains of microorganisms outlined in the approved label.	Raxar (domperidone) PI
Halofantrine	Halfan	Treatment of mild to moderate malaria.	Halfan (halofantrine hydrochloride) PI
Levofloxacin	Levaquin, Tavanic	Treatment of bacterial infections as outlined in the approved label.	Levaquin (levofloxacin) PI
Moxifloxacin	Avelox, Avalox, Avelon	Treatment or prevention of susceptible bacteria in accordance with the approved label.	Avelox (moxifloxacin hydrochloride) PI
Pentamidine	Pentam	Prevention of PJP in high-risk patients.	Pentam (pentamidine isetionate) PI

Generic Name	Brand Name	General Indication [a]	Source [a]
Roxithromycin	Biaxsig, Coroxin, Roxar, Roximycinv, Roxl-150, Roxo, Roxomycin, Rulid, Rulide, Surlid, Tirabicin, Xthrocin	Treatment of bacterial infections as outlined in the approved label.	Biaxsig (roxithromycin) PI
Sparfloxacin	Zagam	Treatment of bacterial infections as outlined in the approved label.	Zagam (sparfloxacin) PI
Cardiac Agents			
Amiodarone	Cordarone, Pacerone, Nexterone	Treatment and/or prophylaxis for (1) recurrent VF, or (2) recurrent hemodynamically unstable VT, in accordance with the approved label.	Nexterone (amiodarone HCL) PI
Bepridil	Vascor	Treatment of angina.	Vascor (imidapril hydrochloride) PI
Disopyramide	Norpace	Treatment of ventricular arrythmias.	Norpace (disopyramide phosphate) PI
Dofetilide	Tikosyn	Maintenance of sinus rhythm in patients at risk for atrial arrhythmia.	Tikosyn (dofetilide) PI
Dronedarone	Multaq	Antiarrhythmic for patients at risk for AFL.	Multaq (dronedarone) PI
Flecainide	Almarytm, Apocard, Ecrinal, Flécaine, Tambocor	Treatment for arrhythmic conditions as outlined in the approved label.	Almarytm (flecainide acetate) PI
Hydroquinidine, dihydroquinidine	Serecor LP, Lentoquine, Idrochinidina Lirca, Austacute	Prevention and treatment of ventricular dysrhythmias in accordance with the approved label.	Serecor LP (hydroquinidine) PI
Ibutilide	Corvert	Treatment of AFIB and AFL.	Corvert (ibutilide fumarate for injection) PI
Procainamide	Pronestyl, Procan	Treatment of ventricular arrhythmias.	Pronestyl (procainamide) PI
Quinidine	Quinaglute, Duraquin, Quinact, Quinidex, Cin-Quin, Quinora	Treatment of (1) AFIB, AFL, VT, or PSVT in accordance with the approved label.	Quinaglute (quinidine) PI
Sotalol	Betapace, Sotalex, Sotacor	Maintainence of sinus rhythm in patients with symptomatic AFIB/AFL.	Betapace AF (sotalol HCl) PI
Gastrointestinal Agents			
Cisapride	Propulsid	Treatment of GERD.	Propulsid (cisapride) SmPC

Generic Name	Brand Name	General Indication [a]	Source [a]
Domperidone	Motilium, Motillium, Motinorm Costi, Nomit	Treatment of various gastric disorders (eg, gastric reflux disease, nausea, vomiting) in accordance with the approved label.	Domperidone SmPC
Ondansetron	Zofran, Anset, Ondemet, Zuplenz, Emetron, Ondavell, Emeset, Ondisolv, Setronax	Prevention of (1) PONV, (2) nausea/vomiting associated with administration of chemotherapy and/or radiation treatment.	Zofran (ondansetron hydrochloride) PI
Psychotropics			
Citalopram	Celexa, Cipramil	Treatment of depression.	Celexa (citalopram hydrochloride) PI
Donepezil	Aricept	Treatment of dementia of the Alzheimer type.	Aricept (donepezil hydrochloride) PI
Escitalopram	Animaxen, Anxiset-E, Cipralex, Elicea, Entact, Esitalo, Esto, Exodus, Lexam, Lexamil, Lexapro, Losita, Nexito, Reposil, Seroplex	Treatment for various psychiatric disorders and related conditions as outlined in the approved label.	Animaxen (escitalopram) PI
Haloperidol	Aloperidin, Bioperidolo, Brotopon, Dozic, Duraperidol, Einalon S, Eukystol, Haldol, Halosten, Keselan, Linton, Peluces, Serenace, Serenase, Sigaperidol	Treatment and management of psychiatric and neuropsychiatric disorders and associated manifestations (eg, schizophrenia, mania, tics secondary to Tourette's Disorder) as outlined in the approved label.	Aloperidin (haloperidol decanoate) PI
Mesoridazine	Serentil	Management of schizophrenia.	Serentil (mesoridazine besylate) PI
Pimozide	Orap	Suppression of motor and phonic tics associated with Tourette's Disorder.	Orap (Pimozide) PI
Sulpiride	Dogmatil, Dolmatil, Eglonyl, Espiride, Modal, Sulpor	Treatment of acute and chronic schizophrenia.	Sulpiride PI
Sultopride	Barnetil, Barnotil, Topral	Control of (1) psychiatric urgencies, (2) psychomotor excitement, (3) acute delusional episodes, or (4) confusional states.	Topral (sultopride) PI
Thioridazine	Mellaril, Novoridazine, Thioril	Treatment of schizophrenia.	Mellaril (thioridazine) PI
Other			
Anagrelide	Agrylin, Xagrid	Treatment of thrombocythemia in accordance with the approved label.	Xagrid (anagrelide) PI

Generic Name	Brand Name	General Indication [a]	Source [a]
Chlorpromazine	Thorazine, Largactil, Megaphen	Treatment of (1) various psychoses, and psychomotor agitation excitement in accordance with the approved label, (2) intractable hiccups, (3) nausea/vomiting associated with terminal illness.	Thorazine (chlorpromazine hydrochloride for injection) PI
Cilostazol	Pletal	Reduction of symptoms related to intermittent claudication.	Pletal (cilostazol) PI
Droperidol	Inapsine, Droleptan, Dridol, Xomolix	**Inaspsine, Droleptan, Xomolix:** reduction of PONV. **Dridol**: treatment of hypoparathyroidism, refractory rickets, and familial hypophosphatemia.	Dridol (droperidol for injection) PI
Levomepromazine	Nosinan, Nozinan, Levoprome	Supportive treatment for terminally ill patients for (1) intractable nausea and vomiting, (2) management of pain,(3) restlessness, and distress.	Levomepromazine (Levomepromazine Maleate) PI
Levomethadyl acetate	Orlaam	For the management of opiate dependencies.	Orlaam (levomethadyl acetate hydrochloride) PI
Levosulpiride	Lesuride, Levazeo, Enliva (with rabeprazole)	Treatment of various psychiatric and GI disorders in accordance with the approved label.	Levosulpiride PI
Methadone	Dolophine, Symoron, Amidone, Methadose, Physeptone, Heptadone	(1)Treatment of severe pain, (2) supportive treatment in the detoxification of opioid addiction.	Dolophine hydrochloride (methadone hydrochloride) PI
Papaverine HCl (Intra-coronary)	None	For treatment of (1) erectile dysfunction, (2) arrhythmias due to MI. Prophylaxis for peripheral atrial catheter patency.	Papaverine HCL PI
Probucol	Lorelco	Treatment for lowering cholesterol.	Lorelco (probucol) PI
Terlipressin	Teripress, Glypressin, Terlipin, Remestyp, Tresil, Teriss, and others	Treatment of bleeding oesophageal varices.	Teripress (teripressin) PI
Terodiline	Micturin, Mictrol (not bethanechol)	Muscle relaxant/bladder spasm	Not available
Ibogaine	None		Not available

AFIB: atrial fibrillation; AFL: atrial flutter; APL: acute promyelocytic leukemia; EES: erythromycin ethylsuccinate; GERD: gastroesophageal reflux disease; GI: gastrointestinal; IBS: irritable bowel syndrome; MI: myocardial infarction; PJP: pneumocystis jiroveci pneumonia; PONV: post-operative nausea and vomiting; PSVT: paroxysmal supraventricular tachycardia; VF: ventricular fibrillation; VT: ventricular tachycardia.

a Refer to the most current package insert/summary of product characteristics as relevant to the specific prescribing agent and region for the approved indication and safety-related dosing guidance.

Appendix G Bayesian Logistic Regression Model

An adaptive BLRM with overdose control will be used to guide dose escalation. BLRM with overdose control principle [23][24] informs dose escalation decisions and MTD estimation, along with consideration of other available information, such as safety, PK and efficacy.

The 2-parameter logistic regression model used is as follows:

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

where π_i is the DLT rate for dose i, dose_{ref} is a reference dose, and ln is the natural log function.

The MTD for TAK-788 in a global study AP32788-15-101 has been identified as 160 mg QD. A total of 38 DLT evaluable patients were enrolled in the global study, and 5 DLTs were observed. There are 3, 3, 5 and 6 evaluable patients at 5 mg, 10 mg, 20 mg and 40 mg, and no DLT was observed for these doses. There are 6 evaluable patients each at 80 mg, 120 mg and 160 mg, and 1 DLT was observed for each of these three doses. Two DLTs were observed among the 3 evaluable patients at 180 mg. The global MTD will be assigned as the reference dose in this study. A post-hoc BLRM analysis was conducted for the DLT data in the global study, and the posterior distribution of ln(α) and ln(β) conditional on the global study data was obtained by using a quantile-based, weakly informative, bivariate normal prior

$$\text{BVN}\left(\begin{pmatrix}-1.33\\-1.27\end{pmatrix}, \begin{bmatrix}3.19 & -4.28\\-4.28 & 20.0\end{bmatrix}\right)$$

for ln(α) and ln(β), which was assigned based on pre-study estimates of median DLT rate (0.02, 0.04, 0.06, 0.08, 0.14, 0.16, 0.18, and 0.4) at doses (5, 10, 20, 40, 80, 120, 160 and 180 mg), as described in Neuenschwander 2008 [23]. The global posterior distribution of ln(α) and ln(β) is

$$\text{BVN}\left(\begin{pmatrix}-1.12\\0.098\end{pmatrix}, \begin{bmatrix}0.38 & 0.45\\0.45 & 2.45\end{bmatrix}\right),$$

which will be assigned as the prior distribution of ln(α) and ln(β) in this study.

The model will be updated after each group of approximately 3-5 patients are enrolled in the current dose. A different cohort size may also be considered. Each subject will participate in only 1 dose cohort. For each dose, the posterior probability of having DLT rates that fall into the following intervals will be estimated:

- [0, 0.21): underdosing.
- [0.21, 0.33): target toxicity.
- [0.33, 1.00]: excessive toxicity.

The next recommended dose will be selected as described in Section 8.3.

The simulation to evaluate the operating characteristics is performed based on provisional doses (40, 80, 120, and 160 mg QD). For each cohort in the simulation, 5 patients will be enrolled and

each patient is assumed to have 80% probability of being DLT evaluable (there is less than 6% chance that the number of evaluable patients will be less than 3, so for simplicity a minimum of 3 DLT evaluable patients was applied in the simulation, however, the study may consider a flexible cohort size), which results in a flexible cohort size of 3-5 evaluable patients. Escalation from 40 mg QD directly to 160 mg QD is not allowed in the simulation. In addition to the MTD rule specified in the protocol, a dose can be claimed as the MTD if the observed DLT rate at that dose is lower than 33%. The simulation is performed based on 5 scenarios of the assumed true DLT rates at doses (40, 80, 120, and 160 mg), representing various distributions of toxicity across doses, detailed as shown in the following:.

Dose Escalation Simulation Study of the Probability of Dose-Limiting Toxicity

Dose Level	True P(DLT) at each scenario				
	1	2	3	4	5
40 mg (a)	0.01	0.05	0.08	0.10	0.15
80 mg	0.05	0.10	0.13	0.15	0.20
120 mg	0.10	0.15	0.20	0.25	0.32
160 mg	0.20	0.23	0.28	0.40	0.45

Abbreviation: P(DLT), probability of a DLT at each DL.
(a) Starting dose.

The trend of the dose-DLT relationship becomes steeper and MTD is reached earlier from Scenario 1 to Scenario 5. The following table shows the operating characteristic results.

Operating Characteristics for BLRM Dose Escalation Rule

Scenario	Probability of recommending a:				Average proportion of patients receiving a:			Average number of patients	
	Low Dose	Target Dose	High Dose	No MTD	Low Dose	Target Dose	High Dose	Per study	Experiencing DLT per study
1	98.7% (a)	NA	NA	1.3%	100%	NA	NA	17.2	2.1
2	25.9%	71.0%	NA	3.1%	57.3%	42.7%	NA	17.8	2.8
3	34.5%	58.1%	NA	7.4%	61.5%	38.5%	NA	18.7	3.8
4	3.4%	49.2%	28.6%	18.8%	24.3%	45.6%	30.1%	20.0	5.1
5	8.9%	46.0%	15.2%	29.9%	28.3%	49.8%	21.9%	20.9	6.3

Abbreviations: DLT=dose limiting toxicity, MTD=maximum tolerated dose,
low dose=true DLT rate is [0, 0.21), target dose=true DLT rate is [0.21, 0.33), high dose=true DLT rate is [0.33, 1.00], no MTD=MTD rule is not met and determination will be based on clinical judgement.
(a) Probability of 76.9% to claim 160 mg as MTD.

In Scenario 1 where all true DLT rates are below 0.33, the probabilities of recommending the highest dose level (160 mg) is 76.9%. In Scenario 1, the average number of DLT evaluable patients required is approximately 17.2 with 2.1 DLTs expected on average. In Scenario 2, there is 25.9% chance of recommending a lower dose as MTD, 71.0% chance of successfully

recommending target dose levels. The average number of patients required is approximately 17.8, with approximately 2.8 DLTs expected on average. In Scenario 3, with faster increase of DLT rate over doses, there is a 58.1% probability of recommending target dose levels. The average number of patients required is approximately 18.7 with 3.8 DLTs expected on average. In Scenario 4, there is 49.2% chance of claiming the target doses as MTD. The average number of patients required is approximately 20.0 with 5.1 DLTs expected on average. In Scenario 5, there is 46.0% chance of claiming the target doses as MTD. The average number of patients required is approximately 20.9 with 6.3 DLTs expected on average.

The average sample sizes across different scenarios range from 17.2 to 20.9. Based on this, a total sample size of approximately 21 DLT evaluable patients is determined. Assuming a 15% drop out rate and potentially up to 5 patients will be enrolled for any cohort to further confirm the safety, the total sample size for this study will be approximately 28-33.

The accuracy of the BLRM recommendation relies on the true DLT rate, thus the safety, PK and efficacy data evaluation are combined to support the dose escalation. As an example, a hypothetical dose escalation step is shown in the following table to illustrate how BLRM guides dose escalation.

Hypothetical Dose Escalation Step

Step	Dose (mg)	#patients (evaluable)	#DLTs	Next Recommended Dose (mg)
1	40	3	0	120
2	40	3	0	
	120	4	1	160
3	40	3	0	
	120	4	1	
	160	5	2	120
4	40	3	0	
	120	8	2	120
	160	5	2	(Claim 120 mg as MTD)

Abbreviation: MTD, maximum tolerated dose.

Appendix H Detailed Description of Amendments to Text

This document describes changes in reference from Protocol Incorporating Amendment No. 05 to Protocol Incorporating Amendment No. 06.

The previous descriptions in Amendment No. 05 are identified using italicized underscore, and the amended descriptions (Amendment 06) are shown with bold letter and underline. Note that, editorial changes are not listed.

Page 1, Cover Page

Existing Text (Amendment 05)

Date: *27 July 2020*

Amendment Number: *05*

Date	Amendment Number	Region
17 October 2018	Initial Protocol	All sites
22 November 2018	Amendment No. 01	All sites
20 December 2019	Amendment No. 02	All sites
27 January 2020	Amendment No. 03	All sites
25 June 2020	Amendment No. 04	All sites
27 July 2020	Amendment No. 05	All sites

Revised Text (Amendment 06)

Date: **12 January 2022**

Amendment Number: **06**

Date	Amendment Number	Region
17 October 2018	Initial Protocol	All sites
22 November 2018	Amendment No. 01	All sites
20 December 2019	Amendment No. 02	All sites
27 January 2020	Amendment No. 03	All sites
25 June 2020	Amendment No. 04	All sites
27 July 2020	Amendment No. 05	All sites
12 January 2022	**Amendment No. 06**	**All sites**

Rationale for Amendment

To amend the protocol.

Page 3, Section 1.2 Approval (SIGNATURES)

Existing Text (Amendment 05)

[redacted]

Revised Text (Amendment 06)

[redacted]

Rationale for Amendment

Change of the person in charge

Page 40, Section 8.1 Study Drug Administration (Phase 2 Part)

Existing Text (Amendment 05)

Phase 2 Part

TAK-788 drug product will be administered orally. TAK-788 will be self-administered by the patient. The dose will be 160 mg orally administered once daily. Each 28-day dosing period is referred to as 1 cycle. Patients will take the prescribed dose with water with or without a low-fat meal (ie, ≤350 kcal and ≤15% of calories from fat). 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). Missed doses should be recorded in an appropriate source record (eg, clinic chart), patient diary, and study drug administration eCRF.

Revised Text (Amendment 06)

Phase 2 Part

TAK-788 drug product will be administered orally. TAK-788 will be self-administered by the patient. The dose will be 160 mg orally administered once daily. Each 28-day dosing period is referred to as 1 cycle. Patients will take the prescribed dose with water with or without a low-fat meal (ie, ≤350 kcal and ≤15% of calories from fat). 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). Missed doses should be recorded in an appropriate source record (eg, clinic chart), patient diary, and study drug administration eCRF.

In case of extenuating circumstances that prevent a patient from attending the study site (eg, the COVID-19 pandemic), drug packs and patient diaries should be returned at the next available on-site clinic visit.

Rationale for Amendment

To ensure patient monitoring and evaluation during the coronavirus disease 2019 (COVID-19) public health emergency.

Page 43, Section 8.4.1.1 Management of Selected Treatment-Related Adverse Events

Existing Text (Amendment 05)

Diarrhea

Based on pre-clinical findings and known class effect, patients should be monitored for the onset of diarrhea. Symptomatic care, such as loperamide, may be given at first evidence of loose stool, increased frequency of bowel movement, or at grade 1 diarrhea, according to the investigator's clinical judgment. For grade 2 diarrhea, administer loperamide at 4 mg, then 2 mg every 2 to 4 hours until the patient is symptom-free for 12 hours. No dose modification is necessary unless the patient does not tolerate TAK-788 or the symptom recurs. For grade ≥3 diarrhea despite loperamide, treatment will be withheld until recovery to grade ≤1 diarrhea. Secondary prophylaxis in patients who have experienced diarrhea with TAK-788 treatment is allowed. Other medications (such as diphenoxylate hydrochloride with atropine sulfate) and supportive care may be added according to the institution's standard of care. Primary prophylactic antidiarrheal medications may be used after discussion with the sponsor.

Revised Text (Amendment 06)

Diarrhea

Based on pre-clinical findings and known class effect, patients should be monitored for the onset of diarrhea. Symptomatic care, such as loperamide, may be given at first evidence of loose stool,

increased frequency of bowel movement, or at grade 1 diarrhea, according to the investigator's clinical judgment **(not to exceed total dose of 16 mg over 24 hours)**. For grade 2 diarrhea, administer loperamide at 4 mg, then 2 mg every 2 to 4 hours until the patient is symptom-free for 12 hours **(not to exceed total dose of 16 mg over 24 hours)**. No dose modification is necessary unless the patient does not tolerate TAK-788 or the symptom recurs. For grade ≥3 diarrhea despite loperamide, treatment will be withheld until recovery to grade ≤1 diarrhea. Secondary prophylaxis in patients who have experienced diarrhea with TAK-788 treatment is allowed. Other medications (such as diphenoxylate hydrochloride with atropine sulfate) and supportive care may be added according to the institution's standard of care. Primary prophylactic antidiarrheal medications may be used after discussion with the sponsor.

Rationale for Amendment

For consistency across the TAK-788 program.

Page 43, Section 8.4.1.1 Management of Selected Treatment-Related Adverse Events

Existing Text (Amendment 05)

N/A

Revised Text (Amendment 06)

Cardiac Events: QTc Interval Prolongation and Heart Failure

TAK-788 dose modification guidelines, outlined in Table 8.c, should be closely followed for patients who experience QTc interval prolongation or heart failure deemed related to TAK-788 dosing. TAK-788 dose reduction levels should follow the schedule outlined in Table 8.b.

Table 8.c TAK-788 Dose Modification for TEAEs of QTc Interval Prolongation and Heart Failure

Toxicity Grade	Parameters	TAK-788 Dose Modification
QTc Interval Prolongation		
Grade 2	QTc Interval of 481 to 500 msec.	First Occurrence: • Withhold TAK-788 dosing until QTc interval recovers to a ≤Grade 1 or baseline. • Once recovered, resume TAK-788 at the most recent dose. Recurrence: • Withhold TAK-788 until ≤ Grade 1 or baseline. • Once recovered, resume TAK-788 dosing at the next lower dose level or permanently discontinue dosing, based on clinical judgement.
Grade 3	≥501 msec *or* Increases of >60 msec from baseline.	First Occurrence: • Withhold TAK-788 until ≤ Grade 1 or baseline. • Once recovered, resume TAK-788 dosing at the next lower dose level, or permanently discontinue TAK-788 dosing, based on clinical judgement. Recurrence: • Permanently discontinue TAK-788 dosing.
Grade 4	Torsades de Pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmias.	Permanently discontinue TAK-788 dosing.
Decreased Ejection Fraction		
Grade 2: Ejection fraction - asymptomatic.	Resting ejection fraction 50% to 40% *or* Decrease from baseline 10% to 19%.	• Withhold TAK-788 until recovered to baseline. • If the patient recovers to baseline within 2 weeks of dose interruption, resume TAK-788 at the most recent dose level or the next lower dose level, in accordance with clinical judgement. • If the patient does not resume to baseline within 2 weeks of dose interruption, permanently discontinue TAK-788 dosing.

Toxicity Grade	Parameters	TAK-788 Dose Modification
≥Grade 3: Ejection fraction - asymptomatic.	Resting ejection fraction ≤39% *or* ≥ 20% decrease from baseline.	Permanently discontinue TAK-788 dosing.
Heart Failure		
Any Grade Heart failure - symptomatic		Permanently discontinue TAK-788 dosing.

QTc: corrected QT interval; TEAE: treatment-emergent adverse event.

Rationale for Amendment

To align the current protocol with newly available safety information, and to ensure consistency in dose modifications guidelines across the TAK-788 program.

Page 50, Section 8.7.3 Concomitant Medications with QTc Interval Prolongation Potential

Existing Text (Amendment 05)

N/A

Revised Text (Amendment 06)

8.7.3 Concomitant Medications with QTc Interval Prolongation Potential

Investigators should provide close oversight of patients when co-dosing TAK-788 with concomitant medications with known QTc inteval prolongation. Additional ECGs, as clinically indicated should be conducted in accordance with the investigator's judgement. Dose modification for patients exhibiting QTc interval prolongation is outlined in Section 8.3.1.5. Restricted concomitant medications with a known risk of Torsades de Pointes are provided in Appendix F.

Rationale for Amendment

To provide additional precautionary guidance for investigators regarding the concomitant dosing of medications with QTc interval prolongation potential.

Page 52, Section 8.13 Storage, Handling, and Accountability

Existing Text (Amendment 05)

The recommended storage condition for TAK-788 drug product is at a temperature thermostatically maintained at the usual customary working environment of 1°C to 30°C, as experienced in pharmacies, hospitals, and warehouses.

The study pharmacist or designee at the site will be responsible for handling and dispensing study drug and completing associated documentary paperwork. Supplies are 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 medication is dispensed to a patient, the following information must be recorded: the patient identification number, drug product strength, quantity dispensed with the corresponding lot number, and the signs 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.

Revised Text (Amendment 06)

The recommended storage condition for TAK-788 drug product is at a temperature thermostatically maintained at the usual customary working environment of 1°C to 30°C, as experienced in pharmacies, hospitals, and warehouses.

The study pharmacist or designee at the site will be responsible for handling and dispensing study drug and completing associated documentary paperwork. Supplies are 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 medication is dispensed to a patient, the following information must be recorded: the patient identification number, drug product strength, quantity dispensed with the corresponding lot number, and the signs 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.

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/IRB, TAK-788 can be shipped DTP from the investigation site to the patient's home address via courier if needed.

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.

Rationale for Amendment

To ensure continuity of TAK-788 treatment due to COVID-19 related quarantines, cancellations of on-site visits, or concerns about possible COVID-19 exposure.

Page 54, Section 9.4 Study Procedures

Existing Text (Amendment 05)

The study procedures to be performed at screening and throughout the entire study are listed in the schedule of events (Appendix A), which is meant to provide a convenient display of the timing and scope of required assessments expected at each visit, but does not provide a

comprehensive description of each assessment. Additional details are provided as necessary in the sections that follow.

The ICF may be signed more than 21 days before C1D1. Screening assessments must be performed within 14 days before C1D1, with the exception of tumor imaging assessment, for which the allowable window is 21 days before C1D1.

Investigators must be familiar with the details of this section and use it in conjunction with the table to adequately carry out the required study assessments. All study assessments should occur within ±3 days of the scheduled study day unless otherwise noted in the schedule of events descriptions or table. A cycle is defined as 28 days.

In Phase 1, patients will be hospitalized during DLT evaluation in Cycle 1. If a patient needs to be discharged temporarily during the period, the investigator must obtain an approval from the sponsor. The investigator must document the confirmation record for stabilization of the patient's symptoms per the available data in an appropriate source record (eg, medical records) before the patient's temporary discharge.

Revised Text (Amendment 06)

The study procedures to be performed at screening and throughout the entire study are listed in the schedule of events (Appendix A), which is meant to provide a convenient display of the timing and scope of required assessments expected at each visit, but does not provide a comprehensive description of each assessment. Additional details are provided as necessary in the sections that follow.

The ICF may be signed more than 21 days before C1D1. Screening assessments must be performed within 14 days before C1D1, with the exception of tumor imaging assessment, for which the allowable window is 21 days before C1D1.

Investigators must be familiar with the details of this section and use it in conjunction with the table to adequately carry out the required study assessments. All study assessments should occur within ±3 days of the scheduled study day unless otherwise noted in the schedule of events descriptions or table. A cycle is defined as 28 days.

In Phase 1, patients will be hospitalized during DLT evaluation in Cycle 1. If a patient needs to be discharged temporarily during the period, the investigator must obtain an approval from the sponsor. The investigator must document the confirmation record for stabilization of the patient's symptoms per the available data in an appropriate source record (eg, medical records) before the patient's temporary discharge.

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. Such instances will be documented in the study records.

Rationale for Amendment

To ensure patient monitoring and evaluation during the coronavirus disease 2019 (COVID-19) public health emergency.

Page 59, Section 9.4.18 Disease Assessment

Existing Text (Amendment 05)

At screening, disease assessment must include imaging of the chest, abdomen, pelvis, and brain using appropriate radiological procedures (computed tomography [CT] scans or magnetic resonance imaging [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.

Patients must have at least 1 measurable lesion per RECIST v1.1 (see Appendix C). Previously irradiated lesions may not be used for target lesions, unless there is unambiguous radiological progression after radiotherapy. For Phase 1 part, brain lesions may be used as target lesions provided they are ≥10 mm and have not been: 1) previously treated with whole brain radiation therapy (WBRT) within 3 months, or 2) previously treated by SRS or surgical resection.

Abbreviated

Revised text (Amendment 06)

At screening, disease assessment must include imaging of the chest, abdomen, pelvis, and brain using appropriate radiological procedures (computed tomography [CT] scans or magnetic resonance imaging [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.

Patients must have at least 1 measurable lesion per RECIST v1.1 (see Appendix C). Previously irradiated lesions may not be used for target lesions, unless there is unambiguous radiological progression after radiotherapy. For Phase 1 part, brain lesions may be used as target lesions provided they are ≥10 mm and have not been: 1) previously treated with whole brain radiation therapy (WBRT) within 3 months, or 2) previously treated by SRS or surgical resection.

Local site investigator/radiology assessment based on RECIST version 1.1 will be used to determine subject eligibility. In extenuating circumstances during the COVID-19 public health emergency, patients may use alternative site for imaging if approved by the sponsor or designee.

Abbreviated

Rationale for Amendment

To ensure patient monitoring and evaluation during the coronavirus disease 2019 (COVID-19) public health emergency.

Page 80, Section 14.1 Study-Site Monitoring Visits

Existing Text (Amendment 05)

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.

All aspects of the study and its documentation will be subject to review by the sponsor or designee including, but not limited to, the investigator's binder, study medication, subject medical records, informed consent documentation, 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.

Revised text (Amendment 06)

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.

All aspects of the study and its documentation will be subject to review by the sponsor or designee including, but not limited to, the investigator's binder, study medication, subject medical records, informed consent documentation, 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.

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.

Rationale for Amendment

To ensure patient monitoring and evaluation during the coronavirus disease 2019 (COVID-19) public health emergency.

Page 102, Appendix F Drugs with a Risk of Torsades de Pointes

Existing Text (Amendment 05)

The website *crediblemeds.org/everyone/composite-list-all-qtdrugs/[Accessed: 7 June 2019]* 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 the table 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.

Drugs Generally Accepted by the CredibleMeds QTDrug List Advisory Board to have 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/ thrombocytemia*
Arsenic trioxide	*Trisenox*	*Anticancer/leukemia*
Astemizole	*Hismanal*	*Antihistamine/allergic rhinitis*
Azithromycin	*Zithromax, Zmax*	*Antibiotic/bacterial infection*
Bepridil	*Vascor*	*Antianginal/angina pectoris (heart pain)*
Chloroquine	*Aralen*	*Antimalarial/malaria*
Chlorpromazine	*Thorazine, Largactil, Megaphen*	*Antipsychotic, Antiemetic/schizophrenia, nausea, many others*
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, Zineryt, 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, Ecrimal, Flécaine*	*Antiarrhythmic/abnormal heart rhythm*
Fluconazole	*Diflucan, Trican*	*Anti-fungal/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*
Ibogaine	*None*	*Psychedelic/narcotic addition, unproven*
Ibutilide	*Corvert*	*Antiarrhythmic/abnormal heart rhythm*
Levofloxacin	*Levaquin, Tavanic*	*Antibiotic/bacterial infection*
Levomepromazine	*Nosinan, Nozinan, Levoprome*	*Antipsychotic/schizophrenia*
Levomethadyl acetate	*Orlaam*	*Opiate agonist/narcotic dependence*
Levosulpiride	*Lesuride, Levazeo, Enliva (with rabeprazole)*	*Antipsychotic/schizophrenia*
Mesoridazine	*Serentil*	*Antipsychotic/schizophrenia*
Methadone	*Dolophine, Symoron, Amidone, Methadose, Physeptone, Heptadone*	*Opiate agonist/pain, narcotic dependence*
Moxifloxacin	*Avelox, Avalox, Avelon*	*Antibiotic/bacterial infection*

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, and others*	*Vasoconsrictor/septic shock*
Terodiline	*Micturin, Mictrol (not bethanechol)*	*Muscle relaxant/bladder spasm*
Thioridazine	*Mellaril, Novoridazine, Thioril*	*Antipsychotic/schizophrenia*
Vandetanib	*Caprelsa*	*Anticancer/cancer (thyroid)*

Revised Text (Amendment 06)

The website **crediblemeds.org/everyone [Accessed: 19 November 2021]** 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.

Drugs with a known risk of Torsades de Pointes are listed in the table 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.

Drugs Generally Accepted by the CredibleMeds QTDrug List Advisory Board to have a Known Risk of Causing Torsades de Pointes; Prohibited in this Study

Generic Name	Brand Name	General Indication [a]	Source [a]
Analgesics/Anethesic			
Cocaine	Numbrino	Local anesthetic for mucus membranes of the nasal cavity (for diagnostic or surgical procedures).	Numbrino (cocaine hydrochloride) PI
Propofol	Diprivan, Propoven	Initiation and maintenance of general anesthesia or sedation in accordance with the approved label.	Diprrivan (propofol) PI
Sevoflurane	Ultane, Sojourn	Induction and maintenance of general anesthesia.	Ultane (sevoflurane) PI
Anti-allergy Agents			
Astemizole	Hismanal	Treatment of allergic rhinitis, allergic conjunctivitis, and chronic urticaria.	Hismanal (astemizole) US PI
Terfenadine	Seldane	Antihistamine/allergic rhinitis	Not available
Anticancer Treatments			
Aclarubicin	Aclacin, Aclacinomycine, Aclacinon, Aclaplastin, Jaclacin	Treatment of malignant blood disorders.	Aclarubicin (aclarubicin hydrochloride) SmPC
Arsenic trioxide	Trisenox	Treatment of APL.	Trisenox (arsenic trioxide for injection) PI
Oxaliplatin	Eloxatin	Treatment of advanced colorectal rectal cancer.	Eloxatin (Oxaloplatin for Injection) PI
Vandetanib	Caprelsa	Treatment of medullary thyroid cancer.	Capresla (vandetanib) PI
Anti-infectives			
Azithromycin	Zithromax, Zmax	Treatment of bacterial infections as outlined in the approved label.	Zithromax (azithromycin) PI
Chloroquine	Aralen	Antimalarial /Treatment of malaria.	Aralen (chloroquine phosphate) PI
Ciprofloxacin	Cipro, Cipro-XR, Neofloxin	Treatment of bacterial infections as designated by the label.	Cipro (ciprofloxacin hydrochloride) PI
Clarithromycin	Biaxin, Prevpac	Treatment of bacterial infections as designated by the label.	Biaxin (clarithromycin) PI

Generic Name	Brand Name	General Indication [a]	Source [a]
Erythromycin	Abboticin, Abboticin-ES, Acnasol, E Base, EES, EMycin, Erycin, Eryc Ranbaxy, Erymax, Erypar, Eryped, Ery-Tab, Erythrocin Stearate Filmtab, Erythrocot, Erythroped, Ilosone, MY-E, Pediamycin, PCE Dispertab, Robimycin, Stiemycine, Tiloryth, Zineryt	Treatment (and for some agents, the prevention) of bacterial infections as outlined in the approved label.	Erycin (erythromycin) PI
Fluconazole	Diflucan, Trican	Treatment for fungal infections as outlined in the approved label.	Diflucan (Fluconazole Tablets) (Fluconazole for Oral Suspension) PI
Gatifloxacin	Tequin	Treatment and prevention of bacterial infections as outlined in the approved package insert.	Tequin (gatifloxcacin) PI
Grepafloxacin	Raxar	Treatment of infections caused by strains of microorganisms outlined in the approved label.	Raxar (domperidone) PI
Halofantrine	Halfan	Treatment of mild to moderate malaria.	Halfan (halofantrine hydrochloride) PI
Levofloxacin	Levaquin, Tavanic	Treatment of bacterial infections as outlined in the approved label.	Levaquin (levofloxacin) PI
Moxifloxacin	Avelox, Avalox, Avelon	Treatment or prevention of susceptible bacteria in accordance with the approved label.	Avelox (moxifloxacin hydrochloride) PI
Pentamidine	Pentam	Prevention of PJP in high-risk patients.	Pentam (pentamidine isetionate) PI
Roxithromycin	Biaxsig, Coroxin, Roxar, Roximycinv, Roxl-150, Roxo, Roxomycin, Rulid, Rulide, Surlid, Tirabicin, Xthrocin	Treatment of bacterial infections as outlined in the approved label.	Biaxsig (roxithromycin) PI
Sparfloxacin	Zagam	Treatment of bacterial infections as outlined in the approved label.	Zagam (sparfloxacin) PI
Cardiac Agents			

Generic Name	Brand Name	General Indication [a]	Source [a]
Amiodarone	Cordarone, Pacerone, Nexterone	Treatment and/or prophylaxis for (1) recurrent VF, or (2) recurrent hemodynamically unstable VT, in accordance with the approved label.	Nexterone (amiodarone HCL) PI
Bepridil	Vascor	Treatment of angina.	Vascor (imidapril hydrochloride) PI
Disopyramide	Norpace	Treatment of ventricular arrythmias.	Norpace (disopyramide phosphate) PI
Dofetilide	Tikosyn	Maintenance of sinus rhythm in patients at risk for atrial arrhythmia.	Tikosyn (dofetilide) PI
Dronedarone	Multaq	Antiarrhythmic for patients at risk for AFL.	Multaq (dronedarone) PI
Flecainide	Almarytm, Apocard, Ecrinal, Flécaine, Tambocor	Treatment for arrhythmic conditions as outlined in the approved label.	Almarytm (flecainide acetate) PI
Hydroquinidine, dihydroquinidine	Serecor LP, Lentoquine, Idrochinidina Lirca, Austacute	Prevention and treatment of ventricular dysrhythmias in accordance with the approved label.	Serecor LP (hydroquinidine) PI
Ibutilide	Corvert	Treatment of AFIB and AFL.	Corvert (ibutilide fumarate for injection) PI
Procainamide	Pronestyl, Procan	Treatment of ventricular arrhythmias.	Pronestyl (procainamide) PI
Quinidine	Quinaglute, Duraquin, Quinact, Quinidex, Cin-Quin, Quinora	Treatment of (1) AFIB, AFL, VT, or PSVT in accordance with the approved label.	Quinaglute (quinidine) PI
Sotalol	Betapace, Sotalex, Sotacor	Maintainence of sinus rhythm in patients with symptomatic AFIB/AFL.	Betapace AF (sotalol HCl) PI
Gastrointestinal Agents			
Cisapride	Propulsid	Treatment of GERD.	Propulsid (cisapride) SmPC
Domperidone	Motilium, Motillium, Motinorm Costi, Nomit	Treatment of various gastric disorders (eg, gastric reflux disease, nausea, vomiting) in accordance with the approved label.	Domperidone SmPC
Ondansetron	Zofran, Anset, Ondemet, Zuplenz, Emetron, Ondavell, Emeset, Ondisolv, Setronax	Prevention of (1) PONV, (2) nausea/vomiting associated with administration of chemotherapy and/or radiation treatment.	Zofran (ondansetron hydrochloride) PI

Generic Name	Brand Name	General Indication [a]	Source [a]
Psychotropics			
Citalopram	Celexa, Cipramil	Treatment of depression.	Celexa (citalopram hydrochloride) PI
Donepezil	Aricept	Treatment of dementia of the Alzheimer type.	Aricept (donepezil hydrochloride) PI
Escitalopram	Animaxen, Anxiset-E, Cipralex, Elicea, Entact, Esitalo, Esto, Exodus, Lexam, Lexamil, Lexapro, Losita, Nexito, Reposil, Seroplex	Treatment for various psychiatric disorders and related conditions as outlined in the approved label.	Animaxen (escitalopram) PI
Haloperidol	Aloperidin, Bioperidolo, Brotopon, Dozic, Duraperidol, Einalon S, Eukystol, Haldol, Halosten, Keselan, Linton, Peluces, Serenace, Serenase, Sigaperidol	Treatment and management of psychiatric and neuropsychiatric disorders and associated manifestations (eg, schizophrenia, mania, tics secondary to Tourette's Disorder) as outlined in the approved label.	Aloperidin (haloperidol decanoate) PI
Mesoridazine	Serentil	Management of schizophrenia.	Serentil (mesoridazine besylate) PI
Pimozide	Orap	Suppression of motor and phonic tics associated with Tourette's Disorder.	Orap (Pimozide) PI
Sulpiride	Dogmatil, Dolmatil, Eglonyl, Espiride, Modal, Sulpor	Treatment of acute and chronic schizophrenia.	Sulpiride PI
Sultopride	Barnetil, Barnotil, Topral	Control of (1) psychiatric urgencies, (2) psychomotor excitement, (3) acute delusional episodes, or (4) confusional states.	Topral (sultopride) PI
Thioridazine	Mellaril, Novoridazine, Thioril	Treatment of schizophrenia.	Mellaril (thioridazine) PI
Other			
Anagrelide	Agrylin, Xagrid	Treatment of thrombocythemia in accordance with the approved label.	Xagrid (anagrelide) PI
Chlorpromazine	Thorazine, Largactil, Megaphen	Treatment of (1) various psychoses, and psychomotor agitation excitement in accordance with the approved label, (2) intractable hiccups, (3) nausea/vomiting associated with terminal illness.	Thorazine (chlorpromazine hydrochloride for injection) PI

Generic Name	Brand Name	General Indication [a]	Source [a]
Cilostazol	Pletal	Reduction of symptoms related to intermittent claudication.	Pletal (cilostazol) PI
Droperidol	Inapsine, Droleptan, Dridol, Xomolix	Inaspsine, Droleptan, Xomolix: reduction of PONV. Dridol: treatment of hypoparathyroidism, refractory rickets, and familial hypophosphatemia.	Dridol (droperidol for injection) PI
Levomepromazine	Nosinan, Nozinan, Levoprome	Supportive treatment for terminally ill patients for (1) intractable nausea and vomiting, (2) management of pain,(3) restlessness, and distress.	Levomepromazine (Levomepromazine Maleate) PI
Levomethadyl acetate	Orlaam	For the management of opiate dependencies.	Orlaam (levomethadyl acetate hydrochloride) PI
Levosulpiride	Lesuride, Levazeo, Enliva (with rabeprazole)	Treatment of various psychiatric and GI disorders in accordance with the approved label.	Levosulpiride PI
Methadone	Dolophine, Symoron, Amidone, Methadose, Physeptone, Heptadone	(1)Treatment of severe pain, (2) supportive treatment in the detoxification of opioid addiction.	Dolophine hydrochloride (methadone hydrochloride) PI
Papaverine HCl (Intra-coronary)	None	For treatment of (1) erectile dysfunction, (2) arrhythmias due to MI. Prophylaxis for peripheral atrial catheter patency.	Papaverine HCL PI
Probucol	Lorelco	Treatment for lowering cholesterol.	Lorelco (probucol) PI
Terlipressin	Teripress, Glypressin, Terlipin, Remestyp, Tresil, Teriss, and others	Treatment of bleeding oesophageal varices.	Teripress (teripressin) PI
Terodiline	Micturin, Mictrol (not bethanechol)	Muscle relaxant/bladder spasm	Not available
Ibogaine	None		Not available

AFIB: atrial fibrillation; AFL: atrial flutter; APL: acute promyelocytic leukemia; EES: erythromycin ethylsuccinate; GERD: gastroesophageal reflux disease; GI: gastrointestinal; IBS: irritable bowel syndrome; MI: myocardial infarction; PJP: pneumocystis jiroveci pneumonia; PONV: post-operative nausea and vomiting; PSVT: paroxysmal supraventricular tachycardia; VF: ventricular fibrillation; VT: ventricular tachycardia.
a Refer to the most current package insert/summary of product characteristics as relevant to the specific prescribing agent and region for the approved indication and safety-related dosing guidance.

Rationale for Amendment

For consistency across the TAK-788 program.